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Welcome

Welcome to the third edition of the *European Medical Journal*, which draws together the latest research findings and important developments from therapeutic medicine. The journal offers an array of high-quality peer-reviewed articles, feature articles, and symposia. Together they provide comprehensive reviews, informative evaluations, and invaluable insights into current and developing research, management, and treatment of diseases and disorders.

Among the peer-reviewed articles is an informative review of stress urinary incontinence in women by Lee and Zimmern, an endemic problem that proves costly on both a personal and social level. The article draws necessary attention to the progress still required from researchers in developing effective and practical approaches to the evaluation of this disorder. From the field of interventional cardiology, Di Gioia et al. provide an important assessment of the clinical features, diagnosis, and treatment of in-stent restenosis. The article emphasises the importance of defining the best approaches to management of this type of restenosis, which complicates the use of stroke-preventing stents. From the field of rheumatology, del Río-Martínez offers a concise update on our current understanding of spondyloarthritis. While highlighting the limitations in what we know of its development, the article also points to the potential impact of environmental triggers.

Also included in the journal are two insightful feature articles. The first, by Kiss, presents an assured discussion of the benefits of awake thoracic surgery to aid the quality of life of chronically ill patients, while also tackling the ethical issues that surround its use. The second, by Ma and Melson, provides an overview of the identification and removal of sessile serrated polyps throughout colonoscopy and post-polypectomy management.

We hope you enjoy the third edition of *European Medical Journal* and that the topics covered create some food for thought over the coming months. Each of our authors and the members of our esteemed Editorial Board have striven to provide you with a collection of the highest quality research and articles that prove to be both informative and insightful. We already look forward to reporting on even more developments and breakthroughs from across the medical field in the next edition of the *European Medical Journal*, due to be published at the end of this year.

Spencer Gore

Director, European Medical Journal

European Medical Journal is published four times a year.
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Front cover and contents artwork: Stacey Rivers/EMJ

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1. Al-Jahdali, et al. Allergy Asthma Clin Immunol. 2013; 9(1): 8. **2.** Melani, et al. Respir Med. 2011; 105(6): 930–8. **3.** Yildiz, et al. Respir Care. 2014; 59: 223–30. **4.** Global Initiative for Chronic Obstructive Lung Disease (GOLD) – Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2016. Available at: http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/. Date accessed: July 2016.

SANOFI

SANGGX.RESP.15.06.0009(1) Date of preparation: July 2016

Foreword

Dr Harry Thirkettle

BSc Hons MBChB Hons MRCS.

Dear Colleagues,

I would like to welcome you all to the third edition of the *European Medical Journal*, which brings you a series of reviews that analyse and synthesise the latest evidence and guidelines for a range of key medical conditions.

In the Editor's Pick, Fleming discusses fibromyalgia, offering insights into the pathogenesis, diagnosis, and management of this enigmatic disease entity. del Río-Martínez reviews spondyloarthritis, giving an excellent overview of the condition and useful information on its investigation and treatment.

There are papers exploring recommendations and advances in the field of interventional cardiology, for example Mallidi and Lotfi look at late and very late stent thrombosis in the context of different drug-eluting stents. Other topics covered include stress urinary incontinence in a state-of-the-art review by Lee and Zimmern, and cirrhosis, which is featured in a fascinating discussion of the clinical aspects and the future of care of patients with this disease provided by Verhelst et al.

> "The Editorial Board wishes you pleasant reading and encourages you to join the discussion and give us your feedback and comments as we strive to bring you relevant, useful, high-quality peer-reviewed content to meet your intellectual and educational needs."

Finally, I am delighted to present our two feature articles. The opening piece by Kiss takes us on a philosophical journey through the challenging terrain of ethical issues surrounding awake thoracic surgery in the palliation of critically ill patients. Considerations include personalised treatment, patient motivations, and management of patient wishes in the context of ethics and legislation. There is also a fascinating evaluation of endoscopic management of sessile serrated polyps of the colon by Ma and Melson.

The Editorial Board wishes you pleasant reading and encourages you to join the discussion and give us your feedback and comments as we strive to bring you relevant, useful, high-quality peer-reviewed content to meet your intellectual and educational needs.

Harry Thirkettle

BSc Hons MBChB Hons MRCS

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Volibris® (Ambrisentan) Prescribing Information Please refer to full Summary of Product Characteristics (SPC) before prescribing. Volibris® 5 mg and 10 mg film-coated tablets. Each tablet contains 5mg and 10mg ambrisentan, respectively.**Uses:** The treatment of patients with pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II and III including use in combination treatment. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease (PAH-CTD). **Dosage and administration:** Treatment must be initiated by a physician experienced in the treatment of PAH. Oral only. The tablet must be taken whole and not split, crushed or chewed. Adults: Monotherapy: Begin at 5mg. Increase to 10mg daily depending on clinical response and tolerability. In combination with tadalafil: Titrate up to 10mg daily. When co-administered with cyclosporine A, limit dose to 5 mg once daily and monitor the patient carefully. 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If clinically significant fluid retention develops undertake further evaluation to determine the cause and the possible need for specific treatment or discontinuation of ambrisentan. The incidence of peripheral oedema increased in combination with tadalafil. This was highest within the first month of treatment. Cases of pulmonary oedema have been reported with vasodilating agents, when used in patients with pulmonary veno-occlusive disease. If patients develop acute pulmonary oedema, the possibility of pulmonary veno-occlusive disease should be considered. Closely monitor when starting treatment with rifampicin. Do not initiate in women of child-bearing potential unless the result of a pre-treatment pregnancy test is negative and reliable contraception is used. Perform monthly pregnancy tests during treatment. Liver function abnormalities have been associated with PAH. Cases consistent with autoimmune hepatitis, hepatic injury and hepatic enzyme elevations related to therapy have been observed. Measure hepatic aminotransferases (ALT and AST) prior to initiation. Monitor ALT and AST monthly. Discontinue if sustained, unexplained, clinically significant ALT and/or AST elevation develop, or if there are also signs or symptoms of hepatic injury (e.g. jaundice). Do not prescribe for patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Tablets contain the azo colouring agent Allura red AC Aluminium Lake (E129), which can cause allergic reactions. **Drug Interactions:** Limit dose to 5 mg once daily when co-administered with cyclosporine A. Caution when co-administering with other treatments for PAH (e.g. prostanoids and soluble guanylate cyclase stimulators) as efficacy and safety has not been evaluated. 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Cases of raised hepatic transaminases reported commonly and autoimmune hepatitis and hepatic injury uncommonly in routine pharmacovigilance and clinical trials. Please refer to SPC for details of other side effects. **Overdose:** Potential for severe hypotension which may require cardiovascular support. **Legal category:** POM. **Presentation and Basic NHS cost:** Film coated tablet. 5mg x 30, £1618.08; 10mg x 30, £1618.08. **Marketing Authorisation (MA):** EU/1/08/451/002, EU/1/08/451/004 **MA Holder:** Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom. **Last date of revision:** December 2015. UK/ABT/0029/15(1)

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References:

1. Galiè N *et al.* Eur Heart J 2016; 37: 67–119. 2. GlaxoSmithKline. Volibris Summary of Product Characteristics. Available at: www.medicines.org.uk/emc [accessed July 2016]. 3. Galiè N *et al.* N Engl J Med 2015; 373: 834–844. 4. Galiè N *et al.* N Engl J Med 2015; 373: 834–844 (supplementary information). 5. Eli Lilly. Adcirca Summary of Product Characteristics. Available at: www.medicines.org.uk [accessed July 2016].

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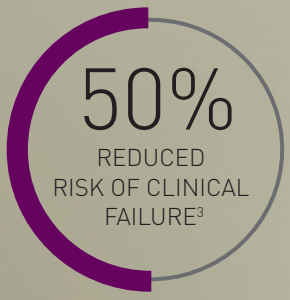

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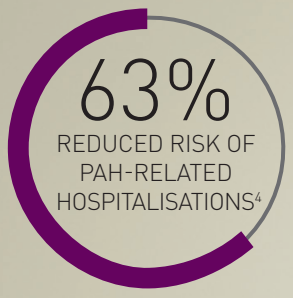

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The use of tadalafil is not recommended in patients chronically taking potent inducers of CYP3A4, such as rifampicin, or concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir. Inform patients not to take tadalafil with other PDE5 inhibitors or other treatments for erectile dysfunction as these combinations have not been studied. Tadalafil co-administered with prostacyclin or its analogues has not been studied in controlled clinical trials. Caution is recommended in case of co-administration. The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated. Tadalafil contains lactose mono-hydrate. Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this product. **Pregnancy and Lactation** There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development. Avoid the use of tadalafil during pregnancy. Tadalafil should not be used during breast-feeding. **Driving, etc** Tadalafil has negligible influence on the ability drive or operate machinery, patients should be aware of how they react to tadalafil before driving or operating machinery. **Undesirable Effects** Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known. *Very common:* Headache[3], flushing, nasopharyngitis (including nasal congestion, sinus congestion, and rhinitis), nausea, dyspepsia (including abdominal pain/discomfort), myalgia, back pain, pain in extremity (including limb discomfort). *Common:* Hypersensitivity reactions, migraine, chest pain[2], palpitations[2], blurred vision, hypotension, epistaxis, vomiting, gastroesophageal reflux, rash, increased uterine bleeding, facial oedema, syncope. *Uncommon:* Seizures, transient amnesia, tinnitus, sudden cardiac death[2], tachycardia[2], hypertension, urticaria, hyperhydrosis (sweating), priapism, haematuria, penile haemorrhage, haematospermia. *Not known*[1]*:* Stroke[2] (including haemorrhagic events), NAION, retinal vascular occlusion, visual field defect, sudden hearing loss, unstable angina pectoris, ventricular arrhythmia, myocardial infarction[2], Stevens-Johnson syndrome, exfoliative dermatitis, prolonged erections, angioedema. [1]Events not reported in registration studies and cannot be estimated from the available data. [2]Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. [3]At the beginning of therapy, headache may occur and decreases over time even if treatment is continued. Adverse reactions reported with tadalafil were transient, and generally mild or moderate. Adverse reaction data are limited in patients >75 years. *For full details of these and other side-effects, please see the Summary of Product Characteristics, which for the UK is available at http://emc.medicines.org.uk/* and for Ireland at http://www.medicines.ie/ **Legal Category** POM **Marketing Authorisation Number** EU/1/08/476/006 **Basic NHS Cost** £491.22 per pack of 56 X 20mg **Date of Preparation or Last Review** August 2015 UK/ADC/0001/15(1) **Full Prescribing Information is Available From** Eli Lilly and Company Limited, Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL. Telephone: Basingstoke (01256) 315 000 E-mail: ukmedinfo@lilly.com Website: www.lilly.co.uk ADCIRCA® (tadalafil) is a registered trademark of Eli Lilly and Company.

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ETHICAL ISSUES ON AWAKE THORACIC SURGERY FOR SERIOUSLY CHRONICALLY ILL PATIENTS

*Gabor Kiss

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Patients of any age with a serious progressive illness and a limited life expectancy that ranges up to a few years can be managed by palliative care. The aim of palliative care is to improve quality of life for patients and their families. In the USA, patients who are willing to forego curative treatment and have a prognosis of survival of ≤6 months live under hospice care. Advanced communication skills have to be used to establish goals of care for patients in palliative and hospice care.[1] Even if these patients have limited life expectancy, they can often remain physically stable and contribute positively to their close environment and to society.

Despite a certain degree of decreased physical capacity, a patient may still want to live longer due to life goals that can involve commitments to full or part-time work such as teaching, or caring for minors or for a disabled family member. The patient may also not wish to miss out on important life occasions, such as witnessing the birth of a child, or they may wish to live longer simply because of a reasonable quality of life in spite of serious illness.

As we do not know how long a patient will live whilst receiving palliative care, we have to treat reversible medical problems if the patient expresses a wish to benefit as much as possible from their remaining life time. This implies that treatment must be individualised and adapted to the patient's needs, requiring a thorough discussion with the patient and their loved ones.[1] Meier and Mandrola,[2] who are specialists in palliative care, have come up with a rule "to manage the person, not the prognosis."

Thoracic surgery is an important therapeutic option in the management of reversible causes of breathlessness and pain, with the aim of relieving acute symptom distress in the palliative patient. In the literature, the treatment of reversible, acute worsening breathlessness is one indication to use awake thoracic surgery (ATS) for patients with severe chronic respiratory disease involving surgery of the pleural space, lungs, and the mediastinum.[3]

General anaesthesia (GA) and intubation remain the last resort for thoracic surgery as these procedures are linked with a high risk of morbidity and mortality in severe chronic respiratory disease patients.[4-9] Consequently, we need to offer the patient less harmful and less invasive alternatives to these anaesthetic techniques such as ATS, before resorting to the use of GA with all of its additional risks.

In the case of acute worsening but surgically reversible dyspnoea in patients with severe chronic respiratory disease, ATS can be used to help achieve the goal of palliative or hospice care in relieving unnecessary suffering and it can limit postoperative complications caused by GA. ATS is indicated if the risks of GA outweigh the benefits and if thoracic surgery under spontaneous respiration is considered of less risk to the patient when compared with ventilation under GA.[3]

Most patients want to spend the rest of their life at home, especially those who benefit from medical care at home and who are well supported by their family, so that they can join their loved ones during their terminal phase.

ATS is part of the focussed care for a good quality of life with the aim of returning the patient to the status quo of stability as it was prior to the acute reversible symptom. This can minimise

hospital stays, leading to quick discharge of the patient, and allowing a quick return to their social environment.

Particularly for patients within a palliative care setting at home, the hospital environment can be seen as a hostile place that risks social isolation, nosocomial infections, sliding into aggressive medical treatment, and exposure to medical errors in a complex hospital system generally characterised by under-staffing and over-stretched resources. Interestingly, hospitalisation has been noted as a major contributor of death in the USA.[10] Consequently, it is imperative to avoid hospitalisation as much as possible by choosing the anaesthetic technique that carries the lowest risk of morbidity. ATS can allow a patient to avoid a long stay in an intensive care unit (ICU), resulting in fewer postoperative complications and less burden to nurses and to the patient's family. In general, ATS has been shown to be safe and safe, and is as efficacious as thoracic surgery under GA, with quicker hospital discharge and lower overall costs.[11,12]

The perioperative goals of ATS are to provide physiological comfort, maintain gas exchange, cardiovascular stability, and psychological comfort by reassurance or, if necessary, by sedation without significantly depressing spontaneous respiration. In light of perioperative sedation, the possibilities of anaesthetic techniques for ATS are still not fully explored, such as the application of hypnosis in an awake patient during ATS.

Table 1: Possible outcomes for anaesthetic management of thoracic surgery for seriously chronically ill patients.

Patient categorically refuses any further therapy and wants limitation of treatment.
Patient wants GA, no ATS, but does accept ICU ventilation.
Patient wants GA, no ATS, and refuses ICU ventilation.
Patient chooses ATS, and accepts conversion to GA with ICU ventilation.
Patient chooses ATS, and accepts conversion to GA but does not accept ICU ventilation.
Patient wants ATS but no GA.[15]

GA: general anaesthetic; ATS: awake thoracic surgery; ICU: intensive care unit.

Not only does hypnosis replace sedation but it can also be therapeutic and improve mental well-being during surgery, in contrast with GA which just leads to a knock-out effect.[13,14]

As healthcare is nowadays under a budgetary pressure, obtaining thorough consent and performing appropriate shared decision making with the severely ill patient can be seen as time-consuming. However, time well spent in thorough discussions that lead to a conscientiously obtained informed consent is also time saved if the outcome does not go the way it was planned. Independent of acute events, the patient has the right to know that they could die at any moment due to the severe chronic disease. If this information is withheld, we deny the person a chance to catch up on missed opportunities both before and after ATS, which the patient still wants to realise in the remaining life time.[2] Telling the full truth to the patient and their family, as far as they can understand and accept it, is imperative to avoid any misunderstanding if things do not go as expected.

During ATS, it is important to keep in mind that at any given moment intubation might be indicated and the patient must know that conversion to GA is not necessarily a failure but a part of the contingency plan, or the next step after ATS. The outcome of a discussion during informed consent can result in different scenarios as described in Table 1.

The management of a patient's refusal of further treatment, such as admission to an ICU, strongly depends on the country's laws. In an ideal world, it should be the rule that doctors in charge have support at hand in case there are legal issues and issues of consciousness, as highlighted in the scenarios in Table 1. In some countries, medical teams are obliged by legislation to pursue treatment even if the patient does not want to continue aggressive treatment.[16] However, there remains a point for all doctors at which treatment can no longer continue against the wish of a severely ill patient when there is no further chance of improvement and when patient decline is rapid and getting out of control. Nevertheless, although doctors are obligated to abide by the law, in order to be of service to the patient they must state during informed consent that conversion to GA during ATS is a step taken to avoid unnecessary suffering, whatever the outcome may be. Once the patient is intubated, their fate may be decided by the natural evolution of the disease

process and its combination with a higher risk of a bad outcome for ventilated patients with severe progressive respiratory disease.[17-20] Patients who understand the high risk of ventilator dependency and have previous experience with long ICU stays, are usually highly motivated to undergo ATS if they have been well informed about its risks and benefits and the potential conversion to GA that also includes the possibility of a bad outcome.[15]

In summary, ATS has been shown to be safe in patients with severe breathlessness, allowing ventilator dependency to be avoided and patient hospitalisation shortened. It contributes to a quick recovery that gives patients the opportunity to join loved ones and even to rewrite some chapters of their life, healing old issues from the past.[2] All palliative patients I have previously dealt with were grateful for undergoing ATS, especially those who still remember their past experience of GA which subsequently confined them for weeks to the ventilator in the ICU.

REFERENCES

1. Kelley AS, Morrison RS. Palliative Care for the Seriously Ill. N Engl J Med. 2015; 373(8):747-55.

2. Meier D, Mandrola J. Palliative Care in Heart Failure: Manage the Person, Not the Prognosis. An interview with Diane Meier. Available at: http://www.medscape.com/viewarticle/859377. Last accessed: 10 March 2016.

3. Kiss G, Castillo M. Nonintubated anesthesia in thoracic surgery: general issues. Ann Transl Med. 2015;3(8):110.

4. Tarhan S et al. Myocardial infarction after general anesthesia. JAMA. 1972;220(11): 1451-4.

5. Yen CR et al. Thoracic epidural anesthesia for a polymyositis patient undergoing awake mini-thoracotomy and unroofing of a huge pulmonary bulla. Acta Anaesthesiol Taiwan. 2008;46(1):42-5.

6. Mineo TC et al. Awake nonresectional lung volume reduction surgery. Ann Surg. 2006;243(1):131-6.

7. Murphy GS et al. Postoperative residual neuromuscular blockade is associated with impaired clinical recovery. Anesth Analg. 2013;117(1):133-41.

8. Castillo M. Regional Anesthesia and thoracic Surgery. Is there a true indication? ASA Congress. San Francisco, 2013.

9. Miñambres E et al. Tracheal rupture after endotracheal intubation: a literature systematic review. Eur J Cardiothorac Surg. 2009;35(6):1056-62.

10. James JT. A new, evidence-based estimate of patient harms associated with hospital care. J Patient Saf. 2013;9(3): 122-8.

11. Pompeo E et al. Feasibility and results of awake thoracoscopic resection of solitary pulmonary nodules. Ann Thorac Surg. 2004;78(5):1761-8.

12. Al-Abdullatief M et al. Awake anaesthesia for major thoracic surgical procedures: an observational study. Eur J Cardiothorac Surg. 2007;32(2):346-50.

13. Musellec H et al. [Ambulatory Essure implant placement sterilization procedure for women: prospective study comparing general anesthesia versus hypnosis combined with sedation]. Ann Fr Anesth Reanim. 2010;29(12):889-96.

14. Meurisse M et al. Hypnosis with conscious sedation instead of general anaesthesia? Applications in cervical endocrine surgery. Acta Chir Belg. 1999; 99(4):151-8.

15. Kiss G et al. Thoracic epidural anaesthesia for awake thoracic surgery in severely dyspnoeic patients excluded from general anaesthesia. Interact Cardiovasc Thorac Surg. 2014;19(5): 816-23.

16. BBC News. Right to die: Court backs France in Vincent Lambert case. Available at: http://www.bbc.com/news/world-europe-33018506. Last accessed: 31 March 2016.

17. de Albuquerque Medeiros R et al. [Postoperative lung complications and mortality in patients with mild-to-moderate COPD undergoing elective general surgery]. Arch Bronconeumol. 2001;37: 227-34.

18. Lindenauer PK et al. Hospital patterns of mechanical ventilation for patients with exacerbations of COPD. Ann Am Thorac Soc. 2015;12(3):402-9.

19. Zafrani L et al. Acute respiratory failure in critically ill patients with interstitial lung disease. PLoS One. 2014;9(8):e104897.

20. Holleman F et al. [The last breath. The decision to ventilate patients with severe chronic obstructive pulmonary disease or not]. Ned Tijdschr Geneeskd. 2002;146(17):785-9.

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ENDOSCOPIC MANAGEMENT OF SESSILE SERRATED POLYPS OF THE COLON

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INTRODUCTION

The scope of this short review is to discuss the current state of practice in detection and removal of sessile serrated polyps (SSPs) during colonoscopy and the post-polypectomy management. SSPs are an important contributor to both sporadic and interval colorectal cancers.[1] The malignant pathogenesis of serrated polyps arises from a molecular pathway alternate to conventional tubular adenomas known as the serrated neoplasia pathway.[2-4] Polyp progression to cancer by this pathway can be rapid. An estimated 20% of all sporadic colorectal cancers but a significantly higher rate of interval cancers arise through the serrated neoplasia pathway.[5,6] Colorectal cancers arising from SSPs are characterised by *BRAF* gene mutation, CpG island hypermethylation in the promotor regions of tumour suppressor genes (i.e. the CpG island methylator phenotype [CIMP]), and microsatellite instability.[1] Moreover, it has been reported that interval colorectal cancers are more likely to exhibit microsatellite instability than non-interval colorectal cancers.[2] Therefore, SSPs are considered to be the most potent candidate lesions of interval colorectal cancers.

Serrated polyps can be categorised into three major subtypes including hyperplastic polyp (HP), traditional serrated adenoma (TSA), and SSP.[7] True HPs are the most common, often diminutive in size and distally located, and thought to pose little risk for further neoplastic progression. Conversely, SSPs, which account for up to 12% of all polyps in an asymptomatic average risk population, have the potential to progress toward dysplasia and malignancy.[8] The extent to which HPs of the right colon (distinct from SSPs) harbour risk for advanced neoplasia is not well defined at this time.

There are two categories of serrated polyps associated with cytological dysplasia. These include: i) SSP with cytological dysplasia and ii) TSA. TSAs were previously known by the term 'serrated adenoma' and considered a variant of conventional tubular adenomas.[4] TSAs are very rare (comprising <1% of all polyps), villiform in histology, and contain premalignant dysplastic features.

PATIENT ASSESSMENT

SSPs appear to be more common in Caucasians and women, contrary to trends seen with conventional tubular adenomas.[9-11] In addition, advanced age, tobacco use, and a higher body mass index have been reported to increase the risk of SSP presence.[12,13]

Serrated polyposis syndrome, previously known as hyperplastic polyposis syndrome, should be considered when multiple serrated polyps are present, especially if proximally located and large in size. The World Health Organization (WHO) defines serrated polyposis syndrome as fulfillment of any of the following criteria: i) at least five serrated polyps proximal to sigmoid, with two or more ≥10 mm; ii) any number of serrated polyps proximal to sigmoid colon with a first-degree relative with serrated polyposis syndrome; and iii) >20 serrated polyps of any size throughout the colon.[7] Serrated polyposis syndrome is associated with an approximately 50% lifetime risk of developing colorectal cancer.[14] Additionally, first-degree relatives of patients with serrated polyposis syndrome have also been shown to have an increased risk of colorectal cancer.

DETECTION UPON COLONOSCOPY

The endoscopic identification of SSP involves careful attention to key features. SSPs are usually

found in the proximal colon. Macroscopically these lesions are flat and can be easily missed due to their subtle appearance with poorly demarcated borders, asymmetric shape, pale colour, and mucus cap on surface.[15-17] There is wide variability in serrated detection rates between colonoscopists likely due to the relatively subtle characteristics of many of these lesions.

Kimura et al.[18] showed that *BRAF* mutation and CIMP-positive serrated lesions have a specific endoscopic pit pattern upon magnification endoscopy referred to as a Type II-O pattern. The pits of the Type II-O pattern have a round open appearance and correspond to dark spots inside the crypts in narrow-band imaging (NBI). Although Type II-O pits may not improve the detection rates of SSPs, they may be useful for distinguishing between SSPs and HPs. How this uniquely described pit pattern upon magnification endoscopy could enhance lesion recognition in typical endoscopic practice is not yet defined.

Detection of proximal serrated lesions has been shown to highly correlate with adenoma detection rates (ADR). One study found the serrated detection rate among experienced gastroenterologists to be between 0% and 2.2%, while another reported a range of 1–18% among 15 endoscopists at a single centre.[19,20] A Japanese prospective study[21] observed a SSP prevalence of at least 5%, while another study found an overall SSP prevalence of 8.1% by a single experienced colonoscopist.[8] Based on ADR targets, Kahi et al.[19] have suggested an equivalent proximal serrated detection rate of 4.5% for both men and women. While there are conflicting results on the effect of NBI compared with white light endoscopy (WLE) on serrated polyp detection, Horimatsu et al.[22] found a significantly higher rate of overall colonic polyp detection with the use of next-generation NBI.

OPTICAL DIAGNOSIS DURING COLONOSCOPY

Hazewinkel et al.[23] derived a systematic validation of specific endoscopic features of SSP using high-resolution WLE and NBI. They determined that the presence of both an indistinctive border and cloud-like surface on high-resolution WLE led to a 77% accuracy in identifying SSP. On NBI, the presence of indistinctive borders, cloud-like surface, irregular shape, and dark spots inside the crypts were independent predictors of SSP histology in multivariate analysis. When all four characteristics were present, this led to an impressive 89% sensitivity, 96% specificity, and 93% accuracy. Furthermore, another study found that dilated and branching vessels during NBI with optical magnification can be a unique feature of SSP and improve positive predictive value.[24] These image enhanced endoscopy features hold potential promises as teachable methods in improving detection of SSP. Further work on describing how interventions might improve SSP detection is needed.

There has been attention to promote cost-effective measures in colonoscopy screening and surveillance including the utilisation of optical diagnosis in implementing a 'resect and discard' strategy for diminutive polyps.[25] The NBI International Colorectal Endoscopic (NICE) classification was developed as a tool for real-time endoscopic assessment of colorectal polyp histology.[26] However it was not designed to differentiate SSPs, but rather HPs, from adenomatous polyps. Kumar et al.[27] found that nearly one-third of SSPs were misinterpreted as HP by community gastroenterologists using the NICE classification. Sano et al.[21] observed an overall 2.7% proportion of SSP in endoscopically diagnosed HPs, with higher rates in the proximal colon and with increasing size.

Recently, IJspeert et al.[28] developed a promising new classification system for optical differentiation of adenomas, HPs, and SSP known as the Workgroup serrAted polypS and Polyposis (WASP) classification. This new classification is a stepwise approach starting with the NICE classification and then incorporating SSP features as described by Hazewinkel et al.[23] When gastroenterologists completed a short training module on the use of the WASP classification, there was a significant increase in accuracy of optical diagnosis overall as well as with SSPs specifically, and the results were sustainable after 6 months.[29]

RESECTION DURING COLONOSCOPY

The prevention of serrated pathway interval cancers requires the complete resection of premalignant lesions. Pohl et al.[30] showed a high rate of incomplete resection with serrated polyps compared with conventional adenomas in the CARE study. SSPs are hypovascular, which makes cold snare polypectomy a safe and effective method of resection for small SSP.[31,32] Endoscopic

mucosal resection (EMR) has become the widely adopted technique for resection of larger lesions. EMR involves submucosal lifting to promote a complete and safe *en bloc* resection.[33] A recent prospective multicentre study evaluated the use of dye-based conventional EMR technique for large laterally spreading lesions greater than 20 mm in size. Pellise et al.[34] found an increased risk of recurrence in conventional adenomatous lesions versus SSPs in the subgroup of 20–25 mm polyps, however the difference was not sustained in the larger subgroups. Large SSP lesions were easier to remove with a similar safety profile compared to adenomatous lesions. This study suggests that standardised dye-based EMR can be a safe and effective mode of resection for large SSPs though this can be technically challenging. Further work in defining how polypectomy techniques can be taught to ensure complete *en bloc* resection is needed.

It is our practice to carefully examine the colon for loss of vascularity and mucus cap where SSPs may be found. Upon finding an area of concern, we use NBI to identify and confirm features consistent with an SSP, as described by Hazewinkel et al.,[23] including irregular shape, cloud-like surface, and dark spots inside crypts. Small lesions (between 6 mm and 10 mm in size) are removed by cautery with a stiff snare. Once there is a high level of confidence for the presence of an SSP and the lesion is ≥1 cm in size, then a dilute indigo carmine solution is injected to create a submucosal cushion and lift the lesion. Frequently the submucosal injectate allows for improved visualisation of the margins of the lesion. With larger lesions, we may opt to use soft coagulation current (using the tip of snare or argon plasma coagulation [APC]) to liberally mark the outer borders of the lesion to ensure complete resection. We usually utilise 'endocut' for resection of these often flat lesions of the right colon to minimise complication risk. In order to minimise post-resection fragmentation of SSP margins, which would limit pathology interpretation assessment of complete resection, we remove larger SSP with retrieval nets rather than attempting retrieval through the suction channel of the colonoscope.

PATHOLOGIC IDENTIFICATION

Beyond the challenges of SSP detection and resection is the appropriate pathologic identification and classification of these lesions, which has implications on timing of follow-up colonoscopy. SSPs are termed histologically from the jaggedness created by in-folding of the crypt endothelium leading to a saw-tooth appearance. The most important histologic features used to define SSPs are the presence of inverted T or L-shaped crypt bases along with hyperserration and columnar dilatation extending into the lower third of the crypts.[4] This abnormal crypt architecture and irregular proliferation differentiate it from typical HPs. TSAs can be recognised by its villiform histology, eosinophilic cytoplasm, and ectopic crypt formation.

Several studies have reported only fair-to-moderate inter-observer concordance among pathologists in distinguishing SSPs from typical HPs.[20,35-37] One study found that large right-sided HPs were reclassified as SSPs in 30–85% of cases upon pathology reinterpretation.[35] Given this variation in interpretation between pathologists, some experts recommend that all serrated lesions ≥10 mm found in the proximal colon be considered SSPs.[38] There is often less misidentification between SSPs and TSAs.[39]

FOLLOW-UP RECOMMENDATIONS

Patients with serrated polyps are at increased risk for synchronous advanced neoplasia and development of neoplasia during surveillance. Large serrated polyps are strongly and independently associated with synchronous advanced neoplasia[13,40] and the risk of colorectal cancer, specifically cancer in the proximal colon.[41] In a meta-analysis, the pooled odds ratio (OR) of synchronous advanced neoplasia for patients with proximal serrated polyps was 2.77 (95% confidence interval [CI]: 1.71–4.46) and with large serrated polyps the OR was 4.10 (95% CI: 2.69–6.26).[42]

There is limited data on the risk of advanced neoplasia on follow-up or surveillance colonoscopy. Schreiner et al.[13] found that patients with advanced adenomas and a concurrent non-dysplastic serrated lesion at baseline have a higher rate of neoplasia and advanced neoplasia compared with patients with advanced adenomas alone. The correlation between proximal large serrated polyps with the occurrence of proximal neoplasia and colorectal cancer suggests a potential common genetic and epigenetic change in the normal colonic mucosa leading to a field defect.[41]

Given the above findings, the US Multi-Society Task Force (USMSTF) first incorporated guidance on post-polypectomy surveillance of serrated lesions in 2012.[43,44] SSPs without cytological dysplasia are, in general, to be managed similarly to conventional tubular adenomas. A 3-year surveillance interval is suggested in patients with high-risk factors including ≥10 mm in size or more than one to two in number. Patients with low-risk SSPs (one to two polyps, each less than 10 mm in size) are recommended a 5-year surveillance interval. The presence of cytological dysplasia confers a more rapid malignant potential and thus should be followed for 1–3 years. A TSA should have an interval colonoscopy every 3 years per USMSTF, or every 3–5 years depending on size per expert consensus. Patients with SSP should be followed annually. Follow-up colonoscopy is generally recommended at a shortened interval (<1 year) if there is any concern about completeness of resection of any neoplastic lesion or poor bowel preparation obscuring visibility.

It is important to recognise that these recommendations were developed based on limited available evidence and that further surveillance studies are much needed. Our group has shown evidence to support a shorter surveillance interval in patients with 'low-risk' SSPs as their risk for development of advanced neoplasia is greater than that observed with low-risk conventional tubular adenomas.[45]

FUTURE DIRECTIONS

In summary, SSPs have gained increasing recognition as an important contributor to interval colorectal cancers. In current endoscopic practice, there is wide variation in reported detection rates of SSPs. Further investigation should be pursued to improve endoscopic detection, complete and safe resection, and determine optimal management and surveillance intervals. Future studies to determine biomarkers for premalignant serrated lesions may also lead to better clinical outcomes. While there are multiple studies demonstrating improved ADRs with implementation of ADR monitoring programmes, correlate results in serrated detection rates are currently not well-described.[29,46] We recommend that colonoscopists begin to monitor their SSP detection rates as an initial first step to improving detection. Teachable methodologies and interventions to improve SSP detection and removal are important areas of further study.

REFERENCES

1. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology. 2010; 138(6):2088-100.

2. O'Brien MJ et al. Comparison of microsatellite instability, CpG island methylation phenotype, BRAF and KRAS status in serrated polyps and traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. Am J Surg Pathol. 2006;30(12):1491-501.

3. Spring KJ et al. High prevalence of sessile serrated adenomas with BRAF mutations: a prospective study of patients undergoing colonoscopy. Gastroenterology. 2006;131(5):1400-7.

4. Torlakovic E et al. Morphologic reappraisal of serrated colorectal polyps. Am J Surg Pathol. 2003;27(1):65-81.

5. Nishihara R et al. Long-term colorectal cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369(12): 1095-105.

6. Farrar WD et al. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol. 2006;4(10): 1259-64.

7. Snover D et al. "Serrated polyps of the colon and rectum and serrated ("hyperplastic") polyposis," Bozman FT et al. (eds.), WHO Classification of Tumours Pathology and genetics Tumours of the digestive system (2010) 4th edition, Lyon: IARC Press.

8. Abdeljawad K et al. Sessile serrated polyp prevalence determined by a colonoscopist with a high lesion detection rate and an experienced pathologist. Gastrointest Endosc. 2015;81(3):517-24.

9. Burnett-Hartman AN et al. Differences in epidemiologic risk factors for colorectal adenomas and serrated polyps by lesion severity and anatomical site. Am J Epidemiol. 2013;177:625-37.

10. Lieberman DA et al. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. JAMA. 2003;290(22): 2959-67.

11. Wallace K et al. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. Cancer Epidemiol Biomarkers Prev. 2009; 18(8):2310-7.

12. Macaron C et al. Risk of metachronous polyps in individuals with serrated polyps. Dis Colon Rectum. 2015;58(8):762-8.

13. Schreiner MA et al. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. Gastroenterology. 2010;139(5):1497-502.

14. Boparai KS et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicenter cohort study. Gut. 2010; 59(8):1094-100.

15. Kashida H et al. Endoscopic characteristics of colorectal serrated lesions. Hepatogastroenterol. 2011;58(109): 1189-92.

16. Tadepalli US et al. A morphologic analysis of sessile serrated polyps observed during routine colonoscopy (with video). Gastrointest Endosc. 2011; 74(6):1360-8.

17. Yamada A et al. Endoscopic features of sessile serrated adenoma and other serrated colorectal polyps. Hepatogastroenterology. 2011;58(105): 45-51.

18. Kimura T et al. A novel pit pattern identifies the precursor of colorectal cancer derived from sessile serrated adenoma. Am J Gastroenterol. 2012; 107(3):460-9.

19. Kahi CJ et al. High colonoscopic prevalence of proximal colon serrated polyps in average-risk men and women. Gastrointest Endosc. 2012;75(3):515-20.

20. Hetzel JT et al. Variation in the detection of serrated polyps in an average risk colorectal cancer screening cohort. Am J Gastroenterol. 2010;105(12): 2656-64.

21. Sano W et al. Prospective evaluation of the proportion of sessile serrated adenoma/polyps in endoscopically diagnosed colorectal polyps with hyperplastic features. Endosc Int Open. 2015;3(4):E354-8.

22. Horimatsu T et al. Next-generation narrow band imaging system for colonic polyp detection: a prospective multicenter randomized trial. Int J Colorectal Dis. 2015;30(7):947-54.

23. Hazewinkel Y et al. Endoscopic features of sessile serrated adenomas: validation by international experts using high-definition white-light endoscopy and narrow-band imaging. Gastrointest Endosc. 2013;77(6):916-24.

24. Yamada M et al. Investigating endoscopic features of sessile serrated adenomas/polyps by using narrow-band imaging with optical magnification. Gastrointest Endosc. 2015;82(1):108-17.

25. Rex DK et al. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointest Endosc. 2011;73(3):419-22.

26. Hewett DG et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology. 2012;143(3):599-607.

27. Kumar S et al. Optical biopsy of sessile serrated adenomas: do these lesions resemble hyperplastic polyps under narrow-band imaging? Gastrointest Endosc. 2013;78(6):902-9.

28. IJspeert JE et al. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps, and sessile serrated adenomas/polyps. Gut. 2015;65(6): 963-70.

29. Coe SG et al. An endoscopic quality improvement program improves detection of colorectal adenomas. Am J Gastroenterol. 2013;108(2):219-26.

30. Pohl H et al. Incomplete polyp resection during colonoscopy- results of the complete adenoma resection (CARE) study. Gastroenterology. 2013;144(1): 74-80.

31. Deenadayalu VP, Rex DK. Colon polyp retrieval after cold snaring. Gastrointest Endosc. 2005;62(2):253-6.

32. Huang CS et al. The clinical significance of serrated polyps. Am J Gastroenterol. 2011;106(2):229-40.

33. Burgess NG et al. Comparison of large sessile serrated adenoma characteristics with conventional advanced mucosal neoplasia resected by wide field endoscopic mucosal resection in a multicenter prospective cohort. Abstract 157. Digestive Disease Week, Orlando, Florida, USA, 18-21 May 2013.

34. Pellise M et al. Endoscopic mucosal resection for large serrated lesions in comparison with adenomas: a prospective multicenter study of 2000 lesions. Gut. 2016. [Epub ahead of print].

35. Khalid O et al. Reinterpretation of histology of proximal colon polyps called hyperplastic in 2001. World J Gastroenterol. 2009;15(30):3767-70.

36. Payne SR et al. Endoscopic detection of proximal serrated lesions and pathologic identification of sessile serrated adenomas/polyps vary on the basis of center. Clin Gastroenterol Hepatol. 2014;12(7):1119-26.

37. Singh H et al. Pathological reassessment of hyperplastic colon polyps in a city-wide pathology practice: implications for polyp surveillance recommendations. Gastrointest Endosc. 2012;76(5):1003-8.

38. Hassan C et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy Guidelines (ESGE) Guideline. Endoscopy. 2013;45(10):842-51.

39. Farris AB et al. Sessile serrated adenoma: challenging discrimination from other serrated colonic polyps. Am J Surg Pathol. 2008;32(1):30-5.

40. Li D et al. Association of large serrated polyps with synchronous advanced colorectal neoplasia. Am J Gastroenterol. 2009;104(3):695-702.

41. Hiraoka S et al. The presence of large serrated polyps increases risk for colorectal cancer. Gastroenterology. 2010; 139(5):1503-10.

42. Gao Q et al. Serrated polyps and the risk of synchronous colorectal advanced neoplasia: a systematic review and meta-analysis. Am J Gastroenterol. 2015; 110(4):501-9.

43. Lieberman DA et al.; United States Multi-Society Task Force on Colorectal Cancer. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143(3):844-57.

44. Rex DK et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol. 2012;107(9):1315-29.

45. Melson J et al. Presence of small sessile serrated polyps increases rate of advanced neoplasia upon surveillance compared with isolated low-risk tubular adenomas. Gastrointest Endosc. 2016;84: 307-14.

46. Ussui V et al. Stability of Increased Adenoma Detection at Colonoscopy. Follow-Up of an Endoscopic Quality Improvement Program-EQUIP-II. Am J Gastroenterol. 2015;110(4):489-96.

REGORAFENIB IN ADVANCED AND REFRACTORY GASTROINTESTINAL CANCERS

Summary of Presentations from the European Society of Medical Oncology (ESMO) 18th World Congress on Gastrointestinal Cancer (WCGI) held in Barcelona, Spain from 28th June–2nd July 2016

Speakers

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MEETING SUMMARY

The European Society for Medical Oncology's (ESMO) 18th World Congress on Gastrointestinal Cancer (WCGI) was held in Barcelona from 28th June–2nd July 2016. Presentations covered gastrointestinal (GI) cancers of every aetiology and site within the GI tract, as well as the major aspects of cancer management from screening to novel therapeutic options. Tyrosine kinase inhibitors (TKIs), with their ability to block key mechanisms required for tumour growth, featured heavily in this year's presentations at WCGI. Data on the oral TKI regorafenib featured prominently in both poster discussion tours and oral presentations, emphasising the continuing interest in the evolution of this therapy within the clinical arsenal of physicians tackling GI cancers.

Introduction

The multikinase inhibitor regorafenib acts on several protein kinases involved in important aspects of tumour growth including angiogenesis (vascular endothelial growth factor [VEGF] receptors 1–3 and TIE2), oncogenesis (*KIT*, *RET*, *RAF1*, *B-RAF*, and *B-RAF V600E*), and the tumour microenvironment (platelet-derived growth factor receptors and fibroblast growth factor receptors).[1] Regorafenib has been approved for treatment of a number of cancers of the GI tract including metastatic colorectal cancer (mCRC) and GI stromal tumours based on the results of Phase III trials.[2,3] Presentations at the 2016 WCGI reflect the continuing efforts to refine and target current regorafenib treatment regimens.

The Effect of Single Nucleotide Polymorphisms on the Efficacy and Safety of Regorafenib in Metastatic Colorectal Cancer

Doctor Deither Lambrechts

Single nucleotide polymorphisms (SNPs) modify susceptibility to a wide range of diseases and also

contribute to the efficacy and side effect profile of therapeutic interventions. Genotyping already drives treatment decisions in the field of GI oncology, for example the TKI imatinib is indicated for use in KIT (CD117)-positive unresectable or metastatic GI stromal tumours.[4] Pharmacogenomics is also already well-established in other fields, with the US Food and Drug Administration (FDA) highlighting the utility of dose adjustment of warfarin based on genotyping of the drug-metabolising enzyme CYP2C9 in the avoidance of side effects.[4]

An analysis of SNPs in the CORRECT cohort (N=760), investigating putative relationships with both efficacy and safety was presented at WCGI. In the pivotal Phase III CORRECT trial,[5] regorafenib significantly improved overall survival (OS) (hazard ratio [HR]: 0.77; 95% confidence interval [CI]: 0.64–0.94; p=0.0052) and progression-free survival (PFS) (HR: 0.49; 95% CI: 0.42–0.58; p<0.0001) versus placebo in patients with mCRC refractory to available therapies.[3] The relationship between angiogenesis-related SNPs in the VEGF and TIE2 signalling pathways and efficacy was assessed, in addition to possible links between SNPs in absorption, distribution, metabolism, and excretion (ADME) genes, and selected Grade 3–4 adverse events (AEs) (diarrhoea, fatigue, mucositis, hypertension, and hand-foot skin reactions).

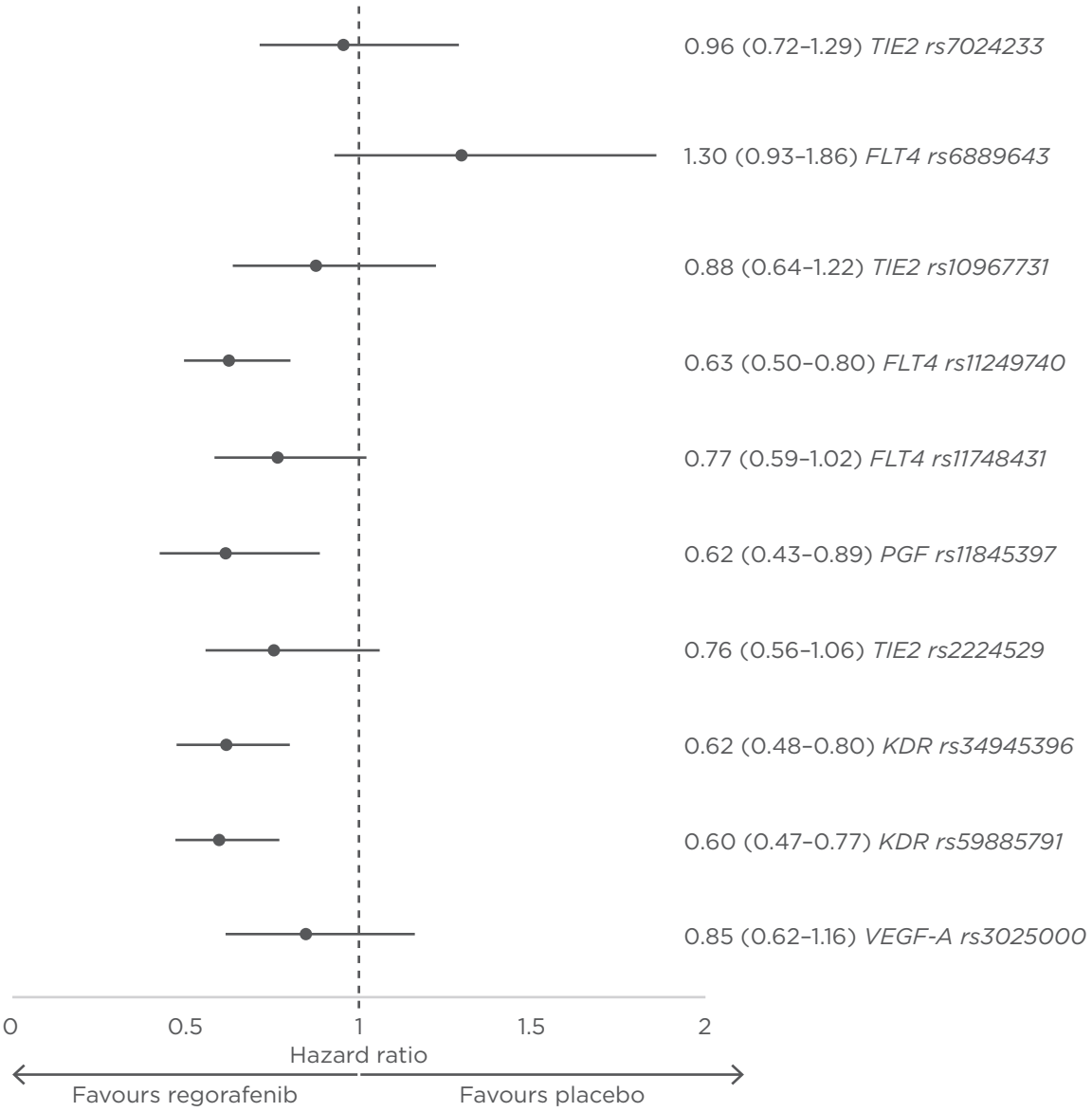

Figure 1: Cox regression analysis on overall survival for regorafenib 160 mg/day versus placebo for major homozygous genotype of all SNPs with an unadjusted p<0.05 and SNPs of special interest.
SNP: single nucleotide polymorphisms; VEGF-A: vascular endothelial growth factor A; FLT: F-fluorothymidine. PGF: placental growth factor; KDR: kinase insert domain-containing receptor.

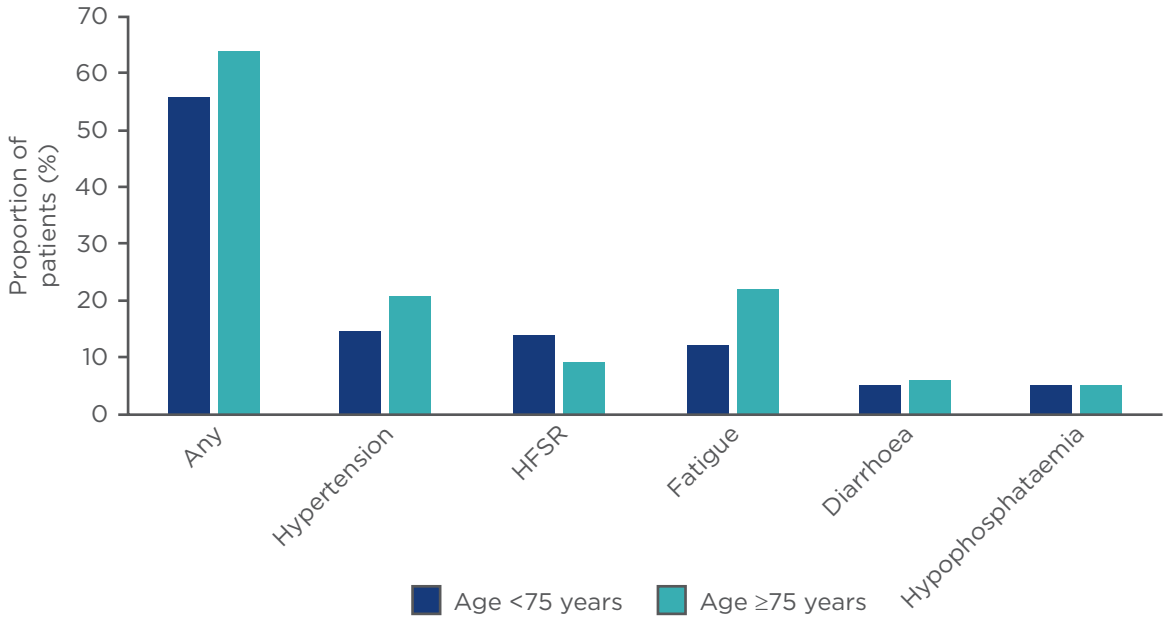

Figure 2: Treatment-emergent adverse events of Grade ≥3.
Adverse events were graded using the NCI-CTCAE v4.0.
HFSR: hand-foot skin reaction; NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events.

Whole-blood genotyping was performed on close to two-thirds of the CORRECT study population. Baseline characteristics and outcomes were similar in the genotyped proportion of the CORRECT population compared with the full population. Notably, none of the eight identified efficacy-related SNPs represented VEGF-A SNPs, which are known to be related to other antiangiogenic therapies such as bevacizumab or aflibercept.[6-8] Furthermore, the results were in line with the diverse nature of regorafenib's TKI blockade resulting in a wider range of efficacy-related SNPs in comparison with bevacizumab, which solely targets VEGF and angiogenesis. SNPs with significant relationships to efficacy were associated with either the *TIE2* gene or the *FLT4* tyrosine kinase receptor gene (Figure 1).

Following statistical analysis for multiple testing only a single SNP in the *TIE2* gene, *rs7024233*, remained significant (Figure 1). However, the level of stringency involved in correcting the large number of angiogenesis-related SNPs (n=258) in this study set an extremely high bar for statistical significance, and further studies may add to the weight of evidence in those SNPs where significance did not survive correction.

A total of 211 VEGF SNPs and 54 ADME SNPs remained following quality control and were included in the analysis. The particular rarity of the ADME SNPs necessitated a combined gene-wise analysis. Following this revised analysis, four genes were found to be significantly associated with specific safety-related events. The combined prevalence of these SNPs was estimated at 10–20%, which is similar to the proportion of patients suffering these Grade 3–4 AEs during regorafenib therapy.[3]

In summary, preliminary exploratory analysis of SNPs in the CORRECT population found that only a single SNP in the *TIE2* gene showed a statistically significant interaction with treatment and OS, following stringent statistical correction methods. Four significant variants in metabolism genes were found, which may have the potential to predict tolerability in patients with mCRC treated with regorafenib. Gene sequencing may allow clinicians to anticipate those patients who will suffer more AEs, enabling early dose adjustment.

Safety and Efficacy of Regorafenib in Elderly Metastatic Colorectal Cancer Patients

Professor Eric van Cutsem

Over the past 15 years, oncologists have seen a large upward shift in the numbers of elderly

patients with mCRC in their clinics. The very definition of elderly appears to have changed over the past 10–15 years, with patients >65 years no longer deemed elderly by some in the clinical community. However, elderly patients may still present treatment challenges due to an increased risk of drug-related toxicity.[9] Specific data are needed in order to aid treatment decisions in elderly patients where expectations from therapy and risk-benefit ratios may be weighted differently. To this end, a study on the efficacy and safety of regorafenib in a subgroup of the CONSIGN-study population aged ≥75 years of age was conducted, following and in complement to a previous analysis presented at ASCO 2016.[10]

The open-label, single-arm, Phase IIIb CONSIGN study[11] (N=2,872) was designed to provide patients with refractory mCRC access to regorafenib prior to market authorisation, following FDA, and European Medicines Agency (EMA) approval based on data from CORRECT. In addition, the CONSIGN study allowed continued assessment of regorafenib safety and efficacy. CONSIGN was conducted in 25 countries in patients ≥18 years of age, with good (≤1) Eastern Cooperative Oncology Group Performance Status (ECOG PS). Patients had experienced progression within 3 months of therapy with approved treatment options and received regorafenib, 160 mg/day on a 3 weeks on, 1 week off cycle. The primary endpoint was safety, and the efficacy outcome was PFS assessed per investigator according to local standards.[12]

Dose interruptions and delays were indicative of similar tolerability in the two age groups. Although the majority of patients underwent some form of treatment interruption or delay, the median duration of these interruptions was low for both groups. Similarly, differences between the two groups in Grade 3 AEs were slight (Figure 2). Some regorafenib-related AEs tended to be somewhat more common in the elderly patient group compared with the younger age group. Treatment-emergent National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 tended to be more common in the younger age group; however, the differences were slight and unlikely to be indicative of a difference in toxicity between the two groups. The sole efficacy outcome assessed in the CONSIGN trial was PFS. Both age groups had a similar median PFS of approximately 2.5 months.

In summary, regorafenib was well-tolerated in the elderly and younger subpopulations of the CONSIGN trial. Treatment modifications and discontinuations were similar between the two groups; the high rates were likely indicative of active management of AEs by physicians, which is key to the management of treatment-emergent AEs during therapy with regorafenib. Given the similar efficacy between the two groups and adequate tolerability profiles, regorafenib appears to be a suitable treatment for elderly patients with previously treated mCRC.

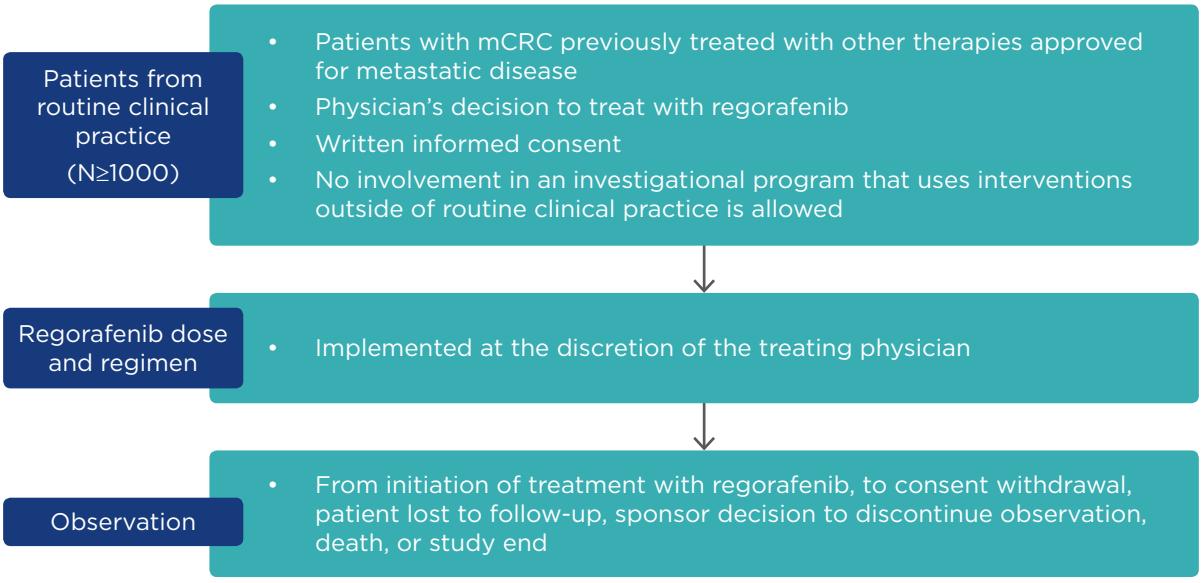

Figure 3: CORRELATE[13] study design.
mCRC: metastatic colorectal cancer.

Regorafenib in Metastatic Colorectal Cancer in Routine Clinical Practice

Professor Michael Ducreux

The CORRELATE trial[13] aims to characterise the safety and efficacy of regorafenib for mCRC in a real-world population in routine clinical practice. CORRELATE is a prospective, observational, multicentre trial conducted in >25 countries in Europe, Latin America, and the Asia-Pacific region. Approximately 1,000 patients with mCRC, selected for regorafenib therapy according to local health authority guidelines, will be recruited. Dose interruptions and reductions will be permitted for the management of AEs (Figure 3).

The primary endpoint is the incidence of treatment-emergent AEs with OS, PFS, disease control rate, health-related quality of life, and healthcare resource use as secondary endpoints. Data will be sourced from medical records, routine measurements, and patient-reported outcomes. Patients receiving at least one dose of regorafenib will be included in the analysis. The final analysis will be performed when all patients have been followed for 6 months from the time they discontinue regorafenib (excluding those withdrawing early due to death, consent withdrawal, or patient/investigator decisions). An interim analysis will occur after 500 patients have been observed for at least 3 months.

As of February 2016, 404 patients have been enrolled with recruitment ongoing. The primary completion date is estimated as September 2017.[14]

Conclusion

Positive data in mCRC continues to accrue with the prospect of genetic screening guiding treatment decisions to promote both safety and efficacy. Regorafenib appears to be an effective treatment option in the sometimes difficult-to-treat elderly population, and data from the ongoing CORRELATE study will add further to the understanding of safety and patient-related outcomes, as well as real-world efficacy, in the near future.

REFERENCES

1. Wilhelm SM et al. Regorafenib (BAY 73-4506): A new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129(1):245-55.

2. Demetri GD et al.; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013; 381(9863):295-302.

3. Grothey A et al.; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.

4. Kitzmiller JP et al. Pharmacogenomic testing: Relevance in medical practice: Why drugs work in some patients but not in others. Cleve Clin J Med. 2011;78(4): 243-57.

5. Bayer. Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. NCT01103323. Available at: https://clinicaltrials.gov/ct2/show/NCT01103323.

6. Giampieri R et al. Angiogenesis genotyping and clinical outcome during regorafenib treatment in metastatic colorectal cancer patients. Sci Rep. 2016; 6:25195.

7. de Haas S et al. Genetic variability of VEGF pathway genes in six randomized phase III trials assessing the addition of bevacizumab to standard therapy. Angiogenesis. 2014;17(4):909-20.

8. Lambrechts D et al. Markers of response for the antiangiogenic agent bevacizumab. J Clin Oncol. 2013;31(9):1219-30.

9. Repetto L. Greater risks of chemotherapy toxicity in elderly patients with cancer. J Support Oncol. 2003;1(4 Suppl 2):18-24.

10. Van Cutsem E et al. Analysis of patients ≥75 years in the open-label phase 3b CONSIGN trial of regorafenib in previously treated metastatic colorectal cancer (mCRC). Abstract 012. ESMO 18th World Congress on Gastrointestinal Cancer, 29 June-2 July 2016.

11. Bayer. Regorafenib in Subjects With Metastatic Colorectal Cancer (CRC) Who Have Progressed After Standard Therapy (CONSIGN). NCT01538680. Available at: https://clinicaltrials.gov/ct2/show/NCT01538680?term=NCT01538680&rank=1.

12. Van Cutsem E et al. Results from the large, open-label phase 3b CONSIGN study of regorafenib in patients with previously treated metastatic colorectal cancer. Ann Oncol. 2015;26(suppl 4):iv118.

13. Bayer. Safety and Effectiveness of Regorafenib (Correlate). NCT02042144. Available at: https://clinicaltrials.gov/ct2/show/NCT02042144?term=NCT02042144&rank=1.

14. Ducreux M et al. A prospective, observational trial to assess the safety and efficacy of regorafenib in patients with metastatic colorectal cancer (mCRC) in routine clinical practice (CORRELATE). Ann Oncol. 2016;27(Supp 2):ii80.

