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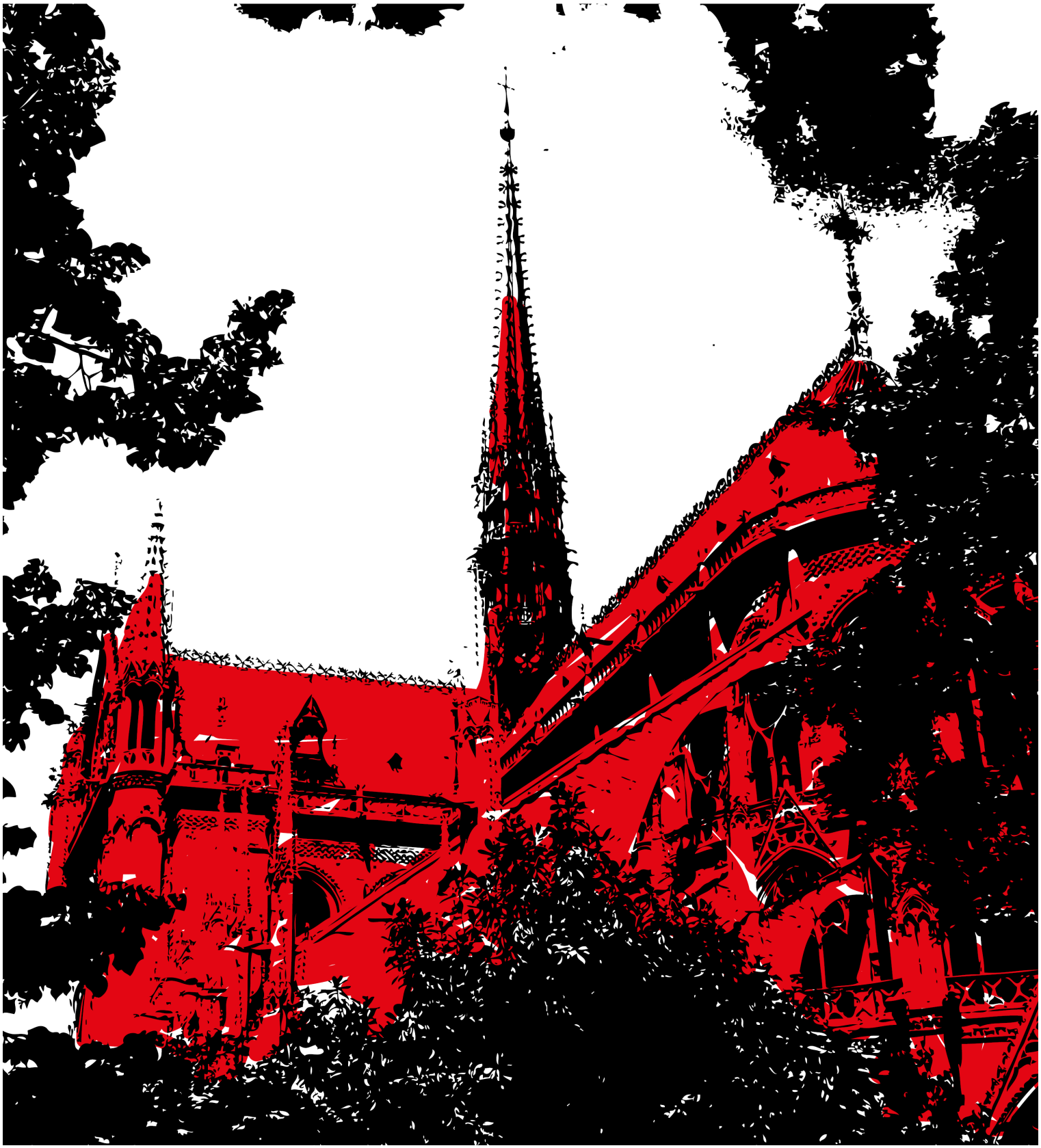

CONTENTS

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Welcome

Hello and welcome to the first edition of *European Medical Journal* for 2017, including a selection of peer-reviewed articles spanning numerous therapeutic areas. This interdisciplinary collection will facilitate the cross-pollination of ideas throughout the therapeutic spectrum.

Encompassed within this issue's array of medical discovery, Estomba et al. document the journey of three-dimensional (3D) printing for biomedical applications, including the exciting prospects for the future, in our Editor's Pick. Balakrishnan et al. discuss both the laboratory and clinical aspects of B cell receptor inhibitors, which have recently advanced the treatment of B cell malignancies, with an emphasis on chronic lymphocytic leukaemia, while Kumar presents a brief review of the literature on haemangiomas followed by a rare case of a calvarial lesion, which was found to be an intraosseous cavernous haemangioma upon excision. The transcatheter repair of congenital heart defects in the young and the anaesthesia techniques utilised in transfemoral transcatheter aortic valve implantation are reviewed by El-Saedi et al. and Aksoy et al.,respectively, while Nilsson provides a brief review depicting the necessary control of cardiovascular risk in Type 2 diabetes mellitus patients, supported by novel trial evidence. In the field of rheumatology, Yılmaz and Yılmaz assess the current evidence surrounding the management and treatment of antiphospholipid syndrome presentation within the lungs, and Watt and Gulati describe the novel drug treatments for osteoarthritis currently in circulation including those set to make an appearance in the near future. Additionally, innovation in Duchenne muscular dystrophy research is analysed by Van Ruiten et al. and Lee and Lee consider the question of whether ethnicity plays a role in lower urinary tract symptoms and metabolic syndrome.

> "In this edition's feature article, Micklewright highlights the impending, yet often overlooked, subject of climate change and its potential impact on the future of global healthcare."

In this edition's feature article, Micklewright highlights the impending, yet often overlooked, subject of climate change and its potential impact on the future of global healthcare. Complementing a brief overview of the issue, the author provides clear steps to follow for clinicians to minimise their impact.

As ever, I would like to acknowledge the contribution of all those who peer-reviewed for this journal, regardless of whether the manuscripts they reviewed were ultimately published. We could not publish high-quality papers without their efforts.

We sincerely hope that you find this edition of *European Medical Journal* a stimulating and insightful read, and one which inspires future discussion and implementation within your clinical practice and future endeavours. With special thanks to our esteemed Editorial Board for their continued support, we look forward to this year's many successes.

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Director, European Medical Journal

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Dose escalation to 600mg once daily was allowed in the phase 2 clinical trial of adult patients with previously treated Ph+ CML who did not experience severe or persistent moderate adverse reactions, and who did not meet certain early efficacy criteria. For details of dose escalation and dose reduction guidelines for non-haematologic adverse reactions and for haematologic adverse reactions, refer to SmPC section 4.2. Patients with serum creatinine >1.5 x ULN were excluded from CML studies. Increasing exposure (AUC) in patients with moderate and severe renal impairment during studies was observed. For details of dosage in patients with moderate and severe renal impairment please refer to SmPC section 4.2. Caution should be exercised in patients with relevant cardiac disorders and in patients with recent or ongoing clinically significant gastrointestinal disorder (see section 4.4 of SmPC). No specific dose recommendation is necessary in the elderly (>65 years). Since there is limited information in the elderly, caution should be exercised in these patients. The safety and efficacy of bosutinib in patients under 18 years of age has not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Hepatic impairment. **Special warnings and precautions for use:** Treatment with bosutinib is associated with elevations in serum transaminases (ALT, AST). Transaminase elevations generally occurred early in the course of treatment. Patients receiving bosutinib should have liver function tests prior to treatment initiation and monthly for the first 3 months of treatment, and as clinically indicated. Treatment with bosutinib is associated with diarrhoea and vomiting, therefore patients with recent or ongoing clinically significant gastrointestinal disorder should use this medicinal product with caution and only after a careful benefit-risk assessment. Patients with diarrhoea and vomiting should be managed using standard-of-care treatment, including an antidiarrhoeal or antiemetic medicinal product and/or fluid replacement. In addition, these events can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see SmPC sections 4.2 and 4.8). The antiemetic agent, domperidone, has the potential to increase QT interval prolongation and to induce "torsade de pointes"- arrhythmias; therefore, co-administration with domperidone should be avoided. It should only be used if other medicinal products are not efficacious. In these situations an individual benefit-risk assessment is mandatory and patients should be monitored for occurrence of QT prolongation. Treatment with bosutinib is associated with myelosuppression, defined as anaemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month and then monthly thereafter, or as clinically indicated. Treatment with bosutinib may be associated with fluid retention including pericardial effusion, pleural effusion and pulmonary oedema. Patients should be monitored and managed using standard-of-care treatment. Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. Bosutinib may predispose patients to bacterial, fungal, viral or protozoan infections. Automated machine-read QTc prolongation without accompanying arrhythmia has been observed. Bosutinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, who have uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia, or who are taking medicinal products that are known to prolong the QT interval. Monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating therapy with Bosutinib and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to bosutinib administration and should be monitored periodically during therapy. Treatment with bosutinib may result in a clinically significant decline in renal function in CML patients. A decline over time in estimated glomerular filtration rate (eGFR) has been observed in patients treated with bosutinib in clinical studies. It is important that renal function is assessed prior to treatment initiation and closely monitored during therapy with bosutinib, with particular attention in those patients who have preexisting renal compromise or in those patients exhibiting risk factors for renal dysfunction, including concomitant use of medicinal products with potential for nephrotoxicity, such as diuretics, ACE inhibitors, angiotensin receptor blockers and nonsteroidal anti-inflammatory drugs (NSAIDs). Bosutinib can induce severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Bosutinib should be permanently discontinued in patients who experience a severe skin reaction during treatment. Due to the possible occurrence of tumour lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of bosutinib (see SmPC section 4.8). Reactivation of hepatitis B (HBV) in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Bosulif. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with Bosulif should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. The concomitant use of bosutinib with strong or moderate CYP3A inhibitors/inducers should be avoided as an increase/decrease in bosutinib plasma concentration will occur. Grapefruit products, including grapefruit juice and other foods that are known to inhibit CYP3A should be avoided. **Drug interactions:** The concomitant use of bosutinib with with strong CYP3A inhibitors (including, but not limited to itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, telithromycin, nefazodone, mibefradil, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, boceprevir, telaprevir, grapefruit products including grapefruit juice) or moderate CYP3A inhibitors (including, but not limited to fluconazole, ciprofloxacin, erythromycin, diltiazem, verapamil, amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir, aprepitant, crizotinib, imatinib) should be avoided, as an increase in bosutinib plasma concentration will occur. Refer to section 4.5 of the SmPC for further details. If a strong or moderate CYP3A inhibitor must be administered during bosutinib treatment, an interruption of bosutinib therapy or a dose reduction in bosutinib should be considered. The concomitant use of bosutinib with strong CYP3A inducers (including, but not limited to carbamazepine, phenytoin, rifampicin, St. John's Wort), or moderate CYP3A inducers (including, but not limited to bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided, as a decrease in bosutinib plasma concentration will occur. Caution should be exercised when administering bosutinib concomitantly with proton pump inhibitors (PPIs). Short-acting antacids should be considered as an alternative to PPIs and administration times of bosutinib and antacids should be separated (i.e. take bosutinib in the morning and antacids in the evening) whenever possible. Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those patients taking anti-arrhythmic medicinal products or other medicinal products that may lead to QT prolongation. Refer to sections 4.4 and 4.5 of the SmPC for further details. **Fertility, pregnancy and lactation:** Not recommended in pregnancy or whilst breast feeding. Bosutinib has the potential to impair reproductive function and fertility. **Driving and operating machinery:** Bosutinib has no or negligible influence on the ability to drive and use machines. **Undesirable effects:** Very common adverse events are: respiratory tract infection, thrombocytopenia, neutropenia, anaemia, leukopenia, decreased appetite, headache, cough, diarrhoea, vomiting, nausea, abdominal pain, alanine aminotransferase increased, aspartate aminotransferase increased, rash, arthralgia, pyrexia, oedema, fatigue. Commonly reported adverse events are: pneumonia, influenza, bronchitis, nasopharyngitis, febrile neutropenia, drug hypersensitivity, dehydration, hyperkalaemia, hypophosphataemia, dizziness, dysgeusia, pericardial effusion, electrocardiogram QT prolonged, hypertension, dyspnoea, pleural effusion, gastritis, hepatotoxicity, hepatic function abnormal, blood bilirubin increased, gamma-glutamyltransferase increased, urticaria, acne, pruritus, myalgia, back pain, renal failure, chest pain, pain, asthenia, lipase increased, blood creatinine increased, blood amylase increased, blood creatine phosphokinase increased. Refer to section 4.8 of the SmPC for further information on side effects, including description of selected adverse reactions. **Legal category:** POM. **Basic NHS price:** Bosulif 100mg, 28 tablets [EU/1/13/818/001] £859.17. Bosulif 500 mg, 28 tablets [EU/1/13/818/003] £3436.67. **Marketing authorisation holder:** Pfizer Ltd, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK.

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1. Pfizer Ltd. Bosulif SPC. Available at: www.medicines.org.uk/emc/

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Foreword

Dr Pierfrancesco Agostoni

Interventional Cardiologist, Department of Cardiology, St. Antonius Hospital, Nieuwegein, Netherlands.

Dear Colleagues,

It is our pleasure to introduce you to this new edition of *European Medical Journal*, the first of 2017.

The current issue covers several aspects of medicine and public health. We start in the featured article with the important topic of climate change and global warming. Micklewright urges doctors (specifically family doctors) to take action and tackle the health concerns that occur hand in hand with this.

Among the highlights of this current edition we would like to signal are the biomedical applications of 3D printing. Estomba and colleagues share insights on this interesting technology aimed at improving preoperative planning, medical education, and, in the long term, patient outcomes.

We also move into the cardiology field to discuss anaesthesia techniques during transcatheter aortic valve replacement. Aksoy and colleagues present a clear review of the available anaesthesia modalities to be applied to transfemoral aortic valve implantation. Furthermore, El-Saiedi and colleagues present the advancements in transcatheter repair of congenital heart defects in young patients. We complete our cardiology topics with an interesting review in which Nilsson displays recent trial evidence showing how cardiovascular outcomes are significantly improved in diabetic patients when diabetes and all other cardiovascular risk factors are better controlled.

“Aksoy and colleagues present a clear review of the available anaesthesia modalities to be applied to transfemoral aortic valve implantation.”

We then cover a broad range of medical topics such as the interaction between chronic lymphocytic leukaemia cells and B cell receptor signalling inhibitors, anti-phospholipid syndrome and the lungs, new drug treatments for osteoarthritis, advances in Duchenne muscular dystrophy, the role of ethnicity in the link between lower urinary tract infections and metabolic syndrome, and haemangiomas (with an interesting case report).

We hope you will enjoy reading this edition of *European Medical Journal*; we believe these articles will be of great help in your clinical practice.

Kind regards,

Pierfrancesco Agostoni

Interventional Cardiologist, Department of Cardiology, St. Antonius Hospital, Nieuwegein, Netherlands.

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- John Hixson

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- Kenneth D. Royal, Mari-Wells Hedgpeth

Light Sheet Fluorescence Microscopy Combined with Optical Clearing Methods as a Novel Imaging Tool in Biomedical Research

- Julia Bode et al.

Virtual Reality Assisted Anaesthesia During Upper Gastrointestinal Endoscopy: Report of 115 Cases

- José Luis Mosso Vázquez et al.

Microbiome: The Missing Link in Neuropsychiatric Disorders

- Alper Evrensel, Mehmet Emin Ceylan

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CLIMATE CHANGE: WHAT CAN DOCTORS DO?

***Thomas Micklewright**

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ABSTRACT

Global warming remains one of the largest global threats to our health. The size of the challenge is immense but political interventions have so far failed to create the drastic changes that are needed to avert this crisis. Concerned by the health risks of climate change, new health groups are emerging to champion this cause, raising awareness, accumulating research data, and influencing public policy. However, there has been less discussion about the role of individual clinicians, particularly family doctors, in addressing this challenge. This article proposes six simple steps that doctors can take to help influence the 'green' behaviour of patients, colleagues, and health systems.

Keywords: Global warming, climate change, general practice, family medicine.

INTRODUCTION

I often wonder if in 20 years' time, we will be telling our children with shame and disbelief of how the world sat back and did nothing about climate change. Despite the Ebola crisis, the obesity epidemic, and nuclear weaponry, global warming could represent the biggest impending threat to public health across the globe.[1] At the end of 2015, the United Nations (UN) met in Paris once again, to reach an agreement on tackling climate change. Described by the French Foreign Minister Laurent Fabius as a 'historic turning point',[2] the agreement that came out of this meeting laid out plans to recreate a space race-like fever in emissions cutting, encouraging countries to make 'green choices' as a matter of national pride. Yet, the agreement is largely non-binding and flexible, relying on countries to determine their own contributions to carbon-cutting and to act solely out of goodwill.[3] If politicians continue to delay action, it may be that individual lifestyle change and grassroots campaigning become our best strategies and doctors are well placed to champion this cause.

HEALTH IMPACTS

Extreme heatwaves will cause increasing deaths from cardiovascular and respiratory disease,[4] especially in the elderly. In Europe, 70,000 deaths were attributed to the heatwave of 2003 alone.[5] Furthermore, an increase in air temperature would increase the mobility of pollen and other aeroallergens, and increase the spread of pollutants through the air.[4] Evidence is accumulating that clearly demonstrates the effect of air pollutants on respiratory and cardiovascular mortality;[4] as temperatures rise and the burning of fossil fuels continues, mortality will only increase.

Variable rainfall patterns are expected to increase both the frequency and intensity of flooding, which as seen during the winter of 2015 across the UK, can be devastating. As well as destroying property and infrastructure and posing a direct threat to life, flooding also can contaminate freshwater and increases the spread of water-borne disease and the breeding of disease-carrying insects such as mosquitoes.[4] In other areas of the world the opposite effect will be seen, with drought and famine threatening human life.

As global air temperatures change, it is expected that patterns of infection will be altered, with some tropical diseases becoming more widespread.[4] The transient changes in temperature from the 1997–1998 El Niño affected the spread of *Plasmodium falciparum* in eastern Africa,[6] schistosomiasis across China,[7] and tick-borne encephalitis in northern Europe,[8] suggesting that infectious disease is already responding to climate change.

Additionally, a secondary effect of climate change is the impact that all of the above will have on global migration and conflict. Flooding, drought, famine, and collapse of infrastructure will all contribute to mass migrations, which risk greater spread of infection and overwhelming the health systems of the receiving countries. What is more, as boundaries are crossed and communities become increasingly protective of their resources, border disputes could occur.

Finally, it is worth noting that although 50% of all emissions are caused by the richest 10% of people,[9] it is those living in developing areas with a weak health infrastructure, limited access to clean water and food, and those living in small island states, that will be most severely affected by the aforementioned changes.[4]

WHAT IS ALREADY BEING DONE

The International Physicians for the Prevention of Nuclear War (IPPNW) was founded during the Cold War and won the Nobel Peace Prize for helping to change public opinion and public policy across the world. They did this by translating scientific jargon into the concrete, personal terms of human health.[10] Joules of force became skull fractures, degrees centigrade became third degree burns. Unable to view nuclear war as an abstract entity anymore, public opinion changed. This same approach is needed now to communicate the harsh realities of climate change but thankfully, health organisations are already taking a stand.

In the UK, the Climate and Health Council was established in 2007 to campaign internationally on the health dangers of climate change and to unite and empower health professionals in this cause.[11] The commissions published in 2009 and 2015[1] marked an international academic collaboration, which mapped out clearly the health impact of climate change and the policy changes needed to protect health worldwide. More recently, the Global Climate and Health Alliance[12] was also founded to raise awareness of the health implications of climate change and to apply political pressure, supported with research, to UN climate negotiations.

Finally, steps have also been taken to reduce the environmental impact of healthcare itself. In 2008, the UK's National Health Service (NHS) Sustainable Development Unit (SDU) was created to help reduce the carbon footprint of health and social care in England, which in 2015, was reported to be 26.6 million tonnes of carbon dioxide equivalent.[13] They have identified carbon 'hot spots' across the NHS,[14] including in pharmaceuticals and medical devices, which commissioners can use to help reach the SDU's 5-year goal of reducing the NHS's carbon footprint by 34%.[15]

WHAT CAN YOU DO?

Below are six steps we each can take as doctors in our daily practice to help in our fight against climate change, adapted from recommendations from The Climate and Health Council in the UK:[16]

1. Encourage patients to walk and cycle whenever possible to benefit both their cardiovascular health and the quality of the air they breathe
2. When offering dietary advice, strongly encourage reduced meat consumption. Farming and meat production is one of the biggest and most overlooked contributors to global warming. If everyone in the UK had one meat-free day per week, this would reduce the same amount of CO_2 emissions as taking 5 million cars off the road,[17] whilst benefiting the cardiovascular health of our patients
3. Community awareness: become aware of local 'green' grants and schemes you can signpost patients towards, especially those who are struggling financially. For instance, look for grants for home insulation or bus passes in your area
4. Social prescribing: volunteering can benefit patients who are socially isolated or struggling with their mental health or self-esteem. Directing these patients to 'green' charities and local environmental projects can give a sense of purpose and social support to these patients whilst also protecting the environment
5. Climate change champion: advocate for climate change to have a place on the agenda of all committees and meetings you attend to help reduce the environmental footprint of healthcare. Argue for the environmental impact of healthcare to become a regular agenda item on all meetings you attend. Recognise your power to influence policy change at a wider level and to leverage the health voice. Consider becoming politically active or joining one of the above national or global campaigns
6. Set an example: try to reduce the energy bill for your own practice, advocate for local and less processed food, drink tap water, and cycle or catch the bus to work

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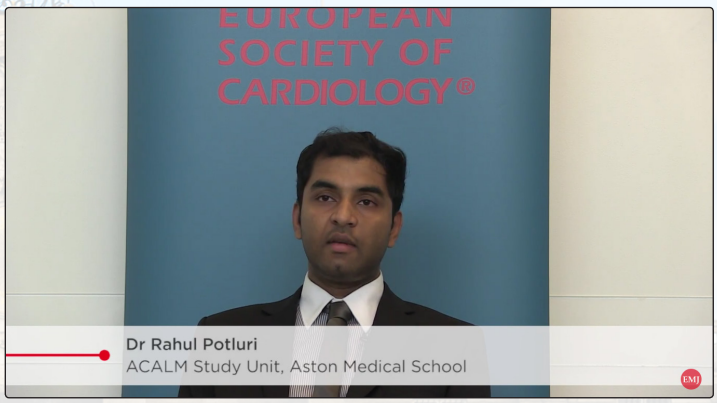

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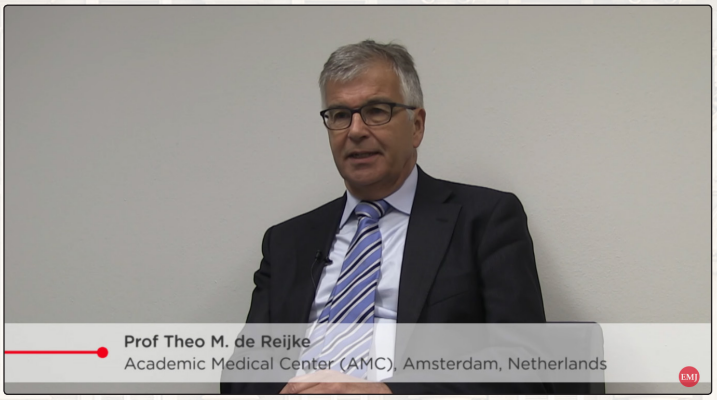

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EDITOR'S PICK

Estomba et al. discuss the applications for additive manufacturing printing technology across the field of medicine, particularly those of three-dimensional (3D) bioprinting. 3D printing has the potential to become a game changer in medicine and surgery by improving the procedural planning of surgical interventions and by helping young doctors to refine their skills in settings where its use may simulate real life scenarios. The welcomed possibility of 3D printing in the design and manufacture of tailored implants and biocompatible scaffolds is also introduced.

Dr Pierfrancesco Agostoni

3D PRINTING FOR BIOMEDICAL APPLICATIONS: WHERE ARE WE NOW?

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ABSTRACT

Three-dimensional (3D) printing is an additive manufacturing process. This technology provides us with the opportunity to create 3D structures by adding material on a layer-by-layer basis, using different kinds of materials such as ceramics, metals, plastics, and polymers. Nowadays, tissue engineering investigations are taking place on a widespread basis in the fields of regeneration, restoration, or replacement of defective or injured functional living organs and tissues. For this reason, it is important to understand the basic concept of 3D bioprinting as a tool for producing a 3D structure combining living cells and biomaterials and controlling cell proliferation, attachment, and migration within 3D structures. There are a variety of applications for additive manufacturing printing technology available to surgeons at this moment, like scaled models for preoperative planning based prosthetics or custom implants and biocompatible scaffolds. Moreover, this technology can be used as a tool to improve surgical and medical education, by using simulation models and utilising its potential to replicate complex anatomy by employing distinct materials that mimic the characteristics of the native tissue in an effort to increase patient safety through repetition of common procedures.

Keywords: Bioprinting, additive, manufacturing, prosthesis.

INTRODUCTION

Three-dimensional (3D) printing technology was first introduced in 1986 by Charles W. Hull,[1] and named stereolithography.[1] Initially, he referred to additive manufacturing and, despite having to start with a slow diffusion, this technology has acquired a major reputation and become widespread over past decades.[2-4] The reason for this is the ability to use this technology to design and fabricate complex anatomical structures as a guide for complex anatomical studies, to reconstruct complex organs

with intricate 3D microarchitecture and fabricate scaffolds for stem cell differentiation.

3D printing is one of many additive manufacturing processes.[5,6] This technology provides us with the opportunity to create 3D structures by adding material layer-by-layer. To do this, different kinds of materials can be used, such as ceramics, metals, plastics, and polymers (synthetic or natural polymers).[7] 3D modelling software, including computer-aided design (CAD) or computed tomography (CT) images, can help us to design our models, use machine equipment, and layer materials.[8] After creating a CAD sketch, 3D printing equipment then reads the data from the CAD file and produces the respective 3D structure.[9]

There are different types of 3D printing technologies available, such as vat photopolymerisation (hardened with ultraviolet [UV] light), material jetting, material extrusion, powder bed fusion, binder jetting, sheet lamination, and directed energy deposition. The most commonly used technologies within this process are stereolithography apparatus (SLA) and digital light processing.[10,11] This method uses a vat of liquid photopolymer resin and produces a 3D structure layer-by-layer cured by a UV laser to create the 3D structures one at a time.[12]

The most commonly used machine in the material extrusion process is that of fused deposition modelling (FDM).[13,14] This is the simplest 3D printing technology and uses a thermoplastic filament as the printing material. The filament is melted in the head of the 3D printer through heating and then 3D structures are created by adding material layer-by-layer. The sheet lamination process includes different materials within the sheet by way of external force. The different materials able to be used to create each sheet include metals, plastics, polymers, etc.[15,16] During the sheet lamination process, the sheets are laminated together using heat and pressure and then cut into the desired shape with a laser or blade. Finally, the directed energy deposition process is mostly used in the high-tech metal industries and in rapid manufacturing applications.[17,18]

CONCEPT OF 3D BIOPRINTING

Nowadays, tissue engineering investigations are widely carried out in the fields of regeneration, restoration, or replacement of defective or injured functional living organs and tissues.[19-21] For this reason, it is important to understand the basic concept of 3D bioprinting as a tool to produce a 3D structure combining living cells and biomaterials and controlling cell proliferation, attachment, and migration within 3D structures.

In this way, biomedical scaffolds made of natural or synthetic polymers can be used in biomedical and tissue engineering applications[22,23] to replace or regenerate the native tissues functionally and structurally. A scaffold has several functions: it should provide internal pathways for the cell attachment and migration, it must transfer various growth factors and waste products, it should keep its shape while the cells are growing, and have adequate mechanical properties.[24] To achieve these functions, biomedical scaffolds for tissue engineering require a highly porous 3D structure that allows cell affinity such as proliferation, migration, attachment, and differentiation, and even enables nutrients and oxygen transport.[25,26]

Advances introduced by 3D bioprinting have importantly enhanced the ability to control pore size distribution, pore volume, and pore interconnectivity of scaffolds. Furthermore, the development of biomaterials in 3D bioprinting is another important field; presently, different 3D printing processes can mix living cells and bioactive molecules in biomaterials (hydrogels) to make successful 3D structures.

TYPES OF 3D PRINTING METHODS USEFUL IN BIOMEDICAL APPLICATIONS (TABLE 1)

Vat Photopolymerisation Method

The vat photopolymerisation process was patented in 1986 by Charles W. Hull.[1] The SLA machine uses UV light to create 3D structures and is based on the vat photopolymerisation principle that monomer resins are photosensitive when exposed to UV light or another similar power source. Photopolymerisation is driven by a chemical reaction that produces free radicals when exposed to certain wavelengths of light. Photons from the light source dissociate the photoinitiator to a high energy radical state and the free radicals induce the polymerisation of the macromer or monomer solution. However, the problem with this photopolymerisation process is that the created free radicals can cause damage to cell membrane, proteins, and nucleic acids. To combat this, hydrogel scaffolds using this technology have been created recently using 3D printing.

Table 1: Types of 3D printing methods useful in biomedical applications.

3D Printing Methods
Vat photopolymerisation method
Fused filament fabrication (FFF) method
Selective laser sintering (SLS) method
Inkjet 3D printing

Figure 1: An example of a 3D printed maxillary bone to use as a guide during surgery.

Fused Filament Fabrication Method

Fused filament fabrication (FFF) printers use a thermoplastic filament; during the process the filament is heated to its melting point and then extruded to prepare a 3D structure. Thermoplastic filaments are extruded onto the substrate to fabricate a 3D structure. All the procedures are controlled by a computer that translates the dimensions of a structure into X, Y, and Z co-ordinates during printing. This technique is a good and reliable option for fabricating 3D scaffolds in tissue engineering applications and many researchers have reported using this method for tissue engineering. The advantages of this method in tissue engineering applications are: ease of use, the variety of biomaterials, good mechanical properties, and that a solvent is not required. The disadvantages are: material restriction related to thermoplastic polymers and the lack of guarantee that that it can be printed with cells effectively due to the high manufacturing temperature.

Selective Laser Sintering Method

The selective laser sintering (SLS) technique uses a laser as a power source to form solid 3D structures, using a high-powered laser for powder sintering to form a scaffold. This method utilises selective laser printing from 3D modelling software on the surface of a powder bed and may print using several different materials, such as ceramics, metals, and polymers. This technology can be used for tissue engineering, creating different scaffold structures from polymeric biomaterials and their composites, like bone.[27] These composite scaffolds are effective at supporting cell adhesion, proliferation, and growth, but have met with limited success in terms of accurately achieving the required porosity levels.[28] Other authors have reported a technique to design and manufacture a customised titanium mesh for minimal bone augmentation of an atrophic maxillary arch, guided by the final position of the prosthesis and according to the implants necessary for its support.[29] The main advantage of this process for tissue engineering applications is the wide range of biomaterials that can be used. The disadvantage of laser printers is that they tend to be large, cumbersome, and expensive.

Inkjet 3D Printing

Inkjet bioprinters are the most commonly used type of printer for biological and non-biological applications. This method creates different structures using a rapid prototyping and layered manufacturing technology and has seen significant developments in the use of polymeric bioink printing for applications in biological and tissue engineering fields. Different kinds of tissue can be created using printable hydrogels, such as retinal tissue and adipose tissue matrix, among others. The advantages of inkjet 3D bioprinting for tissue engineering applications are: patient-customised fabrication, rapid production, the low cost of production, and ease of incorporating both the drug and biomolecules. In addition, it can be printed with the cells. The main disadvantages are the size limitations, biomaterials available, low resolution, and that it has the worst mechanical properties.

WHERE ARE WE NOW IN THE 3D BIOPRINTING WORLD?

Nowadays, 3D printing technology is rapidly becoming easy and inexpensive enough to be used by doctors, students, and engineers;[30,31] the accessibility of downloadable software from online repositories of 3D printing designs has proliferated, largely due to the expanding applications and decreased cost of this technology.[31-33] However, processes are limited to scaffolds for cell support and simple body parts such as bone, and currently

3D bioprinting materials are mostly limited to collagen, gelatin, fibrin, ceramics, thermoplastics, or light-curable composites; this is why the most developed applications for 3D bioprinting are used for prosthetic limbs, orthodontic devices, and bone implants.

However, different universities and companies around the world are working hard to develop different lines of research about 3D bioprinting. Organovo (San Diego, California, USA), one of the biggest bioprinting companies, has created liver bioprinted human tissue models with collagen using proprietary 3D bioprinting technology (ExVive™).[34] The resulting tissues contain accurate and reproducible 3D structures that can remain completely functional and reliable over 40 days. Other authors report the creation of scaffolds for the human kidney using 3D bioprinting technology,[35] while researchers from Cornell University, Ithaca, New York, USA, have reported 3D printed ears similar to the human ear using 3D bioprinting and collagen gels with living cells.[36] So far, as mentioned above, patient customised 3D bioprinting has been studied only in a few laboratories.

There are a variety of applications for additive manufacturing printing technologies available to the surgeon. For example: scaled models of the maxillofacial skeleton for preoperative planning based prosthetics (Figure 1) or custom implants, biocompatible scaffolds, an artificial airway for a newborn with tracheobronchomalacia, or the creation of artificial bone using rapid prototyping technology to reconstruct portions of the skull to orbit/midface and mandible, with a variety of uses for presenting pathology including trauma, osteomyelitis, postsurgical deformity, and hemifacial macrosomia, with satisfactory cosmetic outcomes.

Moreover, some other authors use additive manufacturing 3D printing technology as a tool to improve surgical and medical education, using simulation models and its potential to replicate complex anatomy by employing distinct materials that mimic the characteristics of the native tissue in an effort to increase patient safety through repetition of common procedures.

3D PRINTED ORGANOIDS

Currently, there are several 3D culture methods including scaffold-based models (hydrogels or solid biomaterials) and scaffold-free platforms for spheroid growth. It is likely that 3D culture may provide more reliable cellular models and help to reduce the number of animals used for drug toxicity and efficacy tests.

Newly developed medical treatments of human disease usually have limitations such as individual differences among patients, difficulty with the prediction of outcomes, and time-consuming drug testing. Precision medicine is now coming into focus and becoming more relevant to clinical practice. 3D organoid culture based on a specific disease, and even on a specific individual, is expected to develop into a powerful tool of precision therapy. Primary cancers, infectious diseases, and developmental diseases can be replicated *ex vivo* on biopsy samples, and these kinds of 'live' clinical specimens may become useful for drug testing, gene editing, or for research on prognosis.[37]

BENEFITS OF 3D BIOPRINTING

Using these devices, physicians have the freedom to produce custom-made prosthetics and implants, and provide positive solutions for patients. Moreover, physicians can have access to more affordable models and increase cost efficiency. Another advantage is the time of production, as only a few hours are needed to develop an implant. Finally, there is the opportunity to democratise technology and expand the possibilities to share concepts about research within this field.

Table 2: Current challenges for cell-tissue printing.

Targets	Required improvements
Biocompatible printers	Improve physiological conditions of printing technologies
Biomaterials	Improve functional, mechanical, and supportive properties
Cell sources	Improve source of cells and phenotypes with specific functions
Vascularisation	Development of vascular tissue to support bioprinting tissue
Innervation	Development of a nerve system to improve bioprinting tissue functions

WHAT ARE THE COSTS INVOLVED IN 3D BIOPRINTING?

Customised implants and prosthetics hold significant value for physicians and patients, facilitating improvements in surgical time, surgical tool availability, medical device or surgical success, and patient recovery through the ability to create custom-made devices and surgical tools. These advantages can decrease the length of the patient's hospital stay, surgical tool costs, and treatment failure costs. This method can help with cost-efficiency owing to its potential for low-cost production of items; however, large-scale production is still cheaper via traditional manufacturing approaches. Recent estimations place savings in the cost of surgery around $100 per minute, as well as reducing the risks of long-term anaesthesia. However, high start-up costs continue to limit the implementation of these strategies.

More recently, USA-based biotech startup Aether (San Francisco, California, USA) and BioBots (Philadelphia, Pennsylvania, USA) released two models of low-cost desktop 3D printers for biomaterials, with each costing around $10,000. These two models use FDM technology to produce bioprinting models and have emerged as an option to spread this type of technology and reduce the cost involved in the production of such models.

LIMITATIONS OF 3D PRINTING FOR BIOMEDICAL APPLICATIONS (TABLE 2)

Expectations surrounding this technology are often exaggerated by the media, governments, and even researchers, who promote unrealistic projections of possibilities; therefore, it is necessary to understand the basic limitations of this technique. Anatomical features and tissue architecture may have details on the scale of hundreds of microns; at the moment it is difficult to achieve this with the standard 3D printers available. Moreover, this problem can limit the ability to create small features that survive the fabrication process, as powder particles must be bound together tightly. Another problem is the limited number of biodegradable, biocompatible resins. Advances have been made to synthesise new macromers with biodegradable moieties; however, these materials have not been US Food and Drug Administration (FDA) approved.

Another problem of 3D printing for biomedical applications are the limited materials available, like collagen, gelatin, fibrin, ceramics, thermoplastics, or light-curable composites. To overcome these limitations, the development of new biomaterials that can be printed in conjunction with cells is necessary. However, these biomaterials should be biocompatible, easily manufactured, and have sufficient mechanical properties for cell support and a secure 3D structure.

WHAT IS THE ACTUAL STATUS OF CELL PRINTING?

The recently announced possibility of bioprinting using stem cells unlocks new possibilities within this domain. The world's first ever human mesenchymal stem cells bioink is now offered by the Swedish startup company CELLINK® (Gothenberg, Sweden) and the American stem cell company RoosterBio Inc. (Frederick, Maryland, USA).

A report from China has claimed the availability of 3D bioprinting tissue to recreate parts of the kidney, ears, and livers,[38] although they do not seem to be implantation-ready. Other reports regarding the bioprinting of bones, cartilage, and muscles as well as other tissues are being conducted.

The 3D bioprinting strategy was initiated by Dr Anthony Attala from Wake Forest Institute for Regenerative Medicine Winston-Salem, North Carolina, USA,[39] who applied this technology to manufacture organ tissues for the heart and kidney, and by Gabriel Villard from Oxford University, Oxford, UK, who developed a bioprinter and later, by printing two layers of different cells, for the first time observed changes in specimens after the printing process, later named 4D printing.

Furthermore, one of the major companies in the 3D bioprinting domain is Organovo. Today, it is not yet possible to 3D bioprint any implantable human organ, but at Organovo, they have printed liver and kidney tissues. The printed liver tissue is significantly more effective for drug testing than standard 2D liver culture systems offered by industry as it consists of primary human hepatocytes, stellates, and endothelial cell types, which are found in native human liver enabling drug testing that is stable for at least 42 days. Fully functional printed organs may be possible within the next 10–20 years.[38]

THE FUTURE OF 3D BIOPRINTING

Nowadays, the 3D printing industry only represents a small proportion of the market; however, in the

next 10 years, this proportion is expected to grow. 3D bioprinting has some challenges to overcome, like the development of new biomaterials and improving printers' technology to advance results.

The current 3D bioprinting challenges for cell/tissue printing are: the design of a bioprinter compatible with physiologically relevant materials and cells, increasing the resolution and speed of these machines and their commercial applications, improving biomaterial composition and cell sources, developing vascular and nerve models, and understanding maturation models for every material. Therefore, it is important to understand the future role robotics and nanomedicine have in the development of this technology also.[39] There is a need to improve the biocompatibility and mechanical properties for cell support, which will facilitate the creation of soft tissue and organs that can be directly transplanted into the human body.

The final question surrounds the possibilities of a biofabrication line. A recent analysis published by Mironov et al.[40] addressed this question and concluded that the only economic and reasonable way to commercialise organ-printing technology is to systematically employ scalable, automated robotic technology and to build an integrated organ biofabrication line. The biofabrication of a human organ will require the development of a series of integrated automated robotic devices.

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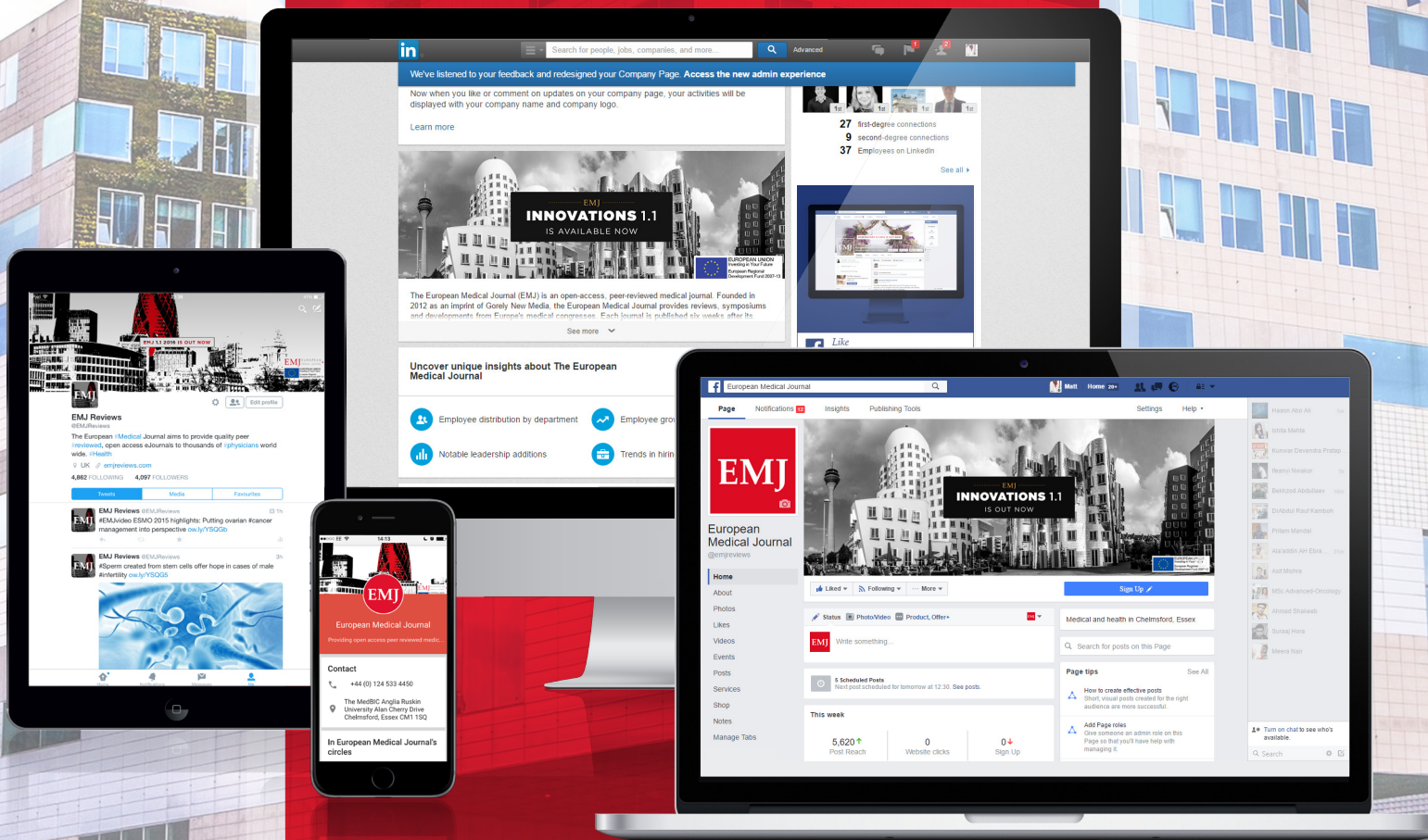

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HIDE AND SEEK: THE GAME BETWEEN CHRONIC LYMPHOCYTIC LEUKAEMIA CELLS AND B CELL RECEPTOR SIGNALLING INHIBITORS

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ABSTRACT

The emergence of B cell receptor (BCR) kinase inhibitors has recently changed the treatment landscape in chronic lymphocytic leukaemia (CLL). The inhibitors that selectively target potential kinases downstream from BCR (particularly Bruton's tyrosine kinase [BTK] and phosphoinositide 3-kinase [PI3K]) have replaced conventional chemotherapy for high-risk CLL. Ibrutinib and idelalisib are the respective first-in-class BTK and PI3K-δ inhibitors that are US Food and Drug Administration (FDA) approved for CLL treatment, with promising second-generation molecules under development. Differing from idelalisib, duvelisib (IPI-145) inhibits both delta and gamma isoforms of PI3K. Kinase inhibitors have gained popularity in the clinic primarily due to their ability to induce remissions in the vast majority of patients, even in patients with high-risk disease features, without causing haematotoxicity. In particular, they interfere with the homing capabilities of CLL cells residing in their respective microenvironments and cause lymphocytosis via redistribution of tissue-resident CLL cells into the peripheral blood. Thereby, BCR inhibitors can seek out and target hiding CLL cells in the lymph node and marrow niches. In this review, we discuss laboratory and clinical aspects of the BCR inhibitors that have recently advanced the treatment of B cell malignancies, with a particular emphasis on CLL. Despite the excitement about this new class of compounds targeting BCR signalling, single agent therapy with kinase inhibitors has limitations, requiring continuous kinase suppression to maintain remissions, which generally are partial remissions, indicating that combination strategies will become important for moving the field forward.

Keywords: Chronic lymphocytic leukaemia (CLL), phosphoinositide 3-kinase (PI3K), duvelisib (IPI-145), apoptosis, B cell receptor (BCR), microenvironment, BCR inhibitors, ibrutinib, idelalisib.

RETHINKING CHRONIC LYMPHOCYTIC LEUKAEMIA BIOLOGY AND RISK FACTORS

Chronic lymphocytic leukaemia (CLL) is a B cell malignancy that is relatively common in the elderly (median age, 71 years), found preferentially in males. Negative prognostic markers for CLL include cytogenetic and molecular markers, including del17p, del11q, and unmutated immunoglobulin (Ig)VH. The clinical outcome or prognosis for patients with these markers is generally poor. Continued clinical and laboratory research has brought the treatment of CLL a long way from the original IFN-α treatments of 30 years ago. For many decades, non-targeted chemotherapeutic agents such as single agent fludarabine,[1] cyclophosphamide, or both in combination,[2] have been the front-line therapy for CLL patients. Over the past decade, the addition of the monoclonal

antibody rituximab in combination with the purine analogue (fludarabine) and alkylator (cytoxan), known as 'FCR', has become a standard-of-care therapy with high efficacy, prolonged overall survival (OS), and acceptable toxicity.[3] Chemo-immunotherapy has improved response rate (RR) and OS[4] with a median disease-free survival of 5 years.[5] Over 50% of patients with IgVH-mutated CLL remained progression-free for >8 years after treatment with FCR.[6,7] However, given the quiescent nature of CLL cells, it is uncertain if non-targeted DNA damaging regimens could be of any real benefit in the targeting of resting CLL B cells. On the same note, identification of new potential targets and target inhibition through a greater understanding of CLL biology have recently transformed the landscape of treatment. In particular, the emergence of targeted therapies like B cell lymphoma-2 (Bcl-2) inhibitors[8,9] (ABT-199, GDC-0199, venetoclax, AbbVie, Chicago, Illinois, USA) and B cell receptor (BCR) kinase inhibitors (ibrutinib and idelalisib)[10-13] have significantly shifted the treatment paradigm for this disease.

B CELL RECEPTOR PATHWAY/B CELL RECEPTOR KINASE INHIBITORS

One broad target of B cell malignancies is those driven by BCR receptor signalling, downstream of which are many potential kinases activated in a cascade fashion, allowing them to significantly drive CLL pathophysiology. Identification of BCR kinases as potential targets for treatment and the discovery of BCR kinase inhibitors to selectively and specifically target BCR pathway kinases have been major breakthroughs in CLL therapy (Figure 1).

IBRUTINIB: FIRST APPROVED BRUTON'S TYROSINE KINASE INHIBITOR

Ibrutinib (marketed as Imbruvica®) is the first-in-class, covalent, small molecule oral inhibitor of Bruton's tyrosine kinase (BTK) inhibitor, a protein downstream of the BCR pathway essential for CLL cell survival and proliferation.[10] Ibrutinib received all four FDA expedited development programmes: Fast Track designation, Breakthrough Therapy designation, Priority Review, and Accelerated Approval[14] for the treatment of previously treated CLL or for the first-line therapy of high-risk CLL with del17p or TP53 mutations. The activity and safety profile of single-agent ibrutinib in CLL with del17p is encouraging, supporting a novel treatment option for patients with high-risk CLL in both first-line and second-line settings.[15] Of note, ibrutinib was also well-tolerated in healthy volunteers.[16]

IBRUTINIB: TARGETS THE HIDING CHRONIC LYMPHOCYTIC LEUKAEMIA CELLS

Rethinking CLL as a dynamic disease has helped in viewing it differently from the perspective of therapeutics. CLL cells often depend on microenvironmental factors for proliferation and survival. In particular, tissue-resident CLL cells exhibit sustained activation of both BCR and NF-κB pathways.[17] A study evaluating *in vivo* effects of ibrutinib on tumour cell activation and proliferation in blood, lymph node, and bone marrow compartments showed a rapid and sustained downregulation of BCR and NF-κB signalling in CLL cells from both the peripheral blood and tissue compartments and decreased tumour proliferation that was independent of prognostic factors such as IgHV status, del17p, or prior treatment history.[18] Another study conducted on serial samples taken from CLL patients before and after initiation of ibrutinib reported a blockage of cell proliferation with a reduction in Ki-67 expression and bromodeoxyuridine incorporation, indicating that ibrutinib classically targets hiding CLL cells (Figure 2).[19]

LYMPHOCYTOSIS: CLASS EFFECT OF B CELL RECEPTOR INHIBITORS

A distinct feature of BCR inhibitors is their ability to cause rapid shrinkage of the lymph nodes within days or weeks upon initiation of treatment. Of note, it was previously known that various other agents such as glucocorticoids, 7-hydroxystaurosporine (UCN-01), and rapamycin (sirolimus) cause similar effects on lymphocyte redistribution, an off-target lymphocytosis effect (as discussed in a recent review).[20] The occurrence of lymphocytosis with BCR signalling inhibitors was first observed with fostamatinib (R788), an inhibitor of spleen tyrosine kinase downstream of BCR. Phase I/II studies of single-agents in patients with relapsed refractory CLL demonstrated an early lymphocytosis of >50% of baseline in 9 of 11 patients, which was associated with a reduction in lymphadenopathy, indicating that inhibition of spleen tyrosine kinase leads to increased trafficking of CLL cells out of the nodal microenvironment and into the peripheral blood where they eventually undergo apoptosis.[21,22]

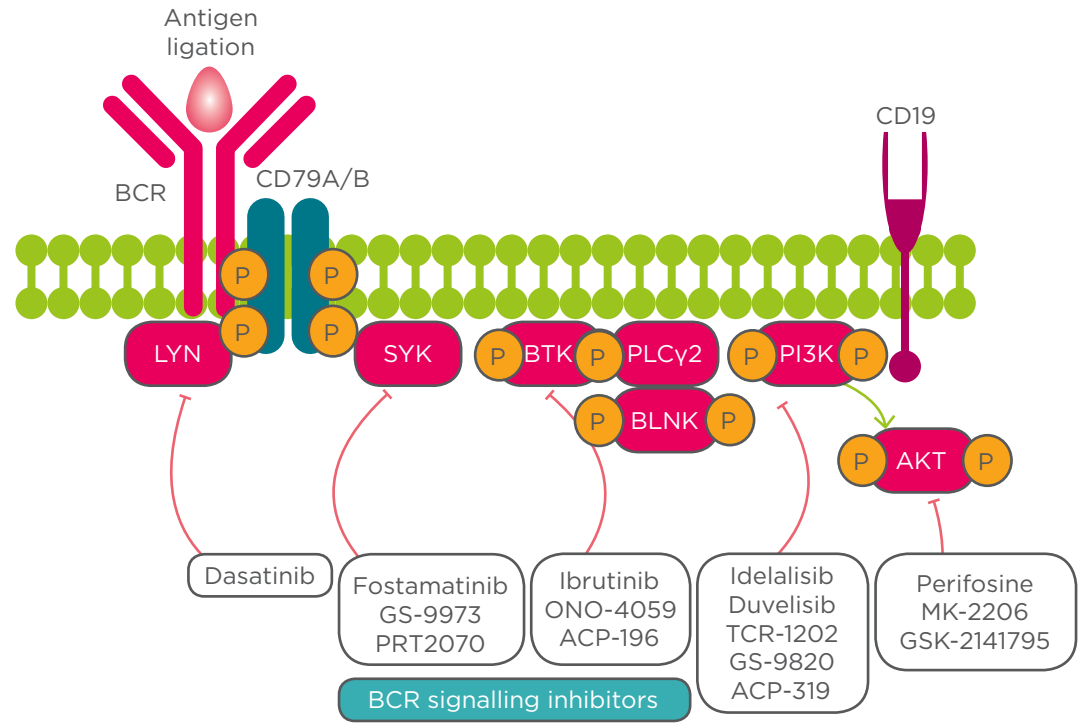

Figure 1: Schematic representing activation of various kinases downstream of the B cell receptor signalling pathway and their inhibitors for therapy of patients with chronic lymphocytic leukaemia. BCR: B cell receptor; BTK: Bruton's tyrosine kinase; SYK: spleen tyrosine kinase; BLNK: B cell linker; PLCγ2: phospholipase Cγ2; PI3K: phosphoinositide 3-kinase.

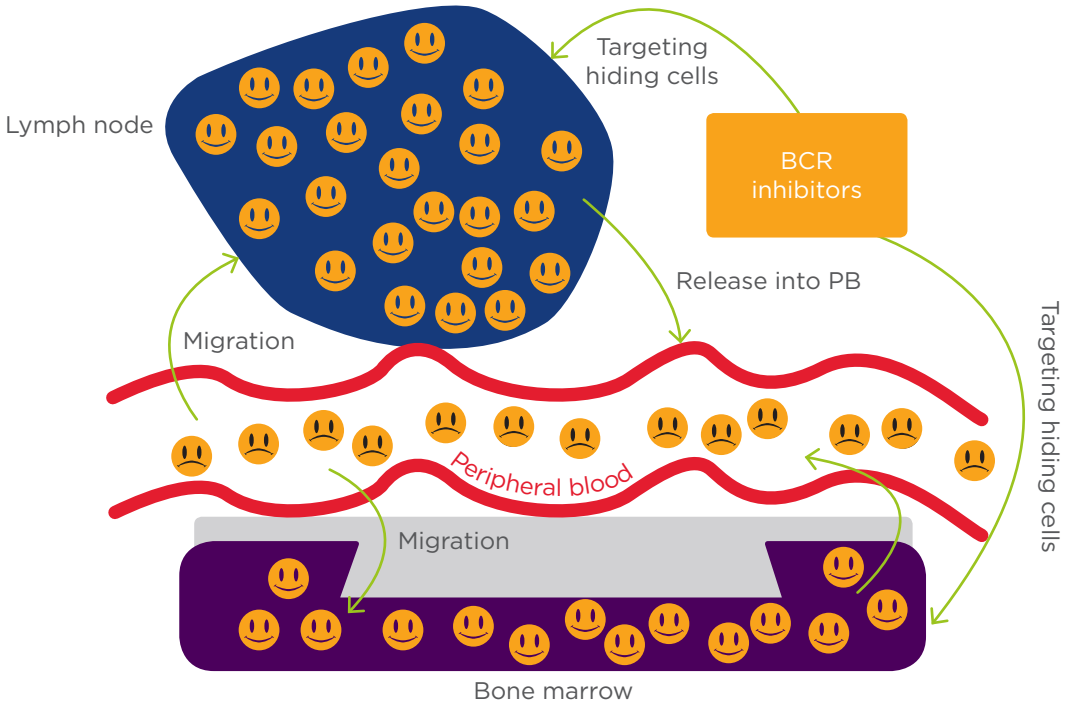

Figure 2: Chronic lymphocytic leukaemia cells migrate towards the chemokines expressed on the tissue microenvironments, such as bone marrow and/or lymph node, where they acquire resistance to conventional chemotherapy. B cell receptor inhibitors are a class of compounds that block the homing capabilities of chronic lymphocytic leukaemia cells and liberate them into the peripheral blood, where they can easily be targeted by other agents.
BCR: B cell receptor; PB: peripheral blood.

The reduction of tumour burden with BCR signalling inhibitors was initially received with great enthusiasm by the patient community and their treating clinicians. Later, it was noted that the lymph node shrinkage is associated with a phenomenon called lymphocytosis i.e. elevation of lymphocyte count in the peripheral blood. Initial doses of ibrutinib peaked at a 66% increase in baseline absolute lymphocyte count in >40% of patients within 24 hours of treatment. Consequently, the observed increase in absolute lymphocyte count was interpreted as a sign of progressive disease and misguidedly viewed as a reason to stop the treatment. Genomic expression profiling studies indicated that the molecular signature of redistributed cells resembled that of cells originating from tissues of the microenvironment (like bone marrow and lymph nodes that serve as havens for CLL cell growth and survival). Circulating CLL cells showed an increased proliferative marker, Ki67, indicating an efflux of leukaemic cells from the tissue compartments into the blood.[23]

Several studies were conducted to understand the event of lymphocytosis and its associated kinetics in the redistribution of CLL cells. Before initiating therapy, the DNA in proliferating cells was labelled with deuterium (patients were asked to drink deuterated water) and the effects of ibrutinib on leukaemia cell kinetics (proliferation and death rates) and redistribution of cells from lymphoid tissues (trafficking) after ibrutinib administration were determined. The data confirmed that after initiation of ibrutinib, there was a rapid increase in radio-labelled CLL cells in the blood rather than the emergence of newly-divided unlabelled cells, indicating mobilisation of CLL cells from proliferating centres.[24] A statistical modelling study conducted to characterise the dynamics of the redistribution phenomenon and pattern of treatment related lymphocytosis demonstrated no significant differences in the pattern of lymphocytosis between cohorts of treatment-naïve elderly CLL, relapsed/refractory CLL, and high-risk CLL, including no detectable dose effect.[25] Another correlative study (using mathematical modelling), between serial lymphocyte counts and volumetric changes in lymph node and spleen sizes during ibrutinib therapy, reported that <2% of peripheral blood CLL cells and <3% of tissue CLL cells underwent apoptosis per day. The fraction of the tissue CLL cells redistributed into the bloodstream during therapy was estimated to be 23% of the total tissue disease burden, indicating that the reduction of tissue disease burden by ibrutinib is primarily due to apoptosis of CLL cells rather than due to their release from the nodal compartments.[26]

These reports clearly indicated that the BCR inhibitors are unique in causing interference between CLL cells and the associated microenvironment by disrupting the migration and homing capabilities of resident cells. It is this novel mechanism of action of the BCR inhibitors that causes reduced homing of leukocytes and CLL cell redistribution from tissue sites into the peripheral blood, contributing to peripheral lymphocytosis. Additionally, the rapid redistribution of cells leading to either a transient or a prolonged event was shown to be associated with favourable prognostic features.[27]

CLINICAL ACTIVITY OF IBRUTINIB

Three years of ibrutinib as a front-line regimen or salvage therapy has demonstrated excellent clinical activity in patients.[28] Studies published on responses to ibrutinib monotherapy[10,15,29] or in combination with rituximab,[30] ofatumumab,[31] rituximab and bendamustine,[32,33] or chemoimmunotherapy[34] have been encouraging. Comparison of ibrutinib to ofatumumab demonstrated ibrutinib as superior to ofatumumab in difficult-to-treat patients with relapsed or refractory CLL as assessed by progression-free survival (PFS), OS, and clinical response.[35] In a recent study, ibrutinib was found superior to chlorambucil in previously untreated patients with CLL as assessed by PFS, OS, RR, and improvement in haematological parameters.[13] A prospective, multicentre, placebo controlled, double-blind Phase III study was subsequently initiated with the objective of comparing the efficacy and safety of ibrutinib to that of a watch-and-wait approach in Binet Stage A CLL.[36]

RESISTANCE MECHANISMS FOR IBRUTINIB

Although ibrutinib induces durable responses in a majority of CLL patients, it also can result in patients developing therapy resistance, especially in patients with del17p and complex cytogenetic abnormalities. Mutation in a cysteine residue of the BTK protein (C481), to which ibrutinib covalently and irreversibly bonds to inhibit its kinase activity,

has been described as a common resistance mechanism. Additional mutations in PLCγ2, which is an immediate downstream target of BTK, were also observed in ibrutinib-resistant patients.[37] Whole-exome, deep sequencing studies conducted to dissect the evolution of ibrutinib resistance resulted in the detection of the BTK-C481S mutation, multiple PLCG2 mutations, and the expansion of clones harbouring del8p with additional driver mutations (EP300, MLL2, and EIF2A), suggesting that ibrutinib therapy favours the selection and expansion of rare sub-clones already present before treatment.[38]

CONTINUOUS KINASE SUPPRESSION REQUIRED

Long-term follow-up results with kinase inhibitors and historical data with ibrutinib suggested a requirement for continuous kinase suppression and other key issues, including response to ibrutinib reintroduction and effect of treatment interruption on secondary resistance to ibrutinib. At the clinical level, responses are partial, indefinite daily use of the drug is required, and the time to secondary resistance was found to increase with duration of treatment. A study comparing the baseline factors in association with discontinuation of ibrutinib reported poor prognosis and disease progression after discontinuation of therapy with associated mutations in BTK and PLCG2.[39] Another study reported that a majority of patients with CLL who discontinued treatment with ibrutinib were found to have high-risk features (94% with unmutated IgVH and 58% with del17p by interphase fluorescence *in situ* hybridisation and 76% of these patients died after discontinuing ibrutinib within a median OS of 3.1 months after discontinuation). Most patients with RR-CLL who prematurely discontinued ibrutinib were difficult to treat and had poor outcomes.[40] Despite this, at current pricing, the average wholesale price of ibrutinib-based treatment in the USA is approximately $118,000 per year and has made a substantial impact on the cumulative cost of CLL care.

IDELALISIB: A PHOSPHOINOSITIDE 3-KINASE DELTA INHIBITOR

Phosphoinositide 3-kinase (PI3K) delta expression, a component of BCR signalling, was found overexpressed in leukocytes, providing a mechanistic rationale for inhibition of the delta isoform in B cell malignancies. Idelalisib (Zydelig R GS-1101, CAL-101) is a first-in-class, targeted, oral inhibitor that selectively inhibits P110δ expression.[11] Preclinical studies demonstrated that idelalisib inhibits BCR signalling and chemokine networks in CLL.[41] The agent is FDA approved in combination with rituximab for the treatment of relapsed CLL.[12] The combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved PFS, RR, and OS among patients with relapsed CLL who were less able to receive chemotherapy. To evaluate idelalisib as an initial therapy, 64 treatment-naïve older patients with CLL were treated with rituximab and idelalisib twice daily continuously for 48 weeks. The median time on treatment was 22.4 months with an overall RR of 97%, and a complete response rate of 19%. Interestingly, the overall RR was 100% in patients with del17p/TP53 mutations and 97% in those with unmutated IgHV. PFS was 83% at 36 months.[42-46]

TOXICITIES FOR B CELL RECEPTOR SIGNALLING INHIBITORS

Despite improved PFS, RR, and OS among patients, resistance and toxicities have been two common companions for these agents as well. Gilead Sciences Inc. (Foster City, California, USA) announced that they are stopping six clinical trials exploring idelalisib in combination with other therapies due to reports of an increased rate of adverse events, especially infectious and autoimmune complications in haematological malignancies. The FDA cautioned clinicians not to prescribe the drug for patients with previously untreated CLL or in combination with other cancer medications until the cause is investigated.

DUVELISIB, PHOSPHOINOSITIDE 3-KINASE DELTA AND GAMMA INHIBITOR

Duvelisib (IPI-145), a potent PI3K inhibitor, is different from idelalisib in that it inhibits both delta/gamma isoforms of PI3K in CLL.[47,48] Even in the setting of BTK C481S mutation, duvelisib proved effective at reducing downstream PI3K signalling as evidenced by diminished AKT phosphorylation.[49] Additional studies indicated that combined inhibition of delta and gamma isoforms of PI3K could be beneficial as each isoform has distinct and non-overlapping functions in CLL biology and hence could enhance the suppression of malignant B cell growth, survival, and migration.[50] Duvelisib is currently in Phase III clinical trials for

haematological malignancies. The results from those studies will determine the future success of this class of agents.

CONCLUSIONS

Many new and effective targeted agents are competing for a role in the treatment of CLL,[51] and whether second-generation molecules prove to be significantly better than the already approved agents (ibrutinib, idelalisib, venetoclax) remains to be seen. Without sufficient long-term follow-up data, it remains difficult to answer questions about the future use, action, and side effects of BCR inhibitors in a definitive fashion. As data emerge from clinical trials with highly active therapies, clinicians caring for patients are left with the question of how to best incorporate these agents into their treatment approaches. Studies combining BCR kinase inhibitors with chemo-immunotherapy (bendamustine and rituximab) demonstrated added toxicity but no clear added benefit from the chemo-immunotherapy in terms of PFS or OS, making it less likely that such combinations will move forward.[32] It is very well possible BCR signalling inhibitors, such as BTK and PI3K inhibitors, will be most effective when given in conjunction with other classes of agents such as antibodies or other targeted therapies (venetoclax; inhibitor of Bcl-2, a guard-rail of apoptosis) that could eventually kill the residual CLL cells efflux to the peripheral blood. In summary, kinase inhibitors have the ability to interfere with the homing capabilities of CLL cells; monotherapy kinase inhibitors have limitations as most responses are partial remissions, suggesting that an appropriate combination of strategies will be critical in moving the field forward.[52,53]

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HAEMANGIOMA: A REVIEW OF THE LITERATURE AND AN UNUSUAL CASE REPORT

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ABSTRACT

Haemangiomas are benign tumours growing by vascular endothelial hyperplasia, commonly occurring in females. The main types diagnosed in children are infantile haemangioma and congenital haemangioma, and these can also be found: in the liver, the gastrointestinal tract, intramuscularly, in vertebrae, intradurally, calvarially, and in the skull base. They can cause functional impairment, high output cardiac failure, and consumption coagulopathy, with current treatment options of corticosteroids, propranolol, embolisation, surgery, and laser treatment. Following a brief review of the literature, a rare case of a calvarial lesion is conveyed. A 57-year-old man presented with a right frontal parasagittal swelling and a computed tomography (CT) scan showed a lesion with a 'honeycomb' appearance. It was excised and the histopathological report received described the lesion as an intraosseous cavernous haemangioma.

Keywords: Infantile haemangioma, congenital haemangioma, propranolol, liver haemangioma, intramuscular haemangioma, vertebral haemangioma, capillary haemangioma, skull haemangioma.

INTRODUCTION

Haemangiomas are benign tumours which arise from the proliferation of endothelial cells surrounding blood-filled cavities. The female to male ratio observed is 3:1, with most haemangiomas presenting soon after birth with gradual involution. Often their rapid growth may interfere with the airways, gastrointestinal tract, and musculoskeletal function, or may cause high output cardiac failure and disseminated intravascular coagulopathy. Additionally, large lesions can trap platelets leading to thrombocytopenia (Kasabach–Merritt syndrome). Haemangiomas of the small bowel, lungs, liver, and mucous membranes can occur in inherited Osler–Weber–Rendu disease.

REVIEW OF THE LITERATURE

Vascular anomalies are congenital lesions of abnormal vascular development.[1] Vascular anomalies were classified in 1982 by Mulliken and Glowacki[2] into vascular tumours, which grow by cellular hyperplasia, and vascular malformations, which represent a localised defect in vascular morphogenesis. Haemangiomas are vascular tumours,[1] with infantile haemangiomas being the most common tumour in infancy.

Infantile haemangiomas arise from haematopoietic progenitor cells in the appropriate milieu of genetic alterations and cytokines. Abnormal levels of matrix metalloproteinases (MMP) and proangiogenic factors (vascular endothelial growth factor [VEGF], basic fibroblastic growth factor [b-FGF], and transforming growth factor beta 1 [TGF-β1]) play a role in haemangioma pathogenesis. Infantile haemangiomas present shortly after birth as well-demarcated, flat, and erythematous red patches. They show three distinct developmental phases: proliferation, quiescence, and involution.