OPTIMISING CANCER IMMUNOTHERAPY: CHALLENGES AND OPPORTUNITIES

Summary of Presentations from a prIME Oncology Scientific Exchange on 21st May 2016 in Amsterdam, Netherlands

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MEETING SUMMARY

Cancer immunotherapy has moved to the forefront in the treatment of patients with cancer, providing a unique opportunity to achieve dramatic and lasting anti-tumour responses in a variety of tumour types. When it comes to patient selection and development of novel immunotherapeutic agents and combinations, so far we have merely scratched the surface of this therapeutic approach. Leading experts in the field of cancer immunotherapy gathered in Amsterdam, Netherlands, on 21st May 2016 for a Scientific Exchange to discuss the current status of immunotherapy within the field of oncology and explore the future of this evolving therapeutic strategy. Current challenges and limitations regarding the use of immunotherapy were addressed for tumour types such as melanoma, lung cancer, bladder cancer, and renal cell carcinoma (RCC). Recent advances and future directions in the areas of immunotherapy biomarkers and mechanisms of resistance were also examined. Current evidence for combination strategies with immunotherapy was highlighted, including combinations with other immunotherapies or with radiotherapy. Below is a summary of the key points discussed during this scientific exchange.

Current Immunotherapy Strategies in the Management of Solid Tumours

Doctor Mario Colombo

The field of cancer immunotherapy is expanding at an extremely rapid pace. After being named the breakthrough of the year in 2013 by *Science*,[1] cancer immunotherapy has continued to revolutionise patient care across an ever-increasing range of malignancies. Immunotherapy seeks to initiate an anti-tumour immune response or augment any existing immune response, ultimately resulting in tumour regression and disease control. This requires cancer antigen presentation, priming and activation of T cells, infiltration of activated T cells into the tumour, and finally recognition and killing of cancer cells.[2] However, the inherent genetic heterogeneity of tumours and the propensity for tumour cells to escape or avoid immune targeting continues to encourage investigation of novel approaches and combination strategies. Several immunotherapies are now available and ongoing clinical trials are exploring a myriad of novel immunotherapeutic approaches, including vaccine therapies, adoptive transfer of tumour-infiltrating lymphocytes (TILs), antibody therapies targeting either immune checkpoints or activation pathways, and chimeric antigen receptor T cells.

Perhaps the most exciting achievement thus far in the use of cancer immunotherapies is the rapid and durable responses observed in a number of tumour types, albeit only in a minority of patients treated.[3] T cell activation, differentiation, and function are controlled by complex interactions between co-stimulatory and co-inhibitory molecules, with overlapping signalling pathways driving an ever-changing tide of immune response.[4] T cell signalling is carefully regulated both transcriptionally and post-transcriptionally. Cell surface expression of co-signalling molecules is continuously modulated within the tumour microenvironment and can differ greatly depending on the milieu of receptors and ligands present on the surface of surrounding cells, including antigen presenting cells (APCs). In addition, several co-signalling receptors can interact with more than one ligand, adding another level of regulation based on the differential expression of specific receptor–ligand pairs that act as either stimulatory or inhibitory signals.

The existence of unique tumour-specific antigens is one of the key premises behind cancer immunotherapy, allowing selective targeting of tumour cells without killing normal host cells. Recent advances in next-generation sequencing and algorithms for epitope prediction have opened the door for rapid identification of tumour neo-antigens.[5] Whole-exome sequencing and *in silico* tools to predict major histocompatibility complex (MHC) Class I molecule presentation can now quickly identify a neoepitope that can then be validated through T cell epitope screening to

assess T cell reactivity.[6] This type of information can be used to identify predictive biomarkers or new targets for immunotherapy, as well as develop neo-antigen vaccines or adoptive cell transfer therapies.

Ongoing research is aimed at expanding and refining the use of immunotherapeutic approaches in the treatment of patients with cancer. While immunotherapy is associated with rapid and durable responses, some patients never respond or develop resistance to these approaches. Improved patient selection is needed, fuelling continued investigation of biomarkers to predict response. Our understanding of resistance mechanisms is also increasing, providing the rationale for novel immunotherapeutic agents and combinatorial strategies.

Experience with Immunotherapy in Clinical Practice: Identifying Limitations and Challenges

Doctor Alexander M. M. Eggermont, Doctor Joachim G. Aerts, Doctor Thomas Powles

Melanoma

Immunotherapy has long been an important part of the treatment landscape for melanoma.[7] Cytotoxic T lymphocyte-associated-protein 4 (CTLA-4) and programmed cell death-protein 1 (PD-1) are negative regulators of T cell activation and can contribute to immune evasion by tumour cells.[8] Monoclonal antibody inhibitors of these checkpoint pathways enhance T cell proliferation and function, perpetuating T cell activation and reawakening the silenced anti-tumour immune response. CTLA-4 is thought to primarily limit early phases of T cell activation, while PD-1 inhibits T cell activity in the effector phase within tissues and tumours.

The CTLA-4-targeted monoclonal antibody ipilimumab became the first immune checkpoint inhibitor approved for the management of previously-treated melanoma and was later approved as first-line treatment, where it has replaced chemotherapy.[7] Long-term survival data with 10 years of follow-up from a pooled analysis of Phase II and Phase III ipilimumab trials demonstrated a prolonged survival benefit for ipilimumab in patients with untreated or pretreated melanoma, and a plateau in the survival curve starting at approximately 3 years with around 20% of patients achieving long-term disease control.[9] A non-randomised subset analysis also showed no significant difference in survival between the 3 mg/kg and 10 mg/kg dosing regimens.

Ipilimumab was also investigated as an adjuvant therapy in the Phase III EORTC 18071 trial.[10] Ipilimumab significantly prolonged median recurrence-free survival compared with placebo, regardless of extent of nodal disease or ulcerative status. Ipilimumab is limited by its adverse event profile, including specific immune-related adverse events (irAEs) such as pruritis, rash, diarrhoea, colitis, hypophysitis, and increases in compounds detected by liver function tests. In the EORTC 18071 trial, most of the Grade 2–5 irAEs had occurred by the fourth or fifth dose of ipilimumab and approximately half of patients receiving ipilimumab had to discontinue therapy due to an adverse event. This implies that the majority of benefit from adjuvant ipilimumab was gained from those first four or five doses.

An important question this study did not address is whether the same magnitude of benefit could be achieved by simply treating patients with ipilimumab at the time of disease progression rather than immediately following surgery. Within the field of melanoma, the clinical value of adjuvant therapy versus salvage therapy at progression continues to be an area of debate. This will be addressed in the Phase III EORTC 1325 trial evaluating adjuvant therapy with the PD-1 inhibitor pembrolizumab in high-risk, Stage III melanoma, as patients will be unblinded at the time of disease relapse and those previously allocated to placebo treatment will be offered pembrolizumab.[11]

The PD-1 checkpoint inhibitors pembrolizumab and nivolumab have demonstrated significant efficacy in patients with ipilimumab-naïve and ipilimumab-pretreated melanoma and were both approved in 2015 for the treatment of patients with unresectable or metastatic disease.[7] Both of these agents demonstrated superiority to chemotherapy in ipilimumab-refractory patients and nivolumab improved overall survival (OS) compared with dacarbazine in treatment-naïve patients.[7,12] The durability of response to PD-1 blockade is similar to that seen with ipilimumab, although the actual response rates tend to be higher with PD-1 inhibitors.[7] In Phase III randomised trials, both pembrolizumab and nivolumab demonstrated superior efficacy to ipilimumab with regards

to overall response rate (ORR) and median progression-free survival (PFS) in patients with advanced melanoma. Pembrolizumab also demonstrated an OS advantage over ipilimumab. In addition, the safety profile of PD-1 inhibition appears to be more favourable than CTLA-4 blockade, further supporting the use of these agents. Based on these data, PD-1 inhibition should be strongly considered as first-line therapy for most patients with advanced melanoma. If a patient has *BRAF*-mutated metastatic disease with a very high tumour load and rapid disease progression, a BRAF inhibitor may be preferred as first-line therapy, with immunotherapy offered later in the disease course.

The combination of ipilimumab and nivolumab was also recently approved for patients with unresectable or metastatic melanoma based on significant improvements in ORR and median PFS over ipilimumab alone in the CheckMate 067 and 069 trials.[13,14] Interestingly, in the CheckMate 067 trial, patients expressing programmed cell death-ligand 1 (PD-L1) showed a similar median PFS with either nivolumab alone or the combination of nivolumab and ipilimumab.[13] This suggests the combination may not be necessary in those expressing PD-L1. In the CheckMate 069 trial, the OS curves for nivolumab plus ipilimumab and ipilimumab alone continue to converge over time, with only a 10% OS benefit for the combination over ipilimumab alone at 24 months.[14] The combination of nivolumab and ipilimumab is also associated with a higher rate of Grade 3 or 4 adverse events (56.5%) compared with nivolumab alone (20%) or ipilimumab alone (27%) and over one-third of patients in the CheckMate 067 trial had to discontinue therapy due to an adverse event.[13] The potential for efficacy and toxicity should be carefully discussed when considering this combinatorial treatment option.

The oncolytic intralesional therapy talimogene laherparepvec (T-VEC) was also recently approved for the treatment of patients with unresectable melanoma. T-VEC is an attenuated oncolytic virus that expresses human granulocyte macrophage-colony stimulation factor (GM-CSF), which is involved in recruitment and activation of APCs and stimulation of tumour-specific T cell response.[15] In the Phase III OPTiM study, intralesional T-VEC was associated with a higher rate of durable and objective responses compared with subcutaneous GM-CSF and prolonged median OS by 4.4 months (p=0.051). Responses to T-VEC were seen in both injected and uninjected lesions and T-VEC was well-tolerated. Ongoing clinical trials are investigating T-VEC in combination with other immunotherapies, including checkpoint inhibitors.[16,17]

Lung Cancer

The vast majority of lung cancers exist in a highly immunosuppressive microenvironment, leading to immune evasion and tumour progression.[18] This has resulted in investigation of several immunotherapy strategies, including vaccines and immune checkpoint inhibitors. PD-1 and PD-L1 inhibitors have demonstrated exciting efficacy and safety in patients with metastatic lung cancer. In a randomised Phase III trial, nivolumab significantly improved ORR, median PFS, and median OS compared with docetaxel in patients with advanced squamous non-small cell lung cancer (NSCLC) with disease progression during or after first-line chemotherapy, reducing the risk of death by 41%.[19] Nivolumab also significantly improved ORR and median OS compared to docetaxel in a Phase III trial of non-squamous NSCLC with progression during or after platinum doublet chemotherapy.[20] This efficacy was particularly evident in patients with higher levels of PD-L1 expression. In both trials, nivolumab was well-tolerated compared with docetaxel, with Grade 3 or 4 adverse events in ≤10% of patients in the nivolumab arms compared to approximately 55% in the docetaxel arms of each trial.[19,20]

The PD-1 inhibitor pembrolizumab and the PD-L1 inhibitor atezolizumab have also demonstrated superiority over docetaxel in patients with previously treated advanced NSCLC expressing PD-L1 in Phase II/III studies.[21,22] Median PFS and OS benefit was most evident in patients with high PD-L1 expression (≥50% of tumour cells expressing PD-L1). Both checkpoint inhibitors were well-tolerated compared with chemotherapy. Updated data from the KEYNOTE-001 trial of pembrolizumab and the POPLAR trial of atezolizumab versus chemotherapy showed favourable long-term OS benefit in patients with PD-L1 plus advanced NSCLC.[23,24]

Close examination of the OS curve for nivolumab in the non-squamous NSCLC trial shows a slight superiority for chemotherapy in the first 6 months after treatment initiation, with slightly more patients in the nivolumab arm dying early in the treatment course,[20] and the survival benefit of nivolumab only appearing after 6 months, by which time one-third of patients had already died.

This calls into question the approach of one-size-fits-all therapy in which every patient receives second-line checkpoint inhibitor therapy. There may be a specific subset of patients who display an unusual immunogenic response, are insensitive to immunotherapy, and may progress too quickly to receive any potential benefits from chemotherapy. The lack of benefit could be related to levels of PD-L1 expression, although further studies are needed. Unfortunately, identification of these patients who may not respond to immunotherapy is difficult given the complex immunosuppressive environment of lung cancer and the limited predictive biomarkers for response to immunotherapy.

Interestingly, there is a further decline in the probability of survival approximately 18 months following initiation of nivolumab for squamous NSCLC, suggesting that many patients that initially responded develop resistance to immunotherapy at around this timepoint.[19] This represents another patient subset needing a biomarker to identify, as these patients may benefit from sequential therapy to boost the anti-tumour response and prolong survival. A good initial tumour response is needed for patients to become long-term survivors, so those with only stable disease at 3 months may need to be considered for combination or sequential therapy. These strategies are currently under investigation, but will need to be carefully evaluated for both efficacy and safety.

Important questions remain, including which patients with lung cancer should be treated with immunotherapy and the optimum duration of treatment. Immunotherapy for all patients with NSCLC may not be ideal, particularly if there is a subset displaying an unusual immunogenic response that is detrimental to their long-term survival. Further studies to identify reliable biomarkers for response and resistance are needed to improve patient selection. Quality of life is also an extremely important factor in the decision to use immunotherapy, as these agents are typically better tolerated than chemotherapy and are often preferred by patients.

Bladder Cancer

The treatment of advanced bladder cancer had seen very little improvement in the last three decades, with limited treatment options and poor patient outcomes until the advent of immunotherapy.[25] Urothelial bladder cancers have high rates of somatic mutations and often express high levels of PD-L1, providing a rationale for the investigation of PD-1 and PD-L1 inhibitors. A Phase II study evaluated first-line atezolizumab in patients ineligible for cisplatin and demonstrated durable response rates and promising effects on survival.[26] This study also showed durable responses (ORR 16%) in a cohort of 310 patients who had progressed following platinum-based chemotherapy.[27] While responses were observed in all PD-L1 patient subgroups, PD-L1 expression on ≥5% of tumour infiltrating immune cells appeared to be an important biomarker for both response and prolonged survival. Exploratory analyses showed that The Cancer Genome Atlas subtypes of bladder cancer were associated with different levels of PD-L1 expression and a corresponding correlation with response to atezolizumab.[28] Mutational load was also predictive of response to this checkpoint inhibitor. Atezolizumab is now approved in the USA for patients with locally advanced or metastatic urothelial carcinoma with progression during or following platinum-based chemotherapy.[29]

Pembrolizumab and the novel PD-L1 inhibitors avelumab and durvalumab have also demonstrated efficacy as monotherapy in Phase I/II trials in advanced urothelial cancer, with response rates of 28–50% in patients with PD-L1-positive tumours.[30-32] Nivolumab elicited responses in 24% of patients with advanced urothelial cancer and promising effects on survival that appeared to be unrelated to PD-L1 status.[33] Ongoing randomised trials are further exploring checkpoint inhibition in bladder cancer, including a trial directly comparing atezolizumab with second-line chemotherapy in patients with metastatic transitional cell carcinoma (TCC) who failed platinum-based chemotherapy.[34] A second randomised study is comparing the PD-L1 inhibitor durvalumab alone versus durvalumab plus the CTLA-4 inhibitor tremelimumab versus chemotherapy for untreated metastatic TCC.[35] Patients will be crossed over at disease progression, providing some insight into the efficacy of sequential therapy using chemotherapy and immunotherapeutic agents. Phase III trials of avelumab maintenance therapy following first-line chemotherapy[36] and of adjuvant atezolizumab or nivolumab post-cystectomy are also ongoing.[37,38]

Renal Cell Carcinoma

In RCC, nivolumab demonstrated superiority to everolimus in patients with advanced disease following one or two prior regimens of

antiangiogenic therapy.[39] Nivolumab significantly improved ORR and prolonged median OS, although unlike in other cancers no plateau was observed in the survival curve for nivolumab, with continuing attrition over time with both treatment approaches. PD-L1 status was prognostic but not predictive of OS benefit. Median PFS was not significantly different between the two treatment arms and further follow-up will be needed to fully understand the survival benefit associated with nivolumab in RCC. The combination of nivolumab and ipilimumab is also under investigation in advanced RCC and has demonstrated preliminary efficacy in a Phase I trial.[40,41]

Tumour angiogenesis is an important driver of RCC progression and antiangiogenic therapy is a key component of the treatment landscape. Antiangiogenic therapies such as bevacizumab have an immunogenic effect and ongoing clinical trials are now evaluating combinations of immunotherapy with antiangiogenic therapy in RCC, including atezolizumab plus bevacizumab.[42] This combination demonstrated promising efficacy in a Phase I trial in advanced RCC, leading to an ongoing Phase II study comparing atezolizumab alone versus atezolizumab plus bevacizumab versus sunitinib in untreated advanced RCC and a Phase III study comparing the combination with sunitinib.[42-44] The anti-PD-L1 therapy avelumab is also being evaluated in combination with axitinib in patients with advanced RCC.[45]

Tumour-associated macrophages promote angiogenesis, invasion, and immunosuppression in a variety of tumour types and may play a particularly important role in RCC.[46] This suggests that second-generation immunotherapy combinations and novel agents targeting macrophages may be needed to see more dramatic efficacy in this tumour type. Inhibitors of macrophage colony stimulating factor 1 (CSF-1) and its receptor (CSF-1R), as well as toll-like receptor and CD40 agonists are under investigation as potential strategies to target tumour-associated macrophages.[2,47] Manipulation of tumour-associated macrophages is complex, as macrophage depletion may inhibit the ability to elicit a strong T cell-mediated response while activation of macrophages can lead to significant production of interleukin-10. Because the immune system is constantly seeking equilibrium, stimulation of one pathway often leads to upregulation of an opposing pathway and can counteract the desired immunogenic effect of the therapy. This complex interplay needs to be carefully considered when designing novel immunotherapies and combinatorial strategies.

Predictive Biomarkers for Cancer Immunotherapy

Doctor Mario Colombo

Despite the success of cancer immunotherapy, not all patients respond to therapy and those who do respond often experience toxicities that can negatively impact on quality of life. Thus the ability to select patients who will most likely benefit from immunotherapy and determine which immunotherapy would work best for an individual, given the expanding number of available agents, is an important objective of current research. High-throughput technologies provide potential tools for immune monitoring and biomarker discovery.[3] One strategy is assessment of TILs, as a lack of T cells within the tumour negatively impacts on the capacity for an immune response. In patients with colorectal cancer, *in situ* immunohistochemical staining and gene expression profiling to evaluate the type, density, and location of immune cells within a tumour sample provided valuable prognostic information.[48] This 'immunoscore' examines the distribution and functional orientation of CD3+ lymphocytes, CD8+ cytotoxic T cells, and memory T cells in the tumour core and invasive margin and has demonstrated superior prognostic utility to the TNM classification system.

PD-L1 expression is an important biomarker for response to PD-1 and PD-L1 inhibitors, although its precise role in specific tumour types is still under investigation.[49] PD-L1 may function primarily as an indicator of immune recognition, reflecting the presence of T cells at the tumour site and sensitivity to interferon gamma. PD-L1 expression patterns differ considerably among the different tumour types, including whether expression is primarily on tumour cells, immune cells, or both. In addition, some tumours display focal PD-L1 expression or show heterogeneous expression across multiple metastases with variation over time. This potentially impacts the utility of PD-L1 as a biomarker for immunotherapy. Increased PD-L1 expression can result from oncogenic signalling or gene mutations within the tumour cell itself (innate resistance) or from activated T cells stimulating surrounding tumour and immune cells to express PD-L1 (acquired resistance).[50]

PD-L1 testing has several technical challenges and can be complicated by the dynamic nature of the immune system.[49] Tumour tissue quantity and quality is important to ensure accurate testing. The percentage cut-offs for PD-L1 positivity are low, sometimes requiring distinction between 1%, 3%, and 5% positive cells within a tumour section. From a biological viewpoint, it is challenging to understand how such small differences in expression can influence responsiveness to immunotherapy. Presumably, PD-1 blockade can create a chain reaction of immune activation from just a small initial population of PD-L1-positive cells that results in clinically meaningful tumour regression. The available diagnostic assays for PD-1/PD-L1 immunohistochemistry differ somewhat with regards to their sensitivity and specificity.[51] While several of the companion diagnostic assays have recently shown comparable PD-L1 staining on the same tissues, suggesting relatively good concordance, careful interpretation, and improved understanding of the inherent differences in these assays is needed.

Mutational load has also been put forth as a potential biomarker for immunotherapy, as increased mutational heterogeneity can create tumour-specific neo-antigens that would potentially elicit an immune response.[52] Tumours with mismatch repair (MMR) deficiencies such as microsatellite instability have particularly high mutational loads, which appears to confer sensitivity to immunotherapy.[53] In support of this, a recent study of the checkpoint inhibitor pembrolizumab demonstrated a response rate of 62% and 60% in MMR-deficient colorectal and non-colorectal tumours, respectively. In contrast, no MMR-proficient colorectal tumours responded to pembrolizumab in this study. However, not all tumour mutations will result in an immunogenic neo-antigen and the challenge lies in being able to accurately identify the appropriate immunologic target.

There are several metabolic enzymes and pathways involved in the control of immune function that represent potential targets for immunotherapy. Tumour cells and nearby immune cells are in continuous competition for nutrients. Studies suggest tumour cells can restrict the availability of glucose to surrounding T cells via PD-L1 signalling, resulting in immunosuppression.[54] Another example is indoleamine 2,3-dioxygenase (IDO), an immune-inhibitory molecule expressed by tumour cells and infiltrating myeloid cells.[55] IDO mediates the kynurenine pathway of tryptophan degradation, resulting in depletion of tryptophan needed for T cell function. This leads to suppression of effector T cells, enhancement of regulatory T cells, and subsequent immune escape. Lastly, in response to signals from activated T lymphocytes, myeloid suppressor cells can block T cell proliferation through manipulation of arginine metabolism by inducing the two enzymes nitric oxide synthase 2 and arginase 1.[56] Induction of either enzyme alone leads to reversible blockade of T cell proliferation, while induction of both enzymes simultaneously results in T cell apoptosis.

There remains a clear unmet need for immunotherapy biomarkers, as it is not realistic to treat every patient with these agents. Ultimately, biomarkers for immunotherapy need to distinguish 'hot' tumours from 'cold' tumours. This might be accomplished with an expanded Immunoscore-type algorithm that takes into account variables such as PD-L1 expression, interferon gamma signatures, MHC Class I and II expression, CD8+ T cell density, mutational load, and other parameters. This readout could provide an 'immune temperature' for each individual tumour to identify responders from non-responders.

Resistance to Immune Checkpoint Blockade

Doctor George Coukos

The exciting efficacy produced by immune checkpoint inhibitors across multiple tumour types is, in most situations, unfortunately coupled with development of resistance to these agents. The precise mechanisms of resistance to immune checkpoint inhibitors are poorly understood, in part due to failure to consistently biopsy and evaluate tumours at progression on immunotherapy. Depending on the tumour type and location, serial biopsies can be very challenging. Liquid biopsies of systemic peripheral blood are much more convenient, can easily be repeated, and may enable prediction of tumour response and/or development of resistance. While peripheral blood samples are unlikely to fully represent the exact immune composition at the tumour site, they could provide important insight into the overall immune environment. A recently published study showed that isolated CD8+, PD-1+ T cells in the peripheral blood of four

patients with melanoma were representative of the TILs recognising specific tumour neo-antigens.[57] Although this was a very small study, it presents the possibility of using peripheral blood as a mirror for the tumour-immune microenvironment. It is important to remember the potential for background noise in peripheral blood samples, as the circulating markers will reflect not only the tumour-specific immune response, but also immune responses to infections, inflammation, and other events. Further study will be required to determine how liquid biopsies and tissue biopsies can best be utilised to fully understand the complex resistance strategies tumours employ to evade immunotherapy.

One of the major mechanisms of resistance to immune checkpoint blockade is absence of tumour-infiltrating T cells. T cells must already be embedded at the tumour site in order to achieve a good anti-tumour immune response. In a retrospective study of ovarian cancer, 5-year OS was significantly higher in patients whose tumours contained infiltrating T cells compared with those without T cell infiltration (74% versus 12%).[58] A meta-analysis performed in 2012 of studies from multiple tumour types also identified the presence of T cells within the tumour as a good prognostic indicator.[59] Mouse models of ovarian cancer and retrospective analysis of melanoma tumour samples clearly showed that the absence of TILs predicted failure of PD-L1 blockade.[60,61] While some tumours have spontaneous infiltration of T cells, 50–70% of solid tumours lack tumour-infiltrating T cells and would not be expected to respond to T cell activation. This potentially explains why only 30–50% of tumours respond to immune checkpoint inhibitor monotherapy. Based on T cell infiltration, tumours can be divided into immunogenic and non-immunogenic. The non-immunogenic group however comprises both tumours that have no T cells at all (immune ignorant or immune desert) and those that only have T cells at the invasive margin (immune exclusion).

Immunogenicity is also related to mutational load and the presence of neo-antigens, as discussed previously, with mutational load predicting for response to pembrolizumab in NSCLC and MMR-deficient tumours.[53,62] Importantly, a linear relationship does not exist between the number of neo-antigens in a tumour and the level of response to PD-1 blockade, indicating that additional factors likely influence tumour immunogenicity and response to therapy. Adding to this complexity, McGranahan et al.[63] recently published a study showing that clonal neo-antigens enhance sensitivity to immune checkpoint inhibitors, while subclonal neo-antigens were associated with a poor response to these agents.[63] Interestingly, administration of chemotherapy appeared only to add subclonal neo-antigens and did not improve response to immunotherapy. Immune targeting of clonal, dominant neo-antigens that are shared by all the branches of the tumour could potentially eliminate all of the tumour clones. In contrast, significant subcloning will create neo-antigens that are not shared universally within the tumour and allow subclones to evade the immune response. These data suggest that administration of immunotherapy earlier in the disease course before subcloning occurs may be more beneficial, although many tumours exhibit significant heterogeneity at diagnosis.

Strategies to improve response to PD-1/PD-L1 blockade in tumours that are already immunogenic include pushing TILs harder to increase the immune response, eliminating more inhibitory signals, or expanding the pool of tumour-reactive T cells. Activating immune receptors such as OX40, GITR, CD137, CD27, and HVEM are potential targets for agonistic antibodies that could be combined with existing immunotherapy to augment immune response (Figure 1).[4] Increased activation of the immune system will undoubtedly result in emergence of further regulatory counterpoints, or 'breaks' to achieve equilibrium. Novel inhibitory receptors beyond CTLA-4 and PD-1, including TIM-3, VISTA, and LAG-3, represent targets for blocking antibodies to eliminate additional inhibitory signals.

As mentioned previously, an apparently important negative regulator of immune response is IDO, which catabolises tryptophan and shuts down T cells. Studies of immune checkpoint blockade in IDO knockout mice showed that upregulation of IDO is a potential mechanism of resistance to agents inhibiting CTLA-4, PD-1, PD-L1, and GITR.[64] Combined blockade of IDO and immune checkpoint signalling appeared to be synergistic in this mouse model, suggesting a rationale for combination therapy strategies that could prevent or overcome resistance to checkpoint blockade monotherapy.

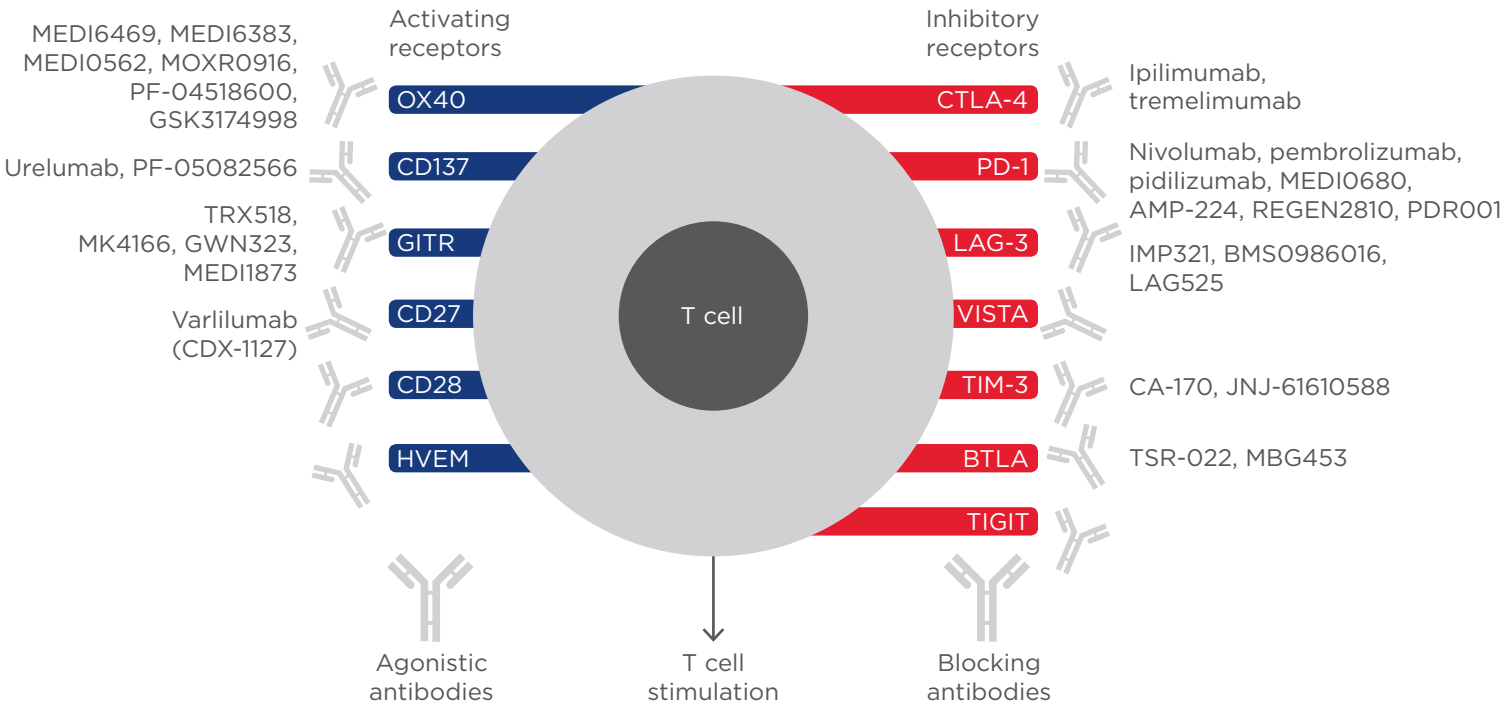

Figure 1: T cell targets for antibody-based immunotherapies.
CTLA-4: cytotoxic T lymphocyte-associated-protein 4; GITR: glucocorticoid-induced tumour necrosis factor-related; TIM-3: T cell immunoglobulin and mucin domain-3; LAG-3: lymphocyte-activation gene 3; PD-1: programmed cell death-protein 1; HVEM: herpes virus entry mediator; BTLA: B and T lymphocyte-associated; TIGIT: T cell immunoreceptor with Ig and ITIM domains.

In order to overcome immune exclusion, the mechanisms of exclusion must first be eliminated to allow infiltration of T cells into the tumour. These T cells could then be activated through immune checkpoint blockade, vaccines, personalised T cell adoptive therapy, etc. One potential mechanism for immune exclusion is through the action of the endothelial barrier. In a study of advanced ovarian cancer tumour samples, those without intratumoural T cells demonstrated increased expression of vascular endothelial growth factor.[58] A study of genomic and transcriptomic signatures in patients with melanoma patients treated with PD-1 blockade also showed that tumours resistant to PD-1 inhibition had upregulation of genes involved in angiogenesis.[65] The tumour endothelium may prevent circulating T cells from transmigrating into the tumour or it may attract T cells and then trigger T cell death through the expression of molecules such as Fas ligand.[66]

Overcoming immune ignorance or the existence of an immune desert within a tumour site represents a difficult challenge in the field of immunotherapy. Current investigations are trying to identify the key signalling pathways responsible for immune ignorance and examine targeted therapies that may reverse this effect. For example, *PTEN* loss is associated with an immune desert phenotype with complete silencing of immune and inflammatory signalling pathways.[67] In preclinical models, loss of *PTEN* led to upregulated expression of immunosuppressive cytokines and proangiogenic signalling, decreased T cell tumour infiltration, and poor response to PD-1 inhibitors. A selective PI3K-β inhibitor improved response to both PD-1 and CTLA-targeted therapy, suggesting a rationale for combinatorial therapy to overcome immune resistance. Radiotherapy may also represent an important strategy to convert a non-immunogenic tumour into a responsive tumour and is discussed below.

There is a clear need for algorithms to assess the potential for response and resistance to immunotherapy, but this will require considerable advances in bioinformatics and identification of reliable biomarkers. A cancer immunogram recently proposed by Blank et al.[68] suggests integration of multiple parameters to assess the capacity for an immune response. Variables include absence of checkpoint markers (PD-L1), immune

cell tumour infiltration, total lymphocyte count, mutational load, sensitivity to immune effectors (MHC expression and interferon gamma sensitivity), absence of inhibitory tumour metabolism (lactate dehydrogenase and glucose utilisation), and absence of soluble inhibitors (interleukin-6 and C-reactive protein). The relationships between these parameters and the hierarchal importance of each will need to be quantified in order to achieve a measurable readout useful for immunotherapy treatment decisions.

Immunotherapeutic Combination Strategies: Where Are We Now and Where Are We Going?

Doctor Ignacio Melero, Doctor Alexander M. M. Eggermont, Doctor Eric Deutsch

Combination of Different Immunotherapeutic Strategies

Integration of cancer immunotherapies into combination and sequential strategies represents an attractive therapeutic strategy to increase the anti-tumour immune response and improve long-term patient outcomes.[69] By carefully selecting agents or treatment modalities with complementary mechanisms of action, synergistic efficacy may be achieved. Tumours with strong endogenous anti-tumour immune response typically exhibit PD-L1 upregulation in the tumour and respond well to anti-PD-1 monotherapy.[52] Tumours with a weak endogenous anti-tumour immune response often lack PD-L1 upregulation and will usually not be responsive to PD-1 blockade. Utilising an inducer of tumour immunity such as a vaccine or co-stimulatory agonist can increase the endogenous anti-tumour immune response, leading to PD-L1 upregulation and reconditioning of the environment to become responsive to PD-1 blockade. This provides an important rationale for sequential or combinatorial immunotherapy strategies to stimulate or reactivate the immune system and boost tumour response.

The number of combination immunotherapy strategies under investigation continues to expand (Figure 2).[69] PD-1/PD-L1 blockade will likely continue to be the foundation for most combinatorial strategies given the efficacy and tolerability these agents have already demonstrated. PD-1/PD-L1 provides a unique common denominator for cancer therapy, with inhibitors of this immune checkpoint targeting a single molecular pathway that plays a role in many different tumour types.[50]

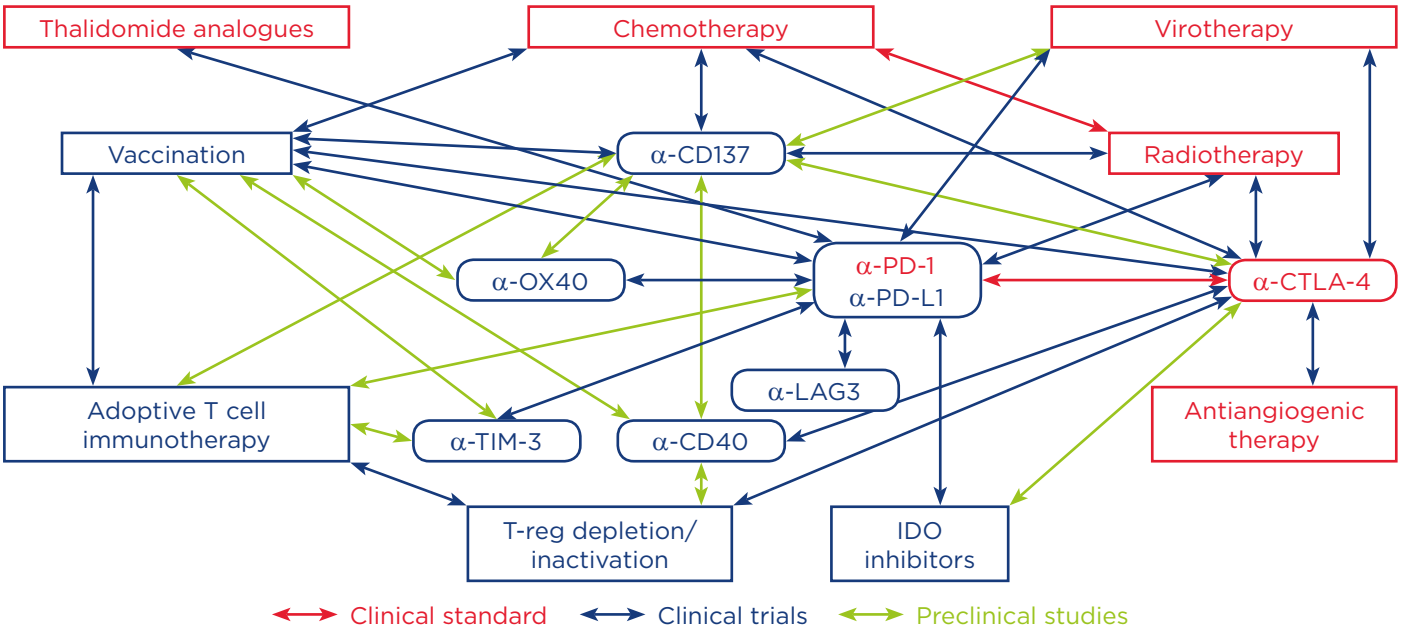

Figure 2: Combination therapy strategies involving cancer immunotherapy.[69]
CTLA-4: cytotoxic T lymphocyte-associated-protein 4; PD-1: programmed cell death-protein 1; PD-L1: programmed cell death-ligand 1; TIM-3: T cell immunoglobulin and mucin domain-3; IDO: indoleamine 2,3-dioxygenase.
Adapted with permission from Melero et al.[69]

PD-1/PD-L1 blockade can then be combined with blockade of other co-inhibitory molecules (CTLA-4, LAG-3, killer immunoglobulin-like receptors), agonists for co-stimulatory molecules (CD137, OX40, CD40, GITR), metabolic targets, vaccination strategies, or adoptive cell therapy.[4]

The success of the checkpoint inhibitors and their complementary mechanisms of action led to investigation of dual checkpoint blockade. As mentioned previously, the combination of ipilimumab and nivolumab demonstrated striking efficacy in patients with advanced melanoma, with durable responses and a significant improvement in PFS for the combination over ipilimumab or nivolumab monotherapy.[7] Importantly however, the superior efficacy of the combination came at the cost of excess toxicity, with 36% of patients discontinuing combination therapy due to treatment-related adverse events. Tolerability represents an important challenge in the use of immunotherapies, particularly when combinatorial strategies are employed. Replacing poorly tolerated immunotherapeutic agents with those that have a more favourable safety profile may improve the therapeutic index of future immune combinations. Sequencing of immunotherapies is clearly an important strategy to evaluate and may provide better disease control with good tolerability and preservation of quality of life.

The tolerability of agents such as ipilimumab may also be improved by re-evaluating the dosing and treatment schedule. For instance, recent data from the expansion cohort of the KEYNOTE-029 trial showed that combining standard-dose pembrolizumab with a reduced dose of ipilimumab (1 mg/kg for four doses) had robust activity and was well-tolerated.[70] Only 25% of patients experienced a Grade 3 or 4 irAE and very few had to discontinue ipilimumab therapy. Results from the ongoing Phase III trial comparing ipilimumab dosing of 3–10 mg/kg will also shed light on the optimum dosing for ipilimumab when given as sequential therapy.[71] Spacing out the doses of ipilimumab, such as administration every 3 months instead of every 3 weeks, may also improve tolerability of combination regimens, particularly for less fit patients.

A novel immunotherapy currently under investigation in combination regimens is the potent oral IDO1 inhibitor epacadostat. This agent demonstrated promising activity and tolerability in combination with ipilimumab in a Phase I/II trial of patients with metastatic melanoma.[72] A second Phase I/II trial is evaluating epacadostat plus pembrolizumab in multiple solid tumour types.[73] The combination is well-tolerated, with only 11% of patients experiencing a Grade 3 adverse event and no Grade 4 events reported. Objective responses were observed in many tumour types, including advanced melanoma, RCC, NSCLC, TCC of the bladder, endometrial adenocarcinoma, and head and neck cancers. In 19 evaluable patients with advanced melanoma, 10 (53%) achieved an objective response, including 2 complete responses.

Another novel immunotherapy target with the potential to make a good partner for immunotherapy combinations is CD137 (also called 4-1BB), which is expressed on activated T cell and natural killer cells.[74] This co-stimulatory molecule binds to the CD137 ligand on APCs, promoting T cell proliferation, cytotoxic activity, and cytokine production, while inhibiting apoptosis. Anti-CD137 agonist therapy overcomes tumour antigen tolerance in a cytotoxic T lymphocyte-dependent manner and enhances natural killer cell antibody-dependent cellular cytotoxicity.[74,75] CD137 co-stimulation is synergistic with adoptive T cell therapy in preclinical models.[76] TILs can be selected for CD137 expression *ex vivo* to enrich for the most potent anti-tumour activity and/or cultured in the presence of anti-CD137 agonist to increase T cell activation. Administration of anti-CD137 agonist therapy at the time of TIL adoptive transfer can also increase T cell activation and tumour infiltration.

Combinations with OX40 targeted antibody therapy are also currently being explored and have shown activity in Phase I trials in solid tumours. For example, the OX40 agonist therapy MOXR0916 demonstrated promising activity and good tolerability in combination with atezolizumab in a Phase Ib dose escalation trial in advanced solid tumours.[77] The ongoing first-in-human ENGAGE-1 trial is examining the OX40 agonist GSK3174998 alone or in combination with pembrolizumab in patients with advanced solid tumours.[78]

The vast number of potential doublet and triplet immunotherapy combinations cannot all realistically be examined in clinical trials. Therefore, biological insight and robust preclinical studies are needed to identify the most promising combination strategies before moving into clinical studies. To assist in this investigation,

a humanised murine model has been developed that will allow the study of human tumours in an immunocompetent setting by transferring human lymphocytes into immunodeficient mice.[79] This will be a useful tool for the evaluation of immune checkpoint inhibitors and combination immunotherapy regimens. Murine tumour models are not ideal however, and due to the considerable differences between human and mouse immune systems, may underestimate or overestimate the potential for immunotherapies and combination regimens.

Combination Strategies with Immunotherapy and Radiotherapy

In addition to its direct anti-tumour effects, radiotherapy can trigger an immune response and mediate tumour regression not only locally but also at distant tumour sites, the so-called abscopal or 'away from the target' response.[80] In murine tumour models, radiotherapy increased PD-L1 expression in the tumour microenvironment and administration of PD-L1 blocking antibody synergised with radiotherapy to amplify the anti-tumour effect. The combination of radiotherapy and anti-PD-L1 therapy activated cytotoxic T cells and reduced the accumulation of myeloid-derived suppressor cells within the tumour, promoting an anti-tumour immune response. A similar study in murine cancer models using low-dose fractionated radiotherapy also showed upregulation of PD-L1 on tumour cells.[81] Interestingly, the synergy between radiotherapy and anti-PD-L1 therapy only prolonged survival when given concurrently, not sequentially. This may have implications for the use of combined immunotherapy and radiotherapy as this strategy moves into clinical practice. However, the half-life of immune checkpoint inhibitors is long enough that administering immunotherapy a few days prior to radiotherapy should be sufficient to ensure appropriate timing of immune stimulation.

The abscopal effect, associated with the combination of immunotherapy and radiotherapy, has been observed in an early proof-of-principle trial using local radiotherapy and GM-CSF in patients with metastatic solid tumours.[82] A total of 27% of the 41 patients demonstrated an abscopal response. A preclinical study in melanoma and RCC models showed that PD-1 expression inhibited the ability of single-dose radiotherapy to induce an abscopal effect.[83] This was reversed with PD-1 blockade therapy, demonstrating a synergistic anti-tumour effect in the primary tumour and an abscopal effect on non-irradiated tumours. A second study using a murine breast cancer model demonstrated similar synergistic responses with radiotherapy and CTLA-4 blockade, including abscopal responses in non-irradiated tumours.[84] However, unlike the previous study, the abscopal effect was seen only when fractionated radiotherapy was used, not single-dose radiotherapy. A small, retrospective melanoma study also demonstrated abscopal responses in patients who received ipilimumab followed by radiotherapy and suggested a survival benefit in patients who experienced abscopal responses compared with those who did not.[85] Larger, randomised trials will be necessary to fully elucidate the long-term benefit of an abscopal response to immunotherapy-radiotherapy combinations.

The largest randomised trial of immunotherapy combined with radiotherapy to date investigated single-dose radiotherapy followed by either ipilimumab or placebo in patients with castration-resistant prostate cancer.[86] Although dramatic, durable responses were observed in the ipilimumab arm: median OS was not significantly prolonged (10.0 months versus 11.2 months; hazard ratio: 0.85; p=0.053). The negative result may be attributed to factors such as suboptimal timing of radiotherapy or selection of the wrong immunotherapeutic agent for this tumour type.

Immunotherapy is also under investigation in combination with stereotactic ablative radiotherapy in several tumour types.[87] Triplet combinations incorporating radiotherapy, CTLA-4 blockade, and PD-1/PD-L1 blockade are also being explored based on data from preclinical murine tumour models.[88] Upregulation of PD-L1 and T cell exhaustion are a mechanism of resistance to radiotherapy and CTLA-4 blockade. The addition of anti-PD-L1 therapy appeared to reverse this effect and promote response and anti-tumour immunity. Combinations of stereotactic ablative radiotherapy with vaccine-based strategies are also under investigation.[89]

Numerous questions remain regarding the combination of radiotherapy with immunotherapies. Clinical trial data are needed to determine the optimal immunotherapy to combine with radiotherapy and the appropriate dose and fractionation schedule for radiotherapy. Further study will be necessary to truly determine whether radiotherapy can turn a non-immunogenic tumour

into an immunogenic tumour to maximise the anti-tumour immune response and careful attention paid to toxicities that may be exacerbated by these combination strategies.

Combination Strategies with Immunotherapy and Chemotherapy or Targeted Agents

Combinations with chemotherapy and targeted agents have also been explored in multiple tumour types, including melanoma and lung cancer.[69] In patients with untreated metastatic melanoma, the combination of ipilimumab with dacarbazine improved median OS compared to dacarbazine alone, but was associated with Grade 3 or 4 immune-mediated hepatitis in 31.6% of patients versus 2.4% with dacarbazine alone.[90] Dacarbazine does not lead to immunogenic cell death and may be a poor partner for novel immunotherapeutic combinatorial strategies. In breast cancer, ongoing studies are evaluating pembrolizumab in combination with agents such as paclitaxel, nab-paclitaxel, capecitabine, carboplatin/gemcitabine, and eribulin mesylate, as well as with poly(ADP-ribose) polymerase inhibitor therapy.[91]

Table 1: Selected ongoing trials of combination approaches with immune checkpoint inhibitors.[91]

Combination approach	Targets	Agents	Phase	Tumour types
Dual checkpoint blockade	PD-1, CTLA-4	Nivolumab + ipilimumab	I, II, III	Melanoma, lung, RCC, sarcoma, breast, colon, liver glioblastoma, gliosarcoma, MDS, lymphoma, myeloma
	PD-1, CTLA-4	Pembrolizumab + ipilimumab	I, II	Melanoma, RCC, lung
	PD-L1, CTLA-4	Durvalumab + tremelimumab	I, II, III	Breast, lung, HCC, gastric, H & N, bladder, melanoma, glioma, mesothelioma, prostate, pancreas
	PD-1, PD-L1	MEDI0680 + durvalumab	I	Selected advanced tumours
	PD-1, LAG-3	Nivolumab + BMS-986106	I	Solid tumours, glioblastoma
	PD-1, LAG-3	Pembrolizumab + IMP321		
	PD-1, LAG-3	PDR001 + LAG525	I, II	Solid tumours
	PD-1, TIM-3	PDR001 + MBG453	I	Advanced tumours
Checkpoint inhibitor plus co-stimulatory receptor agonists	CD137, PD-1	Urelumab + nivolumab	I, II	Solid tumours, glioblastoma
	CD137, PD-1	PF-05082566 + pembrolizumab	I	Solid tumours
	CD137, PD-L1	PF-05082566 + avelumab	I	Solid tumours
	OX40 + CTLA-4 or PD-L1 or CD20	MEDI6469 + tremelimumab or durvalumab or rituximab	I, II	Solid tumours, DLBCL
	OX40, PD-1	GSK3174998 + pembrolizumab	I	Solid tumours
	OX40, PD-L1	PF-04518600 + avelumab	I	Solid tumours
	OX40, PD-L1	MEDI6383 + durvalumab	I	Solid tumours
	OX40, PD-L1	MOXR0916 + atezolizumab	I	Solid tumours
	GITR, PD-1	MK-4166 + pembrolizumab	I	Solid tumours
	GITR, PD-1	GWN323 + PDR001	I	Advanced tumours
	CD27, PD-L1	Varilumab + atezolizumab	I, II	Advanced tumours
	CD40, CTLA-4	CP-870,893 + tremelimumab	I	Melanoma
Checkpoint inhibitor plus innate immune cell stimulators	KIR, CTLA-4	Lirilumab + ipilimumab	I	Solid tumours
	KIR, PD-1	Lirilumab + nivolumab	I	Lymphoma, myeloma, solid tumours
Checkpoint inhibitor plus IDO inhibition	IDO + PD-1 or PD-L1 or CTLA-4	Epacadostat + nivolumab, pembrolizumab, durvalumab, atezolizumab, or ipilimumab	I, II, III	Select advanced cancers, lung, melanoma
	IDO, CTLA-4	Indoximod + ipilimumab	I, II	Melanoma
	IDO, PD-L1	GDC-0919 + atezolizumab	I	Solid tumours

Table 1 continued.

Combination approach	Targets	Agents	Phase	Tumour types
Checkpoint inhibitor plus oncolytic therapy	Viral therapy, CTLA-4 or PD-1	T-VEC + ipilimumab or pembrolizumab	I, II, III	Melanoma
	Viral therapy, CTLA-4 or PD-1	CVA21 + ipilimumab or pembrolizumab	I	Melanoma
	Viral therapy, CTLA-4	HF10 + ipilimumab	II	Melanoma
Checkpoint inhibitor plus targeted therapy	HDAC, PD-1	Entinostat + pembrolizumab	I, II	Lung, melanoma
	HDAC, PD-1	Vorinostat + pembrolizumab	I, II	H & N, salivary gland
	HDAC, PD-1, CTLA-4	Entinostat + nivolumab + ipilimumab	I	Solid tumours, breast
	HDAC, PD-L1	Entinostat + atezolizumab	I, II	Breast
	EGFR, PD-1	Erlotinib or gefitinib or afatinib + pembrolizumab	I, II	Lung
	VEGF, PD-L1	Bevacizumab + atezolizumab	I, II, III	RCC
	VEGFR, PD-1	Axitinib + pembrolizumab	I	RCC
	VEGFR, PD-L1	Axitinib + avelumab	I, III	RCC
	HER2, PD-L1	Trastuzumab/pertuzumab or T-DM1 + atezolizumab	I	HER2+ breast
	PARP, PD-1	Niraparib + pembrolizumab	I, II	Breast
	CDK, PD-1, ER	Palbociclib + pembrolizumab + letrozole	II	ER+ breast
	BRAF, MEK, PD-L1	Dabrafenib + trametinib + durvalumab	I, II	Melanoma
Checkpoint inhibitor plus chemotherapy	PD-1, cytotoxic targets	Nivolumab + platinum doublet chemotherapy	I	Lung
	PD-L1, cytotoxic targets	Atezolizumab + carboplatin/ paclitaxel +/- bevacizumab	III	Lung
	PD-1, cytotoxic targets	Pembrolizumab + paclitaxel, nab-paclitaxel, eribulin mesylate, carboplatin/ gemcitabine, capecitabine,	I, II	Breast
	PD-L1, cytotoxic targets	Atezolizumab + nab-paclitaxel	II, III	Breast
Checkpoint inhibitor plus radiotherapy	PD-L1, PD-1	Chemoradiotherapy + consolidation durvalumab or atezolizumab or nivolumab	II, III	Lung
	PD-L1	Atezolizumab	0	Lung
	CTLA-4	Ipilimumab	I, II	Lung
	PD-1	REGN2810, pembrolizumab	I, II	Lung

BRAF: v-raf murine sarcoma viral oncogene homolog B; CTLA-4: cytotoxic T lymphocyte-associated-protein 4; DLBCL: diffuse large B cell lymphoma; EGFR: epidermal growth factor receptor; GITR: glucocorticoid-induced tumour necrosis factor-related; H & N: head and neck; HCC: hepatocellular carcinoma; HDAC: histone deacetylase; IDO: indoleamine 2,3-dioxygenase; KIR: killer cell immunoglobulin-like receptor; LAG-3: lymphocyte-activation gene 3; MEK: mitogen-activated protein kinase; PD-1: programmed cell death-protein 1; PD-L1: programmed cell death-ligand 1; RCC: renal cell carcinoma; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor; MDS: myelodysplastic syndrome; HER2: human epidermal growth factor receptor 2; ER: estrogen receptors; PARP: poly(ADP-ribose) polymerase.

Atezolizumab is being investigated in combination with nab-paclitaxel, HER2-targeted agents, and HDAC inhibitors. The combination of atezolizumab and nab-paclitaxel demonstrated promising tolerability and efficacy in a recently reported Phase Ib trial in triple-negative breast cancer.[92]

The combination of ipilimumab with paclitaxel/carboplatin was explored in two Phase II trials in patients with chemotherapy-naïve advanced NSCLC or extensive disease SCLC.[93,94] In both trials, 'phased' ipilimumab (two doses of chemotherapy plus placebo, followed by four doses of chemotherapy plus ipilimumab) significantly improved immune-related PFS compared to chemotherapy alone, which was not observed when ipilimumab and chemotherapy were initiated concurrently. In the NSCLC trial, 'phased' ipilimumab with paclitaxel/carboplatin also improved median PFS and ORR compared with chemotherapy alone.[93] A Phase I study of nivolumab in combination with different platinum-based doublet chemotherapy in advanced NSCLC showed ORRs of 33–47%, similar to the efficacy of doublet chemotherapy alone.[95] Another Phase Ib trial evaluated atezolizumab plus carboplatin in combination with either paclitaxel, nab-paclitaxel, or carboplatin as first-line therapy for advanced NSCLC.[96] While the patient numbers are small, the combination of atezolizumab with first-line chemotherapy had a tolerable safety profile and generated durable responses, with ORRs ranging from 60–75%. The combination of pembrolizumab with platinum-based doublet chemotherapy demonstrated ORRs of 48–71% as front-line therapy for advanced NSCLC.[97]

Several ongoing trials of immunotherapy combined with chemotherapy or targeted agents are ongoing or planned in lung cancer, including the Phase III KEYNOTE-189 trial evaluating pembrolizumab with platinum-based doublet chemotherapy as first-line therapy for metastatic non-squamous NSCLC.[91,98] Phase I/II trials are also evaluating checkpoint blockade in combination with erlotinib, gefitinib, or afatinib in patients with *EGFR*-mutated NSCLC.[91] Combinations of immunotherapy with chemotherapy or targeted agents are often associated with considerable toxicity, suggesting these strategies may be more beneficial administered as sequential therapy rather than concomitantly.

Conclusions

Future development of cancer immunotherapy will undoubtedly focus on combination strategies, including combinations of checkpoint inhibitors with other therapies (Table 1).[91] Robust, well-designed clinical trials will be essential to ensure continued progress in cancer immunotherapy. As novel combinations move into early-phase trials, it will be both challenging and critical to identify efficacy signals and detect potential synergy between therapies. Appropriate patient selection is critical, as treating unselected populations with these combinations is unlikely to give a robust survival signal. Emerging biomarkers and algorithms should be rapidly incorporated into clinical trials to increase the probability of detecting an efficacy signal if one is present. It may also be beneficial to initially test novel immunotherapy agents or combinations in patients who do not respond to PD-1/PD-L1 blockade to identify those with significant activity that are worth pursuing. The most promising agents can then be explored in treatment-naïve patients and earlier lines of therapy.

We have only scratched the surface with regard to the potential for cancer immunotherapy. Continued identification of the critical regulators of immune evasion and response will open the door to development of novel immunotherapy strategies and eradication of tumours that currently lack effective treatment options. The next few years will undoubtedly witness a massive expansion in cancer immunotherapies and combination regimens. Only by carefully evaluating these emerging strategies will we be able to effectively incorporate them into clinical practice and improve patient outcomes.

REFERENCES

1. Couzin-Frankel J. Breakthrough of the year 2013: Cancer Immunotherapy. Science. 2013;342(6165):1432-3.
2. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39(1):1-10.
3. Yuan J et al. Novel technologies and emerging biomarkers for personalized cancer immunotherapy. J Immunother Cancer. 2016;4:3.
4. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat Rev Immunol. 2013;13(4):227-42.
5. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy.

Science. 2015;348(6230):69-74.

6. Kvistborg P et al. Immune monitoring technology primer: whole exome sequencing for neoantigen discovery and precision oncology. J Immunother Cancer. 2016;4(22):1-4.

7. Redman JM et al. Advances in immunotherapy for melanoma. BMC Med. 2016;14(1):20.

8. Callahan MK et al. Checkpoint blockade for the treatment of advanced melanoma. Cancer Treat Res. 2016;167:231-50.

9. Schadendorf D et al. Pooled analysis of long-term survival data from phase ii and phase iii trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015;33(17):1889-94.

10. Eggermont AM et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015;16(5):522-30.

11. Merck Sharp & Dohme Corp. Study of Pembrolizumab (MK-3475) Versus Placebo After Complete Resection of High-Risk Stage III Melanoma (MK-3475-054/KEYNOTE-054). Available at: https://clinicaltrials.gov/show/NCT02362594. Last accessed: 26 April 2016.

12. Robert C et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-30.

13. Wolchok JD et al. Updated results from a phase III trial of nivolumab (NIVO) combined with ipilimumab (IPI) in treatment-naive patients (pts) with advanced melanoma (MEL) (CheckMate 067). Abstract 9505. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

14. Postow MA et al. Initial report of overall survival rates from a randomized phase ii trial evaluating the combination of nivolumab and ipilimumab in patients with advanced melanoma. Abstract CT002. American Association for Cancer Research Annual Meeting, New Orleans, Louisiana, USA, 16-20 April 2016.

15. Andtbacka RH et al. Talimogene Laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol. 2015;33(25):2780-8.

16. Puzanov I et al. Survival, safety, and response patterns in a phase 1b multicenter trial of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma. Abstract 9063. 2015 ASCO Annual Meeting, Chicago, Illinois, USA, 29 May-2 June 2015.

17. Long G et al. Primary analysis of MASTERKEY-265 phase 1b study of talimogene laherparepvec (T-VEC) and pembrolizumab (pembro) for unresectable stage IIIB-IV melanoma. Society for Melanoma Research 2015 Congress, San Francisco, California, USA, 18-21 November 2015.

18. Yang L et al. Immunotherapy for lung cancer: advances and prospects. Am J Clin Exp Immunol. 2016;5(1):1-20.

19. Brahmer J et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123-35.

20. Borghaei H et al. Nivolumab versus Docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627-39.

21. Herbst RS et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.

22. Fehrenbacher L et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387(10030):1837-46.

23. Hui R et al. Long-term OS for patients with advanced NSCLC enrolled in the KEYNOTE-001 study of pembrolizumab (pembro). Abstract 9026. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

24. Smith DA et al. Updated survival and biomarker analyses of a randomized phase II study of atezolizumab vs docetaxel in 2L/3L NSCLC (POPLAR). Abstract 9028. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

25. Powles T et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515(7528):558-62.

26. Balar AV et al. Atezolizumab (atezo) as first-line (1L) therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (mUC): Primary analysis of IMvigor210 cohort 1. Abstract LBA4500. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

27. Dreicer R et al. Updated efficacy and > 1-y follow up from IMvigor210: Atezolizumab (atezo) in platinum (plat) treated locally advanced/metastatic urothelial carcinoma (mUC). Abstract 4515. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

28. Rosenberg JE et al. PD-L1 expression, Cancer Genome Atlas (TCGA) subtype, and mutational load as independent predictors of response to atezolizumab (atezo) in metastatic urothelial carcinoma (mUC; IMvigor210). Abstract 104. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

29. FDA Grants Genentech's Cancer Immunotherapy TECENTRIQ (Atezolizumab) Accelerated Approval for People with a Specific Type of Advanced Bladder Cancer. [press release]. Available at: www.gene.com/media/press-releases/14626/2016-05-18/fda-grants-genentechs-cancer-immunothera. Last accessed: 18 June 2016.

30. Plimack ER et al. Pembrolizumab (MK-3475) for advanced urothelial cancer: updated results and biomarker analysis from KEYNOTE-012. Abstract 4502. ASCO Annual Meeting, Chicago, Illinois, USA. 29 May-2 June 2015.