Earlier nomenclature referred to these manifestations as strawberry or capillary haemangioma, cavernous haemangioma, and capillary cavernous haemangioma. Haemangiomas can be superficial, deep, or compound: superficial haemangiomas are red and nodular with no subcutaneous component, a deep haemangioma presents as a protrusion with an overlying bluish tint or telangiectasia, and compound haemangiomas

have both deep and superficial components. Nearly 10% of children require intervention because of bleeding, ulceration, visual axis obstruction, airway obstruction, high-output cardiac failure, or risk of permanent disfigurement. Kasabach–Merritt syndrome, a potentially life-threatening coagulopathy characterised by enlarging haemangioma with severe thrombocytopenia, is associated with kaposiform haemangioendothelioma, tufted angiomas, and rarely with congenital haemangiomas.[3]

Corticosteroids, interferon, and vincristine have been used successfully for substantial and life-threatening disease. Topical corticosteroids have minimal efficacy; intralesional triamcinolone (3 mg/kg) can decrease tumour size in 75% of cases and intralesional steroid treatment is an option for focal haemangiomas of the parotid, nasal tip, subglottis, and eyelid. Oral prednisolone 3 mg/kg/day for 1 month is useful for haemangiomas >4 cm. Surgical management involves excision, laser treatment, or both. For large lesions causing high output cardiac failure, embolisation can be considered for initial control of cardiac overload.

In 2008, regression of a facial haemangioma was noted in a child being treated with propranolol for obstructive hypertrophic myocardiopathy. Since then, propranolol has been introduced as a primary treatment for complicated haemangioma.[4] Propranolol is effective during the proliferative phase of growth and a dosing regimen of 1 mg/kg/day is commenced initially, increased to 2 mg/kg/day at 1 week if this is well tolerated. The indications for therapy are ocular involvement, airway compromise, presence of ulceration, functional impairment, or a combination of the above. Well-documented side effects reported include hypoglycaemia, gastrointestinal upset, and bronchospasm.

Congenital haemangiomas arise in the fetus, are fully grown at birth, and do not have postnatal growth. The major types observed (depending on clinical progression) are: rapidly involuting congenital haemangioma, which involutes within the first few months of life, and non-involuting congenital haemangioma, which is persistent. Partially involuting congenital haemangiomas are congenital haemangiomas with overlapping features,[5] and usually, these do not require resection, however this may be needed in some non-involuting congenital haemangiomas.

Liver haemangiomas are the most common benign liver tumours. These lesions are usually incidental findings of imaging studies of the abdomen performed for other reasons.[6] Hepatic haemangiomas can be classified into three morphological patterns: focal, multifocal, and diffuse. Focal hepatic haemangiomas are the hepatic form of cutaneous, rapidly involuting congenital haemangiomas and focal haemangiomas are fully grown at birth, but regress faster during development. In contrast, multifocal and diffuse hepatic haemangiomas are true infantile haemangiomas, undergoing parallel phases of growth and involution.[7] Liver haemangiomas can be readily diagnosed by ultrasound or multiphase contrast-enhanced helical computed tomography (CT) scans. The indications for surgical resection are progressive abdominal pain in combination with size >5 cm. Haemangioma of the upper gastrointestinal tract is a rare cause of bleeding.[8] Bleeding is often recurrent and diagnosis is often delayed for months to years. It should be considered in patients with recurrent gastrointestinal bleeding and negative conventional investigations. Mesenteric angiography may be the only investigation which will identify these lesions and results after excision are excellent.

Chronic pain and a new mass are the most common presenting symptoms;[9] intramuscular haemangiomas present with muscular pain in particular. Pain is often exacerbated with exercise of the involved muscle due to the vascular dilation and increased regional blood flow. Clinical findings that support the diagnosis of haemangioma include isolated pulsations, extremity enlargement when dependent and regression when elevated, compressibility, increased temperature, muscle contracture, tenderness on palpation, and muscle weakness. Magnetic resonance imaging (MRI) is the diagnostic procedure of choice, as it reliably differentiates haemangiomas from malignant tumours without the need for a biopsy. A T1-weighted axial MRI through the haemangioma is very slightly hyperintense to muscle and shows multiple interlacing vascular channels of the lesion. Conservative management is the first-line of treatment for nearly all isolated intramuscular haemangiomas and rapid tumour growth, intractable pain, risk of local skin necrosis, thrombocytopenia, cosmetic or functional impairment, or suspicion of malignancy may necessitate surgical intervention.

Vertebral haemangiomas are recognised as one of the commonest benign tumours of the vertebral

column.[10] These predominantly affect the thoracic and lumbar vertebrae, with cervical involvement being rarer. These can become symptomatic and cause neurological deficit through any of the following four reported mechanisms: i) epidural extension; ii) expansion of the involved vertebra causing spinal canal stenosis; iii) spontaneous epidural haemorrhage; and iv) pathological burst fracture. The lesion most frequently occurs in the vertebral body and the radiological features of vertebral haemangiomas includes reduced bone density between much denser vertical trabeculae. This 'jailhouse' pattern was reportedly based on the lamellar arrangement of cancellous bone around space containing vessels. Surgical intervention is warranted in vertebral haemangiomas presenting with neurological complications. Decompression of the cord can be accomplished with a laminectomy, or corpectomy with instrumentation.

Capillary or cavernous haemangiomas have been rarely encountered in the spinal intradural space and in the *cauda equina*. Clinical features present as lower back pain, radicular pain, paresthesias, decreased sensation, motor weakness, a positive Lasegue's sign, urinary retention, retrograde ejaculation, and impotence.[11-13] MRI reveals an intradural, well-circumscribed, contrast-enhancing mass, with a surgical approach performed through laminectomy. The appearance of the tumour is pinkish-red and is found attached to one root. Histologically, there is proliferation of capillary-sized vessels lined by flattened endothelial cells, indicating capillary haemangioma.

Intraosseous haemangiomas are rarely seen in the calvarium.[14-16] The parietal bone is the most commonly involved, followed by the frontal bone and less frequently by the occipital and temporal bones. A history of trauma seems to be related in some cases reported within the literature. Loss of vision and proptosis have appeared when the bone lesion involves the orbital, mandibular, or maxillary bones. Excessive bleeding can occur as a major complication at the time of surgery and after tooth extraction. Facial nerve paralysis or hearing loss can develop with temporal bone involvement of intraosseous haemangioma, with CT scans showing osteolytic lesions replacing normal bone tissue. The differential diagnoses for intraosseous haemangioma include fibrous dysplasia, osteoma, Langerhans cell histiocytosis, and multiple myeloma. Fibrous dysplasia exhibits a 'ground glass appearance'; on the other hand, intraosseous haemangioma demonstrates a 'honeycomb' appearance, which is the scattering of radiodense spots within the radiolucent hollow. The treatment of choice for intraosseous haemangioma is en bloc resection with an adequate normal bone margin and the bony defect can be reconstructed by various methods. Other therapeutic methods include curettage, radiotherapy, and embolisation.

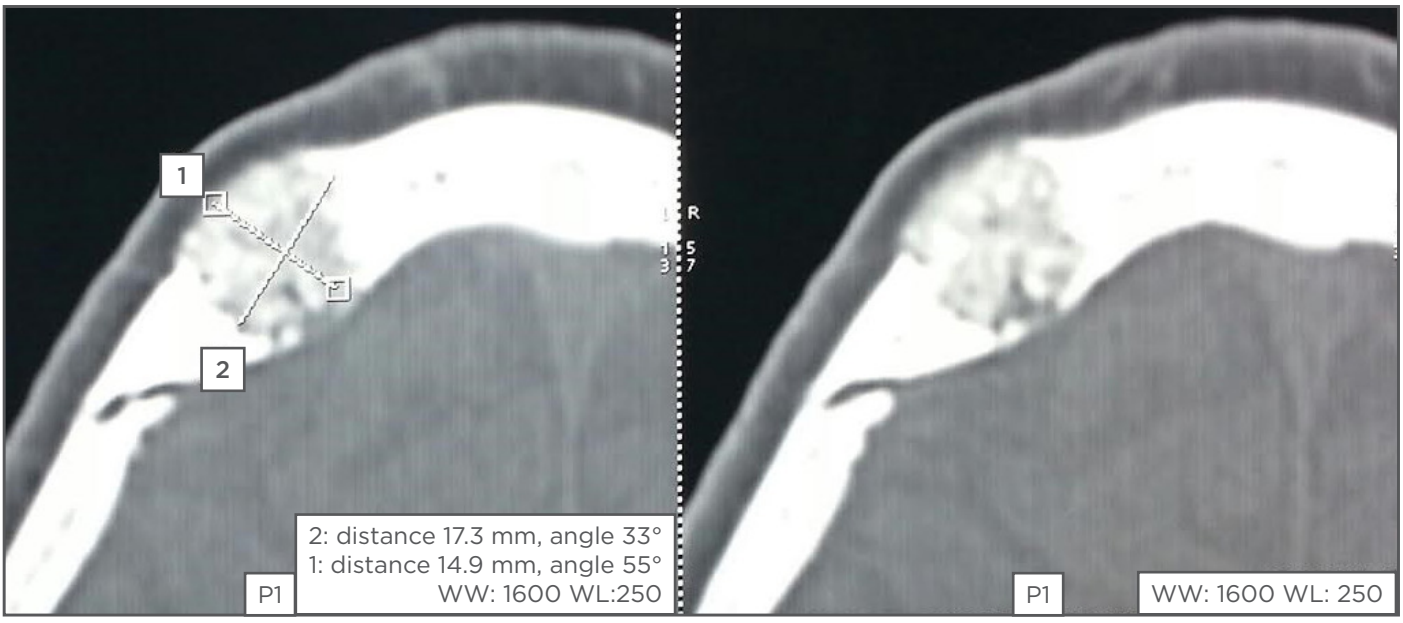

Figure 1: CT scan showing 'honeycomb' lesion of the skull.
CT: computed tomography.

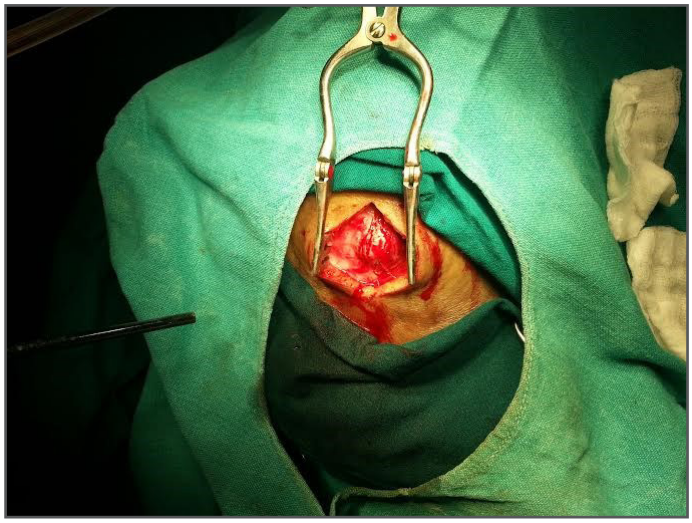

Figure 2: Preoperative picture of swelling.

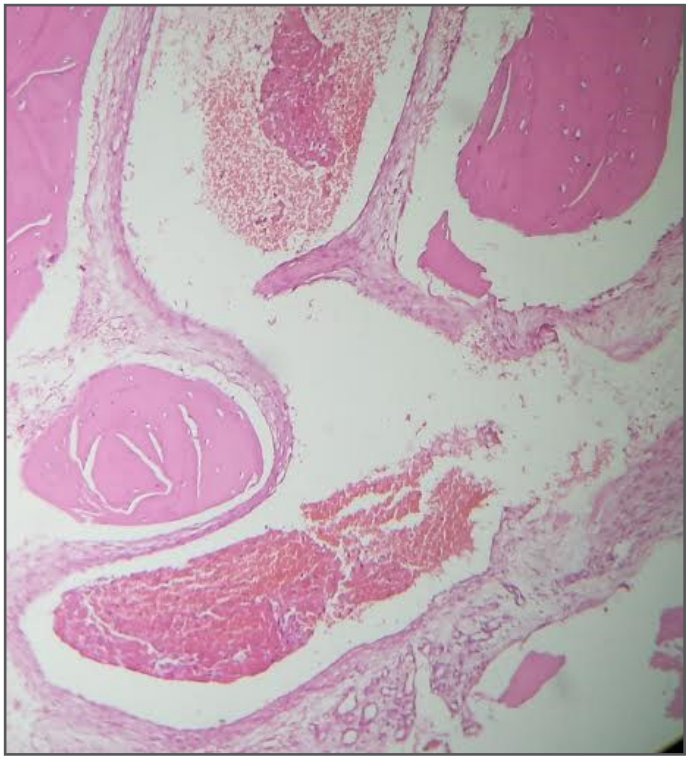

Figure 3: Histopathology of a cavernous haemangioma.
Histopathology performed by Dr Mary Mathew, Consultant Histopathologist, Muthoot Healthcare, Kerala, India.

Skull-base haemangiomas have been reported to arise from the occipital condyle, causing neck pain and torticollis, from the foramen magnum and clivus causing basilar impression, and from the orbitosphenoid ridge and orbital roof causing progressive proptosis and visual loss.[17] In MRI the lesion usually appears mottled and heterogeneous with both increased and decreased signal intensities on both T1 and T2-weighted images. Grossly, it appears as soft, rubbery, vascular tissue separated by thin bony trabeculae. Intraoperatively, the lesion appears as 'moth-eaten' bony interstices or white coral filled with vascular soft tissue. Microscopically, intraosseous cavernous haemangiomas are composed of thin-walled vascular channels lined by a single layer of flattened endothelial cells interspersed among bony trabeculae. The surgical approach becomes more difficult for extensive skull base haemangiomas. Successful excision requires the appropriate microsurgical skull base approach and technique. Radiation therapy remains a viable option for unresectable skull base lesions or residual tumours from subtotal resections.

CASE REPORT

A 57-year-old man presented with right parasagittal swelling which had increased in size. It was measured as 2x2 cm, hard in consistency, and non-mobile. A CT scan showed mixed density swelling in the right high frontal bone, involving the diploë but not eroding into the intracranial space. The appearance was honeycomb-like, with radiodense spots in radiolucency (Figure 1). Surgery was performed under local anaesthesia with a longitudinal incision made. Hard nodular swelling was seen within the skull (Figure 2). It was 'nibbled' and drilled until normal-looking bone was seen around the area. Bone wax was used for haemostasis and the wound healed. Histopathological examination showed bony trabeculae separated by widened marrow spaces containing scanty marrow elements. The marrow was replaced by a cavernous type of vascular spaces lined by plump endothelial cells and filled with blood, diagnostic of intraosseous cavernous haemangioma (Figure 3).

CONCLUSION

Haemangiomas, although benign tumours of the vascular endothelium, can cause functional impairment and life-threatening complications. Medical, surgical, and embolisation treatments are current options. Haemangiomas of the liver, gastrointestinal tract, muscle, vertebra, cauda equina, calvarium, and the skull base have been described, although skull haemangiomas are rare; the treatment for these is excision.

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TRANSCATHETER REPAIR OF CONGENITAL HEART DEFECTS IN THE YOUNG

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ABSTRACT

In recent decades, tremendous medical advances have been made. Therapeutic cardiac catheterisation for repair of congenital heart defects has become the standard mode of therapy. Catheter techniques have progressed. They now provide temporary palliation, prepare the patient for surgical reconstruction, or offer a definitive repair. The main advantages of non-surgical procedures are avoidance of thoracotomy and cardiopulmonary bypass, together with a shorter hospitalisation period and speedier convalescence.

Paediatric interventions include: transcatheter device closure of congenital cardiac defects, balloon angioplasty and valvuloplasty, atrial septostomy, patent ductus arteriosus stenting in the neonatal period, vessel embolisation, and many others. Topping those interventions is the introduction of transcatheter valve replacement. The aim of this article is to review these interventions and present them in a simplified, vibrant, and up-to-date fashion.

In conclusion, paediatric cardiac interventions have established their reliability and ever-expanding scope in the setting of congenital heart disease management. Nevertheless, success is dependent on selecting the proper procedure for each condition, which may also vary with each patient. Thus, it is highly dependent on the experience and expertise of the operator. With the current rate of technological innovation, more and more surgical procedures will eventually be replaced by catheter-based interventions with a great degree of safety and efficacy.

Keywords: Interventional cardiology, paediatric cardiac interventions, congenital heart defects (CHD), congenital heart disease, cardiac devices, septal defects.

INTRODUCTION

The last five decades have witnessed the most remarkable advances in the management of congenital heart defects (CHD). In the last two decades these advances have become so safe and effective that they are becoming an attractive alternative to surgery, sparing patients the surgical scars. The patient is usually mobile the very same day and thereafter; most of these patients remain unaffected for the rest of their lives.[1] From the most common defect, atrial septal defect (ASD), to the rarest defect, aortico-ventricular tunnel, every unwanted defect in the cardiovascular system can be closed with various types of devices. As a result of the tremendous progress in the field of interventional cardiology, the scope for application of transcatheter procedures has widened.[2]

DEVICE CLOSURE OF ATRIAL SEPTAL DEFECTS

The ostium secundum type of ASD can be closed by the transcatheter technique. Different devices were used in the past.[3] Dr Kurt Amplatz, former Professor of Radiology at the University of Minnesota, Minneapolis, Minnesota, USA, has developed the new self-centring device (Amplatzer™ septal occluder) to overcome the limitation of all earlier devices. It consists of a self-expandable

double disc nitinol mesh. The device is securely screwed into a delivery cable and loaded into a long introducer sheath that passes from a femoral vein to cross the ASD. The distal disc is released in the left atrium, pulled against the septum, then the rear disc is released in the right atrium. When secured in place it is disconnected. The procedure is monitored by either transthoracic echo, transoesophageal echo (Figure 1A), or by intracardiac echocardiography.[4] Recently, 3D reconstruction has helped tremendously in visualising the device after delivery and its relation to all surrounding structures (Figure 1C).

Some ASDs are considered difficult to work with, including those that are >26 mm. However, it should be noted that it is possible to close ASDs as large as 36 mm; balloon sizing is recommended in such cases (Figure 1B). Multiple ASDs can be closed as effectively with multiple devices, the smaller device sandwiched by the bigger device or large patent foramen ovale (PFO) device can cover all the multiple fenestrations.[5] Symptomatic PFO patients with a history of cryptogenic stroke and PFO patients with a septal aneurysm can be closed with a PFO device.[6] A septal aneurysm by itself is considered a challenge.

At least a 5 mm rim of atrial septum around the defect is needed as a prerequisite for device closure. A deficient or absent rim is anything <3 mm. However, the device design would not require the anterior rim for anchoring as it would splay around the posterior wall of the aorta.[7] Some techniques were developed to aid the operator when attempting closure of defects with deficient rims, the most famous of which are the pulmonary vein approach, the Hausdorf sheath, and the balloon-assisted techniques.[8-10]

The other type of ASD devices are the patch devices, such as the Gore® Helex® Septal Occluder and some of the newer devices with biodegradable matrix that are being tried in animal models. The bioengineered collagen occluder is ideal for septal occlusion. The tissue scaffold promotes the healthiest and most complete healing response, excellent biocompatibility, and full resorption of material, leaving only native tissue.[11]

Atrial Septal Defect Closure in Special Situations: Infants, Elderly, and Pulmonary Atresia with Intact Ventricular Septum

Evidently, ASD must be closed in symptomatic infants with right ventricular volume overload, symptoms of pulmonary over-circulation, evidence of pulmonary hypertension, failure to thrive, or inability to wean off the ventilator. In this group of patients, surgical closure may pose some morbidity or even mortality. Therefore, efforts should be made to close them either percutaneously or utilising a hybrid approach, avoiding the complication of bypass and shortening the recovery period.[12]

An interatrial communication is usually present in cases of pulmonary atresia with intact interventricular septum for decompression of right chambers or increasing the left ventricular output. Ideally, atrial shunt closure should always be performed in these patients after they undergo right ventricular decompression if they have mild-to-moderate systemic desaturation (>85%) with bidirectional atrial shunt. However, it is absolutely contraindicated to close this communication if the shunt is still exclusively right to left.[13]

DEVICE CLOSURE OF VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects (VSD) are the second most common CHD, accounting for ~20% of cases. About 75% of them are perimembranous and the remaining are muscular VSDs (mVSDs). Surgical closure of mid-mVSD, especially multiple defects, has high incidence of recurrence and is associated with high risk of morbidity and mortality.[1] Today, mid-mVSDs or apical VSDs can be safely closed with the mVSD occluder. This device has a retention skirt 8 mm larger than the central waist and the length of the waist is 7 mm to fit in the thick interventricular septum well. The device can be effectively positioned after securing an arteriovenous circuit. More recently, the sole use of the transvenous approach has been attempted. The relatively small delivery system (6–9 Fr) allows the device to be placed even in small infants.[14]

Patients with haemodynamically significant mVSDs may be offered percutaneous or hybrid-approach device closure.[15] Periventricular device closure of mVSDs is effective and safe, which makes it the approach of choice for small infants.[16] Multiple mVSDs are difficult to manage as they develop pulmonary hypertension early. Today these multiple VSDs are closed by multiple VSD devices.[17]

Perimembranous VSD closure is challenging because of the thin membranous septum and its proximity to both the aortic and tricuspid valves. There is a higher possibility that it will impinge on the aortic valve, causing aortic regurgitation or

compression of the AV node and subsequently cause atrioventricular block. It has been shown recently that perimembranous VSDs can be closed successfully using several devices: the perimembranous VSD device,[18] the Amplatzer™ Duct Occluder I[19] (Figure 2A and Figure 2B) or even the Amplatzer™ Duct Occluder II[20] (Figure 2C and Figure 2D), and lastly the PFM medical coil occluder.[21]

DEVICE CLOSURE OF PATENT DUCTUS ARTERIOSUS

Percutaneous attempts to close the patent ductus arteriosus (PDA) started with the Ivalon plug in 1971. This prototype led to the development of a number of devices, like the Sideris button device and Rashkind's umbrella devices. Nevertheless, these devices needed relatively large delivery systems.

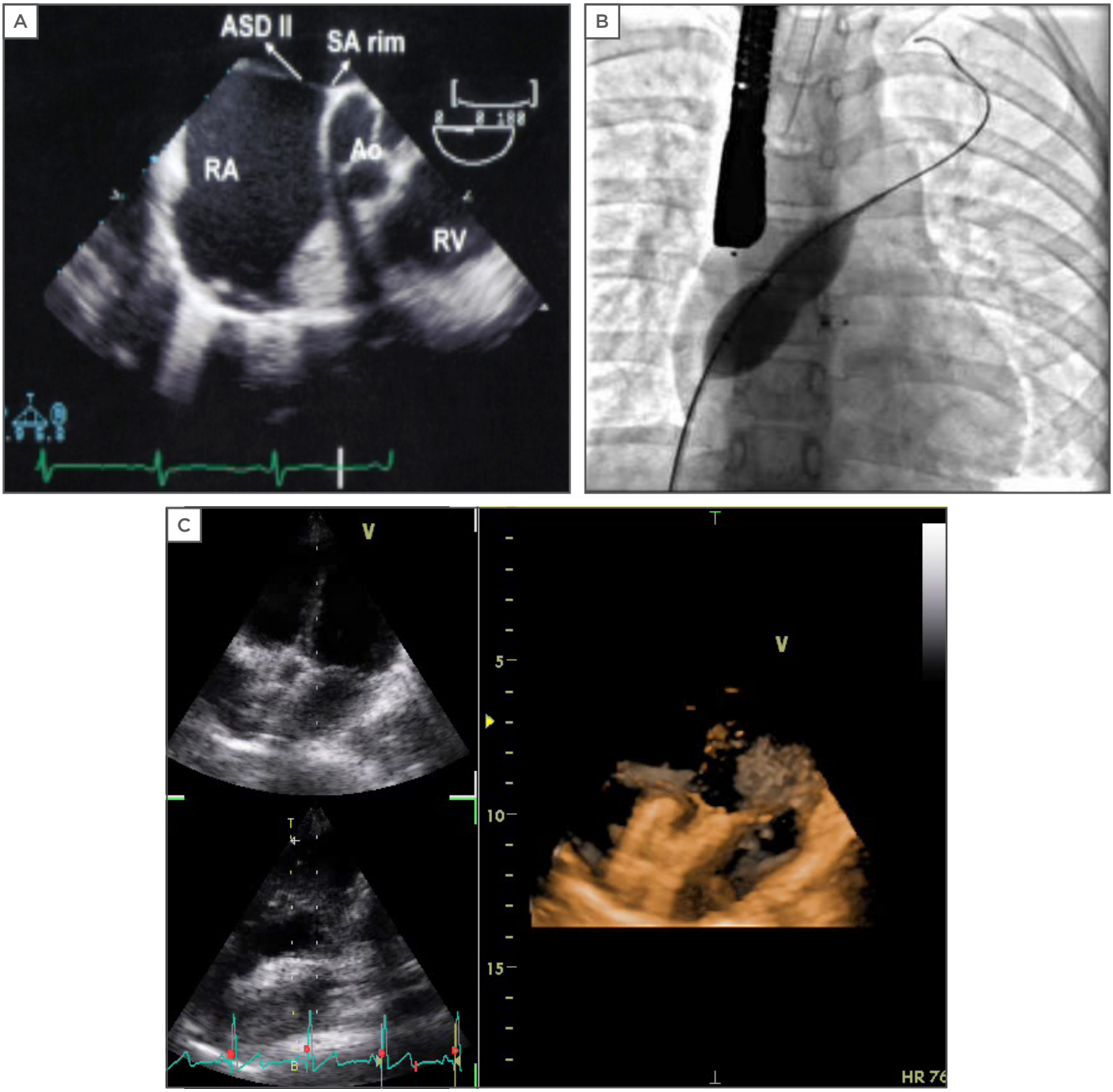

Figure 1: Imaging and device placement for an atrial septal defect.
A) Transoesophageal echocardiography showing ASD secundum; B) Balloon sizing as seen in catheterisation laboratory; C) 3D imaging showing an ASD device *in situ* with no residual shunt.
ASD: atrial septal defect; RV: right ventricle RA: right artery; SA rim: superior anterior rim; AO: aorta.

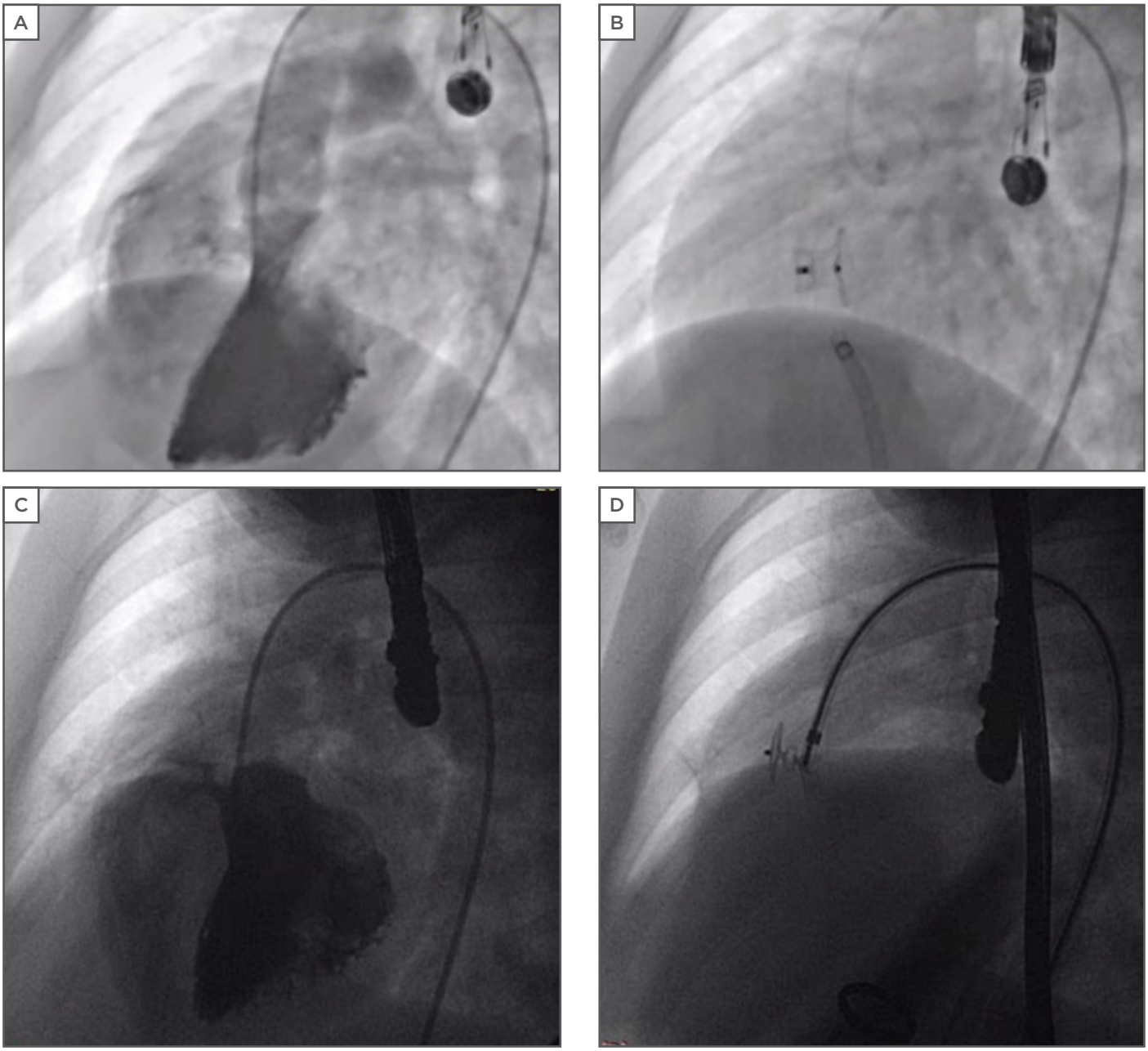

Figure 2: Device closure of a ventricular septal defect.
A) Moderate sized perimembranous VSD; B) VSD closed by ADO I; C) Small perimembranous VSD; D) VSD closed by ADO II.
VSD: ventricular septal defect; ADO: Amplatzer Duct Occluder.

Then coils with thrombogenic strands, which can be delivered at the PDA through 5–6 Fr catheters became available. The success of these simple, safe, and cheap coils has opened the doors for newer detachable coils with smaller delivery systems using screws, which offered safe and controlled coil detachment. These coils can be relocated or withdrawn during the procedure if they are not in optimum position.[22] The development of the Amplatzer Duct Occluder made it safe and easy to close the larger ducts.

Indications for duct occlusion are mainly to prevent the development of pulmonary vascular disease and to eliminate the possibility of infective endocarditis. Today transcatheter closure of PDA has become the standard of care replacing surgery, except in very low birth weight patients or those with complex anatomy. The choice of the device to use during PDA closure depends mainly on the experience and preference of the operator, but the general consensus is:

a) Small PDA <3 mm are closed with Cook's coils, which have thrombogenic strands and are cheap and effective. The coils can be delivered both antegradely and retrogradely. The success rate reported for coils is up to 95%[23]
b) For moderately large PDAs (3–6 mm) we now have the Nit-Occlud® PDA occlusion system (Figure 3A and Figure 3B) which consists of a spiral coil made of nitinol with graduated stiffness and compact winding with memory. It mechanically occludes the duct as there are no thrombogenic strands[24]
c) For larger PDAs (4–14 mm), Amplatzer Duct Occluder is available.[25] The transvenous approach is used to deliver the aortic skirt in the ampulla
d) Recently, the Amplatzer Duct Occluder II and Amplatzer AS have been specially designed for infants, mostly <6 kg. This newer generation of devices are self-expanding with two retention discs (at both aortic and pulmonary ends) that articulate with a central plug. The advantage of these newer devices is that they have low profile and can be easily delivered through a 4 or 5 Fr sheath in infants. As these devices have a retention skirt on either side, they can be delivered either antegradely or retrogradely[26]
e) Closing tubular PDA in infants is still a very challenging task; Amplatzer™ Vascular Plug II and IV are safely used with 100% occlusion rates[27,28]

AORTOPULMONARY WINDOW

The aortopulmonary window is a communication between the ascending aorta and the pulmonary trunk and/or right pulmonary branch. It is rare, occurring in 0.2–0.6% of patients with CHD.[29] In general, these malformations initiate significant left-right shunt with congestive heart failure in the first days or months of life, and early development of severe pulmonary hypertension.[30] Several isolated reports were published showing the effective transcatheter closure of aortopulmonary window with different devices like the Amplatzer Septal Occluder and Amplatzer Duct Occluder II.[31]

CATHETER CLOSURE OF CORONARY ARTERY FISTULAE

Coronary artery fistulae are rare anomalies characterised by direct communication between one or more coronary arteries and a cardiac chamber or a great vessel bypassing the capillary network. Most fistulae arise from the right coronary artery and less frequently from the left coronary artery or the circumflex artery.[32] Most cases are small and asymptomatic accordingly. Indications for closure are: heart failure, cardiomegaly or dilated left ventricle on echocardiography, aneurysmal fistula, coronary fistula in the setting of single coronary, and evidence of myocardial steal on stress electrocardiogram.[33] Multislice computed tomography prior to procedure gives detailed anatomical information about the fistulae, drainage, and the narrowest site. This information helps in planning and preparation of the devices that are appropriate for the procedure.[34] The device is chosen according to the size and shape of the fistulae, this can be coils intertwined together, vascular plugs, or nitinol occluder devices.

VESSEL EMBOLISATION OF PULMONARY ARTERIOVENOUS MALFORMATIONS, AORTOPULMONARY COLLATERAL ARTERIES, AND VENOVENOUS COLLATERALS

Pulmonary arteriovenous malformations are direct communications between the pulmonary arteries and veins bypassing the capillary bed.[35] Embolisation is recommended in symptomatic patients or when the feeding arteries are >3 mm in diameter.[36] Aortopulmonary collateral arteries can be detected in association with various CHD, especially complex cyanotic heart defects. In those patients, aortopulmonary collateral arteries can relieve systemic hypoxaemia prior to surgical correction. Surgical ligation is technically challenging. Indications of transcatheter embolisation are large left-right shunting, resulting in congestive heart failure, pulmonary over-circulation, respiratory compromise, and pleural effusion or protein-losing enteropathy.[15]

Venovenous collaterals are found most often in children with a univentricular heart after a bidirectional Glenn or modified Fontan procedure. The resulting increased systemic venous pressure after these palliations allows for flow through the pulmonary vasculature.[37] Transcatheter embolisation is indicated if the collateral vessels are clinically relevant, causing significant cyanosis or increasing risk of systemic embolism.[15] The embolising material for all these vessels includes coils, vascular plugs, and nitinol occluders.