31. Apolo AB et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with metastatic urothelial carcinoma from the JAVELIN solid tumor phase 1b trial: Analysis of safety, clinical activity, and PD-L1 expression. Abstract 4514. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

32. Massard C et al. Safety and efficacy of durvalumab (MEDI4736), an anti-PD-L1 antibody, in urothelial bladder cancer. Abstract 4502. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

33. Sharma P et al. Efficacy and safety of nivolumab monotherapy in metastatic urothelial cancer (mUC): results from the phase I/II CheckMate 032 study. Abstract 4501. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

34. Hoffman- La Roche. A Study of Atezolizumab Compared With Chemotherapy in Patients With Locally Advanced or Metastatic Urothelial Bladder Cancer [IMvigor211]. Available at: https://clinicaltrials.gov/show/NCT02302807. Last accessed: 20 June 2016.

35. AstraZeneca. Study of MEDI4736 With or Without Tremelimumab Versus Standard of Care Chemotherapy in Bladder Cancer. Available at: https://clinicaltrials.gov/show/NCT02516241. Last accessed: 20 June 2016.

36. Pfizer. A Study Of Avelumab In Patients With Locally Advanced Or Metastatic Urothelial Cancer (JAVELIN Bladder 100). Available at: https://clinicaltrials.gov/show/NCT02603432. Last accessed: 20 June 2016.

37. Hoffman-La Roche. A Phase III Study of Atezolizumab Treatment Versus Observation as Adjuvant Therapy in Patients With PD-L1 Positive, High Risk Muscle Invasive Bladder Cancer After Cystectomy [IMvigor010]. Available at: https://clinicaltrials.gov/show/NCT02450331. Last accessed: 20 June 2016.

38. Bristol-Myers Squibb. A Study of Adjuvant Nivolumab Versus Placebo Post-Surgical Removal of High Risk Invasive Urothelial Carcinoma (CheckMate 274). Available at: https://clinicaltrials.gov/show/NCT02632409. Last accessed: 20 June 2016.

39. Motzer RJ et al. Nivolumab

versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015; 373(19):1803-13.

40. Hammers HJ et al. Expanded cohort results from CheckMate 016: a phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). Abstract 4516. ASCO Annual Meeting, Chicago, Illinois, USA. 29 May-2 June 2015.

41. Bristol-Myers Squibb. Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214). Available at: https://clinicaltrials.gov/show/NCT02231749. Last accessed: 20 June 2016.

42. Sznol M et al. Phase Ib evaluation of MPDL3280A (anti-PDL1) in combination with bevacizumab (bev) in patients (pts) with metastatic renal cell carcinoma (mRCC). Abstract 410. 2015 Genitourinary Cancers Symposium, Orlando, Florida USA.

43. Hoffman-La Roche. A Phase 2 Study of Atezolizumab (an Engineered Anti-PDL1 Antibody) as Monotherapy or in Combination With Avastin (Bevacizumab) Compared to Sunitinib in Patients With Untreated Advanced Renal Cell Carcinoma [IMmotion150]. Available at: https://clinicaltrials.gov/show/NCT01984242. Last accessed: 20 June 2016.

44. National Institutes of Health. A Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma. Available at: https://clinicaltrials.gov/show/NCT02420821. Last accessed: 20 June 2016.

45. Larkin JMG et al. Avelumab (MSB0010718C; anti-PD-L1) in combination with axitinib as first-line treatment for patients with advanced renal cell carcinoma. Abstract TPS4580. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

46. Santoni M et al. Emerging role of tumor-associated macrophages as therapeutic targets in patients with metastatic renal cell carcinoma. Cancer Immunol Immunother. 2013;62(12): 1757-68.

47. Ries CH et al. CSF-1/CSF-1R targeting agents in clinical development for cancer therapy. Curr Opin Pharmacol. 2015;23: 45-51.

48. Kirilovsky A et al. Rational bases for the use of the Immunoscore in routine clinical settings as a prognostic and predictive biomarker in cancer patients. Int Immunol. 2016;28(8):373-82.

49. Topalian SL et al. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer. 2016;16(5):275-87.

50. Topalian SL et al. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27(4):450-61.

51. Ratcliffe M et al. A comparative study of PD-L1 diagnostic assays and the classification of patients as PD-L1 positive and PD-L1 negative. Abstract LB-094. 107th Annual Meeting of the American Association for Cancer Research, New Orleans, Louisiana, USA, 16-20 April 2016.

52. Pardoll DM. Immunotherapy overview: mechanisms and modalities. ASCO Annual Meeting, Chicago, Illinois, USA, 29 May-2 June 2015.

53. Le DT et al. PD-1 blockade in tumors with mismatch repair deficiency. Abstract LBA100. ASCO Annual Meeting, Chicago, Illinois, USA, 29 May-2 June 2015.

54. Sukumar M et al. Nutrient competition: a new axis of tumor immunosuppression. Cell. 2015;162(6):1206-8.

55. Moon YW et al. Targeting the indoleamine 2,3-dioxygenase pathway in cancer. J Immunother Cancer. 2015;3:51.

56. Bronte V et al. L-arginine metabolism in myeloid cells controls T-lymphocyte functions. Trends Immunol. 2003;24(6):301-5.

57. Gros A et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Nat Med. 2016;22(4):433-8.

58. Zhang L et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med. 2003;348(3):203-13.

59. Fridman WH et al. The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer. 2012; 12(4):298-306.

60. Duraiswamy J et al. Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T-cell rejection function in tumors—response. Cancer Res. 2014;74(2):633-4.

61. Tumeh PC et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568-71.

62. Rizvi NA et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015; 348(6230):124-8.

63. McGranahan N et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science. 2016;351(6280): 1463-9.

64. Holmgaard RB et al. Indoleamine 2,3-dioxygenase is a critical resistance mechanism in antitumor T cell immunotherapy targeting CTLA-4. J Exp Med. 2013;210(7):1389-402.

65. Hugo W et al. Genomic and Transcriptomic features of response to anti-PD-1 Therapy in metastatic melanoma. Cell. 2016;165(1):35-44.

66. Motz GT et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. Nat Med. 2014;20(6):607-15.

67. Peng W et al. Loss of PTEN promotes resistance to T cell-mediated immunotherapy. Cancer Discov. 2016; 6(2):202-16.

68. Blank CU et al. CANCER IMMUNOLOGY. The "cancer immunogram". Science. 2016;352(6286):658-60.

69. Melero I et al. Evolving synergistic combinations of targeted immunotherapies to combat cancer. Nat Rev Cancer. 2015;15(8):457-72.

70. Long GV et al. Pembrolizumab (pembro) plus ipilimumab (ipi) for advanced melanoma: Results of the KEYNOTE-029 expansion cohort. Abstract 9506. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

71. Bristol-Myers Squibb. Phase 3 Trial in Subjects With Metastatic Melanoma Comparing 3 mg/kg Ipilimumab Versus 10 mg/kg Ipilimumab. Available at: https://clinicaltrials.gov/show/NCT01515189. Last accessed: 20 June 2016.

72. Gibney G et al. Updated results from a phase I/II study of epacadostat (INCB024360) in combination with ipilimumab in patients with metastatic melanoma. Abstract 511. European Cancer Congress, Vienna, Austria, 25-29 September 2015.

73. Gangadhar TC et al. Preliminary results from a phase I/II study of epacadostat (incb024360) in combination with pembrolizumab in patients with selected advanced cancers. J Immunother Cancer. 2015;3(suppl 2):O7.

74. Melero I et al. Multi-layered action mechanisms of CD137 (4-1BB)-targeted immunotherapies. Trends Pharmacol Sci. 2008;29(8):383-90.

75. Houot R et al. Targeting immune effector cells to promote antibody-induced cytotoxicity in cancer immunotherapy. Trends Immunol. 2011; 32(11):510-6.

76. Weigelin B et al. Anti-CD137 monoclonal antibodies and adoptive T cell therapy: a perfect marriage? Cancer Immunol Immunother. 2016;65(5):493-7.

77. Infante JR et al. A phase Ib dose escalation study of the OX40 agonist MOXR0916 and the PD-L1 inhibitor atezolizumab in patients with advanced solid tumors. Abstract 101. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

78. Infante JR et al. ENGAGE-1: A first in human study of the OX40 agonist GSK3174998 alone and in combination with pembrolizumab in patients with

advanced solid tumors. Abstract TPS3107. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

79. Sanmamed MF et al. Nivolumab and urelumab enhance antitumor activity of human t lymphocytes engrafted in Rag2-/-IL2Rγnull immunodeficient mice. Cancer Res. 2015;75(17):3466-78.

80. Deng L et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014;124(2):687-95.

81. Dovedi SJ et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res. 2014;74(19):5458-68.

82. Golden EB et al. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. Lancet Oncol. 2015;16(7):795-803.

83. Park SS et al. PD-1 Restrains radiotherapy-induced abscopal effect. Cancer Immunol Res. 2015;3(6):610-9.

84. Dewan MZ et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res. 2009;15(17):5379-88.

85. Grimaldi AM et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. Oncoimmunology. 2014; 3:e28780.

86. Kwon ED et al.; CA184-043 Investigators. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014; 15(7):700-12.

87. Bernstein MB et al. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach. Nat Rev Clin Oncol. 2016. [Epub ahead of print].

88. Twyman-Saint Victor C et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015;520(7547):373-7.

89. Mondini M et al. Synergy of radiotherapy and a cancer vaccine for the treatment of HPV-associated head and neck cancer. Mol Cancer Ther. 2015;14(6):1336-45.

90. Robert C et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364(26):2517-26.

91. National Institutes of Health. ClinicalTrials.gov. Available at: https://clinicaltrials.gov. Last accessed: 29 June 2016.

92. Adams S et al. Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC). Abstract 1009. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

93. Lynch TJ et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol. 2012;30(17):2046-54.

94. Reck M et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol. 2013;24(1):75-83.

95. Antonia SJ et al. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) in advanced non-small cell lung cancer (NSCLC). Abstract 8113. ASCO Annual Meeting, Chicago, Illinois, USA, 30 May-3 June 2014.

96. Liu SV et al. Safety and efficacy of MPDL3280A (anti-PDL1) in combination with platinum-based doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). Abstract 8030. ASCO Annual Meeting, Chicago, Illinois, USA, 29 May-2 June 2015.

97. Gadgeel SM et al. Pembrolizumab (pembro) plus chemotherapy as front-line therapy for advanced NSCLC: KEYNOTE-021 cohorts A-C. Abstract 9016. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

98. Hall RD et al. Phase 3 study of platinum-based chemotherapy with or without pembrolizumab for first-line metastatic, nonsquamous non-small cell lung carcinoma (NSCLC): KEYNOTE-189. Abstract TPS9104. ASCO Annual Meeting, Chicago, Illinois, USA, 3-7 June 2016.

CHALLENGES AND CONSIDERATIONS IN THE MANAGEMENT OF HYPERKALAEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

This CME symposium took place on 23rd May 2016 as a part of the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA) Congress 2016 in Vienna, Austria

Chairperson

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Speakers

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MEETING SUMMARY

Prof David Goldsmith opened the symposium by highlighting the objectives of the meeting. The education objectives of the symposium were to summarise the mechanisms that regulate potassium balance, specifically highlighting how these mechanisms are affected by inhibition of the renin-angiotensin-aldosterone system (RAAS); to examine the pathophysiology of hyperkalaemia and illustrate the impact on clinical outcomes; to evaluate current clinical evidence and outline key considerations that help determine the urgency; and to describe recent clinical trial data on investigational oral ion exchangers and the potential future role of these emerging therapies in clinical practice.

In the first presentation, Prof Johannes F. E. Mann discussed the predisposing factors of hyperkalaemia by presenting a case of a heart failure (HF) patient with Stage 3 chronic kidney disease (CKD), and also discussed the epidemiology and pathophysiology of hyperkalaemia. Dr Martin H. de Borst then discussed the current therapeutic options available for the outpatient treatment of hyperkalaemia, along with recent clinical data on novel treatments, in particular patiromer and zirconium cyclosilicate (known as ZS-9).

Pathophysiology and Risk of Hyperkalaemia

Professor Johannes F. E. Mann

Prof Mann presented the case of a male patient with known congestive HF and CKD Stage 3 (creatinine in the range of 2 mg/dL) to highlight the predisposing factors of hyperkalaemia. The patient was admitted with general muscular weakness, and his underlying diseases included ischaemic heart disease and Type 2 diabetes mellitus (T2DM). He was appropriately treated with ramipril, eplerenone, furosemide, bisoprolol, digioxin, and more recently hydrochlorothiazide plus amiloride (prescribed by his family physician). The patient's laboratory results revealed a high serum potassium level (6.7 mmol/L), substantial metabolic alkalosis (pH: 7.53; HCO_3: 33 mmol/L), recovery of serum creatinine to 4.3 mg/dL, and blood glucose 120 mg/dL. Although the patient's serum potassium level was not exceedingly high and his prior electrocardiogram (ECG) was normal, ECG results at presentation showed a wide QRS complex (left bundle branch block) and a PQ interval at the higher end. As a result, the patient underwent dialysis, leading to a reduction in his serum potassium and ECG normalisation post-dialysis; this indicated that his hyperkalaemia was responsible for the observed left bundle branch block.

With regards to his medications, all were considered likely contributors to his hyperkalaemia, except for furosemide and hydrochlorothiazide. However, careful evaluation is required to ensure that discontinuation of any medications accounting for hyperkalaemia will not have an adverse impact on clinical outcome. For example, angiotensin-converting enzyme (ACE) inhibitors like ramipril have been shown to improve both survival in patients with HF[1,2] and renal outcomes in patients with or without diabetes,[3,4] while eplerenone also improves survival in HF patients.[5] Additionally, the β-blocker, bisoprolol, has been associated with improved survival in patients with HF, including those with renal impairment.[6,7] In contrast, the DIG study[8] demonstrated that digoxin provided symptomatic improvements but had no effect on survival. Similarly, furosemide and amiloride do not contribute to improvement of survival nor do they preserve renal function. As a result, the discontinuation of furosemide, amiloride, and digoxin may be appropriate given that these agents are unlikely to contribute to his outcomes. Taken together, this case highlights two major predisposing factors for hyperkalaemia, the patient's underlying diseases (i.e. congestive HF, CKD, ischaemic heart disease, T2DM) and the use of medications that may have interfered with potassium disposal. This is supported by a recent large, nested, case-control study, which identified renal failure, T2DM, and current use of potassium-sparing diuretics as significant risk factors for hyperkalaemia in patients with newly diagnosed HF.[9]

The epidemiology of hyperkalaemia can be best described by its prevalence in large clinical trials of relevant patient populations (i.e. cardiovascular disease [CVD], diabetes, CKD). In the HOPE trial evaluating RAAS inhibition with ramipril in >9,000 patients at high cardiovascular risk over approximately 4.5 years, the incidence of hyperkalaemia (serum potassium >5.0 mmol/L) in the ramipril and placebo arms were 8.7% and 6.5%, while 1.2% and 0.7% of patients had serum potassium ≥5.5 mmol/L, respectively.[10] Substantial rates of hyperkalaemia were also reported in the ONTARGET trial of >25,000 high-risk patients with CVD or diabetes, with serum potassium >5.0 mmol/L being observed in 3.7% and 5.7% of patients in the ramipril and ramipril plus telmisartan treatment arms, respectively; serum potassium ≥5.5 mmol/L was reported in 1.6% and 2.7% of patients, respectively.[11] It should be noted that active study treatment was administered to all patients during the run-in phase of both studies, which resulted in approximately 1% of patients being excluded from both studies due to hyperkalaemia; this may in part account for the high incidence of hyperkalaemia in the placebo arm of the HOPE trial. The findings of these two studies highlight the increased risk of hyperkalaemia following RAAS inhibition in the cardiology setting, particularly during intensive blockade with dual therapy.

The prevalence of hyperkalaemia is high in the nephrology setting, as demonstrated by data from the RENAAL trial, which evaluated losartan versus placebo in >1,000 patients with T2DM and nephropathy.[12,13] In the overall RENAAL population, 30.6% of patients had serum potassium ≥5.0 mmol/L, comprising 38.4% of patients in the losartan and 22.8% in the placebo arms; serum potassium ≥5.5 mmol/L was reported in 10.8% and 5.1% of patients, respectively.[12,13] Importantly, the incidence of hyperkalaemia was high in the placebo arm of this study despite patients not being allowed concomitant use of RAAS inhibitors, indicating that both diabetes and renal impairment

(i.e. low glomerular filtration rate [GFR]/proteinuria) contributed to an increased risk of hyperkalaemia. Indeed, data from the AASK database demonstrate the association between low estimated GFR (eGFR) and hyperkalaemia, with a high incidence of hyperkalaemia in non-diabetic patients with hypertensive CKD and eGFR <40 mL/min/1.73 m^2 having serum potassium >5.5 and >6.0 mmol/L (14.9% and 4.7%, respectively).[14] Furthermore, data from the ONTARGET trial indicated that elevated urinary albumin increases the risk of hyperkalaemia, particularly in the presence of low eGFR, with >10% of patients with macroalbuminuria and eGFR <60 mL/min/1.73 m^2 having serum potassium levels in excess of 5.5 mmol/L.[15] The findings of these studies emphasise the challenges faced by clinicians when treating patients at high cardiovascular and/or renal risk. Although pharmacological RAAS inhibition carries a risk of hyperkalaemia, one must consider if the major renal and cardiovascular benefits of inhibiting the RAAS outweighs the risk of hyperkalaemia.

An important issue in the management of hyperkalaemia is to determine if there is a threshold at which hyperkalaemia is considered dangerous, warranting prompt intervention. This issue was addressed in a recent study that analysed data from >50,000 ambulatory CKD patients (eGFR <60 mL/min/1.73 m^2).[16] In this study, serum potassium 5.5–5.9 and ≥6.0 mmol/L were associated with significant increases in mortality,[16] thus indicating that serum potassium >5.5 mmol/L may be considered a threshold for intervention of a patient's hyperkalaemia.

Pseudohyperkalaemia as a result of the tourniquet-and-fist-clenching technique during phlebotomy can best describe the pathophysiology of hyperkalaemia.[17] In this small study, the application of a tourniquet in addition to fist clenching resulted in a transient increase in serum potassium levels by >1 mmol/L as a result of local potassium release due to contraction of the forearm muscles.[17] Potassium in the diet is absorbed via the gastrointestinal tract, with 98% of the body's potassium being stored intracellularly. Potassium uptake from the blood into the intracellular space is regulated by the ion transporter, sodium-potassium ATPase, which is upregulated by the sympathetic nervous system through β-receptors and insulin. Potassium disposal is regulated by aldosterone and occurs through the kidneys in the distal tubules of the nephron. The secretion of potassium via the distal tubules is a critical step to its excretion given that potassium is freely filtered and fully reabsorbed in the proximal tubules. This step requires the presence of sufficient sodium levels and energy provided by sodium-potassium ATPase, which removes sodium and drives potassium into the cell and the urine. Therefore, impaired renal potassium excretion is key to the pathophysiology of hyperkalaemia.

One example of pharmacological interference of the mechanism involved in renal potassium disposal is volume depletion due to intensive diuretic therapy in chronic heart failure patients, which results in substantial increases in proximal tubular sodium reabsorption, leading to reduced delivery of sodium into the distal tubule cells via the epithelial sodium channel, thus decreasing potassium secretion. Other drugs that interfere with the epithelial sodium channel include amiloride, triamterene, trimethoprim, tacrolimus, and cyclosporine. Given that aldosterone is a major regulator of potassium excretion, drugs or diseases (e.g. diabetes, hyporeninaemic hypoaldosteronism) that result in low aldosterone levels can lead to decreased expression of the sodium channel. Finally, digitalis compounds are a potent inhibitor of sodium-potassium ATPase and β-blockers interfere with this pump. Therefore, there are multiple ways where drugs, including RAAS inhibitors, can interfere with potassium excretion in the kidneys. Insulin deficiency, β-blocker therapy and the presence of CKD can also decrease the activity of sodium-potassium ATPase in cells outside of the kidney, thus reducing the cellular uptake of potassium.

Current and Emerging Options for Outpatient Treatment of Hyperkalaemia

Doctor Martin H. de Borst

Dr de Borst opened his presentation by referring to Prof Mann's case study to discuss approaches to the acute management of hyperkalaemia. Initial management of the patient would likely include a calcium infusion and a combined insulin-glucose infusion, which both have a rapid onset of effect. However, these acute interventions are short-lasting, and hyperkalaemia will eventually reoccur. As previously mentioned, starting haemodialysis is another approach with a rapid effect. Following these strategies, a current possibility would be the use of an ion exchanger, such as sodium polystyrene sulphonate (SPS) or a calcium-containing

alternative (CPS) available in some countries, which has an onset of effect of 2–4 hours with a duration of action of 4–6 hours. Additional interventions that may also be initiated in the acute setting based on the specific properties of this patient include fluid supplementation to manage dehydration, diuretic therapy, correction of metabolic acidosis with bicarbonate supplementation, and salbutamol or fludrocortisone to promote rapid potassium excretion. Lastly, close monitoring of the patient is required, potentially in the intensive care unit, involving the monitoring of ECG and laboratory results.

The chronic management of hyperkalaemia involves three major approaches: management of potassium intake, metabolism, and excretion (Figure 1). Potassium intake can be managed by dietary restriction of potassium-rich fruits (e.g. bananas, apples, mangoes). However, avoiding these foods on a daily basis may not always be beneficial as they may also contain vitamins, fibre, and other nutrients that are essential for a healthy diet. Indeed, findings of the international PURE study in >100,000 individuals from the general population demonstrated that a very low potassium intake using the surrogate measure of 24-hour potassium excretion may also be associated with an increased risk of death or cardiovascular events.[18] Furthermore, the U-shaped association of serum potassium levels with mortality in the CKD population indicated that both very high (≥6 mmol/L) and very low (<3.5 mmol/L) serum potassium levels significantly increased mortality risk,[16] suggesting that high and low intake of potassium should be avoided. Therefore, although the management of potassium intake may be appropriate in most patients at risk of hyperkalaemia, careful consideration must be undertaken before prescribing daily restriction of potassium in the diet.

The chronic management of hyperkalaemia may also require the correction of coexisting metabolic abnormalities. The presence of metabolic acidosis may be corrected by sodium bicarbonate supplementation, which has also been previously shown to retard CKD progression and renal function loss.[19] Additionally, the correction of hyperglycaemia will have a beneficial impact on serum potassium levels. Furthermore, medications that influence potassium homeostasis should be reassessed to determine if their use may be temporarily or permanently discontinued. While RAAS inhibitors (ACE inhibitors and angiotensin II receptor blockers) and mineralocorticoid receptor antagonists can increase the risk of hyperkalaemia, the discontinuation of these drugs may not be appropriate as they provide long-term preservation of renal function. Other medications contributing to hyperkalaemia that should be reassessed include diuretics, antibiotics, non-steroidal anti-inflammatory drugs, β-blockers, heparin, digitalis, calcineurin inhibitors, and potassium-containing supplements.

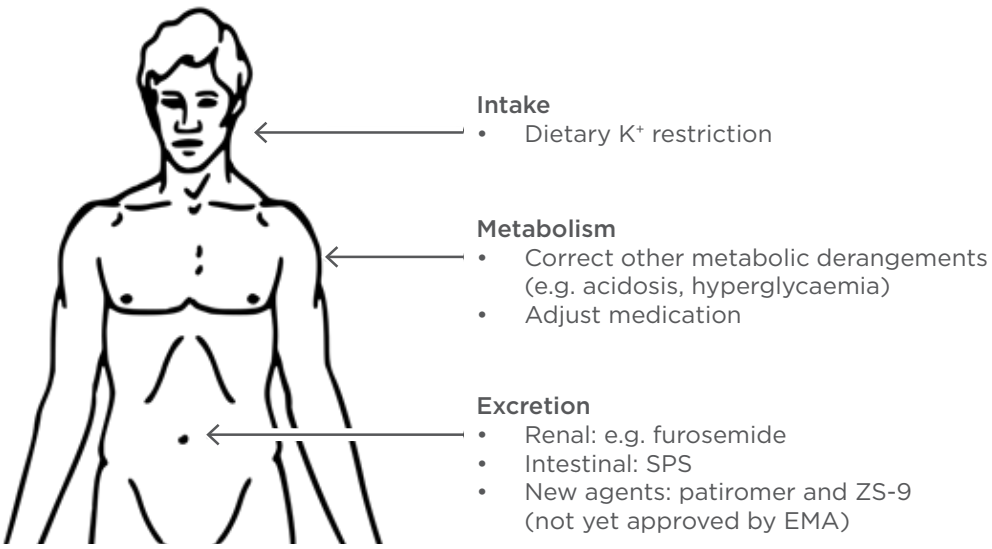

Figure 1: Chronic management of hyperkalaemia.
SPS: sodium polystyrene sulphonate; ZS-9: sodium zirconium cyclosilicate; EMA: European Medicines Agency.

With regards to the excretion of potassium, treatment with diuretics in patients with fluid overload and/or hypertension may promote renal potassium excretion, but this approach is limited in patients with advanced CKD. Mineralocorticoid stimulation with drugs such as fludrocortisone may promote intestinal potassium excretion, but is offset by the potential complication of sodium retention. As previously mentioned, SPS is a resin ion exchanger commonly used to treat hyperkalaemia, along with the alternative CPS; these two compounds promote intestinal potassium excretion by exchanging potassium for sodium (SPS) or calcium (CPS). To date, the clinical data for SPS in the management of hyperkalaemia are limited to early open-label studies reporting reductions in serum potassium of >1 mmol/L,[20,21] and a recent small randomised controlled trial reporting a reduction in potassium of 1.04 mmol/L (95% CI: -1.37 to -0.71) in outpatients with CKD and mild hyperkalaemia (5.0–5.9 mmol/L).[22] Safety data did not reveal clear differences in tolerability between SPS and placebo in this study.[22] However, the taste of SPS may be an important tolerability issue, making its long-term use less than ideal in this setting. Therefore, additional strategies targeting the excretion of potassium are needed.

Two novel drugs were recently developed for the treatment of hyperkalaemia. Patiromer is a spherical non-absorbed polymer that exchanges potassium for calcium, while ZS-9 is a non-absorbed oral powder that acts as a potassium selective ion trap.[23,24] Patiromer was recently approved by the US Food and Drug Administration (FDA) for the treatment of hyperkalaemia, but ZS-9 has yet to receive FDA approval; neither agent has been approved by the European Medicines Agency (EMA).

Two recent clinical trials evaluated the efficacy and safety of patiromer in the CKD setting. The short-term efficacy of patiromer was evaluated in the 2-part, pivotal OPAL-HK trial (N=237).[25] CKD patients who were using RAAS inhibitors and had a potassium of 5.1 to <6.5 mmol/L were initially treated with patiromer for 4 weeks. Serum potassium levels were significantly reduced by approximately 1 mmol/L from 5.6 to 4.6 mmol/L at Week 4. Furthermore, a target potassium level of 3.8 to <5.1 mmol/L was achieved by 76% of patients during the initial treatment phase. A total of 107 patients reached the target potassium level and were subsequently randomised to patiromer or placebo for 8 weeks in Part 2 of the trial. During this phase, recurrent hyperkalaemia was reported in 60% of placebo recipients, compared with 15% of patiromer recipients, at Week 8.

The long-term treatment effects of patiromer were evaluated for 52 weeks in the Phase II, open-label AMETHYST-DN trial (N=306),[26] which randomised patients with T2DM and kidney disease (eGFR: 15 to <60 mL/min/1.73 min^2; serum potassium: >5.0 mmol/L) to one of three patiromer dosages, titrated to reach serum potassium <5.1 mmol/L; all patients received RAAS inhibitors before and during treatment. A reduction from baseline in serum potassium was observed at Week 4, which persisted through Week 52; however, patiromer withdrawal resulted in the return of serum potassium to approximately 5.0 mmol/L. Safety data in both patiromer clinical trials indicated that gastrointestinal adverse events (AEs; constipation, diarrhoea, and nausea) were the most common events, occurring in approximately 3–5% of patients; hypomagnesaemia was also reported in approximately 7% of patients from the AMETHYST-DN trial.[25,26]

ZS-9 has been evaluated in two randomised, double-blind, placebo-controlled, Phase III trials. The HARMONIZE trial evaluated the short-term efficacy of ZS-9 therapy for 28 days in 258 patients with hyperkalaemia (potassium ≥5.1 mmol/L).[27] During an initial 48-hour open-label phase, ZS-9 reduced serum potassium from 5.6 mmol/L at baseline to 4.5 mmol/L at 48 hours; analysis by patient subgroup demonstrated the consistent short-term potassium-lowering effect of ZS-9 (approximately 1 mmol/L) in patients with CKD, HF, diabetes, and those receiving RAAS inhibitors. During the randomised phase, ZS-9 was associated with significant dose-dependent reductions in potassium levels from Days 8–29, compared with placebo.

In the second Phase III trial by Packham et al.[28] (N=753), initial treatment with ZS-9 at four dosages also effectively reduced serum potassium levels in a dose-dependent manner at 48 hours in patients with hyperkalaemia (5.0–6.5 mmol/L), with sustained normokalaemia (3.5–4.9 mmol/L) observed through 12 days of maintenance therapy in both the 5 and 10 g ZS-9 arms, which remained significant versus placebo; however, withdrawal of ZS-9 resulted in the return of serum potassium levels similar to that of the placebo arm.[28]

Safety data from the two ZS-9 studies indicated that treatment during the short-term period was well-tolerated, with AE rates of 7.8% and 12.9% in the HARMONIZE trial[27] and the Packham et al.[28] study. The incidence of AEs increased during the maintenance phases of both studies (29.4% and 25.1%, respectively), but rates were similar to that of placebo. As with patiromer, gastrointestinal complaints (diarrhoea and constipation) were the most notable side effects in both studies; however, a high incidence of oedema was reported in the 15 g ZS-9 arm (14%) of HARMONIZE.[27,28]

To date, the current chronic treatment options for hyperkalaemia, particularly in the outpatient setting, are suboptimal and hyperkalaemia limits the optimal dosing of renoprotective therapy. The introduction of novel agents, such as patiromer and ZS-9, is likely to improve the management of hyperkalaemia, which may enable renoprotective therapy to be optimised in the long-term. Clinical trials of these novel compounds have established their short-term efficacy and safety, and long-term data appears to warrant further investigation. However, head-to-head studies comparing these agents with SPS are lacking, and there has been discussion on possible interactions with the uptake or bioavailability of other medications. Nevertheless, patiromer and ZS-9 represent a new and emergent therapeutic paradigm in the management of hyperkalaemia. Future research should focus on the potential clinical implications of these novel compounds when used in conjunction with RAAS inhibitors. Will management of hyperkalaemia with patiromer or ZS-9 improve the safety of RAAS inhibitors, allowing these agents to be used at higher dosages or as combination therapy, and will this lead to improvements in clinical outcomes?

Conclusions

Hyperkalaemia is a common complication in many patient populations, including those with CVD, diabetes, and CKD. In particular, patients with renal impairment and the concomitant use of drugs that may increase serum potassium levels (i.e. RAAS inhibitors) or interfere with potassium disposal (i.e. amiloride) are associated with an increased risk of hyperkalaemia. A critical aspect to the pathophysiology of hyperkalaemia involves impaired potassium excretion, highlighting the need for agents that target this key pathway. Current treatment options for the chronic management of hyperkalaemia are suboptimal. Although dietary restriction can manage potassium intake, this may interfere with a healthy diet. Furthermore, strategies targeting potassium excretion, such as SPS, appear to be efficacious, but are poorly tolerated and thus less ideal for long-term treatment. The need for new agents to effectively treat hyperkalaemia has seen the recent development of two novel therapies, patiromer and ZS-9, which have both demonstrated acceptable short-term efficacy and safety, along with promising long-term data. Their incorporation into clinical practice will represent a new treatment paradigm in the management of hyperkalaemia, thus allowing optimal dosing of renoprotective therapy with RAAS inhibitors in patients with CKD or those at high renal risk.

REFERENCES

1. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet. 1993;342(8875):821-8.

2. Hall AS et al. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction Ramipril Efficacy. Lancet. 1997;349(9064):1493-7.

3. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet. 1997; 349(9069):1857-63.

4. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet. 2000; 355(9200):253-9.

5. Zannad F et al.; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;363(1):11-21.

6. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.

7. Castagno D et al. Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial. Eur J Heart Fail. 2010;12(6):607-16.

8. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336(8):525-33.

9. Michel A et al. Risk factors for hyperkalaemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. Eur J Heart Fail. 2015;17(2):205-13.

10. Mann JF et al. Serum potassium,

cardiovascular risk, and effects of an ACE inhibitor: results of the HOPE study. Clin Nephrol. 2005;63(3):181-7.

11. Heerspink HJ et al. The effect of ramipril and telmisartan on serum potassium and its association with cardiovascular and renal events: results from the ONTARGET trial. Eur J Prev Cardiol. 2014;21(3): 299-309.

12. Miao Y et al. Increased serum potassium affects renal outcomes: a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. Diabetologia. 2011;54(1):44-50.

13. Appel GB et al. Analysis of metabolic parameters as predictors of risk in the RENAAL study. Diabetes Care. 2003; 26(5):1402-7.

14. Weinberg JM et al. Risk of hyperkalemia in nondiabetic patients with chronic kidney disease receiving antihypertensive therapy. Arch Intern Med. 2009;169(17):1587-94.

15. Tobe SW et al. Cardiovascular and renal outcomes with telmisartan, ramipril, or both in people at high renal risk: results from the ONTARGET and TRANSCEND studies. Circulation. 2011;123(10):1098-107.

16. Luo J et al. Association between Serum Potassium and Outcomes in Patients with Reduced Kidney Function. Clin J Am Soc Nephrol. 2016;11(1):90-100.

17. Don BR et al. Pseudohyperkalemia caused by fist clenching during phlebotomy. N Engl J Med. 1990;322(18): 1290-2.

18. O'Donnell M et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med. 2014;371(7):612-23.

19. de Brito-Ashurst I et al. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. 2009;20(9):2075-84.

20. Scherr L et al. Management of hyperkalemia with cation-exchange resin. N Engl J Med. 1961;264:115-9.

21. Flinn RB et al. Treatment of the oliguric patient with a new sodium-exchange resin and sorbitol; a preliminary report. N Engl J Med. 1961;264:111-5.

22. Lepage L et al. Randomized Clinical Trial of Sodium Polystyrene Sulfonate for the Treatment of Mild Hyperkalemia in CKD. Clin J Am Soc Nephrol. 2015; 10(12):2136-42.

23. Li L et al. Mechanism of Action and Pharmacology of Patiromer, a Nonabsorbed Cross-Linked Polymer That Lowers Serum Potassium Concentration in Patients With Hyperkalemia. J Cardiovasc Pharmacol Ther. 2016;21(5):456-65.

24. Stavros F et al. Characterization of structure and function of ZS-9, a K+ selective ion trap. PLoS One. 2014; 9(12):e114686.

25. Weir MR et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3):211-21.

26. Bakris GL et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. JAMA. 2015;314(2):151-61.

27. Kosiborod M et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA. 2014; 312(21):2223-33.

28. Packham DK et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med. 2015;372(3):222-31.

EDITOR'S PICK

In this specially selected article, Fleming gives a fascinating insight into the controversial field of fibromyalgia and polysymptomatic distress disorders. These conditions present with a diverse array of symptoms posing diagnostic challenges which many clinicians will face at some point in their career. The unifying central sensitisation theory discussed provides solace for patients and physicians alike, potentially elucidating the pathophysiology of the disorders and their medically unexplained symptoms. The author goes on to provide useful diagnostic and management strategies which have the potential to raise the standard of care in these common, yet poorly understood, conditions.

Dr Harry Thirkettle

CLINICAL MANAGEMENT OF FIBROMYALGIA AND THE CONTINUUM OF POLYSYMPTOMATIC DISTRESS DISORDERS

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ABSTRACT

The evaluation of patients with fibromyalgia (FM) and other functional somatic syndromes can appear intimidating, but a high index of suspicion and a more systematic approach can improve provider efficiency, reduce frustration, and improve the care experience. FM is a dimensional rather than a categorical disorder, reflecting a continuous spectrum of physical symptoms; it is formally diagnosed after reaching a critical mass of widespread pain and symptom severity. Central sensitisation is a maladaptive neuroplastic response in the higher brain neural pain network that accounts for FM symptoms. Rheumatologists are a scarce medical resource, so their involvement in FM can be considered along 'focussed factory' or 'solution shop' approaches. Multimodal FM treatments should include pharmacologic and nonpharmacologic therapies including cognitive therapies, graded exercise, and stress management.

Keywords: Central sensitisation (CS), fibromyalgia (FM), polysymptomatic distress (PSD), systems approach.

BACKGROUND

Physicians are frequently faced with patients bearing symptoms that lack the confirmatory or exclusionary tests found in categorical disorders such as hip fracture or myocardial infarction. When individuals present with chronic widespread pain, they often have other medically unexplained symptoms (MUS), referring to symptoms that have little or no apparent basis in organic disease. The reported burden of symptoms is out of proportion with what is expected by examination and testing. While some symptoms may be nonspecific and ambiguous, other MUS present along a continuum of organ or system-specific features and may meet diagnostic classifications for fibromyalgia

(FM), chronic fatigue syndrome (CFS), chronic pelvic pain, chronic abdominal pain, irritable bowel syndrome (IBS), or chronic dizziness. Notably, the prior diagnosis of somatisation has been reclassified as 'somatic symptom disorder,' now referring more to the distress of bodily symptoms (i.e. health anxiety) than to their organicity.[1]

Physicians encountering MUS may develop a 'negative empathy' toward patients, which interferes with the consultation.[2] This unwarranted antipathy can be traced to a myriad of symptoms without explanation, high patient expectations, lengthy visits, and heavy practice demands. Very often, this results in unmet expectations and dissatisfaction with the services provided, however extensive.[3] The difficulty in providing help to these patients may foster negative feelings (counter-transference), stigmatisation, and isolation, to which system constraints and physician attributes are often contributory.[4] For clinical staff, such encounters can result in emotional frustration and burn-out. By recognising the risks for unprofessional behaviour and changing strategies, one can improve the therapeutic alliance and repair the clinical encounter. In this article, we review the shared pathology of patients with MUS and offer a systematic approach to increase provider efficiency, streamline testing, and improve the care experience.

DIAGNOSTIC CONTROVERSY

The symptoms accompanying the primary musculoskeletal complaints in FM overlap considerably with other disorders, such as CFS, IBS, chronic pelvic pain, chronic daily headache, interstitial cystitis, temporomandibular disorder (TMD), and other unexplained symptoms.[5-7] Indeed, the 2010 American College of Rheumatology (ACR) Diagnostic Criteria for Fibromyalgia includes chronic widespread pain, but replaced the 1990 tender point requirement with a Symptom Severity Scale (SSS). This scale includes fatigue, unrefreshed sleep, cognitive complaints, and multiple somatic symptoms. The working diagnoses in patients with MUS can depend on the patient's cardinal complaint, organ system clusters, diagnostic bias, and clinician subspecialty.[8] Patients with one diagnostic category are frequently diagnosed with other functional syndromes.[9] Historically, patients with MUS have been diagnosed with hysteria, functional nervous disorder, traumatic neurosis, psychosomatic disorder, hypochondriasis, somatisation, somatoform disorder, and functional somatic symptoms.[2,10] The favoured terminology depends on the prevailing medical, cultural, legal, and employment environment, with a bias toward Cartesian dualism. However, patients often reject diagnoses suggesting psychological origins.[10]

RECONCEPTUALISING FIBROMYALGIA

The stakes are high. Annually, FM patients average 5.5 million outpatient visits, direct healthcare costs reach $9,000, and indirect costs (absenteeism, disability, unemployment, early retirement) approach $30,000.[11,12] The functional syndromes share diagnostic overlap because they are consanguine dimensional disorders rather than categorical diseases with discrete pathologic causes, reflecting a continuous spectrum of sensitivity to physical symptoms which are formally diagnosed after reaching a critical mass.[13] Patients frequently have a myriad of complaints unexplained by physiological or structural pathology, but often have recognisable symptom clusters (FM, IBS, chronic pelvic pain). A polysymptomatic distress (PSD) score can be calculated by taking the sum of the two scores from the 2010 ACR FM diagnostic criteria, namely the Widespread Pain Index (WPI) and the SSS.[14,15] Patients meeting the 2010 ACR FM criteria will have a PSD score of ≥12 (WPI ≥3). The PSD score represents a measure of 'fibromyalgianess'.[13]

For patients with PSD, the physician must provide a plausible explanation for their symptoms beyond listing negative findings, or the residual uncertainty reduces clinical trust. The neurophysiological process called central sensitisation (CS), may fill that explanatory gap. CS is currently felt to be a centralised pain state reflecting a progressive process whereby the central nervous system (CNS) amplifies pain and other stimuli across many organ systems.[16] In this model, it is postulated that there are peripheral and central components to the abnormal sensory processing, a neuroplastic maladaptation effecting spinal sensitisation, and a disproportionately augmented response in the higher brain pain network. Cellular processes alter nociceptive neuronal function, and repeated nociception induces an increased response termed sensitisation. CNS glial cells release proinflammatory cytokines, which help initiate and maintain central sensitivity and chronic pain. These immunologic processes undermine the usual dichotomy of inflammatory versus non-inflammatory pain in FM versus rheumatologic disorders.

Table 1: Features of central sensitisation.[10,21-40]

- Increased neural membrane excitability
- Facilitation of neural synaptic strength
- Decreased inhibitory transmission
- Affected neurons display spontaneous activity, reduced activation threshold, enlarged receptive fields
- Neuronal memory
- Elevated serum neuropeptides: substance P, corticotropin-releasing hormone, haemokinin-1
- Elevated serum and cerebrospinal fluid inflammatory cytokines
- Activation of spinal cord glial cells
- Dorsal horn sensitisation
- Spinal sensitisation: enhanced temporal summation
- Increased sensitivity for future stimulation
- Non-painful stimuli activate nociceptive specific dorsal horn cells
- Heightened activity in ascending pathways
- Reduced descending inhibitory pathway response
- Increased/no change in descending facilitatory pathway response
- Reduced efficiency of conditioned pain modulation, psychophysical responses
- Autonomic dysregulation (lower baseline parasympathetic activity, elevated baseline sympathetic activity or predominance, reduced heart rate variability, orthostatic hypotension/tachycardia
- Hypothalamic–pituitary axis dysregulation: impaired cortisol reductions during sleep, low cortisol response to stress, defects in growth hormone and insulin-like growth factor–paracrine axis
- Increased growth hormone, decreased cortisol after exercise intervention in fibromyalgia
- Hyper-responsive central neural network (sensory and discriminative, affective and motivational, cognitive and evaluative), amplifying pain perception
- Cognitive–emotional amplification and extension of pain (catastrophising, fear of movement)
- Altered regional cerebral blood flow (pain, cognition)
- Spinal and supraspinal mechanisms treat all sensory input as salient
- Lowered thresholds for stimulus tolerance
- Amplification of painful stimuli (hyperalgaesia); regional/widespread
- Amplification of nonpainful stimuli (allodynia)
- Visceral hypersensitivity
- Insomnia: disrupted, fragmented, nonrestorative sleep
- Lower sleep efficiency (more Stage N1, poor sleep continuity)
- Dermatographia, livedo reticularis

Over time, perceptions become uncoupled from the intensity, duration, or even the presence of noxious peripheral stimuli. Hypersensitivity amplifies and distorts sensations elicited by innocuous stimuli and normal body sensations; more pain-related activity ascends, unimpeded by descending pain inhibition. This produces a disparity between stimulus and perception, reduced sensory tolerance, increased pain sensitivity, widespread hyperalgesia experienced clinically as pain, and other somatic complaints (Table 1).[9,16-20]

A UNIFYING DIAGNOSIS

CS-produced symptoms occur along a continuum, and frequently overlap. Indeed, somatic functional disorders often share diagnostic criteria and core symptoms.[13] Patients are frequently diagnosed with more than one such disorder, whether initially or progressively over time.[5,14] However, there is a heterogeneity of symptom expression; diagnoses occur in clinical clusters, and sensitivity to stimuli is not uniform across functional syndromes.[6,8]

Patients who meet 2010 ACR FM criteria have a PSD score of ≥12, but there is a bell curve distribution of symptom severity and the cut-off for FM diagnosis is designated as the extreme end of that spectrum.[10,13] There are similar distributions of severity in IBS,[41] TMD,[42] burning mouth syndrome,[43] and postural orthostatic tachycardia syndrome.[44]

Patients with functional syndromes frequently report multiple medication allergies or intolerances. These are often non-allergic hypersensitivity reactions to several classes of chemically unrelated agents.[45] The mechanism is unclear, but CS-mediated visceral and sensory hypersensitivity seems likely. One should consider the presence of multiple drug, food, and environmental intolerances as indicative of CS.[46,47]

Regardless of whether it is known as MUS, functional somatic syndrome, PSD,[13] or bodily distress syndrome,[48] CS serves as an organising principle by being descriptive and avoiding psychological or tautological terminology.

The current hypothesis is that the continuum of CS appears to be the common process linking these disorders, and may be a heritable 'vulnerability phenotype' for developing FM and related syndromes.[9] CS offers a feasible explanatory neurophysiologic model that is readily understood by patients, providing a useful cognitive anchor for future management. This explanation has proven helpful in our clinic by fostering patients to move from a diagnostic mindset (i.e. requesting more tests and consultations) to rehabilitative and recovery approaches. Whether considered as one disorder or many, differentiation remains useful, whilst remaining aware of diagnostic overlap, the continuum of symptoms, and the maladaptive neuroplastic process of CS. Despite this proposed clinical utility, CS remains theoretical, and the science must be consistently updated for patients so that it does not become a Kiplingesque 'Just So' story, which would harm the therapeutic relationship.

A SYSTEMS APPROACH

Focussed Factory Versus Solution Shop

Rheumatologists are a scarce medical resource. A workforce study projected a deficit of 2,600 adult rheumatologists by the year 2025. As of 2010, regional shortages of rheumatologists were already identified, with limited access for cities with populations of <50,000. Some regions with populations of >200,000 had no practicing rheumatologists.[49,50] As a result, rheumatology practices must clarify their service lines. Some rheumatologists prefer to be 'focussed factories', limited to specialty care (e.g. lupus, rheumatoid arthritis [RA], mixed connective tissue disease). Others may prefer to take all comers, the 'solution shop' approach.[51] Alternatively, a focussed factory specific to FM could be considered.

Notably, many physicians report being uncomfortable diagnosing FM. In one study, 53% of doctors found FM somewhat or very difficult to diagnose, citing inadequate training or knowledge.[52] Nonspecialists rarely or improperly use ACR FM criteria, and delayed or misdiagnosis is frequent.[53] As a result, referrals for FM diagnosis are likely to persist. Notably, FM affects 12–17% of RA patients, and FM pain maybe misinterpreted as active disease in RA (i.e. 'fibromyalgic RA').[54] Systemic lupus erythematosus (SLE) autoantibodies lead to chronic pain, arthralgia, morning stiffness, fatigue, and damage to the renal and CNSs. SLE can be difficult to differentiate from FM due to provider inexperience, higher FM prevalence (10-fold greater than SLE), and early symptoms that do not meet SLE diagnostic criteria.[55] The differentiation between SLE and FM among subjects that are antinuclear antibody positive is beyond the scope of this article, but FM affects 13–33% of patients with SLE, and is more likely to develop in the later stages of the disease. FM is also found in systemic sclerosis and Sjögren's syndrome.[18,56,57]

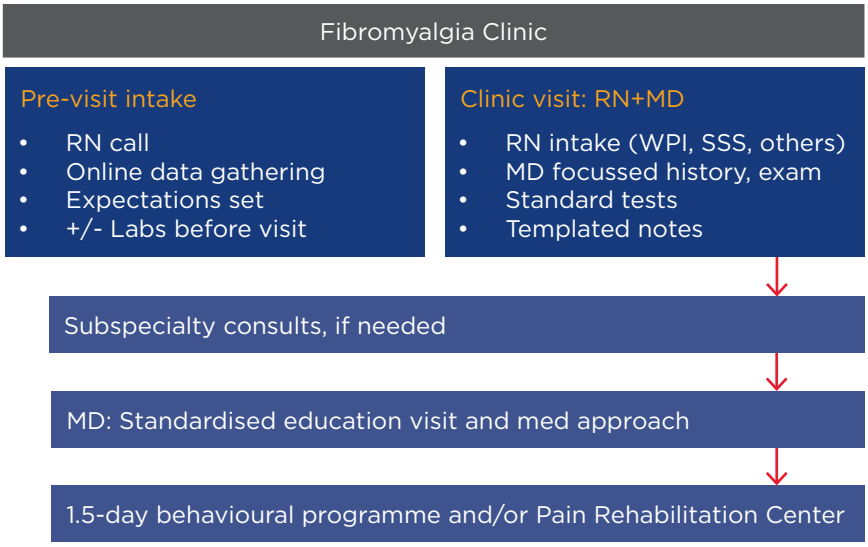

Figure 1: Mayo Clinic Fibromyalgia and Chronic Fatigue Clinic standardised assessment.
(Mayo Foundation©).
RN: registered nurse; MD: medical doctor; WPI: Widespread Pain Index; SSS: Symptom Severity Scale.

Consequently, patients with organic rheumatologic disease may have or develop CS pain and PSD disorders such as FM. The correct interpretation of the FM symptoms is crucial in avoiding overtreatment because concomitant FM can simulate flares of pain in rheumatologic disorders.

RECOMMENDATIONS

Filtering

Excluding patients with MUS requires gathering data to reduce the likelihood of the prospective patient having a functional somatic disorder.

- Screening laboratory tests can be a useful filter, restricting consultations to patients with abnormal rheumatologic serologies or inflammatory markers. Cut-off levels may risk missing false negatives, which should prompt repeated requests for consultation. False positives would not be discovered without more extensive pre-consultation testing
- Requiring written referrals can provide a filter, especially in closed networks. However, this can be labour intensive, and can risk false positives and false negatives
- Patient narratives regarding the clinical question can help determine whether to offer a rheumatology appointment. Queries can be limited to a few written paragraphs and be provided online. Automated scripts could flag keywords and phrases for review
- High PSD values are correlated with FM and functional disorders. An arbitrary PSD cut-off score of >12 would reduce (but not eliminate) the most severe cases. Cut-offs may be modified by regional experience and clinical volume
- Given the significant overlap among functional syndromes, screening for their presence may similarly predict the likelihood of CS[7]
- Current narcotic use can also be discriminative
- Precautions:
  i) Patients with RA and degenerative joint disease often have varying degrees of FM. Patients would still require management of their 'fibromyalgianess', but earlier attention may forestall progression
  ii) To avoid exclusion, patients may under report or misrepresent symptoms and prior diagnoses. This can limit the utility of PSD screening, but patients who do so risk a negative clinic experience. This can be made explicit (and acknowledged) when completing these forms
  iii) In regions with limited access to rheumatologists or FM/chronic pain treatment programs, filtering patients may leave them without adequate care

Rheumatologists using the solution shop or mixed approach must integrate FM into the practice, including the continuum of PSD, but an alternative system of care delivery is useful. The Mayo Clinic Fibromyalgia and Chronic Fatigue Clinic employs a standardised assessment of FM patients (Figure 1). This applies a focussed factory approach, dividing labour to reduce the workload and improve staff retention.

Pre-Visit Work

External records

- Performed by patient
- Limit material to past 2 years, maximum 50 pages
- Do not mail; records will not be reviewed prior to visit
- Discard blank/illegible/non-medical notes and duplicates
- Put in chronological order
- If not done in time for the visit, records may not be reviewed
- Failure to complete these tasks may result in delays, rescheduling, or limited record review
- If available, have non-physician personnel confirm compliance; separate laboratory, procedures, and image reports

Medications

- Prior medications, narcotics, psychoactive medications for rheumatologic diagnosis (start/stop dates, compliance, side effects, degree of benefit, reason for discontinuation)
- Supplements
- Self-reported allergies and intolerances

Prescheduling

- To complete the clinician assessment efficiently, desired laboratory tests are best done prior to the visit
- If the patient wants other PSD complaints evaluated, the practice must decide whether to:
  a) Make recommendations to be completed elsewhere
  b) Complete the tests at this episode of care, thus requiring prescheduled tests and consultations. This should be focussed on the most concerning or worrisome complaints

The fibromyalgia/polysymptomatic distress visit

In order to manage expectations, the time available (both prior to and at the visit) must be made explicit. Focus on the current symptoms of concern and reduce time spent discussing a medicalised history, which is often obfuscated rather than clarified by these data. Rheumatologists will narrow the inquiry to the cardinal symptoms, but remain alert to symptoms that might pose significant risks.

After sufficient review, past treatment options should be explored, including medications and surgeries. These data could be gathered online (pre-visit), by questionnaire, or by medical assistants. It is important to note whether or not the intervention changed the symptoms (range 0–100% better; or got worse). CS syndromes are often characterised by brief intervals of improvement, perhaps a few weeks or months, followed by recurrence (placebo effect).

SPECIAL ISSUES IN POLYSYMPTOMATIC DISTRESS

Comorbid Psychiatric Disorders

Individuals presenting with PSD often have accompanying psychiatric disorders associated with a range of coping and self-regulation deficits that increase the sensitivity to stress. Anxiety, depression, personality disorders, and self-critical perfectionism have been correlated with various chronic pain and functional somatic syndromes.[58-60] However, not all patients with PSD have diagnosable psychiatric disorders. In one study of patients with functional somatic syndromes, depression was absent in as many as two-thirds, and no anxiety was found in upwards of 72%.[48] Many patients assert that depression arose because of their symptoms. Avoid narrowing the interview to psychiatric dysfunctions, especially early on, as this may disrupt the discussion ("You think it's all in my head").

Traumatic Events

FM and other PSD syndromes tend to have a female predominance and are closely associated with significant stressors such as physical or sexual abuse, catastrophic events (war, natural disasters), infections, and peripheral pain triggers.[61,62] The association between abuse/trauma and CS, and the subsequent development of chronic pain/PSD functional disorders is important. However, the rheumatologist should avoid focussing on trauma, except briefly in the context of discussing CS, where alluding to the connection is sufficient. One can point the direction without requiring the patient to acknowledge or divulge such a history. Previously unaddressed or ongoing/current abuse warrant further referral.

Despite the relationship between trauma history and CS, the evidence for a direct causal association between specific traumas and FM is controversial, perhaps even 'weak to nonexistent'.[63] Lawsuits and disability claims may be seeking a level of certainty from healthcare providers regarding 'direct causation' that cannot be provided. The temporal association to a single trauma (e.g. car accident) is often uncertain or remote, premorbid CS complaints are frequent, and symptoms are often in excess of identifiable physical pathology. Traumatic events may represent a tipping point rather than the discrete onset of CS. Being a dimensional rather than categorical disorder, CS origins are multifactorial, influenced by the complex interplay of genetics, biological factors, the environment, events, and psychosocial responses progressing along multiple causal paths (Table 2). The ways in which the courts, insurance, and employment realms manage this complexity is beyond the scope of this article, but assigning causation to specific traumatic events or psychiatric disorders is often inconsistent with the current medical evidence.

TREATMENT

Given the diagnostic overlap of functional disorders, their treatment suggests a similar management overlap. Single modality treatments (medications, physical therapy) for FM have limited benefit. Multimodality treatments (education, physical therapy, cognitive behavioural therapy) are advised and evidence for their positive effects in FM have been reported.[64,65] This can, however, be logistically difficult, and access to multidisciplinary pain centres can be rather limited. Initial FM treatment should include symptom validation, understanding the stress response, the maladaptive nature of CS (especially how it can cause pain and other symptoms of bodily distress), and hope for improvement. The basics of neuroanatomy, the stress response, neuroplasticity, and their relationships to pain and symptom management can be simplified and readily understood by most adults.

Table 2: Mayo Clinic fibromyalgia self-management group programme.

1. Fibromyalgia diagnosis
• Diagnostic criteria • Self-management
2. Stress neurobiology
• Stress response • Autonomic nervous system • Acute versus chronic pain • Central sensitisation • Neuroplasticity
3. Pain cycle
• Symptom-focussed behaviours, somatic hypervigilance • Relationships • Cycle of chronic pain with example, activity when timely • Goal setting
4. Moderation
• Time management • Energy conservation • Graded exercise
5. Grief, spirituality, mood
• Grief and loss • Forgiveness, spirituality • Cognitive behavioural therapy • Behavioural activation • Effective and ineffective interventions • Depression, anxiety • Managing stress
6. Nutrition, sleep, cognition
• Nutrition • Sleep hygiene • Brain fog: improving cognitive performance • Humour • Relaxation • Mindfulness • Paced breathing
7. Additional resources
• Non-pharmacological treatments i) Biofeedback ii) Complementary therapies iii) Creative work iv) Hypnotherapy v) Mind–body techniques vi) Meditative movement (tai chi) • Medications • Opioid-induced hyperalgaesia • Difficult day planning

Finally, the concepts of moderation, graduated exercise, and reduced somatic hypervigilance are employed.

Non-pharmacological therapies can be targeted to pain generators, deconditioning, and loss of function (physical therapy, massage, acupuncture). Cognitive behavioural therapies are key for somatic symptoms and mood disorders. Psychotherapy may be helpful for depression and anxiety. Pharmacological and dietary therapies can be targeted at symptomatic relief of common symptom clusters (e.g. IBS, bladder pain). Management literature on specific functional syndromes and local expertise can be helpful. Central pharmacotherapies for functional syndromes have modest efficacy, with the greatest success from tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and alpha 2 delta ligands.[66]

Table 3: Central sensitisation: Multifactorial aetiology.

• Genetic influence
• Biologic vulnerability
• Hypersensitivity phenotype
• Hormonal/gender influence
• Infections
• Autonomic dysfunction
• Prolonged pain generators (arthritis, neuropathy)
• Environmental factors
• Prolonged stressors (physiological, psychosocial)
• Mood disturbances
• Cultural factors
• Sleep disorders

Long-term use of narcotics should be avoided due to side effects, tolerance, dependence, opioid induced hyperalgaesia, and increased mortality.[67,68] At our medical centre, patients participate in a 1.5-day multimodality treatment programme for FM which has a significant positive effect. The programme includes an evaluation with a care team for diagnosis/confirmation of FM, followed by FM education and an interactive self-management session. Participants report significant improvements in physical functioning, work status, pain, stiffness, fatigue, anxiety, depression, sleep, and overall well-being (Table 3).[69,70]

CONCLUSION

Functional syndromes arise from a nociceptive disorder with disruptions of pain neurotransmitters, the hypothalamic–pituitary axis, autonomic system, and sleep that produces bodily distress. FM is a dimensional disorder where complaints fall on a continuum of PSD. Although the clinical definitions of functional disorders have symptom overlap, they are based on cardinal complaints and clinical/organ system clusters, and reflect a degree of severity that interferes with normal social roles and employment. Patients often have more than one such diagnosis, and these disorders often complicate other medical illnesses such as RA and even cancer.

FM will continue to involve rheumatologists as some providers remain uncomfortable confirming the diagnosis, especially when tests are not completely normal and there are numerous non-rheumatological symptoms. Subspecialists also have practical experience regarding the amelioration of FM complaints. Nevertheless, there are standard approaches to FM that can be undertaken by non-specialists. Multimodal approaches best include pharmacological and non-pharmacological therapies, e.g. cognitive therapies, graded exercise, and stress management. A systems approach can improve the FM care process.

REFERENCES

1. Isaac M et al. Medically Unexplained Symptoms. Med Clin N Am. 2014;98(3):663-72.

2. Cohen M et al. Stigmatization of patients with chronic pain: the extinction of empathy. Pain Med. 2011;12(11):1637-43.

3. Butler CC, Evans M. The 'heartsink' patient revisited. The Welsh Philosophy and General Practice discussion Group. Br J Gen Pract. 1999;49(440):230-3.

4. Chepenik L. Difficult Patient Encounters: Medical Education and Modern Approaches. Curr Emerg Hosp Med Rep. 2015;3(4):195-201.

5. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med. 2001;134(9 Pt 2):868-81.

6. Yunus M. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):339-56.

7. Fleming K, Volcheck M. Central Sensitization Syndrome and the Initial Evaluation of a Patient with Fibromyalgia: A Review. Rambam Maimonides Med J. 2015;6(2):e0020.

8. Fink P, Rosendal M. Recent developments in the understanding and management of functional somatic symptoms in primary care. Curr Opin Psychiatry. 2008;21(2):182-8.

9. Bourke J et al. The common link between functional somatic syndromes may be central sensitisation. J Psychosomatic Res. 2015;78(3):228-36.

10. Stone J et al. What should we say to patients with symptoms unexplained by disease? The "number needed to offend." Br Med J. 2002;325(7378):1449.

11. Bernatsy S et al. Co-morbidity and physician use in fibromyalgia. Swiss Med Wkly. 2005;135(5-6):76-81.

12. Chandran A et al. The comparative economic burden of mild, moderate, and severe fibromyalgia: results from a retrospective chart review and cross-sectional survey of working-

age U.S. adults. J Manag Care Pharm. 2012;18(6):415-26.

13. Wolfe F et al. Fibromyalgia Prevalence, Somatic Symptom Reporting, and the Dimensionality of Polysymptomatic Distress: Results From a Survey of the General Population. Arthritis Care Res. 2013;65(5):777-85.

14. Wessely S, Hotopf M. Is fibromyalgia a distinct clinical entity? Historical and epidemiological evidence. Baillieres Best Pract Res Clin Rheumatol. 1999;13(3): 427-36.