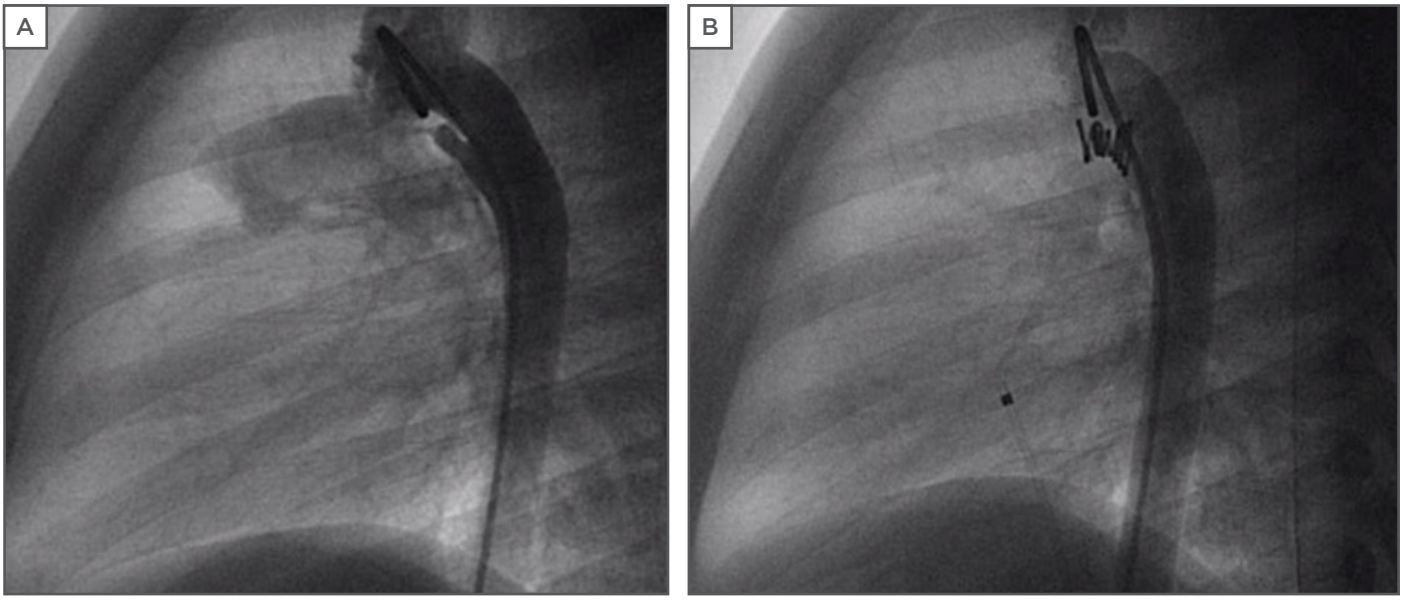

Figure 3: Device closure of a patent arteriosus ductus.
A) Elongated conical PDA on angiogram; B) Nit-Occlud PDA device *in situ.*
PDA: patent arteriosus ductus.

Transcatheter Interruption of Antegrade Pulmonary Artery Flow in Status Post-Bidirectional Glenn

The key to a successful Fontan-type operation is low pulmonary artery pressure (PAP) and low pulmonary resistance. According to the classical indications for the Fontan operation, mean PAP should be <15 mmHg. Recent case reports have shown children with elevated mean PAP after a Glenn procedure, with additional antegrade pulmonary flow through the band, that could be treated successfully with transcatheter closure of this communication using occluder devices like ASD, VSD, or PDA.[38]

Transcatheter Completion of Fontan

Surgeons and interventionists have been collaborating to avoid repeated surgeries by developing new techniques that surgically precondition the heart prior to transcatheter completion. Special occluding stents have been reported to establish inferior vena cava: right atrium to pulmonary artery connection.[39,40]

Fontan Fenestration Closure

Lateral tunnel Fontan baffle fenestration and subsequent catheter closure was first described in 1990 to increase postoperative survival and decrease postoperative morbidity in patients at high-risk for transformation to this type of circulation.[41] This results in decompression of systemic venous channel into the left atrium in cases with borderline Fontan physiology. Patients with chronic Fontan baffle leak with favourable dynamics and tolerating baffle occlusion testing can undergo transcatheter closure for the purpose of relieving cyanosis.[15]

LIFESAVING NEONATAL PALLIATIVE PROCEDURES

Transcatheter Balloon Atrial Septostomy

Enlarging of the ASD by rapidly pulling a balloon filled with radiopaque dye across the restrictive PFO was described by Rashkind and Miller in 1966.[42] Since then thousands of neonates have been saved by this technique all over the world. Balloon atrial septostomy is a lifesaving procedure for severely hypoxic and acidotic neonates with congenital cyanotic heart diseases like transposition of great arteries, tricuspid, mitral atresia, and pulmonary atresia.[2]

Patent Ductus Arteriosus Stenting

This represents another neonatal lifesaving procedure described rather recently and replacing the need for quick surgical intervention in the neonatal period.[43] The procedure allows the patient to stabilise and develop before returning

after several months for a bilateral cavopulmonary (Glenn) shunt to be established and later completion of Fontan. The present coronary stents have better profile, flexibility, and tractability that can be delivered safely through a 4–5 Fr sheath. Tortuous PDA still represents a technical challenge.[44]

Ballooning/Stenting for Coarctation

Endovascular stents are used in conjunction with balloon dilatation to treat coarctation (native or post-surgical) and lately even in neonatal cases.[45,46] Stents prevent recurrence of coarctation, recoil, and vascular proliferative responses. Stents can also prevent aortic dissection and aneurysm formation.

BALLOON DILATATION OF STENOTIC VALVES

Pulmonary Balloon Valvuloplasty

Kan et al.[47] reported the technique of balloon dilatation of the stenotic valve with a significant reduction in the right ventricular pressure. Today, percutaneous balloon valvuloplasty is the treatment of choice for isolated pulmonary stenosis (PS) and neonates with critical PS. Pulmonary valvuloplasty is indicated for a patient with critical pulmonary valve stenosis (defined as PS present at birth with cyanosis and evidence of PDA dependency), at any age post-neonatal with or without right ventricle dysfunction and a peak-to-peak catheter gradient or echocardiographic peak instantaneous gradient of >40 mmHg, with the patient fully sedated.[15]

The balloon chosen should be from 1.2–1.6-times the pulmonary annulus measurement. High pressure balloons are chosen for dysplastic valves with tendency to recoil. The best results are obtained in doming valves with neither sub-valvular nor supra-valvular obstruction. Perforation of the pulmonary valve in the setting of pulmonary atresia/intact ventricular septum has made it possible to transform the pulmonary atresia to severe stenosis and thereafter proceeding with percutaneous balloon valvuloplasty.[48]

Balloon Valvuloplasty for Aortic Stenosis

Aortic valve balloon valvuloplasty is an effective and safe procedure for which the results are comparable to those of surgical aortic valvotomy. In neonates presenting with left ventricular failure, balloon valvuloplasty is lifesaving. It not only reduces the gradient across the aortic valve but also improves the left ventricular function and postpones the need for definite procedure-like valve replacement so that if required it can be replaced by a bigger adult size prosthetic valve or homograft.[2,49]

Indications for intervention include: a) critical aortic stenosis in the neonate with left ventricle dysfunction and PDA dependency; and b) aortic stenosis in childhood with peak systolic gradient >50 mmHg in symptomatic patients, patients with electrocardiogram changes, or peak systolic gradient >70 mmHg in asymptomatic patients with no electrocardiogram changes.[50] The procedure is better done under pacing of the heart and the balloon annulus ratio should not exceed 0.9.

BALLOON/STENT ANGIOPLASTY FOR STENOSIS OF PULMONARY ARTERY BRANCHES

Peripheral pulmonary artery stenosis may be congenital or acquired (postoperative). Significant stenosis requiring intervention is when there are gradients of 20–30 mmHg across the stenotic area, when there is elevation of the right ventricle or proximal main PAP to greater than one-half of systemic pressure secondary to the distal obstruction, or when there is relative flow discrepancy between the lungs of 35/65% or worse.[15] Surgical treatment of these stenoses is difficult and frustrating with very high incidence of recurrence. Recently, 3D reconstructed rotational angiography has facilitated balloon angioplasty with or without stenting, single or multiple, and has shown efficacy, becoming a new hope to these patients with peripheral pulmonary artery stenosis.[51]

TRANSCATHETER PULMONARY VALVE REPLACEMENT

Free pulmonary regurgitation may result in progressive right ventricle dilation and failure, arrhythmias, and progressive widening of the right ventricular outflow tract, leading eventually to death. Previously, these patients needed surgical valve implantation to preserve the ventricular function. Bonhoeffer et al.[52] were the first to report on a novel percutaneous pulmonary valve technique. This technique is being refined regularly, aiming to use smaller sheaths and to ensure fewer complications like stent fracture, arrhythmia, homograft rupture, and coronary artery compression. An example of this is the newly introduced Venus P-Valve™ system.[53]

Currently, this procedure can only be done for children >5 years and weighing >25 kg, following multislice computed tomography and cardiac magnetic resonance imaging for reconstruction of the outflow tracts to aid accurate choice of the size to be used and the proper plane of valve deployment.

CONCLUSION

Transcatheter interventions have transformed the management of CHD. Device closure of various defects has provided spectacular improvement in patient care. Other interventions are increasing in popularity, such as neonatal PDA stenting, whereas older interventions like ballooning of narrowed valves have become well established. The success rate is rising as operators' experience is increasing. These procedures are safe, effective, and are an attractive alternative to cardiac surgery. In some circumstances they have replaced surgery and in other situations they provide a bridge to surgery or a useful adjunct. Device closures and valve replacement have supplanted surgery in many countries, but the major constraint in some areas remains the cost of the devices and the lack of tertiary care centres that are dedicated to such procedures and have the trained personnel. The goal of reaching the perfect device/procedure still leaves much to be accomplished in the future.

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ANAESTHESIA TECHNIQUES IN TRANSFEMORAL TRANSCATHETER AORTIC VALVE IMPLANTATION: A BRIEF REVIEW

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) is an alternative, less invasive method to use for aortic valve replacement in high-risk patients. This operation allows a faster recovery, reduced tissue damage, less postoperative pain, increased patient satisfaction, reduced intensive care unit (ICU) stay, avoidance of ICU admission, reduced hospital stay, and reduced wound infection rates. A retrograde transfemoral approach is commonly used in TAVI procedures. The role of the anaesthetist is important for a successful outcome. General or local anaesthesia, with or without conscious sedation, may be used according to patient characteristics, the presence of comorbidities, and the preference of the surgical team. There is no general consensus regarding which patients should receive general or local anaesthesia during TAVI operations; therefore, the surgical team's preference has an important influence on the selection of anaesthetic technique. There are many studies in the literature relating to the anaesthesia technique used in TAVI operations. No matter which technique is used, anaesthetists should provide and maintain optimal haemodynamic stability during the procedure. On the other hand, anaesthetists should be cautious of possible procedural complications, such as hypotension, ventricular fibrillation, permanent pacemaker requirement, and emergency aortic valve replacement requirement.

Keywords: Aortic valve stenosis, transcatheter aortic valve implantation (TAVI), transfemoral approach, anaesthesia techniques.

INTRODUCTION

Aortic stenosis is an acquired degenerative valvular disease and is frequently seen in the elderly population, who commonly have medical comorbidities such as severe left ventricular dysfunction and renal and respiratory diseases. Patients diagnosed with aortic stenosis have a high mortality rate (4–18%) for open-heart surgery.[1] Transcatheter aortic valve implantation (TAVI) is an alternative, less invasive method for high-risk patients, compared with surgical aortic valve replacement (SAVR).[2] This procedure results in a faster recovery, reduced tissue damage, less postoperative pain, increased patient satisfaction, reduced intensive care unit (ICU) stay, avoidance of ICU admission, reduced hospital stay, reduced wound infection, reduced sternal dehiscence, avoidance of resternotomy, no activation of coagulation cascade, reduced bleeding, reduced release of vasoactive substances, reduced myocardial dysfunction after cross clamp, and a reduced use of resources. On the other hand, TAVI may cause serious complications, including haemodynamic instability requiring inotropic support, embolisation of aortic material, aortic regurgitation, complete heart block requiring a permanent pacemaker, vascular access damage and haemorrhage, or the metal frame stent may be placed incorrectly.[3] A co-ordinated multidisciplinary approach, including a cardiologist, cardiothoracic surgeon, anaesthetist, perfusionist, and cautious anaesthetic management are essential for the success of TAVI.[4]

THE IMPORTANT ROLE OF THE ANAESTHETIST IN TRANSCATHETER AORTIC VALVE IMPLANTATION

Anaesthetists who provide support for TAVI have critical responsibilities before, during, and after the procedure. The anaesthetist should be knowledgeable of cardiothoracic anaesthesia, fluoroscopy, and echocardiography. Primarily, good preoperative risk evaluation should be provided by the anaesthetist to reduce the morbidity and mortality risk associated with TAVI. Anaesthetists should identify risk factors such as previous interventional procedures, signs of congestive heart failure, and laboratory evaluations, and discuss these risk factors with the procedure team and the patient beforehand.[5] They should develop strategies to make the procedure as safe as possible and should also communicate clearly with the procedure team. On the other hand, the anaesthetist should provide haemodynamic stability and stay alert for complications, such as severe haemodynamic instability, haemorrhage/hypovolaemia, major vascular rupture, left ventricle perforation, hypothermia, conduction block/arrhythmias, cerebrovascular accidents, incorrect placement of the valve/paravalvular regurgitation, coronary ostial occlusion, or embolisation, that may occur during TAVI.[6] After the procedure, the anaesthetist should be careful to stay aware of complications such as bleeding from the cannulation site and arrhythmias.[5,6]

ANAESTHESIA TECHNIQUES

Transfemoral, subclavian, axillary, direct aortic, apical, and transcaval approaches have all been described for the TAVI procedure.[2,7] The retrograde transfemoral approach is the most commonly used.[2] The role of the anaesthetist is important for a successful outcome because elderly patients often have multiple comorbidities and organ dysfunction.[1] Inadequate haemodynamic management during the TAVI procedure may lead to morbidity and mortality and the postoperative period may be complicated. Therefore, optimal haemodynamic stability should be maintained throughout.[3]

General anaesthesia (GA) or local anaesthesia (LA) with conscious sedation (LACS) may be used according to patient characteristics, the presence of comorbidities, and the preference of the surgical team.[4] GA was preferred in the initial learning process in clinics and later preferred in patients with coexisting diseases such as heart failure, obesity, pulmonary disease, and cardiogenic shock.[8,9] Covello et al.[8] analysed 69 patients (42 patients received LACS and 27 received GA) who underwent TAVI. They concluded that GA or LACS were both valid alternative techniques that can be titrated according to patient characteristics. Bergmann et al.[9] performed TAVI under sedation in 100 patients. Sedation alone was required in 83 patients; in 17 patients sedation had to be converted to GA due to interventional complications. There were no significant differences between LACS and GA groups in terms of procedural or postoperative results (length of ICU stay, 30-day and 1-year mortality). They concluded that TAVI can safely be facilitated by sedation in the majority of patients. Oguri et al.[10] compared the clinical outcomes in patients who underwent transfemoral-TAVI under GA or LACS. They reported no significant differences in terms of Valve Academic Research Consortium (VARC)-defined complications (myocardial infarction, stroke, and vascular and bleeding complications), other procedural complications, procedure success, or cumulative 30-day and 1-year survival rates. On the other hand, they found more common post-procedural aortic regurgitation ≥mild in the LACS group, compared with the GA group. They thought that transoesophageal echocardiography (TOE) support during TAVI might reduce the incidence of post-procedural aortic regurgitation. Indeed, Berry et al.[11] have reported that TOE provides key anatomical and functional information during TAVI procedures. In the period prior to the procedure TOE is used to assess aortic valves, to measure aortic root diameters and left ventricular outflow tract dimensions, to evaluate left ventricular structures and mitral valve functions, and to evaluate thoracic aortas anatomically. During the procedure, TOE provides visualisation of the prosthetic valve position, the effects of the balloon valvuloplasty, and rapid diagnosis of complications (such as pericardial effusion and iatrogenic mitral regurgitation). In the period after the procedure, prosthetic valve assessment, measurement of aortic root diameters and left ventricular outflow tract dimensions, and evaluations of left ventricular structure, mitral valvefunction, and thoracic aorta are performed via TOE.[11]

In a recent study,[12] we presented short-term results of the first TAVI applications used in our institute. An Edwards SAPIEN valve was implanted, followed by a balloon aortic valvuloplasty via transfemoral

approach for all patients. All procedures were performed under GA accompanied by TOE. There were no mortality or serious complications during the procedures and the success rate was 100% at our institute. In addition, we reported a low mortality rate in the first 30 days (4%) and 6 months (16%). Gümüş et al.[13] also performed all approaches under GA with fluoroscopic and TOE guidance reported a 7% mortality rate in the first 30 days. However, Dehédin et al.[14] applied transfemoral TAVI using GA or LACS. They reported lower intraoperative catecholamine requirements and volume expansion, shorter procedure durations, and shorter hospital stays in the LACS group, compared with the GA group. They found similar periprocedural outcomes, 30-day mortality rates, and lengths of stay in the ICU in both groups.

There is no consensus regarding which patients should receive GA or LA during TAVI operations. Therefore, the surgical team's preference has an important effect on the selection of anaesthetic technique. GA requires tracheal intubation and mechanical ventilation, which leads to respiratory compromise, delayed extubation, haemodynamic instability, prolonged ICU stays, and haemodynamic instability. However, the GA technique is preferred by surgical teams in the initial learning process because it facilitates the management of procedural complications due to the patient's immobility and allows the use of TOE. On the other hand, LA provides simple neurological monitoring, improved patient satisfaction, and reduced morbidity. However, LA catheter placement may cause patient discomfort, and possible patient movement may increase the risk of prosthesis misplacement.[4] Vavuranakis et al.[15] published initial experiences in a total of 30 patients treated with TAVI using only LACS. They reported that TAVI, without GA, using a CoreValve® prosthesis, is a safe procedure. In another study,[16] a similar procedural success rate, 30-day mortality, and 30-day combined safety were reported in patients undergoing TAVI with GA or LACS. In addition, the LACS group had a shorter procedural time, ICU stay, and hospital stay, unlike the GA group.

Table 1: Mentioned studies comparing local anaesthesia with conscious sedation versus general anaesthesia in patients undergoing transcatheter aortic valve implantation.

Author year	Total number of patients	Number of GA	Number of LACS	Conclusion
Covello et al.[8] 2010	69	42	27	GA or LACS are both valid alternative techniques that can be titrated according to patient characteristics
Bergmann et al.[9] 2011	100	17	83	TAVI can safely be facilitated by sedation in the majority of patients
Oguri et al.[10] 2014	2,326	1,377	949	The less invasive transfemoral-TAVI under LA is preferred in clinical settings
Dehédin et al.[14] 2011	125	91	34	LA is associated with less intraoperative haemodynamic instability and a significant shortening of the procedure and hospital stay
Yamamoto et al.[16] 2013	174	44	130	Transfemoral TAVI with the patient under LACS could successfully be performed in most patients, with the advantage of early recovery
Ben-Dor et al.[17] 2012	92	22	70	TAVI can be performed in the majority of cases with controlled monitored anaesthesia care, resulting in a shorter procedure time and in-hospital length of stay
Motloch et al.[18] 2012	74	33	41	TAVI under LACS is as effective and safe as TAVI under GA
Attizzani et al.[19] 2015	251	91	160	TAVI under LACS is associated with a shorter post-procedural hospital stay, lower costs, and a similar safety profile
Petronio et al.[22] 2016	1,316	355	961	The use of LA can be associated with good clinical outcomes

TAVI: transcatheter aortic valve implantation; GA: general anaesthesia; LACS: local anaesthesia with conscious sedation; LA: local anaesthesia.

Ben-Dor et al.[17] also demonstrated the feasibility and safety of performing TAVI guided by TOE without the necessity of GA. In a similar study, Motloch et al.[18] found significantly less periprocedural adrenergic support, shorter intervention times, and lower labour costs in patients undergoing TAVI under LACS compared to the patients under GA. Attizzani et al.[19] reported shorter post-procedural hospital stays, lower costs, and similar safety profiles in patients who received LACS compared to patients receiving conventional strategies.

In a recent study, Piayda et al.[20] evaluated the safety and feasibility of TAVI via femoral access, under LA only (without concomitant sedation) in a total of 215 patients. Of these patients, 40 (18.6%) received additional sedation during the procedure due to inadequate pain control or agitation, and conversion to GA was applied in 7 patients (3.3%). They reported a significantly longer duration of ICU stay in the group requiring additional sedation, compared with patients who only received LA or GA. They suggest that TAVI with LA alone may be considered as the primary option in many patients. Goren et al.[21] assessed the feasibility and safety of TAVI under sedation in an observational study. They reported significantly less catecholamine and intravenous fluid requirements, a shorter total procedural time, and less post-procedural pulmonary complications in the sedation group. In another study, Petronio et al.[22] assessed the safety and non-inferiority of LA versus GA in a large cohort of patients undergoing TAVI. They observed a shorter procedural time, lesser use of a surgical vascular access, a lower incidence of acute kidney injury Stage 3, a lower rate of bleeding and major vascular access-site complications, and a shorter length of hospital stay in the LA group. They concluded that TAVI under LA is as effective and safe as TAVI under GA in experienced centres. Greif et al.[23] achieved good clinical outcomes with TAVI under LA performed with only mild analgesic medication under fluoroscopic guidance. The Sentinel European TAVI Pilot Registry analysed 2,807 patients from ten participating countries treated transfemorally with either LA (1,095 patients, 39%) or GA (1,712 patients, 61%). They found an increase in LA use over time, and contrary to other results similar death and survival rates for the two approaches in the first year of the study. In another report, Mayr et al.[25] researched the effect of sedation and GA on cerebral oxygen saturation and neurocognitive outcomes in patients undergoing TAVI. In this randomised controlled trial, they reported similar cumulative cerebral desaturation and neurocognitive function levels between groups. However, they observed a higher incidence of adverse events (bradypnea: the need for airway maneuvers and bag-mask ventilation) in the sedation group. In a meta-analysis, Fröhlich et al.[26] compared LA with monitored anaesthesia care (MAC) versus GA in patients undergoing transfemoral TAVI. MAC was defined as cardiovascular and respiratory monitoring of the patient by a qualified anaesthetist, who may or may not be administering concomitant sedation. They reported similar mortality and safety endpoints in both and that patients with GA were more likely to need catecholamine support. Also, they observed a shorter procedural times and in-hospital stays in patients undergoing TAVI with MAC, compared with GA.

CONCLUSION

TAVI continues to be an alternative to SAVR for high-risk patients. There are many studies in the literature related to the anaesthesia technique used in TAVI operations (Table 1). Based on the results of these studies, LA with only mild analgesic medication, LACS, or GA may be used successfully in selected cases undergoing TAVI. The use of LA techniques in TAVI operations has been steadily increasing over past years, and has been associated with improved clinical outcomes. In the selection of the most appropriate anaesthetic technique for a patient, the first step is an attentive preoperative assessment with the anaesthetist evaluating patient comorbidities and haemodynamic status. The procedure team's experience is another factor for the selection of an appropriate anaesthesia technique. No matter what technique is used, the anaesthetist should provide and maintain optimal haemodynamic stability during the procedure. On the other hand, the anaesthetist should be cautious for possible procedural complications such as hypotension, ventricular fibrillation, permanent pacemaker requirement, and emergency SAVR requirement. If LACS is used, the anaesthetist must be ready to perform full GA at any moment during the procedure. Further studies are needed to determine whether the anaesthesia technique used may improve short and long-term clinical outcomes of TAVI.

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NEW DRUG TREATMENTS FOR OSTEOARTHRITIS: WHAT IS ON THE HORIZON?

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ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis, yet has historically lagged far behind rheumatoid arthritis in terms of drug development. Despite the many challenges presented by clinical trials in OA, improvements in our understanding of disease pathogenesis and a move to treat pain, as well as underlying disease process, mean there are now many new pharmacological therapies currently in various stages of clinical trials. The medical need for these therapies and the evidence for recent tissue and molecular targets are reviewed. Current therapeutic examples in each area are discussed, including both novel therapeutics and existing agents which may be repurposed from other disease areas. Some challenges remain, but opportunities for improving symptoms and disease process in OA in the clinic with new pharmacological agents would appear to be on the close horizon.

Keywords: Osteoarthritis (OA), drug, clinical trial, treatment.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, causing enormous suffering and healthcare cost; one-third of those aged >45 years seek treatment for OA and 81% of these have constant pain or limitation of activities,[1] with 7.5 million working days lost per annum in the UK alone. The majority of joint replacements can be attributed to OA pain. By 2030, it is expected that 560,000 hip replacements each year will occur within the USA.[2] This being said, OA has historically lagged behind rheumatoid arthritis (RA) in levels of research and drug development. With an ageing and increasingly obese population, incidence of symptomatic OA and joint replacements are increasing year-on-year, associated with increasingly unsustainable costs.[3] OA is now becoming a disease seen in younger people, in their 40s and 50s, who are not yet appropriate for joint arthroplasty. This has led to a clear and increasing unmet need for new pharmacological treatments. In previous decades, the desire to demonstrate structural modification has been hampered by several factors: the limited impact new agents have on the US Food and Drug Administration (FDA)-required endpoint joint space width on X-ray,[4] toxicity issues in some promising drug classes such as MMP inhibitors,[5] and the realisation that the placebo effect in OA (as in many diseases), is substantial and needs careful consideration in trial design.[6] However, there is now great momentum internationally to develop better drug treatments for the condition, aided by significant advances in our understanding of disease pathogenesis. A number of agents across several drug classes seem set to transform the way we think about the medical treatment options of OA.

The Medical Need for New Pharmacological Agents for Osteoarthritis

Drug treatments for OA can be divided into those which improve pain or symptoms (SYMOADs) and those which improve structure, or slow progression,

with or without an effect on pain (DMOADs). Existing guidelines for the management of OA include several pharmacological therapies;[7-9] education, weight loss, and exercise advice should always precede and accompany any drug treatment of the disease. In those whose pain is not adequately controlled, first-line, evidence-based analgesia includes topical non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (paracetamol). Oral NSAIDs and cyclooxygenase-II (COX-II) inhibitors, opiates, or intra-articular steroids can all be considered if these first-line agents fail. However, even the best of these agents only gives clinically meaningful efficacy in half of those taking the drug[10] and the side effects and potential toxicities limit their use in a population who often have associated comorbidities. Several non-pharmacological treatments also exist, but are not the focus of this review. For those with advanced radiographic disease, substantial pain, and impaired quality of life, total knee or hip replacement gives substantial improvement in symptoms in the majority but carries the associated costs and risks of a large operation.[3] Nonetheless, there still remains a significant treatment gap: those who are younger (<~55) with symptomatic disease and those of any age who have symptomatic disease which is not considered radiographically advanced enough for joint replacement (Figure 1). It is important to note that not all those with radiographic disease progress; new medical treatments might increase this group and reduce the numbers ultimately requiring surgery.

Scope of this Review

Progress has been reviewed from the last 5 years; only human, double-blind, randomised controlled trials (RCTs) published in peer-reviewed journals, or with published protocols or registration on clinical trials websites have been included. This is not intended to be an exhaustive, systematic review, but rather to encompass the key areas of interest with relevant examples. Many more targets are apparent from preclinical models that have not entered human studies; past experience tells us only a minority of these will prove translatable. All peripheral joints and stages of disease have been considered, however it is apparent that well-established/advanced knee OA is studied most commonly, with some studies in hip or hand OA.

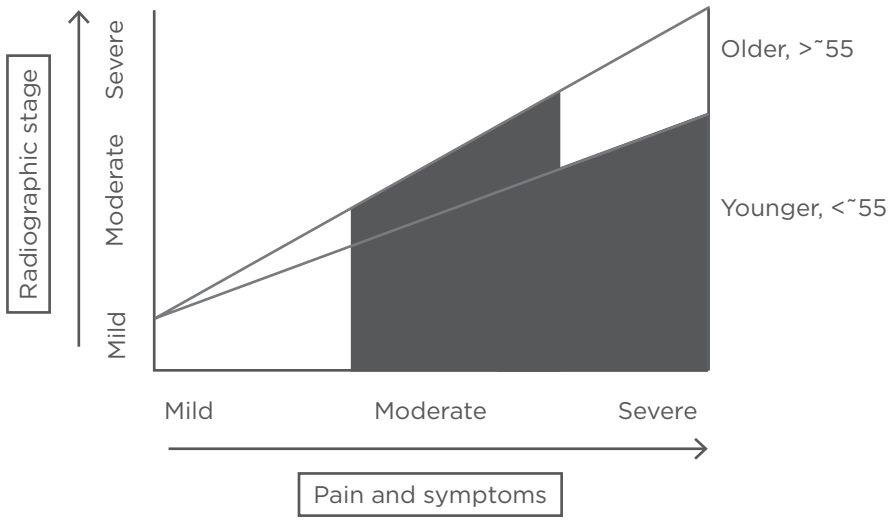

Figure 1: The medical treatment gap in osteoarthritis.
Existing, evidence-based treatments are often effective in those with early disease where there are mild symptoms, and also in older individuals with advanced radiographic disease with severe pain or other symptoms severely affecting quality of life (for whom joint replacement is a highly effective treatment). The medical need for novel pharmacological agents arises in those whose symptoms have not responded adequately to existing evidence-based interventions including existing pharmacological choices, or in whom these are contraindicated or not tolerated: younger patients with moderate-to-severe symptoms, with any radiographic stage of disease (for whom joint replacement surgery is not indicated); and also those older patients with moderate radiographic disease only, or those who do not wish for surgery. Marked in black, pharmacological interventions for the condition are likely to be aimed at the above treatment gap.

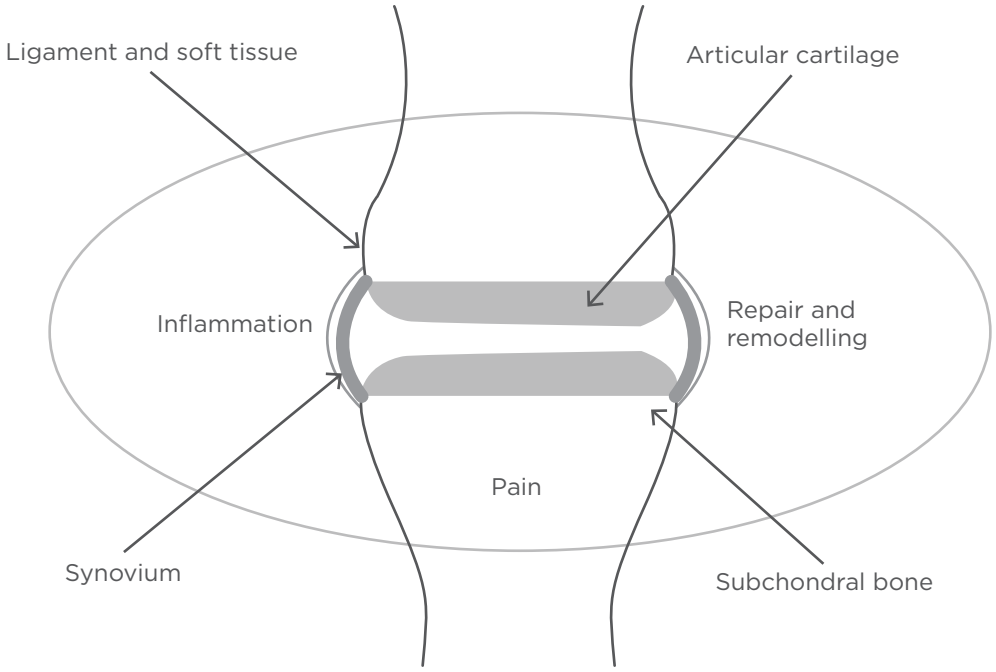

Figure 2: Tissue and molecular targets in osteoarthritis.
Osteoarthritis is a disease of the whole joint, with processes affecting articular cartilage, subchondral bone, synovium and ligament, and other soft tissue such as meniscus in the knee, all shown to be important in the pathogenesis of the disease. Three related molecular processes, inflammation, repair and remodelling, and pain-generating pathways, are important molecular targets in all of these joint connective tissues.

New formulations of drug classes in current clinical use, notably NSAIDs, steroids, or viscosupplementation, have not been included. Similarly, nutraceuticals and botanicals are not reviewed here, as they are subject to different regulation, and often have ill-defined and potentially multiple active ingredients which make them difficult to assess pharmacologically; an excellent review of this area has been carried out recently.[11] Stem cell and cell-based therapies and platelet-rich plasma therapy are beyond the scope of this review.

TISSUE AND MOLECULAR TARGETS FOR OSTEOARTHRITIS

Overview

OA is now considered a disease of the whole joint, with most of the affected connective tissues being targets for novel therapeutics (Figure 2).[12] Changes within articular cartilage occur early in the disease and include excessive action of proteinases (aggrecanases and collagenases) causing loss of proteoglycan and Type II collagen, both critical matrix molecules. Structurally compromised articular cartilage is then vulnerable to further damage.[13,14] Bone remodelling occurs early in the disease, and closely mirrors changes within the articular cartilage.[15] Bone marrow lesions (BMLs) evident on magnetic resonance imaging (MRI) are associated with pain and progression[16,17] and new bone formation occurs, including osteophyte formation. This process has been somewhat underestimated on two-dimensional imaging and is often extensive and a hallmark of disease.[18] Such remodelling appears to be a repair attempt; whether this is sometimes beneficial, stabilising or splinting a joint, or whether it is always a primary driver of pain and other symptoms, is a matter of debate.

Therapeutic targets will be reviewed relevant to cartilage, bone, inflammation/repair, and pain, with examples of drugs targeting pain, structure, or both.