15. Wolfe F. New American College of Rheumatology criteria for fibromyalgia: A twenty-year journey. Arthritis Care Res (Hoboken). 2010;62(5):583-4.

16. Clauw D. Fibromyalgia: A Clinical Review. JAMA. 2014;311(15):1547-55.

17. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-15.

18. Di Francoa M, Bazzichi L. Pain in systemic connective tissue diseases. Best Pract Res Clin Rheumatol. 2015;29(1): 53-62.

19. Wallace D, Gavin I. Cytokine and chemokine profiles in fibromyalgia, rheumatoid arthritis and systemic lupus erythematosus: A potentially useful tool in differential diagnosis. Rheumatol Int. 2015;35:991-6.

20. Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. Best Pract Res Clin Rheumatol. 2007;21(3):481e97.

21. Latremoliere A, Woolf CJ. Central sensitization: A generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10(9):895-926.

22. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. Curr Opin Anaesthesiol. 2010;23(5):611-5.

23. Samad T et al. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature. 2001;410(6827): 471-5.

24. Cao H, Zhang Y. Spinal glial activation contributes to pathological pain states. Neurosci Biobehav Rev. 2008;32(5): 972-83.

25. Ingvar M. Pain and functional imaging. Philos Trans R Soc Lond B Biol Sci. 1999;354(1387):1347-58.

26. Borsook D et al. Neuroimaging revolutionizes therapeutic approaches to chronic pain. Mol Pain. 2007;3:25.

27. Eisenlohr-Moul T et al. Parasympathetic Reactivity in Fibromyalgia and Temporomandibular Disorder: Associations With Sleep Problems, Symptom Severity, and Functional Impairment. J Pain. 2015;16(3):247-57.

28. Meeus M et al. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: A systematic review. Semin Arthritis Rheumatism. 2013;43(2):279-87.

29. Giovengo S et al. Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. J Rheumatol. 1999;26(7):1564-9.

30. Generaal E et al. Basal inflammation and innate immune response in chronic multisite musculoskeletal pain. Pain. 2014;155(8):1605-12.

31. Tsilioni I et al. Neuropeptides CRH, SP, HK-1 and inflammatory cytokines IL-6, TNF are increased in serum of patients with Fibromyalgia Syndrome implicating mast cells. J Pharmacol Exp Ther. 2016. [Epub ahead of print].

32. Kosek E et al. Evidence of different mediators of central inflammation in dysfunctional and inflammatory pain — Interleukin-8 in fibromyalgia and interleukin-1 β in rheumatoid arthritis. J Neuroimmunol. 2015;280:49-55.

33. Fatima G et al. Circadian Rhythm of Serum Cortisol in Female Patients with Fibromyalgia Syndrome. Indian J Clin Biochem. 2013;28(2):181-4.

34. Paananen M, O'Sullivan P. A low cortisol response to stress is associated with musculoskeletal pain combined with increased pain sensitivity in young adults: a longitudinal cohort study. Arthritis Res Ther. 2015;17:355.

35. Martinez-Lavin M et al. Circadian studies of autonomic nervous balance in patients with fibromyalgia. A heart rate variability analysis. Arthritis Rheum. 1998;41(11):1966-71.

36. Cuatrecasas G et al. Growth hormone treatment for sustained pain reduction and improvement in quality of life in severe fibromyalgia. Pain. 2012;153(7):1382-9.

37. Diaz-Piedra C et al. Sleep disturbances in fibromyalgia syndrome: the role of clinical and polysomnographic variables explaining poor sleep quality in patients. Sleep Med. 2015;16(8):908-9.

38. Montoro C et al. Aberrant cerebral blood flow responses during cognition: Implications for the understanding of cognitive deficits in fibromyalgia. Neuropsychol. 2015;29(2):173-82.

39. Kwiatek R et al. Regional cerebral blood flow in fibromyalgia. Arthritis Rheum. 2000;43(12):2823-33.

40. Littlejohn G. Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. Nat Rev Rheumatol. 2015;11:639-48.

41. Lackner J et al. Multidomain Patient-Reported Outcomes of Irritable Bowel Syndrome: Exploring Person-Centered Perspectives to Better Understand Symptom Severity Scores. Value Health. 2013;16(1):97-103.

42. Kotiranta U et al. Subtyping Patients with Temporomandibular Disorders in a Primary Health Care Setting on the Basis of the Research Diagnostic Criteria for Temporomandibular Disorders Axis II Pain-Related Disability: A Step Toward Tailored Treatment Planning? J Oral Facial Pain Headache. 2015;29(2):126-34.

43.Sun A et al. Burning mouth syndrome: a review and update. J Oral Pathol Med. 2013;42(9):649-55.

44. Lewis I, Pairman J. Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. J Intern Med. 2013;273(5): 501-10.

45. Schiavino D et al. Multiple-drug intolerance syndrome: clinical findings and usefulness of challenge tests. Ann Allergy Asthma Immunol. 2007;99(2): 136-42.

46. Palmquist E et al. Overlap in prevalence between various types of environmental intolerance. Int J Hyg Environ Health. 2014;217(4-5):427-34.

47. Kraus JE. Sensitization phenomena in psychiatric illness: lessons from the kindling model. J Neuropsychiatry Clin Neurosci. 2000;12(3):328-43.

48. Fink P, Schröder A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. J Psychosom Res. 2010;68(5):415-26.

49. Deal C et al. The United States rheumatology workforce: Supply and demand, 2005–2025. Arthritis Rheum. 2007;56(3):722-9.

50. Arthritis & Rheumatism/American College of Rheumatology. Press Release: Shortage of Rheumatologists–In Some U.S. Regions Closest Doctor May Be 200 Miles Away. November 27, 2013. Available at: http://www.wiley.com/WileyCDA/PressRelease/pressReleaseId-109897.html. Last Accessed: 16th February 2016.

51. Cook D et al. From 'Solution Shop' Model To 'Focused Factory' In Hospital Surgery: Increasing Care Value And Predictability. Health Aff. 2014;33(5): 746-55.

52. Perrot S et al. Survey of physician experiences and perceptions about the diagnosis and treatment of fibromyalgia. BMC Health Serv Res. 2012;12:356.

53. Baron R et al. Improving the primary care physicians' decision making for fibromyalgia in clinical practice: development and validation of the Fibromyalgia Detection (FibroDetect®) screening tool. Health Quality Life

Outcome. 2014;12:128.

54. Pollard L et al. Fibromyalgic rheumatoid arthritis and disease assessment. Rheumatology (Oxford). 2010;49(5):924-8.

55. Wallace D, Silverman S. Systemic lupus erythematosus and primary fibromyalgia can be distinguished by testing for cell-bound complement activation products. Lupus Sci Med. 2016;3(1):e000127

56. Haliloglu S, Carlioglu A. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. Rheumatol Int. 2014;34(9): 1275-80.

57. Choi BY, Oh HJ. Prevalence and clinical impact of fibromyalgia in patients with primary Sjogren's syndrome. Clin Exp Rheumatol. 2015;34(2 Suppl 96):9-13.

58. Kempke S et al. Self-critical perfectionism and its relationship to fatigue and pain in the daily flow of life in patients with chronic fatigue syndrome. Psychol Med.2013;43(5):18.

59. Taiminen T et al. Psychiatric (axis I) and personality (axis II) disorders in patients with burning mouth syndrome or atypical facial pain, Scand J Pain. 2011;2(4):155-60.

60. Fietta P, Manganelli P. Fibromyalgia and psychiatric disorders. Acta Biomed. 2007;78(2):88-95.

61. Ablin JN et al. Holocaust survivors: the pain behind the agony. Increased prevalence of fibromyalgia among Holocaust survivors. Clin Exp Rheumatol. 2010;28(6 Suppl 63):S51-6.

62. Häuser W et al. Emotional, physical, and sexual abuse in fibromyalgia syndrome: A systematic review with meta-analysis. 2011;63(6):808-20.

63. Wolfe F et al. Fibromyalgia and Physical Trauma: The Concepts We Invent. The J Rheumatol. 2014;41(9):1737-45.

64. Arnold L, Clauw D. A Framework for Fibromyalgia Management for Primary Care Providers. Mayo Clin Proc. 2012;87(5):488-96.

65. Hauser W et al. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. Arthritis Rheum. 2009;61(2):216-24.

66. Henningsen P et al. Management of functional somatic syndromes. Lancet. 2007;369(9565):946-55.

67. Yi P, Pryzbylkowski P. Opioid Induced Hyperalgesia. Pain Med. 2015;16(S1):S32-6.

68. Chou R et al. The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4):276-86.

69. Oh T et al. Predictors of Clinical Outcome in Fibromyalgia After a Brief Interdisciplinary Fibromyalgia Treatment Program: Single Center Experience. PM R. 2012;4(4):257-63.

70. Pfeiffer A et al. Effects of a 1.5-Day Multidisciplinary Outpatient Treatment Program for Fibromyalgia: A Pilot Study. Am J Phys Med Rehabil. 2003;82(3): 186-91.

AVANAFIL: THE SECOND-GENERATION TREATMENT OF ERECTILE DYSFUNCTION

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ABSTRACT

The main objectives of erectile dysfunction (ED) management are to control and reduce associated organic cardiovascular risk factors and to restore the capacity to obtain and maintain a rigid penile erection.

Since oral phosphodiesterase (PDE)-5 inhibitors have a demonstrated efficiency in the number and duration of erections in patients with ED with a favourable benefit-to-risk ratio, they have been recommended in European guidelines as the first-line medical therapy for ED.

In January 2016, we published a comprehensive review and meta-analysis on the safety and efficacy of avanafil, a novel second-generation PDE-5 inhibitor. This review aims to shed a special spotlight on the key aspects of this meta-analysis and to discuss how avanafil can provide an added value in the management of ED over first-generation agents.

Keywords: Erectile dysfunction (ED), avanafil, phosphodiesterase (PDE)-5 inhibitors.

INTRODUCTION

Erectile dysfunction (ED) is defined by the National Institutes of Health (NIH) as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance. This self-reported condition is the main complaint in male sexual medicine.[1] The incidence of ED is 26 new annual cases per 1,000 men,[2] for a worldwide ED prevalence evaluated at 37–52% of adults aged ≥40 years old and that is projected to increase by 2025 to approximately 322 million.[3] Of note, ED prevalence and severity is strongly associated with age.[4-11]

ED must be considered a multidimensional disorder deriving from a general (or stepwise) perturbation of all the components involved in the erectile response including organic (the body), relational (the couple), and intra-psychic (the mind).[12-18] ED may arise from the alteration of any one of these components (as a precipitating event) but sooner or later it will involve the other components in a redundant way, having negative effects on quality of life, interpersonal relationships, and mood.[9,19-24]

Despite this evidence, it is important to recognise that organic components and in particular cardiovascular risk factors such as smoking,[25,26] hypertension,[27,28] diabetes,[29,30] dyslipidaemia,[27] obesity, and sedentary lifestyle,[31,32] are major contributors to the pathogenesis of ED. In fact, arteriogenic ED, usually assessed through penile

colour Doppler ultrasound, is associated with a relevant increase in cardiovascular disease risk.[33,34]

THE PHARMACOLOGICAL MANAGEMENT OF ERECTILE DYSFUNCTION

The main objectives of ED management are to control and reduce associated organic cardiovascular risk factors and to restore the capacity to obtain and maintain a rigid penile erection. Due to the great variability of underlying aetiologies and the subjective aspects of ED, medical therapy depends on the patients' (and their partners') characteristics and comorbidities.[10,35,36]

Androgens are considered the major hormonal regulator of penile physiology.[37-40] Hypogonadism is a frequent condition in subjects seeking medical care for ED.[41] Testosterone replacement therapy in hypogonadal men (total testosterone <12 nM) is associated with significant increases in self-reported measures of erectile function.[39,40] Hence, according to the 4th International Consultation on Sexual Medicine (ICSM), testosterone assessment must precede any pharmacological intervention of ED subjects.[40]

Oral pharmacological management with phosphodiesterase (PDE)-5 inhibitors is the first-line modality, before other methods, which comprise penile self-injections with vasoactive drugs, intraurethral or intracavernosal alprostadil (a prostaglandin E1), vacuum-assisted erection devices, and penile prosthesis.[10,35,36,42-44] Only oral PDE-5 inhibitors that have been approved in Europe will be discussed in this article. These drugs act with a predominantly peripheral mechanism potentiating the nitric oxide (NO) pathway. Sexual stimulation generates a local production of NO which after binding to its intracellular receptors, activates the enzyme guanylate cyclase, leading to increased levels of cyclic guanosine monophosphate (cGMP). cGMP can engage a number of downstream targets, leading eventually to smooth muscle relaxation and penile erection. PDE-5 inhibition, by blocking cGMP degradation, can therefore increase NO signalling and induce smooth muscle relaxation.[45-47]

Oral PDE-5 inhibitors have a demonstrated efficiency in the number and duration of erections in patients with ED, with a favourable benefit-to-risk ratio, and hence they have been recommended in European guidelines as the first-line medical therapy for ED.[48] In January 2016, we published a comprehensive review and meta-analysis on the safety and efficacy of avanafil, a novel second-generation PDE-5 inhibitor. This review aims to shed a special spotlight on the key aspects of this meta-analysis and to discuss how avanafil can provide an added value in the management of ED over first-generation agents.

FIRST-GENERATION PHOSPHODIESTERASE 5 INHIBITORS

Sildenafil (Viagra®) was approved by the European Medicines Agency (EMA) in 1998 as the first oral PDE-5 inhibitor for ED and has been explored in a plethora of clinical trials.[49,50] Market authorisations for two other agents, vardenafil and tadalafil, were then subsequently granted by the EMA. The main characteristics of PDE-5 inhibitors are summarised in Table 1.[35,46,50-77] Adverse events (AEs) reported with first-generation PDE-5 inhibitors are generally mild, mostly transient, and self-limited; the most commonly-reported being headache, flushing, dyspepsia, nasal congestion, and dizziness with tadalafil also being associated to myalgia and back pain.[35,60,73,78-80]

All PDE-5 inhibitors are contraindicated with the use of nitrates or NO-donor drugs due to the risk of severe hypotension which can sometimes be life-threatening. PDE-5 inhibitors are to be used with caution with non-selective alpha-blockers and potent CYP3A4 inhibitors.[81] In addition, precaution is recommended for vardenafil in patients taking Type 1A anti-arrhythmics (such as quinidine or procainamide) or Type 3 anti-arrhythmics (such as sotalol or amiodarone) due to a possible causal association with QT prolongation.[82]

AVANAFIL: A SECOND-GENERATION PHOSPHODIESTERASE 5 INHIBITOR

Drug Characteristics

Avanafil (Spedra®) is the newest available PDE-5 inhibitor having been approved by the EMA in June 2013. It is a second-generation PDE-5 inhibitor along with lodenafil, mirodenafil, and udenafil (the last two are marketed in South Korea) but is the only one approved in Europe to date.[83,84]

Avanafil has a demonstrated high potency with a 50% inhibitory concentration (4.3–5.2 nM).[55-57] This compound is highly selective for PDE-5 as opposed to other PDE-5 inhibitors. *In vitro* studies evidenced less inhibition of PDE-1 (>10,000-fold;

present in the heart), PDE-6 (120-fold, present in the retina), and PDE-11 (>10,000-fold, present in the testicles). Furthermore, approximately 20,000-fold selectivity for the PDE-5 versus PDE-3 enzyme is found in the heart and blood vessels, which is important because PDE-3 is involved in control of cardiac contractility.[85] This high selectivity may confer and/or contribute to an improved safety profile over other PDE-5 inhibitors (Table 1).[51-54]

Avanafil is available in Europe as 50, 100, or 200 mg oral tablets. The recommended dose is 100 mg, taken as needed approximately 15–30 minutes before sexual activity; sexual stimulation is required for a response to treatment. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. The maximum recommended dosing frequency is once per day.[51]

Table 1: Main characteristics and isozyme selectivity of phosphodiesterase 5 inhibitors.

	Sildenafil[50,66-68]	Vardenafil[35,46,69-74]	Vardenafil[75-77]	Tadalafil[35,59-65]	Avanafil[51-58]
Brand name	Viagra®	Levitra®		Cialis®	Spedra®
Generation	First-generation				Second-generation
Galenic form	Film-coated tablets	Film-coated tablets	Orodispersible tablets	Film-coated tablets	Tablets
Year of European market authorisation	1998	2003	2010	2003	2013
Recommended dose	50 mg (may be increased to 100 mg or decreased to 25 mg based on efficacy and tolerability)	10 mg (may be increased to 20 mg or decreased to 5 mg based on efficacy and tolerability)		10–20 mg (also available as doses of 2.5 and 5 mg for once-daily dosing)	100 mg (may be increased to 200 mg or decreased to 50 mg based on efficacy and tolerability)
Maximum recommended dose	100 mg	20 mg		20 mg	200 mg
Onset of action	60 minutes	25–60 minutes	<30 minutes	30 minutes	Approximately 15–30 minutes
Onset of action delayed due to fatty meal or alcohol consumption?	Yes	Yes	No	No	Yes
Duration of action	About 4 hours Some reports of durations of action for up to 12 hours	About 4 hours		Up to 36 hours	>6 hours in some patients
PDE selectivity (fold-difference) 1	375	1,012		10,500	10,192
2	39,375	273,810		>25,000	9,808
3	16,250	26,190		>25,000	>19,231
4	3,125	14,286		14,750	1,096
5	1	1		1	1
6	16	21		550	121
7	13,750	17,857		>25,000	5,192
8	>62,500	1,000,000		>25,000	2,308
9	2,250	16,667		>25,000	>19,231
10	3,375	17,857		8,750	1,192
11	4,875	5,952		25	>19,231

PDE: phosphodiesterase.

Table 2: Efficacy and safety parameters for avanafil 100/200 mg versus placebo.

Parameter	Avanafil 100 mg versus placebo	Avanafil 200 mg versus placebo
Efficacy parameters	**OR (95% CI)**	
Successful intercourse (SEP3)	2.51 (1.85–3.41)	2.87 (2.23–3.69)
Successful intercourse (SEP3) within 15 minutes	4.72 (2.08–10.71)	4.21 (1.44–12.28)
Normalisation of IIEF (>26)	3.54 (2.14–5.87)	3.19 (1.93–5.29)
Successful vaginal penetration (SEP2)	2.20 (1.74–2.84)	2.57 (1.99–3.32)
Safety parameters	**OR (95% CI)**	
Serious AEs	1.99 (0.67–5.93)	1.70 (0.54–5.31)
Any drug-related AEs	2.07 (1.23–3.48)	2.10 (1.35–3.26)
AEs leading to drug discontinuation	1.45 (0.52–4.03)	1.24 (0.44–3.50)
Flushing	6.17 (2.08–18.32)	7.91 (2.71–23.04)
Headache	4.57 (1.91–10.94)	10.21 (4.50–23.17)
Nasal congestion	2.81 (0.99–8.01)	2.63 (0.89–7.73)
Back pain	1.74 (0.53–5.72)	1.24 (0.32–4.83)

SEP3: "Did your erection last long enough for you to have successful intercourse?" and SEP2: "Were you able to insert your penis into your partner's vagina?"
Data are derived and adapted from the meta-analysis of the available randomised placebo-controlled trials. Reproduced with permission from Corona G et al.[88]
SEP: sexual encounter profile; IIEF: International Index of Erectile Function; OR: odds ratio; CI: confidence interval; AEs: adverse events.

Dose adjustments are not required in patients aged 65 years and older. However, the available data on patients aged ≥70 years old is limited.[51] Similarly, dose adjustments are not required in patients with diabetes mellitus or mild-to-moderate renal impairment. It is to be noted that in Phase III studies, decreased efficacy was observed in the latter patient category, as compared with patients with normal renal function.[52,53] In patients with mild-to-moderate hepatic impairment (Child–Pugh Class A or B), treatment should be initiated with the minimum efficacious dose and posology should be adjusted based on tolerance.[52,53] Avanafil is contraindicated in patients with severe renal impairment (defined as creatinine clearance <30 mL/min) and severe hepatic impairment (Child–Pugh Class C) due to lack of specific data in these conditions.[52,53,86,87]

Meta-Analysis of Clinical Efficacy and Safety Data to Date

We conducted a meta-analysis of all available randomised clinical trials to date on the efficacy and safety of avanafil 100 and 200 mg.[88] A comprehensive search was conducted on the MEDLINE, EMBASE, and Cochrane databases. Five placebo-controlled randomised clinical trials of avanafil in ED were included in the analysis, reporting data on a total of 1,379 and 605 patients in the active and placebo arms, respectively.[58,89-92] Since only one study out of five reported on the 50 mg dosage, the authors chose to focus their analyses on the 100 and 200 mg dosages. In the overall cohort, mean ED duration was 65.5 months and the prevalence of severe ED was 42.9%.[88]

Clinical Outcomes

Efficacy: Successful intercourse

In the meta-analysis cited above, according to the evaluation of Sexual Encounter Profile (SEP)-3, avanafil 100 and 200 mg were significantly superior (3-fold increased probability to normalise erectile function) over placebo in improving successful sexual intercourse (Table 2), independently of baseline severity or duration of ED but also of comorbidities (high body mass index, diabetes, and hypertension). Both doses were also significantly superior to placebo with a 4-fold increased likelihood of a successful intercourse within 15 minutes.[88]

Of note, the efficacy of the 100 mg dosage was lower in elderly patients but this effect was not observed with the 200 mg dose. In addition, avanafil 100 and 200 mg were associated with a significantly higher International Index of Erectile Function (IIEF) versus placebo, with a better score for avanafil 200 mg (3.92 [range: 2.68–5.15] and 4.92 [range: 3.66–6.19], respectively, for the 100 and 200 mg doses; both p<0.0001).[88]

Onset and duration of action

Avanafil has a more rapid onset of action than the older PDE-5 inhibitors (within 15 minutes).[53,56,88,93-95] The rapid onset of action was demonstrated during a randomised, double-blind, placebo-controlled registrative clinical trial involving 646 ED patients over 12 weeks (67% and 71% of successful intercourse attempts with 100 and 200 mg avanafil versus 27% with placebo, respectively).[58]

In a newly published randomised, double-blind, placebo controlled, 12-week study, men were either assigned to placebo, avanafil 100 mg, or avanafil 200 mg.[91] Successful intercourse attempts within approximately 15 minutes after dosing were significantly higher with avanafil 100 mg (mean: 25.9%) and 200 mg (mean: 29.1%) than with placebo (mean: 14.9%, p=0.001 and <0.001, respectively). A statistically significant difference between avanafil and placebo was observed for successful intercourse attempts as early as 10 and 12 minutes in the 200 mg and 100 mg groups, respectively. The erectogenic effect of avanafil has been reported beyond 6 hours in some subjects.[51,58]

Safety Profile of Avanafil

Common class-related AEs reported with avanafil include headache, flushing, and nasal congestion.[51,58,89-91,96] Unsurprisingly, In the meta-analysis both avanafil 100 and 200 mg dosage forms were associated with an increased rate of reported drug-related AEs over placebo (especially flushing and headache but no differences for nasal congestion and back pain were observed; Table 2). However, the rate of discontinuations due to AEs for both active doses were similar to those for placebo.[88] An interesting finding was that no difference was observed between the 100 and 200 mg dosages and placebo in terms of serious AEs (odds ratio: 1.99 [0.67–5.93] and 1.70 [0.54–5.31] for avanafil 100 and 200 mg, respectively, both with a non-significant p-value).

Avanafil at its maximum dosage has a comparable efficacy but an improved safety profile over first-generation PDE-5 inhibitors.[53,56,88,93-95] In another meta-analysis published by Chen et al.,[42] the frequency of AEs for each PDE-5 inhibitor when used at their maximum dosage demonstrated a favourable safety profile with avanafil 200 mg versus tadalafil 20 mg (p<0.02), vardenafil 20 mg (p=0.001), and sildenafil (p=0.0001).[88] However head-to-head trials or longer duration studies on the safety of avanafil are needed to ascertain this suggested advantage.[10,88]

CHOICE OF THERAPY AND PRACTICAL CONSIDERATIONS FOR REAL-WORLD PATIENTS: THE ADDED VALUE OF AVANAFIL

The efficacy and safety of PDE-5 inhibitors has been highly documented. However, beyond the first year of therapy with a PDE-5 inhibitor, a substantial proportion of men discontinue treatment prematurely.[10,88,97,98] It therefore appears ineluctable that in order to improve treatment adherence, clinicians should try to better understand patient expectations to help refine the choice of PDE-5 therapy on an individual basis, and tailor therapy according to the patient's/couple's characteristics and expectations.

Although there is no head-to-head data from double-blind randomised trials comparing PDE-5 inhibitors against each other, all four drugs are effective within an acceptable safety profile.[35,99] Guidance from both the American College of Physicians (ACP; 2009) and the European Association of Urology (EAU; 2016) recommend that the choice of PDE-5 inhibitor be based on patient's preferences, costs, ease of use, frequency of intercourse, desired onset, and duration of action as well as AEs.[48,79,100,101]

While the therapeutic armamentarium may seem homogenous, different pharmacokinetic properties and selectivity differences are at the core of the choice for the most appropriate drug.[99,102] Indeed, pharmacokinetic differences translate into different onset and duration of action parameters. Sildenafil, film-coated vardenafil, and tadalafil should be taken 30–60, 25–60, and 30 minutes before desired sexual activity, respectively. Orodispersible vardenafil can be taken only 30 minutes before sexual intercourse; avanafil has the shorter onset of action with a delay of action of only 15 minutes

which is of particular interest for couples seeking a very spontaneous sex life. With this very short onset of action, avanafil is the closest PDE-5 inhibitor to a 'natural' occurrence.[51,59,63,66,69,74]

According to a large online survey (N=1,534) initiated to better understand patients' needs and expectations of sexual activity and ED management, 38% of men considered an ideal onset of action of oral therapies to be of 'about 15 minutes' giving them 'the ability to respond immediately to their partner's sexual wishes and requests' and 'allowing a certain degree of spontaneity'. As we previously commented in our meta-analysis, in the context of ED a drug with a rapid onset can generate better spontaneous sexual interaction.[88] Furthermore, the short delay provided by avanafil could help reduce the psychological impact of ED (couple-related problems, low self-esteem), improve treatment satisfaction, and therefore solidify treatment adherence.

With respect to available dosage forms, avanafil 200 mg could provide an added value in elderly (>65 years old) ED patients in achieving successful sexual encounters. Indeed, in the meta-analysis, while the efficacy of the 100 mg dosage was lower in the elderly than in younger patients, this effect was not observed with the 200 mg dose which was still demonstrated to be as safe as the 100 mg dose.[88] Elderly patients can present several comorbidities and risk factors, and thus the fact that avanafil at its maximum dosage has a comparable efficacy but fewer AEs than first-generation PDE-5 inhibitors, is of particular interest. This safer profile could increase physician confidence in prescribing an on-demand but long-term therapy, as can be the case with elderly ED patients. Likewise, as suggested by some experts and our clinical practice, the maximum dosage of 200 mg could be directly prescribed to complicated subjects in order to obtain the best initial treatment success and generate a strong patient adherence to therapy from the beginning.[88]

CONCLUSION

This new meta-analysis further ascertains the safety and efficacy of avanafil, as evaluated by SEP-3, SEP-2, and IIEF scores in the studied populations. While avanafil has comparable efficacy outcomes with the three older PDE-5 inhibitors, its improved safety profile (due to a higher selectivity) can be of particular interest for clinicians. Furthermore, as a consequence of unique pharmacokinetic properties, this compound provides added value due to its rapid onset of action and reasonable duration of action.

These factors could translate into higher patient compliance and treatment satisfaction thus adherence, and help reduce treatment discontinuations (e.g. due to AEs).[79,103] Second-generation PDE-5 inhibitors are a welcome addition to the therapeutic landscape of ED and can contribute to a more individually-tailored ED therapy.

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REFERENCES

1. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA. 1993;270(1):83-90.

2. Johannes CB et al. Incidence of erectile dysfunction in men 40 to 69 years old: Longitudinal results from the Massachusetts male aging study. J Urol. 2000;163(2):460-3.

3. Ayta IA et al. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int. 1999;84(1):50-6.

4. Litwin MS et al. Health-related quality of life in men with erectile dysfunction. J Gen Intern Med. 1998;13(3):159-66.

5. Jønler M et al. The effect of age, ethnicity and geographical location on impotence and quality of life. Br J Urol. 1995;75(5):651-5.

6. Jackson SE, Lue TF. Erectile dysfunction: Therapy health outcomes. Urology. 1998;51(6):874-82.

7. Fugl-Meyer AR et al. On life satisfaction in male erectile dysfunction. Int J Impot Res. 1997;9(3):141-8.

8. Laumann EO et al. Sexual dysfunction in the United States: Prevalence and predictors. JAMA. 1999;281(6):537-44.

9. Feldman HA et al. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. J Urol. 1994;151(1):54-61.

10. Kim SC et al. Reasons and predictive factors for discontinuation of PDE-5 inhibitors despite successful intercourse in erectile dysfunction patients. Int J Impot Res. 2014;26(3):87-93.

11. Corona G et al. Sexual function of the ageing male. Best Pract Res Clin Endocrinol Metab. 2013;27(4):581-601.

12. Boddi V et al. "It takes two to tango": The relational domain in a cohort of subjects with erectile dysfunction (ED). J Sex Med. 2012;9(12):3126-36.

13. Corona G et al. SIEDY scale 3, a new

instrument to detect psychological component in subjects with erectile dysfunction. J Sex Med. 2012;9(8): 2017-26.

14. Corona G et al. Risk factors associated with primary and secondary reduced libido in male patients with sexual dysfunction. J Sexual Med. 2013;10(4):1074-89.

15. Corona G et al. Assessment of the relational factor in male patients consulting for sexual dysfunction: The concept of couple sexual dysfunction. J Androl. 2006;27(6):795-801.

16. Lotti F et al. Clinical correlates of erectile dysfunction and premature ejaculation in men with couple infertility. J Sex Med. 2012;9(10):2698-707.

17. Balercia G et al. Sexual symptoms in endocrine diseases: Psychosomatic perspectives. Psychother Psychosom. 2007;76(3):134-40.

18. Corona G et al. How to recognize late-onset hypogonadism in men with sexual dysfunction. Asian J Androl. 2012; 14(2):251-9.

19. Jannini EA et al. Organic vs. psychogenic? The Manichean diagnosis in sexual medicine. J Sex Med. 2010; 7(5):1726-33.

20. Lindau ST et al. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357(8):762-74.

21. Fisher WA et al. Erectile dysfunction (ED) is a shared sexual concern of couples I: Couple conceptions of ED. J Sex Med. 2009;6(10):2746-60.

22. Salonia A et al. Is erectile dysfunction a reliable proxy of general male health status? The case for the International Index of Erectile Function-Erectile Function domain. J Sex Med. 2012;9(10):2708-15.

23. Nurnberg HG et al. Depression, antidepressant therapies, and erectile dysfunction: Clinical trials of sildenafil citrate (Viagra) in treated and untreated patients with depression. Urology. 2002; 60(2 Suppl 2):58-66.

24. Clayton AH et al. Sexual dysfunction associated with major depressive disorder and antidepressant treatment. Exp Opin Drug Saf. 2014;13(10):1361-74.

25. Derby CA et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology. 2000; 56(2):302-6.

26. Corona G et al. Psychobiological correlates of smoking in patients with erectile dysfunction. International journal of impotence research. 2005;17(6): 527-34.

27. Seftel AD et al. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. J Urol. 2004;171(6 Pt 1):2341-5.

28. Corona G et al. Pulse pressure independently predicts major cardiovascular events in younger but not in older subjects with erectile dysfunction. J Sex Med. 2011;8(1):247-54.

29. Corona G et al. Sexual dysfunction at the onset of type 2 diabetes: The interplay of depression, hormonal and cardiovascular factors. J Sex Med. 2014; 11(8):2065-73.

30. Corona G et al. The SUBITO-DE study: Sexual dysfunction in newly diagnosed type 2 diabetes male patients. J Endocrinol Invest. 2013;36(10):864-8.

31. Corona G et al. Hypogonadism as a possible link between metabolic diseases and erectile dysfunction in aging men. Hormones (Athens). 2015;14(4):569-78.

32. Corona G et al. Erectile dysfunction and central obesity: An Italian perspective. Asian J Androl. 2014;16(4):581-91.

33. Corona G et al. Penile doppler ultrasound in patients with erectile dysfunction (ED): Role of peak systolic velocity measured in the flaccid state in predicting arteriogenic ED and silent coronary artery disease. J Sexual Med. 2008;5(11):2623-34.

34. Rastrelli G et al. Flaccid penile acceleration as a marker of cardiovascular risk in men without classical risk factors. J Sex Med. 2014;11(1):173-86.

35. Montague DK et al. Chapter 1: The management of erectile dysfunction: an AUA update. J Urol. 2005;174(1):230-9.

36. Costa P, Potempa AJ. Intraurethral alprostadil for erectile dysfunction: A review of the literature. Drugs. 2012; 72(17):2243-54.

37. Carosa E et al. The ontogenetic expression pattern of type 5 phosphodiesterase correlates with androgen receptor expression in rat corpora cavernosa. J Sex Med. 2009;6(2): 388-96.

38. Isidori AM et al. A critical analysis of the role of testosterone in erectile function: From pathophysiology to treatment-a systematic review. Eur Urol. 2014;65(1):99-112.

39. Isidori AM et al. Outcomes of androgen replacement therapy in adult male hypogonadism: Recommendations from the Italian society of endocrinology. J Endocrinol Invest. 2015;38(1):103-12.

40. Corona et al. Endocrinologic Control of Men's Sexual Desire and Arousal/ Erection. J Sex Med. 2016;13(3):317-37.

41. Maseroli E et al. Prevalence of endocrine and metabolic disorders in subjects with erectile dysfunction: A comparative study. J Sex Med. 2015;12(4):956-65.

42. Chen J et al. Sildenafil versus the vacuum erection device: Patient preference. J Urology. 2001;166(5): 1779-81.

43. Pinsky MR et al. Intracavernosal therapy and vacuum devices to treat erectile dysfunction. Arch Esp Urol. 2010; 63(8):717-25.

44. Corman A et al. [Importance of patient's choice in the treatment of erectile dysfunction]. Presse Med. 2012; 41(6 Pt 1):593-7.

45. Dolci S et al. Subcellular localization and regulation of type-1C and type-5 phosphodiesterases. Biochem Biophys Res Commun. 2006;341(3):837-46.

46. Palit V, Eardley I. An update on new oral PDE5 inhibitors for the treatment of erectile dysfunction. Nat Rev Urol. 2010; 7(11):603-9.

47. Boolell M et al. Sildenafil, a novel effective oral therapy for male erectile dysfunction. Br J Urol. 1996;78(2):257-61.

48. Hatzimouratidis K et al. EAU Guidelines on Male Sexual Dysfunction. Updated 2016. Available at: http://uroweb.org/guideline/male-sexual-dysfunction/. Last accessed: 19 July 2016.

49. Goldstein I et al. Oral sildenafil in the treatment of erectile dysfunction. 1998. J Urol. 2002;167(2 Pt 2):1197-204.

50. Fink HA et al. Sildenafil for male erectile dysfunction: A systematic review and meta-analysis. Arch Intern Med. 2002;162(12):1349-60.

51. EMA. Spedra: EPAR- Product Information- European Medicine Agency. Updated March 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002581/WC500145206.pdf. Last accessed: 19 July 2016.

52. Smith WB 2nd et al. PDE5 inhibitors: Considerations for preference and long-term adherence. Int J Clin Pract. 2013; 67(8):768-80.

53. Kyle JA et al. Avanafil for erectile dysfunction. Ann Pharmacother. 2013; 47(10):1312-20.

54. Katz EG et al. Avanafil for erectile dysfunction in elderly and younger adults: Differential pharmacology and clinical utility. Ther Clin Risk Manag. 2014;10: 701-11.

55. Kotera J et al. Avanafil, a potent and highly selective phosphodiesterase-5 inhibitor for erectile dysfunction. J Urol. 2012;188(2):668-74.

56. Wang R et al. Selectivity of avanafil, a PDE5 inhibitor for the treatment of erectile dysfunction: Implications for clinical safety and improved tolerability. J Sex Med. Aug 2012;9(8):2122-9.

57. Allison M et al. Pharmacokinetics of avanafil, a novel, rapidly absorbed, selective PDE5 inhibitor for the treatment of mild to severe erectile dysfunction. J Sex Med. 2011;8(suppl 5):S466.

58. Goldstein I et al. A randomized, double-blind, placebo-controlled evaluation of

the safety and efficacy of avanafil in subjects with erectile dysfunction. J Sex Med. 2012;9(4):1122-33.

59. EMA. Cialis: EPAR- European Medicines Agency. Updated September 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000436/WC500026318.pdf. Last accessed: 19 July 2016.

60. Curran M, Keating G. Tadalafil. Drugs. 2003;63(20):2203-12; discussion 2213-4.

61. Coward RM, Carson CC. Tadalafil in the treatment of erectile dysfunction. Ther Clin Risk Manag. 2008;4(6):1315-30.

62. Forgue ST et al. Tadalafil pharmacokinetics in healthy subjects. Br J Clin Pharmaco. 2006;61(3):280-8.

63. Tadalafil (Cialis) once a day for erectile dysfunction. Med Lett Drugs Ther. 2008;50(1283):27-8.

64. Porst H et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: Results of a multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol. 2006;50(2):351-9.

65. Shabsigh R et al. Efficacy and safety of once-daily tadalafil in men with erectile dysfunction who reported no successful intercourse attempts at baseline. J Sex Med. 2013;10(3):844-56.

66. EMA. Viagra: EPAR- European Medicines Agency. Updated November 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000202/WC500049830.pdf. Last accessed: 19 July 2016.

67. Moncada I et al. Efficacy of sildenafil citrate at 12 hours after dosing: Re-exploring the therapeutic window. Eur Urol. 2004;46(3):357-60; discussion 360-1.

68. McCullough AR et al. Randomized, double-blind, crossover trial of sildenafil in men with mild to moderate erectile dysfunction: Efficacy at 8 and 12 hours postdose. Urology. 2008;71(4):686-92.

69. Vardenafil (levitra) for erectile dysfunction. Med Lett Drugs Ther. 2003; 45(1166):77-8.

70. Porst H et al. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: The first at-home clinical trial. Int J of Impot Res. 2001;13(4):192-9.

71. Klotz T et al. Vardenafil increases penile rigidity and tumescence in erectile dysfunction patients: A RigiScan and pharmacokinetic study. World J Urol. 2001;19(1):32-9.

72. Hellstrom WJ et al. Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: Results of a randomized, double-blind, 26-week placebo-controlled pivotal trial. Urology. 2003;61(4 Suppl 1):8-14.

73. Keating GM, Scott LJ. Vardenafil: A review of its use in erectile dysfunction. Drugs. 2003;63(23):2673-703.

74. EMA. Levitra: EPAR- Product Information- European Medicine Agency. Updated April 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000475/WC500039992.pdf. Last accessed: 19 July 2016.

75. Debruyne FM et al. Time to onset of action of vardenafil: A retrospective analysis of the pivotal trials for the orodispersible and film-coated tablet formulations. J Sex Med. 2011;8(10): 2912-23.

76. Sanford M. Vardenafil orodispersible tablet. Drugs. 2012;72(1):87-98.

77. Wang H et al. The effectiveness and safety of avanafil for erectile dysfunction: A systematic review and meta-analysis. Curr Med Res Opin. 2014;30(8):1565-71.

78. Giuliano F et al. Safety of sildenafil citrate: Review of 67 double-blind placebo-controlled trials and the postmarketing safety database. Int J of Clin Pract. 2010;64(2):240-55.

79. Tsertsvadze A et al. Oral sildenafil citrate (viagra) for erectile dysfunction: A systematic review and meta-analysis of harms. Urology. 2009;74(4):831-36.e8.

80. Chung E, Broc GB. A state of art review on vardenafil in men with erectile dysfunction and associated underlying diseases. Expert Opin on Pharmacothe. 2011;12(8):1341-8.

81. Jackson G et al. The second Princeton consensus on sexual dysfunction and cardiac risk: New guidelines for sexual medicine. J Sex Med. 2006;3(1):28-36.

82. Corona G et al. The use of phosphodiesterase 5 inhibitors with concomitant medications. J Endocrinol Invest. 2008;31(9):799-808.

83. Kang SG, Kim JJ. Udenafil: efficacy and tolerability in the management of erectile dysfunction. Ther Adv Urol. 2013; 5(2):101-10.

84. Bruzziches R et al. An update on pharmacological treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors. Expert Opin Pharmacother. 2013;14(10):1333-44.

85. Knight W, Yan C. Therapeutic potential of PDE modulation in treating heart disease. Future Med Chem. 2013; 5(14):1607-20.

86. Vecchio M et al. Interventions for treating sexual dysfunction in patients with chronic kidney disease. Cochrane Database Syst Rev. 2010(12):CD007747.

87. Navaneethan SD et al. Prevalence and correlates of self-reported sexual dysfunction in CKD: a meta-analysis of observational studies. Am J Kidney Dis. 2010;56(4):670-85.

88. Corona G et al. The safety and efficacy of Avanafil, a new 2(nd) generation PDE5i: Comprehensive review and meta-analysis. Expert Opin Drug Safety. 2016;15(2): 237-47.

89. Goldstein I et al. Avanafil for the treatment of erectile dysfunction: A multicenter, randomized, double-blind study in men with diabetes mellitus. Mayo Clinic Proc. 2012;87(9):843-52.

90. Mulhall JP et al. A phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. J Urol. 2013;189(6): 2229-36.

91. Hellstrom WJ et al. Efficacy of Avanafil 15 Minutes after Dosing in Men with Erectile Dysfunction: A Randomized, Double-Blind, Placebo Controlled Study. J Urol. 2015;194(2):485-92.

92. Zhao C et al. Efficacy and safety of avanafil for treating erectile dysfunction: Results of a multicentre, randomized, double-blind, placebo-controlled trial. BJU Int. 2012;110(11):1801-6.

93. Hellstrom WJ et al. A phase II, single-blind, randomized, crossover evaluation of the safety and efficacy of avanafil using visual sexual stimulation in patients with mild to moderate erectile dysfunction. BJU Int. 2013;111(1):137-47.

94. Kedia GT et al. Avanafil for the treatment of erectile dysfunction: Initial data and clinical key properties. Ther Adv Urol. 2013;5(1):35-41.

95. Limin M et al. Avanafil, a new rapid-onset phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction. Expert opinion on investigational drugs. 2010;19(11):1427-37.

96. Belkoff LH et al. An open-label, long-term evaluation of the safety, efficacy and tolerability of avanafil in male patients with mild to severe erectile dysfunction. Int J of Clin Pract. 2013;67(4):333-41.

97. Conaglen HM, Conaglen JV. Couples' reasons for adherence to, or discontinuation of, PDE type 5 inhibitors for men with erectile dysfunction at 12 to 24-month follow-up after a 6-month free trial. J Sex Med. 2012;9(3):857-65.

98. Jannini EA et al. Health-related characteristics and unmet needs of men with erectile dysfunction: A survey in five European countries. J Sex Med. 2014;11(1):40-50.

99. Tsertsvadze A et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile

dysfunction: a systematic review and meta-analysis. Ann Internal Med. 2009; 151(9):650-61.

100. Qaseem A et al. Hormonal testing and pharmacologic treatment of erectile dysfunction: A clinical practice guideline from the American College of Physicians. Ann Intern Med. 2009;151(9):639-49.

101. Jannini EA et al. How to evaluate the efficacy of the phosphodiesterase type 5 inhibitors. Journal Sexual Med. 2012;9(1):26-33.

102. Burke RM, Evans JD. Avanafil for treatment of erectile dysfunction: Review of its potential. Vasc Health Risk Manag. 2012;8:517-23.

103. Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? Drugs. 2005;65(12):1621-50.

NEW EVIDENCE FOR EXOGENOUS GLYCOSAMINOGLYCANS TREATMENT OF 'CYSTITIS': IS THE FUTURE NOW?

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ABSTRACT

Chronic cystitis may be due to different known causes. Current basic science research has revealed a wide consensus that chronic cystitis may arise from a primary defective urothelium lining and in particular from a damage of its glycosaminoglycans (GAGs) component. The GAG layer is composed mainly of heparin, dermatan, the glycosaminoglycans, chondroitin sulphate (CS), and hyaluronic acid (HA) which adhere to the surface of the urothelium. The main components, CS and HA, play a central role in the urine barrier and antibacterial defence mechanisms. When the GAG layer loses its protective barrier function it translates into increasing permeability of the urothelium. The main consequence of this is that bladder inflammation may arise. Exogenous restoration of the GAG layer has recently become a new opportunity for the treatment of recurrent urinary tract infections, painful bladder syndrome or interstitial cystitis, and lower urinary tract symptoms after chemotherapy or pelvic radiotherapy. The aim of this paper is to update the literature about the use of exogenous for the treatment of cystitis.

Keywords: Urothelium, cystitis, intravesical instillation, sodium hyaluronate, chondroitin sulfate (CS), Ialuril®.

INTRODUCTION

Chronic cystitis may be due to different known causes such as recurrent urinary tract infections (UTIs), chemical or physical irritants, resulting from chemotherapy and radiotherapy for pelvic tumours, or to uncertain causes and aetiology as in the case of painful bladder syndrome and interstitial cystitis (PBS/IC). Although in the past the urinary bladder epithelium was classically thought of as a simple passive barrier, current basic science research has revealed a wide consensus that chronic cystitis may arise from a primary defective urothelium lining and in particular from damage of its glycosaminoglycans (GAGs) component.[1-3] In normal conditions, the GAG layer consists of a thick mucus layer of glycoproteins and proteoglycans on the surface of the urothelial cells. The GAG layer is also located in between the cells lines and even in the entire bladder wall. Within the mucus is a hydrophilic mucin layer in which water molecules are embedded, providing a good barrier against ions, solutes, water, and pathogens. The GAG layer is composed mainly of heparin, dermatan, the glycosaminoglycans, chondroitin sulphate (CS) and hyaluronic acid (HA) which adhere to the surface of the urothelium. The main components, CS and HA, play a central role in the barrier against urine and antibacterial defence mechanisms. These components do not simply float on the surface but instead are 90% attached to transmembrane proteins, core protein chains, and proteoglycans so that they are stabilised on the surface and allow water molecules to be embedded. During dysfunction of the GAG layer, the GAG layer loses its protective barrier function leading to increased permeability into the deep layers of the urothelium and bladder and consequently to inflammation

(cystitis). Exogenous restoration of the GAG layer has recently become a new opportunity for the treatment of recurrent UTIs, PBS/IC, and lower urinary tract symptoms after chemotherapy or pelvic radiotherapy. Recently, Lazzeri et al.[4] provided an update on the clinical use of GAG therapy starting in such different clinical conditions.

In 2016, two new and well-designed papers dealt with the role of GAGs in the treatment of cystitis. Ciani et al.[5] addressed the role of Ialuril® for the treatment of recurrent UTIs and Gacci et al.[6] reported the clinical use of exogenous GAGs in patients with post-radiation cystitis. The aim of this paper is to update the literature about the use of exogenous GAGs for the treatment of cystitis starting from the pathophysiology of GAGs dysfunction.

PATHOPHYSIOLOGY OF GLYCOSAMINOGLYCANS DAMAGE

Different causes may be considered in the early stage of GAG injury. Autoimmune diseases, chronic bacterial infections, chemicals such as anticancer drugs (cyclophosphamide or bacillus Calmette–Guérin [BCG] exposure), or radiation exposure can all result in urothelial GAG loss. Damaging this shielding layer would result in the loss of protective function and would allow both the normal (i.e. H+, K+, Na+, Cl-) and abnormal constituents of urine (i.e. metabolites of cytotoxic drugs or toxic substances excreted in urine) to come into direct contact with the subepithelial layers. This infiltration through the GAGs barrier defect can cause subepithelial layer inflammation and delay or prevent the healing of both the damaged bladder urothelial cells as well as the GAGs.[7] The GAGs healing failure, due to chronic pathological stimuli (i.e. recurrent UTIs or radiotherapy), leads to the activation of a specific subset of unmyelinated C fibres in the suburothelium.[8] They are peptide-containing fibres (substance P, neurokinin A and B, calcitonin gene-related peptide, and Bradykinin) and although they serve as primary afferents, they may play an important role in the regulation of the lower urinary tract by an efferent function.[8] The afferent function, mediated by the release of neuropeptides from their central endings, is involved in the regulation of the micturition reflex, pain sensation, and activation of the visceral reflex. The efferent function due to the release of substance P, calcitonin gene-related peptide, and tachykinins from peripheral endings regulate the smooth muscle contraction, immune cell migration, mast cells degranulation, and neurogenic inflammation. There is robust evidence supporting their role in bladder chronic inflammation.[4]

Furthermore, when the GAGs defect persists or its healing process fails, chronic stimulation of suburothelial tissues may result in visceral hypersensitivity of bladder C fibre nociceptors.[9] Clinically, the neuronal hypersensitivity, i.e. the exaggerated perception to normal stimuli, leads to allodynia: the perception of nociceptive stimulation which occurs for stimuli that would usually evoke an innocuous sensation (i.e. pain during bladder filling). It also leads to hyperalgesia: exaggerated pain sensation to a stimulation which is normally mildly noxious (i.e. high pain intensity for mild inflammation).

Based on such evidence the use of exogenous GAGs for early repair of the GAG layer has been suggested and investigated. The hypothetical mechanisms of action are complex and include inhibition of adherence of immune complexes to polymorphonuclear cells, inhibition of leukocyte migration, and aggregation, regulation of fibroblast and endothelial cell proliferation, and enhancement of connective tissue healing.[10]

UP-TO-DATE: THE CLINICAL EVIDENCE

Urinary Tract Infections

Almost 50% of women will experience at least one UTI in their lifetime and in 20–50% of these, the episode is followed by a second infection within 6 months.[11] In the USA, up to 15% of women develop UTIs each year, and one in four of those will have one or more recurrences. This condition however is not restricted to women, and it is estimated that the annual incidence of UTIs in males aged 17–79 years in the USA is 2.2%.[12] The symptoms of UTI, particularly when recurrent, impact on quality of life and productivity, affecting physical and emotional functioning, vitality, sexual and social functioning, and general health perceptions.[13]

Eradication of the infection has been the aim of current management strategies. Continuous or patient-initiated antimicrobial therapy is the current standard management practice for the treatment of acute UTIs and the prophylaxis of recurrent UTIs.[14] Agents include trimethoprim with or without sulphamethoxide, nitrofurantoin, cefaclor, cephalexin, norfloxacin, ciprofloxacin, and fosfomycin. Disadvantages of this choice of

treatment include the adverse effects associated with the antimicrobial agents and the increasing drug resistance.[15]

Despite our broad array of very successful antimicrobial agents, UTIs remain a complex clinical condition. Urothelial GAGs also play an important role in fending off infection, by virtue of forming a physical barrier as well as binding and encapsulating bacteria.

Currently, there are a range of commercially available intravesical formulations of exogenous GAGs. There are formulations containing a low concentration of HA (0.08%), a low concentration of CS (0.2%), or a high concentration of CS (2%). Exogenous GAGs, especially in the combination of HA and CS (Ialuril®, IBSA), were originally investigated for efficacy in patients with PBS/IC who had not benefited from other therapies.[16] Recently, Ialuril® showed efficacy and safety for the prevention of recurrent UTIs.[17]

Earlier observational studies showed that exogenous intravesical HA markedly reduced recurrences of UTIs[18,19] and were followed by a prospective study of the combination of HA and CS in patients with recurrent UTIs.[17] This randomised, double-blind, placebo-controlled trial of Ialuril® (four instillations at weekly intervals, then five instillations at monthly intervals) monitored the 28 patients randomised to Ialuril® and the 29 patients randomised to placebo for 12 months. Patients treated with active drug had fewer UTI recurrences, a longer time to recurrence, and a greater improvement in quality of life than patients in the placebo group. They experienced fewer episodes of UTI and a longer mean time-to-recurrence than patients receiving placebo (87% versus 10% and 185 versus 53 days; p<0.05, for both); the total number of UTIs experienced at 6 and 12 months was also significantly less (p<0.05) in the Ialuril® group. Symptoms (according to the Pelvic Pain and Urgency/Frequency [PUF] score) improved significantly and quality of life was also improved at 12 months (p<0.001).

De Vita et al.[20] compared exogenous intravesical GAGs to antibiotic prophylaxis for recurrent UTIs in 28 women; the intravesical treatment significantly reduced the recurrence of UTIs and improved urinary symptoms, quality of life, and cystometric capacity at 12-month follow-up. Results in the GAGs (Ialuril®) and antibiotic groups were: number of recurrences (1 versus 2.3; p=0.02), mean 3-day voiding (17.8 versus 24.2; p=0.04), symptoms according to visual analogue scale (VAS) score (pain: 1.6 versus 7.8; p<0.001), PUF score (11.2 versus 19.6; p<0.001), King's Health Questionnaire score (18.4 versus 47.3; p<0.001), and maximum cystometric capacity (380 versus 229 mL; p<0.001). As in the Damiano et al.[17] study, tolerability of Ialuril® formulation was good with no serious adverse events reported. Recently Cicione et al.[21] assessed the effectiveness of intravesical instillation of HA and CS as a non-antibiotic treatment option for prophylaxis of recurrent UTIs in female patients at seven European institutions.[21] They used an intravesical instillation of 50 mL HA 1.6% and CS 2% solution in 157 women with recurrent UTIs. UTI episodes decreased from 4.13±1.14 to 0.44±0.50 (p=0.01) at 12 months, while recurrent UTI time prolonged from 94.8±25.1 days to 178.4±37.3 days (p=0.01) at 12 months. An improvement in symptoms and quality of life was achieved.

The critical analysis of these studies offers some considerations. The number of instillations seems to be an important marker of success for intravesical administration therapy. Furthermore, in contrast to what happens with antibiotic prophylaxis owing to side effects and development of resistance, the effectiveness of GAG reinstatement therapy improves over time, with an even better expected comparative effectiveness profile in the long-run as showed by Ciani et al.[5]

Painful Bladder Syndrome and Interstitial Cystitis

To improve the integrity and function of the bladder lining, exogenous intravesical GAG replacement therapies are one of the treatment options for patients with PBS/IC, generally refractory to conventional therapy.[14]

Morales et al.[22] found a complete or partial response rate of 71% for up to 1 year. Recently Engelhardt et al.[23] observed a 50% complete bladder symptom remission after intravesical HA. Those patients who responded did not use additional therapy during the 5-year follow-up; 41.7% with symptom recurrence improved with HA maintenance.[23] Hanno et al.[24] reached a different conclusion. They carried out a double-blind, placebo-controlled, multicentre clinical study of different HA preparations (40 or 200 mg/cm^3) and they did not find any significant efficacy of sodium hyaluronate compared with placebo.

Steinhoff et al.[25] investigated the exogenous CS therapy efficiency by an open-label 12-month study. The authors found a response rate for symptom improvement of 67% in 18 patients with 40 mL instillations of CS 0.2% weekly for 4 weeks and then monthly for 12 months. A recently published randomised controlled trial (RCT) failed to show superiority of CS 2.0% over control after 6 weeks of treatment.[26]

Porru et al.[27] investigated the efficiency of intravesical CS/HA combination in 20 PBS/IC patients. A VAS for pain and urgency, number of void per day, mean voiding volume, Interstitial Cystitis Symptom Index, and PUF score improved compared with baseline. Cervigni et al.[28] seemed to confirm such results. They reported the long-term results of intravesical CS/HA therapy in 12 patients and showed the sustained efficiency for 3 years in terms of mean number of voids per day and mean volume per void with the confirmation of quality of life assessments. The same author confirmed such results in 2014.[29] In this study, 74 patients were treated with Ialuril® and 36 with RIMSO-50®. At baseline, mean pain VAS scores of 65.53 (standard deviation [SD]: 21.00) and 64.58 (SD: 20.53) were reported in the Ialuril® and the RIMSO-50 group, respectively. At the end-of-treatment visit, the response to treatment in terms of pain decrease from baseline was statistically significant in both groups, with a VAS score reduction of -39.27 (SD: 24.52) for Ialuril® and of -31.00 (SD: 26.38) for RIMSO-50. For the 59 patients in the Ialuril® and 31 patients in the RIMSO-50 group completing the follow-up period, the mean VAS reduction was of -43.71 (SD: 28.56) and of -33.65 (SD: 31.31), respectively. The results from voiding diaries and the questionnaire scores were consistent with pain reduction. There was a higher proportion of patients with adverse events in the RIMSO-50 (30.56%; 95% confidence interval [CI]: 13.61–43.45) than in the Ialuril® (14.86%; 95% CI: 6.86–23.27) group. A case of strangury and a case of suprapubic pain, both treatment-related, led to withdrawal of two patients, one per group.

Despite the limitations of most of those studies, findings confirmed the role of combination therapy with HA and CS as a safe and effective option for the treatment of patients with refractory PBS/IC.

Chemo and Radio-Induced Cystitis

Cystitis can be induced by both radiotherapy and chemotherapy, and can be either acute or chronic.[30] The condition often results in storage-type lower urinary tract symptoms and haematuria. It is generally thought that damage to the GAG layer coating the urothelium is the initial trigger for development of cystitis. In order to prevent and/or treat such conditions GAG replenishment therapy with CS, heparin, HA, and a new combination of CS and HA (Ialuril®) have been used.

Shao et al.[31] randomised 36 patients undergoing radiotherapy for gynaecological malignancies to receive either HA or hyperbaric oxygen therapy. They found no significant differences between the two groups in terms of haematuria, voiding frequency, or VAS pain at 6, 12, and 18 months after treatment, except for a decreased frequency of voiding at 12 months in the HA group. Sommariva et al.[32] studied the effects of intravesical HA+CS in patients with symptomatic late radiation tissue cystitis. In this 12-month, prospective, longitudinal, non-randomised, investigative pilot study, patients with severe haematuria received daily instillations 5 days/week in Month 1, 3 days/week in Month 2, 2 days/week in Month 3, once weekly in Months 4–6, every 2 weeks in Months 7–8, every 3 weeks in Months 9–10, and monthly/bimonthly for 1 year. Patients with or without occasional haematuria received instillations 3 days/week in Month 1, 2 days/week in Month 2, 1 day/week in Months 3–4, every 2 weeks in Months 5–6, every 3 weeks in Months 7–8, and monthly/bimonthly for 1 year. A total of 32 patients were enrolled. Authors found interesting results. Starting from a mean baseline of 66.9 mL, bladder capacity significantly increased to 101.9 mL at 3 months and to 174.4 mL at 12 months ($p<0.001$ for both versus baseline). Voiding frequency also significantly decreased from 14.6/day at baseline to 10.5 at Month 3 and 8.8 at Month 12 ($p<0.001$ for both versus baseline). Significant increases were observed after 3 and 12 months for the quality of life as measured by the European Quality of Life 5-Dimensions (EuroQol-5D) and the EuroQol-5D VAS.

Giannessi et al.[33] investigated a group of patients with cystitis and nocturia related to post-radiation bladder pain. This study evaluated the impact of HA+CS on symptoms and bother related to nocturia in men with bladder pain syndrome. Authors concluded that HA+CS was effective in reducing nocturia and related bother after radiotherapy. Gacci et al.[34] confirmed such results. Although bladder instillation treatment with a combination of HA and CS can be considered effective in reducing nocturnal voiding frequency

in men with post-radiation bladder pain following prostate cancer, RCTs with sham treatment are needed to extend and validate results.

BCG-induced chemical cystitis unresponsive to conventional therapies represents a considerable challenge for clinicians. While BCG is considered to be an effective treatment to reduce recurrence and progression of non-muscle-invasive bladder cancer, it is indeed associated with local treatment-related side effects that can lead to discontinuation or interruption.

Imperatore et al.[35] investigated the effect of treatment for BCG-induced chemical cystitis unresponsive to traditional treatments with intravesical administration of HA+CS. At all follow-up times, significant improvements were seen in VAS scores for pain and urgency, voids per 24 hours, and urine volume per void. Significant improvements were observed throughout the 12-week study period. These authors concluded that intravesical instillation of HA+CS is an efficacious strategy for refractory BCG-induced chemical cystitis with results that appear to be long-lasting.

Finally, Topazio et al.[36] investigated if sequential administration of HA could reduce the side effects related to BCG. A total of 30 consecutive subjects undergoing BCG intravesical administration for high-risk non-muscle-invasive bladder cancer were randomised to receive either BCG alone or BCG+HA. Mean VAS score for pain was significantly lower in the group receiving the combination of BCG+HA. International Prostate Symptom Score and number of daily micturitions were all significantly lower in the group receiving BCG+HA.

All these approaches are very interesting and could offer a real alternative or a new protective treatment to post-radiotherapy tissue damage. However, most of the studies are not RCTs and do not include a control group. For this reason, caution is necessary in interpreting them. Furthermore, some open issues remain. The undefined schedule treatment, the prevalence of male population, different types of tumours, and small sample size requires new information before the introduction of this treatment to clinical practice. Currently an international study using Ialuril®, IBSA for the prevention of post-radiation pelvic syndrome is ongoing and results are expected in the next months.