Cartilage

There has been long-standing emphasis on disease modification in articular cartilage. It was demonstrated in two reports in 2005 that the key enzyme responsible for the specific cleavage of aggrecan seen in mouse OA was a disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5); knockout of this gene significantly inhibited OA development.[19,20] This also appears

to be the important aggrecanase in humans.[21,22] Several pharmaceutical companies have developed and tested antibodies or small molecule inhibitors to ADAMTS-5 or both ADAMTS-4/5 for their disease-modifying effects in OA.[21,23] However, difficulties in demonstrating structural modification and potential toxicities have, to date, hampered successful outcome for any of these agents; aggrecanases are found at low levels in cardiovascular and nervous systems. However, some agents remain in clinical trials at present. Given that cartilage is aneural, it might be supposed that these agents may slow down progression but have no direct effect on pain. Promotion of pathways which regulate aggrecanase activity may prove more tractable in the future.

The Wnt signalling pathway is known to play a central role in joint tissue formation, including cartilage and bone, and altered Wnt signalling has been associated with cartilage loss. Some improvement in cartilage thickness and in knee pain has recently been reported in a small study of an intra-articular injection of Wnt inhibitor SM04690.[24]

Bone

The two drug classes lending strongest support to bone as a therapeutic target are bisphosphonates and strontium ranelate. Previous trials of risedronate did not meet primary endpoints on structure, but had significant effects on some secondary patient-reported outcomes and also had suppressive effects on C-terminal crosslinking telopeptide of collagen Type II (CTX-II), a qualified biomarker of cartilage turnover, which may also reflect changes in bone.[4,25] More recently, two trials of systemically administered bisphosphonates reported significant effects on OA pain. Laslett et al.[26] reported that individuals treated with intravenous zoledronate had reduced visual analogue scale (VAS) pain and BMLs over 1 year. Neridronate improved VAS pain and BMLs on whole organ MRI score.[27] Intra-articular clodronate has also shown benefit.[28] Bisphosphonate use was also associated with reduction in knee pain over 3 years in the Osteoarthritis Initiative (OAI) cohort.[29]

In an osteoporosis RCT, it was noted that there was substantial radiographic improvement of OA with strontium ranelate.[30] In a subsequent RCT in knee OA (SEKOIA trial), effects of 1 g or 2 g of the drug were examined.[31] Paradoxically, structure improved most at 1 g dosing, but pain benefit was only seen with 2 g. Bruyère et al.[32] noted a clinically meaningful improvement in pain, function, and stiffness at the 2 g dose. In post-hoc analyses using MRI outcomes, both doses had significant effects on BMLs.[33] Similarly, if patients were stratified post-hoc by meniscal extrusion, there was quantitative MRI evidence of structural disease slowing.[34] In 2014, the drug was restricted for its primary indication of osteoporosis, due to safety concerns relating to risk of venous thromboembolism and myocardial infarction. As a result the programme in OA is currently on hold.

There have also been negative studies in this area. Salmon calcitonin, another osteoporotic agent, did not show significant difference from placebo in a trial of knee OA.[35] There was much circumstantial evidence that vitamin D would reduce pain and potentially disease-modify. However, in two recent studies, oral vitamin D raised serum levels significantly, but had no significant difference on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) classified pain or cartilage volume.[36,37]

Inflammation

Inflammation in OA remains a surprisingly contentious topic. There is evidence that inflammation is important in initiation of disease, in early disease, and in late disease. Mechanical activation of inflammatory signalling pathways and inflammatory response genes in joint connective tissues appears necessary to drive a process leading to OA in preclinical models.[38,39] In longitudinal studies, elevated systemic levels of inflammatory cytokines (such as interleukin [IL]-6 and tumour necrosis factor [TNF]-α) are associated with disease progression.[40,41] These molecules are capable of inducing activation of aggrecanases. A number of connective tissues including cartilage are capable of their synthesis.[42,43] In established disease, synovial and fat pad inflammation would appear to be one of the strongest predictors of both pain and progression.[44,45] Existing drugs with proven efficacy on pain by anti-inflammatory action (NSAIDs, steroids) are not thought to be disease-modifying.

Several anti-cytokines licensed for use in RA have also been studied in OA. Perhaps the only surprise is that there is still an incomplete picture. In a small RCT of the anti-TNF adalimumab in hand OA, 50% pain reduction was seen in 35.1% of the active arm and 27.3% of the placebo arm, with the conclusion that adalimumab was not superior to placebo.[46]

In a previous study Verbruggen et al.[47] had reported a subgroup of hand OA with palpable soft tissue swelling (at highest risk of erosion) had statistically less radiological progression in the first 6 months if treated with adalimumab. Subcutaneous etanercept was not significantly better than placebo in a RCT in erosive hand OA on the primary outcome of hand pain. However, when analysed per protocol, the etanercept group with symptomatic disease who completed the study had significantly improved pain and less structural damage.[48] More recently, a small study of a single injection of intra-articular etanercept for knee OA showed significant reduction in pain VAS compared with intra-articular hyaluronan.[49] To date in knee OA, there has only been an open label study of a systemically administered anti-TNF.[50] A human monoclonal antibody to IL-1R1 was reported as showing no discernible benefit versus placebo in 159 individuals with knee OA over 12 weeks.[51] A Phase IIa RCT of the safety and efficacy of ABT-981 (neutralising antibody to IL-1α and IL-1β) in hand OA is ongoing.[52] An IL-6 receptor antagonist is also being investigated in hand OA in a French study.[53] The effects of this drug class on large joint OA are unreported. A selective oral inducible nitric oxide synthase (iNOS) inhibitor, cindunistat, showed no slowing of joint space narrowing and no impact on pain or function.[54]

Such cytokines may implicate innate immunity including macrophages in OA development. New Phase II trials of an antagonist of granulocyte macrophage-colony stimulating factor (GM-CSF) are being carried out in hand OA, in addition to RA.[55] The NALP3 inflammasome, which is implicated in gout, appears to be activated in OA by crystals or activation by danger-associated molecular patterns.[56-58] Colchicine is an old drug which has its effect partly via the inflammasome. The efficacy of this drug on symptomatic post-menopausal knee OA is being assessed.[59] Impaired microvasculature may be important in predisposing individuals to OA.[60] It is possible that other drugs which have a vascular anti-inflammatory effect may benefit OA: atorvastatin, low molecular weight heparin,[61] the aldosterone antagonist spironolactone,[62] and the sodium channel blocker VX-150[63] have been, or are being, tested for their effects on OA.

Inhibition of synovial inflammation is likely to be an important mode of action for some of these agents. Repurposing studies have been carried out of existing anti-synovial agents to assess their effect on painful OA. In an Egyptian RCT in a pre-defined group with knee OA and inflammatory signs such as effusion, 25 mg methotrexate was superior to placebo on knee pain and function; it also reduced ultrasound-evident inflammation.[64] A further UK-based trial assessing this drug in a wider knee OA population non-responsive to existing therapies, is in progress.[65] Hydroxychloroquine was not found to be acceptable or show pain improvement in a small study which was terminated early.[66] Two large European trials have subsequently assessed this drug in somewhat different populations with hand OA; in a multicentre RCT, hydroxychloroquine was not significantly different to placebo on the primary outcome of average hand pain and no differences could be seen in a subgroup with inflammatory change on ultrasound at baseline.[67-69]

Repair

Pro-repair and anti-catabolic pathways are activated as part of the inflammatory response; harnessing the effects of these pathways may be therapeutically important. Two well-described reparative or anti-catabolic pathways activated in OA and injured connective tissues, are fibroblast growth factor (FGF) and transforming growth factor beta (TGF-β). There is much to learn about the relative roles of multiple family members and their receptors. Both pathways are pleiotropic: knocking out FGF-2 accelerates murine OA, but FGFs contribute to the inflammatory signalling response to connective tissue injury.[43,70] Similarly, TFG-β and its family may be anti-catabolic for articular cartilage and promote cartilage growth, but also promote bone growth (promoting osteophytes) and fibrosis.[71] The first published clinical trial in this area tested intra-articular FGF-18 (sprifermin) in knee OA; the agent was well-tolerated. The primary quantitative MRI endpoint was not met; however, all active treatment groups had improved pain scores, with significant difference from placebo at 12 months.[72] Post-hoc analysis showed reduced cartilage loss and increased cartilage thickness in the active arm.[73] As such, the drug will proceed to Phase III assessment. Antibodies to TGF-β exist and are also of therapeutic interest, but arguably only if they can be targeted to act in a tissue-specific manner.[71]

Pain

Pain as a primary outcome in clinical trials is now more accepted and tractable than structural modification in established disease, and has led to a recent increase of RCTs within this area.

Pain is the leading symptom for patients; whilst it may be driven by changes in specific joint tissues such as bone and synovium, there is evidence that targeting primary neurotrophic pathways activating sensory afferents may be a highly effective way of relieving pain in this and other chronic painful conditions. There is evidence from mouse models that nerve growth factor (NGF) and other neurotrophins are over-expressed in symptomatic disease, and are synthesised by the joint connective tissues themselves.[74] NGF causes allodynia and hyperalgesia is often associated with the disease. Inhibition of NGF or calcitonin gene related peptide (CGRP) reduces pain behaviour in preclinical models.[75,76]

In humans, the most studied area is NGF inhibition.[77] In a seminal RCT in 2010, Lane et al.[78] showed that subcutaneous administration of tanezumab, a monoclonal antibody to NGF, brought about significant, dose-related, clinically substantial relief of pain on walking in knee OA when compared with placebo. Subsequent trials have demonstrated superiority to NSAIDs and opiates.[79,80] Other monoclonal antibodies to NGF such as fasinumab and soluble tropomyosin receptor kinase A (TrkA) receptor fusion proteins have demonstrated similar effects.[81-83] An FDA halt to Phase III trials due to a potential safety signal of osteonecrosis has now been lifted. Two out of eighty-seven adjudicated cases were likely due to osteonecrosis. Most were in fact cases of rapidly progressive OA (RPOA), which was primarily associated with concurrent chronic NSAID administration.[84] There was also increased risk on the highest dose (10 mg of tanezumab), or where there was identifiable risk for RPOA (subchondral insufficiency fractures, very advanced radiographic disease). There was no apparent association with greater pain relief or anaesthesia in these individuals. New Phase III trials mitigating against RPOA risk, with increased neurological monitoring have now recommenced.[77,84] Small molecule inhibitors selectively inhibiting the NGF receptor, TrkA that are orally available and shorter-acting are also being tested; safety considerations will need to be similar for all of these agents.

Despite promise from preclinical models, a monoclonal antibody to CGRP (LY2951742) showed no dose response, and no superiority to celecoxib.[85] An inotropic glutamate receptor antagonist failed to meet its primary endpoint. This was a short study with an active comparator, pregabalin.[86] The selective serotonin re-uptake inhibitor (SSRI) duloxetine has been more extensively studied. Two studies showed significantly improved pain compared with placebo, but no benefit of 120 mg over 60 mg.[87,88] Further studies are comparing the effects of pregabalin and duloxetine in hand OA[89] and their mechanism of action.[90]

LIMITATIONS AND PERSPECTIVES

We continue to learn lessons from recent clinical trials in OA: firstly, that we must continue to understand the basic mechanisms in the disease to predict drug effects. Structure-modifying agents could potentially be combined with a pain-relieving agent to improve patient acceptability, but the anti-NGF trials tell us we must first fully appreciate potential interactions. Secondly, there is always a balance to find in acceptability, safety, and effectiveness. What is acceptable risk in conditions such as OA? Some patients may accept a very low risk of acceleration of their disease towards joint replacement or other potential toxicity, if a drug provides markedly improved quality of life. A high level of patient involvement in assessing acceptability and approval of new drugs for OA is needed, bench-marking on existing drug classes such as NSAIDs and opiates. Repurposing of existing agents (with acceptable safety profiles for other indications and potentially relevant effects in OA) is likely to be an expanding and cost-effective area.

Design of OA trials has in recent years been a bigger challenge than the identification of novel targets.[91] Better trial design needs to take account of and minimise placebo response; we need better, more reliable patient and disease-relevant outcome measures. One of the biggest challenges in this area is the heterogeneity of the disease, in its phenotype and progression. We need to be able to stratify patients in our recruitment to trials, enriching for those at highest risk of progression (of symptoms or structure) or with relevant disease phenotype.[92] Better prognostic modelling is being developed.[12,93] These groups may include those with early disease, or those at risk of disease, such as those with knee trauma, where ~50% of individuals will develop symptomatic radiographic disease.[94] The gain may arguably be larger in these groups, in advance of extensive irreversible structural damage. Most trials to date have been in the knee and hip. The noticeable increase in trials of agents in hand OA will diversify the field; we may discover that some agents have site-specific effects. It may be necessary to revisit some failed trials once we have better ways of assessing effects of some of these agents.

Who will benefit from these drugs? The majority of patients with OA may not need these drugs. Rather, they will be reserved for those with highly symptomatic and/or progressive disease who have failed to respond to primary interventions.[7] We will need to personalise certain treatments to particular groups, by better defining disease phenotypes, with valid biomarkers for disease processes or response to a particular drug class.[95] More expensive biological interventions will only find their place if they prove to be cost-effective, for example if they delay or reduce the need for joint replacement or other comorbidity or mortality risk associated with OA.[96] Specialist drugs will likely require eligibility assessment and monitoring, much like DMARDs and biologics for RA: we need to develop a readiness to think about the care of this disease in a different way.

CONCLUSIONS

Opportunities for modifying symptoms and disease process in OA with new pharmacological agents would appear to be on the close horizon. There are a variety of tissue and molecular targets, old and new. A renewed focus on patient-reported symptoms, particularly pain, has brought about the possibility of new drug classes for OA. The question would appear not to be whether, but simply when; a new approved class would seem likely within 5–10 years. Understanding what impact new agents have on the underlying disease process, and what they can teach us about disease pathogenesis is an essential part of their assessment.

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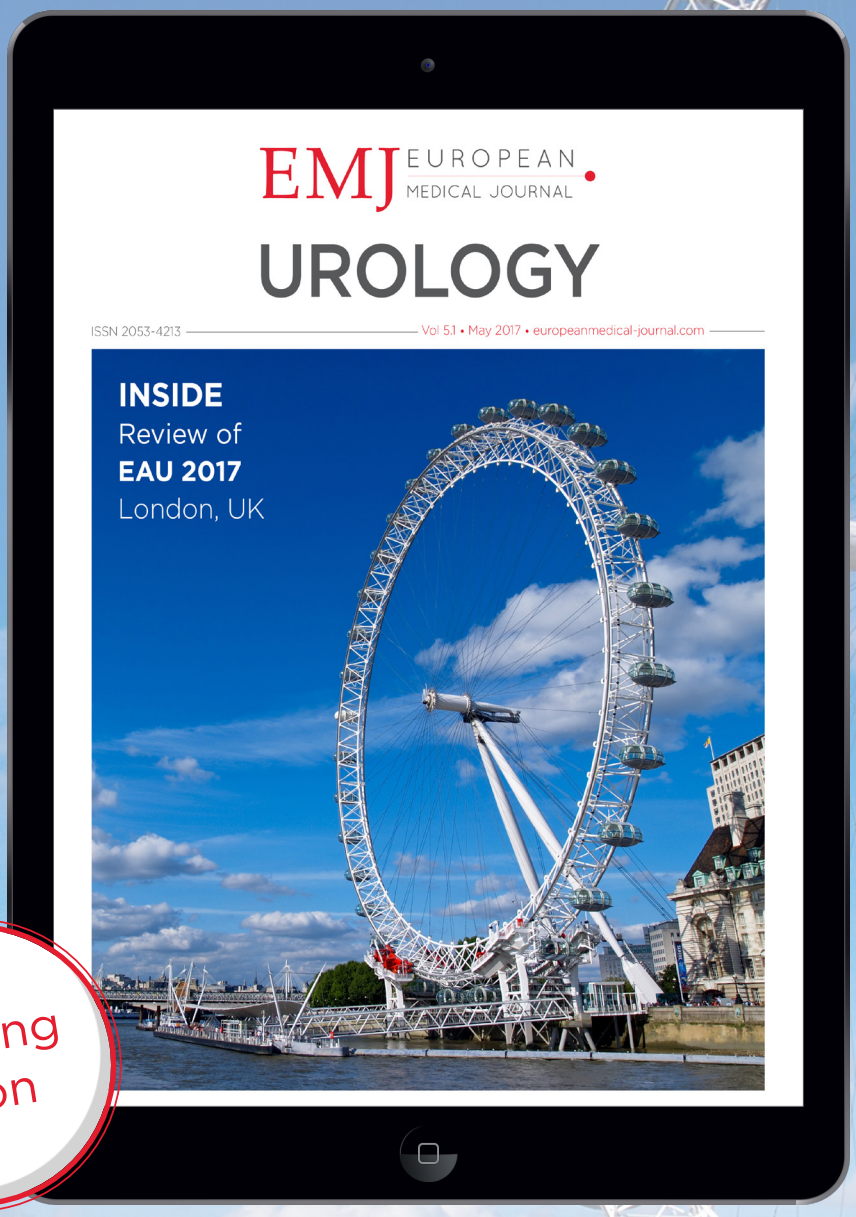

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CONTEMPORARY DRUG-ELUTING STENTS AND VASCULAR RESPONSE

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ABSTRACT

Cardiovascular disease is a leading cause of death and disability worldwide. Current treatment strategies aimed at treating the consequences of coronary artery disease have embraced both optimal medical therapy and catheter based percutaneous coronary intervention with drug-eluting stents (DES). Current-generation DES elute predominantly mammalian target of rapamycin (mTOR) inhibitors, which act primarily as a cytostatic agent that retards vascular smooth muscle cell proliferation and migration; this occurs in response to injury and thus prevents restenosis. While DES have reduced restenosis, the use of first-generation DES was associated with an increased risk of late stent thrombosis and accelerated neointimal atherosclerosis (i.e. neoatherosclerosis), both major contributors to late stent failure. The underlying substrate of late DES failure is likely related to vascular endothelial dysfunction, which occurs after DES implantation. Initial concerns with first-generation DES have led to improvements in stent design, polymer load and biocompatibility, and pharmacologic agents, all of which have helped to improve healing responses, lessen late stent failure, and result in an overall improved safety profile. The armamentarium of DES has expanded from the current-generation durable polymer DES to bioresorbable polymer DES, polymer-free DES, and lastly totally bioresorbable vascular scaffolds with a goal of improving vascular responses and endothelial function while preserving anti-restenotic efficacy. We will review these contemporary DES in relation to their short and long-term effects on vascular biocompatibility and healing responses.

Keywords: Restenosis, mammalian target of rapamycin (mTOR) inhibitors, endothelialisation, neoatherosclerosis.

INTRODUCTION

Drug-eluting stents (DES) are endovascular devices designed to prevent restenosis through inhibition of smooth muscle cell proliferation that is incited by vascular injury from initial device deployment.[1] Since their introduction into clinical use, major advances have occurred in the DES design involving thinner metal scaffolds with preserved radial strength, more biocompatible polymers, and advancement in mammalian target of rapamycin (mTOR) inhibitor analogues, allowing for better drug retention in the vessel reducing the total amount of drug load needed per device. Each improvement in these DES components has, for the most part, improved the vascular responses to current-generation devices, lessening the delay in re-endothelialisation of stent struts and reducing the thrombotic risk. Despite these improvements, overall signs of vascular dysfunction still occur in current-generation metallic DES including inhibition of normal coronary vasomotion (largely due to the encasement of the vessel within a metallic cage) and the accelerated development of collections of foamy macrophages within the neointima (termed neoatherosclerosis). The latter may be due to incomplete endothelial junction formation and promotes the development of accelerated atherosclerosis leading to restenosis, late stent failure, and the need for target lesion revascularisation.[2,3] This suggests that certain

components in the DES system (e.g. the metallic backbone, mTOR inhibitors, and drug carrier polymers) may be the major contributors to endothelial dysfunction after DES deployment. Recent advancements in DES technology have aimed to reduce the vessel exposure to both carrier polymers, anti-proliferative agents, and even the metallic backbone itself. This has led to the development of newer endovascular devices such as the bioresorbable vascular scaffold (BVS), bioresorbable polymer DES (BP-DES), and polymer-free DES (PF-DES).[4-7] Whilst current research into endovascular devices focusses on both metal backbone of the device itself as well as polymers used to deliver drugs from them, there have been advancements in the evolution of anti-proliferative agents for DES beyond limus-based derivatives. We will review current and future DES design and long-term risk for endothelial dysfunction and adverse clinical events.

CONTEMPORARY STENT DESIGN

Contemporary DES contain three primary components: a metallic backbone, polymer coating (which may or may not be absorbable), and lastly the anti-proliferative agent itself. For the sake of this discussion we will review the design of the three durable polymer DES (DP-DES) and one BP-DES currently approved by the US Food and Drug Administration (FDA) for human use. We will briefly touch upon the design of PF-DES and BVS systems, the latter of which was recently approved for clinical use in the USA. An overview of stent design elements by device type is shown in Table 1.

Stent Platforms

Stent platforms currently in use in DP-DES, BP-DES, and PF-DES consist of cobalt nickel, cobalt chromium, or platinum-chromium alloys, providing an increased radial strength and radiopacity compared with stainless steel. All current-generation platforms are biocompatible and composed of thin struts (74–89 µm) which reduce inflammation and arterial injury and re-endothelialise at a faster rate than previous stents.

Polymers

Polymers applied to the surface of DES are designed to help control drug release. Polymers themselves can be immunogenic, generating hypersensitivity responses, which may result in delayed healing and in some cases stent thrombosis, as has been previously reported for both first and second-generation DP-DES.[2,8] Even low-grade inflammations generated in response to polymers are thought to promote cell proliferation and intimal formation as has been shown in the porcine coronary model where first-generation sirolimus-eluting stents (SES) showed significant reduction in neointimal formation at 28 days compared to bare-metal stents (BMS) but this reduction was not sustained in the later time points.[9] This was accompanied by evidence of increasing inflammation (i.e. granulomas and eosinophilic reactions) as well as cell proliferation, suggesting polymer induced inflammation as the cause of increasing intimal formation over time. This so-called late catch up phenomenon has been seen in both our human pathology DES registries as well as in clinical trials.[10]

The goal of polymer design for DP-DES has been to improve biocompatibility to help improve outcomes. Durable polymers such as polyvinylidene difluoride (PVDF) on the XIENCE™ Alpine (Abbott Vascular, Santa Clara, California, USA) and PROMUS Element™ (Boston Scientific, Marlborough, Massachusetts, USA) stents as well as the BioLinx™ polymer on the Resolute Integrity™ Stent (Medtronic, Minneapolis, Minnesota, USA). The BioLinx polymer consists of hydrophobic long-chain methacrylate esters, hydrophilic polar N-vinylpyrrolidone, vinyl acetate, and poly (n-butyl methacrylate), all of which have improved biocompatilibility compared to first-generation DES polymers. PVDF-coated stents had significantly lower thrombosis and platelet deposition compared with their bare-metal counterparts in experimental settings.[11] In this regard, they have also been shown to elicit reduced platelet aggregates in blood contact applications.[12] Whether other polymers used in DP-DES have similar effects remains incompletely explored.

The only FDA approved BP-DES in the USA is the SYNERGY™ stent system (Boston Scientific, Marlborough, Massachusetts, USA) which consists of a poly(lactic-co-glycolic acid) (PLGA) copolymer in which everolimus is released over the course of 3 months and the abluminal polymer layer becomes fully degraded by 4 months when PLGA biodegrades by hydrolysis of its ester linkages. Vascular responses were reported to be similar between SYNERGY, polymer-only stents, and corresponding BMS at 270 days in the porcine coronary model.[13] These data reinforce the rationale for BP-DES wherein by eliminating long-term polymer exposure arterial inflammation is similar to BMS.

Table 1: Comparison of contemporary drug-eluting platforms.

Platform	Trade name	FDA approval	Polymer	Scaffold component	Scaffold thickness	Drug	Elution
DP-DES	Resolute, XIENCE, Promus	Yes	BioLinx (Resolute), PBMA + PVDF-HFP (Promus and Xience)	CoCr (Resolute, XIENCE) PtCr (Promus)	81 µm	Everolimus (XIENCE, Promus), Zotarolimus (Resolute)	90% in 30 days (XIENCE and Promus) 50% by 30 days and 100% by 180 days (Resolute)
BP-DES	SYNERGY	Yes	PLGA	PtCr	74 µm	Everolimus	90% in 30 days
PF-DES	Biofreedom™	No	None (reservoirs)	Stainless steel (316 L)	114 µm	Biolimus A9	90% in 30 days
BVS	Absorb 1.1	Yes	PLLA + PDLLA	See polymer	156 µm	Everolimus	90% in 30 days

DES: drug-eluting stents; DP: durable polymer; BP: bioresorbable polymer; PF: polymer free; PBMA: poly n-butyl methacrylate; PVDF-HFP: polyvinylidene fluoride and hexafluoropropylene monomers; PLGA: poly(lactic-co-glycolic acid); PLLA: poly-L-lactic acid; PDLLA: poly-D,L-lactide; CoCr: cobalt chromium; PtCr: platinum chromium; BVS: bioresorbable vascular scaffolds; FDA: US Food and Drug Administration.

Bioresorbable Vascular Scaffold

BVS were designed to overcome the limitations of metallic stents including impaired coronary vasomotion and preclusion of bypass surgery for stented segments. The ability to provide transient scaffolding during repair of injured segments while minimising the risk of restenosis is the goal of BVS therapies. The development of the everolimus eluting Absorb™ (Abbott Vascular, Santa Clara, California, USA) BVS represents the most advanced attempt to bring such a system to clinical use. The bioabsorbable stent consists of a 150 µm thick poly-L-lactide scaffold with a poly-D-L-lactide coating. With the polylactic acid family of polymers molecular weight degradation occurs predominantly through hydrolysis, which includes a reduction in molecular weight first, followed by mass loss eventually leading to degradation of monomers (L-lactate) into pyruvate, which enters the Krebs cycle and is converted into carbon dioxide and water; practically speaking, the system takes 36–42 months to fully absorb. Long-term preclinical models utilising the Absorb system show promising results, but still raise interesting clinical questions. In the porcine model vascular responses to Absorb versus current-generation DP-DES (XIENCE V, Abbott Vascular) were comparable at all time points although inflammation scores and percent area stenosis were greater for Absorb versus XIENCE V from 6–36 months.[7] In the rabbit iliac model of stenting, there was comparable endothelialisation of Absorb versus a first-generation DES (Cypher™, Johnson and Johnson, New Brunswick, New Jersey, USA) at 1 month with slight improvement at 36 months in addition to lower inflammation scores but greater area stenosis at the later time point.[14] The greater area of stenosis was thought to be mainly due to its thicker struts. This suggests that BVS is least comparable to first-generation DES, however there are still concerns as to its readiness for clinical use compared with current-generation DES.[15]

Anti-Proliferative Drugs

DES utilise anti-proliferative agents to prevent restenosis. These anti-proliferative agents mainly consist of two classes: mTOR inhibitors and the taxol derivative paclitaxel. Initially first-generation DES utilised the mTOR inhibitor, sirolimus, in 2003 (Cypher, Johnson and Johnson), and soon after paclitaxel was used in 2004 (Taxus®, Boston Scientific, Marlborough, Massachusetts, USA). Since then the number of mTOR inhibitors has expanded in subsequent second and third-generation DES to become the predominant anti-proliferative agent eluted from these devices. Their use has extended into newer endovascular devices such as the BVS, BP-DES, and PF-DES.

The use of newer, lipophilic-limus based mTOR inhibitors (i.e. everolimus, zotarolimus, umirolimus ['biolimus A9™']) have also allowed lower drug concentrations lessening drug toxicity when compared to the prototype, sirolimus. While both sirolimus and everolimus have been used both systemically and locally, newer analogues (such as zotarolimus and umirolimus) have been specifically developed for local elution in vascular stents.

The development of locally eluted sirolimus analogues has been initiated by the modification of the C40 or C42 moiety on the macrocyclic ring of the sirolimus backbone with a lipophilic group. In preclinical studies, zotarolimus with a tetrazole modification to C42 had the highest lipophilicity compared with sirolimus and paclitaxel, allowing for rapid vascular wall uptake and pharmacokinetic titration. In *in vitro* modelling of both endothelial proliferation and migration, sirolimus appeared to have more anti-proliferative and anti-migratory effects on endothelial cells versus everolimus.[16]

VASCULAR RESPONSES TO FIRST AND SECOND-GENERATION DURABLE POLYMER DRUG-ELUTING STENTS

Human pathologic studies looking at the vascular responses from patients with first-generation DP-DES demonstrated delayed arterial healing as defined by persistent fibrin, minimal neointimal formation, and incomplete endothelialisation in DP-DES compared to BMS cases at similar time points after stenting.[8] Endothelialisation was complete in most BMS sections by 3–4 months while in first-generation DP-DES some samples remained unhealed as much as 40 months after implantation. Late stent thrombosis was defined as any platelet rich thrombus occupying 25% of lumen 30 days after DP-DES implantation, and was observed in >50% of patients receiving DP-DES.[17] The major pathologic finding distinguishing late thromboses from patient DP-DES was evidence of a significantly greater delay in arterial healing characterised by lack of endothelialisation and persistent fibrin deposition at a mean of approximately 6 months after DES implantation.[17] These data suggested that lack of complete arterial healing after DES was the common factor underlying all cases of DES late stent thrombosis. Further clinical data continued to demonstrate increased thrombotic events in patients receiving first-generation DES and indicated the most important risk factor for such events was withdrawal of dual antiplatelet therapy.[18] Data from the SIRTAX and Post-SIRTAX registries in Bern and the RESEARCH and T-SEARCH registries in Rotterdam and Amsterdam indicated that stent thromboses continued to occur steadily, at a constant rate of 0.6% per year at least out to 4 years after stent implantation and perhaps beyond.[19] Thus it seemed clear that in some patients receiving first-generation DES, arterial healing continued to be delayed for many years.

Second-generation DES such as everolimus-eluting stents (EES), Endeavor zotarolimus-eluting stents (E-ZES) (Medtronic), and Resolute Integrity zotarolimus-eluting stents (R-ZES) (Medtronic) were designed with thinner strut backbone stents, reduced polymer and drug loading, and eluted analogues of sirolimus such as everolimus and zotarolimus, which in some cases have improved lipophilicity as well as potentially increasing tissue retention and cellular targeting. In preclinical models of arterial stents, EES, E-ZES, and R-ZES demonstrate superior endothelialisation to first-generation DES at similar time points. In human autopsy samples of first-generation DES compared to second-generation DES (i.e. EES) EES demonstrated superior strut coverage at similar timepoints.[2,8,20] Although head-to-head trials of first-generation DES (i.e. SES) versus EES have not conclusively shown a reduced incidence of stent thrombosis, all have probably been underpowered to reach such an endpoint. Optical coherence tomography (OCT) studies in patients receiving these stents have also been conducted and suggest superior strut coverage, a surrogate measure for endothelial coverage, in EES.[21,22]

VASCULAR RESPONSES TO ELIMINATING POLYMERS AND SCAFFOLD: BIORESORBABLE POLYMER DRUG-ELUTING STENTS, POLYMER-FREE DRUG-ELUTING STENTS, AND BIORESORBABLE VASCULAR SCAFFOLD

Despite evidence of improved endothelial recovery in second-generation DP-DES versus first-generation DP-DES, concerns about polymer induced inflammation as a cause of late catch up in both first and second-generation DP-DES prompted innovation in the design of metallic DES with the goal of limiting polymer exposure through either BP-DES or PF-DES. Of additional concern were rare reports of adverse effects of carrier polymers, such as hypersensitivity reactions with predominant eosinophilic infiltration and resulting intra-strut protrusions seen in OCT studies.[23]

Platforms involving BP-DES (SYNERGY) and PF-DES (Biofreedom™, Biosensors, Singapore) are in clinical use throughout the world though only SYNERGY is currently approved in the USA. Most BP-DES act similarly to DP-DES with less exposure of carrier polymer (degrades within 4 months) and similar

efficacy.[24] Vascular responses in the porcine model are similar between SYNERGY and control BMS, though SYNERGY showed mild increases in fibrin at early timepoints.[13] Long-term inflammation was not reported in this particular study.

One particular issue of importance for BP-DES is how to show a definitive advantage in clinical endpoints versus second-generation DP-DES. In the EVOLVE II clinical trial of SYNERGY versus PROMUS (DP-DES), at 24 months, SYNERGY was non-inferior to PROMUS for target lesion failure (8.5% versus 9.4%, respectively). There were no significant differences in all-cause death (1.7% versus 2.1%), myocardial infarction (5.5% versus 5.3%), target lesion revascularisation (4.3% versus 3.1%), or stent thrombosis (0.4% versus 0.8%). It remains to be seen whether longer-term follow-up will demonstrate any clinically relevant differences. In the absence of data showing accelerated healing in SYNERGY versus DP-DES, dual antiplatelet duration is likely also to remain similar to current-generation DP-DES given similar drug elution characteristics (Table 1).

PF-DES also provides an interesting alternative combining the lack of polymer with the benefits of anti-proliferative drugs. Drug elution is through reservoirs within the metal scaffolding, which elutes the drug over a period of 30 days.[25] With the Biofreedom PF-DES, studies have suggested that given this elution profile and absence of polymer, dual antiplatelet duration can be shortened to 1 month, similar to BMS with similar cardiovascular outcomes when compared to BMS in patients at a high risk of bleeding.[25] In the porcine model, the Biofreedom stent demonstrated equivalent early reduction of intimal formation with improved late efficacy compared to the SES. At 180 days SES showed delayed healing and persistent inflammation compared with Biofreedom.[26]

One of the more innovative devices is the fully BVS which eliminates the long-term disadvantages of a metallic scaffold.[7] Implantation of BVS is thought to restore the vasomotor integrity of the underlying vasculature seen in preclinical animal models.[27] Because polymer is not as strong as metal, BVS has considerably thicker struts to improve its radial strength. Moreover, as stated earlier, polylactic acid degrades mainly by hydrolysis with complete degradation taking >32 months in animal models.[7]

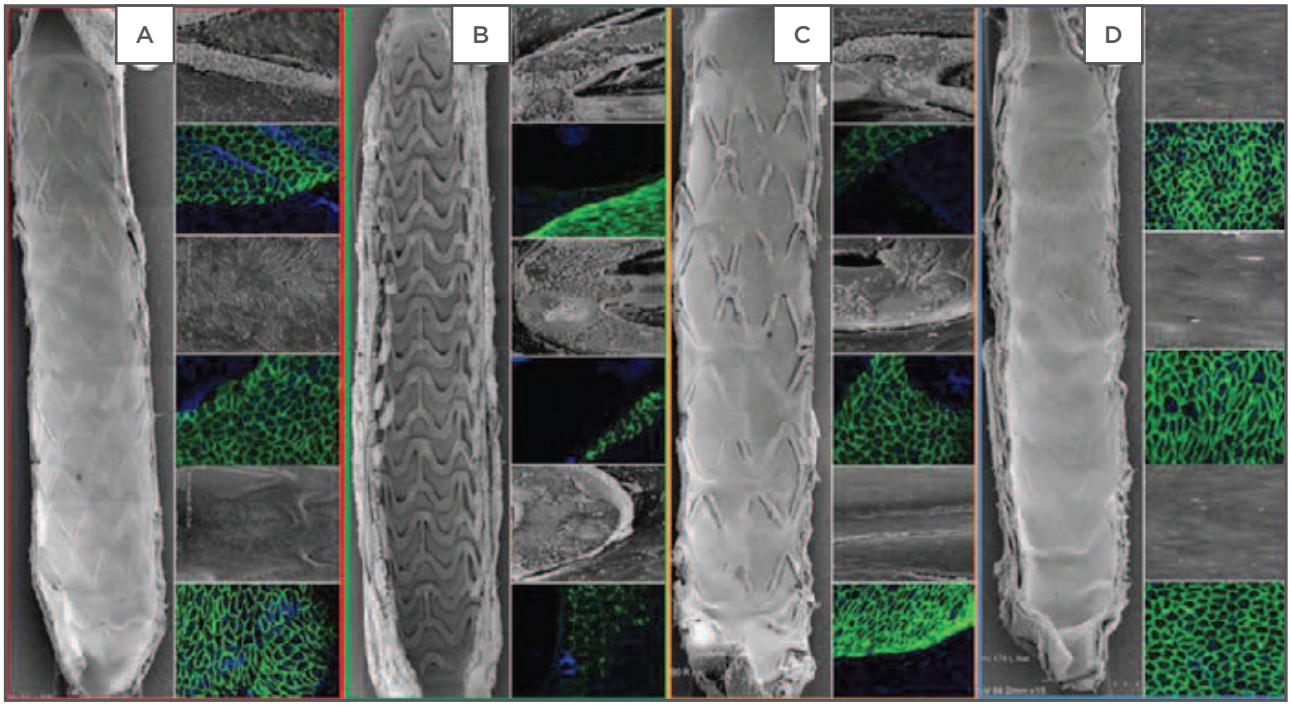

Figure 1: Representative images of endothelial coverage at Day 28 in a rabbit iliac artery model at 15x SEM (far right panel) and 200x SEM images (grey inset) and confocal microscopy (green stain) with endothelial protein staining (CD31/PECAM-1 expression).

A) Bioresorbable polymer everolimus-eluting stent; B) Everolimus-eluting bioresorbable vascular scaffold; C) Bioresorbable polymer biolimus-eluting stent; D) Bare-metal stent.

SEM: scanning electron microscopy.

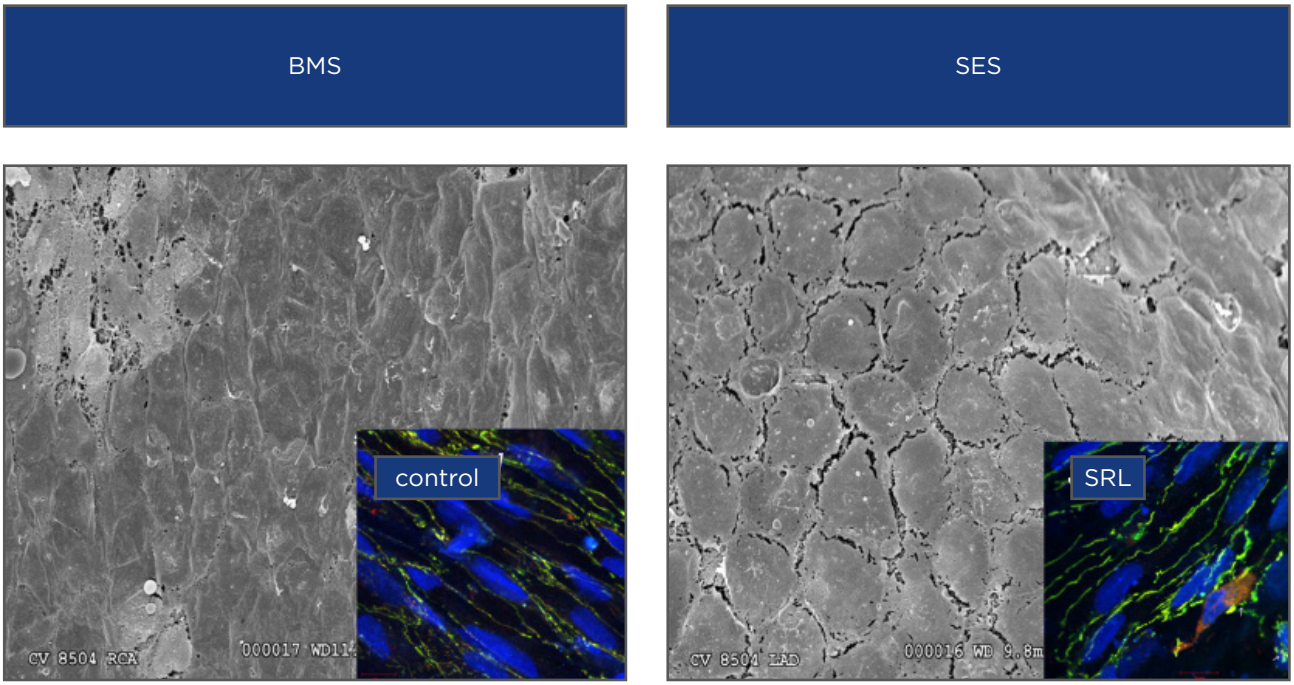

Figure 2: Poorly formed endothelial cell junctions following stent placement.
When compared with BMS, scanning electron microscopy of rabbit iliacs treated with SES have poorly formed endothelial junctions compared with BMS treated arteries and subsequent endothelial barrier dysfunction. Insets show immunohistochemistry of key endothelial barrier proteins with better formed junctions in control treated human endothelial cells compared with those treated with SRL.
BMS: bare-metal stents; SES: sirolimus-eluting stents; SRL: sirolimus.

In the rabbit model, endothelialisation, while similar to first-generation DES,[14] is slower and more dysfunctional at 28 days as compared to DP-DES[28] (Figure 1). A recent meta-analysis of BVS compared with current-generation DP-DES suggests that although target lesion revascularisation rates are equivalent, there is an increased risk of stent thrombosis compared with second-generation DP-DES (XIENCE).[29] While BVS (Absorb, Abbott Vascular) provides a novel treatment of symptomatic coronary artery disease,[29,30] it in many ways mirrors first-generation DP-DES in that the strut thickness is about twice that of current-generation DP-DES (Table 1) and thus it is not surprising that delayed healing is an issue with this device. BVS, like first-generation DP-DES, will likely undergo improvement in scaffold design leading to thinner struts with preserved radial strength.

While all these novel platforms provide different attributes compared to DP-DES, mTOR inhibitors remain a constant in all and its presence not only contributes to impaired initial endothelialisation but subsequent endothelial barrier dysfunction with acceleration of neoatheroma formation (i.e. neoatherosclerosis).

MECHANISMS OF IMPAIRED ENDOTHELIALISATION

Most current-generation DES used in clinical practice are designed to elute pharmacologic agents such as sirolimus that inhibit the mTOR, a member of the phosphatidylinositol kinase-related family of serine/threonine kinases. Although animal studies suggest that inhibitors of mTOR delay endothelial cell growth and recovery, the precise cellular mechanisms are still being elucidated.

mTOR interacts with several proteins to form two distinct complexes named mTOR complex 1 (mTORC1) and 2 (mTORC2), each of which has distinct sensitivities to rapamycin. Each mTOR complex integrates information from upstream signalling and activates downstream effectors to control distinct cellular mechanisms needed for arterial repair. mTORC1 is the better characterised of the mTOR complexes and integrates signalling from multiple signals including growth factors released upon arterial injury to affect process critical for endothelial coverage after injury such as migration and proliferation. The regulation of proteins critical (i.e. S6K1) for cell proliferation and migration might

in fact be the most important mechanism by which mTORC1 regulates endothelialisation.[3,16,25,31,32]

Other factors also affect endothelial recovery. Local drug concentrations are increased by overlapping DES, encountered in approximately one-quarter of interventional procedures which may lead to an increased percentage of uncovered stent struts.[33] However, the use of newer, lipophilic-limus based mTOR inhibitors (e.g. everolimus, zotarolimus) have also allowed lower drug concentrations, lessening drug toxicity when compared to the prototype, sirolimus. Furthermore, everolimus has been shown to have a more favourable vascular response in a preclinical diabetic animal model after DES implantation suggesting it may have a role in promoting endothelial integrity.[5] Outside of pharmacological factors related to eluted drugs, various mechanical factors are related to poor endothelial healing and late stent failure. These factors include polymer hypersensitivity leading to eosinophilic infiltration, a rare but clinically important finding, and persistently poor endothelial healing due to either stent malapposition or underlying penetration of struts in necrotic core rich lesions.[2] To some extent, these factors have been overcome by advances in stent technology in newer-generation DES with more biocompatible polymers and newer alloys and stent designs.

While improvements in design (i.e. mechanical and biological) factors may have largely addressed aetiologies of poor endothelial coverage after first-generation DES placement, an intact endothelium may display poor endothelial barrier function that may act as a substrate for neointimal atherosclerosis known as neoatherosclerosis (Figure 2). Neoatherosclerosis is the development of foamy macrophages within the neointima which overlies the deployed stent and is accelerated in DES compared with BMS. The use of limus-based DES may contribute to poor endothelial barrier function, leading to neoatherosclerosis, which is increasingly seen as a common substrate that underlies late stent failure leading to in-stent restenosis and thrombosis.

NEOATHEROSCLEROSIS

Post-mortem studies of patients with late stent failure/stent related deaths have demonstrated both: i) poor endothelial coverage and ii) neointimal atherosclerosis (neoatherosclerosis) as common substrates of late sent failure. Key features of neoatherosclerosis include foamy macrophages, thin cap fibroatheroma, and lipid infiltration or plaque rupture. Accelerated neoatherosclerosis is seen with first-generation DES placement (mean ~420 days) and BMS (mean ~2,160 days) and may play a role in the greater observed incidence of late and very late stent thrombosis in DES versus BMS. We previously reported in an autopsy series of first and second-generation DES that the incidence of neoatherosclerosis was approximately 30% in both first and second-generation (i.e. EES) DES.[2] There is a growing body of evidence that points towards the eluted limus-based agents as contributors to late events through a common pathologic pathway involving the accelerated neoatherosclerosis formation. The occurrence of accelerated atherosclerosis within DP-DES might be due to impaired endothelial barrier formation, which would allow transudation of lipid and immune cells into the arterial wall. We recently demonstrated that mTOR inhibitors can impair endothelial barrier formation both in cultured cells, mice, and human aortic specimens exposed to sirolimus *ex vivo*. We showed that sirolimus-FKBP12 interaction impairs barrier formation by increasing intracellular calcium via destabilisation of ryanodine intracellular calcium release channels and subsequent activation of calcium sensitive protein kinase C alpha (PKC-α), a serine/threonine kinase important in vascular endothelial cadherin barrier function through its interaction with a key endothelial junctional protein, p120-catenin (p120).[3] This study demonstrated that the impairment in barrier formation that occurs after endothelial cells are treated with mTOR inhibitors occurs because of off-target effects of the drug itself rather than as a direct consequence of mTOR inhibition. These differences are likely exacerbated by diabetes where PKC activation is also associated with accelerated atherosclerosis suggesting that neoatherosclerosis is likely a major contributor to in stent restenosis, especially in diabetes. These data may also explain why the incidence of neoatherosclerosis is not different between first and second-generation DP-DES and will likely occur in newer stent platforms since all employ mTOR inhibitors.

While many believe BP-DES and BVS might obviate the formation of neoatheroma by eliminating vascular exposure to polymer, it has been observed clinically within the latter stent system.[34] Overall it remains to be seen whether these newer stent systems alleviate the incidence of neoatherosclerosis.[2]

Recently we demonstrated a mechanism by which limus-based mTOR inhibitors inhibit

endothelial barrier formation and likely contribute to neoatherosclerosis formation.[3,16] We showed that sirolimus-FKBP12 interaction impairs barrier formation by increasing intracellular calcium via destabilisation of ryanodine intracellular calcium release channels and subsequent activation of calcium sensitive PKC-α, a serine/threonine kinase, important in vascular endothelial cadherin barrier function through its interaction with a key endothelial junctional protein, p120-catenin (p120).[3] This study demonstrated that the impairment in barrier formation that occurs after endothelial cells are treated with limus-based agents occurs because of off-target effects of the drug itself rather than as a direct consequence of mTOR inhibition, suggesting that the different limus agents will likely result in similar rates of neoatherosclerosis. These differences are likely exacerbated by diabetes where PKC activation is also associated with accelerated atherosclerosis suggesting that neoatherosclerosis is a major contributor to in stent restenosis, especially in diabetes.[35] These data may also explain why the incidence of neoatherosclerosis is not different between first and second-generation DES since all employ mTOR inhibitors which utilise similar mechanisms (i.e. FKBP12) to inhibit mTOR.[2] Although neoatherosclerosis has been observed with BVS, future studies will elucidate the overall incidence compared with current-generation DP-DES.

CONCLUSION

Current-generation DP-DES and newer DES platforms (BP-DES, PF-DES, BVS) have the advantage of long-term patency rates (i.e. low target vessel revascularisation) with suppression of restenosis and an overall low rate of in stent thrombosis. Newer platforms attempt to obviate risk by eliminating the polymer, removing the metal scaffold in BVS and using newer lipophilic mTOR inhibitors. While current clinical data suggest newer platforms are non-inferior to DP-DES, their potential advantages have yet to materialise and may depend on a unique clinical situation. While PF-DES may have a definite use in high-risk bleeding patients, the advantage of BP-DES and first-generation BVS compared with current-generation DP-DES has not yet been fully elucidated. BVS may have the greatest therapeutic potential as compared to DP-DES because they offer the potential of restoration of normalising vasomotion and vessel remodelling.[27] The main concern with BVS is its structural design, with thicker stent struts and compromised radial strength preventing complete endothelialisation and inadequate stent expansion. This has led to an overall observed increase in stent thrombosis in first-generation BVS. Further improvement in novel stent/scaffold design may likely lead to clinical improvements, however it may take long-term follow-up to elucidate reduction in target lesion revascularisation and reduction in long-term vascular effects such as neoatherosclerosis.

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DOES RACE/ETHNICITY HAVE A ROLE IN A LINK BETWEEN LOWER URINARY TRACT SYMPTOMS AND METABOLIC SYNDROME?

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ABSTRACT

Metabolic syndrome (MS) is a highly prevalent disease related to the risk of cardiovascular disease and diabetes. A large body of evidence has suggested a link between MS and the components of MS with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) complex. The pathogenesis of MS is complex and not fully understood. Furthermore, recent results from epidemiological studies, including multiple Asian reports, have not been consistent. The risk of BPH is lower in Asian men compared with white men and the prevalence of MS varies by race and ethnicity. An elevated risk of Type 2 diabetes mellitus, hypertension, and dyslipidaemia is closely related to MS and is observed in Asian men even if their body mass index is low. However, the role of race and ethnic disparity in the link between MS and LUTS secondary to BPH is not elucidated. It has been suggested that the pathogenesis of LUTS is multifactorial rather than developing from BPH, which is the traditional concept. Lifestyle and genetic factors may substantially modify the risk of MS and LUTS/BPH. This comprehensive literature review summarises the scientific evidence of the racial/ethnic disparity regarding the association between MS and LUTS/BPH in order to improve current understanding of this controversial issue.

Keywords: Metabolic syndrome (MS), lower urinary tract symptoms (LUTS), ethnicity, benign prostatic hyperplasia (BPH).

INTRODUCTION

A cluster of multiple risk factors including obesity, insulin resistance, hypertension, and dyslipidaemia that are related to an increased risk of cardiovascular disease has been termed metabolic syndrome (MS).[1] The MS and benign prostatic hyperplasia (BPH) complexes are prevalent diseases that increase with age in older men. Hammarsten and Högstedt[2] first suggested that components of MS constituted risk factors for the development of BPH. Clinical and epidemiological evidence have suggested that the risk of lower urinary tract symptoms (LUTS)/BPH is associated with MS, or individual components of MS such as obesity, diabetes, and hypertension.[3,4] Conversely, other studies, including multiple Asian epidemiologic investigations, did not demonstrate a link between MS and LUTS.[5-7]

In a multi-ethnic study in the USA, the estimated prevalence of MS was about half as likely in non-Hispanic black males when compared with non-Hispanic white males.[8] Race and socioeconomic status are independently associated with BPH. The severity of LUTS is greater in American black men than American white men.[9,10] In contrast, no significant difference in the prevalence of symptomatic BPH between these two races of American men was observed in the National Health and Nutrition Examination Survey (NHANES) III.[11] Black men are approximately half as likely to be diagnosed with BPH than white men, despite being more likely to undergo surgical treatment.[12] In a recent cross-sectional study, multi-ethnic Asian men and Malay men were groups found to be significantly associated with LUTS, particularly post-micturition symptoms among Malay, Chinese, and Indian men.[13] The results suggest that the

findings can be attributed to religious custom. However, the impact of genetic factors was not clear for this disparity. It is well described that racial variations exist with regard to the age-specific prostate specific antigen (PSA) level, prostate volume, and the prevalence of obesity and diabetes, which are also variables related to the association between MS and LUTS.[14-16]

There is thus an emerging concern regarding whether race/ethnic differences have a role in the conflicting observations regarding the link between MS and LUTS/BPH. Race/ethnicity reflects any combination of genetic and environmental influence including cultural, lifestyle, and socioeconomic state, both separately and jointly.[17] However, little information for racial/ethnic difference with regard to this issue is available. This review provides an overview of the pathway linking variables related to ethnicity with underlying factors between MS and LUTS, with regard to the role of race/ethnicity in their association.

RACIAL DIFFERENCE OF BENIGN PROSTATIC HYPERPLASIA AND SECONDARY LOWER URINARY TRACT SYMPTOMS

Race/ethnicity is associated with the risk of BPH. The risk of BPH has been found to be 41% higher among black and Hispanic men when compared with white men.[9] Prostate volume is greater in Caucasian men than in Asian men, consistent with increasing age. In a Japanese study, the mean prostate volume was 20.3 mL in Japanese men and 29.6 mL in American men.[15] This observation was confirmed by autopsy.[18] The prostate volume was suggested to be related to different cellular composition.[19] The prostate volume appears to increase steadily at about 1.6% per year in randomly selected communities of men.[20] However, changes in prostate size are highly variable at an individual level. In the Baltimore Longitudinal Study of Aging, at a median follow-up of 4.3 years prostate size had increased in 61.9% of men and remained stable or decreased in 38.1%.[21] MS and its components, particularly dyslipidaemia, central obesity, and hyperinsulinaemia, are strongly associated with greater prostate volume increments[22,23] and increased risks of symptomatic BPH and LUTS.[3,24] The Boston Area Community Health (BACH) survey involving a population-based random sample of a multi-ethnic population found the prevalence of LUTS was consistent according to race/ethnicity.[25] Remarkably, an increasing prevalence of LUTS severity is concomitant with ageing, but not with prostate volume, without ethnic disparity.[23] In a meta-analysis, although men with MS had a significantly higher total prostate volume than those without MS, the differences between patients with or without MS for LUTS severity was not significant.[23]

RACE/ETHNIC DIFFERENCE AND OBESITY

The prevalence of obesity varies according to race/ethnic groups, age, and sex.[16,26] Strong genetic components in the aetiology of obesity have also been demonstrated.[27] Genetic factors may contribute 70% of the variation in body mass index (BMI). Race has been shown to modify the relationship between androgenic steroids and metabolic variables associated with the risk of diabetes. NHANES data has shown that the prevalence of being overweight among men increased significantly while a race/ethnicity disparity remained.[28] The highest prevalence of obesity was observed in black men. The prevalence of obesity in men peaked among men aged 40–59 years old at 36.8%.

Asian men possess higher visceral adipose tissue levels than white European men.[29] Furthermore metabolic complications of obesity such as insulin resistance, dyslipidaemia, and Type 2 diabetes mellitus have been shown to occur at lower BMI levels among obese Asian men compared with their Caucasian counterparts. It is suggested that with limited superficial subcutaneous fat stores in Asian men, excessive fat deposits more readily in the presence of a positive energy balance.

With a similar BMI, Asian people have a higher cardiovascular risk than Caucasian people, and cardio-metabolic risk is significantly higher in white people than in African Americans.[30] A World Health Organization (WHO) expert consultation proposed that the BMI cut-off points, defined by the WHO (25.0–29.9 kg/m^2 for overweight, ≥30.0 kg/m^2 for obesity) as international classifications, are applicable to Asians.[30] The prevalence of obesity is related to ethnic sociocultural differences including diet and physical activity. Specifically, visceral obesity rates in Japanese men are significantly higher than Mongol groups, although the two groups are considered genetically similar. However, the prevalence of individual metabolic abnormalities within each of the groups was

similar to each other and also to the reported prevalence rates in the USA.[31] Urbanisation and an unhealthy diet may have contributed to an increased prevalence of obesity in Mongolian men. Despite the strong influence of genes on obesity, the non-genetic determinants of obesity and weight change in adulthood, such as dietary behaviour, lifestyle, and physical activity, play an important role in the development of the condition.[32]

Racial Difference and Diabetes

The prevalence of diabetes was higher in Asia than in the USA.[33,34] The prevalence of Type 2 diabetes mellitus has rapidly increased in native and migrant Asian populations and it is very high among Pima Indians. Three developing Asian countries: India, China, and Pakistan, make up 21%, 12%, and 5% of these rates, respectively. One of the hallmarks of diabetes in Asian countries is the rapidly increasing prevalence of Type 2 diabetes in young patients.[34] The mechanism of the underlying development of diabetes is complex. Hyperinsulinaemia, a characteristic of insulin resistance, is common among Asian people.[35] Asian populations are more insulin resistant when BMI is lower than people of many other races. Diabetes develops at least a decade earlier in Asian people than in white people. The rapidly increasing rate of diabetes in Asia may be associated with genetic and environmental interaction, which is influenced by lifestyle and diet changes caused by urbanisation, and the longevity of life.[36] Epidemiologic studies have consistently reported diabetes or glucose levels to be associated with an increased risk of LUTS, regardless of BPH.[9]

RACIAL DIFFERENCE AND METABOLIC SYNDROME

In NHANES III and NHANES 1999–2006, a persistent increase of MS (from 29.1% to 34%, age adjusted) among different races/ethnicity has been observed.[26] Mexican-Americans showed the highest prevalence but had the least change in this time. An increase in MS prevalence is likely related to an increase in diabetes prevalence. However, the prevalence of MS among men without diabetes did not significantly change.

Diabetes and obesity are major components of MS. In Caucasian people the prevalence of MS decreased by approximately half when compared with Caucasians with diabetes.[37,38] A markedly lower prevalence of MS in Asian ethnic groups was observed. The prevalence of MS in Japan and in Mongolia, according to Adult Treatment Panel (ATP) III criteria, was 6% and 12%, respectively. In contrast, these rates increased by 13% and 52%, respectively, when based on ATP III WPRO (Regional Office for the Western Pacific Region of WHO) criteria.[30] A distinct difference between Japanese and Mongolian populations is the metabolic variable of obesity and dyslipidaemia rates. This finding is attributed to a difference in diet and lifestyle.

A consistent epidemiological finding is that the prevalence of MS peaks in people who are middle-aged, followed by its decline or equilibrium in men aged 70 years or older.[37,39-41] The trend of a declining prevalence of MS among older-aged men was similar across different races.

The prevalence of MS gradually increased in men from 20 years old up to 50–59 years old according to the Japan Metabolic Syndrome Criteria Study Group guidelines, or up to 60–69 years according to the United States National Cholesterol Education Program (NCEP) guidelines, followed by a decline at 70 years and older.[39] The highest prevalence rate of obesity and dyslipidaemia was observed at around 50 years of age, while the prevalence of hypertension increased in both genders from 20 years through to 80 years of age.

In a Korean cohort study, the prevalence of MS showed a peak in those aged 65–74 years old following which it then gradually decreased in older men but increased in older women.[41] The prevalence of hypertension and diabetes increased in men aged ≥65 years old. Dyslipidaemia rates remained constant in the older-aged men. In Asian populations, it is considered that an increased prevalence of MS is attributed to an increase in the prevalence of obesity-related diabetes mellitus.

RACIAL DIFFERENCE OF PROSTATE SPECIFIC ANTIGEN LEVELS

Prostate volume and PSA level were shown to be the most powerful predictors of BPH progression.[14,42] In a large study, among unselected populations of healthy ageing-men, elevated levels of free PSA independently increased the risk for clinical BPH over 9 years of follow-up.[43] In a 15-year longitudinal community-based study of Japanese men, LUTS and quality of life deteriorated, prostate volume and PSA level increased, and maximum flow rate decreased.[44] Racial differences

in the age-specific PSA reference range is well known. Asian men had lower PSA values than white and African American men of similar age.[14,45] In a cross-sectional study in Malaysia among multi-ethnic groups, the median PSA level of Malay, Chinese, and Indian men was 1.00 ng/mL, 1.16 ng/mL, and 0.83 ng/mL, respectively.[46] Indians had a relatively lower median PSA level and prostate volume than Malay and Chinese men. Asian American men had the highest PSA level, and the lowest PSA levels were observed in the Chinese men within the Asian men cohort.[45] The results indicated that environmental and dietary factors may influence the serum PSA level.

A prospective longitudinal study demonstrated that at the baseline, median PSA level in white men did not differ from the levels in African American men.[47] However, African American men had a much more rapid increase in the PSA level over time when compared with white men. This suggests that genetic and epigenetic factors may contribute to racial/ethnic differences in the serum PSA level.

Multifactorial Aetiology of Lower Urinary Tract Symptoms

LUTS is not a definitive diagnosis and is subject to complex symptoms, with LUTS pathologies affecting prostate and bladder function. A traditional concept of LUTS in elderly men refers to bladder outlet obstruction caused by benign prostatic enlargement. This view did not involve the ageing bladder as a possible cause of LUTS. Age and bladder outlet obstruction are independently associated with detrusor overactivity in men with BPH.[48] In a prospective cohort study of BPH treatment effectiveness, LUTS was not associated with prostate volume, however a reduction in symptoms following treatment correlated with uroflowmetry results.[49]

Poor correlation with symptoms suggested that LUTS defined by the International Prostate Symptom Score (IPSS) was an unreliable measurement of pathophysiological phenomena regarding prostatism.

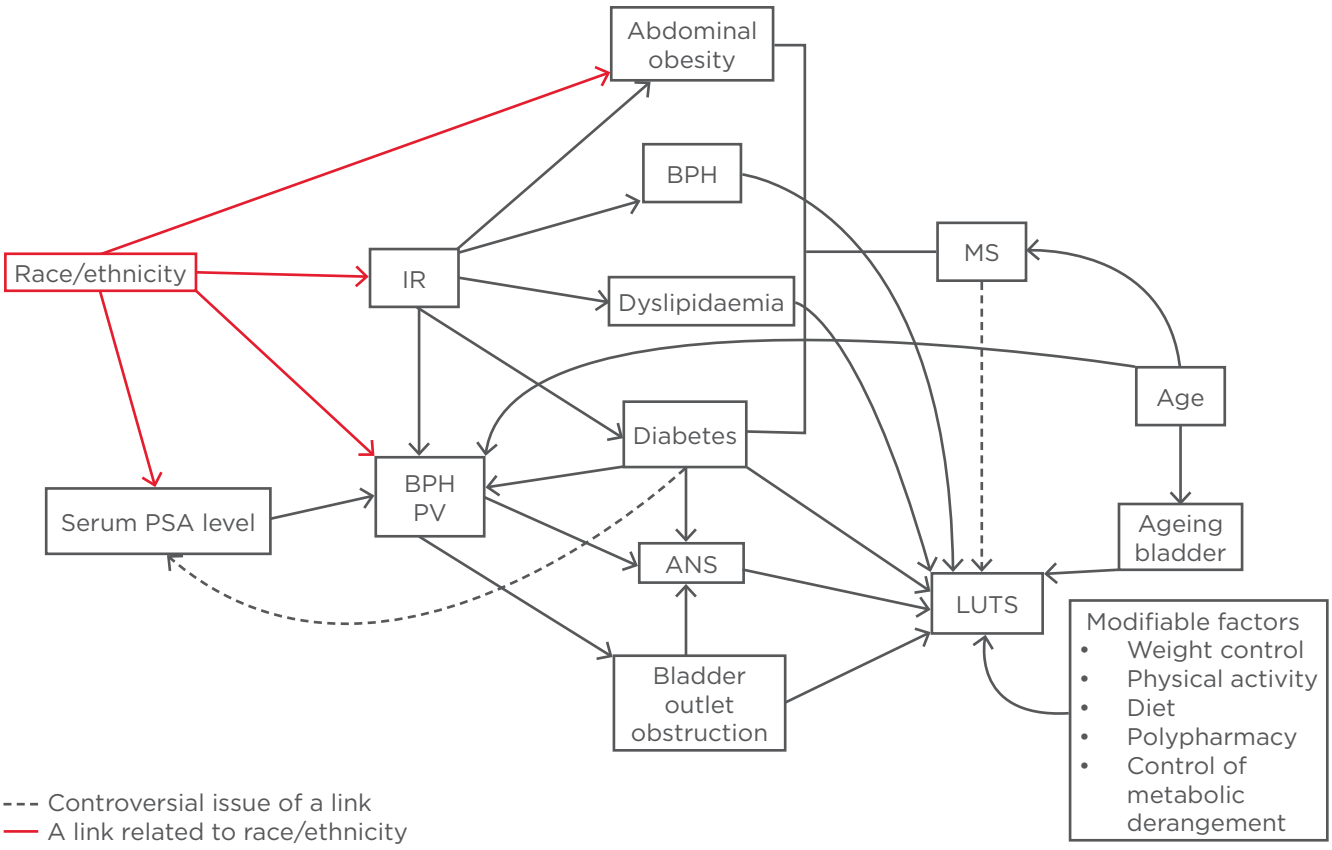

Figure 1: The association between variables related to ethnicity and underlying factors relating to metabolic syndrome and lower urinary tract syndrome.

IR: insulin resistance; MS: metabolic syndrome; PV: prostate volume; ANS: autonomic nervous system; BPH: benign prostatic hyperplasia. PSA: prostate specific antigen; LUTS: lower urinary tract benign prostatic hyperplasia.

Autonomic nervous system hyperactivity is significantly associated with LUTS.[50] The distribution of weak stream frequency was greater in the Japanese than in American men, despite smaller prostates.[14] The results support that LUTS are associated with a non-obstructive causal relationship.

LIFESTYLE/MODIFIABLE RISK FACTORS AND LOWER URINARY TRACT SYMPTOMS

Lifestyle interventions such as weight loss, increased physical activity, and healthier dietary habits substantially alter the risks of symptomatic BPH and LUTS.[25,43,51] In a meta-analysis, the intensity of exercise was related to the reduction of risk of prostate enlargement.[23] High-energy intakes, particularly with a high consumption of protein and polyunsaturated fatty acid, led to a greater risk of developing BPH.[52] Interestingly, a protective effect of alcohol intake on BPH/LUTS was consistently observed in various studies.[51] The impact of modifiable risk factors on LUTS secondary to BPH seems to be similar across different races. The use of prescribed medication that potentially contributes to LUTS as adverse effects was associated with LUTS.[53]

DISCUSSION

In an epidemiological study, race/ethnicity may not reflect the genotype if categorisation of race/ethnicity is defined by phenotype or social group. The relationship between individual metabolic components of MS and LUTS/BPH is complex (Figure 1). Basic and clinical investigation demonstrated that metabolic components including obesity, diabetes, and BPH are substantially influenced by genetic and shared environmental factors such as dietary habits and physical activity.[54] Although there is a strong genetic influence on the development of obesity and diabetes, the role of ethnic disparity in the link between MS and LUTS may overlap genetic variations, lifestyle, and socioeconomic factors. There are environmentally determined differences across different population groups observed over time. Recently, increases in the prevalence of overweight and obese adolescents and children have been observed in many countries throughout the world.[55] This increased trend is attributed to environmental factors. The emerging high prevalence of obesity in Asia is based on factors other than ethnicity such as urbanisation, nutrition transition, and socioeconomic status.

Epidemiological data from the USA and Asia suggest that despite the unrelenting increase in the prevalence of obesity, rates of MS and obesity are dependent on age, through middle-age when these rates peak and begin to either decrease or remain constant in older-age across different racial groups. It is remarkable that the prevalence of overweightness among children and adolescents along with obesity among men increased significantly among different races.[55] Trends did not differ significantly by age or racial/ethnic group. In a Korean community-based study the rate of MS decreased among men aged ≥70 years old. The prevalence of obesity plateaued at 36.2% in 2007 and 37.8% in 2012. Age-specific prevalence of hypertension and diabetes remained constant, while the prevalence of obesity and dyslipidaemia decreased in old-age (>70 years). This finding may be linked to increased rates of regular heath examinations which reached >70% in old age males. These results might be attributable to lifestyle changes and better control of blood glucose and blood pressure in accordance with improved socioeconomic status in older age. In Korea, regular heath examination rates substantially reached >70% in older males (≥65 years old).[41]

In Asian populations the prevalence of diabetes has greatly increased. The risk of central obesity in Asian populations is higher due to genetic influences. The rapidly increasing rate of diabetes in Asia is associated with genetic factors and environmental interaction. Epidemiological studies have demonstrated that the environmental impact on the risk factors of diabetes may be similar across different races.