CONCLUSION

Robust evidence indicates that a defective urothelial barrier may underlie or be involved in the pathogenesis of several chronic bladder conditions, such as PBS/IC, recurrent UTIs, and chemical and radiation cystitis. These different clinical entities that were in the past considered distinct diseases can now be viewed as diseases caused as a result of the dysfunction of a common physiological element, the urothelium and associated GAG lining.

This renewed approach to looking at the pathophysiology of these GAG disorders will allow the development of more effective treatments for these debilitating and sometimes chronic diseases. Preliminary studies of the intravesical instillation of a combined solution containing a high concentration of HA and CS as GAG replacement therapy suggest that this formulation has efficacy potential in both UTIs and PBS/IC. Importantly, the safety profile of this combination has been reported to be very favourable, without adverse events of particular significance. New emerging oral formulations could be a non-invasive and complementary approach, although no evidence exists till now.

REFERENCES

1. Parsons CL. The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis. Urology. 2007;69(4 Suppl):9-16.

2. Hauser PJ et al. Abnormalities in Expression of Structural, Barrier and Differentiation Related Proteins, and Chondroitin Sulfate in Feline and Human Interstitial Cystitis. J Urol. 2015;194(2): 571-7.

3. Engles CD et al. Intravesical chondroitin sulfate inhibits recruitment of inflammatory cells in an acute acid damage "leaky bladder" model of cystitis. Urology. 2012;79(2);483.

4. Lazzeri M et al. Managing chronic bladder diseases with the administration of exogenous glycosaminoglycans: an update on the evidence. Ther Adv Urol. 2016;8(2):91-9.

5. Ciani O et al. Intravesical administration of combined hyaluronic acid (HA) and chondroitin sulfate (CS) for the treatment of female recurrent urinary tract infections: a European multicentre nested case-control study. BMJ Open. 2016;6(3):e009669.

6. Gacci M et al. Bladder Instillation Therapy With Hyaluronic Acid and Chondroitin Sulfate Improves Symptoms of Postradiation Cystitis: Prospective Pilot Study. Clin Genitourin Cancer. 2016. [Epub ahead of print].

7. Hurst RE et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis.

Urology. 1996;48(5):817-21.

8. Maggi CA, Meli A. The sensory efferent function of capsaicin-sensitive neurons. Gen. Pharmac. 1988;19(1):1-43.

9. Dinis P et al. Anandamide-evoked activation of vanilloid receptor 1 contributes to the development of bladder hyperreflexia and nociceptive transmission to spinal dorsal horn neurons in cystitis. J Neurosci. 2004;24(50): 11253-63.

10. Iavazzo C et al. Hyaluronic acid: an effective alternative treatment of interstitial cystitis, recurrent urinary tract infections, and hemorrhagic cystitis? Eur Urol. 2007;51(6):1534-40.

11. Laupland KB et al. Community-onset urinary tract infections: a population-based assessment. Infection. 2007;35(3):150-3.

12. Guay DR. Contemporary management of uncomplicated urinary tract infections. Drugs. 2008;68(9):1169-205.

13. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med. 2002;113 Suppl 1A:5s-13s.

14. European Association of Urology. EAU Guideline 2015. Available at: www.uroweb.org. Last accessed: 25 July 2016.

15. Sorlozano A et al. Evolution of the resistance to antibiotics of bacteria involved in urinary tract infections: a 7-year surveillance study. Am J Infect Control. 2014;42(10):1033-8.

16. Cervigni M et al. A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(7):943-7.

17. Damiano R et al. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. Eur Urol. 2011;59(4):645-51.

18. Constantinides C et al. Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: a pilot study. BJU Int. 2004;93(9):1262-6.

19. Lipovac M et al. Prevention of recurrent bacterial urinary tract infections by intravesical instillation of hyaluronic acid. Int J Gynaecol Obstet. 2007;96(3):192-5.

20. De Vita D et al. Prospective observational study of intravesical sodium hyaluronate and chondroitin sulfate in women with chronic cystitis, recurrent bacterial cystitis: preliminary data. 86th SIGO Congress, Milan, Italy, 14-17 November 2010.

21. Cicione A et al. Intravesical treatment with highly-concentrated hyaluronic acid and chondroitin sulphate in patients with recurrent urinary tract infections: Results from a multicentre survey. Can Urol Assoc J. 2014;8(9-10):E721-7

22. Morales A et al. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol. 1996;156:45-8.

23. Engelhardt PF et al. Long-term results of intravesical hyaluronan therapy in bladder pain syndrome/interstitial cystitis. Int Urogynecol J. 2011;22:401-5.

24. Hanno P et al., "Painful bladder syndrome (including interstitial cystitis)," Abrams PH et al., (eds.), Incontinence (2005) 3rd Edition, Paris: Health Publications Limited, pp.1456-520.

25. Steinhoff G et al. The efficacy of chondroitin sulphate 0.2% in treating interstitial cystitis. Can J Urol. 2002; 9(1):1454-8.

26. Nickel JC et al. A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulphate versus vehicle control in patients with interstitial cystitis/painful bladder syndrome. Urology. 2010;76(4):804-9.

27. Porru D et al. Impact of intravesical hyaluronic acid and chondroitin sulphate on bladder pain syndrome/interstitial cystitis. Int Urogynecol J. 2012;23(9): 1193-9.

28. Cervigni M et al. Intravesical hyaluronic acid and chondroitin sulphate for bladder pain syndrome/interstitial cystitis: Long-term treatment results. Int Urogynecol J. 2012;23(9):1187-92.

29. Cervigni M et al. A randomized, open-label, multicentre study of efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate (HA 1.6% and CS 2%) vs dimethyl sulfoxide (DMSO 50%) in women with Bladder Pain Syndrome/ Interstitial Cystitis (BPS/IC). Abstract 464. EAU Annual Meeting, Stockholm, Sweden, 2014.

30. Payne H et al. Chemical- and radiation-induced haemorrhagic cystitis: Current treatments and challenges. BJU Int. 2013;112:885-97.

31. Shao Y et al. Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. BJU Int. 2012;109(5):691-4.

32. Sommariva ML et al. Intravesical hyaluronic acid and chondroitin sulphate improve symptoms and quality of life in patients with late radiation tissue cystitis: An investigative pilot study. Eur J Inflammation. 2014;12:177-85.

33. Giannessi C et al. Nocturia related to post radiation bladder pain can be improved by hyaluronic acid chondroitin sulfate (Ialuril®). Abstract 592. Eur Urol Suppl. 2014;13:e592.

34. Gacci M et al. Sodium hyaluronate and chondroitin sulfate replenishment therapy can improve nocturia in men with post-radiation cystitis: results of a prospective pilot study. BMC Urol. 2015;15:65.

35. Imperatore V et al. Intravesical instillation of sodium hyaluronate–chondroitin sulfate in patients with bacillus calmette-guérin-induced chemical cystitis unresponsive to conventional therapies: Preliminary experience with 1 year follow-up. Eur Urol Suppl. 2014;13:e466.

36. Topazio L et al. Could hyaluronic acid (ha) reduce bacillus calmette-guerin (bcg) local side effects? Results of a pilot study. BMC Urol. 2014;14:64.

THE EVOLVING BIOSIMILAR LANDSCAPE: APPROVAL OF THE FIRST ETANERCEPT BIOSIMILAR IN EUROPE AN INTERVIEW WITH EMILIO MARTÍN-MOLA

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ABSTRACT

On January 14th 2016, SB4 (Benepali®) received marketing authorisation application approval from the European Commission (EC). It is the first biosimilar to etanercept available in Europe as well as the first subcutaneous anti-tumour necrosis factor biosimilar. Benepali® was approved for the treatment of rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic spondyloarthritis), and plaque psoriasis.

SB4 adds to the available biologic armamentarium of biosimilars in rheumatology, which also includes two infliximab biosimilars; one under the brand names Remsima® and Inflectra®, and the other under the brand name Flixabi®. Unlike infliximab biosimilar, which is a chimeric monoclonal antibody, SB4 is a fusion protein.

We aimed to review the current European Medicines Agency (EMA) requirements for the approval of biosimilars and how these products can integrate into daily clinical practice in rheumatology.

To that effect, we recently discussed with Dr Emilio Martín-Mola about the European framework for approval of biosimilars and the controversies that may surround this new category of medicinal products. We discussed how the advent of biosimilars in rheumatology has the potential to truly be a game-changer for both physicians and patients.

Keywords: Biosimilars, biologics, disease-modifying anti-rheumatic drugs (DMARDs), SB4 (Benepali®), entanercept (Enbrel®), rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondylitis, plaque psoriasis (PP), European Medicines Agency (EMA).

About Dr Emilio Martín-Mola

- Dr Emilio Martín-Mola is Head of the Rheumatology Unit at Hospital Universitario La Paz, Madrid, Spain.
- He has more than 35 years of experience in rheumatology, following a doctorate degree *cum laude* from the Faculty of Medicine of the University of Navarra, Pamplona, Spain.
- He is a member of various national and international scientific societies, including past tenures as President of the Spanish Society of Rheumatology (SER) and Executive Committee member and Treasurer of the European League Against Rheumatism (EULAR).
- Dr. Martín-Mola has authored more than 300 scientific articles for international journals and participated in EULAR consensus documents for the diagnosis and treatment of rheumatoid arthritis and osteoarthritis.

INTRODUCTION

In 2013, the European Commission (EC) approved CT-P13 (Remsima®/Inflectra®) as the first biosimilars to the reference infliximab (Remicade®). CT-P13 is the first monoclonal antibody (mAb) biosimilar approved by the EC (Table 1).[1,2]

Likewise, on January 14th 2016, SB4 (Benepali®) received marketing authorisation application (MAA) approval from the EC following a positive opinion from the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) in November 2015. Benepali® is the first biosimilar to etanercept available in Europe, as well as the first subcutaneous anti-tumour necrosis factor biosimilar.[3,4]

Benepali® was approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (ankylosing spondylitis [AS] and non-radiographic axial spondyloarthritis [nr-axSpA]), and plaque psoriasis (PP). This MAA applies to all 28 European Union (EU) member states as well as Norway, Iceland, and Liechtenstein.

Since the biologic armamentarium in rheumatology is rapidly expanding with these successive approvals of biosimilars, here we aim to review the current EMA requirements for the MAA of biosimilars and how these products can integrate into daily clinical practice in rheumatology.

To that effect, we recently discussed with Dr Emilio Martín-Mola about the European framework for biosimilar approval and the controversies that may surround this new category of medicinal products. We discussed how the advent of biosimilars in rheumatology has the potential to truly be a game-changer for both physicians and patients.

Table 1: Current biosimilar landscape in Europe for the treatment of rheumatic diseases.[1-5]

INN (Reference drug name)	Chemical structure	Mode of administration	Biosimilar brand name	Indications	MAA holder	EMA status
Etanercept (reference medicinal product, Enbrel®)	Human TNF receptor p75 Fc fusion protein produced by recombinant DNA technology in a CHO mammalian expression system	Subcutaneous (pre-filled syringe or pen)	Benepali® (SB4)	• RA • PsA • axSpA (AS and nr-axSpA) • PP	Samsung Bioepis	Approved MAA on 14th January 2016[3]
Infliximab (reference medicinal product, Remicade®)	Chimeric human-murine IgG1 mAb produced in murine myeloma cells by recombinant DNA technology	Powder for concentrate for solution for infusion	Remsima® (CT-P13)	• RA • AS • CD/UC (adult and paediatric) • PsA • PP	Celltrion Healthcare	Approved MAA on 10th September 2013
			Inflectra® (CT-P13)		Hospira UK Limited	Approved MAA on 10th September 2013
Infliximab (reference medicinal product, Remicade®)	Chimeric human-murine IgG1 mAb produced in CHO cells by recombinant DNA technology	Powder for concentrate for solution for infusion	Flixabi® (SB2)	• RA • AS • CD/UC (adult and paediatric) • PsA • PP	Samsung Bioepis	Approved MAA on 30th May 2016

AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; CD/UC: Crohn's disease/ulcerative colitis; CHO: chinese hamster ovary; IgG1: immunoglobulin G1; INN: international non-proprietary name; MAA: marketing authorisation application; mAb: monoclonal antibody; nr-axSpA: non-radiographic axial spondyloarthritis; PP: plaque psoriasis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; TNF: tumour necrosis factor.

Box 1: How are biosimilars defined? Key characteristics of biosimilars.

- A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicine (the 'reference medicinal product').[6]
- The World Health Organization (WHO) defines biosimilars as "biotherapeutic products that are similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product."[7]
- After the expiration of the patent period (usually 20 years after filing date of the patent application) of a licensed reference medicinal product, biosimilars can be marketed following a positive assessment of a marketing application by the European Medicines Agency (EMA).
- Available biosimilars in rheumatology are administered either through intravenous infusions or subcutaneous injections, since biological disease-modifying anti-rheumatic drugs (DMARDs) cannot be administered orally. Enzymes in the stomach degrade proteins.
- Since biosimilars are biologics, they inherit the variability of any biologic. This means that even minor changes in the manufacturing process may alter their biological function and/or immunogenicity profile. EMA takes rigorous measures to guarantee this will have no meaningful clinical impact.
- Post-translational alterations can occur in both reference medicinal products and biosimilars due to the use of different cell lines and manufacturing processes, resulting in products that are highly similar, but not identical.[8]
- As per EMA guidelines, a biosimilar must demonstrate biosimilarity based on a comprehensive comparability analysis to the reference medicinal product for the following criteria: quality characteristics, biological activity, safety, and efficacy.[9]
- The pre-authorisation procedures ensure that the differences between the reference medicinal product and the biosimilar have no relevant impact on safety or clinical efficacy.[9]

Box 2: How do biosimilars differ from generics?

- Due to their complexity in production and the nature of the products, biosimilars cannot be compared to generic drugs.
- Indeed, a generic drug is usually a chemical compound that is very easy to synthesise by pharmaceutical companies. On the contrary, a biosimilar is a biological product, usually a protein with a much higher molecular weight (200–1,000 times the size of a chemical compound).[10]
- As opposed to chemically-synthesised medicines, biologics and biosimilars are manufactured in living cells, extracted, then purified, which complicates the manufacturing processes and large-scale production.[11,12] Furthermore, the conformational structure of a protein is fragile, requiring special handling and storage to reduce the risk of adverse events and immune responses.

INTERVIEW WITH DR EMILIO MARTÍN-MOLA

Caroline Charles (CC): Good afternoon Dr Martín-Mola, let us talk on the advent of biosimilars in rheumatology. First, can you elaborate on the process of the clinical development programme of a biosimilar in the European context?

Emilio Martín-Mola (EMM): The clinical development programme of a biosimilar is different from that of a reference medicinal product (Table 2). Specific evaluation pathways for biosimilars have been developed by the EMA.

The EMA defines biosimilars as: "Biological medicinal products that contain a version of the active substance of an already authorised, original biological medicinal product (reference medicinal product). A biosimilar agent is similar to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise."[6]

EMA guidance documents contain both non-clinical and clinical requirements and all translate into one single objective: to ensure that the biosimilar has no clinically meaningful differences from the originator.

At the inception of biosimilar development is an extensive analytical comparability exercise and characterisation to demonstrate that the biosimilar

is highly similar for all critical quality attributes, for example, in terms of physicochemical attributes and mode of action/non-mode of action-related biological activity. Analytical data are key to establishing biosimilarity, since the conformational structure of a protein influences its binding affinity to the target, thus potentially impacting clinical efficacy and safety.

Manufacturing a biosimilar mainly comprises circular iterations based on non-clinical physicochemical and biological characterisation to refine such structural considerations (Figure 1). The *in vitro* testing steps are usually more extensive than those required for the development of a reference medicinal product, so as to compare the results of receptor binding, cell proliferation, and cell potency assays with the targeted reference medicinal product.

Then, non-clinical animal testing (if needed) can be conducted in order to establish a comparative pharmacokinetics profile, though the latter is usually ascertained in clinical Phase I studies in healthy volunteers or patients. Finally, clinical comparative Phase III studies, namely equivalence design trials, are conducted to establish efficacy and safety comparability with the reference medicinal product in one sensitive indication that has been agreed with the EMA.

Following MAA, pharmacovigilance plans and post-marketing studies are required as they are for the reference medicinal product. These steps aim to detect any late developing adverse events (AEs) and additional immunogenicity aspects.

CC: What evidence is needed for the EMA to grant approval of an advanced biosimilar medicine such as a monoclonal antibody or fusion protein?

EMM: The EMA has published several general and specific guidelines for the development of biosimilars (Table 3). The criteria and processes can be applicable to all biosimilars in development or to a specific therapeutic class (e.g. mAbs). Such a framework is essential to provide manufacturers with guidance to establish similarity in terms of quality, safety, and efficacy. These regulatory pathways and processes are, in my opinion, absolutely acceptable as they are now.

CC: Certain clinicians have expressed some fears over the approval and use of biosimilars in Europe. Why is that and what is your personal opinion on the matter?

EMM: Biosimilars can be confused with what we call 'intended copies' or 'biomimics' that exist in countries with less stringent regulation (i.e. some Latin American countries, India, China).

Table 2: Is the development programme of a biosimilar different from that of its reference biologic? Overview of European Medicines Agency biosimilar regulatory guidelines.[13-15]

Non-clinical aspects	• Target binding, signal transduction, functional activity/viability of cells of relevance must be evaluated • If *in vitro* comparability is satisfactory, animal studies may not be required • Potency must be the same as the reference medicinal product • Route of administration (galenics) must be the same as the reference medicinal product • Higher-order structures, post-translational modifications must be as similar as possible, and demonstrate no impact on the clinical efficacy and safety
Clinical aspects	Comparability confirmed by a stepwise process: • Pharmacokinetics: the biosimilar should be used at the same dose as the reference product (Phase II studies are not needed because dose-response was established for the reference product) • Pharmacodynamics (if feasible) • Clinical efficacy and safety (Phase I/III) (in a sensitive indication and sensitive population)
Naming	• Commercial name, appearance, and packaging should differ from reference product • INN should be the same for related reference medicinal product
Pharmacovigilance	• Risk management pharmacovigilance plan (as for any biologic, i.e. reference medicinal products or biosimilars) must be submitted • Clinical safety monitored closely after MAA approval

INN: international non-proprietary name; MAA: market authorisation approval.

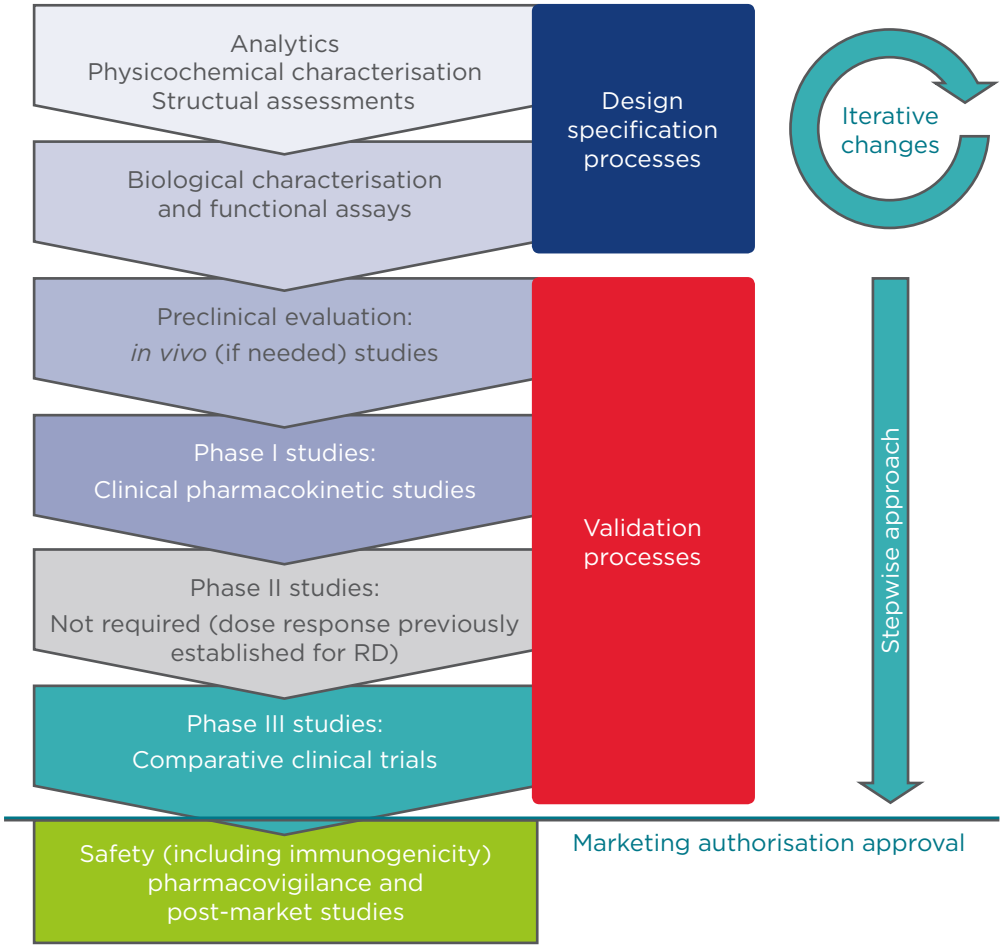

Figure 1: General development steps for biosimilars in Europe.
RD: rheumatic disease.
Modified from McCamish and Woollett.[16]

I think that apprehension might stand in some cases for the confusion between copies and biosimilars. But intended copies have nothing to do with biosimilars: copies have been used in Latin American countries for several years prior to the establishment of regulatory guidelines, thus without robust clinical trials and thorough evaluation as we see now for European MAA of biosimilars. Some of the copies are still on the market in some Latin American countries as well as in India and China, and unsurprisingly, local rheumatologists have observed some safety issues.[14,17]

I believe these fears also come from the fact that studies for biosimilars are often conducted in only one indication, i.e. RA. I can understand how gastroenterologists could be sceptical about the use of a biosimilar in Crohn's disease (CD) when the equivalence studies have been conducted only in RA. On one hand, determination of the key disease in which to conduct a clinical equivalence or non-inferiority Phase III trial for the development of a biosimilar is a difficult and challenging decision that should be discussed and agreed with the EMA. On the other hand, for a biologic that has several different indications, it is absolutely impossible to conduct many different clinical trials simultaneously.

Extrapolation is a concept adopted by the EMA as part of their biosimilar approval process to respond to this impossibility of conducting, as an example, eight Phase III trials for the approval of an infliximab biosimilar. The rationale set forth by the EMA is that a reference indication can be extrapolated if the mechanism of action for all indications is the same, among several other considerations.[6] In rheumatology, the reference disease to conduct such studies so far has been RA, but some authors have claimed that other rheumatologic diseases or even plaque psoriasis should be the reference disease for Phase III biosimilar studies.

Table 3: European Medicines Agency Guidelines relevant for biosimilar approval processes in rheumatology.

Overarching biosimilar guidelines (all biosimilar products)	**Guideline on similar biological medicinal products**[6] CHMP/437/04 Rev 1 (30 April 2015) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf **Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues**[13] EMEA/CHMP/BMWP/42832/2005 Rev1 (1 July 2015) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf **Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues** EMA/CHMP/BWP/247713/2012 Rev.1 (1 December 2014) www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf
Product-specific guidelines	**Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues** EMA/CHMP/BMWP/403543/2010 (1 December 2012) www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf
Other guidelines relevant for biosimilars	**Comparability of biotechnological/biological products ICH Topic Q 5 E** CPMP/ICH/5721/03 (June 2005) www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002805.pdf **Comparability of biotechnology-derived medicinal products after a change in the manufacturing process: non-clinical and clinical issues** EMEA/CHMP/BMWP/101695/2006 (1 November 2007) www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003935.pdf **Immunogenicity assessment of biotechnology-derived therapeutic proteins** EMEA/CHMP/BMWP/14327/2006 (April 2008) www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003946.pdf **Immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use** EMEA/CHMP/BMWP/86289/2010 (1 December 2012) www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099362.pdf
Draft guidelines (under public consultation) relevant for biosimilars	**Draft guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins** EMEA/CHMP/BMWP/14327/2006 Rev. 1 www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf **Draft concept paper on the need for a reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development** EMA/297149/2013 www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144945.pdf

CHMP: Committee for Medicinal Products for Human Use; EMEA: European Agency for the Evaluation of Medicinal Products; BMWP: Biosimilar Medicinal Products Working Party; EMA: European Medicines Agency; CPMP: Committee for Medicinal Products; ICH: International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

CC: Can you elaborate on the topic of extrapolation?

EMM: The argument that states that the behaviour of the drug should be similar in all the indications is very simple. Extrapolation of safety and efficacy has emerged as an important way to simplify biosimilar development. However, a few issues happened with the biosimilar for infliximab. It was shown that CT-P13 had a lower *in vitro* antibody-dependent cell-mediated cytotoxicity (ADCC). That was the only difference between the reference product and this biosimilar.

The EMA did not consider this difference relevant and extrapolated the indications of this biosimilar to inflammatory intestinal diseases. However, the EMA required that the company perform a randomised double-blind study in patients with CD

and a prospective observational study to assess the effectiveness and safety of this drug in CD and ulcerative colitis (UC).

Initially, Health Canada, the regulatory agency from Canada, based on these *in vitro* studies, did not approve the extrapolation for inflammatory intestinal diseases. However, following a review of additional data, Health Canada very recently approved the infliximab biosimilar Inflectra in three extra indications, namely CD, fistulising CD, and UC.[18]

Furthermore, both the US Food and Drug Administration (FDA) and the Australian regulatory agency, the Therapeutic Goods Administration (TGA), recently approved the extrapolation for the same diseases that the EMA did.[19,20]

CC: How do you see this evolving?

EMM: Eventually, clinicians will overcome these unfounded concerns. Once a drug has been approved by the EMA as a biosimilar, there is no reason not to be confident with it, because the steps and the regulatory processes are both numerous and stringent, and ensure security of use. I think those fears stem from a lack of education in the process of biosimilar approval: specialists in Europe should be better informed about the processes and the numerous steps and checkpoints set in place to ensure biosimilar quality, efficacy, and safety.

Of course, we also have to keep in mind that over time pharmaceutical companies have gained the trust of physicians due to their solid history with the patented originator drug. Some physicians may want to rely on the reference medicinal product, but I think medical education on biosimilars is crucial to making physicians more confident about using biosimilars.

CC: Are there any other topics of discussion on biosimilars?

EMM: Some patients generate an immune response to biologics (characterised by the production of anti-drug antibodies [ADAs]), which can potentially limit clinical efficacy and increase the risk of AEs.

Box 3: Main SB4 clinical and safety data from equivalence study with Enbrel®.

- The clinical and safety outcomes of SB4 were evaluated in a Phase III, randomised, double-blind, parallel-group, multicentre equivalence study,[25] which included 596 patients with moderate-to-severe active rheumatoid arthritis (RA) despite methotrexate therapy, randomised 1:1 to receive a weekly dose of 50 mg SB4 subcutaneously (n=299) or etanercept reference medicinal product (n=297).[23]
- SB4 resulted in equivalent primary endpoint American College of Rheumatology ACR20 response rates at Week 24 compared to Enbrel.®
- The ACR20 was 78.1% for SB4 and 80.3% for the reference medicinal product (per-protocol patient set from the final analysis set). The 95% confidence interval of the adjusted treatment difference was −9.41% to 4.98%, which was well contained within the predefined equivalence margin of −15% to +15%, indicating therapeutic equivalence between both products. Other efficacy endpoints and pharmacokinetic endpoints were comparable.
- The incidence of treatment emergent adverse events at Week 24 was comparable between both arms (55.2% in SB4 versus 58.2% in Enbrel®). Both drugs were well tolerated.
- The immunogenicity profiles appeared to be significantly different (incidence of anti-drug antibody development up to Week 24 was 0.7% versus 13.1% in SB4 compared with etanercept), but according to the European Public Assessment Report (EPAR), this was considered to have minimal clinical significance.[4]
- After a 52-week follow-up, the ACR20 response rate was 80.8% in the SB4 arm and 81.5% in the reference medicinal product arm.[26] The safety and efficacy of continuing SB4 and transitioning from reference etanercept to SB4 was evaluated in an open-label, 48-week extension study period. The results were reported at EULAR 2016.[27] Data showed comparable safety, immunogenicity, and efficacy between patients who continued receiving SB4 and those who transitioned from the reference product to SB4. SB4 was well-tolerated and effective over the 2-year period in patients with moderate-to-severe RA. This 48-week extension transition study provided clear evidence that switching from reference etanercept to SB4 produced no new treatment emergent issues, such as an increase in adverse events, an increase in immunogenicity, or loss of efficacy. These and other coming data will further increase our knowledge and confidence of switching patients from reference products to biosimilars.[27,28]

Immunogenicity is a crucial issue for all biologics; any therapeutic protein injected in the body can be immunogenic. These ADAs can be neutralising (i.e. suppress the drug's activity by competing with the binding site for tumour necrosis factor or other targets and lead to a clinical non-response) or non-neutralising (not affecting the drug's efficacy). One of the requirements of the EMA for biosimilar approval is that the biosimilar must have the same or lower immunogenicity profile as the reference medicinal product. Both the etanercept reference medicinal product and SB4 have a low immunogenicity profile with non-neutralising ADAs.

We also have to be careful with interchangeability issues. When a biosimilar is available, patients may be switched from a reference medicinal product to a biosimilar or the other way around. In this context, when a patient is started on a biologic therapy, it would be wise to treat from the beginning either with a biosimilar or a reference medicinal product, because if we interchange therapies and AEs occur, it might be difficult or impossible to establish which of both drugs is responsible. We need safety data of interchangeability and at present, in Norway and Denmark, studies are being conducted on interchangeability safety. Until these data are available to guide us, it could be wise to keep giving the same drug that the patient received since the beginning of treatment. Of note, the Spanish Society of Rheumatology (SER) stated that until pharmacovigilance practices improve, we should be prudent in all decisions related to interchangeability concerns.[21]

I anticipate biosimilars to be integrated into current treatment algorithms just as well as reference medicinal products, and as first-line treatment choices in treatment-naïve patients due to healthcare costs, so as to 'bypass' switching issues right from the start.

CC: Benepali® (SB4) has recently been approved as a biosimilar of etanercept. What data are available to show equivalence to the reference etanercept (Enbrel®)?

EMM: SB4 (Benepali®) is a biosimilar to etanercept reference medicinal product (trade name, Enbrel®) and is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system. Pharmacokinetic equivalence was demonstrated in a Phase I study conducted in healthy male subjects.[22]

SB4 exhibits similar structural, physiochemical (except for a single amino acid), and biologic properties and has demonstrated therapeutic equivalence to etanercept reference medicinal product.[4,23,24] The clinical outcomes of SB4 were demonstrated as equivalent to its reference medicinal product, Enbrel®, in a Phase III clinical trial (Box 3).

CC: How will biosimilars, such as Benepali®, be used in rheumatology clinical practice?

EMM: Since etanercept is an excellent drug for RA with a very good track record and is well known by physicians, I think its biosimilar, Benapali®, will be a success and, because of the reduced prices, it will drive down healthcare costs for both patients and healthcare payers. This will undoubtedly increase patient access to biologics and the number of patients receiving a biotherapy in rheumatology will be expanded. This drug should increase the access to biologics in countries where, for economic reasons, there are restrictions to receive biologics.

CC: What benefits will biosimilars bring to rheumatologists? Do you anticipate biosimilars to change the treatment landscape for patients with rheumatic diseases?

EMM: As of now, in Europe, three advanced biosimilars have been approved, but physicians can expect several other biosimilars on the market in the next few years due to the expiration of many patents for biologics, including some used in rheumatic diseases.

I think biosimilars will change the landscape of the management of rheumatic diseases, since these drugs are disease-modifying anti-rheumatic drugs. The introduction of high-quality, well-tolerated, and effective biosimilars has the potential to increase access to biotherapies and, as patients from a wider demographic will receive proper treatment, stringent regulatory pathways will ensure continuity without reducing the quality of care. Since patients with rheumatic diseases are prescribed long-term treatment with individualised drug regimes, biosimilars will undoubtedly change the clinical landscape and help close the affordability gaps of biologics access.

REFERENCES

1. European Medicines Agency. Summary of the European public assessment report (EPAR) for Remsima. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002576/human_med_001682.jsp&mid=WC0b01ac058001d124. Last accessed: 19 July 2016.

2. European Medicines Agency. Summary of the European public assessment report (EPAR) for Inflectra. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002778/human_med_001677.jsp&mid=WC0b01ac058001d124. Last accessed: 19 July 2016.

3. Samsung Bioepis. Samsung Bioepis Enters the European Biopharmaceutical Market with Benepali®, the First Fusion Protein Biosimilar Approved by the European Commission. Available at: http://www.businesswire.com/news/home/20160116005013/en/Samsung-Bioepis-Enters-European-Biopharmaceutical-Market-Benepali%C2%AE. Last accessed: 19 July 2016.

4. European Medicines Agency. Summary of the European public assessment report (EPAR) for Benepali. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004007/human_med_001944.jsp&mid=WC0b01ac058001d124. Last accessed: 19 July 2016.

5. European Medicines Agency. Summary of the European public assessment report (EPAR) for Flixabi. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004020/human_med_001980.jsp&mid=WC0b01ac058001d124. Last accessed: 19 July 2016.

6. European Medicines Agency. Guideline on similar biological medicinal products CHMP/437/04 Rev 1. 30 April 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf. Last accessed: 20 July 2016.

7. World Health Organization; Expert Committee on Biological Standardization. Guidelines on evaluation of similar biotherapeutic products (SBPs). 2009. Available at: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf. Last accessed: 20 July 2016.

8. Dorner T et al. The role of biosimilars in the treatment of rheumatic diseases. Ann Rheum Dis. 2013;72(3):322-8.

9. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. (EMEA/CHMP/BMWP/42832/2005). 22 February 2006. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf. Last accessed: 20 July 2016.

10. Kozlowski S et al. Developing the nation's biosimilars program. N Engl J Med. 2011;365(5):385-8.

11. Dranitsaris G et al. Biosimilars of biological drug therapies: regulatory, clinical and commercial considerations. Drugs. 2011;71(12):1527-36.

12. Crommelin DJ et al. Shifting paradigms: biopharmaceuticals versus low molecular weight drugs. Int J Pharmaceutics. 2003;266(1-2):3-16.

13. European Medicines Agency; Committee for Medicinal Products for Human Use (CHMP) (2014). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf. Last accessed: 20 July 2016.

14. Mysler E et al. Clinical and regulatory perspectives on biosimilar therapies and intended copies of biologics in rheumatology. Rheum Int. 2016;36(5):613-25.

15. McCamish M, Woollett G. Worldwide experience with biosimilar development. mAbs. 2011;3(2):209-17.

16. McCamish M, Woollett G. The state of the art in the development of biosimilars. Clin Pharmacol Ther. 2012;91(3):405-17.

17. Barile-Fabris LA et al. Incidence of adverse events in patients treated with intended copies of biologic therapeutic agents in Colombia and Mexico. Abstract 1506. American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting, Boston, Massachusetts, USA, 11-16 November 2014.

18. Generics and Biosimilars initiative. Health Canada approves Inflectra biosimilar for extra indications. Available at: http://gabionline.net/Biosimilars/News/Health-Canada-approves-Inflectra-biosimilar-for-extra-indications. Last accessed: 29 June 2016.

19. Celltrion. FDA's Arthritis Advisory Committee Recommends Approval of Celltrion's CT-P13, a Proposed Biosimilar Infliximab, for All Indications. Available at: http://www.businesswire.com/news/home/20160209006848/en/FDA%E2%80%99s-Arthritis-Advisory-Committee-Recommends-Approval-Celltrion%E2%80%99s. Last accessed: 19 July 2016.

20. Generics and Biosimilars initiative Australian approval for infliximab biosimilar. Available at: http://www.gabionline.net/Biosimilars/General/Australian-approval-for-infliximab-biosimilar. Last accessed: 19 July 2016.

21. Abad Hernández MÁ et al. Position paper from the Spanish Society of Rheumatology on biosimilar drugs. Reumatol Clin. 2015;11(5):269-78.

22. Lee YJ et al. A randomized phase I pharmacokinetic study comparing SB4 and etanercept reference product (Enbrel®) in healthy subjects. Br J Clin Pharmacol. 2016;82(1):64-73.

23. Emery P et al. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2015. [Epub ahead of print].

24. Cho IH et al. Evaluation of the structural, physicochemical, and biological characteristics of SB4, a biosimilar of etanercept. mAbs. 2016. [Epub ahead of print].

25. Samsung Bioepis Co., Ltd. A Study Comparing SB4 to Enbrel® in Subjects With Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy. NCT01895309. https://clinicaltrials.gov/ct2/show/NCT01895309.

26. Samsung Bioepis Co., Ltd. Samsung Bioepis Receives Positive CHMP Opinion for the First Etanercept Biosimilar in the European Union. Available at: http://www.businesswire.com/news/home/20151120005300/en/Samsung-Bioepis-Receives-Positive-CHMP-Opinion-Etanercept. Last accessed: 19 July 2016.

27. Emery P et al. Long-term safety and efficacy of SB4 (etanercept biosimilar) in patients with rheumatoid arthritis: comparison between continuing SB4 and switching from etanercept reference product to SB4. Ann Rheum Dis. 2016;75(Suppl 2):236.

28. Generics and Biosimilars initiative. Samsung adds 48-week extension to SB4 biosimilar study. Accessible at: http://www.gabionline.net/Biosimilars/News/Samsung-adds-48-week-extension-to-SB4-biosimilar-study. Last accessed: 19 July 2016.

LATE AND VERY LATE STENT THROMBOSIS IN THE ERA OF SECOND-GENERATION DRUG-ELUTING STENTS

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ABSTRACT

Stent thrombosis is a life-threatening complication of percutaneous coronary intervention that often results in ST-segment myocardial infarction or sudden cardiac death. First-generation drug-eluting stents (DESs) are associated with an increased risk of late and very late stent thrombosis compared with bare-metal stents due to delayed endothelialisation of the stent struts. The second-generation DES design includes a number of improved features (thinner stent struts, fluorinated copolymers, and different anti-proliferative agents) to decrease the risk of late stent thrombosis. Currently, the cobalt-chromium everolimus-eluting stent, a second-generation stent, has the lowest risk of stent thrombosis when compared with the available alternatives. Given the improved design of second-generation stents, a shorter duration of dual antiplatelet therapy of 6 months may be enough to reduce the rate of bleeding complications without increasing the risk of adverse cardiovascular events. Future large-scale randomised trials are required to evaluate the safety and efficacy of third-generation DESs which feature bioresorbable polymers and scaffolds.

Keywords: Stent thrombosis, drug-eluting stent (DES).

INTRODUCTION

Percutaneous coronary intervention (PCI) is a common procedure performed worldwide as part of the treatment for coronary artery disease. In the UK alone, 92,589 PCIs were performed in 2013 (1,444 per million annually), with drug-eluting stents (DESs) used in 82% of PCIs perfomed.[1] While the first-generation DESs (Cypher® sirolimus-eluting stents [C-SES] and Taxus® paclitaxel-eluting stents [PESs]) significantly reduced the restenosis rates compared with bare-metal stents (BMSs),[2] there was concern regarding the resulting increased rate of late and very late stent thrombosis.[3,4]

Stent thrombosis is a potentially life-threatening complication of PCI that often causes acute closure of the vessel and, as a result, can cause ST-segment elevation myocardial infarction or sudden cardiac death. Despite rapid access to PCI, stent thrombosis is associated with a high 30-day mortality rate of 10–25%.[5] Though a rare complication, given the large number of PCIs performed annually, the absolute number of patients with stent thrombosis is substantial. The concern relating to risk of late stent thrombosis with first-generation DESs prompted the development of second-generation DESs using different drugs (everolimus or zotarolimus), different stent platforms (thinner stent struts), and a more biocompatible polymer. This article will summarise the existing literature regarding the relative risk of stent thrombosis with second-generation DESs and review the optimal duration of dual antiplatelet therapy (DAPT) to reduce the risk of stent thrombosis in the era of second-generation DESs.

Definition of Stent Thrombosis

In order to standardise the definition of stent thrombosis, the Academic Research Consortium (ARC) was formed in 2007 as part of a collaborative effort between the academic research organisations in the USA and Europe.[6] Stent thrombosis was categorised based on the certainty of evidence from angiographic and pathological data as 'definite' (confirmed by angiography in addition to clinical or pathological acute coronary

syndrome), 'probable' (any unexplained death ≤30 days after stent placement or myocardial infarction documented in a territory of the implanted stent without angiographic confirmation), or 'possible' (unexplained death ≤30 days of intracoronary stenting). Based on the timing of occurrence, stent thrombosis can be classified as acute (≤24 hours), sub-acute (between 24 hours and 30 days), late (30 days–1 year), and very late (≥1 year).[6]

Mechanism and Pathophysiology of Late Stent Thrombosis

The pathophysiology of late stent thrombosis in first-generation DESs is related to chronic inflammation, persistent fibrin deposition, and delayed arterial healing, resulting in incomplete endothelialisation of the stent struts into the arterial wall.[7] First-generation DESs are covered with potent anti-proliferative agents such as sirolimus and paclitaxel. These drugs impede the smooth muscle cell proliferation, suppress neointimal formation, and delay the normal healing process of the injured arterial wall.[7] Hence, the percentage of uncovered stent struts exposed directly to the blood stream and serving as a nidus for thrombus formation, is higher after implantation of DESs.

In order to determine the pathological correlates of late stent thrombosis, Finn et al.[8] studied 62 coronary lesions from 46 human autopsy cases with first-generation DESs implanted for >30 days. Endothelial coverage was noted as the most significant histological predictor of stent thrombosis.[8] The average stent length without neointimal coverage was significantly higher in thrombosed DESs lesions.[8] The odds ratio (OR) for thrombosis was 9.0 (95% confidence interval [CI]: 3.5–22.0) for a stent with >30% uncovered struts compared with a stent with complete coverage.[8]

Incomplete, non-uniform healing of the injured arterial wall following DES implantation is triggered by several factors: lesion characteristics, drug properties, total drug dose, drug release profile and distribution, and polymer biocompatibility.[7] In a study of 127 patients with sirolimus or paclitaxel coated stents who died >30 days after implantation, incomplete stent strut coverage was more frequently noted in stents deployed in bifurcation lesions, bypass grafts, restenosed lesions, chronic total occlusions, left main lesions, or lesions >30 mm.[9]

In summary, the underlying mechanism of late stent thrombosis after DES implantation relates to delayed arterial healing, chronic inflammation, fibrin deposition, and impaired endothelialisation of the stent struts. However, the final triggering event is governed by multiple factors including lesion type, the drug, and stent characteristics as described above.

Features of Second-Generation Drug-Eluting Stents Contributing to Decreased Risk of Late Stent Thrombosis

Second-generation DESs have been designed with specific features to overcome the issue of delayed endothelialisation noted with first-generation DESs (Figure 1). The current US Food and Drug Administration (FDA)-approved DESs with specific design features are listed in Figure 2.

Thinner stent struts

Second-generation stents have thinner stent struts (81–91 μm) compared with the first-generation stents (100–140 μm). In a study of 72 patients with *de novo* lesions undergoing DESs implantation, using optical coherence tomography, Tada et al.[10] showed that the number of uncovered struts was significantly higher with thick strut DESs than with thin strut DESs at 6–8 months. In another study using *ex vivo* flow set up to study device thrombogenicity, Kolandaivelu et al.[11] demonstrated that thicker stent struts were 49% more thrombogenic as they caused flow disruption and stagnation. In order to reduce strut thickness while preserving the radial strength and radio opacity of the stents, newer alloys were used in second-generation DESs (chromium cobalt: Xience V®, Xience Prime™, Endeavor®, and Resolute™; and platinum chromium: Promus Element®) instead of the stainless steel used in first-generation DESs.

Fluorinated copolymer

Hypersensitivity reactions to non-erodible polymers used in first-generation DESs (poly[ethylene-co-vinyl acetate] and poly-n-butyl methacrylate in the Cypher stent, and poly[styrene-3-isobutylene-8-styrene] in the Taxus stent) resulted in chronic inflammation with eosinophil deposition, causing delayed healing and late or very late stent thrombosis.[7,12-14] More biocompatible polymers (e.g. fluorinated copolymer consisting of vinylidene fluoride and hexafluoropropylene in Xience everolimus-eluting stents [EESs], and phosphorylycholine in Endeavor zotarolimus-eluting stents [E-ZES]) are used in second-generation DESs to decrease the hypersensitivity

response.[7,15-17] In an autopsy study consisting of 204 lesions, the cobalt-chromium everolimus-eluting stent (CoCr-EES) showed a lower inflammation score with no hypersensitivity, decreased fibrin deposition, and a lower rate of late and very late stent thrombosis compared with SESs and PESs.[14]

Difference in anti-proliferative drugs

The first-generation DESs used either sirolimus (also known as rapamycin) or paclitaxel as the anti-proliferative agent. Sirolimus is a macrolide antibiotic that binds to FK506-binding protein 12 and blocks the mammalian target of rapamycin.[16] The G1/S phase transition in the cell cycle is blocked, resulting in inhibition of smooth muscle migration and proliferation. Paclitaxel inhibits the mitotic process, blocking the transition from G2 to G1 phase by stabilising the microtubules and preventing depolymerisation.[16]

The second-generation stents use different anti-proliferative agents: everolimus (Xience V, Xience Prime, and Promus Element) and zotarolimus (Endeavor and Resolute). Everolimus is a hydroxyethyl derivative of sirolimus and has a similar mechanism of action.[16] However, the dose of everolimus used in the CoCr-EES is lower than that of sirolimus (88 µg for a 3.0x18.0 mm stent versus 150 µg of sirolimus for the same stent).[17]

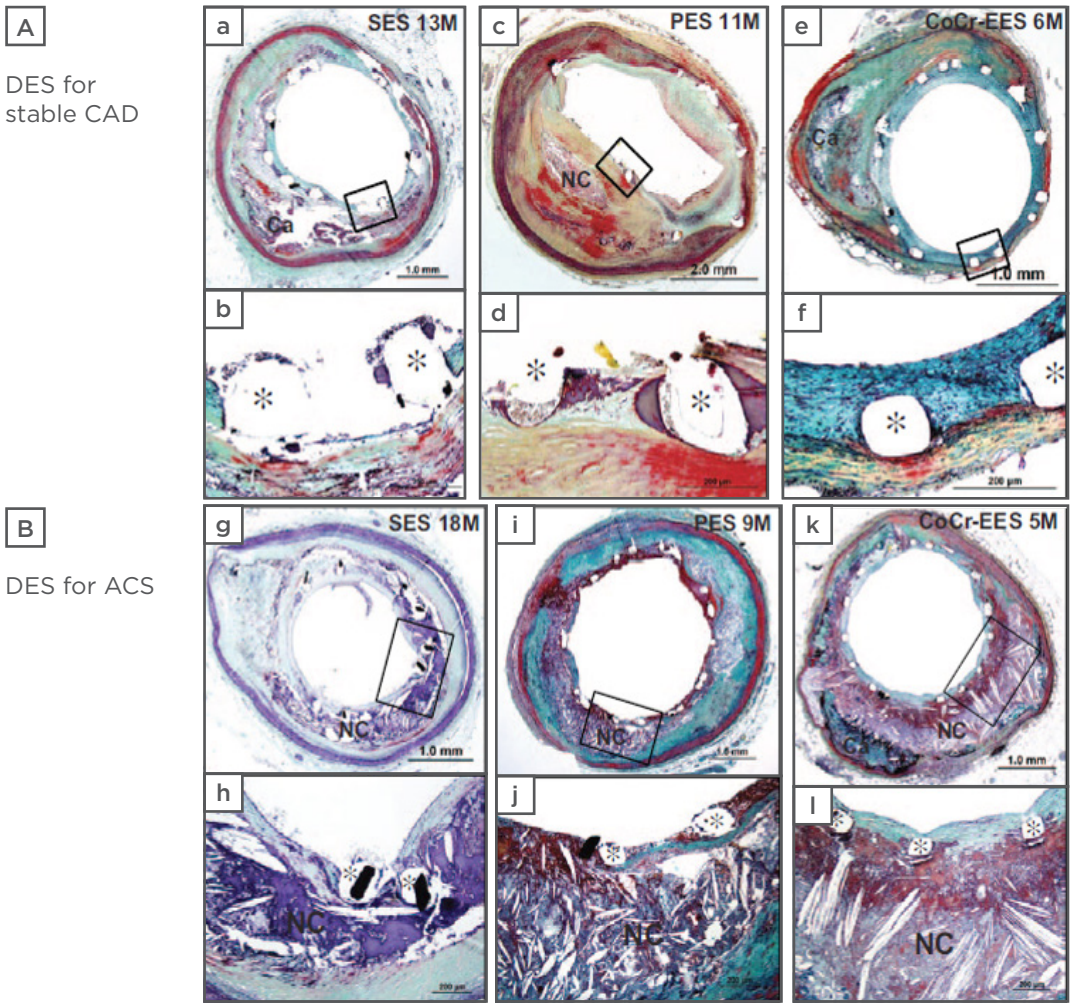
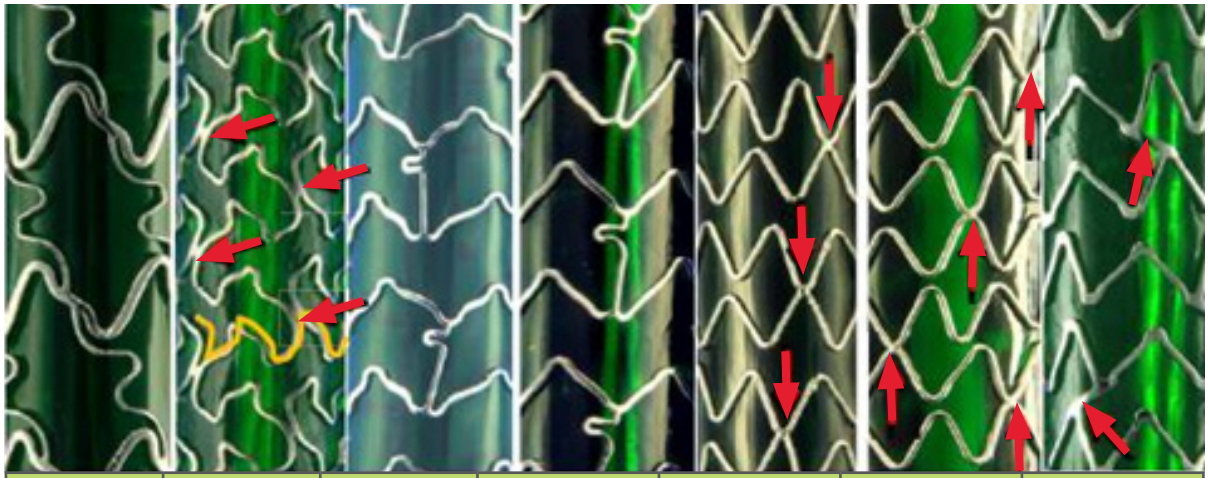


Figure 1: Histopathology comparing first and second-generation drug-eluting stents.
Representative images of sirolimus-eluting stents (SESs), paclitaxel-eluting stents (PESs), and cobalt-chromium everolimus-eluting stents (CoCr-EESs) implanted for: A (a–f): stable coronary artery disease (CAD); and B (g–l): acute coronary syndrome (ACS). Histology sections from:
(a, b): a 53-year-old patient with an SES implanted in the proximal left anterior descending coronary artery at 13 months. a) Low power image showing mild neointimal growth and underlying fibrocalcific plaque. b) High power image showing focal uncovered struts.
(c, d): a 71-year-old man with a PES implanted in the right coronary artery 11 months *antemortem*. c) Low power image showing mild-to-moderate neointimal proliferation and underlying fibroatheroma. d) High power image showing uncovered struts with persistent peri-strut fibrin deposition shown.

(e, f): a 60-year-old man who received a CoCr-EES in the mid left circumflex artery 6 months *antemortem*. e) A low power image showing mild neointimal proliferation and underlying fibrocalcific plaque. All struts are covered with proteoglycan-rich neointima with absence of fibrin, highlighted in f), a high-power image.
(g, h): a 74-year-old woman who received a SES in the proximal left anterior descending coronary artery for acute myocardial infarction 18 months *antemortem* and died of diffuse severe CAD. g) A low-power image showing mild neointimal proliferation with h) focal uncovered struts and strut penetration into the necrotic core (NC).
(i, j): a 64-year-old woman with a PES implanted in the right coronary artery for acute myocardial infarction 9 months *antemortem* who died of congestive heart failure. i) A low power image shows patent lumen with stent struts surrounded by fibrin and an underlying NC. j) Uncovered struts with fibrin deposition that overlie the NC.
(k, l): a 67-year-old man who received a CoCr-EES in the proximal left anterior descending coronary artery for non-ST segment elevation acute myocardial infarction 5 months *antemortem* who died of non-cardiac causes. k) A low-power image showing mild neointimal proliferation and an underlying large NC.
All struts are covered with a thin neointima overlying the NC, highlighted in the high-power image in l).
Histological sections stained with Movat pentachrome.
*Stent strut.
DES: drug-eluting stent.
Used with permission, taken from Otsuka F et al.[14]



Cyper Select	Liberte	Vision Xience V	MultiLink 8 Zience Prime	Driver Endeavor	Integrity Resolute	Omega Promus Elem
First-generation	First-generation	Second-generation	Second-generation	Second-generation	Second-generation	Second-generation
Stainless steel	Stainless steel	Cobalt chromium	Cobalt chromium	Cobalt chromium	Cobalt chromium	Platinum chromium
140 µm	100 µm	81 µm	81 µm	91 µm	91 µm	81 µm
Sirolimus	Paclitaxel	Everolimus	Everolimus	Zotarolimus	Zotarolimus	Everolimus
PEVA and PBMA polymers	SIBS triblock copolymer	Fluorinated copolymer	Fluorinated copolymer	Polyphosphorylcholine	BioLinx polymer	Fluorinated copolymer

Figure 2: Comparison of various features of currently approved drug-eluting stents.
Photographs of stent designs and names and the metal they are constructed from, strut thickness in microns, anti-proliferative agent, and the polymer used in each stent. Red arrows represent the welds between the sinusoidal hoops of the stent struts.
PEVA: poly(ethylene-vinyl acetate); PBMA: poly(butyl methacrylate); SIBS: styrene-b-isobutylene-b-styrene.
Modified from Ormiston JA et al.[53]

Zotarolimus is a semisynthetic derivative of sirolimus in which the tetrazole group has replaced the hydroxyl group, making it more lipophilic and enhancing the absorption of the drug across the cell membrane.[16] These differences in the type of anti-proliferative agent, drug load, and kinetics may also contribute to the reduced rates of late stent thrombosis seen in second-generation DESs.[18]

Clinical Trials Comparing Second-Generation Drug-Eluting Stents with First-Generation Drug-Eluting Stents and Bare-Metal Stents

Everolimus-eluting stents

In a meta-analysis of the 3-year results from the SPIRIT II, III, and IV clinical trials, the rate of stent thrombosis was significantly lower with EESs compared with PESs (0.7% versus 1.7%, p=0.003).[19] In another randomised study involving 1,800 patients (COMPARE), EESs were associated with lower rate of definite or probable stent thrombosis at 5 years compared with PESs (3.1% versus 5.9%, p=0.005).[20]

The differences in clinical outcomes were less apparent in randomised trials comparing EESs with SESs than with PESs. In the SORT OUT IV trial, 1,390 patients with coronary artery disease were randomised to either an EES or SES. At 18 months, the rate of definite stent thrombosis was lower with EESs compared with SESs (0.2% versus 0.9%, 95% CI: 0.07–0.88).[21] In contrast, in a large prospective randomised study, BASKET PROVE, there was no significant difference between the rates of stent thrombosis in SESs and EESs at 2 years.[22]

In the EXAMINATION trial, 1,504 patients with ST-segment elevation myocardial infarction were randomised to EESs or BMSs.[23] At 1 year, stent thrombosis rates were significantly lower in the EES group (0.5% versus 1.9% with definite stent thrombosis and 0.9% versus 2.5% with definite or probable stent thrombosis, p=0.019).[23] In a meta-analysis of five randomised trials involving a total of 4,896 patients, EESs were associated with a significant reduction in definite stent thrombosis (OR: 0.41, CI: 0.22–0.76, p=0.005) and definite or probable stent thrombosis (OR: 0.48, 95% CI: 0.31–0.73, p<0.001).[24]

Zotarolimus-eluting stents

The clinical trials that support the superiority of ZESs are not as robust as those which support the use of EESs. The two FDA-approved ZESs are Endeavor and Resolute. Resolute ZESs use a BioLinx tripolymer coating instead of the phosphorylcholine polymer used in E-ZES, which extends the elution of zotarolimus to a longer period of time (180 days versus 30 days).[25]

ENDEAVOR IV is a large randomised trial comparing E-ZES with PESs.[26] At 5 years, the overall definite/probable stent thrombosis rates were similar between the two groups (1.3% versus 2%, p=0.042).[26] However, the rate of very late stent thrombosis was significantly lower with ZESs than with PESs (0.4% versus 1.8%, p=0.012).[26] Similarly, in a randomised trial conducted in China, there was no difference between the two stents in the rates of definite or probable stent thrombosis, or late stent thrombosis at the end of 1 year.[25]

The superiority of E-ZES in comparison to C-SES in terms of reducing the rate of stent thrombosis has not yet been established. In the ENDEAVOR III trial, 436 patients were randomised to E-ZES or C-SES.[27] At 5 years, though the pre-specified end points of all-cause mortality and myocardial infarction were significantly lower in E-ZES, the rates of stent thrombosis were very low and similar in both groups (0.7% ZESs versus 0.9% SES, p=1.0).[27] In another randomised study of 1,162 patients, SORT OUT III, the rate of very late stent thrombosis beyond 12 months was similar between E-ZES and C-SES.[28] Similar results were observed in a very large randomised trial, PROTECT, involving 8,791 patients.[29] At 3 years, the rates of definite or probable stent thrombosis did not differ between E-ZES and C-SES (1.4% E-ZES versus 1.8% for C-SES, p=0.22).[29] To date, there are no large-scale clinical trials directly comparing Resolute ZESs to C-SES.

In a study combining patient-level data from 6 prospective randomised trials involving 2,132 patients treated with E-ZES and 596 patients treated with a BMSs, no difference in the rate of definite or probable stent thrombosis was observed at 5 years (0.8% versus 1.7%, p=0.21).[30] There are no trials comparing Resolute ZESs directly with BMSs.

Given the low incidence of stent thrombosis, large sample sizes are required to detect significant differences in rates between stents. Most of the trials noted above were not powered sufficiently for this. Hence, a large network meta-analysis including a total of 49 randomised trials and 50,844 patients was conducted by Palmerini et al.[31] to investigate if there was a significant difference in stent thrombosis rates. At 1 year, CoCr-EESs were associated with a significantly lower rate of

stent thrombosis compared with BMSs (OR: 0.27, 95% CI: 0.08–0.74), PESs (OR: 0.28, 95% CI: 0.16–0.48), SESs (OR: 0.41, 95% CI: 0.24–0.70), E-ZES (OR: 0.21, 95% CI: 0.10–0.44), and Resolute ZESs (OR: 0.14, 95% CI: 0.03–0.47).[31] At 2 years, CoCr-EESs were associated with a lower rate of stent thrombosis than BMSs, results that have not been seen with other DESs.[31] Even at 2 years, the sustained reduction in stent thrombosis incidence in patients with a CoCr-EES compared with BMS has been pivotal in the evolution of PCI, proving the relative safety and efficacy of second-generation DESs compared with BMSs.[18]

Optimal Duration of Dual Antiplatelet Therapy for Prevention of Stent Thrombosis in the Era of Second-Generation Drug-Eluting Stents

The optimal duration of DAPT after PCI with second-generation DESs in order to balance the risk of stent thrombosis and bleeding complications is currently controversial. While 2014 European Guidelines on Myocardial Revascularisation changed the duration of DAPT to 6 months after PCI with second-generation DESs in patients with stable coronary artery disease, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on PCI recommend 6–12 months of DAPT.[32,33] The prior recommendation of extending DAPT to ≥1 year was based on observational studies with first-generation DESs.[34,35]

Recently, several randomised trials performed in patients with second-generation DESs showed non-inferiority in a shorter duration DAPT (3 months or 6 months) compared with longer duration DAPT (12 months or 24 months).[36-41] Consistently in these trials, the risk of major cardiovascular adverse events and stent thrombosis was not different, while the risk of bleeding increased with longer duration DAPT (Table 1).

Table 1: Randomised trials of second-generation drug-eluting stents (DESs) comparing shorter and longer duration of dual antiplatelet therapy.

Study	Stent	Number of patients in each treatment group (n)	Primary end point	Follow-up duration after randomisation	Results of primary end point	Any significant difference in rates of stent thrombosis?
SECURITY, 2014[36]	Any second-generation DES	6 months (682) 12 months (717)	Cardiac death, MI, CVA, stent thrombosis, bleeding	1 year	Non-inferiority proved	No (0.3 % vs. 0.4%, p=0.694)
ITALIC, 2014[39]	Everolimus-eluting stent	6 months (953) 24 months (941)	Death, MI, CVA, TVR, bleeding	1 year	Non-inferiority proved	No (0 patients in 6 month group vs. 3 in 24 month group)
ISAR-SAFE, 2014[40]	Everolimus-eluting stent	6 months (1,997) 12 months (2,003)	Death, MI, CVA, stent thrombosis, bleeding	9 months	Non-inferiority proved	No (0.3 % vs. 0.2 %, p=0.49)
OPTIMIZE, 2013[38]	Zotarolimus-eluting stent	3 months (1,563) 12 months (941)	Death, MI, CVA, major bleeding	1 year	Non-inferiority proved	No (0.3% vs. 0.1%, 95% CI: 0.44–35.49)
RESET, 2012[37]	Endeavor Zotarolimus-eluting stent	3 months (1,059) 12 months (1,058)	Cardiac death, MI, stent thrombosis, TVR, major bleeding	1 year	Non-inferiority proved	No (0.2% vs. 0.3%, p=0.65)
EXCELLENT, 2012[41]	Everolimus-eluting stent	6 months (722) 12 months (721)	Cardiac death, MI, TVR, stent thrombosis	1 year	Non-inferiority proved	No (0.9% vs. 0.1%, p=0.10)

MI: myocardial infarction; CVA: cerebrovascular accident; TVR: target vessel revascularisation.

However, it is important to note that these trials are not powered adequately to determine a significant difference in the rate of stent thrombosis. Hence, despite the results of these randomly controlled trials (RCTs), the optimal duration remains controversial. In a recent large, multicentre trial, 9,961 patients with DESs (46.7% EES, 26.9% PES, 12.8% ZES, and 11.5% SES) were randomised to 12 or 30 months of DAPT.[42] While the rates of stent thrombosis and myocardial infarction were significantly reduced as the duration of DAPT increased, the rate of moderate-to-severe bleeding increased.[42] The rate of death from any cause was higher in the longer DAPT therapy group, despite reduced rates of stent thrombosis and myocardial infarction (2.0% versus 1.5%, p=0.05).[42] Similar results were noted in a meta-analysis of 11 RCTs involving 31,666 patients.[43] Though longer DAPT (≥1 year) reduces the risk of myocardial infarction and stent thrombosis, it is associated with increased risk of bleeding complications and mortality from non-cardiovascular causes.[43] In patients with stable coronary artery disease, a shorter DAPT duration of 3–6 months is recommended, especially if the patient is at high risk of bleeding and has a second-generation DESs. After PCI for acute coronary syndrome, DAPT for a duration of 1 year is recommended regardless of the type of stent.

Consideration of the optimal duration of DAPT after PCI is further complicated by recent increases in the use of new P2Y12 inhibitors (prasugrel and ticagrelor). Compared with clopidogrel, these newer agents demonstrate a more potent suppression of platelet activity and are associated with significantly reduced rates of stent thrombosis and increased rates of bleeding complications.[44,45] Studies of the optimal duration of DAPT with these newer agents are limited. The current guidelines do not differentiate the duration of DAPT based on the antiplatelet agent used.[32,33] In a recent large-scale multicentre trial involving 21,162 patients who presented with myocardial infarction >1 year previously, patients were randomised to ticagrelor 90 mg or 60 mg twice daily for a median duration of 33 months or placebo; results demonstrated an association between ticagrelor and a significant reduction in the risk of cardiovascular death, myocardial infarction, or stroke, and an increased risk of bleeding, when compared with placebo.[46] Given the increased risk of bleeding complications and mortality from non-cardiovascular cause, DAPT therapy for ≥1 year should be individualised based on clinical and anatomical risk factors.

Future Directions

The success of biocompatible fluorocopolymers in reducing the rate of stent thrombosis has facilitated the next-generation DESs with either biodegradable polymers (third-generation DESs) or bioresorbable vascular scaffolds (BVS; considered fourth-generation DESs).

Third-generation drug-eluting stents

Third-generation stents consist of a metallic stent platform, with the drug being delivered from an ultra-thin bioabsorbable polymer applied to the outer stent surface. Once the drug is eluted, the polymer is completely reabsorbed, leaving behind the endothelialised BMSs struts. Though designed to reduce the risk of stent thrombosis, such a reduction has not yet been demonstrated in randomised trials. In a recent trial comparing the Synergy™ stent (a platinum chromium metal alloy with bioabsorbable poly[D,L-lactide-co-glycolide] abluminal everolimus-eluting polymer) with EES, the rate of definite stent thrombosis was similar after 12 months (2.6% versus 1.7%, p=0.21).[47] Future randomised studies are needed to evaluate long-term outcomes regarding late stent thrombosis with these stents.

Bioresorbable vascular scaffolds

BVSs are made of lactic acid or magnesium-based polymers. These stents are designed to restore normal vasomotor tone and increase the lumen calibre through positive remodelling following degradation of the stent. Theoretically, the risk of late stent thrombosis should be reduced as no metallic stent struts remain exposed to the blood stream after stent degradation. The initial data from large registry studies showed significant increases in the rate of device-related early or sub-acute stent thrombosis with BVSs compared with metallic stents.[48-50] However, in the recent randomised ABSORB III trial, where everolimus-eluting BVSs (Absorb BVS) were compared with CoCr-EESs in 2,008 patients, there was no significant difference in the rate of stent thrombosis at 12 months (1.5% versus 0.7%, p=0.13).[51] In a recent patient-level pooled meta-analysis of four randomised trials, there was a non-significant increase in the rate of stent thrombosis with BVS.[52] Though shown to be non-inferior when compared with second-generation DESs in terms of major cardiovascular events at 1 year in the ABSORB III trial[51] and in the recent meta-analysis,[52] the deliverability and radial strength of these stents may be factors which

limit their widespread usage. Future stent designs should aim at reducing strut thickness while maintaining radial and longitudinal strength to improve deliverability of BVS. Currently, the optimal duration of DAPT for BVS or stents with biodegradable polymers is unknown. Future large-scale randomised trials are needed to address these issues.

CONCLUSION

Stent thrombosis is an uncommon but life-threatening complication of PCI. Late and very late stent thrombosis was a major concern with first-generation DESs. With the improved features of the second-generation DESs (thinner stent struts, biocompatible fluorocopolymers, and use of different anti-proliferative agents) the rate of stent thrombosis has dramatically decreased. Currently, CoCr-EESs have produced the lowest rate of stent thrombosis within 2 years of placement of all available stents including BMSs. Though the optimal duration of DAPT in patients with second-generation DESs is still controversial, 6-month therapy might result in reduced bleeding complications without increasing the occurrence of major cardiovascular events. The next-generation DESs include stents with biodegradable polymers and bioresorbable scaffolds. However, large-scale randomised trials are needed to definitively evaluate the efficacy and safety of these third and fourth-generation stents in the future.

REFERENCES

1. Ludman P et al. National Audit of Percutaneous Coronary Interventions. Annual Public Report. January 2013 – December 2013. Available at: http://www.ucl.ac.uk/nicor/audits/adultpercutaneous/documents/2013_annual_report_pdf. Last accessed: 24 November 2015.

2. Cutlip DE et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. J Am Coll Cardiol. 2002;40(12):2082-9.

3. Camenzind E et al. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation. 2007;115(11):1440-55.

4. Wenaweser P et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol. 2008; 52(14):1134-40.

5. Burzotta F et al. Angiographic and clinical outcome of invasively managed patients with thrombosed coronary bare metal or drug-eluting stents: the OPTIMIST study. Eur Heart J. 2008;29(24):3011-21.

6. Cutlip DE et al.; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115(17):2344-517.

7. Finn AV et al. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol. 2007;27(7):1500-10.

8. Finn AV et al. Pathological correlates of late drug-eluting stent thrombosis strut coverage as a marker of endothelialization. Circulation. 2007;115(18):2435-41.

9. Nakazawa G et al. Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. J Am Coll Cardiol. 2011;57(4):390-8.

10. Tada T et al. Impact of stent strut thickness on arterial healing after drug-eluting stents implantation assessed by optical coherence tomography. Eur Heart J. 2013;34(Suppl 1):3935.

11. Kolandaivelu K et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation. 2011;123(13):1400-9.

12. Virmani R et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation. 2004;109(6):701-5.

13. Nebeker JR et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol. 2006;47(1):175-81.

14. Otsuka F et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. Circulation. 2014;129(2):211-23.

15. Hezi-Yamit A et al. Impact of polymer hydrophilicity on biocompatibility: implication for DES polymer design. J Biomed Mater Res A. 2009;90(1):133-41.

16. Price MJ, Mosley WJ. "Fundamentals of Drug- Eluting Stent Design," Matthew J Price (ed.), Coronary Stenting: A Companion to Topol's Textbook of Interventional Cardiology (2012), Philidelphia: Elsevier Saunders, pp.13-27.

17. Kukreja N et al. Xience V everolimus-eluting coronary stent. Expert Rev Med Devices. 2009;6(3):219-29.

18. Palmerini T et al. Stent thrombosis with drug-eluting stents: is the paradigm shifting? J Am Coll Cardiol. 2013;62(21):1915-21.

19. Dangas GD et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv. 2013;6(9):914-22.

20. Smits PC et al. Final 5-Year Follow-Up of a Randomized Controlled Trial of Everolimus- and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice: The COMPARE Trial (A Trial of Everolimus-Eluting Stents and Paclitaxel Stents for Coronary Revascularization in Daily Practice). JACC Cardiovasc Interv. 2015;8(9):1157-65.

21. Jensen LO et al.; Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV) Investigators. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation. 2012;125(10):1246-55.

22. Kaiser C et al.; BASKET–PROVE Study Group. Drug-eluting versus bare-metal stents in large coronary arteries. N Engl J Med. 2010;363(24):2310-9.

23. Sabate M et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction

(EXAMINATION): 1 year results of a randomised controlled trial. Lancet. 2012; 380(9852):1482-90.

24. Valgimigli M et al. Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis. BMJ. 2014;349:g6427.

25. Gujja K et al. "Efficacy and safety of bare metal and drug eluting stents." Matthew Price (ed.), Coronary stenting: a companion to Topol's Textbook of interventional cardiology (2012), Philidelphia: Elsevier Saunders, pp.81-92.

26. Kirtane AJ et al.; ENDEAVOR IV Investigators. The "final" 5-year follow-up from the ENDEAVOR IV trial comparing a zotarolimus-eluting stent with a paclitaxel-eluting stent. The "final" 5-year follow-up from the ENDEAVOR IV trial comparing a zotarolimus-eluting stent with a paclitaxel-eluting stent. JACC Cardiovasc Interv. 2013;6(4):325-33.

27. Kandzari DE et al. Late-term clinical outcomes with zotarolimus- and sirolimus-eluting stents. 5-year follow-up of the ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv. 2011;4(5):543-50.

28. Rasmussen K et al.; SORT OUT III study group. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. Lancet. 2010;375(9720):1090-9.

29. Camenzind E et al.; PROTECT Steering Committee and Investigators. Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial. Lancet. 2012; 380(9851):1396-405.

30. Eisenstein EL et al. Long-term clinical and economic analysis of the Endeavor drug-eluting stent versus the Driver bare-metal stent: 4-year results from the ENDEAVOR II trial (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv. 2009;2(12): 1178-87.

31. Palmerini T et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet. 2012; 379(9824):1393-402.

32. Windecker S et al. 2014 ESC/EACTS guidelines on myocardial revascularization. Rev Esp Cardiol. 2015;68(2):144.

33. Levine GN et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv. 2013;82(4):E266-355.

34. Bavry AA et al. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med. 2006;119(12):1056-61.

35. Daemen J et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet. 2007;369(9562):667-78.

36. Colombo A et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014; 64(20):2086-97.

37. Kim BK et al; RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol. 2012;60(15):1340-8.

38. Feres F et al; OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013;310(23):2510-22.

39. Gilard M et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol. 2015;65(8):777-86.

40. Schulz-Schüpke S et al. Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) Trial Investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J. 2015;36(20): 1252-63.

41. Gwon HC et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125(3):505-13.

42. Mauri L et al.; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371(23):2155-66.

43. Palmerini T et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet. 2015;385(9985):2371-82.

44. Wallentin L et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361(11):1045-57.

45. Wiviott SD et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357(20):2001-15.

46. Bonaca MP et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372(19):1791-800.

47. Kereiakes DJ et al. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II Randomized Trial. Circ Cardiovasc Interv. 2015;8(4). doi: 10.1161/CIRCINTERVENTIONS.114.002372.

48. Capodanno D et al. Percutaneous coronary intervention with everolimus-eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry. EuroIntervention. 2015;10:1144-53.

49. Kraak RP et al. Initial experience and clinical evaluation of the Absorb bioresorbable vascular scaffold (BVS) in real-world practice: the AMC Single Centre Real World PCI Registry. EuroIntervention. 2015;10(10):1160-8.

50. Jaguszewski M et al. Feasibility of second-generation bioresorbable vascular scaffold implantation in complex anatomical and clinical scenarios. Clin Res Cardiol. 2015;104(2):124-35.

51. Ellis SG et al; ABSORB III Investigators. Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease. N Engl J Med. 2015;373(20):1905-15.

52. Stone GW et al. 1-year outcomes with the Absorb bioresorbable scaffold in patients with coronary artery disease: a patient-level, pooled meta-analysis. Lancet. 2016. doi: 10.1016/S0140-6736(15)01039-9. [Epub ahead of print].

53. Ormiston JA et al. Stent Longitudinal Integrity. Bench Insights into a clinical problem. JACC Cardiovasc Interv. 2011; 4:1310-7.

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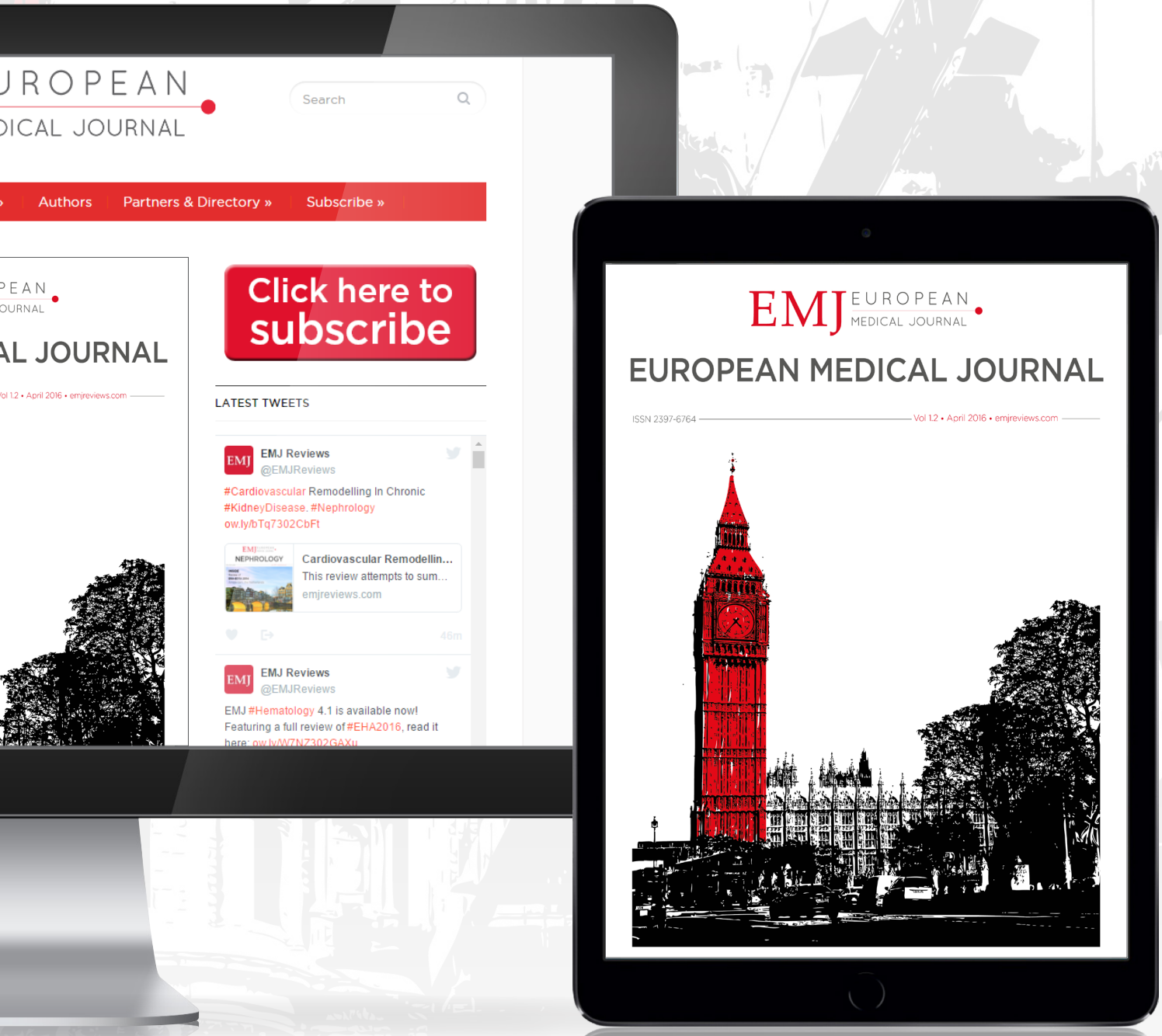

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SPONDYLOARTHRITIS: PATHOGENESIS, CLINICAL MANIFESTATIONS, DIAGNOSIS, AND MANAGEMENT

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ABSTRACT

The term spondyloarthritis (SpA) is used to describe a heterogeneous group of diseases sharing certain characteristics. Traditionally, patients with SpA have been classified in five subgroups: ankylosing spondylitis (AS), psoriatic arthritis, arthritis associated with inflammatory bowel disease (IBD), reactive arthritis, and undifferentiated SpA. The pathogenesis of SpA is still not entirely clear; it is considered to be multifactorial, the result of interaction between genetic risk factors and environmental triggers that lead to activation of autoinflammation and autoimmunity. This group of diseases is characterised by a chronic inflammation in entheses and other anatomical structures, leading to their main clinical features: sacroiliitis, enthesitis, and peripheral arthritis. An association with extra-articular manifestations such as psoriasis, uveitis, and IBD is also a distinctive feature of SpA.

Several diagnostic and classification criteria have been proposed over time. However, all of these criteria have a main limitation, which is the difficulty to identify patients at an early stage of the disease. The Assessment of Spondyloarthritis International Society (ASAS) proposed the ASAS classification criteria that introduced two major changes: first, the classification of patients with SpA based on the predominant symptoms (axial or peripheral); second, the introduction of magnetic resonance imaging, which allows detection of sacroiliitis at the early stages of the disease. Nowadays, the ASAS criteria classify SpA in two groups: axial SpA, including classical AS and non-radiographic axial SpA, and peripheral SpA. The therapy for SpA has evolved dramatically over time. The introduction of biological therapy in recent years, which has continuously progressed, has improved the functional and clinical prognosis of SpA patients.

Keywords: Spondyloarthritis (SpA), clinics, review.

INTRODUCTION

The term spondyloarthritis (SpA) is used to describe a heterogeneous group of diseases that share certain characteristics that differentiate them from other rheumatic diseases: familial history, common pathogenesis, *HLA-B27* association, relation with gastrointestinal or genitourinary infections, and similar clinical features mainly characterised by the presence of enthesitis, sacroiliitis, and arthritis.[1]

The group includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), reactive arthritis, and undifferentiated SpA.[1] However, at an early stage of the disease it may be difficult to classify patients into a definitive category. The Assessment of Spondyloarthritis International Society (ASAS) criteria allows classification of SpA patients through the use of predominant symptoms in axial (Figure 1) and peripheral SpA (Figure 2).[2-4] This review analyses the clinical manifestations, pathogenesis, diagnosis, and treatment of SpA.

EPIDEMIOLOGY

The prevalence of SpA depends on the genetic background, especially *HLA-B27* frequency,

ethnicity, and geographical distribution of the population under study. Therefore, the prevalence varies, and it is estimated to be 0.1–2.5%. The prevalence reported in Europe of AS is 0.3–1.8%, considering the factors commented above.[5]

PATHOGENESIS

The pathogenesis of SpA is not entirely clear. It is the result of a complex interaction between genetic risk factors and environmental triggers that leads to the activation of autoimmunity and autoinflammation.

Genetic Risk Factors

The mode of inheritance is polygenic and related to several genetic factors. Estimated heritability in AS is >90%, and this condition increases with several clinical manifestations of AS such as radiographic damage, age of onset, and BASDAI.[6] First, second, and third-degree relatives of patients with AS have a relative risk of 94%, 25%, and 4%, respectively of developing the disease.[7]

The principal genetic factors associated with SpA are:

MHC genes

HLA-B27 is the most important genetic factor in AS. It is present in 85–95% of white patients with AS, although only 7–8% of *HLA-B27* carriers in general population develop AS.[8] *HLA-B27* is also associated with other forms of SpA to a lesser degree.[7,9] *HLA-B27* is encoded by an allele of the major histocompatibility complex (MHC) class I HLA-B region, and all the molecules of this group share a common canonical structure that allows presenting antigenic peptides to the T cell receptors of CD8+ lymphocyte. Several different hypotheses have been suggested to explain the role of *HLA-B27* in the pathogenesis of SpA:

Arthritogenic peptide hypothesis

Certain microbial peptides very similar to self-peptides could mimic them and cause reactivity of T lymphocytes, leading to autorreactivity and autoimmune disease.[10-12] The validity of this hypothesis is questioned by the fact that *HLA-B27* rats can still develop arthritis in the absence of T CD8+ cells.[13]

Heavy chain homodimer hypothesis

HLA-B27 heavy chains can form stable dimers that can engage receptors of several types of cells in a way different from the canonical structure, so that they can be recognised by natural killer (NK) receptors, developing an inflammatory process. Leukocyte receptors that could recognise homodimers are: LILRA1, LILRB2, KIR3DL1, and KIR3DL2.[14]

HLA-B27 misfolding hypothesis

Due to several reasons, the folding process of *HLA-B27* is slower than other HLA alleles, and could generate misfolding proteins that accumulate in the endoplasmic reticulum, leading to activation of autophagy and IL23/17 pathway.[14]

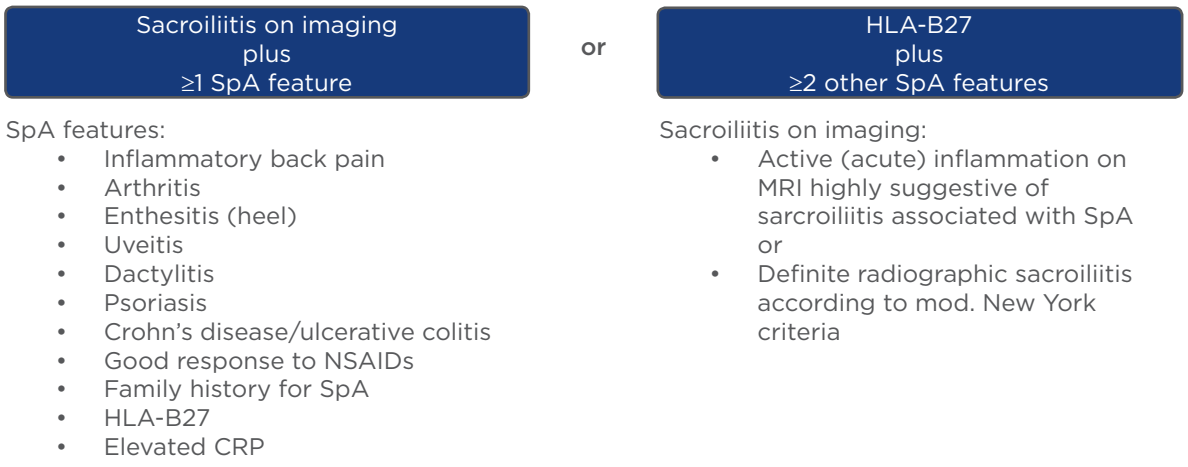

Figure 1: Assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis.

For use in patients with back pain ≥3 months and an age of onset <45 years of age.

NSAIDs: non-steroidal anti-inflammatory drugs; MRI: magnetic resonance imaging; CRP: c-reactive protein.

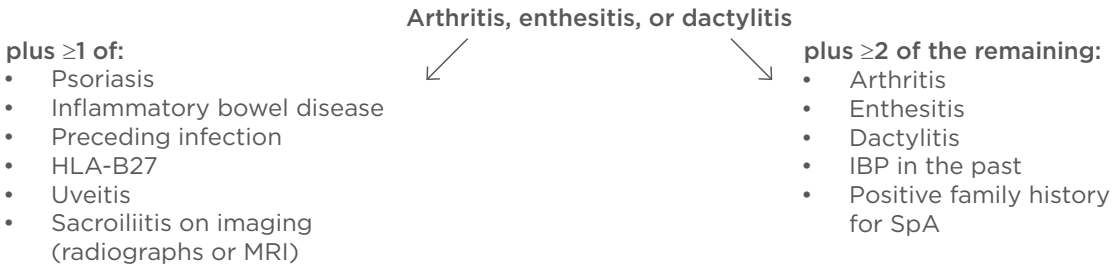

Figure 2: Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis.
MRI: magnetic resonance imaging; IBP: inflammatory back pain; SpA: spondyloarthritis.

More than 100 subtypes of *HLA-B27* have been characterised, however not all of them have the same degree of association with SpA/AS. *B27:02, 04*, and *05* are strongly associated with AS. Other HLA-B alleles such as *HLA-B60, B39, B38*, and *B40* have been associated with AS.[14]

Non-MHC genes

Genome-wide association studies (GWAS) have involved several genes in the pathogenesis of SpA grouped into several functional categories.

Polymorphisms in the endoplasmic reticulum aminopeptidase 1 and 2 (*ERAP1* and *ERAP2*) are strongly associated with SpA. The mechanism by which ERAP1 predisposes to SpA remains unknown. One hypothesis suggests that *ERAP1* alters *HLA-B27* peptide presentation. *ERAP1* variants found in patients with AS are present mostly in patients who are *HLA-B27* positive rather than in *HLA-B27* negative.[15] The mechanism by which *ERAP2* affects disease risk remains unclear.

IL17/23 pathway

GWAS have identified association with genes for the IL23 receptor (IL23R) as well as tyrosine kinase 2 (TYK2), and signal transducer and activator of transcription (STAT3), which are involved in the IL23R pathway. New therapeutic options against these targets have shown efficacy.[16]

Other non-MHC genes implicated have been the tumour necrosis factor (TNF) receptor gene family and the genes modulating activation and differentiation of CD4+ or CD8+ lymphocytes.

Environmental Triggers

The important role of abnormal intestinal microbiota and infections in the development of joint disease has been confirmed in several studies. Of the patients with IBD, 10–20% develop sacroiliitis, and many patients with AS show microscopic inflammatory lesions in the biopsy without intestinal symptoms, this may be due to the two diseases sharing a common pathogenetic cause. In other cases, such as reactive arthritis and Reiter's syndrome, arthritis develops a short-time after a gastrointestinal or genitourinary infection.[16]

The role of mechanical stress in inflammation and bone formation has been widely discussed in the literature regarding pathogenesis of SpA. The 'synovio-entheseal complex' represents the sophisticated integration between insertions and the adjacent synovium. The fibrocartilages at insertions are prone to microdamage and/or aberrant tissue repair that may manifest as adjacent tenosynovitis or synovitis, due to the synovium being rich in immune cells and its ability to undergo hyperplasia and vessel ingrowth.[17] This makes the 'enthesis organ' a place where molecules from bacteria may be preferentially deposited. Microdamage and bacterial deposition in the context of HLA-B27 could lead to the characteristic inflammatory changes of AS. The sequence of entheseal inflammation followed by new bone formation is not formally proven, although magnetic resonance imaging (MRI) studies suggest that new bone formation preferentially occurs in advanced inflammatory spinal lesions, characterised by reparative processes such as bone sclerosis.[18] Acute lesions resolve without sequelae, but in chronic inflammatory lesions, resolution of the process results in fat metaplasia and bone formation, therefore mechanical stress is involved in disease progression.[19]

Animal models have showed the multifactorial aetiology of SpA with genome (*HLA-B27*), microbial, and biomechanical stress models shaping the disease phenotypes. At a molecular

level, there is evidence with TNF and IL23/IL17. Additionally, at the cellular level, resident entheseal IL-23R+, CD3+/CD4-/CD8- T cells have been identified, although their role still remains unclear. However, selection of animal models must be careful due to high sensitivity to environmental changes and different genetic backgrounds.[20]

CLINICAL FEATURES

Patients with axial SpA characteristically have chronic lower back pain. Patients with either axial or peripheral SpA can present arthritis, enthesitis, and dactylitis.

Lower Back Pain

Chronic lower back pain affects approximately 20% of the general population, but a reduced percentage of these patients have axial SpA.[21] Therefore, the lower back pain in axial SpA is described as 'inflammatory low back pain'. It is present in 70–80% of patients with axial SpA, and characterised by:[22] age of onset <45 years, insidious onset, evolution >3 months, improving with movement and non-steroidal anti-inflammatory drugs (NSAIDs), but not with rest. It is associated with morning stiffness and pain at night. The early stage of the illness is quite intense and can irradiate to the dorsal spine or pelvis. Sacroiliitis can manifest as alternating left-right gluteal region pain and it is very specific for axial SpA and AS.

The cervical spine, and less frequently the thoracic spine, can also be affected, especially in AS, with loss of range of motion.

Peripheral Arthritis

This often involves the lower extremities, especially knees and ankles, and is associated with swelling. Its pattern is acute, non-erosive, asymmetrical, and oligoarticular.[23] Hip and shoulder arthritis are frequent in AS.[24]

Enthesitis

Enthesitis is characteristic of SpA. Enthesis is the site of insertion of ligaments, tendons, joint capsule, or fascia to bone. The most common site of enthesitis is the Achilles tendon. Iliac crests, costochondral junctions at the sternum, the greater trochanters, and the tibial plateaus can also be affected. Enthesitis produces swelling and tenderness on palpation.[24]

Dactylitis

Dactylitis is the global inflammation of fingers and toes, which can make them look like sausages. Dactylitis is particularly characteristic of PsA and reactive arthritis but is not a specific characteristic of SpA. It is observed in syphilis, tuberculosis, and sarcoidosis.[25] It can be acute (with inflammatory signs) or chronic (often not painful). Dactylitis can affect one or more fingers and/or toes asymmetrically.

Non-Articular Features

These are characteristic of SpA spectrum disease:

- Eye involvement: Acute unilateral anterior uveitis is a symptom of SpA, especially in HLA-B27 patients, and may be the presenting problem. It usually responds to local therapy. Non-purulent, transient conjunctivitis could also be associated[26,27]
- Inflammatory bowel disease: Articular disease related to SpA is the most common extra-intestinal feature in IBD, although the clinical course of both diseases is independent. IBD has been diagnosed in 10% patients with AS. On the other hand, AS is diagnosed in 3–10% patients with IBD, although 15–50% patients have sacroiliitis on imaging. Sixty percent of patients with AS show microscopic inflammation of bowel mucosa without IBD symptoms[28,29]

Other Clinical Features

These include aortic insufficiency, conduction abnormalities, neurological manifestations secondary to spinal fractures or atlantoaxial subluxation, amyloidosis, and osteoporosis.[20]

DIAGNOSIS

Laboratory Findings

There are no laboratory findings absolutely specific for SpA. HLA-B27, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are the markers most commonly used in clinical practice.

In most ethnic groups, >90% of AS and 50–70% of patients with other forms of SpA are positive for HLA-B27, and it is included in the ASAS criteria. However, HLA-B27 positivity is not diagnostic by itself of either AS or SpA. HLA-B27 is particularly helpful in diagnosis of non-radiographic axial SpA in combination with MRI. The combination of severe sacroiliitis on MRI with

HLA-B27 positivity is an excellent predictor of future AS development.[30]

CRP and ESR have both low sensitivity and specificity and they do not represent the disease process or activity in AS and SpA. Elevated CRP is included in axial ASAS SpA classification; however, elevated CRP or ESR are only present in 40–50% of patients with AS.[31] This percentage may be greater in peripheral forms such as PsA. Thus, normal ESR or CRP levels do not rule out active disease or AS diagnosis.

Other markers such as cytokines, matrix metalloproteinases, osteoprotegerin, or calprotectin are under investigation.[32]

Radiographic Findings

Plain radiographs

There are several characteristic findings that may be observed in patients with SpA, although these are not present in early stages of the disease. In axial SpA, the most specific finding is sacroiliitis, and this has been included in many classification criteria. According to grading of radiographic sacroiliitis (Figure 3) there is positive evidence for sacroiliitis at Grade 2 or higher bilaterally, or Grade 3 unilaterally. Patients considered as non-radiographic axial SpA do not have definite plain radiographic findings of sacroiliitis. Syndesmophytes (ossification originating from the intervertebral ligaments that may bridge vertebral bodies) are also very specific for axial SpA, and can be observed in the absence of sacroiliitis.[31,33]

Radiographs of peripheral joints and entheses show variation in the degree and kind of radiographic changes seen in different types of SpA. In axial SpA, the most severe peripheral joint involvement observed is in the hip joints, where extensive destructive changes may occur.[31] Radiographic changes in peripheral joints are common in patients with PsA, even at early stages of the disease. These changes are very characteristic of PsA, showing the coexistence of erosive changes and new bone formation within the same joint or in different joints within the same digit. Fluffy erosions can be observed in areas of enthesitis in patients with SpA, such as the heels, although these findings are not specific for SpA.[34]

Magnetic resonance imaging

MRI has become an important tool in the diagnosis of patients in the early stage of disease, without abnormalities on plain radiographs, allowing an early diagnosis. MRI findings in sacroiliac joints are included in ASAS criteria. These findings include active inflammatory lesions of sacroiliac joints, observed as high-intensity bone marrow oedema on short-tau inversion recovery (STIR) or on T2 with fat absorption images. Bone marrow oedema is not exclusive for SpA and could appear in malignancies, infections, and osteitis condensans ilii. Findings on MRI of the spine show lesions that are triangular in shape at one or more corners of the vertebrae.[31]

Other imaging techniques

Computed tomography scanning and scintigraphy are less frequent used. Ultrasonography is useful for enthesitis, showing hypoechogenicity, increased thickness of the tendon insertion, calcifications, enthesophytes, and power Doppler activity.[35]

Classification Criteria

Classification criteria for SpA and AS were developed for use in epidemiological and clinical research. Currently ASAS criteria have replaced older classification criteria. Although there are specific criteria for different types of SpA, such as the ClASsification criteria for Psoriatic ARthritis (CASPAR) for PsA, it may be difficult to classify a patient into a definitive SpA disease group, especially at onset. ASAS criteria allow the classification of practically all patients with SpA according to predominant symptoms in axial or peripheral SpA. These classifications also include MRI findings allowing classification of early and non-radiographic forms. ASAS criteria for axial SpA have a sensitivity of 82.95% and a specificity of 84.4%. For peripheral SpA, ASAS criteria have an estimated sensitivity of 75% and specificity of 82.2%.[2-4]

- Grade 0: Normal
- Grade 1: Suspicious changes
- Grade 2: Minimal abnormality, small localised areas with erosions or sclerosis, without alteration in the joint width
- Grade 3: Unequivocal abnormality, moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis
- Grade 4: Severe abnormality, total ankylosis

Figure 3: Grades of sacroiliitis based upon the presence of the characteristic radiographic findings.

TREATMENT

The main goal of SpA management is to reduce disease activity and control joint damage, improving quality of life and preserving functional abilities, autonomy, and social participation of patients.

The management of axial SpA is different, in terms of pharmacological treatment, from peripheral SpA. NSAIDs and anti-TNF blockers are the cornerstone in treatment of axial SpA. Although these treatments have also demonstrated efficacy in peripheral SpA, non-biological disease-modifying anti-rheumatic drugs (nb-DMARDs) are an essential tool in peripheral SpA.

Non-Steroidal Anti-Inflammatory Drugs

According to ASAS and the European League against Rheumatism (EULAR), NSAIDs, including the selective cyclo-oxigenase-2 antagonists, are the first-line therapy of SpA, especially axial SpA.[36] There is often clinical improvement of lower back pain in patients with AS treated with NSAIDs, with a clinically significant response in >70% of the patients compared with patients with mechanical back pain.

Corticosteroids

Intra-articular injections of steroids can be used in monoarthritis, enthesitis, and dactylitis. Systemic steroids are not usually recommended in the treatment of axial involvement due to a lack of efficacy in axial symptoms. In the case of peripheral SpA, systemic steroids may be useful in short-term treatment in severe forms with the lowest possible dosage.[37]

Non-Biologic Disease-Modifying Anti-Rheumatic Drugs

Methotrexate, leflunomide, and sulfasalazine are generally ineffective for axial manifestations, but are useful in peripheral SpA. Although methotrexate is the most widely nb-DMARD used, the choice may be based on the patient's clinical profile, considering also the coexistence of extra-articular manifestations. Methotrexate can improve psoriasis and methotrexate and sulfasalazine are useful if uveitis and/or bowel disease are present.[37,38]

Biological Disease-Modifying Anti-Rheumatic Drugs

TNF-α blocking therapies are currently the only effective treatment available for patients with axial SpA who are unresponsive to the first-line therapy with NSAIDs. Each of the currently available TNF blocking agents (adalimumab, infliximab, etanercept, golimumab, and certolizumab pegol) has a strong and similar clinical efficacy in active AS.[28] The choice of a TNF blocker depends on the patient preference, experience of the medical professional with the drug, comorbidities, and extra-articular manifestations. Adalimumab and etanercept are useful when treating psoriasis. Infliximab and adalimumab have been demonstrated to improve uveitis. Infliximab and adalimumab are used in IBD (Crohn´s disease and ulcerative colitis). Golimumab has been shown to improve ulcerative colitis and certolizumab pegol to improve Crohn´s disease.[8,27,28]

All the TNF-α blockers are also effective in the control of peripheral disease unresponsive to nb-DMARDs. Ustekinumab, a fully human immunoglobulin monoclonal antibody direct against IL-12 to 23 is effective in the treatment of PsA and psoriasis.[29] The investigation of new targets for SpA treatment is in constant evolution, and many new drugs will be available in a short period of time, improving the therapeutic tools for SpA.

REFERENCES

1. Khan MA. Update on Spondyloarthropathies. Ann Intern Med. 2002;136(12):896-907.

2. Rudwaleit M et al. The development of Assessment of SpondyloArthritis. International Society classification criteria for axial spondyloarthritis (part I): Classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis. 2009;68(6):770-6.

3. Rudwaleit M et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): Validation and final selection. Ann Rheum Dis. 2009;68(6):777-83.

4. Rudwaleit M et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25-31.

5. Stolwijk C et al. The global prevalence of spondyloarthritis: A systematic review and meta-regression analysis. Arthritis Care Res (Hoboken). 2015. [Epub ahead of print]

6. Thomas GP, Brown MA. Genetics and genomics of ankylosing spondylitis.

Immunol Rev. 2010;233(1):162-80.

7. Brown MA et al. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. Arthritis Rheum. 1997;40(10):1823.

8. van der Heijde D et al.; Assessment of SpondyloArthritis international Society (ASAS). ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:1811-8.

9. Brown MA et al. Recurrence risk modelling of the genetic susceptibility to ankylosing spondylitis. Ann Rheum Dis. 2000;59(11):883-6.

10. Reveille JD. Biomarkers for diagnosis, monitoring of progression, and treatment responses in ankylosing spondylitis and axial spondyloarthritis. Clin Rheumatol. 2015;34:1009-18.

11. Ben Dror L et al. The HLA-B*2705 peptidome. Arthritis Rheum. 2010;62: 420-9.

12. López de Castro JA. The HLA-B27 peptidome: building on the cornerstone. Arthritis Rheum. 2010;62(2):316-9.

13. Sorrentino R et al. HLA-B27 and antigen presentation: at the crossroads between immune defense and autoimmunity. Mol Immunol. 2014;57(1):22-7.

14. Castro-Santos P et al. [Genetics of ankylosing spondylitis]. Rev Med Chil. 2014;142:1165-73.

15. Yamaguchi A et al. Association of HLA-B39 with HLA-B27-negative ankylosing spondylitis and pauciarticular juvenile rheumatoid arthritis in Japanese patients. Evidence for a role of the peptide-anchoring B pocket. Arthritis Rheum. 1995;38(11):1672-7.

16. Giovannini L et al. One year in review 2015: Spondyloarthritis. Clin Exp Rheumatol. 2015;33:769-78.

17. Benjamin M, McGonagle D. The enthesis organ concept and its relevance to the spondyloarthropathies. Adv Exp Med Biol. 2009;649:57-70.

18. Maksymowych WP et al. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. Ann Rheum Dis. 2013;72(1):23-8.

19. Jacques P, McGonagle D. The role of mechanical stress in the pathogenesis of spondyloarthritis and how to combat it. Best Pract Res Clin Rheumatol. 2014; 28:703-10.

20. Vieira-Sousa E et al. Review: animal models as a tool to dissect pivotal pathways driving spondyloarthritis. Arthritis Rheum. 2015;67(11):2813-27.

21. Reveille JD, Weisman MH. The epidemiology of back pain, axial spondyloarthritis and HLA-B27 in the United States. Am J Med Sci. 2013;345:431.

22. Rudwaleit M et al. How to diagnose axial spondyloarthritis early. Ann Rheum Dis. 2004;63(5):535-43.

23. Vander Cruyssen B et al. Hip involvement in ankylosing spondylitis: Epidemiology and risk factors associated with hip replacement surgery. Rheumatology (Oxford). 2010;49(1):73-81.

24. Jacques P et al. Proof of concept: Enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. Ann Rheum Dis. 2014;73:437.

25. Healy PJ, Helliwell PS. Dactylitis: Pathogenesis and clinical considerations. Curr Rheumatol Rep. 2006;8(5):338-41.

26. Muñoz-Fernández S, Martín-Mola E. Uveitis. Best Pract Res Clin Rheumatol. 2006;20(3):487.

27. Ali A, Samson CM. Seronegative spondyloarthropathies and the eye. Curr Opin Ophthalmol. 2007;18:476.

28. Mielants H et al. Course of gut inflammation in spondyloarthropathies and therapeutic consequences. Baillieres Clin Rheumatol. 1996;10:147-64.

29. Stolwijk C et al. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: A systematic review and meta-analysis. Ann Rheum Dis. 2015;74(1):65.

30. Brown MA. Human leucocyte antigen-B27 and ankylosing spondylitis. Intern Med J. 2007;37(11):739-40.

31. Sieper J et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: A guide to assess spondyloarthritis. Ann Rheum Dis. 2009; 68 Suppl 2:ii1-44.

32. Rojas-Vargas M et al. First signs and symptoms of spondyloarthritis--data from an inception cohort with a disease course of two years or less (REGISPONSER-Early). Rheumatology (Oxford). 2009;48:404.

33. Siannis F et al. Clinical and radiological damage in psoriatic arthritis. Ann Rheum Dis. 2006;65(4):478-81.

34. Delle Sedie A, Riente L. Psoriatic arthritis: What ultrasound can provide us. Clin Exp Rheumatol. 2015;33:S60-5.

35. Braun J et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011;70(6):896-904.

36. Caso F et al. Pharmacological treatment of spondyloarthritis: Exploring the effectiveness of nonsteroidal anti-inflammatory drugs, traditional disease-modifying antirheumatic drugs and biological therapies. Ther Adv Chronic Dis. 2015;6:328-38.

37. Rios Rodriguez V, Poddubnyy D. Old and new treatment targets in axial spondyloarthritis. RMD Open. 2015; 1(Suppl 1):e000054.

38. Poddubnyy D et al. Ustekinumab for the treatment of patients with active ankylosing spondylitis: Results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). Ann Rheum Dis. 2014;73(5):817-23.

EVALUATION OF STRESS URINARY INCONTINENCE: STATE-OF-THE-ART REVIEW

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ABSTRACT

Stress urinary incontinence (SUI) in women is an endemic and costly problem. It is associated with a significant burden on both a personal and community level. Despite its association with a poor quality of life, many women choose to live with the condition without seeking medical attention. The incidence of SUI, however, is escalating, and it is most evident in women living in residential aged care facilities.

In most instances, diagnosis of SUI patients is straightforward with a demonstrable urinary leak upon coughing or employment of the Valsalva manoeuvre with a relatively full bladder. In these situations, further investigation with formal urodynamics is a matter of debate and there is no standard practice due to a lack of robust data to guide physicians. This review examines the pathophysiology and basic evaluation of SUI, and the current evidence supporting the utility of invasive urodynamic testing.

Keywords: Female stress urinary incontinence (SUI), evaluation, urodynamics.

INTRODUCTION

The 2010 joint report by the International Urogynecological Association (IUGA) and International Continence Society (ICS) defined stress urinary incontinence (SUI) as the 'involuntary loss of urine on effort, physical exertion, or on sneezing or coughing'.[1] Urinary incontinence (UI) is an endemic and costly problem, and is associated with a significant burden on both a personal and community level. The prevalence escalates with increasing age; approximately 25% of young women, and up to 75% of older women experience some involuntary urine loss.[2,3] The burden of UI is high in both human and financial terms.[4] UI has a negative impact on health-related quality of life (HRQoL)[5] and contributes to depression[6] and admission to a nursing home.[7] The estimated direct cost of UI care in the USA alone is US$19.5 billion.[4] Despite the association of UI with a poor quality of life (QoL), many women choose to live with the condition without seeking medical attention.[8]

For those who do seek medical help there has been considerable debate as to whether a basic office evaluation suffices, or if formal invasive urodynamic studies (UDS) are required before surgical management is considered. In clinical practice, the utilisation of invasive UDSs for the evaluation of UI is not well defined and varies considerably in the community. In addition to the invasive nature of the study, there is also a financial consideration; healthcare spending attributable to UDS has been estimated at approximately $400 million, at a cost of approximately $1,000 per study.[9] In 2012, the American Urological Association (AUA) and the Society of Urodynamics and Female Urology (SUFU) produced a document on UDS guidelines to guide physicians with evidence-based clinical recommendations.[10]

SUI in women relates to numerous current controversial topics within urology, and so this review aims to provide an update on the pathophysiology and basic evaluation of SUI, and the role of UDS prior to surgical intervention.

Table 1: Features of urethral biology contributing to urinary continence in women, and their comprising elements.

Factor	Elements
Mucous membrane seal	Mucosa and submucosal[11]
Urethral length	-
Urethral sphincter	External - rhabdosphincter[11] Internal - smooth muscle
Integrity of nerve innervations[11]	-
Anatomical support	Petros and Ulmsten integral theory[12,13] DeLancey's hammock theory[12]

Table 2: Risk factors for stress urinary incontinence.

Factors
• Pregnancy • Route of delivery (vaginal > caesarean delivery > nulliparous) • Menopause • Hysterectomy • Advanced age • Family history • Obesity

PATHOPHYSIOLOGY OF STRESS URINARY INCONTINENCE

There are variable contributing factors to the mechanism of continence in females. Static and dynamic components are in constant interplay to prevent urine escaping from the bladder during periods of increased abdominal pressure. These measures are dependent on equal transmission of pressure to the bladder, bladder neck, and the intra-abdominal portion of the urethra arising from optimal anatomical support. Additional contributing factors arise from supportive structures that provide a mucosal seal for optimal urethral coaptation. Such factors include the urothelial lining and the underlying connective tissue layer, the external striated and internal smooth muscle sphincters, and an intact and coordinated neural circuit.[11] Table 1 summarises the elements contributing to urinary continence.

Two significant theories of urinary continence that have improved our understanding of the structural support of the urogenital diaphragm have emerged within the last three decades. The first is DeLancey's hammock theory, where pelvic floor muscles and fasciae act as a 'hammock' that supports the bladder neck and the upper urethra. Functionally, the urethral closing pressure is dependent upon transmission of pressure to the bladder neck and the proximal urethra against the rigid support of the pelvic floor muscles, fasciae, and anterior vaginal wall.[12] More recently, Petros and Ulmsten proposed the integral theory, in which urinary continence depends upon three factors: 1) the pubococcygeus muscle, which lifts the anterior vaginal wall to compress the urethra; 2) the pelvic floor muscles that draw the hammock upwards closing the bladder neck; and 3) a taut anterior vaginal wall.[13]

RISK FACTORS

The aetiology of an incontinent urethra is not completely understood. However, some risk factors for SUI have been established, including pregnancy, the mode of delivery, menopause, hysterectomy, advanced age, family history, and obesity.

Modifiable Factors

Pregnancy and mode of delivery

Women who have experienced a vaginal delivery are at a much higher risk of SUI than nulliparous women or those who underwent a caesarean section (Table 2). In a Scandinavian study of more than 15,000 women, the prevalence of UI among nulliparous women was 10%, versus 16% in the caesarean delivery group, and 21% in the vaginal delivery group.[14] This may be the result of pregnancy and labour-induced pelvic floor musculature and connective tissue injury, in addition to nerve damage. Similarly, in a registry based national cohort study by Gyhagen et al.[15] using Swedish Pregnancy, Obesity, and Pelvic Floor (SWEPOP) data, the prevalence of UI 20 years after childbirth in singleton primiparae vaginal delivery was associated with a 67% increased risk of UI, and UI >10 years increased by 275% compared with caesarean section. However, the data indicate that eight or nine caesarean sections were required to avoid one case of UI.[15]

Hysterectomy

The role of hysterectomy in the development of SUI is poorly understood but again, may be related to direct damage to the pelvic floor.

Table 3: Preoperative evaluation.

History
• Onset/duration • Severity, pads per day • Impact on quality of life • Questionnaires - UDI-6, IIQ-7, PFDI-20 • Prolapse symptoms • Obstetrics history • Medications • Previous surgeries
Physical examination
• Cough stress test • Urethral mobility • Vaginal prolapse/atrophy • Kegel exercise • Neurological symptoms
Urinalysis
• Haematuria, pyuria
Uroflow/Post-void residual
• Flow rate/chronic retention
Bladder diary*
• Input/output • Frequency of leakage
Cystoscopy*
• Urethral stenosis/bladder lesions/haematuria
Urodynamics*
• Confirmation of SUI • Urethral function, leak point pressure • Bladder compliance • Pressure/flow parametres

*Optional (physician discretion)
UDI-6: Urogenital Distress Inventory-6; IIQ-7: Incontinence Impact Questionnaire-7; PFDI-20: Pelvic Floor Distress Inventory-short form; SUI: stress urinary incontinence.

Similarly, there is an association with vaginal prolapse, probably due to the common risk factor of pelvic floor muscles weakening.[16,17] Kudish et al.[18] reported on a Women's Health Initiative (WHI) observation study between 1993 and 1996. Post-menopausal women (aged 50–79 years) with (n=53,569) and without (n=38,524) uteri were assessed. Baseline UI incidence rate was 66.5%, with 27.3% of participants demonstrating SUI, 23% urgency urinary incontinence (UUI), and 12.4% mixed urinary incontinence (MUI). Multivariate analysis showed an association between hysterectomy and a higher incidence of an UUI and SUI episode at 3 years.[18]

Obesity

Obesity is a pandemic global health issue and has a deleterious effect on the lower urinary tract (LUT) with increased prevalence of both SUI and UUI.[19] Obesity causes chronically high intra-abdominal pressures, leading to weakening of the pelvic floor musculature and innervation. Multiple studies have shown a clear relationship between weight loss from lifestyle modification and improved UI. In a randomised controlled trial (RCT) by Subak et al.[20] 338 obese women randomised to one of two weight-loss programmes with a mean weight loss of 8 kg and 1.6 kg after 6 months had a corresponding reduction in SUI of 58% and 33%, respectively. Auwad et al.[21] also demonstrated the positive effects of weight loss from lifestyle modification, with ≥5% weight loss translating to a statistically significant improvement in both SUI (pad weight) and QoL (King's Health Questionnaire).

Non-Modifiable Factors

Advanced age is associated with both SUI and UUI.[22] In addition, there is a genetic link as women with a family history of incontinence are more likely to develop UI than those without.[23] Hormonal factors have been implicated as a contributing factor to overall urinary continence, such as oestrogen and vasogenic adrenergic receptors which are found readily in both the urethra and bladder neck. However, the magnitude of their overall influence on the continence mechanism has yet to be fully elucidated, though the higher prevalence of SUI in post-menopausal women at least suggests an indirect causal relationship.[24]

DIAGNOSIS/INVESTIGATIONS

Basic Evaluation

Given the high prevalence and personal cost of UI, it is somewhat surprising that no specific screening recommendations have been advocated by major health organisations. As many women experience infrequent leakage and choose to live with the condition, screening is likely to benefit those who are motivated to seek medical attention when their QoL is affected by UI. Each woman affected by SUI should have a comprehensive medical history and physical exam with urinalysis, post-void residual (PVR) measurements, and if appropriate, functional testing with UDS. Bladder diaries and pad usage are important adjunctive assessments (Table 3).

Recently, the American College of Obstetricians and Gynecologists (ACOG) and the American Urogynecology Society (AUGS) issued a joint document on the current understanding of UI in women, and outlined guidelines for diagnosis and management that were consistent with the best available scientific evidence. They recommended six basic clinical steps in the evaluation of female UI, which addressed: 1) history; 2) urinalysis; 3) physical examination; 4) demonstration of stress incontinence; 5) assessment of urethral mobility; and 6) PVR.[25]

History

The onset, severity, and context of UI (stress alone, urgency alone, or both) should be fully explored. Associated urinary symptoms such as frequency, urgency, haematuria, recurrent urinary tract infections, and nocturia should also be elucidated. Symptom severity can be assessed with daily pad usage and the type of pads used (pantiliners, menses pads, incontinence pads, or diapers). Relevant risk factors and gynaecological and obstetric history should be assessed. It is important to enquire about medications and prior surgical history as this can impact on treatment. Symptoms of pelvic organ prolapse (POP) with vaginal bulge are highly associated with SUI and should be explored.[17]

Questionnaires

Validated questionnaires are helpful to establish the baseline severity of UI and measure condition-specific impact on HRQoL. These can also be utilised for objective outcome measures subsequent to interventions. Numerous validated questionnaires are available to clinicians and some of the most readily used tools include: the Urogenital Distress Inventory (UDI) and Incontinence Impact Questionnaire (IIQ), especially the short forms (UDI-6, IIQ-7), which are easy to administer even in a busy practice.

Other questionnaires on UI relate to association with pelvic floor dysfunction, such as the Pelvic Floor Distress Inventory short form (PFDI-20) and the Pelvic Floor Impact Questionnaire short form (PFIQ-7),[26,27] which evaluate the relative proportion of stress versus urge (e.g. the MESA questionnaire), or focus on QoL or degree of improvement after intervention (e.g. the Patient Global Impression of Improvement [PGI-I] questionnaire).

Physical Examination

A comprehensive pelvic examination is important to establish the degree of urethral support and concurrent POP, as well as a woman's ability to perform 'Kegel' exercises. This should be established before initiating pelvic floor muscle training for treatment.[28] The POP quantification system was devised to standardise reporting of vaginal prolapse anatomically at straining in relation to a fixed reference point i.e. vaginal introitus. The classification uses six points along the vagina (two points each on the anterior, middle, and posterior compartments), measured in relation to the vaginal introitus. It is the only prolapse quantification system from the ICS, the AUGS, and the Society of Gynecology Surgeons for the quantification of POP.[29]

Applied with a reasonably full bladder (200–300 mL), a cough stress test (CST) will identify the presence of SUI in most cases. This is performed in the supine or standing position. A positive test is defined as involuntary leakage from the urethra synchronous with effort or physical exertion (straining), or sneezing or coughing. This may be repeated in the standing position if supine CST is negative. If vaginal prolapse is present, the cough test should be repeated following reduction of the prolapse for SUI assessment. Swift et al.[30] have previously reported the test-retest reproducibility of CST in the evaluation of SUI. In a cohort of 50 incontinent women, patients were tested with a CST with a bladder volume of 300 mL or at maximum capacity at the time of cystometry and this was repeated 1–4 weeks later. The conclusion indicated that the CST was most reliable in women with pure SUI (100%) and less so in those with MUI (80%).[30]

Advanced vaginal prolapse can mask SUI as it can kink the urethra resulting in outlet obstruction which protects against UI. It is not uncommon for *de novo* SUI to ensue following prolapse repair; the Colpopexy and Urinary Reduction Efforts (CARE) trial[31] and Outcomes following vaginal Prolapse repair and mid Urethral Sling (OPUS) trial[32] have shown such findings. The optimal methodology for assessing occult SUI in women with vaginal prolapse has not, however, been adequately studied. Most of the studies evaluating this have been in conjunction with prolapse reduction during urodynamics testing and not with clinical testing alone. To date, there is no clear evidence to suggest that assessment of occult SUI on clinical

testing with CST and prolapse reduction alone is comparable to UDSs.

The Q-tip cotton swab test for urethral hypermobility (normal mobility is defined as a resting angle or displacement angle of the urethra–bladder neck with maximum Valsalva of at least 30° from the horizontal) is seldom used as it can cause patient discomfort, and other methods such as point Aa of the POP Quantification system can be used instead.[33] Overall cognitive status should be assessed, along with a neurological examination. Urine analysis should be performed in all patients to assess for microscopic haematuria, glucose, protein, leukocytes, nitrites, and to exclude infection as an acute cause of UI.[34]

Post-Void Residual Urine Volume

The definition of a high PVR has not been standardised but the cut-off threshold based on the Value of Urodynamic Evaluation (ValUE) trial is generally accepted; a PVR <150 mL measured by bladder ultrasonography or catheter indicates adequate bladder emptying in women seeking to undergo SUI surgery.[34] For any discordant readings, the PVR should be repeated. An elevated PVR in the absence of POP is uncommon and warrants further evaluation of the bladder emptying mechanism with UDS.

Bladder Diary

A bladder diary can be a useful adjunct for quantifying symptoms with voided times and voided volumes and can act as a record of the number of UI episodes. A 3-day voiding diary is sufficient in most instances for assessment, accounting for daily variation in activities.[35]

Urodynamics

UDSs are a series of tests that evaluate the function of the LUT. Some components of the testing are invasive (i.e. require catheterisation) and some are non-invasive. The good UDS practice guideline established in 2002 set the benchmark for how this test should be performed. There are two phases to the testing; the cystometry phase (filling) and the pressure-flow (voiding) study. Both of these evaluate the pressure/volume relationships during bladder filling, storage, and emptying in search of a functional diagnosis.[36]

SUI is a condition of urethral dysfunction where the outlet resistance to abdominal pressure has been compromised resulting in urinary leakage. To this end, invasive urodynamics attempts to evaluate the relative condition of the outlet that may inform clinicians of treatment choices. Urethral dysfunction has been traditionally assessed with two parameters: 1) urethral pressure profile (UPP) and 2) Valsalva leak point pressure (VLPP). Urodynamics data reported by Lemack et al. from the Stress Incontinence Surgical Treatment Efficacy trial (SISTEr) (which evaluated Burch colposuspension and autologous fascial pubovaginal sling) using VLPP as a marker of severity did not find correlations with several indices of SUI severity on physical examination or UDS parameters.[37] Similarly, in the Trial Of Mid-Urethral Slings (TOMUS: a RCT of the retropubic mid-urethral sling versus the transobturator mid-urethral sling), preoperative UDSs in women with low VLPP did not impact on surgical outcome. UDS data from the TOMUS trial also suggested a limited future for the UPP in clinical practice.[38]

Whether to consider UDS testing in patients with UI has been a matter of considerable debate. The AUA/SUFU guidelines have summarised the clinical utility of UDSs for the following situations: '1) to identify factors contributing to LUT dysfunction and assess their relevance; 2) to predict the consequences of LUT dysfunction on the upper tracts; 3) to predict the consequences and outcomes of therapeutic intervention; 4) to confirm and/or understand the effects of interventional techniques; and 5) to investigate the reasons for failure of a treatment or treatments'.[10] However, with the lack of Level 1 evidence supporting routine use, the current position of invasive urodynamic testing in the diagnostic pathway for UI remains controversial and, as stated previously, practices vary considerably. This disconnect between clinicians and evidence-based application of invasive testing has led to several key randomised studies. The first is the Value of Urodynamic Evaluation (ValUE) trial; a non-inferiority RCT undertaken by the Urinary Incontinence Treatment Network with a non-inferiority margin of 11% (equivalent to a standardised difference of <0.8).