The correlation of diabetes to prostate volume is not clear. Unexpectedly, in the BACH survey when controlling for age, men with diabetes had a 21.6% lower mean PSA level than men without diabetes.[56] It is suggested that serum testosterone levels and diabetes medication are associated with a decrease in PSA level. A multi-ethnic community-based study showed that the presence of diabetes may be less related to prostate volume, but more so to LUTS, irritative symptoms, and nocturia.[47]

LUTS are strongly dependent on age and the presence of MS. The possible mechanism of the link between MS and LUTS is that of hyperinsulinaemia, which is an underlying feature of MS and is

causally related to the development of BPH by an increased sympathetic nerve activity in men with BPH.[2] However, conflicting results were observed in linking LUTS to prostate volume. The amount that prostate volume increases with advancing age is highly variable between different individuals.[21] Development of BPH is traditionally related to genetic predisposition which is an unmodifiable factor. MS and its components are associated with a greater prostate volume.[22,23] Increased physical activity and dietary changes modify the risk factors of BPH/LUTS.

As defined by the IPSS, LUTS presents dynamic aspects over time across a person's life.[21] In a 3-year follow-up of Japanese men, LUTS worsened in approximately one-third of the participants, remained the same in one-third, and improved in one-third.[15] In a USA longitudinal study, at a 4.2-year follow-up, about 20% of men in the community showed an increase of IPSS points and about 16–23% had an increase in prostate volume.[57] Age-specific IPSS is higher in Japanese men than American men despite a lower prostate volume than American men.[58] The prevalence of LUTS is variable with age; the prevalence of moderate-to-severe LUTS ranges from 22% in men aged 50–59 years old, to 45% in men aged 70–80 years old. Inconsistent results in the link between MS and LUTS may be attributed to the interaction of hereditary and environmental factors. The dynamic nature of individual metabolic components impacts the association between MS and LUTS.

CONCLUSION

In epidemiological investigations, racial and ethnic categories are social and not genetic. The inconsistent results concerning the link between MS and LUTS reflects the diversity in genetic and socioenvironmental factors associated with it. Although there is a strong influence from genetic impacts on obesity and diabetes, the role of ethnic disparity in the link between MS and LUTS may overlap genetic variations, lifestyle, and socioeconomic factors. A tangled web of relationships between LUTS and metabolic variables may hamper the impact of race/ethnicity on the link between LUTS and MS. Emerging new concepts on pathophysiology of LUTS and lifestyle factors may provide new targets for modifying the risk factors of MS. Longitudinal studies are needed for a better understanding of the relationship between MS and LUTS.

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ANTIPHOSPHOLIPID SYNDROME AND THE LUNGS

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ABSTRACT

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by recurrent thromboembolic events (arterial or venous) and/or morbidity in pregnancy (fetal loss, premature birth, or recurrent embryonic losses) in the presence of laboratory evidence of antiphospholipid antibodies (aPL). APS is a multisystem disorder. Several lung manifestations may develop in patients with APS including pulmonary embolism (PE)/infarction; thromboembolic and non-thromboembolic pulmonary hypertension (PH) (pulmonary arterial hypertension); pulmonary microthrombosis; acute respiratory distress syndrome associated with catastrophic APS; diffuse alveolar haemorrhage; and pulmonary capillaritis. Postpartum syndrome and cryptogenic fibrosing alveolitis (CFA) can be associated with APS. Pulmonary manifestations are relatively rare but are more likely to be life-threatening compared with other complications of APS. Particularly in the presence of aPL, pulmonary manifestations should be suspected in any systemic lupus erythematosus patient with clinical findings such as chest pain, dyspnoea, tachypnoea, and haemoptysis. Early diagnosis and treatment of pulmonary manifestations in APS are essential for improving mortality rates in patients with this condition. The purpose of this review is to assess current evidence around the diagnosis, prognosis, and management of patients with common and rare pulmonary manifestations of APS.

Keywords: Antiphospholipid syndrome (APS), pulmonary embolism (PE), pulmonary hypertension (PH), alveolar haemorrhage, antiphospholipid antibodies (aPL), systemic lupus erythematosus (SLE).

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by recurrent thromboembolic events (arterial or venous) and/or morbidity in pregnancy (fetal loss, premature birth, or recurrent embryonic losses) in the presence of laboratory evidence of antiphospholipid antibodies (aPL); including anticardiolipin antibodies (aCA), anti-beta 2 glycoprotein 1 antibodies (aβ2GP1), and lupus anticoagulant (LAC).[1,2] LAC effects the surface phospholipids thus disrupting the clotting time measured by the activated partial thromboplastin time. aCA and aβ2GP1 have roles in the control of coagulation-like complexes of phospholipids and protein or cofactors.[3] aPL are evaluated by two different methods: first a functional, activated partial thromboplastin time-based method for LAC, and second an immune assay for both aCA and aβ2GP1.[4]

aPL can be detected in the absence of thrombosis or fetal loss during infectious diseases, drug use, and even in healthy individuals. In this situation, it is clinically important to apply the diagnostic criteria.[3] The preliminary criteria, developed in 1999, and the classification criteria (Sapporo criteria) were modified in 2006.[2] When a patient fulfills the criteria they can be diagnosed as having autoimmune disease-associated APS if a condition such as systemic lupus erthematous (SLE) is present or primary APS if there is no concomitant disorder.[5] APS is a multisystem disorder. In a study including 1,000 patients with either primary or autoimmune disease-associated APS, various complications were found such as deep vein

thrombosis (DVT), thrombocytopenia, livedo reticularis, stroke, superficial thrombophlebitis, pulmonary embolism (PE), fetal loss, and transient ischaemic attack.[6] Several lung manifestations may develop in patients with APS, including PE/infarction, thromboembolic andnon thromboembolic pulmonary hypertension (PH) (pulmonary arterial hypertension), pulmonary microthrombosis, acute respiratory distress syndrome, diffuse alveolar haemorrhage (DAH), and pulmonary capillaritis.[7,8] Moreover, postpartum syndrome and cryptogenic fibrosing alveolitis (CFA) can be associated with APS.[9] Patients who develop two or more of these pulmonary manifestations synchronously can be described as having antiphospholipid lung syndrome.[7] The purpose of this study is to review the diagnosis, prognosis, and management of patients associated with common and rare pulmonary manifestations in APS.

PULMONARY EMBOLISM AND INFARCTION

The pulmonary manifestations secondary to APS may show a wide variability, but the common complications in the lung involve pulmonary thromboembolism and its associated sequelae, such as infarction and PH.[7] aPLs are associated with thrombosis; aβ2GP1 antibodies are not only a marker of thrombophilia, but moreover contribute to hypercoagulability.[10] In a study, venous thrombosis was independently associated with LAC.[11] PE may be the first manifestation of APS. Cervera et al.[12] prospectively examined the morbidity and mortality in 1,000 APS patients over a 10-year period. They found that 14.1% of patients had PE at initial diagnosis and incidence of new PE was 3.5% over the 10-year follow-up. PE-associated mortality occurred in 5.4% of the patients.[12] DVT, sometimes accompanied by PE, is the most common manifestation of APS. DVT occurs in 55% of APS patients and approximately half of these patients demonstrate PE (30%).[13,14] Furthermore, in a cohort study the PE recurrence rate in APS patients was observed to be as high as 7.5% in the first 5 years after the initial thrombotic event.[4]

The differential diagnosis of PE from pleuritis or pneumonitis can be difficult. Particularly in the presence of aPL, PE should be suspected in any SLE patients with clinical findings such as chest pain, dyspnoea, tachypnoea, and haemoptysis.[14] The first step in diagnosis of suspected PE is with clinical probability scoring, followed by D-dimer levels in blood, if appropriate, and chest radiography. Echocardiography, ventilation perfusion scintigraphy, and/or computed pulmonary angiography are essential for definitive diagnosis. Diagnosis of DVT can be made using Doppler ultrasound.[15]

PULMONARY HYPERTENSION

PH may be present as a separate entity or as a consequence of various clinical conditions such as PE in APS patients. In particular, recurrent pulmonary emboli may give rise to PH.[16] In addition, the microscopic pathogenesis of PH is characterised by vascular endothelial and smooth muscle proliferation, *in situ* thrombosis, development of plexogenic lesions of small pulmonary arteries, and fibrinoid vasculitis that can include all types of medium-sized arteries.[17] A recent study summarised the pathogenesis of PH in APS into three components: a) a cross-reactivity between aCA and anti-endothelial cell antibodies, b) the actions of aPL on the endothelium, and c) the plausible pathogenic role of anti-endothelial cell antibodies in PH.[8]

Transthoracic echocardiography (TTE) allows for estimates of pulmonary arterial pressure which can be confirmed by right heart catheterisation (RHC). Definitive diagnosis of PH requires an increase in mean pulmonary arterial pressure ≥25 mmHg at rest, measured by RHC.[18] It is suggested that aPL in SLE patients increase the risk of PH, a rare and life-threatening complication with poor prognosis.[8,19] In a study, the PH frequency was found to be higher in aPL positive than aPL negative SLE patients (25% and 2%, respectively).[20] Similarly to a previous study, Kamel et al.[21] found that patients with PH were most likely to have aCA positivity in comparison with those without PH. Conversely, Hübbe-Tena et al.[22] found no significant relationship between aPL and unlikely, possible, or likely groups of PH in SLE patients. The reported prevalence of PH in APS patients varies widely between studies, from 2–24%.[6,23] The discrepancies in these findings could be the result of different clinical features of patients at inclusion and/or different diagnostic methods, such as TTE and RHC, which can affect the prevalence of PH.

Five groups of disorders that cause PH have been described: pulmonary arterial hypertension (Group 1); PH due to left heart disease (Group 2); PH due to chronic lung disease and/or hypoxia

(Group 3); chronic thromboembolic PH (CTEPH) (Group 4); and PH due to unclear multifactorial mechanisms (Group 5).[24] Most PH patients associated with aPL are classified to Group 4 and a smaller percentage to Group 1.[25]

CTEPH is a pulmonary vascular disease caused by chronic obstruction of the major pulmonary arterial bed by organised thrombi.[24] Wolf et al.[26] found that 20% of CTEPH patients tested positive for aPL. An important study conducted by Martinuzzo et al.,[27] demonstrated higher rates of aPL positivity in patients with CTEPH compared with those with primary or secondary PH. Finally, aPL positive patients have a high-risk of PE, therefore the patients with CTEPH should be screened for thrombophilia, involving aPL (aCA, LAC).[8,18] Kanakis et al.[25] suggested that in patients with CTEPH, the presence of aPL would classify them as having APS, if they meet the clinical and laboratory criteria.

In patients with suspected PH the initial diagnostic tests include chest radiography, TTE, RHC, and pulmonary function tests. Ventilation perfusion lung scans are preferred over computed tomographic pulmonary angiography (CTPA) as the initial test because they detect CTEPH with greater sensitivity.[28]

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME AND ACUTE RESPIRATORY DISTRESS SYNDROME

A small number of patients with APS (1%) develop a fulminant clinical presentation of catastrophic APS (CAPS). CAPS has a mortality rate of approximately 50% and comprises of with widespread multiple small blood vessel thrombosis, circulating aPL, and multi-organ infarction in days to weeks.[29,30] The main pulmonary complication of CAPS is acute respiratory distress syndrome (ARDS), with PE and alveolar haemorrhage occurring less commonly.[31]

ARDS is a severe life-threatening disease due to a known clinical insult, with new or worsening respiratory symptoms within 1 week: respiratory failure due to an infection or injury (not fully explained by cardiac failure or fluid overload) and refractory arterial hypoxaemia requiring supplemental oxygen treatment. ARDS can be categorised as mild, moderate, or severe, with mortality rates around 27%, 32%, and 45%, respectively. Radiographical findings include bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules.[32] The aetiology of ARDS in CAPS is unclear. In the acute phase of ARDS, the permeability of the alveolar-capillary membrane is increased, so proteinaceous oedema fluid, neutrophils, red blood cells, and immunoglobulins accumulate in the alveolar space.[33] In addition, pulmonary microembolism may cause vascular injury and elevated transport of proteins through the pulmonary microvascular barrier in the parenchyma.[34] aPL have also been found in the bronchoalveolarlavage (BAL) fluid of a patient with ARDS and APS. These results support the hypothesis that aPL could promote the process of ARDS in CAPS patients.[35]

DIFFUSE ALVEOLAR HAEMORRHAGE AND PULMONARY CAPILLARITIS

DAH is a syndrome of the lungs characterised by bleeding into the alveolar spaces, due to disruption of the alveolar-capillary basement membrane. This deterioration is caused by injury or inflammation of the arterioles, venules, or alveolar septal (alveolar wall or interstitial) capillaries.[36] Haemoptysis is the most common presenting symptom although it is absent in 33% of cases, even when haemorrhaging is severe. It is common for patients to initially present with cough, haemoptysis, fever, dyspnoea, and pleuritic chest pain. DAH may cause acute severe respiratory distress, requiring immediate ventilatory support with mechanical ventilation.[31]

Laboratory findings often demonstrate anaemia and elevated white blood cell count, but these are not essential to the diagnosis. Coagulation abnormalities should be excluded by checking a platelet count, prothrombin time, international normalised ratio, and partial thromboplastin time.[36] Chest radiographs usually show bilateral alveolar infiltrates, however the changes can be subtle, thus abnormalities are more reliably detected with computed tomography scanning.[37] Bronchoscopy and BAL, with or without biopsy, often aid in confirmation of the diagnosis. Diagnosis is characterised by increasing haemorrhagic appearance on serial BAL, serial increase in red blood cell counts, and presence of haemosiderin-laden macrophages in the BAL fluid.[38]

The exact incidence of DAH in patients with APS is unclear; it may be the initial manifestation of APS and a life-threatening situation. Yachoui et al.[39] found that DAH is a rare complication of primary APS that can also arise *de novo* in aPL positive individuals. Pulmonary capillaritis is one

of three different histopathological patterns seen in DAH and it appears to be the histopathological form occurring in APS patients with circulating aPL.[37] It is characterised by neutrophilic infiltration of the alveolar septum with associated oedema into the lung interstitium, causing structural necrosis, loss of capillary integrity, and haemorrhage.[40,41] Some authors observed that capillaritis does not appear to be the predominant pathology and believe that capillaritis in the setting of APS is likely an unrelated and coincidental phenomenon. Although this opinion is less frequently seen in literature, bland haemorrhage, another histopathological pattern of DAH, was found, rather than pulmonary capillaritis, in five out of six lung biopsies of APS patients.[39,42] Asherson and Greenblatt[43] also showed that alveolar haemorrhage and microvascular thrombosis could occur with or without pulmonary capillaritis in APS patients. Nonetheless, the most common trend is that capillaritis causes DAH in APS patients. In a case series, Cartin-Ceba et al.[44] found pulmonary capillaritis in three patient lung biopsies. Also, Deane and West[37] found DAH due to pulmonary capillaritis in the setting of high titres of aPL in four primary APS patients. They speculate that aPL can induce pulmonary capillaritis to tissue injury in non-thrombotic manifestations of primary APS, whilst thrombosis remains most common cause of lung injury. aPL cause upregulation of vascular endothelial cell adhesion molecules, therefore neutrophils are recruited and migrate into the alveolar septae with resulting tissue destruction and subsequently, extravasation of red blood cells occurs into the alveoli.[37]

The vasculitis/capillaritis leading to DAH may be limited to the lungs.[41] Most of the lung tissue may comprise small capillaries, allowing for greater contact between neutrophils and endothelial cells. Although unproven, this may be preferential to the binding of the β2GP1 antigen to endothelial cells, especially in the lung environment. It was reported that aPL can rarely lead to vasculitis in organs other than the lung.[45]

FIBROSING ALVEOLITIS

CFA (also called idiopathic pulmonary fibrosis) is a specific form of chronic, progressive, fibrosing, interstitial pneumonia of unknown cause, occurring in adults and limited to the lungs.[46] The literature regarding CFA as a rare pulmonary manifestation of APS is limited, however we were able to identify three relevant studies. The first was a case report on a patient with primary APS who developed insidious diffuse pulmonary infiltrates.[47] The second was a case report of a patient with CFA, PE, and myocardial infarction in the presence of APS.[48] The third involved a cohort of 329 APS patients. It found significant associations between the presence of medium aCA immunoglobulin (Ig)G levels and medium β2GP1 IgM levels with CFA in APS patients ($p=0.002$ and $p=0.00001$, respectively). The correlation among CFA and IgG, aCA, and β2GP1 IgM levels supports the notion of a causative relationship between these types of circulating antibodies and such lesions. The number of patients with CFA was not mentioned in this latter example, limiting the extent of conclusions that can be drawn.[9]

POSTPARTUM SYNDROME

Postpartum syndrome is a distinctly rare clinical pulmonary manifestation of APS and in the setting of aPL is an entity reported only twice in the medical literature. In the first report, Kochenour et al.[49] detected three patients with postpartum syndrome. The clinical features are characterised by pleuritis, cyclic fever, and dyspnoea. Diffuse, patchy pulmonary infiltrates and pleural effusions were found in the radiological evaluation. One patient was also found to have cardiomyopathy.[49] Kupferminc et al.[50] identified a postpartum woman who developed fever, pulmonary infiltrates, cardiac conduction defects, and renal insufficiency following severe pre-eclampsia.[50] These obstetric cases are predisposed to a catastrophic APS-like syndrome with multiorgan system dysfunction driven by microangiopathy, including pulmonary parenchyma and vessels. Since 1994, there have been no new patients described in the literature. Although unproven, there may be a lack of awareness about this syndrome, or these patients may be evaluated as CAPS.

MANAGEMENT OF PULMONARY MANIFESTATIONS IN ANTIPHOSPHOLIPID SYNDROME PATIENTS

The therapy for non-obstetric APS patients is largely the same regardless of whether the disorder is classified as primary APS or autoimmune disease-associated APS. The treatment must be individualised according to the patient's current

clinical status and recurrence of thrombotic events. CAPS patients have to be carefully observed and treated, often in an intensive care unit. Incidentally found serum aPL positive asymptomatic patients do not require specific treatment.

The therapy for PE is the same in patients with APS as in the general population. The mainstay of treatment for APS includes antithrombotic medications like low molecular weight heparin, unfractionated heparin, warfarin, and aspirin. Heparin is generally administered alongside warfarin until the international normalised ratio (INR) has been within the target range of 2.0–3.0 for 2 consecutive days.[51] After the first thromboembolic event, the optimal duration of anticoagulation is uncertain in APS. However, Ruiz-Irastorza et al.[52] recommended anticoagulation duration for 3–6 months, if it is the first venous event with a known transient precipitating factor and a non-diagnostic or low-risk aPL profile (an isolated, intermittently positive, low-to-medium titre aCA or aβ2GP1).

Somers et al.[53] followed 412 patients with first venous thromboembolic events, finding that in the presence of aPL, the risk of recurrent thrombosis was doubled at the end of 6 months of antithrombotic therapy (29% versus 14%). Therefore, for many patients lifelong therapy is prudent. Some studies suggest that aspirin alone has minimal or no benefit for the prevention of thrombotic APS manifestations in patients who have experienced previous events.[54,55] However, in another study they found that aspirin (81 mg/day) reduced the risk of thrombosis in aPL positive individuals. Hydroxychloroquine (HCQ) may have some benefit for complications in SLE associated with APS patients; although it is unproven whether they benefit from HCQ, the control of SLE, or through aPL-mediated thrombosis.[56]

In the case of treatment failure, if recurrent thrombotic events occur despite the target range of 2.0–3.0, there are some alternative treatments, such as increasing the target of INR (3.1–4.0) or adding low-dose aspirin, low molecular weight heparin, or HCQ.[52]

Recently, new oral anticoagulants (i.e. direct thrombin inhibitors and factor Xa inhibitors) can be considered in patients who are warfarin intolerant/allergic or have difficulties with anticoagulant control.[57,58] Rituximab can be tried for recurrent thrombosis, despite sufficient anticoagulation. Nalli et al.[59] also showed that rituximab was effective for noncriteria aPL clinical manifestations (i.e. thrombocytopenia and skin ulcers). Some studies reported that glucocorticosteroids and other immunosuppressive therapies such as azathioprine, cyclophosphamide, and methotrexate could decrease the titres of aPL, but do not seem to reduce thrombotic risk.[60,61]

Early diagnosis and aggressive therapy is essential to the management of CAPS, ARDS, and DAH because the mortality rates are high. Generally, the aim of CAPS treatment is to reduce thrombotic events and suppress cytokine cascade. The treatment of CAPS includes a combination of anticoagulants, systemic glucocorticoids, plasma exchange, and intravenous Ig (400 mg/kg/day for 5 days). Also, it is reported that intravenous Ig might prevent recurrent thrombotic events like PE in APS patients. High doses of systemic glucocorticoids, 1 mg/day methylprednisolone intravenously for 3 days, followed by oral or parenteral 1 mg/kg/day prednisone have been recommended for CAPS patients. Also, high doses of glucocorticoids may be useful in ARDS, pulmonary microthrombosis, and DAH. After cessation of the corticosteroids, DAH may recur; in this situation other immunomodulatory therapy such as cyclophosphamide, cyclosporine, and mycophenolate should be used. Cyclophosphamide has also been used successfully in CAPS patients with SLE.[31,37,62-64] In management of ARDS patients, adding pulse cyclophosphamide and plasmapheresis to anticoagulation and a high-dose corticosteroid therapy may be required.[62]

In APS patients, pulmonary endarterectomy (PEA) is a choice for treatment of CTEPH. PEA requires careful assessment of the risks and benefits. It must be a multidisciplinary approach to limit the risk of thrombosis or bleeding and to manage possible thrombocytopenia.[8] Some studies recommended pulmonary arterial vasodilators such as bosentan and iloprost for patients with aPL-associated PH.[65,66] Inferior vena cava filters can be another treatment approach. Zifman et al.[67] identified 10 patients with APS and recurrent thrombotic events. They underwent inferior vena cava placement; 5 of the 10 patients died, 2 of them suddenly, and PE could not be excluded.

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CARDIOVASCULAR RISK FACTOR CONTROL IN TYPE 2 DIABETES MELLITUS AND NEW TRIAL EVIDENCE

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ABSTRACT

The micro and macrovascular complications of Type 2 diabetes mellitus are influenced by several well described cardiovascular risk factors such as hyperglycaemia, hypertension, hyperlipidaemia, and smoking alongside age, sex, and diabetes duration. Modern guidelines have defined treatment and goals for these risk factors based on evidence. As new trials are constantly published, these risk factors must be analysed for evidence to contribute to guidelines that are being revised. During recent years three new trials (EMPA-REG, LEADER, and SUSTAIN-6) have shown that treatment of hyperglycaemia with new anti-diabetic drugs has been able to reduce a composite cardiovascular endpoint. This is a great achievement and is the focus of this review, which also summarises developments in the treatment of other relevant risk factors. Ultimately, a high-quality level of diabetes care also needs to involve a well-informed and motivated patient; if compliance is suboptimal the benefits of modern treatment will not be reached.

Keywords: Cholesterol, diabetes, drugs, glucose, hypertension, lipids, trials.

INTRODUCTION

Type 2 diabetes mellitus is associated with increased cardiovascular risk as documented in numerous observational studies. This is caused by the impact of cardiovascular risk factors such as hypertension, hyperlipidaemia, hyperglycaemia, and increased risk of thrombosis besides the influence of age, sex, and diabetes duration. The mechanisms linking these risk factors with disease manifestation of micro and macrovascular complications are based on gene-environmental interactions, where a less healthy lifestyle, for example smoking, lack of physical exercise, or unhealthy eating habits, result in obesity.

Several international guidelines have addressed the challenge of screening, diagnosing, and treating these risk factors, not only in patients with Type 2 diabetes mellitus but also in subjects with impaired fasting glucose or impaired glucose tolerance.[1] In the USA, the American Diabetes Association (ADA) published the annual 'Standards of Medical Care' in 2016, where updated recommendations for the treatment of Type 2 diabetes mellitus and risk factor control were stated.[2] Within these guidelines goals have been set for the control of glycaemia, blood pressure, lipids, and smoking cessation.[1,2] A summary of current goals set for risk factor control in Europe along with some comments are listed in Table 1.[1]

During 2013–2016 several important new clinical intervention trials in patients with Type 2 diabetes mellitus have been published to expand the evidence base for how to deal with the risk factors regarding drug therapy. This is not a way to diminish the important role of lifestyle modifications but the evidence from drug interventions should now be updated and critically discussed. In this brief review some of the newer studies have been reviewed for their main findings and commented upon, with a focus on newer anti-diabetic drugs.

TREATMENT OF HYPERGLYCAEMIA

The new drug alternatives to treat Type 2 diabetes mellitus have been tested in several recent large-scale intervention trials in recent years. Of these

trials, three have included a dipeptidyl peptidase 4 (DPP-4) inhibitor versus placebo, three a glucagon-like peptide-1 (GLP-1) receptor agonist/analogue (GLP-1 RA) versus placebo, and one a sodium/glucose cotransporter 2 (SGLT2) inhibitor versus placebo. The patients with diabetes recruited have generally been high-riskpatients and in most cases, with a previous cardiovascular disease (CVD) manifestation. This is both a merit and a problem, as it is not self-evident that findings in these high-risk patients can be extrapolated to other patients with diabetes but at a lower cardiovascular risk (Table 2).

Table 1: Treatment goals for risk factor control in patients with Type 2 diabetes mellitus.[1]

Risk factor	Treatment goal	Comments
Hyperglycaemia	HbA_{1c} <7.0%	Less strict in the elderly and frail
Hypertension	<140/85 mmHg	Lower in patients with macroalbuminuria
Hyperlipidaemia	LDL-C <2.5 mmol/L, but <1.8 mmol/L in patients at very high-risk	Risk markers such as triglyceride levels and HDL-C should also be considered
Smoking	No tobacco use	Risk reduction with a lesser amount smoked is a possible step in the process
Obesity	Weight stabilisation	Reduction of HbA_{1c} with some anti-diabetes drugs may increase body weight

LCL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Table 2: Summary of outcome trials with new anti-diabetic drugs.

Study	Patients	Drug/placebo	Outcome	Result	Strength	Limitation
SAVOR-TIMI[3]	16,492 T2DM, 2.1 years	Saxagliptin 5 mg o.d. per oral*	Composite CV outcome	1.00 (0.89 to 1.12; p=0.99 for superiority; p<0.001 for non-inferiority)	Large RCT	Mostly high-risk T2DM patients and those with a CHF risk
EXAMINE[4]	5,380 T2DM, 18 months	Alogliptin 25 mg o.d. per oral*	Composite CV outcome	0.96 (one-sided repeated confidence interval, 1.16; p<0.001 for non-inferiority)	Large RCT	Only high-risk T2DM patients
TECOS[5]	14,671 T2DM, 3.0 years	Sitagliptin 50–100 mg o.d. per oral*	Composite CV outcome	0.98 (0.88– 1.09; p<0.001 for non-inferiority)	Large RCT	Only high-risk T2DM patients
EMPA-REG OUTCOME[9]	7,020 T2DM, 3.1 years	Empagliflozin 10 or 15 mg o.d. per oral	Composite CV outcome	0.86 (0.74–0.99; p=0.04 for superiority)	Large RCT	Only high-risk T2DM patients
ELIXA[6]	6,068 T2DM, 25 months	Lixisenatide 10–20 mg o.d. subcutaneous	Composite CV outcome	1.02 (0.89–1.17; p<0.001 for non-inferiority and p=0.81 for superiority)	Medium RCT	Only high-risk T2DM patients
LEADER[7]	9,340 T2DM, 3.8 years	Liraglutide 1.8 mg o.d. subcutaneous	Composite CV outcome	0.87 (0.78–0.97; p<0.001 for non-inferiority; p=0.01 for superiority)	Large RCT	Only high-risk T2DM patients
SUSTAIN-6[8]	3,297 T2DM, 2.0 years	Semaglutide 0.5 or 1.0 mg once weekly, subcutaneous	Composite CV outcome	0.74 (0.58–0.95; p<0.001 for non-inferiority)	Large RCT	Only high-risk T2DM patients

Risk ratios with 95% confidence intervals and significance testing for non-inferiority and superiority.
*Reduced dosage in patients with impaired renal function estimated glomerular filtration rate (eGFR) 30–60 mL/min.
T2DM: Type 2 diabetes mellitus; CHF: congestive heart failure; RCT: randomised controlled trial; CV: cardiovascular; o.d.: once daily.

The three DPP-4 inhibitor trials were SAVOR-TIMI 53,[3] EXAMINE,[4] and TECOS,[5] with an overall favourable safety profile, the only exception being the increased risk of congestive heart failure as noted in the SAVOR-TIMI 53 trial.[3] In all three trials, non-inferiority against placebo was shown but the cardiovascular event risk was not different from placebo. Thus, these drugs are generally safe but did not provide added benefits for cardiovascular prevention. The next set of trials were the three GLP-1 RA studies ELIXA,[6] LEADER,[7] and most recently the SUSTAIN-6 study,[8] from which the latter two will be related in more detail due to their positive outcomes. On the other hand, the ELIXA study showed non-inferiority and safety but no added cardiovascular prevention versus placebo in patients with Type 2 diabetes mellitus and a recent event of an acute coronary syndrome as inclusion criterion.[6] Finally, the EMPA-REG OUTCOME trial tested the new class of SGLT2 inhibitors for non-inferiority and cardiovascular effects versus placebo.[9] This trial will also be described more in detail.

LEADER

In the double-blind LEADER trial, patients with Type 2 diabetes mellitus and high cardiovascular risk were randomised to receive liraglutide or placebo.[7] The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The primary hypothesis was that liraglutide would be non-inferior to placebo regarding the primary outcome, with a margin of 1.30 for the upper boundary of a 95% confidence interval (CI) of the hazard ratio (HR). A total of 9,340 patients underwent randomisation with a median follow-up of 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4,668 patients [13.0%]) than in the placebo group (694 of 4,672 [14.9%]) (HR: 0.87; 95% CI: 0.78–0.97; p<0.001 for non-inferiority; p=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (HR: 0.78; 95% CI: 0.66–0.93; p=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (HR: 0.85; 95% CI: 0.74–0.97; p=0.02). The rates of non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for heart failure were non-significantly lower in the liraglutide group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The authors concluded that the rate of the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke among patients with Type 2 diabetes mellitus at high-risk was lower with liraglutide than with placebo.[7]

The reduction of cardiovascular mortality is an important achievement taking into consideration that the patients in LEADER were mostly well treated already at baseline by several drugs for secondary prevention of CVD. For example, a very high proportion of the patients were treated with statins or renin-angiotensin system-blocking agents. An important contributing factor could be the weight loss induced by liraglutide (a mean difference of 2.3 kg at 36 months versus placebo [95% CI: 2.5-2.0])

SUSTAIN-6

The most recent GLP-1 RA trial was SUSTAIN-6, presented at the European Association for the Study of Diabetes (EASD) 52nd Annual Meeting in Munich, Germany, September 2016, and published simultaneously.[8] The rationale was that the cardiovascular effects of semaglutide, a GLP-1 RA with an extended half-life of approximately 1 week, in Type 2 diabetes mellitus were unknown. A total of 3,297 patients with Type 2 diabetes mellitus on a standard-care regimen were randomly assigned to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. It was hypothesised that semaglutide would be non-inferior to placebo for the primary outcome. The non-inferiority margin was 1.8 for the upper boundary of the 95% CI of the HR. At baseline, 2,735 of the patients (83.0%) had established CVD, chronic kidney disease, or both. The primary outcome occurred in 108 of 1,648 patients (6.6%) in the semaglutide group and in 146 of 1,649 patients (8.9%) in the placebo group (HR: 0.74; 95% CI: 0.58–0.95; p<0.001 for non-inferiority). Non-fatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (HR: 0.74; 95% CI: 0.51–1.08; p=0.12); non-fatal stroke occurred in 1.6% and 2.7%, respectively (HR: 0.61; 95% CI: 0.38–0.99; p=0.04). Rates of death from cardiovascular causes were

similar in the two groups. Rates of new or worsening nephropathy were lower in the semaglutide group but rates of retinopathy complications (vitreous haemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (HR: 1.76; 95% CI: 1.11–2.78; p=0.02). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal. The authors concluded that in patients with Type 2 diabetes mellitus who were at high cardiovascular risk, the rate of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the non-inferiority of semaglutide.[8]

An astonishing fact is the significant reduction of stroke events despite a minimal blood pressure reduction in the actively treated arm. As a risk of stroke is strongly dependent on the influence of hypertension or dysregulated haemodynamic control, further mechanistic studies to evaluate these aspects are called for, preferably by use of 24-hour ambulatory blood pressure monitoring and evaluation of central haemodynamics as well as arterial stiffness in the aorta. The increased risk of retinopathy is an unexpected finding that needs further evaluation as there is no real explanation at present, as a similar (non-significant) trend was also seen in the LEADER Study. The mean body weight in the semaglutide group, as compared with the placebo group, was 2.9 kg lower in the group receiving 0.5 mg and 4.3 kg lower in the group receiving 1.0 mg (p<0.001 for both comparisons).

EMPA-REG OUTCOME

Another class of anti-diabetic drugs are the SGLT2-inhibitors, promoting glucosuria. One member drug of this class, empagliflozin, was tested in a trial including patients with Type 2 diabetes mellitus at a high cardiovascular risk and then published in 2015.[9] Patients were randomised to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke, as analysed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalisation for unstable angina. A total of 7,020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4,687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2,333 patients (12.1%) in the placebo group (HR: 0.86; 95.02% CI: 0.74–0.99; p=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7% versus 5.9% in the placebo group; 38% relative risk reduction), hospitalisation for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (p=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events. The effect on body weight was modest. The conclusion from the study was that patients with Type 2 diabetes mellitus at a high risk of cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care.[9]

In a further analysis from the EMPA-REG OUTCOME study of effects on renal protection, pre-specified renal outcomes included incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal replacement therapy, or death from renal disease) and incident albuminuria.[10] The results indicated that incident or worsening nephropathy occurred in 525 of 4,124 patients (12.7%) in the empagliflozin group and in 388 of 2,061 (18.8%) in the placebo group (HR 0.61; 95% CI: 0.53–0.70; p<0.001). Doubling of the serum creatinine level occurred in 70 of 4,645 patients (1.5%) and in 60 of 2,323 (2.6%) in the placebo group, a significant relative risk reduction of 44%. Renal-replacement therapy was initiated in 13 of 4,687 patients (0.3%) in the empagliflozin group and in 14 of 2,333 patients (0.6%) in the placebo group, representing a 55% lower relative risk in the empagliflozin group. There were no significant between-group differences in the rates of incident albuminuria. The conclusion reached was that empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than the placebo, when added to standard care.[10]

TREATMENT OF HYPERTENSION

Elevated blood pressure is a frequent companion to obesity and hyperglycaemia in Type 2 diabetes mellitus, as influenced by insulin resistance and associated abnormalities. The control of hypertension is one of the cornerstones of risk factor control in these patients, as stated in European guidelines from 2013.[1,11] The goal for blood pressure control in these guidelines is set to <140/85 mmHg, with a corresponding goal of <140/80 mmHg (but <130/80 mmHg in specified subgroups) in USA guidelines from 2016.[2] More recently a systematic review and meta-analysis has documented the importance of targeting patients with diabetes and a baseline systolic blood pressure ≥140 mmHg, but not to treat patients with a baseline systolic blood pressure <140 mmHg due to increased risk of myocardial infarction and cardiovascular mortality.[12] This was challenged by another observational study from the Swedish National Diabetes Register (NDR) that showed a linear and increasing relationship between observed systolic blood pressure levels and risk of complications already from levels <120 mmHg in patients free from CVD.[13] On the other hand, no specific analysis was made for patients already treated for hypertension and thus this observational study merely echoes the findings from an earlier observational publication from The UK Prospective Diabetes Study (UKPDS) with a similar design.[14]

Recently the publication of the SPRINT study in the USA has provoked a heated debate on blood pressure goals in hypertensive patients.[15] Even if no patients with diabetes were included in SPRINT, arguments have been raised for implementing more strict blood pressure goals in patients with Type 2 diabetes mellitus, for example, the goal of <120 mmHg systolic blood pressure that proved more successful than the goal of <140 mmHg systolic blood pressure. On the other hand, the blood pressure methodology used in SPRINT was unusual and this could hamper any comparison with other similar intervention studies and also preclude from applying the findings in SPRINT when guidelines will be revised.[16] In fact, the methodology used in SPRINT was to ask the patient to do a self-measurement of blood pressure while sitting alone in a room and using an automatic blood pressure device. This could have introduced bias as such a way to measure blood pressure could be 15–16 mmHg lower for systolic blood pressure as compared to office blood pressure recordings.[17]

Many experts thus think that current blood pressure goals for patients with diabetes should be kept, even if a minority of experts have argued for adopting the more stringent blood pressure goals from the SPRINT study.

TREATMENT OF HYPERLIPIDAEMIA

The cornerstone of lipid regulation in patients with Type 2 diabetes mellitus is still statins, used in effective dosages and based on a solid evidence base.[18] The most effective statin is rosuvastatin and its preventative effects, as well as that of other statins, overshadows some other effects promoting glycaemia and increase of HbA_{1c}.[19] The mechanism behind this effect has been shown to be as a result of dual effects on glucose homeostasis by rosuvastatin, where insulin sensitivity is improved but beta cell function is impaired during *in vitro* experiments.[20] Guidelines recommend a target for low-density lipoprotein (LDL) cholesterol to be <2.5 mmol/L for most patients with diabetes and <1.8 mmol/L for patients at a very high risk,[1,2] for example, with a previous manifestation of a cardiovascular event motivating secondary prevention. Sometimes combination therapy, such as combining a statin with fibrates or cholesterol uptake inhibitors (ezetimibe), can also be an option.

An emerging and promising class of lipid-lowering drugs are the proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors,[21] with a lowering effect on LDL cholesterol of about 60%. The first clinical outcome study is the FOURIER trial, expected to report in early 2017.[22] FOURIER is a randomised, placebo-controlled, double-blind, parallel-group, multinational trial testing the hypothesis that adding evolocumab to statin therapy will reduce the incidence of major adverse cardiovascular events in patients with clinically evident vascular disease. The study population consists of 27,564 patients who have had a myocardial infarction, an ischaemic stroke, or symptomatic peripheral artery disease.[22] If the clinical benefits dominate adverse effects this new class of drugs may prove to be beneficial in subgroups of patients with diabetes at very high risk, or who are statin intolerant.[23] Recently, the GLAGOV study[24] was presented where it was shown that among 968 patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in percentage of atheroma volume after 76 weeks of treatment. However, further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.

SUMMARY

To protect patients with Type 2 diabetes mellitus from micro or macrovascular complications a wide and effective approach for overall risk factor control is recommended, as shown in the long-term follow-up of the Danish STENO-2 study.[25] In this landmark study, it was concluded that at 21.2 years of follow-up after 7.8 years of intensified, multifactorial, target-driven treatment of Type 2 diabetes mellitus with microalbuminuria, there was a median of 7.9 years of gain of life. The increase in lifespan is matched by time free from incident CVD.

A rigid control of hypertension and hyperlipidaemia has long been recognised, and now three new large clinical trials have proven the benefits of glycaemic control by use of newer agents such as SGLT2 inhibitors (empagliflozin) or GLP-1 RAs (liraglutide, semaglutide). These drugs may also have some other, less well-defined beneficial effects on vascular and haemodynamic function, as manifested in successful reduction of congestive heart failure and stroke. Further studies should look more into the mechanisms explaining these beneficial effects that do not seem to be fully explained by weight reduction only.

In the future, the hope for a personalised 'precision medicine' bears hope also for the treatment of hyperglycaemia and risk factors in patients with Type 2 diabetes mellitus.[26] However, sophisticated methods and new drugs cannot overcome an old but intrinsic problem in diabetes care; to increase the quality of the consultation based on understanding, support, and trust. A well-informed and motivated patient with Type 2 diabetes mellitus will most likely adhere to a healthy lifestyle and drug medication for risk factor control. Sadly, the opposite is often true in many fields of diabetes care and has to be improved based on a team approach in which physicians work together with diabetes nurses, dieticians, and other experts, but most importantly with the patient and his/her family within social networks to improve standards of care.

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STATE-OF-THE-ART ADVANCES IN DUCHENNE MUSCULAR DYSTROPHY

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a severe and fatal muscle condition affecting young children. Without interventions, affected boys lose the ability to walk independently by the age of 10 and develop progressive cardiac and respiratory failure. The last 20 years have seen a change in the natural history of DMD following improvements in clinical care and proactive interventions to manage complications of the disease. An international collaboration of DMD experts has created care imperatives for best practice in DMD; these are now available in 30 different languages and are disseminated worldwide. An update of these care recommendations is currently under review.

More recently, the field has seen encouraging scientific progress in regard to new therapeutic approaches of which a large number are currently being evaluated in clinical trials. With time, improvements in clinical care and access to new treatments and innovations are changing the natural course of DMD, from a relentless progressive illness with death in teenage years to a more chronic illness with a good quality of life and increased life expectancy. This is a particularly encouraging time for DMD, and experiences built in the muscular dystrophy field are likely to be of benefit to the development of new approaches and therapies in other rare diseases.

Keywords: Duchenne muscular dystrophy (DMD), dystrophin, genetic diagnosis, standards of care, clinical trials.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most severe and common muscular dystrophy in children affecting approximately 1 in 3,500–10,000 male births.[1] It is an X-linked recessive condition affecting mostly boys. Clinically, it presents with progressive muscle weakness and wasting affecting all body muscles, including the heart and the respiratory muscles. Historically, boys with DMD lost the ability to walk independently by the age of 10 years and progressively developed heart and respiratory insufficiency, eventually leading to death in their late teens or early 20s. In recent years, there have been significant developments in both clinical care and scientific research in DMD. Following the implementation of care recommendations, including corticosteroids, respiratory and cardiac management, orthopaedic intervention, and rehabilitation, the natural history of DMD has changed from a rapidly progressive and life-limiting condition to a more chronic illness with an increase in life expectancy.[2-3] Recent studies have reported a good quality of life,[4] with the research field of DMD thriving, and the hope of finding a disease-modifying drug which will further slow the deterioration in muscle function. In this article, we summarise recent developments in the diagnosis and management of DMD and provide an update on clinical research in the field.

DUCHENNE MUSCULAR DYSTROPHY

Pathogenesis

DMD is caused by mutations in the dystrophin gene, the largest gene in the human genome, consisting of 79 exons. The mutation rate of the dystrophin

gene is relatively high and about one-third of cases are caused by new (*de novo*) mutations.[5] In the remaining two-thirds of patients, the mutation is passed on from the mother (X-linked), who usually does not show any clinical manifestation of the condition (asymptomatic carrier). The size of the gene, together with the high mutation rate, explains the variability of mutations in DMD including large deletions (68%), duplications (11%), and small mutations (20%).[5] Small mutations include small deletions, insertions, and point mutations, resulting in stop codons or disrupted splicing.

The hotspot for mutations in the dystrophin gene lies between exon 45 and 55 (deletions) and exons 2 and 10 (duplications), but mutations have been reported along the entire gene. There are no strict correlations between the location of the mutation and the severity of the clinical presentation, although several exceptions to this general rule have now been described.[5-8] Mutations causing an interruption of the 'reading frame' (out-of-frame) lead to DMD because protein synthesis is disrupted, resulting in the total absence of the encoded protein, dystrophin. Mutations in the same gene which do not alter the reading frame (in-frame mutations) lead to the production of a shorter but still partially functioning protein and result in a milder phenotype (Becker muscular dystrophy).

The protein dystrophin is expressed in skeletal muscles, the heart, and the brain. In muscles, dystrophin acts as a shock absorber during muscle contraction; in its absence, muscle fibres undergo membrane fragility, inflammation, chronic damage, and finally replacement by fibrotic tissue and fat. These pathological changes manifest clinically with progressive loss of muscle strength and mass. Although the role of dystrophin in the brain remains largely unknown, intellectual impairment is reported in about 30% of DMD subjects.[9]

CLINICAL FEATURES

The hallmark of DMD is progressive muscle wasting and weakness. Although the pathological changes start *in utero*, the condition does not usually manifest clinically until the age of 2–4 years. It can present with a delay in motor milestones or with symptoms of muscle weakness. Typical early clinical features of DMD include difficulty getting up from the floor (Gower's manoeuvre), difficulties with running, jumping, hopping, an abnormal or tip-toe gait, and frequent falls. On examination, calf hypertrophy, hypotonia, and neck flexor weakness can be detected from an early age.[10] Speech and language delay and behavioural problems, including autistic spectrum disorders, have also been described and can present before muscle weakness has become apparent. With the progression of the disease, muscle weakness affects all skeletal muscles, leading to loss of independent walking, reduced motor function in the upper limbs, and scoliosis due to axial weakness. Joint contractures result from a combination of reduced mobility and changes in muscle structure, following replacement of muscle fibres with connective tissue. The heart and the respiratory muscles undergo similar pathological changes, leading to progressive dilated cardiomyopathy, arrhythmia, and restrictive lung disease.[10]

Early heart involvement has been reported in DMD, although generally the incidence of cardiomyopathy increases with age.[11] The clinical challenge remains recognising heart failure in DMD, which often is asymptomatic, even at late stages. Respiratory insufficiency in DMD is more predictable, usually presenting after the loss of independent ambulation. The diaphragmatic involvement significantly contributes to the drop in forced vital capacity, observed as an early sign of respiratory impairment, increasing susceptibility to chest infections, and sleep-disordered breathing.[12,13]

DIAGNOSIS

If there is a clinical suspicion of DMD, a blood test to measure creatine kinase (CK) levels should be promptly arranged as the first screening test. CK is a muscle enzyme which is released in the blood stream as a response to muscle damage. CK levels are always significantly elevated in DMD, and values in the thousands should trigger the diagnosis, although other neuromuscular diseases might also be considered. CK testing has been used for neonatal screening, as increased levels are present from birth. CK newborn screening was in place in some countries e.g. Wales and the USA, however at present it has been discontinued due to concerns regarding its sensitivity and specificity when performed around the time of birth.[14-16] At the time of writing, CK neonatal screening is not routinely adopted in any country.

A child with clinical evidences of muscle weakness and elevated CK levels should be referred to a neuromuscular centre for genetic testing for dystrophin gene mutations. Multiplex ligation-dependent probe amplification[17] is the most

reliable and cost-effective test to detect deletions and duplication, analysing all exons of the dystrophin gene. If multiplex ligation-dependent probe amplification does not identify any mutation, gene sequencing will allow the identification of small deletions/insertions and point mutations, although it is more expensive, time-consuming, and available only in specialised laboratories.

Muscle biopsy, which historically represented the diagnostic test for DMD showing the total absence of dystrophin expression in muscle fibres associated with utrophin upregulation, is today often avoided and replaced by genetic testing in centres where this is available. A muscle biopsy can still be useful in some rare cases when genetic testing does not reveal a mutation but the patient shows a clear DMD phenotype or when there is a discrepancy between the reading frame rule and the clinical presentation.

Delays in Diagnosis of Duchenne Muscular Dystrophy

Despite the tremendous advances in the management of DMD for children over the last decade, published data show that there is still a delay in the diagnosis of the condition across different countries.[18-23] This is due to both presentational delay (time from onset of symptoms to presentation to a health professional) and diagnostic delay (time from first medical assessment to genetic diagnosis). The mean age at diagnosis ranges from 4.3–4.11 years and has not significantly improved over the past 20 years.[18-23] Recommendations to lower the age of diagnosis include raising awareness of DMD in the community, primary care to ensure DMD is recognised as a differential diagnosis in children presenting with signs of muscle weakness and/or speech delay, and promoting early CK level testing as a cost-effective, readily available screening tool for DMD. To reach these targets, a mnemonic (MUSCLE: Motor milestone delay, Unusual gait, Speech delay, CK ASAP, Leads to Early diagnosis of DMD) has been developed for use in primary care to improve the diagnostic process in DMD.[18]

Establishing an accurate genetic diagnosis of DMD at a young age is important as it allows genetic counselling and family carrier testing, prenatal diagnosis, early access to treatment, consideration for mutation specific therapeutic options (e.g. ataluren), or participation in clinical trials with new investigational drugs.

MEDICAL MANAGEMENT

Corticosteroids

Corticosteroids are currently the only medication available to all patients with DMD to slow down the progression of the condition and are part of the care recommendations. Although the benefits of corticosteroids are well-documented, they only postpone disease milestones without altering the natural course of the disease. Moreover, corticosteroids are associated with several side effects which limit their prescription worldwide.

Corticosteroids have been shown to prolong ambulation and stabilise respiratory function.[24-27] In addition, corticosteroids have cardio-protective properties and prevent or reduce the need for spinal (scoliosis) surgery.[25,28,29] The most frequently prescribed corticosteroids in DMD are prednisone (or prednisolone) (0.75 mg/kg/day) and deflazacort (0.9 mg/kg/day), with several regimes currently used.[30] Corticosteroids are generally introduced when the child's motor skills plateau, around the age of 4–5 years. Emerging evidence suggests that early treatment might be associated with better long-term outcomes, including prolonged ambulation, however further research is needed to evaluate the impact of early and prolonged corticosteroid treatment in a growing child.[31]

Although corticosteroids have been prescribed for >20 years in DMD, a worldwide debate is ongoing as to which corticosteroid should be prescribed, which regime, from what age, and for how long. The main concerns are related to the management of steroid-related adverse effects which have led to inconsistency in prescribing practices across different centres and different countries. The more common steroid-related side effects and their management strategies according to the care recommendations are summarised in Table 1.[3] Daily regimes appeared to be more effective but with more frequent side effects compared with intermittent regimes.[32] Limited data comparing the effects of different corticosteroids are available: there are some indications that deflazacort is associated with less weight gain and possibly a better effect on muscle strength and function, but longer term longitudinal data are awaited.[33-35]

A double-blind randomised control study FOR DMD is ongoing to compare the three most commonly prescribed corticosteroid regimes in DMD regarding efficacy and side effect profile (NCT01603407).[35]

Table 1: Summary of adverse effects of corticosteroid therapy and their management.

Steroid-related adverse effects	Management
Cosmetic (cushingoid features, weight gain, hirsutism, skin changes)	Offer dietary advice and review acceptability of the changes
Adverse behavioural changes (mood changes, emotional lability, hyperactivity)	Often worsen in first weeks of starting corticosteroids. If prolonged, refer for behavioural management, consider assessment for DMD-related behavioural disorders (30% of children with DMD), and refer appropriately
Immune suppression	Ensure immunity to varicella, avoid live vaccines, proactive approach in managing infections (early antibiotics)
Adrenal suppression	Additional steroid cover in illness/surgery. Be alert about missed doses (if not tolerating steroids, consider intramuscular/intravenous steroids)
Hypertension	Blood pressure monitoring at each clinic visit. Use age-appropriate blood pressure centile charts. If BP >99th centile, advise weight loss, salt reduction in diet, or medical treatment
Glucose intolerance	Urine dipstick at each clinic visit. If positive for glucose, check fasting blood glucose
Gastric reflux and peptic ulcer disease	Enquire about symptoms at each clinic visit, and advise to avoid NSAIDs. Manage symptoms and signs with ranitidine or proton pump inhibitor
Cataracts	Yearly ophthalmology review. Cataracts more common with deflazacort. If present, refer for ophthalmology for assessment and treatment if necessary
Bone demineralisation (increased risk of fractures)	Ensure high calcium intake with diet and adequate vitamin D levels. Annual bone density scan (DEXA). Review fracture history carefully. Consider bisphosphonate treatment for vertebral fractures
Growth retardation and delayed puberty	Monitor height at each clinic visit; if static (<2 cm per year), refer to endocrinology. Assess puberty and if delayed consider endocrine assessment and testosterone treatment if appropriate

DMD: Duchenne muscular dystrophy; BP: blood pressure; NSAIDs: non-steroidal anti-inflammatory drugs; DEXA: dual energy X-ray absorptiometry.

The study aims to clarify the long-standing equipoise of the use of corticosteroids in DMD, and provide families and clinicians a (long-awaited) evidence-based recommendation on the use of corticosteroids and standardised management of steroid-related side effects. Whilst awaiting the outcome of this study, the choice of treatment is currently made based upon personal experience of the clinician in charge, availability of the formulation (e.g. deflazacort is not available in the USA), and patient and family's choice. An informed discussion on benefits and side effects with the family is mandatory to ensure compliance with the treatment and the management of side effects. Whichever steroid and regime is prescribed, the potential risk of adrenal failure should be considered when the child is unwell, in case of surgery and prior to anaesthetics. Each patient should be provided with an up-to-date alert card which details steroid treatment (including regime) and offers advice with regards to steroid replacement in emergencies.

Clinical Care Recommendations for Duchenne Muscular Dystrophy

As established by the care recommendations published in 2010, DMD is a complex multi-system disorder and requires a multidisciplinary approach. This involves different specialities such as neuromuscular specialists, paediatrics, cardiology, respiratory, orthopaedics, endocrinology, physiotherapy, occupational therapy, speech and language therapy, and psychology.[2,3] The role of each speciality team varies according to the disease stage the patient is in and the progression of the symptoms, however all teams should be involved from the point of diagnosis. The role of the tertiary neuromuscular team is co-ordinating the patient care and ensuring that the right specialists are involved at the correct time to provide a proactive model of clinical care in which interventions (such as cardiac medications, access to non-invasive ventilation, etc.) can be swiftly organised when needed. Surveillance in DMD is

centred around early detection of disease complications but also ensuring that patient-specific needs are identified and managed in order to optimise their physical, social, educational, and psychological status. The best practice of care in DMD has been translated into 30 different languages and a summary outlining the imperatives in DMD care has recently been published[36] to facilitate optimal care to families living with DMD worldwide (Table 2). An update of the care recommendations is currently in progress reflecting the more recent changes and improvements in patient management.

Regardless of the extensive effort in disseminating the DMD care recommendations worldwide, a recent survey has shown an unexpected discrepancy between the published recommendations and care provision as reported by patients and families across different countries.[37] The survey highlighted concerns in all countries regarding access to routine follow-up by neuromuscular, cardiac, and respiratory specialists, physiotherapy, and access to medical devices. In addition, the survey showed a worrying lack of access to psychosocial therapy in DMD: this is of particular relevance in view of the continuous improvement in life expectancy for this patient population, leading to a new adult group of patients who live with a chronic and disabling condition and for whom psychological and social support will become essential to ensure good quality of life.

Table 2: Imperatives in Duchenne muscular dystrophy care.

Imperatives in DMD	
Diagnosis	• When to suspect DMD • Importance of early CK testing • Genetic diagnosis
Support groups	• Encourage parents to seek support from online resources and trustworthy patient organisations
Corticosteroids	• Start early • Discuss benefits and side effects of steroids • Review response and side effects of steroids regularly
Heart	• Regular cardiac review, including echocardiogram • Start cardiac medication early if any evidence of left ventricular dysfunction • Screen for arrhythmia (sign of heart failure)
Respiratory	• Yearly lung function tests, flu, and pneumococcal vaccinations • Low threshold for treating respiratory infections • At later stages, discuss cough assists and review need for assisted ventilation
Mechanical diagnosis and therapy (physiotherapy, occupational therapy, rehabilitation)	• Regular review by physiotherapy • Discuss stretching exercises, contracture devices, wheelchairs, and home adaptations (adapted beds, hoists, etc.) based on disease stage
Bone density	• If taking steroids, review vitamin D status yearly, and provide supplements if needed • Regular bone density scans, and review spine for scoliosis and vertebral fractures
Mental health	• Consider presence of learning disabilities • Review emotional and mental status at each visit
6-monthly clinic reviews	• Monitor: weight (under or overweight), other side effects of corticosteroids (hypertension, cataract, behavioural problems, abdominal pain and gastro-oesophageal reflux, glycosuria, delayed puberty), diet, swallowing difficulties
Final stage	• Provide each patient with a DMD alert card, detailing steroid treatment and plan for emergencies • Be aware of risk of anaesthetics in DMD

DMD: Duchenne muscular dystrophy, CK: creatine kinase.

Table 3: List of Duchenne muscular dystrophy studies open (actively recruiting or active) as per April 2016.

Approach	Target	Selected population	Current studies
Exon skipping	Exon 51 skippable mutations	Ambulant, 4–6 years old	A Phase II, open-label, safety, tolerability, and efficacy study with eteplirsen in ambulant DMD subjects (USA)
		Ambulant, 7–16 years old	A Phase III, confirmatory efficacy study with eteplirsen in ambulant DMD subjects (USA)
		Non-ambulant, 7–21 years old	A Phase II, open-label, safety and tolerability study with eteplirsen in non-ambulant DMD subjects (USA)
		Ambulant and non-ambulant, 7–13 years old	A Phase IIb, open-label extension study to assess the ongoing efficacy, safety, and tolerability of treatment with eteplirsen in DMD subjects who have previously received eteplirsen (USA, Canada)
		Ambulant, >5 years old	A Phase III, open-label extension study to assess safety and efficacy of drisapersen in DMD subjects who previously participated in a drisapersen study (USA)
	Exon 53 skippable mutations	Ambulant, 6–15 years old	A randomised, double-blind, placebo-controlled, safety and tolerability study followed by an open-label efficacy and safety evaluation with *SRP-4053* (morpholino AON) in ambulant DMD subjects (EU)
		Ambulant, 5–18 years old	A Phase I/II, open-label study to assess safety and efficacy of *PRO053* in ambulant DMD subjects (EU)
	Exon 45 skippable mutations	Ambulant, >5 years old	A Phase IIb, open-label study to assess safety and efficacy of *PRO045* in ambulant DMD subjects (EU)
		Ambulant, 5–10 years old	A Phase I/II study to evaluate the safety, tolerability, efficacy, and pharmacokinetic profile of DS-5141b in patients with DMD and to determine the dosage for subsequent studies (Japan)
	Exon 44 skippable mutations	Ambulant and non-ambulant, 9–20 years old	Open-label extension study to assess the ongoing efficacy, safety, and tolerability of treatment with PRO044 in DMD subjects who have previously received PRO044 (EU)
Stopcodon read-through	Nonsense point mutations	Ambulant, >5 years old	A Phase III extension study to evaluate safety and efficacy of ataluren in ambulant DMD subjects who took part in the Phase III ACT DMD study (worldwide)
		Ambulant and non-ambulant, >5 years old	A Phase III, open-label extension saftey and efficacy study for subjects previously treated with ataluren (worldwide)
Gene-therapy	All	Non-ambulant, >7 years old	A Phase I pilot study to evaluate safety and biological activity of the rAAVrh74.MCK.micro-Dystrophin vector administered by an intramuscular route in subjects with DMD
	All	>7 years old	A Phase I/II clinical intramuscular gene transfer of rAAV1.CMV.huFollistatin344 trial to DMD subjects
	All	Non-ambulant, >9 years old	A Phase I safety and tolerability study with intramuscular injection of rAAVrh74.MCK.GALGT2 in non-ambulant DMD patients (USA)
Stem cells	Subjects with confirmed DMD associated cardiomyopathy	Ambulant and non-ambulant, >12 years old	A randomised, open-label study of the safety and efficacy of multi-vessel intracoronary delivery of allogeneic cardiosphere-derived cells in patients with cardiomyopathy secondary to DMD
	Available haplotype-compatible donor	>16 years old	A Phase I/II study to evaluate safety and local effects on muscle strength of normal myoblast transplantation in DMD (Canada)
Anti-myostatin	All	Ambulant, 6–10 years old	A Phase II, randomised, double-blind, placebo-controlled study with *PF-06252616* in ambulant DMD subjects (worldwide)
	All	Ambulant, 5–10 years old	A multi-site, randomised, placebo-controlled, double-blind, multiple ascending subcutaneous dose study to evaluate the safety tolerability and pharmacokinetics of *BMS-986089* in ambulatory boys with DMD (US, Canada)
	All	Ambulant, >4 years old	A randomised, double-blind, placebo-controlled, multiple ascending-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of *ACE-031 (ActRIIB-IgG1)* in subjects With DMD (Canada) - Terminated based on preliminary safety data

Table 3 continued.

Approach	Target	Selected population	Current studies
Utrophin upregulation	All	Ambulant, 5-10 years old	A Phase II proof of concept study with SMT-*C1100* in ambulant DMD subjects (UK)
NK-B inhibition	Steroid naïve	Ambulant, 4–7 years old	A Phase IIa, open-label, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys with DMD (USA)
	Steroid naïve	Ambulant, 4–7 years old	A Phase I/II, open-label study to assess safety of *CAT-1004* in ambulant DMD subjects (USA)
Anti-inflammatory/ anti-fibrosis	Steroid naïve	Ambulant, 4–7 years old	A double-blind, randomised study to investigate efficacy and side effect profile of the three most commonly prescribed corticosteroid regimes in ambulant DMD subjects (FOR DMD) (worldwide)
	All	Ambulant, 6–14 years old	A Phase Ib, open-label study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending oral doses of rimeporide in patients with DMD (EU)
	All	6–10 years old	A Phase II HT-100 study to evaluate long-term safety and pharmacodynamics of *HT-100* in patients with DMD who have previously received *HT-100* (USA)
	All	Ambulant, 7–11 years old	A Phase I/II study to assess the safety and tolerability, pharmacokinetics, and effects on histology and different clinical parameters of givinostat in ambulant children with DMD (Part II) (Italy)
	All	Non-ambulant, >12 years old	A Phase II, open-label, single arm trial of *FG-3019* to estimate FG-3019's efficacy in non-ambulatory subjects with DMD.
Anti-oxidants	All	Ambulant, 5–10 years old	A Phase II/III, double-blind, placebo control study to assess safety and efficacy of Sunphenon Epigallocatechin-Gallate (*EGCg*) in ambulant DMD (Germany)
Neuronal nitric oxide synthase activators	All	Ambulant, 7–10 years old	A double blind randomised placebo controlled efficacy and safety study of L-citrulline and metformin in ambulant subjects with DMD (Switzerland)
	All	Ambulant, 7–14 years old	A randomised, double-blind, placebo-controlled, safety and efficacy Phase III trial of tadalafil for DMD (US and EU) - terminated for lack of efficacy
Cardio-protection	Absence of cardiomyopathy	Ambulant and non-ambulant, 2–45 years old	A Phase IV randomised prospective study to compared the effect of carvedilol and Ramipril on heart function in DMD subjects (Italy)
	All	Non-ambulant, >10 years old	A Phase III non-inferiority study of spironolactone vs. eplerenone in preserving cardiac and pulmonary function in patients with preserved left ventricular ejection fraction (USA)
	Absence of cardiomyopathy	Ambulant and non-ambulant, 10–15 years old	A Phase III randomised, double-blind, placebo-controlled, study to evaluate the effect of nebivolol, for the prevention of ventricular systolic dysfunction in DMD subjects, recruiting (France)
Other	Confirmed delayed puberty	Ambulant and non-ambulant, 12–17 years old	An observational study of clinical outcomes for testosterone treatment of pubertal delay in DMD (UK)

Studies non-specific for DMD (e.g. also recruiting patients with other neuromuscular conditions) are not included. Completed studies are not listed with the exception of two studies which were terminated only recently. Due to the continuous progress of the research in the field, this list is likely to change quickly and should therefore only be used as an indicator or number of studies in DMD and current approaches. Full details of clinical trials in DMD can be found on www.clinicaltrials.gov

DMD: Duchenne muscular dystrophy; AON: antisense oligonucleotide; NK-B: neurokinin-B.

PROGNOSIS

Life expectancy for patients with DMD has increased dramatically over the last 20 years, with a mean age of survival currently between 23.0–27.8 years.[38-41] The prolonged survival is the result of improved disease management leading to a delay in the development of complications.

This includes clinical care, corticosteroid treatment, proactive cardiac monitoring and treatment, access to respiratory interventions, rehabilitation, and orthopaedic procedures. The main cause of death in DMD remains progressive cardiorespiratory failure, although the percentage of primary cardiac deaths in DMD is rising because management of respiratory complications has improved.[42-44] Cardiac abnormalities in DMD progress with age and are characterised by initial left ventricular enlargement, followed by dilated cardiomyopathy with left ventricular dysfunction, arrhythmia, and heart failure.[43] Whether prophylactic cardiac treatment is able to prevent or postpone the onset of cardiac involvement still needs to be demonstrated. Early onset cardiomyopathy has been associated with poor response to treatment, and worse prognosis.[45]

Early access to overnight ventilatory support has been the most successful intervention so far in prolonging survival in DMD.[38] However, in practice this intervention is not always well-tolerated and therefore may be refused or delayed, increasing the risk of severe respiratory complications and death. Respiratory physiotherapy and proactive management of chest infection with up-to-date vaccinations, low threshold for antibiotic treatment, and devices to assist cough (e.g. Ambu bag, cough assist machine) can also impact outcomes.

Even with this positive trend and the continuous increase in survival rates in DMD, unexpected young deaths have been anecdotally reported. Teenage years seem to be a particularly fragile phase in this population and increased surveillance might be required in patients showing an unexpected deterioration around this time. Although the causes of these young deaths often remain largely unclear, several risk factors have been suggested. These include insidious worsening of respiratory function, presence of malnutrition, subtle cardiac arrhythmia, stress-induced adrenal failure in patients undergoing long-term corticosteroids treatment, fat embolism following trauma, psychological distress, and poor attendance to follow-up appointments. Awareness of these risk factors is important in order to minimise the risk of an untimely (sudden) death in DMD.[46]

THE FUTURE OF DUCHENNE MUSCULAR DYSTROPHY

The last 10 years have seen an enormous effort in developing new therapeutic approaches for DMD. Improvements in clinical care have already significantly changed the natural course of the disease, and recent investments in new potential treatments for the condition mean a promising future lies ahead. Several clinical trials in DMD are currently running, offering different approaches. These range from mutation-specific strategies aiming to correct the underlying genetic cause of the disease (exon skipping, reading through), to gene and stem cell therapy and non-mutation-dependent strategies directed to address downstream pathological pathways (anti-myostatin, utrophin, vamorolone, etc.).[47] One of these approaches, tested in clinical trials, has led to the successful approval of a drug for DMD by the European Medicines Agency (EMA) called ataluren (Translarna™, conditional approval). Moreover, parallel studies investigating new treatments for the cardiac and respiratory complications (e.g. idebenone, eplerenone, nebivolol, etc.) have been developed in recent years. This illustrates that the clinical multidisciplinary approach also extends into the field of research. A list of the currently open studies is summarised in Table 3, however the list will continue to evolve over time.

The rapid development of research in DMD has raised concerns on feasibility of multiple clinical trials in rare diseases where the patient population is limited, especially for targeted approaches (e.g. mutation-specific interventions). This is further complicated by the current requirements of a very narrow patient population (with regard to eligibility criteria; e.g. age, stage of the disease, mutation, etc.) being recruited in clinical trials, in order to reach study primary outcomes timely and efficiently. Currently a number of clinical trials exclude participants who have previously received any investigational drug, further obstructing recruitment and drug development in rare diseases. Although the results of some of the recent studies have been disappointing, lessons have been learnt from the clinical trial experience with the disease over the past years. This has raised awareness of the gaps which need to be addressed in order to ensure more cost-effective studies in the future and the ability to provide clearer outcomes on safety and efficacy of new investigational drugs. This includes: the importance of patient registries to allow identification of patients for large international studies; a better understanding of outcome measures for DMD; the impact of age, corticosteroid treatment, provision of standardised care on motor performance, and outcome measures. Other factors to take into consideration include

the importance of disease-specific biomarkers breaching clinical outcomes; the possible impact of mutation type and location on clinical severity; the ethical requirement to involve older patients in clinical research, and the current lack of longitudinal natural history outcome data on this non-ambulatory population; the need for harmonisation of the regulatory processes, and requirements to facilitate the conduct of international studies in rare diseases. Finally, the need to develop a new health economic model applicable to rare diseases, and to ensure objective evaluation of the clinical effectiveness of investigational drugs without discouraging future drug development.[48]

CONCLUSION

Historically, DMD was considered an incurable condition and as such was approached with very limited proactive management. The development and dissemination of care recommendations for DMD has significantly changed this approach, leading to improved survival and quality of life, and allowing the prospect of an adult life for most patients diagnosed today. The field has seen large investments in terms of new therapeutic approaches which have now been taken into clinical trials and have resulted in one of the tested drugs receiving conditional approval by the EMA. Finally, there is hope that the future for boys and young men with DMD will significantly improve in the upcoming years. This leads to a new set of challenges, including social and psychological impacts of longer-term survival which need to be addressed in parallel with the continued improvement in care and treatment. The experience built over the last 20 years in DMD (implementation of diagnosis, dissemination of care recommendations, acquiring essential natural history data, and delivery of clinical research with investigational drugs) is likely to be of extreme value for the future of DMD patients. It also provides a learning experience for the development of new therapeutic approaches in other rare diseases.

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