In the ValUE study, 630 women with a clinical diagnosis of SUI or stress-predominant MUI, with clinically demonstrable stress leakage, were randomised to either no further assessment or to undergo urodynamic investigation prior to their SUI corrective surgeries. The primary endpoint was treatment success defined as a ≥70% reduction in the baseline score of the urogenital distress inventory, and a PGI-I response of 'much better'

or 'very much better'. At 12 months, treatment success was equivocal in both arms; 76.9% in the urodynamic testing group versus 77.2% in the office evaluation group. Secondary outcomes included cost and utility of performing UDSs in those that had preoperative UDSs with findings of stress predominant incontinence. Again at 12 months, there was no difference between the two groups in Incontinence Severity Index, PGI-I, and global QoL measures, with both groups having similar rates of positive provocative stress tests. The report concluded that UDSs did not improve the rate of treatment success in women with uncomplicated SUI (defined as PVR urine volume <150 mL, negative urinalysis result, a positive CST result, and no POP beyond the hymen), and a well-performed office-based evaluation (including demonstration of SUI) was sufficient.[34]

Almost concurrently, a multicentre study in the Netherlands also evaluated urodynamics in similar patient groups using the Value of Urodynamics prior to Stress Incontinence Surgery (VUSIS-1), but this trial was terminated prematurely due to poor recruitment; an alternative design resulted in the VUSIS-2.[39] In this study, all women underwent invasive urodynamic testing, and only those with discordant clinical and urodynamic findings were randomised between mid-urethral sling (as dictated by their clinical assessment) or 'individual treatment' (dictated by the combination of clinical and urodynamic results). Individual treatment could include pessary, medical treatment, physiotherapy, or surgery at the discretion of the provider. Neither the participants nor healthcare professionals involved were blind to the urodynamic results in either group. The primary outcome in the VUSIS studies was based on the Dutch version of the long form UDI score at 12 months, with a secondary outcome being cost. The conclusion of the study was that in women with uncomplicated SUI, an immediate mid-urethral sling operation is not inferior to individually tailored treatment based on urodynamic findings.[39]

A recent systematic review by Rachaneni et al.[40] on whether preoperative UDSs improved surgical outcomes compared to office evaluation in women with SUI or SUI-predominant MUI (including the aforementioned two trials) reported no benefit with preoperative invasive UDSs overall in women who had a normal bladder capacity and PVR at the time of office evaluation. They further postulated that office evaluation alone may significantly impact on the delivery and cost of continence services, and has no detriment for health with the avoidance of UDSs, which some women undoubtedly see as an unpleasant and embarrassing procedure. However, this review concluded that more robust RCTs and longer-term outcomes are warranted to assess whether the current outcomes are consistent.[40]

Current guidance from the UK National Institute for Health and Care Excellence (NICE) suggests that invasive cystometry is not required prior to conservative treatments for UI, or prior to surgery where the diagnosis of SUI is clear on clinical grounds (i.e. where there are no symptoms of overactive bladder or voiding dysfunction, no anterior compartment prolapse, and no previous surgery for SUI).[28]

The Cochrane review on urodynamic investigation for the management of UI in adults and children was first reported in 2002, and the latest citations in 2012 report similar findings. The Cochrane review authors' conclusions included the following: "When women with incontinence are assessed using urodynamics in addition to clinical methods, they are more likely to receive different treatment, and to have their management plan changed. However, the evidence was not conclusive in showing whether these differences in management resulted in differences in health outcomes such as incontinence, QoL, or economic outcomes after treatment compared to women who did not have urodynamic tests." Further robust research confirming clinical utility is highly recommended.[41]

As stated, the AUA/SUFU urodynamics guidelines have made the following recommendations for SUI:[10]

1. Clinicians who are making the diagnosis of urodynamic stress incontinence should assess urethral function. (Recommendation; Evidence Strength: Grade C)
2. Surgeons considering invasive therapy in patients with SUI should assess PVR urine volume. (Expert Opinion)
3. Clinicians may perform multichannel urodynamics in patients with both symptoms and physical findings of stress incontinence who are considering invasive, potentially morbid, or irreversible treatments. (Optional; Evidence Strength: Grade C)
4. Clinicians should perform repeat stress testing with the urethral catheter removed in patients suspected of having SUI who do not demonstrate this finding with the catheter in place during urodynamic testing. (Recommendation; Evidence Strength: Grade C)

5. Clinicians should perform stress testing with reduction of the prolapse in women with high-grade POP but without the symptom of SUI. Multichannel urodynamics with prolapse reduction may be used to assess for occult stress incontinence and detrusor dysfunction in these women with associated LUTS. (Optional; Evidence Strength: Grade C)

Ambulatory urodynamics have not been particularly favoured for investigation of SUI and hence are not part of the recommendation by the International Consultation on Incontinence (ICI) for routine investigation of SUI. For the most part, it remains a research tool and the procedure is time-consuming, technically challenging, and expensive. The clinical usefulness of ambulatory urodynamics for the detection and treatment of bladder dysfunction has not been studied in detail but studies indicate that it is more sensitive in detecting detrusor muscle overactivity[42] and in those who have already undergone conventional urodynamics, particularly in the case of patients with suspected bladder acontractility and incontinence of unclear origin.[43] NICE states that ambulatory urodynamic monitoring should be used as a second-line investigational modality.[44] Further study is required to determine the clinical implications of these findings and their relationship with treatment outcome.

CONCLUSION

SUI is an endemic condition that harbours a significant personal and socioeconomic burden. The pathophysiology of SUI has evolved over past decades but remains unclear in part. Based on Level 1 evidence, basic office evaluation including a positive CST, a negative or low PVR urine volume, a negative urinalysis, and no significant prolapse was found to be non-inferior to urodynamic testing. Preoperative invasive multichannel urodynamic testing may not be necessary before planning primary anti-incontinence surgery in women with uncomplicated SUI (defined as PVR <150 mL, negative urinalysis result, and positive CST). Progress is needed to develop better tools to assess urethral function and more studies will be necessary to further clarify the role of UDSs in the evaluation of SUI.

Take-Home Messages

- SUI is a highly prevalent condition in the community and incidence continues to rise
- SUI is associated with substantial morbidity with a high impact on personal and financial cost
- Invasive urodynamic study is not required in the evaluation of women with uncomplicated SUI or SUI predominant MUI
- Invasive urodynamic study does not improve outcomes in women undergoing surgical management compared to those that had office evaluation
- More robust RCTs with longer-term follow-up are required to assess that this current trend is consistent.

REFERENCES

1. Haylen BT et al. An International Urogynecological Association (IUGA)/ International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J. 2010;21(1):5-26.

2. Carls C. The prevalence of stress urinary incontinence in high school and college-age female athletes in the midwest: implications for education and prevention. Urol Nurs. 2007;27:21-24, 39.

3. Kinchen KS et al. The prevalence, burden, and treatment of urinary incontinence among women in a managed care plan. J Womens Health (Larchmt). 2007;16: 415-22.

4. Anger JT et al.; Urologic Diseases of America Project. Increasing costs of urinary incontinence among female Medicare beneficiaries. J Urol. 2006;176(1):247-51.

5. Hunskaar S, Vinsnes A. The quality of life in women with urinary incontinence as measured by the sickness impact profile. J Am Geriatr Soc. 1991;39(4):378-82.

6. Nygaard I et al. Urinary incontinence and depression in middle-aged United States women. Obstet Gynecol. 2003;101(1): 149-56.

7. Thom DH et al. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. Age Ageing. 1997;26(5):367-74.

8. Harris SS et al. Care seeking and treatment for urinary incontinence in a diverse population. J Urol. 2007; 177(2):680-4.

9. Ward RM et al. The impact of multichannel urodynamics upon treatment recommendations for female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(9):1235-41.

10. Winters JC et al; American Urological Association, Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. Urodynamic studies in adults: AUA/SUFU guideline. J Urol. 2012;188(6 Suppl):2464-72.

11. Rovner ES et al. The UCLA approach to sphincteric incontinence in the female. World J Urol. 1997;15(5):280-94.

12. DeLancey JO. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. Am J Obstet Gynecol. 1994;170(6): 1713-20.

13. Ulmsten U, Petros P. Intravaginal

slingplasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence. Scand J Urol Nephrol. 1995;29:75-82.

14. Rortveit G et al. Urinary incontinence after vaginal delivery or cesarean section. N Engl J Med. 2003;348(10):900-7.

15. Gyhagen M et al. The prevalence of urinary incontinence 20 years after childbirth: a national cohort study in singleton primiparae after vaginal or caesarean delivery. BJOG. 2013;120(2): 144-51.

16. Brown JS et al. Hysterectomy and urinary incontinence: a systematic review. Lancet. 2000;356(9229):535-9.

17. Zargham M et al. The role of pelvic organs prolapse in the etiology of urinary incontinence in women. Adv Biomed Res. 2013;2:22.

18. Kudish BI et al. Hysterectomy and urinary incontinence in postmenopausal women. Int Urogynecol J. 2014;25(11): 1523-31.

19. Parazzini F et al.; VIVA Study Group. Risk factors for stress, urge or mixed urinary incontinence in Italy. BJOG. 2003; 110(10):927-33.

20. Subak LL et al. Weight loss to treat urinary incontinence in overweight and obese women. N Engl J Med. 2009; 360(5):481-90.

21. Auwad W et al. Moderate weight loss in obese women with urinary incontinence: a prospective longitudinal study. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(9):1251-9.

22. Sampselle CM et al. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. Obstet Gynecol. 2002;100(6):1230-8.

23. Hannestad YS et al. Familial risk of urinary incontinence in women: population based cross sectional study. BMJ. 2004;329(7471):889-91.

24. Cardozo L. Discussion: the effect of estrogens. Urology. 1997;50(6A suppl):85.

25. [No authors listed]. Urinary Incontinence in Women. Female Pelvic Med Reconstr Surg. 2015;21(6):304-14.

26. Uebersax JS et al. Short forms to assess life quality and symptom distress for urinary incontinence in women: the incontinence impact questionnaire and the urogenital distress inventory. Continence Program for Women Research Group. Neurourol Urodynam. 1995;14(2):131-9.

27. Avery KN et al. Questionnaires to assess urinary and anal incontinence: review and recommendations. J Urol. 2007;177(1):39-49.

28. National Institute for Health and Care Excellence. Urinary incontinence: the management of urinary incontinence in women. Clinical Guideline 171. 2013. Available at: www.nice.org.uk/Guidance/CG171. Last accessed: 9 March 2016.

29. Kobashi KC, "Evaluation of patients with urinary incontinence and pelvic prolapse", Wein AJ et al. (eds.), Campbell-Walsh Urology (2012) 10th edition, Philadelphia, PA: Elsevier-Saunders pp. 348-50.

30. Swift SE, Yoon EA. Test-retest reliability of the cough stress test in the evaluation of urinary incontinence. Obstet Gynecol. 1999;94(1):99-102.

31. Visco AG et al.; Pelvic Disorders Network. The role of preoperative urodynamic testing in stress-continent women undergoing sacrocolpopexy: the Colpopexy and Urinary Reduction Efforts (CARE) randomized surgical trial. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(5):607-14.

32. Wei JT et al.; Pelvic Floor Disorders Network. A midurethral sling to reduce incontinence after vaginal prolapse repair. N Engl J Med. 2012;366(25):2358-67.

33. Zyczynski HM et al.; Urinary Incontinence Treatment Network (UITN). Correlation of Q-tip values and point Aa in stress-incontinent women. Obstet Gynecol. 2007;110(1):39-43.

34. Nager CW et al.; Urinary Incontinence Treatment Network. A randomized trial of urodynamic testing before stress-incontinence surgery. N Engl J Med. 2012;366(21):1987-97.

35. Tincello DG et al. Urinary diaries: a comparison of data collected for three days versus seven days. Obstet Gynecol. 2007;109(2 Pt 1):277-80.

36. Schafer W et al.; International Continence Society. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn. 2002;21(3):261-74.

37. Albo ME et al. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007;356(21):2143-55.

38. Richter HE et al. Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med. 2010; 362(22):2066-76.

39. van Leijsen SA et al. Value of urodynamics before stress urinary incontinence surgery: a randomized controlled trial. Obstet Gynecol. 2013; 121:999-1008.

40. Rachaneni S, Latthe P. Does preoperative urodynamics improve outcomes for women undergoing surgery for stress urinary incontinence? A systematic review and meta-analysis. BJOG. 2015;122(1):8-16.

41. Clement KD et al. Urodynamic studies for management of urinary incontinence in children and adults. Cochrane Database Syst Rev. 2013;10:CD003195.

42. Pannek J, Pieper P. Clinical usefulness of ambulatory urodynamics in the diagnosis and treatment of lower urinary tract dysfunction. Scand J Urol Nephrol. 2008;42(5):428-32.

43. Rademakers KL et al. Differentiation of lower urinary tract dysfunctions: The role of ambulatory urodynamic monitoring. Int J Urol. 2015;22(5):503-7.

44. Chester J et al. The role of ambulatory urodynamics in investigation of female urinary incontinence. Int Urogynecol J. 2016;27(3):381-6.

CIRRHOSIS: REVIEWING THE LITERATURE AND FUTURE PERSPECTIVES

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ABSTRACT

Cirrhosis is the final stage of chronic liver disease and has many causes, including viral hepatitis, excessive alcohol intake, and non-alcoholic steatohepatitis. When decompensated cirrhosis develops, complications occur that affect quality of life and patient survival. Cirrhosis has a large burden of disease and is responsible for almost 2% of deaths in Europe. Cirrhotic patients are in need of early diagnosis and a careful follow-up for the prevention and detection of complications. The ultimate treatment for end-stage cirrhosis is liver transplantation. This review will cover clinical aspects of cirrhosis and uncover future trends in the care of these patients.

Keywords: Cirrhosis, diagnosis, treatment.

INTRODUCTION

Cirrhosis is the final stage of chronic liver disease. It results in distortion of the hepatic architecture by fibrosis, and the formation of regenerative nodules.[1] It is the result of progressive liver fibrosis caused by chronic liver diseases, including viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), autoimmune liver disease, and genetic disorders, amongst others. Recent reports support the finding that the early stages of cirrhosis are reversible on a microscopic level with adequate treatment of the underlying liver disease.[2] However, at more advanced stages, cirrhosis is considered irreversible. Cirrhosis is the source of a variety of complications, which result in a reduction in the life expectancy of these patients.[3] At this stage, liver transplantation is the only curative treatment option.[4]

EPIDEMIOLOGY AND AETIOLOGY

Cirrhosis has a large burden of disease. It is the eighth leading cause of death and is responsible for 1.2% of all deaths in the USA.[5] According to the Global Burden of Disease study, the worldwide prevalence of cirrhosis is increasing.[6] In the USA, the most common causes of cirrhosis are chronic hepatitis C virus (HCV), alcoholic liver disease, and non-alcoholic liver disease.[7] In Europe, liver cirrhosis accounts for 1.8% of all deaths, amounting to 170,000 deaths per year.[3] Worryingly, the reported incidence of cirrhosis remains stable or is increasing in several countries, including both the UK[8] and Ireland.[3] In Europe, the main causes are alcoholic liver disease, NASH, and HCV.[3] The four most frequent causes of cirrhosis worldwide are chronic hepatitis B virus (HBV) and HCV, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and haemochromatosis. A variety of other diseases can result in cirrhosis, although these are less frequent.[9]

Alcohol

Excessive alcohol intake remains the number one cause of cirrhosis in Western countries. A daily intake of ≥60 g/day for men, and ≥40 g/day for women is considered harmful. Chronic intake of alcohol can also accelerate the natural progression of chronic HBV or HCV,[10] and haemochromatosis. Alcohol abstinence is the cornerstone of treatment and can reverse the disease course.[11]

Viral Hepatitis

Chronic HBV and HCV are leading causes of cirrhosis, especially in endemic regions like South

East Asia and Sub-Saharan Africa. According to the disease stage, finite treatment with pegylated interferon or long-term therapy with nucleos(t)ide analogues is appropriate in HBV patients.[12] The introduction of interferon-free treatment for HCV has been important, as it has resulted in improved treatment response without significant side effects.[13] However, access to these new direct-acting agents remains a challenge due to high costs. Hepatitis A and E do not develop into chronic hepatitis in immunocompentent patients and are not considered risk factors for cirrhosis.

Non-Alcoholic Fatty Liver Disease

NAFLD is related to the presence of metabolic syndrome in association with obesity, diabetes, and/or arterial hypertension. A subset of these patients will develop signs of NASH, which can lead to the development of fibrosis and subsequently cirrhosis.[14,15] It is an increasing health problem, especially in the Western world.[6] Treatment is based on dietary measures and exercise.[14]

Haemochromatosis

Hereditary haemochromatosis is an autosomal recessive disorder characterised by excessive intestinal absorption of dietary iron, which results in a pathological increase in total body iron stores.[16] End-organ liver damage can occur, in turn leading to cirrhosis. Phlebotomy has been indicated to remove excessive iron stores.[17]

Autoimmune Hepatitis

Autoimmune hepatitis is a rare disease affecting 16–18 cases per 100,000 inhabitants in Europe. More than 30% of adult patients and ~50% of children have cirrhosis at diagnosis, due to an insidious disease course.[18] Treatment is based on immunosuppressive agents including corticosteroids and azathioprine.[18]

Primary Biliary Cholangitis and Primary Sclerosing Cholangitis

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are autoimmune diseases that affect the small and the large bile ducts, respectively. PBC can lead to progressive fibrosis resulting in cirrhosis. In PSC patients, prolonged extrahepatic cholestasis can induce the development of portal fibrosis leading to cirrhosis.[19] Ursodeoxycholic acid can slow down disease progression in PBC and can be used in PSC.[20] In PBC, newer agents, like obeticholic acid, are promising treatment options.[21]

Rare Causes of Cirrhosis

Other causes of cirrhosis include a reaction to drugs, Budd-Chiari syndrome, Wilson's disease, alpha-1 antitrypsin deficiency, granulomatous liver diseases, right-sided heart failure, and veno-occlusive disease amongst others.[9] A specific aetiology can be determined in 85–90% of patients.[22]

CLINICAL MANIFESTATION

Cirrhosis can be compensated without overt complications, or decompensated with the appearance of complications. The three major complications of cirrhosis are the consequences of portal hypertension (e.g. ascites, variceal bleeding, etc.), hepatocellular insufficiency (e.g. icterus), or the appearance of hepatocellular carcinoma (HCC).

Patients with compensated cirrhosis may present with nonspecific symptoms or may even be asymptomatic. They can complain of anorexia, weight loss, or fatigue. When decompensation develops, patients may present with jaundice, pruritus, signs of upper gastrointestinal bleeding, abdominal distension due to ascites, or confusions due to hepatic encephalopathy.[23] Hypogonadism may occur in men, which can manifest as impotence, infertility, or loss of libido.[24] In women, amenorrhoea or irregular menstrual bleeding are common.[25] Typical signs at clinical examination include jaundice, stellate angiomas, palmar erythema, foetor hepaticus, asterixis, signs of hypogonadism, and feminisation in males. Other signs include indicators of portal hypertension such as ascites, cutaneous collateral venous circulation, and splenomegaly.[23]

DIAGNOSIS

Laboratory Findings

Laboratory abnormalities may be the first indication of liver cirrhosis. Though bilirubin levels may be normal in compensated cirrhosis, the levels rise as cirrhosis progresses. Levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are moderately elevated in cirrhosis; however, normal aminotransferase levels do not exclude cirrhosis. Alkaline phosphatase is usually mildly elevated in cirrhosis. Levels higher than 2 or 3-times the upper limit of normal suggest an underlying cholestatic liver disease, such as

PSC or PBC.[20] Gamma-glutamyl transpeptidase levels correlate well with alkaline phosphatase, but are more elevated in alcohol induced chronic liver disease.[26]

Once the synthetic function of the liver is affected, albumin levels decrease and prothrombin time levels increase as key proteins involved in the coagulation cascade are produced in hepatocytes. Low platelets can appear in the case of hypersplenism.[27]

Imaging

Ultrasonography is the first step in liver imaging. It is non-invasive, widely available, affordable, and well accepted by patients. Liver volume can be normal, enlarged, or diminished, especially in advanced cirrhosis.[28] Often a nodular deformation of the liver can be observed. Other typical signs include atrophy of the right lobe of the liver, and hypertrophy of the caudate or left lobes.

When portal hypertension develops, Doppler imaging can reveal an enlarged portal vein, enlarged collateral veins, and decreased portal flow.[29] Ultrasonography is useful for the detection of hepatic nodules and is the backbone of screening programmes for the early detection of HCC.[30,31] Detection of hepatic nodules demands further characterisation using computed tomography or magnetic resonance imaging.

Non-Invasive Markers of Cirrhosis

Hepatologists are increasingly adopting the use of non-invasive markers of fibrosis and cirrhosis. These include biological markers and transient elastography (TE). Liver fibrosis can be staged using 1-dimensional ultrasound (FibroScan®, Echosens, France),[32] which measures the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver. The stiffer the tissue, the faster the shear wave propagates. Ultrasound elastography can currently be performed based on two physical principles: strain displacement/imaging, and shear wave imaging and quantification.[33] The latter includes point shear wave elastography (pSWE), also known as acoustic radiation force impulse imaging (ARFI; Virtual touch tissue quantification™, Siemens Healthcare; elastography point quantification, ElastPQ™, Philips) and 2D-shear wave elastography (2D-SWE; Aixplorer™ Supersonic Imagine, France). A major advantage of pSWE/ARFI is that it can be easily implemented on modified commercial ultrasound machines (Acuson 2000/3000 Virtual Touch™ tissue quantification, Siemens Healthcare, Germany; ElastPQ, iU22xMATRIX, Philips, Netherlands). This results in a combined approach of conventional ultrasonography with TE.[34] Correct interpretation of pSWE/ARFI results should systematically take into account potentially confounding parameters: fasting for at least 2 hours, levels of transaminases (<5-times the upper limit of normal), absence of extrahepatic cholestasis, and absence of right heart failure.[33] According to the European Association for the Study of the Liver (EASL) clinical practice guidelines, TE is a reliable method for the diagnosis of cirrhosis in patients with chronic liver diseases. TE is generally better at ruling-out rather than suggesting cirrhosis and has a negative predictive value >90%.[34]

FibroTest©, a patented biomarker (combining six serum markers with the age and gender of the patient: alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, gamma-glutamyl transpeptidase, total bilirubin, and ALT), and APRI (AST to Platelet Ratio Index calculator) are the most widely used and validated biological markers.[35] Fibrotest and APRI show an area under a receiver operating characteristic curve (AUROC) of 0.86 and 0.84,[36] respectively, for the diagnosis of cirrhosis.

Liver Biopsy

The gold standard for the diagnosis of cirrhosis is a histological examination. However, this should not be performed in all cirrhotic patients. A biopsy should be considered in patients in whom the diagnosis is in question, and when knowledge of a specific diagnosis is likely to alter the management of the disease.[37] A liver biopsy can be performed percutaneously, transjugularly, or laparoscopically. There is an inherent risk of bleeding, and severe bleeding occurs in between 1 in 2,500 and 1 in 10,000 biopsies performed using an intercostal percutaneous approach.[37]

MAJOR COMPLICATIONS

Cirrhotic patients are at risk for the development of complications, therefore cirrhotic patients should be observed more closely for decompensated cirrhosis. Once decompensation develops, the patient should be considered for liver transplantation.[4] Many complications of cirrhosis develop as a result of portal hypertension, an increased pressure in the portal circulation defined as an elevation of the hepatic venous pressure

gradient to >5 mmHg.[38] The haemodynamic abnormalities associated with portal hypertension cause the most severe complications of cirrhosis, including ascites, hepatic encephalopathy, and bleeding from gastro-oesophageal varices.

Ascites is the accumulation of fluid in the peritoneal cavity. It is treated with diuretics and sodium restriction. Some patients require repeated therapeutic paracentesis, or transjugular intrahepatic portosystemic shunt (TIPS) placement.[39] In patients with ascites, spontaneous bacterial peritonitis (SBP) may occur. Patients may be asymptomatic, present with altered mental status, or be seriously ill with a high fever, abdominal tenderness, and pain. The diagnosis is established by an elevated ascitic fluid absolute polymorphonuclear leukocyte count (≥250 cells/mm^3). The mortality is high if prompt antibiotic treatment and albumin substitution are not initiated.[39]

Hepatorenal syndrome (HRS) can develop in patients with advanced cirrhosis. HRS is the development of renal failure in patients with advanced chronic liver disease who have portal hypertension and ascites.[40] Around 40% of these patients will develop HRS during the natural history of their disease. It is caused by vasoconstriction of the renal circulation and intense systemic arteriolar vasodilatation, which results in reduced systemic vascular resistance and arterial hypotension. Following liver transplantation, the histological appearance of the kidneys is normal and the kidneys often resume normal function.[39] Treatment of HRS is based on the treatment of the precipitating factors; adequate volume replacement with albumin and vasoconstriction therapy with vasopressin analogues, such as terlipressin.[39]

Variceal haemorrhage is a dramatic event that typically presents as haematemesis and/or melaena. The mortality rate is high (20%, 30-day mortality) and treatment requires a multidisciplinary approach[41] including antibiotic treatment and endoscopic haemostasis. In selected patients, early TIPS placement can increase survival.[42]

A typical complication of cirrhosis is the occurrence of portal vein thrombosis (PVT). According to a large prospective trial in France, the 5-year cumulative incidence of PVT was 10.7%.[41] PVT is associated with the severity of liver disease at baseline and anticoagulation is indicated in patients waiting for liver transplantation.[43]

Hepatic encephalopathy encompasses a spectrum of potentially reversible neuropsychiatric abnormalities including confusion, altered level of consciousness, and coma.[44] Signs can easily be overlooked when they are limited to psychomotor slowing, a lack of attention, or sleep disturbances. Hepatic encephalopathy can be scored using the West Haven criteria. A typical sign of encephalopathy is the presence of asterixis. Treatment is based upon addressing the precipitating factors using synthetic disaccharides (e.g. lactulose) and nonabsorbable antibiotics (e.g. rifaximin).[44]

Liver cirrhosis is the most important risk factor for the development of HCC. HCC represents up to 85% of the primary liver cancer burden.[45] In patients with compensated cirrhosis the annual incidence of HCC ranges from 1–8%.[46] It is mandatory for an ultrasonography to be taken every 6 months to ensure early detection of HCC.[47,48]

FOLLOW-UP, PREVENTION OF COMPLICATIONS, AND TREATMENT

The natural course of cirrhosis is variable and can be well tolerated for many years. In these patients the primary goal should be to prevent the occurrence of complications. Slowing or even reversing the progression of liver disease can be achieved by addressing the underlying liver disease. Abstinence from alcohol improves survival in alcoholic cirrhosis.[49] Achieving a sustained viral response in HCV with antiviral treatment lowers liver-related mortality.[50]

The presence of impaired hepatic metabolism and renal excretion denotes a need for caution with many medications, which may subsequently necessitate dose adjustments or should even be avoided.[49,51] Nephrotoxic agents can precipitate HRS and should be used cautiously. Careful monitoring for the development of complications and, if possible, the prevention of complications, is the cornerstone of the treatment of a cirrhotic patient. Cirrhotic patients should undergo screening for oesophageal varices with upper endoscopy. However, according to the recent Baveno VI guidelines, patients with a liver stiffness <20 kPa, and a platelet count >150,000 can avoid screening.[52] Patients with medium or large varices require primary prevention with non-selective beta blockers or endoscopic band ligation. The role of carvedilol remains unclear.[52] Furthermore, platelet levels <100,000 can increase risk for surgery.

In a study, it was demonstrated that in patients with ascitic fluid protein <15 g/L and without prior SBP, norfloxacin (400 mg/day) reduces the risk of SBP and improves survival. In these patients, long-term primary prophylaxis should be considered.[41] Empirical antibiotics should be started immediately following the diagnosis of SBP. Furthermore, albumin (1.5 g/kg at diagnosis and 1 g/kg on Day 3) should be administered in order to decrease the risk of HRS.[41]

The presence of hepatic encephalopathy can be extremely subtle. Precipitating factors including dehydration, infection, and variceal bleeding should be avoided or addressed as soon as possible. The ultimate treatment for cirrhosis is liver transplantation, and excellent long-term results have been demonstrated.[53] It should be considered in patients with decompensated cirrhosis. The final decision depends upon the severity of the liver disease and the absence of contraindications.[4]

Patients who develop HCC should be managed according to the Barcelona Clinic Liver Cancer (BCLC) staging system.[31] Single HCC lesions in Child–Pugh A patients are eligible for resection or ablation. Intermediate stage disease patients are offered locoregional therapy including transarterial chemoembolisation or radioembolisation. In advanced or metastatic disease, sorafenib is the only remaining option; it improves median overall survival from 6 to 9 months. In patients with lesions that meet the 'Milan criteria' liver transplantation should be considered.[31]

PROGNOSIS

The prognosis of patients with compensated cirrhosis is excellent. Transition from the compensated to the decompensated stage occurs at a rate of 5–7% per year.[11] The median survival rate in compensated cirrhosis is >12 years.[11] Once patients develop complications of cirrhosis, such as ascites, variceal bleeding, or HRS, they are considered to have decompensated cirrhosis and their prognosis is worse.

Two models are commonly used for prognosis evaluation: the Child–Pugh classification and the Model for End-Stage Liver Disease (MELD). The Child–Pugh classification includes the variables serum albumin and bilirubin, ascites, encephalopathy, and prothrombin time.[54] The ranges from 5 to 15, and patients are divided into Child–Pugh A (score 5–6), B (score 7–9), or C (score 10–15). One-year survival rates for Child–Pugh A, B, and C patients are 100%, 80%, and 45%, respectively.[55] MELD score is calculated using bilirubin levels, creatinine, and international normalised ratio.[56] It is now used for prioritising patients on the liver transplant waiting list. Patients with a MELD score of >10 should be referred to a liver transplant centre for evaluation.

There is a growing interest in the use of non-invasive tests for the prognosis of chronic liver disease, particularly for TE in patients with cirrhosis.[34] The Baveno VI consensus paper[52] introduced the term 'compensated advanced chronic liver disease' (cACLD). This term applies to patients with chronic liver disease at increased risk of developing clinically significant portal hypertension, defined as a hepatovenous pressure gradient of ≥10 mmHg. TE values <10 kPa in the absence of other known clinical signs rule out cACLD. Values between 10–15 kPa are suggestive of cACLD but need confirmation. Values >15 kPa are highly suggestive of cACLD. Patients with cACLD are at an increased risk for complications and should be referred to a liver disease specialist.[52]

CONCLUSION

Cirrhosis is the final stage of chronic liver disease. The aim of a clinician dealing with cirrhosis should be to prevent the development of major complications. A new trend in this field is the adoption of non-invasive techniques, e.g. TE for diagnosis of cirrhosis and follow-up of cirrhotic patients, as they are an emerging tool for risk stratification. In cirrhotic patients the performance of an ultrasonograph every 6 months remains of utmost importance for early detection of HCC. Decompensated patients have a dismal prognosis and should be referred to a specialised hepatological centre, as liver transplantation should be considered in these patients.

REFERENCES

1. Anthony PP et al. The morphology of cirrhosis. Recommendations on definition, nomenclature, and classification by a working group sponsored by the World Health Organization. J Clin Pathol. 1978;31(5):395-414.

2. Buti M et al. Long-term clinical outcomes in cirrhotic chronic hepatitis B patients treated with tenofovir disoproxil

fumarate for up to 5 years. Hepatol Int. 2015;9(2):243-50.

3. Blachier M et al. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol. 2013; 58(3):593-608.

4. Murray KF, Carithers RL. AASLD practice guidelines: Evaluation of the patient for liver transplantation. Hepatology. 2005;41(6):1407-32.

5. Murray CJ et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA. 2013;310(6): 591-608.

6. Vos Tet al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(9995):743-800.

7. Wong RJ et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148(3):547-55.

8. Fleming KM et al. Incidence and prevalence of cirrhosis in the United Kingdom, 1992-2001: a general population-based study. J Hepatol. 2008; 49(5):732-8.

9. Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. Am Fam Physician. 2006; 74(5):756-62.

10. Frieden TR et al. Chronic liver disease in central Harlem: the role of alcohol and viral hepatitis. Hepatology. 1999;29(3):883-8.

11. D'Amico G et al. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol. 2006;44(1):217-31.

12. Lampertico P et al. Optimal management of hepatitis B virus infection – EASL Special Conference. J Hepatol. 2015;63(5):1238-53.

13. European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2014;60(2):392-420.

14. Ratziu V et al. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol. 2010;53(2):372-84.

15. Marchesini G et al. Diet, Weight Loss, and Liver Health in NAFLD: Pathophysiology, Evidence and Practice. Hepatology. 2015. [Epub ahead of print].

16. Kanwar P, Kowdley KV. Diagnosis and treatment of hereditary hemochromatosis: an update. Expert Rev Gastroenterol Hepatol. 2013;7(6):517-30.

17. Brissot P. Optimizing the diagnosis and the treatment of iron overload diseases. Expert Rev Gastroenterol Hepatol. 2015:1-12. [Epub ahead of print].

18. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015;63(4):971-1004.

19. Boonstra K et al. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol. 2012;56(5):1181-8.

20. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. J Hepatol. 2009;51(2): 237-67.

21. Trivedi PJ et al. Obeticholic acid for the treatment of primary biliary cirrhosis. Expert Rev Clin Pharmacol. 2016;9(1): 13-26.

22. Charlton MR et al. Liver transplantation for cryptogenic cirrhosis. Liver Transpl Surg. 1997;3(4):359-64.

23. Peck-Radosavljevic M et al. Managing complications in cirrhotic patients. United Eur Gastroenterol J. 2015;3(1):80-94.

24. van Thiel DH et al. Patterns of hypothalamic-pituitary-gonadal dysfunction in men with liver disease due to differing etiologies. Hepatology. 1981;1(1):39-46.

25. Burra P et al. Sexual dysfunction in chronic liver disease: is liver transplantation an effective cure? Transplantation. 2010;89(12):1425-9.

26. Goldberg DM. Structural, functional, and clinical aspects of gamma-glutamyltransferase. CRC Crit Rev Clin Lab Sci. 1980;12(1):1-58.

27. Chrostek L, Panasiuk A. Liver fibrosis markers in alcoholic liver disease. World J Gastroenterol. 2014;20(25):8018-23.

28. Benhamou JP et al., "Cirrhoses," Maladies Du Foie et Des Voies Biliaires (2008), Paris: Médecine-sciences Flammarion, pp.82-6.

29. Zwiebel WJ. Sonographic diagnosis of hepatic vascular disorders. Semin Ultrasound CT MR. 1995;16(1):34-48.

30. Trinchet JC et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: A randomized trial comparing 3- and 6-month periodicities. Hepatology. 2011;54(6):1987-97.

31. Llovet JM et al. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012; 56(4):908-43.

32. Sandrin L et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol. 2003;29(12):1705-13.

33. Bamber J et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med. 2013;34(2):169-84.

34. Castera L et al. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015;63(1):237-64.

35. Castera L, Bedossa P. How to assess liver fibrosis in chronic hepatitis C: serum markers or transient elastography vs. liver biopsy? Liver Int. 2011;31 Suppl 1:13-7.

36. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med. 2013;158(11):807-20.

37. Rockey DC et al. Liver biopsy. Hepatology. 2009;49(3):1017-44.

38. de Franchis R et al. Definitions, methodology and therapeutic strategies in portal hypertension. A Consensus Development Workshop, Baveno, Lake Maggiore, Italy, April 5 and 6, 1990. J Hepatol. 1992;15(1-2):256-61.

39. Ginès P et al. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397-417.

40. Salerno F et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Postgrad Med J. 2008;84(998):662-70.

41. Nery F et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015;61(2):660-7.

42. Francoz C et al. Portal vein thrombosis, cirrhosis, and liver transplantation. J Hepatol. 2012;57(1):203-12.

43. Colle I et al. "Varices, Portal hypertensive gastropathy and GAVE," Lee S, Moreau R, (eds.), Cirrhosis. A Practical Guide to Management (2015), Chichester: John Wiley & Sons Inc, pp. 137-50.

44. García-Pagán JC et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010;362(25):2370-9.

45. Vilstrup H et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol. 2014;61(3): 642-59.

46. Perz JF et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45(4): 529-38.

47. Pellicoro A et al. Liver fibrosis and repair: immune regulation of wound healing in a solid organ. Nat Rev Immunol. 2014;14(3):181-94.

48. Bruix J, Sherman M. AASLD PRACTICE GUIDELINE Management of Hepatocellular Carcinoma : An Update. Hepatology. 2010;42:1-35.

49. Mathurin P, Bataller R. Trends in the management and burden of alcoholic liver disease. J Hepatol. 2015;62(1 Suppl):S38-S46.

50. Singal AG et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol. 2010;8(3):280-8.

51. Lewis JH, Stine JG. Review article: prescribing medications in patients with cirrhosis - a practical guide. Aliment Pharmacol Ther. 2013;37(12):1132-56.

52. de Franchis R. Expanding Consensus in Portal Hypertension: Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015; 63(3):743-52.

53. Adam R et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol. 2012;57(3):675-88.

54. Pugh RN et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-9.

55. Infante-Rivard C et al. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. Hepatology. 7(4):660-4.

56. Kamath PS et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464-70.

IN-STENT RESTENOSIS AFTER CAROTID ARTERY STENTING: FROM DIAGNOSIS TO TREATMENT

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ABSTRACT

Although carotid artery stenting is a safe and effective treatment for preventing ischaemic stroke in significant carotid atherosclerotic disease, it can be complicated by in-stent restenosis (ISR). Factors involved in the ISR process are both mechanical and patient-related, but the most important is the neo-intimal thickening within stent struts, leading to lumen reduction. Overall incidence of carotid ISR is low and related embolic risk seems to be lower than native disease. Digital subtraction angiography is the gold standard for diagnosis. Nowadays, Doppler ultrasound should be considered the first-line investigation, due to its non-invasiveness and reproducibility. Computed tomography angiography remains useful when Doppler ultrasound is inconclusive. Indication and modality of treatment of ISR are still debated: both surgery (carotid endarterectomy with stent removal in most cases) or interventional procedures such as percutaneous transluminal angioplasty with simple balloon, cutting-balloon, drug-eluting balloon, and stenting, showed safety and efficacy in follow-up. Surgery is currently reserved for selected cases. Carotid ISR is an overall rare complication which can be easily identified at routine follow-up. This paper is a literature review and state-of-the-art assessment of ISR, clinical features, diagnosis, and treatment.

Keywords: Carotid artery stenting (CAS), carotid in-stent restenosis (ISR), Doppler ultrasound (DUS).

BACKGROUND

Ischaemic stroke represents a major health problem and is an important cause of long-term disability in developed countries. Mortality ranges between 10% and 30%[1] considering both myocardial infarction (MI) and recurrent stroke. Atherosclerosis from supra-aortic vessels and especially from the common carotid bifurcation is a major cause of recurrent ischaemic stroke, accounting for approximately 20% of all strokes,[2] nearly 80% of which may occur without warning. Carotid endarterectomy (CEA) is currently the established treatment for significant carotid stenosis. Randomised controlled trials show that CEA is safe and effective, reducing the risk of ischaemic stroke in both symptomatic and asymptomatic patients. Percutaneous carotid artery stenting (CAS) was initially proposed as an alternative treatment for high-risk patients, but accumulating data from a recent randomised controlled trial[3,4] suggest that CAS and CEA achieve similar long-term outcomes in terms of ischaemic stroke reduction. Compared with CEA, endovascular treatment is associated with significantly lower risks of MI (odds ratio [OR]: 0.44), cranial nerve palsy (OR: 0.08), and access site haematoma (OR: 0.37).[5] Restenosis after CAS is a poorly described phenomenon. Poor and discordant data are available on incidence, predictors, diagnostic approach, and therapeutic strategies.

IN-STENT RESTENOSIS: INCIDENCE AND PATHOPHYSIOLOGY

In-stent restenosis (ISR) likely results from vessel trauma causing physical irritation, endothelial dysfunction, and chronic inflammation leading to subsequent neo-intimal hyperplasia. It generally occurs <24 months after the first procedure or as *de novo* atherosclerosis.[6,7] The real incidence of ISR after CAS is unclear, with reports ranging from <5% to >21%.[8-11] Lal et al.[6] observed an incidence of 42.7% of patients with restenosis causing >40% diameter reduction and 16.4% with restenosis causing >60% diameter reduction at 5-year follow-up. Data from a retrospective investigation involving 3,179 CAS procedures, reporting the incidence of restenosis (defined as narrowing of ≥50% and peak systolic velocity [PSV] >175 cm/s), showed an acceptable rate of annual ISR >50% of 1.49% and a cumulative rate at 5 years of 6%.[12]

Suggested predictors of ISR after CAS are advanced age, female sex, implantation of multiple stents, prior revascularisation treatment, suboptimal result with residual stenosis, elevated post-procedural serum levels of acute phase reactants, asymptomatic lesion, use of balloon-expandable stents,[11] and stent sub-expansion.[13] The clinical impact of significant ISR is uncertain, but neo-intimal hyperplasia seems to be associated with a reduced potential of embolisation compared with native lesions.[6,14] In most trials the higher incidence of ISR during follow-up was not found to have an impact on complication rates. It has therefore been postulated that restenosis might be a relatively benign disease.[7,15,16] In contrast, a study involving 215 patients and 12 reported cases of restenosis support showed that during the long-term follow-up period, the combined rate of ipsilateral stroke and death was significantly higher in the restenosis group (33.3% versus 10.8%).[17] In addition, de Donato et al.[12] demonstrated that stroke rate in the group of ISR patients was slightly superior to patients without ISR. Regarding stent technology, two types of stents have been mainly used until now: open-cell and close-cell stents. Open-cell stents are designed to keep some of the segments free from the adjacent rings, allowing greater adaptation to the vessel anatomy but less plaque coverage and higher risk of tissue prolapse. Closed-cell stent designs are characterised by a higher density of bridge interconnection, which reduces their conformability and increases the probability of malapposition but at the same time offers greater plaque coverage. Most registries show poor correlation between in-hospital and 30-day mortality, and stent design.[18,19] A study with intravascular optical coherence tomography after CAS confirmed that stent malapposition is more frequent with closed-cell stents, while plaque prolapse is more common with open-cell stents.[20] Long-term differences in terms of restenosis between open-cell and closed-cell stents have yet to be well evaluated. De Donato et al.[12] showed that post-procedural complication rates (stroke, transient ischaemic attack, death) are higher for the open-cell types and increase with larger free cell area. No difference in terms of restenosis was present in long-term follow-up; it has been suggested that after complete endothelisation of the stent, differences in stent type probably no longer play an important role.[21] A recent non-randomised, retrospective study comparing stent types by multidetector computed tomography angiography (CTA) showed that at follow-up, ISR was more common in the open-cell stent group (16 of 91 patients with open-cell stents and 3 of 84 patients with closed-cell stents had focal restenosis), without differences in clinical outcomes.[22]

A novel carotid stent design has recently been developed: the double layer mesh stent, which includes features of both stent types. It comprises an internal micromesh layer for plaque coverage and an external self-expanding nitinol layer for scaffolding, offering the flexibility that characterises open-cell design stents; in an initial experiment with seven patients this stent seemed to be safe and effective in the treatment of extracranial internal carotid artery (ICA) stenosis but further data are necessary.[23]

FROM DIAGNOSIS...

Digital subtraction angiography (DSA) is the gold standard for diagnosis of carotid ISR but it is associated with several complications such as access site haemorrhage, risk of thromboembolism, and iodinated contrast medium adverse reactions. It also carries a significant risk of morbidity and mortality, ranging from 1–4%.[24] Doppler ultrasound (DUS) is frequently used for routine follow-up after CAS because it is an easily used and non-invasive diagnostic tool. The degree of lumen diameter reduction, PSV, end-diastolic velocity (EDV), and the ratio of peak ICA to common carotid artery (CCA) velocity (ICA/CCA ratio)

are the most common parameters used for stenosis quantification. Accuracy of DUS compared with DSA has been evaluated in several studies. Keberle et al.[25] demonstrated a correlation between the two techniques of 97% (r=0.97; p<0.001). The sensitivity and specificity in the detection of high-degree stenosis were 100% and 93.3%, respectively. Cumbie et al.[26] found that a PSV ≥205 cm/s had a sensitivity and specificity of 100% and 96%, respectively, in detecting ISR ≥80%, whereas an ICA/CCA ratio ≥2.6 yielded sensitivity and specificity of 100% and 94%, respectively. They also found that EDV was not a good predictor of significant ISR, while the combination of PSV and ICA/CCA had 100% sensitivity and 97% specificity. When compared with CTA, DUS showed a specificity of 97.7%, sensitivity of 100%, a positive predictive value of 98.4%, and a negative predictive value of 100% for the detection of ICA restenosis.[27] A study involving 814 CAS procedures, 6,427 DUS examinations, and 1,123 angiographies found ISR ≥70% and ISR ≥50% in 22 patients and in 73 patients, respectively; DUS analysis using a combination of the three parameters (PSV, EDV, and ICA/CCA) achieved a specificity of 99% and a sensitivity of 98% for ISR ≥70% compared with angiography.[28]

Criteria for diagnosis of restenosis are not well established. Many studies have reported different parameters and cut-off values for ISR definition. Moreover, a stented artery has different biomechanical properties that make it comparable to a rigid tube, with the enhanced stiffness resulting in increased velocity. Lal et al.[29] showed that as the elastic modulus increases after stenting, the compliance of the vessel decreases. According to this evidence, they proposed adjusted criteria for the definition of stenosis in stented arteries, validated by angiography (Table 1).[30] A review[31] of 14 studies showed that, with computed tomography and angiographic control, DUS threshold values indicating a significant restenosis with a diameter reduction of 70%, 75%, or 80% were PSV threshold at 300–350 cm/s consistently, while EDV thresholds varied slightly more at 90–140 cm/s; the ICA/CCA ratio varied from 3.8–4.7. It was suggested to record the Doppler parameters of the stented vessel early after CAS and use them as a new starting point. This new baseline can help the subsequent follow-up, which should be as regular as possible since few data are available on the course of ISR. Lal et al.[6] also suggested a classification model for ISR based on morphology (Figure 1). The pattern of ISR together with the elevation in PSV and ICA/CCA ratios are indicative of the severity of ISR. According to this classification, Type III and IV lesions need treatment more frequently when associated with an 80% lumen stenosis. Regarding the clinical relevance of types of restenosis, they also showed that diffuse proliferative (Type IV) ISR lesions (and diabetes) were important determinants of long-term outcome after CAS.

CTA is a non-invasive technique with high resolution and quick acquisition times. In native lesions, it is the imaging technique of choice in the case of tortuous carotid, severe calcification, short neck, and high bifurcation.[32] Sensitivity of this technique is 100% for severe native stenosis (≥70%), with a specificity of 63%; the negative predictive value of CTA demonstrating <70% carotid artery stenosis was 100%.[33] For ISR detection CTA has some limitations such as beam hardening from the metallic stent, which may make evaluation of the residual lumen difficult. Furthermore, the need for external beam radiation and injection of intravenous iodinated contrast medium limit the use of CTA for selected cases. New evidence is needed from selected studies involving patients with carotid ISR to assess the real diagnostic value of computed tomography in this setting.

Magnetic resonance angiography (MRA) is a safe, non-invasive, and high resolution imaging technique for carotid artery stenosis, with no need for radiation. MRA in native carotid lesions has a pooled sensitivity and specificity of 95% and 90%, compared with DSA in detecting stenosis ≥70% versus <70%, whereas in the same study DUS showed a sensitivity and specificity of 96% and 100%, respectively.[34] For detecting occlusion, both DUS and MRA are very accurate. Contrast enhanced MRA appears to overcome the limitations seen with unenhanced MRA; however, it does not offer significant advantages over two dimensional time of flight MRA.[35] Metallic related artefacts can hamper the use of MRA for evaluation of ISR. Thus, CTA is preferred to MRA for surveillance of carotid ISR,[36] and we can assert that DUS is the first test for imaging follow-up in patients treated with carotid stents.

In selected cases, when results of DUS are inconclusive, CTA is required. Discrepancies in results with either of these techniques should be confirmed using DSA.

Table 1: Comparison of parameters for defining stenosis between native and stented carotid artery as criteria for diagnosis.

Reduction in vessel diameter from stenosis (%)	Native carotid artery	Stented carotid artery
0–19	PSV <130 cm/sec	PSV <150 cm/sec ICA/CCA ratio <2.15
20–49	PSV 130–189 cm/sec	PSV 150–219 cm/sec
50–79	PSV 190–249 cm/sec EDV <120 cm/sec	PSV 220–339 cm/sec ICA/CCA ratio ≥2.7
80–99	PSV ≥250 cm/sec EDV ≥120 cm/sec ICA/CCA ratio ≥3.2	PSV ≥340 cm/sec ICA/CCA ratio ≥4.5

CCA: common carotid artery; EDV: end-diastolic velocity; ICA: internal carotid artery; PSV: peak systolic velocity.
PSV and EDV measurements for stented carotid arteries are performed within the stented segments.
Adapted from Lal BK et al.[30]

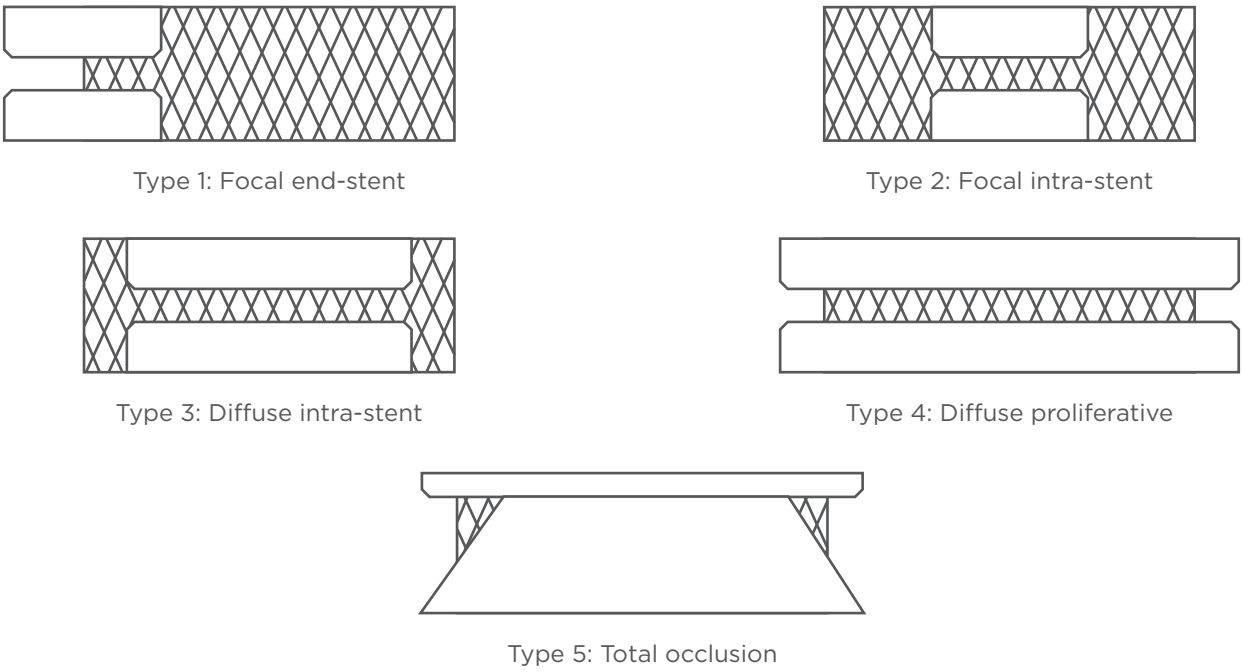

Figure 1: Morphologic description and classification of in-stent restenosis.
Adapted from Lal BK et al.[30]

...TO TREATMENT

The treatment of choice for ISR is still largely debated and no indications have been clearly established, due to the lack of sufficient data. Surgeons currently base their choice on the angiographic appearance of the lesions and the operators' experience. Surgical treatment options include CEA with stent removal or artery bypass. Percutaneous interventional approaches include balloon angioplasty alone (percutaneous transluminal angioplasty [PTA]), cutting balloon angioplasty (CB-PTA), stenting, brachytherapy, and more recently drug-eluting balloon (DEB) angioplasty.

The first step in preventing ISR is to reduce modifiable clinical risk factors. Diabetes, dyslipidaemia, and smoking are independent predictors of restenosis or occlusion after CAS procedures.[37] For this reason it is reasonable to think that a good glycaemic control and low levels

of HbA1c should be a strong recommendation to these patients; in fact in coronary ISR, low levels of HbA1c are related to reduced major adverse cardiac events at long-term follow-up, mainly for reduction in target vessel revascularisation.[38] Topakian et al.[39] showed that high post-procedural high density lipoprotein cholesterol level, measured 1 month after CAS, is a weak, but independent, predictor of carotid stent patency at 1 year; they also showed that ISR was significantly associated with continuous smoking. The authors of this study therefore suggest a strict control of cholesterol levels and cessation of smoking. Use of statins is associated with decreased peri-operative and late ischaemic stroke risk and reduced mortality rates in patients undergoing CAS, but lacks a significant benefit in terms of reduction of restenosis rate.[40]

Although there is no specific pharmacological therapy to reduce incidence of carotid ISR, cilostazol seems to have a positive impact. A recent meta-analysis including seven studies and 1,297 patients treated with CAS showed a significantly lower ISR rate with cilostazol treatment after a mean follow-up of 20 months, without affecting MI/stroke/death events, both in the early and late settings.[41]

Several studies indicate that endovascular treatment, including balloon angioplasty and CB-PTA alone or in conjunction with additional stenting, is the preferred strategy to treat carotid ISR.[42] A review[43] of several studies involving patients with carotid ISR treated with percutaneous approach revealed that after ISR intervention, recurrent restenosis occurred in 12 of 84 cases (14%): 8 after repeat PTA and 4 after repeat CAS placement. One study enrolled 16 cases of ISR (on 482 primary CAS procedure); 13 (81.3%) patients were treated with balloon angioplasty and 3 (18.7%) had the stent removed: patency rates were 68.8% and 81.3%, respectively. These data show that ISR is an ongoing process that requires frequent repeated interventions due to recurrence after primary treatment by balloon angioplasty alone.[44] Recently, a balloon-expandable zotarolimus-eluting stent (ZES) was used by Tekieli et al.[45] to treat significant ISR after CAS in seven patients; at long-term follow-up (mean 17 months) five patients revealed no evidence of restenosis or stent fracture/deformation. In the other two patients the ZES was implanted at the distal edge and protruded beyond the original carotid stent, causing deformation/kinking of the segment and leading to symptomatic stent occlusion over time. This suggests that ZES treatment is feasible and effective if it is placed within the original stent. Evidence is accumulating to support the efficacy of DEBs as a new endovascular strategy for ISR treatment.[46] Montorsi et al.[47] treated seven carotid ISR patients with DEB and there was no ISR recurrence, as measured by DUS, at a mean follow-up of 13.7 months. Vajda et al.[48] recently reported DEB treatment of intracranial stent restenosis in 51 patients. Compared to conventional balloons, the ISR recurrence rate was significantly lower with DEB (9% versus 50%) at 8-month follow-up. Limited data exist on the use of DEB as a treatment of ISR in extracranial CAS. Gandini et al.[49] analysed seven patients treated with DEB for recurrent ISR after a previous endovascular treatment for carotid ISR; over a mean follow-up of 36.6±2.7 months, ultrasound imaging identified recurrent ISR in only three patients at 32 months after DEB angioplasty. The target vessel revascularisation rate was 33.3% at 36 months, concluding that DEB may have a potential role in improving outcomes of those patients treated for early recurrent carotid ISR. Few cases have been treated with brachytherapy.[50]

Regarding surgical treatment, CEA with stent removal is the most frequently used technique: it is reserved for heavily calcified lesions with suboptimal primary stenting results, pre-occlusive lesions no longer approachable by PTA, stent technical failure, and primary stent thrombosis. Endovascular treatment is usually preferred when surgical limitations on stented carotid artery are present, mainly: 1) carotid artery dissection may be difficult or even impossible owing to an intense peri-arterial inflammatory process that may envelop the vessels after CAS; 2) the inflammatory reaction within the stented artery causes tight stent adherence to the arterial wall, making identification of the endarterectomy plane very difficult; 3) the use of a long stent makes it difficult to dissect out the entire stent and sometimes it is impossible to safely gain proximal and/or distal control of the CCA and ICA; 4) the difficulty involved in cutting the artery caused by the metallic stent; and 5) the care required during removal of the stent to avoid vessel wall penetration because of the vessel wall thinning from the stent coils. A recent review[51] collected 41 cases of ISR in the literature treated with CEA

and stent removal; primary closure of the arteriotomy was performed in 5 patients; 3 patients (7.3%) needed graft interposition; and 33 (80.5%) were closed with a venous or prosthetic patch. A good postoperative outcome was achieved in 85.4% of cases (without ischaemic events or neck haematoma); 7.3% of patients presented transient ischaemic stroke in the early period after surgery; neck haematoma requiring surgical revision was present in 7.3% of patients. In long-term follow-up (mean 15.3 months) no adverse neurological events or recurrent restenosis were reported.

A consensus on the best treatment modality in different cases of carotid ISR is not currently available. New DUS criteria enables the selection of patients with a particularly high-risk lesion; in these cases, medical therapy should be chosen only when invasive treatment is high-risk, based mainly on clinical status and comorbidities. Invasive treatment should be planned by a multidisciplinary team, involving interventional cardiologists, vascular surgeons, DUS experts, radiologists, and anaesthesiologists to discuss both patient and plaque features, along with local resources. In general, endovascular treatment is recommended as the first choice wherever possible, mainly because it is the less invasive option and has good results. The choice should be made on a case-by-case basis with a careful analysis of the lesion features mentioned previously, along with a patient-specific consideration of the advantages and disadvantages of both endovascular and surgical treatment.

CONCLUSION

Restenosis after CAS is a developing and complex process which occurs in 5% to >20% of patients. We suggest a careful selection of patients with native atherosclerotic carotid lesions suitable for endovascular treatment, in order to avoid high-risk procedures for mechanical complication and subsequently ISR. Several diagnostic techniques are available to accurately diagnose ISR; DUS is frequently used as a baseline diagnostic tool because it is non-invasive, easy to perform, and reproducible at follow-up. Using the new ISR patterns classification we are able to recognise patients who need invasive therapy, or determine the correct timing of the next follow-up investigation. ISR is a phenomenon under investigation, and the treatment of choice is still largely debated. Lack of sufficient data implies that no clear indications have been established, although non-invasive strategies show encouraging results when used after an appropriate selection of cases. A multidisciplinary expert team is the best way to choose the optimal treatment modality. ISR after CAS represents a challenge for the application of new techniques in the field.

REFERENCES

1. Mohr JP et al. The Harvard Cooperative Stroke Registry a prospective registry. Neurology. 1978;28(8):754-62.

2. Veith FJ et al. Current status of carotid bifurcation angioplasty and stenting based on a consensus of opinion leaders. J Vasc Surg. 2001;33(2 Suppl):S111-6.

3. Bonati LH et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. Lancet. 2015,385(9967):529-38.

4. Brott TG et al. Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis. N Engl J Med. 2016;374(11):1021-31.

5. Bonati LH et al. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev. 2012;9: CD000515.

6. Lal BK et al. Patterns of in-stent restenosis after carotid artery stenting: classification and implications for long-term outcome. J Vasc Surg. 2007;46(5): 833-40.

7. Eckstein HH et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. Lancet Neurol. 2008;7(10):893-902.

8. Diethrich EB et al. Stenting in the carotid artery: initial experience in 110 patients. J Endovasc Surg. 1996;3(1):42-62.

9. Yadav SS et al. Elective stenting of the extracranial carotid arteries. Circulation. 1997;95(2):376-81.

10. Leger AR et al. Poor durability of carotid angioplasty and stenting for treatment of recurrent artery stenosis after carotid endarterectomy: an institutional experience. J Vasc Surg. 2001; 33(5): 1008-14.

11. Christiaans MH et al. Restenosis after carotid angioplasty and stenting: a follow-up study with duplex ultrasonography. Eur J Vasc Endovasc Surg. 2003;26(2): 141-4.

12. de Donato G et al. Long-term results of carotid artery stenting. J Vasc Surg. 2008; 48(6):1431-40.

13. Di Gioia G et al. Percutaneous Treatment of Recurrent In-Stent Restenosis of Carotid Artery Stenting: A Case Report and State-of-the-Art Review. Am J Case Rep. 2015;(16):558-62.

14. Van Laanen K et al. Factors influencing restenosis after carotid artery stenting. J Cardiovasc Surg (Torino). 2008;49(6): 743-7.

15. Arquizan C et al; EVA-3S Investigators. Restenosis is more frequent after carotid stenting than after endarterectomy: the EVA-3S study. Stroke. 2011;42(4):1015-20.

16. Naylor AR. Stenting versus endarterectomy: the debate continues. Lancet Neurol. 2008;7(10):862-4.

17. Wasser K et al. Clinical impact and predictors of carotid artery in-stent restenosis. J Neurol. 2012;259(9): 1896-902.

18. Jim J et al. Society for Vascular Surgery Vascular Registry evaluation of stent cell design on carotid artery stenting outcomes. J Vasc Surg. 2011;54(1):71-9.

19. Timaran CH, Rosero EB, Higuera A, Ilarraza A, Modrall JG, Clagett GP. Randomized clinical trial of open-cell vs closed-cell stents for carotid stenting and effects of stent design on cerebral embolization. J Vasc Surg. 2011;54(5): 1310-16.

20. De Donato G et al. Optical coherence tomography after carotid stenting: rate of stent malapposition, plaque prolapse and fibrous cap rupture according to stent design. Eur J Vasc Endovasc Surg. 2013;45(6):579-87.

21. Bosiers M et al. Does free cell area influence the outcome in carotid artery stenting? Eur J Vasc Endovasc Surg. 2007;33(2):135-41; discussion 142-3.

22. Alparslan B et al. The Effect of Stent Cell Geometry on Carotid Stenting Outcomes. Cardiovasc Intervent Radiol. 2016;39(4):507-13.

23. Hopf-Jensen S et al. Initial clinical experience with the micromesh Roadsaver carotid artery stent for the treatment of patients with symptomatic carotid artery disease. J Endovasc Ther. 2015;22(2):220-5.

24. Hankey GJ et al. Complications of cerebral angiography for patients with mild carotid territory ischaemia being considered for carotid endarterectomy. J Neurol Neurosurg Psychiatry. 1990; 53:542-8.

25. Keberle M et al. [Comparison of 3D power Doppler ultrasound, color Doppler ultrasound and digital subtraction angiography in carotid stenosis]. Rofo. 2001;173(2):133-8.

26. Cumbie T et al. Utility and accuracy of duplex ultrasonography in evaluating in-stent restenosis after carotid stenting. Am J Surg. 2008;196(5):623-8.

27. Aleksic N et al. Color duplex sonography in the detection of internal carotid artery restenosis after carotid endarterectomy: comparison with computed tomographic angiography. J Ultrasound Med. 2011;30(12):1677-82.

28. Setacci C et al. Grading carotid intrastent restenosis: a 6-year follow-up study. Stroke. 2008;39(4):1189-96.

29. Lal BK et al. Carotid artery stenting: is there a need to revise ultrasound velocity criteria? J Vasc Surg. 2004;39(1):58-66.

30. Lal BK et al. Duplex ultrasound velocity criteria for the stented carotid artery. J Vasc Surg, 2008;47(1):63-73.

31. Pizzolato R et al. Imaging challenges of carotid artery in-stent restenosis. J Neurointerv Surg. 2014;6(1):32-41.

32. Corti R et al. Spiral computed tomography: a novel diagnostic approach for investigation of the extracranial cerebral arteries and its complementary role in duplex ultrasonography. Circulation. 1998;98(10):984-9

33. Josephson SA et al. Evaluation of carotid stenosis using CT angiography in the initial evaluation of stroke and TIA. Neurology. 2004;63(3):457-60.

34. Nederkoorn PJ et al. Duplex ultrasound and magnetic resonance angiography compared with digital subtraction angiography in carotid artery stenosis: a systematic review. Stroke. 2003;34(5): 1324-32.

35. Babiarz LS et al. Contrast-enhanced MR angiography is not more accurate than unenhanced 2D time-of-ight MR angiography for determining >=70% internal carotid artery stenosis. AJNR Am J Neuroradiol. 2009;30(4): 761-8.

36. Goldman CK et al. Surveillance imaging for carotid in-stent restenosis. Cath Cardiovasc interv. 2006;67(2): 302-8.

37. Lal BK et al; CREST Investigators. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. Lancet Neurol. 2012;11(9):755-63.

38. Kassaian SE et al. Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. Cardiovasc Diabetol. 2012;11:82.

39. Topakian R et al. Postprocedural high-density lipoprotein cholesterol predicts carotid stent patency at 1 year. Eur J Neurol. 2008;15(2):179-84.

40. Verzini F et al. Effects of statins on early and late results of carotid stenting. J Vasc Surg. 2011;53(1):71-9.

41. Galyfos G et al. Meta-Analysis of Studies Evaluating the Effect of Cilostazol on Major Outcomes After Carotid Stenting. J Endovasc Ther. 2016;23(1):186-95.

42. Groschel K et al. Systematic review of early recurrent stenosis after carotid angioplasty and stenting. Stroke. 2005; 36(2):367-73.

43. Van Haaften AC et al. Therapeutic options for carotid in-stent restenosis: review of the literature. J Vasc Interv Radiol. 2010;21(10):1471-7.

44. Donas KP et al. Balloon angioplasty for in-stent stenosis after carotid artery stenting is associated with an increase in repeat interventions. J Endovasc Ther. 2011;18(5):720-5.

45. Tekieli L et al. Zotarolimus-eluting stent for the treatment of recurrent, severe carotid artery in-stent stenosis in the TARGETCAS population. J Endovasc Ther. 2012;19(3):316-24.

46. Gray WA, Granada JF. Drug-coated balloons for the prevention of vascular restenosis. Circulation. 2010;121(24): 2672-80.

47. Montorsi P et al. Drug-eluting balloon for treatment of in-stent restenosis after carotid artery stenting: preliminary report. J Endovasc Ther. 2012;19(6):734-42.

48. Vajda Z et al. Neurovascular in-stent stenoses: treatment with conventional and drug-eluting balloons. Am J Neuroradiol. 2011;32(10):1942-47.

49. Gandini R et al. Long-term results of drug-eluting balloon angioplasty for treatment of refractory recurrent carotid in-stent restenosis. J Endovasc Ther. 2014; 21(5):671-7.

50. Chan AW et al. Carotid Brachytherapy for In-Stent Restenosis. Catheter Cardiovasc Interv. 2003;58(1):86-9.

51. Zheng J et al. Carotid Endarterectomy with Stent Removal in Management of In-stent Restenosis: A Safe, Feasible, and Effective Technique. Eur J Vasc Endovasc Surg. 2014;47(1):8-12.

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HEPATITIS C: IS REGRESSION OF ADVANCED FIBROSIS POSSIBLE AFTER TREATMENT?

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ABSTRACT

Liver cirrhosis represents a severe complication for hepatitis C patients. Patients with cirrhosis require immediate treatment; a sustained virological response has been demonstrated to reduce the probability of complications and to improve the prognosis. The optimal outcome of treatment is regression, which in many cases is difficult to achieve due to histological changes. Nevertheless, cirrhosis regression has been reported in >50% of patients treated with antiviral drugs who were assessed by biopsy both before and after treatment. Similar results were obtained when transient elastography was used to estimate fibrosis stage. However, more studies with longer follow-up periods are necessary to confirm whether the decrease in liver stiffness resulting from a sustained virological response to a direct-acting antiviral is correlated with improved clinical outcomes.

Keywords: Hepatitis C, liver cirrhosis, regression fibrosis, liver biopsy, elasticity imaging techniques, therapy.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide. Its long-term impact ranges from minimal damage to extensive fibrosis and cirrhosis, which is sometimes accompanied by hepatocellular carcinoma (HCC).[1]

The objective of chronic hepatitis C (CHC) treatment is to achieve a sustained virological response (SVR), defined as the absence of viral replication 12 or 24 weeks after treatment completion. A SVR which is stable over time, reduces morbidity and mortality, and is considered in most cases to be equivalent to cured HCV infection.[2,3] However, complications such as HCC can emerge in patients with a SVR following treatment.[4-7] Studies are still needed to determine whether the life expectancy of these subjects is similar to that observed in the general population.[8]

Many causes of chronic liver disease, including autoimmune hepatitis, haemochromatosis, total parenteral nutrition-related cirrhosis, and primary biliary cholangitis result in cirrhosis that may regress.[9] It has been shown that in some cases, viral suppression in chronic hepatitis B, and SVR in CHC, improve fibrosis and cirrhosis,[10] however definitive data is lacking.

FROM THE NORMAL LIVER TO CIRRHOSIS

Although cirrhosis is the end-stage of every chronic liver disease, its natural history varies significantly. An asymptomatic or 'compensated' phase of cirrhosis is rapidly followed by a progressive stage that is marked by the development of portal hypertension related complications and/or liver dysfunction, called 'decompensated cirrhosis'.[11] Evidence suggests that cirrhosis is an extremely heterogeneous pathological condition that is neither static nor regularly progressive but rather dynamic and bidirectional with a wide spectrum of clinical manifestations.

The liver is organised into lobes, with blood streaming from the portal tract to the central vein throughout the hepatocyte trabecula. A normal liver contains no fibrous tissue, which is formed when repetitive injury drives an unregulated healing response, resulting in an imbalance in

the extracellular matrix and the progressive replacement of functional liver parenchyma with fibrous tissue.[8,12,13]

During the compensated stage, pre-clinical cirrhosis is defined histologically (using the METAVIR and Ishak scoring systems) as a diffuse process in which the normal anatomical lobules are replaced by architecturally abnormal nodules separated by fibrous tissue.[8,13,14] The histological progression of viral hepatopathies is characterised by the formation of fibrous tissue around the portal tract, and of fibrotic bridges between the portal tract and the nearby central vein.[14] Fibrosis is scored in stages, whereas necroinflammation is evaluated by grade. Stratification of fibrosis is defined by the amount of fibrosis and the degree of architectural disorganisation. These semiquantitative histological classifications are widely used.[13,14]

In cirrhotic patients (F4 in the METAVIR classification), functional liver tissue is replaced by fibrous tissue composed of different molecules, including highly cross-linked collagen.[13,14] Cirrhosis is characterised by annular fibrosis that is associated with architectural reorganisation, which drives a shift from lobular to nodular organisation.[12] Other commonly observed abnormalities include: angiogenesis, vascular remodelling, sinusoidal capillarisation, and perisinusoidal fibrosis. All of these processes lead to portal hypertension and, finally, liver decompensation.[13,14] Moreover, two different substages (1 and 2) have been identified based on the absence or presence of gastro-oesophageal varices, resulting in different outcomes.[8]

IS CIRRHOSIS REVERSIBLE?

Cirrhosis represents the final form of fibrosis in almost every chronic hepatopathy.[13] Until recently, fibrosis and cirrhosis were considered irreversible, and the goal of treatment was to halt the progression of these conditions.[9] It has since been demonstrated, in both animal and human models, that cirrhosis may regress or revert in some cases, but it is first necessary to eliminate the causative injury.[10,13,15,16]

Mechanisms of fibrosis have focussed on hepatic stellate cells, which become fibrogenic myofibroblasts during injury through 'activation'. Recent studies have clarified pathways of stellate cell gene regulation and epigenetics, emerging pathways of fibrosis regression through the recruitment and amplification of fibrolytic macrophages, nuanced responses of discrete inflammatory cell subsets, and the identification of the 'ductular reaction' as a marker of severe injury and repair.[17] Most of this attention has been focussed on stellate cell and myofibroblast responses given their critical roles in extracellular matrix production, yet liver injury elicits a complex multicellular response involving other resident cells, such as hepatocytes, macrophages, sinusoidal endothelium, and distinct families of infiltrating immune cells including B cells, natural killer (NK) and NK T cells, and myeloid-derived suppressor cells.[17]

Three conditions must be met for the reversion of fibrosis to occur: a) fibrous tissue must be degraded, b) fibrosis must be replaced by newly formed hepatocytes (i.e. regeneration), and c) normal lobular architecture must be restored.[13] The first condition for reversion, fibrotic septal degradation, is achieved via metalloprotease digestion.[18] Some hallmarks of evolved fibrosis, such as the presence of extensive collagen crosslinking or accumulated elastic fibres, may impair enzymatic degradation by the metalloproteases. It is therefore reasonable that recently established cirrhosis reverts more easily than long-term cirrhosis.[13] The second condition for reversion, regeneration of hepatocytes, requires the downregulation of the inflammatory response. In CHC, the inflammatory response stops when a SVR has been achieved. Both age and the number of necrosis and regeneration cycles have been implicated as factors in the regenerative capacity of hepatocytes. In atrophic cirrhosis, the capacity to regenerate hepatocytes is decreased, and cirrhosis reversion is improbable.[19] Finally, the most restrictive factor in cirrhosis regression is the ability to revert to a lobular organisation from a nodular one.[12] Portal tracts can emerge after fibrosis reabsorption, but this process is improbable in cases of portal venous or central thrombosis.

In summary, regression is more likely in cases of recent cirrhosis, controlled aetiology, and extant regenerative capacity, as well as in the absence of portal thrombosis.[13] Furthermore, in decompensated cirrhotic patients, the effect of treating fibrosis has not been yet studied; until recently, interferon (INF) treatment was the only accepted care regimen for CHC, though it is contraindicated in decompensated patients.[10] Therefore, the exact point at which cirrhosis becomes irreversible remains unknown.[8]

Table 1: Rates of cirrhosis regression measured by liver biopsy in hepatitis C virus patients who achieved sustained virological response with interferon-based therapy.

Study	Patients with cirrhosis, n	Fibrosis scoring system	Regression rates, n (percentage of total cohort, %)
Arif et al.[36]	6	Ishak	5 (83)
George et al.[5]	8	Ishak	6 (75)
Maylin et al.[38]	14	Metavir	9 (64)
Pol et al.[37]	17	Metavir	4 (24)
Shiratori et al.[34]	24	Metavir	11 (46)
Poynard et al.[35]	37	Metavir	25 (68)
D'Ambrosio et al.[39]	38	Metavir	23 (61)
Mallet et al.[4]	39	Metavir	17 (44)

HOW CAN CIRRHOSIS REGRESSION BE DEMONSTRATED?

Hepatic fibrosis stage is the principal predictor of liver disease progression and determines the treatment regimen.[20] Historically, liver biopsy has been the gold standard for staging liver fibrosis.[20] However, because it is an invasive and expensive technique that is marred by sampling error as well as intra and inter-observer variability, non-invasive methods, such as the FibroTest or transient elastography (TE), are currently preferred for patients with CHC.[21-24] Moreover, the current histological classification system was not designed to assess cirrhosis regression. Recently, the use of the Laennec classification has been proposed for this purpose, as follows: F4a: cirrhosis with macronodules and thin septa; F4b: cirrhosis with micronodules and thick septa; and F4c: atrophic cirrhosis with small nodules and large, thick fibrotic septa. The last class is least likely to regress.[25]

Currently, non-invasive methods are preferred for measuring liver fibrosis because they pose fewer risks, are better tolerated by patients, and are suitable for longitudinal study of changes in fibrosis in HCV patients.[26,27] TE is the most accurate non-invasive method for detecting cirrhosis in patients with viral hepatitis and it can be considered the non-invasive standard for the measurement of liver stiffness (LS).[28] LS is correlated with liver fibrosis and cirrhosis, as determined by liver biopsy.[27,29] Its values are strongly correlated with the METAVIR fibrosis stages. However, a substantial overlap of LS values was observed between lower fibrosis stages so TE performs better for detection of cirrhosis than for detection of significant fibrosis.[28] Thus, TE is considered a surrogate marker of fibrosis.[30,31] TE has been validated for the diagnosis of liver-related complications and has high prognostic value for predicting liver-related death and overall survival.[8,25,27,32-34] However, the use of TE is problematic in some cases; an improvement in fibrosis might be confused with a decrease in inflammation after treatment; might not appear the same in cases of obesity or ascites; and can yield false positives in cases of acute hepatitis, extrahepatic cholestasis, or hepatic congestion.[11,25,28,29,35] Despite their advantages over liver biopsy, the use of non-invasive methods to evaluate the evolution of long-term fibrosis and cirrhosis after treatment has not been sufficiently validated.[25,36]

The following section will discuss the lines of evidence supporting cirrhosis regression in some patients with CHC after treatment, including data obtained via liver biopsy and non-invasive methods such as TE.

Cirrhosis Regression Defined by Liver Biopsy

Several studies have used liver biopsy to assess the evolution of liver fibrosis after antiviral treatment of CHC with INF or pegylated interferon (PEG-INF), either with or without ribavirin (RBV). These studies have demonstrated that antiviral therapy can improve liver histology[4,5,36-44] although few cirrhotic patients have been evaluated[45] (Table 1).

In a recent meta-analysis of six studies involving 137 patients with cirrhosis who achieved a SVR following PEG-INF and RBV treatment, the

regression of cirrhosis was assessed by performing a biopsy before and after antiviral therapy.[45] The regression of cirrhosis was defined as a reduction of the METAVIR stage to ≤F3 or of the Ishak fibrosis score to ≤4. In this meta-analysis, liver biopsies obtained from patients who had achieved a SVR revealed the regression of cirrhosis in 73 cases (53%). However, the cirrhosis regression rates among the included studies varied widely, ranging from 24–83%. The authors observed that SVR led to an almost 3-fold increase in the chance of cirrhosis regression, and found that the severity of liver disease is a good predictor of antiviral response. Furthermore, regression may be less likely in patients with more advanced or established cirrhosis.

TRANSIENT ELASTOGRAPHY ASSESSMENT OF THE IMPACT OF TREATMENT AND SUSTAINED VIROLOGICAL RESPONSE ON FIBROSIS AND CIRRHOSIS

Several studies have assessed the validity of TE for evaluating longitudinal disease regression and the progression of fibrosis in patients with CHC of any genotype who were treated with PEG-INF-α and RBV.[8,31,46-54] These studies utilised different designs and treatment regimens, and follow-up periods ranged from 24 weeks[50] to 4 years.[49] Previous studies demonstrated a significant reduction in LS in treated patients compared with untreated controls,[27,29] although the use of control patients cannot currently be justified.

The most important finding in the majority of studies was the significant decrease of LS and biomarker values compared with baseline in patients with HCV who had achieved SVR after PEG-INF and RBV treatment.[8,20,36,47-54] For example, when TE is used as a marker of fibrosis, the cirrhosis regression rate appeared to be higher, ranging from 60–89% in a recent systematic review of three studies involving 56 patients.[10] The high regression rates and variability between studies warrant cautious interpretation; to date, the number of patients evaluated has been limited and different techniques for measuring fibrosis have been used, along with different cut-offs and follow-up periods.

Other studies have reported the regression of advanced fibrosis using other non-invasive markers. A large retrospective study with a 10-year mean follow-up period found that after treatment, fibrosis, as measured by the FibroTest, improved in 49% of patients with advanced baseline fibrosis who had achieved a SVR.[7]

Impact of New Antivirals on Liver Fibrosis Measured by Transient Elastography

The development of direct antiviral agents (DAAs) has increased the SVR rate in patients with HCV and has resulted in faster viral clearance than previous treatments have achieved.[55] Recently, our group used TE to evaluate fibrosis regression in patients treated with HCV protease inhibitors (PIs).[56] The authors of this paper are not aware of any other studies that have evaluated DAAs or other INF-free treatment in this manner.

This study sought to determine whether LS decreased after treatment with a first-generation PI (e.g. boceprevir or telaprevir) in conjunction with PEG-INF and RBV in patients with the HCV genotype 1. Only patients with advanced fibrosis were analysed (TE >9.5 kPa, equivalent to an F3 and F4 classification) because they had a greater risk of developing complications, thus it was imperative that they achieved SVR and decreased fibrosis.[26,56] Patients with decompensated cirrhosis were excluded.

A decrease in LS by the end of the follow-up period compared with the baseline was observed in 77% of patients overall. This decrease was equivalent to >30% of the baseline fibrosis level in almost half of cases; a somewhat higher figure of 42% was reported by Hèzode et al.[50] who used a PEG-INF and RBV treatment. After PI triple therapy, fibrosis measured by TE decreased in almost 90% of patients with a SVR (Figure 1). The decrease in LS was significantly greater in patients who had achieved a SVR (Figure 2).

In both univariate and multivariate analyses SVR alone was correlated with improved fibrosis, which was consistent with other studies.[7,50] In this study, when all other variables were held constant, SVR increased the odds of decreasing fibrosis by 18.85-fold.

An improvement in LS was also observed in some non-SVR patients.[49] This finding, which has no clear explanation, suggests an effect of treatment on fibrosis different from that of SVR. This finding has already been shown for PEG-INF and RBV treatments, which resulted in improvements in cases of relapse,[30] and, to a lesser extent, in non-responders.[31,58] This could be due to an antifibrotic effect of PEG-INF and may be unrelated to SVR.[7]

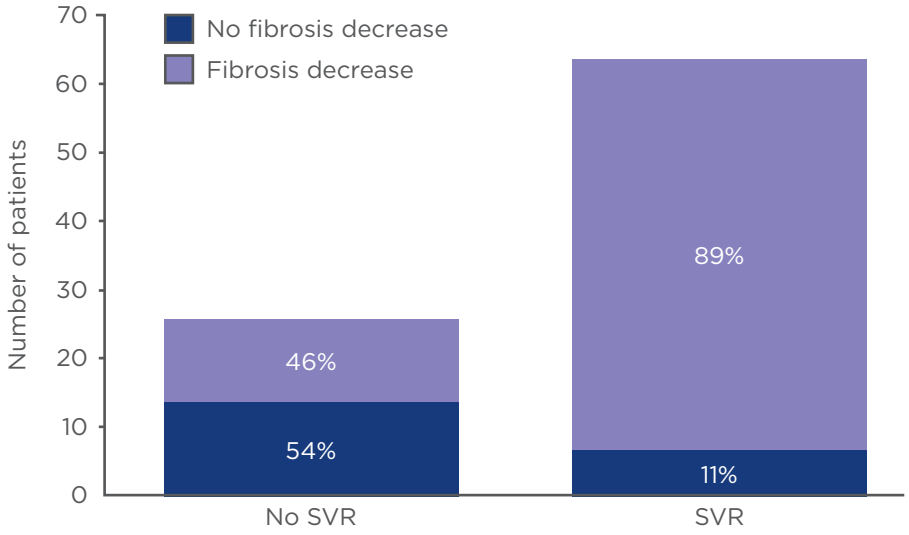

Figure 1: Number and percentage of patients with a decrease in fibrosis as measured by transient elastography in the groups with and without sustained virological response.
SVR: sustained virological response.

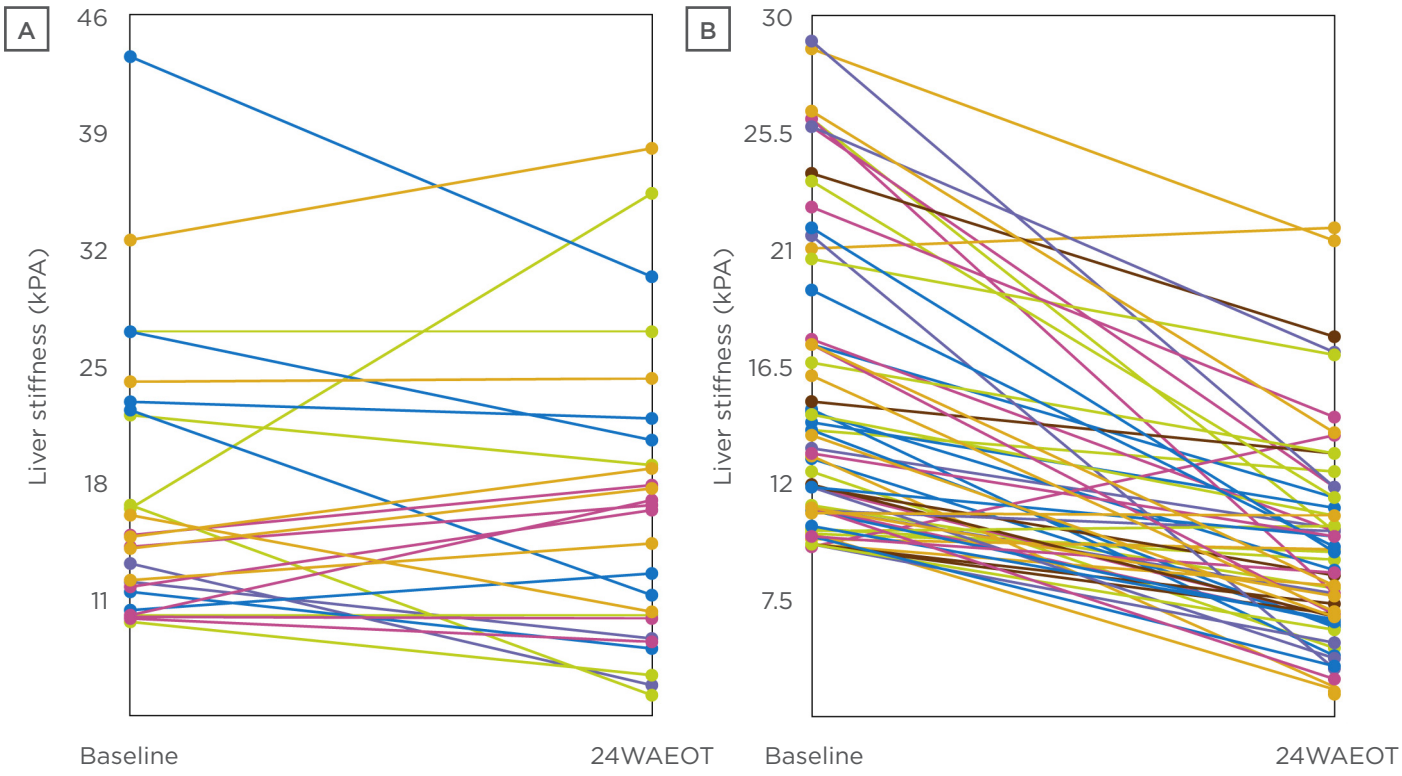

Figure 2: Individual liver stiffness changes relative to baseline at 24 weeks after treatment.
A) Patients who did not achieve sustained virological response (SVR). B) Patients who achieved SVR. Two outliers are not included in the graph.
24WAEOT: 24 weeks after the end of treatment.

In this study, LS decreased in all but one patient with cirrhosis, suggesting a decrease in fibrosis after treatment. Perhaps the most significant finding of this study was that 57% of cirrhosis patients with SVR demonstrated cirrhosis regression by TE.

WHAT IS THE CLINICAL RELEVANCE OF CIRRHOSIS REGRESSION?

SVR is considered a first step towards the reduction of future mortality in HCV-infected patients.

In cirrhotic patients, SVR improves prognosis because it reduces decompensation and the need for a liver transplant, thereby improving survival.[2,3,28]

As mentioned above, SVR is also associated with a reduction of fibrosis and the regression of cirrhosis in many patients. Nevertheless, it remains unknown whether the improvement in fibrosis is a consequence of SVR or is an independent predictive factor of a positive clinical outcome.[9] The mechanisms of hepatitis B and C treatments are different, so cirrhosis regression must be explained by different factors.[10] Current hepatitis B antiviral therapies work by chain termination thereby promoting the cessation of viral replication, but they cannot eliminate covalently closed circular DNA in the liver and even long-term treatment may not eradicate the virus, whereas DAAs against HCV may induce a virus-free state if a SVR is accomplished with only short duration of treatment.[60]

Once viral replication is suppressed in hepatitis B patients, the risk of decompensation and HCC decreases. In contrast, therapies for HCV have revolved around the use of INF, which has been limited in patients with decompensated liver disease as it results in worsening liver function.[10]

Preliminary data has shown that with the introduction of new INF-free therapies, some combinations of DAAs are indicated in decompensated cirrhosis, and involve an improvement in MELD (Model for End-stage Liver Disease) scores of ~70% only 4 weeks after treatment finalisation.[60]

Moreover, the pathogenesis of HCC is less dependent on viral replication than on the presence of cirrhosis.[10] Even in the presence of a SVR, patients with cirrhosis continue to be at risk for HCC.[10] Nowadays, patients with advanced liver disease may be treated with new INF-free antiviral treatments, for which the effects on HCC and cirrhosis regression are unknown. However, it is certain that the assessment of residual liver fibrosis in patients who achieve SVR is important for determining prognosis and for defining cost-effective surveillance programmes for liver-related complications.[42]

In decompensated HCV patients, it is still uncertain whether the severe fibrosis could be reversed to some extent. Although successful treatment outcomes in HCV-induced cirrhosis have been shown to reduce rates of HCC, it is not clear at the moment whether DAA treatment for decompensated patients confers the same benefit.[60] Some studies[7,50,56] report that LS values remained significantly higher after the SVR in patients with baseline cirrhosis compared with those without baseline cirrhosis. In addition, for reasons not yet known, advanced fibrosis and cirrhosis did not regress or progress in some patients, despite the presence of a SVR;[7,50] these patients have an increased risk of HCC compared with those in whom fibrosis had stabilised or regressed.[44] Comorbidities such as alcohol consumption, diabetes, or obesity probably play a major role in the progression of liver disease in SVR patients.[59] Screening for HCC every 6 months by ultrasound or monitoring oesophageal varices is recommended for all cirrhotic patients with an eradicated or inactive viral disease.[5,7,36]

Further investigation is needed to determine whether fibrosis amelioration and cirrhosis regression persist over a longer period of time. Data describing cirrhosis regression may play an important role in predicting long-term prognosis, assessing clinical follow-ups, and establishing the frequency of HCC screening.[10] However, more long-term studies are necessary to confirm whether the decrease in LS after achieving a SVR with DAA is correlated with improved clinical outcomes.[59]

REFERENCES

1. European Association for Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2014;60(2):392-420.

2. Singal AG et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol. 2010;8(3):280-8.

3. van der Meer AJ et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012; 308(24):2584-93.

4. Mallet V et al. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. Ann Intern Med. 2008;149(6):399-403.

5. George SL et al. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. Hepatol. 2009; 49(3):729-38.

6. Aleman S et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infectious Dis. 2013;57(2):230-6.

7. Poynard T et al. Slow regression of liver fibrosis presumed by repeated biomarkers after virological cure in patients with chronic hepatitis C. J

Hepatol. 2013;59(4):675-83.

8. Bruno S et al. Is the benefit of treating patients with cirrhosis proven? Liver int. 2016;36 Suppl 1:21-7.

9. Aghemo A, Colombo M. Cirrhosis regression in chronic hepatitis C: an old tale with a new ending. Gastroenterol. 2009;136(4):1447-9.

10. Manne V et al. Cirrhosis regression in patients with viral hepatitis B and C: a systematic review. J Clin Gastroenterol. 2014;48(9):e76-84.

11. D'Amico G et al. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44(1):217-31.

12. Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterol. 2008;134(6): 1655-69.

13. Bedossa P. Reversibility of hepatitis B virus cirrhosis after therapy: who and why? Liver Int. 2015;35 Suppl 1:78-81.

14. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatol. 1996;24(2):289-93.

15. Calvaruso V, Craxi A. Regression of fibrosis after HBV antiviral therapy. Is cirrhosis reversible? Liver Int. 2014;34 Suppl 1:85-90.

16. Kim JH et al. Clinical application of transient elastography in patients with chronic viral hepatitis receiving antiviral treatment. Liver Int. 2015;35(4):1103-15.

17. Lee YA et al. Pathobiology of liver fibrosis: a translational success story. Gut. 2015;64(5):830-41.

18. Arthur MJ. Collagenases and liver fibrosis. J Hepatol. 1995;22(2 Suppl):43-8.

19. Paradis V et al. Replicative senescence in normal liver, chronic hepatitis C, and hepatocellular carcinomas. Hum Pathol. 2001;32(3):327-32.

20. Ghany MG et al.; American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. Hepatol. 2009;49(4): 1335-74.

21. Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. J Viral Hepat. 2009;16(5):300-14.

22. Castera L, Pinzani M. Non-invasive assessment of liver fibrosis: are we ready? Lancet. 2010;375(9724):1419-20.

23. Sebastiani G et al. Chronic hepatitis C and liver fibrosis. World J Gastroenterol. 2014;20(32):11033-53.

24. Vergniol J et al. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. Hepatol. 2014; 60(1):65-76.

25. Kim SU et al. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol. 2012;57(3):556-63.

26. Friedrich-Rust M et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterol. 2008;134(4):960-74.

27. Yoshioka K et al. Transient elastography: Applications and limitations. Hepatol Res. 2008;38(11):1063-8.

28. Castera L et al. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015;63(1):237-64.

29. Afdhal NH et al. Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study. Clin Gastroenterol Hepatol. 2015;13(4):772-9.

30. Coco B et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat. 2007; 14(5):360-9.

31. Martinez SM et al. Longitudinal liver stiffness assessment in patients with chronic hepatitis C undergoing antiviral therapy. PloS One. 2012;7(10):e47715.

32. de Ledinghen V, Vergniol J. Transient elastography (FibroScan). Gastroenterol Clin Biol. 2008;32(6 Suppl 1):58-67.

33. Pang JX et al. Liver stiffness by transient elastography predicts liver-related complications and mortality in patients with chronic liver disease. PloS One. 2014;9(4):e95776.

34. Poynard T et al. Staging chronic hepatitis C in seven categories using fibrosis biomarker (FibroTest) and transient elastography (FibroScan(R)). J Hepatol. 2014;60(4):706-14.

35. Sagir A et al. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. Hepatol. 2008;47(2):592-5.

36. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterol. 2012; 142(6):1293-302.

37. Shiratori Y et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. Ann Intern Med. 2000;132(7):517-24.

38. Poynard T et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterol. 2002;122(5):1303-13.

39. Arif A et al. Regression of fibrosis in chronic hepatitis C after therapy with interferon and ribavirin. Dig Dis Sci. 2003;48(7):1425-30.

40. Pol S et al. Reversibility of hepatitis C virus-related cirrhosis. Hum Pathol. 2004;35(1):107-12.

41. Maylin S et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroenterol. 2008;135(3):821-9.

42. D'Ambrosio R et al. A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. Hepatol. 2012;56(2):532-43.

43. D'Ambrosio R et al. The diagnostic accuracy of Fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. J Hepatol. 2013;59(2):251-6.

44. Tachi Y et al. Progressive fibrosis significantly correlates with hepatocellular carcinoma in patients with a sustained virological response. Hepatol Res. 2015;45(2):238-46.

45. Akhtar E et al. Cirrhosis regression in hepatitis C patients with sustained virological response after antiviral therapy: a meta-analysis. Liver Int. 2015; 35(1):30-6.

46. Vergniol J et al. Changes of non-invasive markers and FibroScan values during HCV treatment. J Viral Hepat. 2009;16(2):132-40.

47. Arima Y et al. Reduction of liver stiffness by interferon treatment in the patients with chronic hepatitis C. Hepatol Res. 2010;40(4):383-92.

48. Wang JH et al. Liver stiffness decrease after effective antiviral therapy in patients with chronic hepatitis C: Longitudinal study using FibroScan. J Gastroenterol Hepatol. 2010;25(5):964-9.

49. Andersen ES et al. Lower liver stiffness in patients with sustained virological response 4 years after treatment for chronic hepatitis C. Eur J Gastroenterol Hepatol. 2011;23(1):41-4.

50. Hézode C et al. Liver stiffness diminishes with antiviral response in chronic hepatitis C. Aliment Pharmacol Ther. 2011;34(6):656-63.

51. Ogawa E et al. Longitudinal assessment of liver stiffness by transient elastography for chronic hepatitis B patients treated with nucleoside analog. Hepatol Res. 2011;41(12):1178-88.

52. Crisan D et al. Prospective non-invasive follow-up of liver fibrosis in patients with chronic hepatitis C. J Gastrointestin Liver Dis. 2012;21(4):375-82.

53. Calvaruso V et al. Fibrosis evaluation by transient elastography in patients with long-term sustained HCV clearance. Hepat Mon. 2013;13(5):e7176.

54. Stasi C et al. Longitudinal assessment of liver stiffness in patients undergoing antiviral treatment for hepatitis C. Dig Liver Dis. 2013;45(10):840-3.

55. Ghany MG et al.; American Association for Study of Liver Disease. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatol. 2011;54(4):1433-44.

56. Saez-Royuela F et al. Evaluation of advanced fibrosis measured by transient elastography after hepatitis C virus protease inhibitor-based triple therapy. Eur J Gastroenterol Hepatol. 2015. [Epub ahead of print].

57. Ogawa E et al. The longitudinal quantitative assessment by transient elastography of chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin. Antiviral Res. 2009;83(2):127-34.

58. Backus LI et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9(6):509-16.

59. Serfaty L. Follow-up of patients with chronic hepatitis C and a sustained viral response. Liver Int. 2016;36 Suppl 1:67-71.

60. Ohkoshi S. Direct antiviral agent treatment of decompensated hepatitis C virus-induced liver cirrhosis. World J Gastrointest Pharmacol Ther. 2015;6(4):114-9.

CHRONIC TOTAL OCCLUSION IN PATIENTS AFTER CORONARY ARTERY BYPASS GRAFTING: A REVIEW OF POSSIBLE INTERVENTIONS AND RESULTS WITH A CASE STUDY

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ABSTRACT

Within 10 years following a coronary artery bypass graft (CABG), only 60% of vein grafts and 90% of internal mammary artery (IMA) grafts remain patent. Chronic total occlusion (CTO) in patients after a CABG exhibits more advanced stable atherosclerosis. Although the precise mechanism of atherosclerosis in these patients is unknown, several clinical studies have reported that atherosclerotic progression occurs more rapidly in grafted arteries than in non-grafted arteries. These data support the fact that the IMA has a favourable metabolic effect not only in the bypass, but also in the bypassed artery, which is defined by nitric oxide products.

The occlusion frequency of the initial stenotic artery in the proximal or distal segment was ~22% after application of the IMA, and on average 48% after an autovenous bypass. In multivariate analyses, bypass interventions are independently associated with higher hospital mortality and peri-operative complications. Mortality was 2.6% if artery recanalisation was successful, 5.2% in the case of partial success, and 8.2% in the case of failure.

However, due to the difficulty of access, spastic reactions, the small diameter of the artery, and a large area of myocardium that feeds the IMA, use of the IMA for CTO recanalisation is limited. A case study of CTO intervention is used to describe the retrograde approach to CTO of the left anterior descending coronary artery through the IMA and diagonal branch in a patient after a CABG 10 years ago. Two microcatheters were used, and the operation was successfully completed in two stages because of unstable patient condition.

Keywords: Chronic total occlusion (CTO), coronary artery bypass graft (CABG), venous graft, internal mammary artery (IMA), retrograde approach.

INTRODUCTION

The need for repeated interventional/surgical procedures in patients after a coronary artery bypass graft (CABG) is determined by the condition of the coronary bypass grafts and progressive atherosclerosis of the native coronary arteries. Within 10 years following a CABG, only 60% of vein grafts and 90% of internal mammary artery (IMA) grafts remain patent. According to other data, up to 20% of autovenous grafts occlude within the first post-operative year.[1-3] Results of a post-operative coronarography show an accelerated progression of the process in the bypassed coronary artery, which leads to the progression of stenotic lesions to total coronary occlusion, which is determined not so much by the progression of the atherosclerotic process itself, but by changes to intracoronary circulation after the insertion of bypasses. With the improvement of interventional techniques, the number of repeat CABGs at recurrence clinics has declined

significantly and are carried out in 3% of all repeated interventions. A repeat CABG carries a higher risk than an initial CABG. Percutaneous coronary intervention (PCI) is the most common revascularisation procedure after a CABG.

Occlusions of coronary arteries following a repeat CABG surgery are different from those in patients without a previous CABG. Chronic total occlusion (CTO) in patients after a CABG exhibited more advanced stable atherosclerosis. Although the precise mechanism of atherosclerosis in these patients is unknown, several clinical studies have reported that atherosclerotic progression occurs more rapidly in grafted arteries than in non-grafted arteries.[4-6] Blood stasis and low shear stress resulting from competitive flow between native and bypass grafts may serve as the underlying mechanism of greater calcification in the grafted native arteries. Furthermore, the progression from severe atherosclerosis to total occlusion, which is usually located proximal to the anastomosis, is common in grafted arteries.[7-9] PCI on such occlusions are usually more time consuming and more difficult for recanalisation, which partly defines solid 'distal cup' occlusion, formed under the influence of high perfusion pressure, supported by functioning grafts.[10]

CTO treatment of native coronary arteries in patients after a CABG is less effective and more frequently performed by retrograde access through both collaterals and functioning or stenosed venous bypasses.[11-13] Interventions on stenotic venous anastomosis are quite often performed with an efficiency comparable to native coronary arteries, but with a slightly higher rate of complications.[14] Lesions of the IMA in patients after bypass surgery occurs less frequently, but artery stenting is also possible.

Most PCIs performed in prior CABG patients are undertaken in native coronary artery lesions. Compared with native PCI, bypass graft PCI is independently associated with higher in-hospital mortality.[15] As has been demonstrated, with any CTO intervention, patients in whom CTO PCI was successful had better outcomes compared with those in whom CTO PCI failed. The presence of CTO may adversely affect outcomes in patients who develop an acute coronary syndrome, as this may affect an even larger myocardial area than the target-vessel distribution.[16-18] Treatment of a native coronary artery CTO has been described for an acutely thrombosed saphenous vein graft that could not be recanalised, but it can be a challenging procedure requiring specialised equipment and expertise.[19-21]

Calcification is also associated with difficulty in obtaining success during PCI in CTO. Extensive and larger areas of calcification may explain the lower success rate of PCI in CTO patients with a prior CABG (>2 years ago) compared with CTO without a prior CABG.[8,9]

PHYSIOLOGICAL EFFECTS OF GRAFTS ON NATIVE CORONARY ARTERIES

The main advantages of a CABG with IMA use are determined not only by the duration of the bypass operation itself, but also by differences in endothelial metabolic effects of the IMA, venous bypass, and the stented segment, especially in patients with severe coronary endothelial dysfunction or in diabetes patients with multivessel disease.

In 1990, Werner et al.[22] investigated the vasoactive properties of the IMA and venous bypass in CABG patients after acetylcholine indication and found that the IMA is biologically more active than venous bypass because of more active production of endothelial factors.[6] Moreover, the study by Kitamura[23] defines different responses of the lumen depending on the artery bypassed; the presence of the IMA graft resulted in vasodilation of the bypassed coronary artery by an average of 7%, whereas the use of venous bypass leads to narrowing of the bypassed artery by 9% ($p<0.018$).[23] These data support the fact that the IMA has a favourable metabolic effect not only in the bypass, but also in the bypassed artery, which, according to the authors, is defined by nitric oxide (NO) products.[24]

Contemporary data suggest that negative remodelling of human CTOs occurs in two phases. In the early phase, a fibrin-rich, organising thrombus becomes a proteoglycan-rich thrombus. In the late phase, the proteoglycan-rich thrombus becomes replaced by dense collagen within the CTO. Furthermore, there was significantly less negative remodelling in calcified CTOs than in non-calcified, collagen-rich CTOs; severe calcification may provide a solid frame that prevents the CTO vessels from negative remodelling. As CTO with a CABG had the highest calcification, severe calcification may explain the moderate negative remodelling observed in CTOs with a CABG,

compared with the CTOs without a CABG and severe negative remodelling.[8]

CHRONIC TOTAL OCCLUSION PATTERNS IN PATIENTS AFTER CORONARY ARTERY BYPASS GRAFTS

The occlusion cups are known to influence CTO recanalisation success. Sakakura et al.[4] analysed the lumen of coronary segments proximal and distal to CTOs to determine the nature of the lumen (abrupt or tapering). The reported prevalence of the proximal abrupt lumen pattern by angiography varied from 39.1–66.1%. The prevalence of the proximal abrupt pattern was highest in CTOs with CABG surgery (58.8%). Results demonstrated that the majority of distal segments of CTO have a tapered pattern, explaining why the true lumen position of wire is greater in the retrograde approach. Additionally, the tapered pattern of a CTO lumen is a better predictor of successful PCI based on a more favourable accessibility of guidewires into true lumens. Histological correlates of angiographic CTOs have shown the influence of the duration of total occlusion on the presence of calcification, inflammation, and neovascularisation. Another important finding in angiographic CTOs was the absence of complete occlusion on histological examination (70%). The presence of a microchannel diameter of 160–230 μm in a human pathological study has thus encouraged the development of corresponding equipment.[4,7]

PROGRESSION OF NATIVE CORONARY ARTERY OBSTRUCTION

A number of researchers have studied the frequency and characteristics of lesion progression in the vessel-recipient with regard to the type of anastomosis used. The occlusion frequency of the initial stenotic artery in the proximal or distal segment was ~22% after the application of IMA, and 48% on average after autovenous bypass.[2,3,5]

Similar results were obtained by Kitamura,[23] who observed occlusion frequencies of 18% and 46%, respectively. Kitamura also provides the results of similar studies for comparison: Loop F et al. found 39% versus 67%; Manninen H et al. 26% versus 45%; and Hamada Y et al. 12% versus 38% for IMAs and the venous bypass procedure, respectively.

One explanation for these differences may be the greater blood flow in the bypass compared with the IMA and the associated reduced blood flow in the stenotic segment of the coronary artery, leading to the total coronary obstruction. On the other hand, factors produced by the endothelium of IMA may have a protective effect against the progression of coronary stenosis, possibly due to higher levels of NO production than observed in autovenous bypass.

INTERVENTIONS

Brilakis et al.[10] analysed a National Cardiovascular Data Registry report that provided results of PCI in 300,902 patients that had undergone a prior CABG. PCI of native coronary arteries was carried out in 62.5% of patients, and intervention was performed on bypasses in the remaining patients, 34.9% of whom had venous bypass PCI and 2.5% of whom had arterial bypass PCI. The study found that bypass interventions were more frequently performed in males, incurred more risk factors, and cases of acute myocardial infarction often occured.[10] In a multivariate analysis, bypass interventions were independently associated with higher hospital mortality and peri-operative complications.[10] CTO PCI in native coronary arteries in patients who underwent a CABG was performed for 16,376 patients (5.4%) and was successful in 76.6% of cases; however, there was high hospital mortality in this subgroup (3.4%). Mortality was 2.6% if artery recanalisation was successful, 5.2% in the case of a partial success, and 8.2% in the case of failure.[10,25,26]

According to contemporary data, in the absence of a prior CABG, CTO is determined in 18.4% of patients through routine coronary angiography. The effectiveness of CTO revascularisation using modern recanalisation equipment exceeds 85%. In the case of previous myocardial bypass surgery, more than half of patients with recurrent symptoms have chronic coronary artery occlusion. Recanalisation of the occluded artery in this setting causes a number of complications, and the effectiveness of revascularisation is ~80%.

Literary sources indicate that retrograde access at recanalisation of chronic occlusions of coronary arteries is more common in patients after a CABG.[27,28] The modern concept of a retrograde approach was proposed and justified by Japanese operators in 2005, and its use has since increased.[19] The methodology is constantly being refined to improve patient experience, and the creation and clinical implementation of better recanalisation equipment is ongoing.

Currently, the retrograde approach can be classified by the following conditions: direct retrograde wire crossing, kissing wire crossing, controlled antegrade and retrograde subintimal tracking (CART), and reverse CART. In accordance with the data from the Japanese retrograde registry 2009–2011, during retrograde access the septal collaterals were used in 60–65% of cases, the epicardial in 30–40% of cases, and coronary bypasses in 2–3% of cases.[15,29] Important new opportunities in the implementation of retrograde recanalisation appeared after the introduction into clinical practice of a microcatheter 'Corsair' (Asahi Intecc Co.), that allowed safer crossing of the collateral channels.[11,14,21,28]

The possibility of PCI in patients after a CABG with arterial anastomosis also warrants discussion. In contrast to venous bypasses, IMA is less prone to atherosclerotic changes, yet is more prone to spasm. The left anterior descending artery (LAD), bypassed by the internal thoracic artery, remains prone to atherosclerotic processes even with a patent IMA, and could lead to a deterioration of the clinical condition of the patient.[30,31] In addition, septal collaterals may be the only point of access for retrograde recanalisation of the right coronary artery (RCA) and the left circumflex (LCX) artery.

In view of the difficulty of access, spastic reactions, small diameter of the artery, and the large area of myocardium that feeds the IMA, use of the IMA for CTO recanalisation is limited. Nevertheless, such cases have long been described in the literature. Taking into account a long route from the origin of the IMA to the LAD lesions, the need for use of special equipment may occur.

In the literature, there are sporadic references to an effective CTO recanalisation in patients after a CABG, with access through the use of the IMA or vein bypass. Michael et al.[32] reported two cases of successful intervention in patients after CABG surgery using the retrograde approach and technology: the first case introduced the recanalisation equipment through the internal thoracic artery, and the second, in which the internal thoracic artery was used as a source of imaging in recanalisation of chronic coronary occlusion of RCA through collaterals from the native LAD, used three points of access. Torii et al.[33] described a case of successful RCA retrograde recanalisation in patients after CABG surgery and Q-wave myocardial infarction. For retrograde access septal collaterals were used, bypassed by the IMA and LAD. Access was carried out using a 5 Fr guide catheter, deeply intubating the IMA. Advance of the guiding catheter was carried out with the support of the microcatheter and stiff wire 'Grand Slam' (Asahi Intecc). Mibiki et al.[34] describe the case of successful recanalisation of CTO of the LAD via the gastroepiploic artery graft to the RCA. In this case, a 4 Fr guiding catheter was applied to the twisted gastroepiploic artery, which provided sufficient support for the recanalisation equipment.[34]

Park et al.[35] of University Hospital, Geneva, discussed the use of the 'Guideliner' catheter (Vascular Solutions Inc.) to ensure safe and successful advance of the equipment with adequate back-up. In addition, the use of 'mother and child technology' can be applied where there is insufficient visualisation of the distal part of the LAD with the existing competitive bloodstream through the left internal mammary artery (LIMA). It is worth noting that PCIs through the LIMA often pose a challenge. The procedure can be dangerous as the artery develops, straightening and accordioning after the guidewire and balloon are placed in the graft, preventing angiographic assessment if there is no flow through the graft.[30-32] In our practice, we have seen cases of significant spastic reactions during interventions in patients with distal anastomosis disease.

CASE STUDY

A 50-year-old man with a prior CABG 10 years ago (one IMA and four venous grafts) presented with severe angina and onsets of pulmonary oedema (Killip Class II) despite optimal medical treatment. A hypertension 2D echocardiography test showed an ejection fraction of 35% with anterior and inferior hypokinesia.

Coronary angiography revealed RCA CTO with graft occlusion and left main artery CTO. A venous graft to the LCX artery with 70% stenosis was patent. LIMA to the LAD was patent, but the LAD itself was diffusely diseased and occluded (Figure 1A).

After circumflex venous graft stenting, we started LAD recanalisation through the LIMA graft using a 7 Fr guiding catheter. We began with an antegrade approach, using a Corsair microcatheter (150 cm) and a 'Sion' wire, which easily navigated the large diagonals, connected by collaterals with the apical part of the occluded LAD. During our operation,

the patient experienced angina, particularly during the contrast injection. Avoiding excessive use of the contrast media injection, which can cause ischaemia and haemodynamic instability, and considering the negative aspects of subintimal LAD tracking in such a patient, we easily crossed the collaterals from the diagonal branch to the LAD retrogradely, and left the wire in the distal part of the LAD as a marker (Figure 1B). The size of the mammary artery allowed us to use one more microcatheter, the 'Finecross' (150 cm) (Terumo Interventional Systems) with a Fielder XT wire. With use of the kissing wire technique we recanalised the LAD with antegrade wire. After that, dilatation with a 1.5 mm balloon 'Trek' (Abbott Vascular) was performed. We left the Corsair in the diagonal branch to visualise the LAD without using a contrast injection through the guiding catheter (Figure 1C).

At that time the patient suffered a pulmonary oedema. We stopped the operation and started again the following day, at which point the patient's condition was stable. A coronarography demonstrated patent LAD with subocclusion at the apical part. We performed LAD stenting with Xience 2.25 mm/23 mm (Abbot Vascular) and a drug-eluting balloon angioplasty 2.0 mm/20 mm at the apical part with an acceptable angiographic and clinical result (Figure 1D).

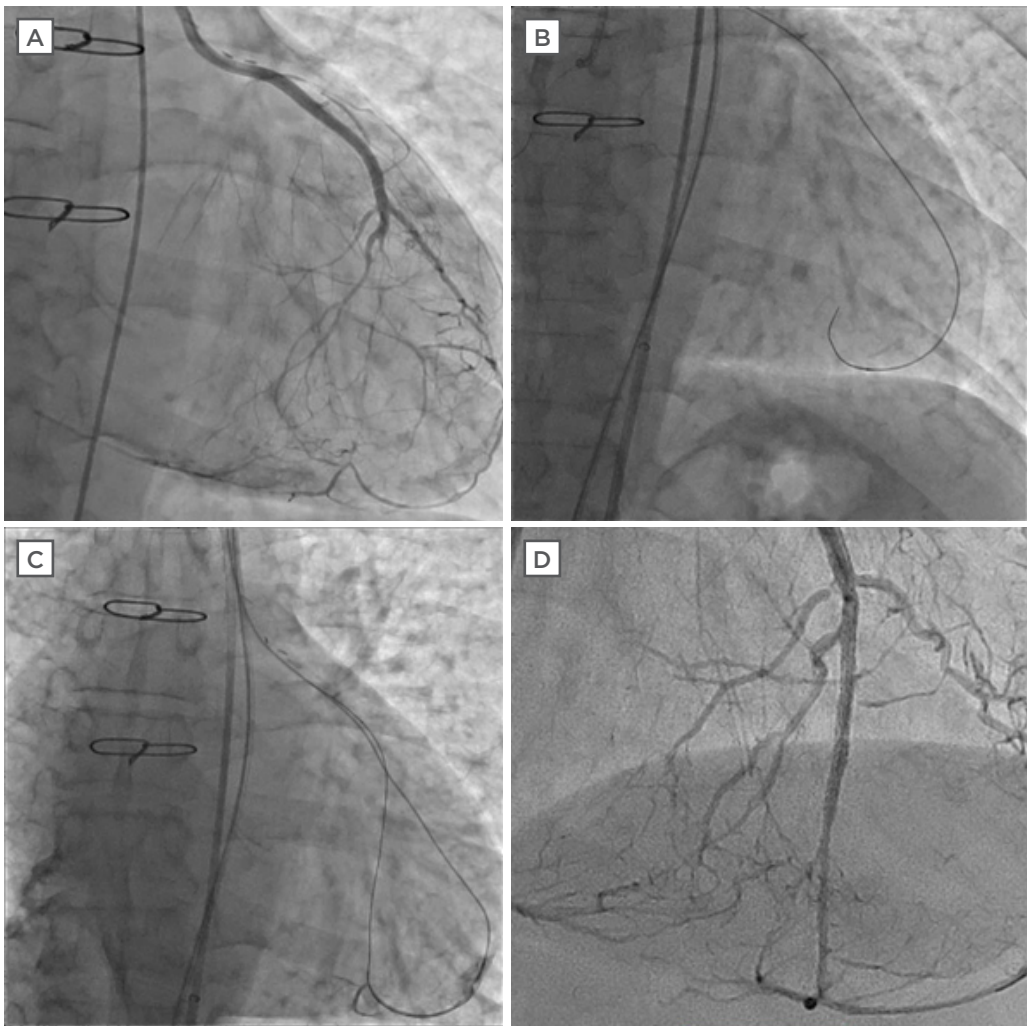

Figure 1: Case pictures.
1A: Left main total occlusion. Patent left internal mammary artery (IMA) to diffusely stenosed and occluded LAD. Retrograde collateralisation from diagonal branch to apical part of LAD; 1B: Mammary graft started using the retrograde approach with Corsair 150 cm + Sion wire through diagonal to distal LAD. Guidewire in LAD was used as a marker; 1C: Complete antegrade LAD recanalisation through IMA graft using Finecross microcatheter + Fielder XT wire. Visualisation performed using Corsair in diagonal branch; 1D: Final result. LAD stented with Xience 2.25 mm/23 mm + DEB 2.0 mm/20 mm at apical part.
DEB: drug-eluting balloon; LAD: left anterior descending artery.

CONCLUSION

- CTOs after a CABG have worse lesion characteristics and are more technically demanding than CTO without prior CABG
- Both arterial and venous grafts, either patent or occluded, can be used for retrograde interventions on native coronary arteries
- According to limited literary sources and personal experience, IMA bypass grafts are the least preferred route for retrograde wiring. Insertion of equipment into the IMA graft could result in pseudolesion formation and antegrade flow cessation. Additionally, disruption of the IMA graft may have catastrophic consequences
- Secondary interventions in patients with bypass graft failure can produce a marked influence on quality of life and also affect prognosis

REFERENCES

1. Goldman S et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. J Am Coll Cardiol. 2004;44(11):2149-56.

2. Hwang M et al. Progression of native coronary artery disease at 10 years: insights from a randomized study of medical versus surgical therapy for angina. J Am Coll Cardiol. 1990;16(5):1066-70.

3. Borges JC et al. Five-year follow-up of angiographic disease progression after medicine, angioplasty, or surgery. J Cardiothorac Surg. 2010;5:91.

4. Sakakura K et al. Comparison of pathology of chronic total occlusion with and without coronary artery bypass graft. Eur Heart J. 2014;35(25):168393.

5. Chen L et al. Angiographic features of vein grafts versus ungrafted coronary arteries in patients with unstable angina and previous bypass surgery. J Am Coll Cardiol. 1996;28(6):1493-9.

6. Chiu JJ, Chien S. Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. Physiol Rev. 2011;91(1): 327-87.

7. Maurer BJ et al. Changes in grafted and nongrafted coronary arteries following saphenous vein bypass grafting. Circulation. 1974;50(2):293-300.

8. Hsu JT et al. Impact of calcification length ratio on the intervention for chronic total occlusions. Int J Cardiol. 2011;150(2):135-41.

9. Burke AP et al. Pathophysiology of calcium deposition in coronary arteries. Herz. 2001;26(4):239-44.

10. Brilakis ES et al. Percutaneous coronary intervention in native arteries versus bypass grafts in prior coronary artery bypass grafting patients: a report from the National Cardiovascular Data Registry. JACC Cardiovasc Interv. 2011;4(8):844-50.

11. Yang CF et al. Successful Revascularization of Chronic Total Occlusion in Native Coronary Arteries through an Occluded Saphenous Bypass Vein Graft: A Retrograde Alternative Approach. Acta Cardiol Sin. 2014;30: 485-9.

12. Lee MS et al. Saphenous vein graft intervention. JACC Cardiovasc Interv. 2011;4(8):831-43.

13. Michael TT et al. Impact of prior coronary artery bypass graft surgery on chronic total occlusion revascularisation: insights from a multicentre US registry. Heart. 2013;99(20):1515-8.

14. Brilakis ES et al. Retrograde recanalization of native coronary artery chronic occlusions via acutely occluded vein grafts. Catheter Cardiovasc Interv. 2010;75(1):109-13.

15. Joyal D et al. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. Am Heart J. 2010;160(1):179-87.

16. Takagi Y et al. Successful recanalization of chronic total occlusion using retrograde approach in a patient with acute coronary syndrome due to aortosaphenous vein graft occlusion. J Cardiol Cases. 2010;1(2):e112-5.

17. Al Suwaidi J et al. Primary percutaneous coronary interventions in patients with acute myocardial infarction and prior coronary artery bypass grafting. Am Heart J. 2001;142(3):452-9.

18. Abdel-Karim AR et al. Percutaneous intervention of acutely occluded saphenous vein grafts: contemporary techniques and outcomes. J Invasive Cardiol. 2010;22(6):253-7.

19. Rathore S et al. Retrograde percutaneous recanalization of chronic total occlusion of the coronary arteries: procedural outcomes and predictors of success in contemporary practice. Circ Cardiovasc Interv. 2009;2(2):124-32.

20. Alhejily WA et al. Retrograde approach to coronary chronic total occlusion via an occluded saphenous bypass graft: a case report. Clin Case Rep. 2013;1(2):54-8.

21. Touma G et al. Chronic total occlusions — Current techniques and future directions. IJC Heart & Vasculature. 2015;7:28-39.

22. Werner GS et al. Effect of acetylcholine on arterial and venous grafts and coronary arteries in patients with coronary artery disease. Eur Heart J. 1990;11(2):127-37.

23. Kitamura S. Physiological and metabolic effects of grafts in coronary artery bypass surgery. Circ J. 2011;75(4):766-72.

24. Tarr FI et al. Evidence of nitric oxide produced by the internal mammary artery graft in venous drainage of the recipient coronary artery. Ann Thorac Surg. 2005;80(5):1728-31.

25. Marmagkiolis K et al. Saphenous vein graft perforation during percutaneous coronary intervention: a case series. J Invasive Cardiol. 2013;25(3):157-61.

26. Peterson ED et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol. 2010;55(18):1923-32.

27. Varghese I et al. Comparison of percutaneous coronary intervention in native coronary arteries vs. bypass grafts in patients with prior coronary artery bypass graft surgery. Cardiovasc Revasc Med. 2009;10(2):103-9.

28. Sekiguchi M et al. Retrograde percutaneous coronary intervention via critically degenerated saphenous vein grafts for chronic total occlusion in native coronary arteries. WJCD. 2013;3(3):261-5.

29. Sianos G et al. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. EuroIntervention. 2012;8(1):139-45.

30. Sharma S, Makkar RM. Percutaneous intervention on the LIMA: tackling the tortuosity. J Invasive Cardiol. 2003;15(6):359-62.

31. Lichtenwalter C et al. Dual guide catheter technique for treating native coronary artery lesions through tortuous internal mammary grafts: separating

equipment delivery from target lesion visualization. J Invasive Cardiol. 2010;22(5):E78-81.

32. Michael TT et al. Role of internal mammary artery bypass grafts in retrograde chronic total occlusion interventions. J Invasive Cardiol. 2012;24(7):359-62.

33. Torii S et al. Retrograde approach via left internal mammary artery using a 5 Fr guiding catheter. Cardiovasc Interv Ther. 2015. [Epub ahead of print].

34. Mibiki Y et al. Percutaneous coronary intervention by retrograde approach for chronic total occlusion of the proximal left anterior descending artery via a gastroepiploic artery graft. Cardiovasc Interv Ther. 2013;28(1):91-7.

35. Park CI et al. Guideliner microcatheter to improve back-up support during a complex coronary stenting procedure through a tortuous left internal mammary graft. J Invasive Cardiol. 2012;24(4):E77-9.