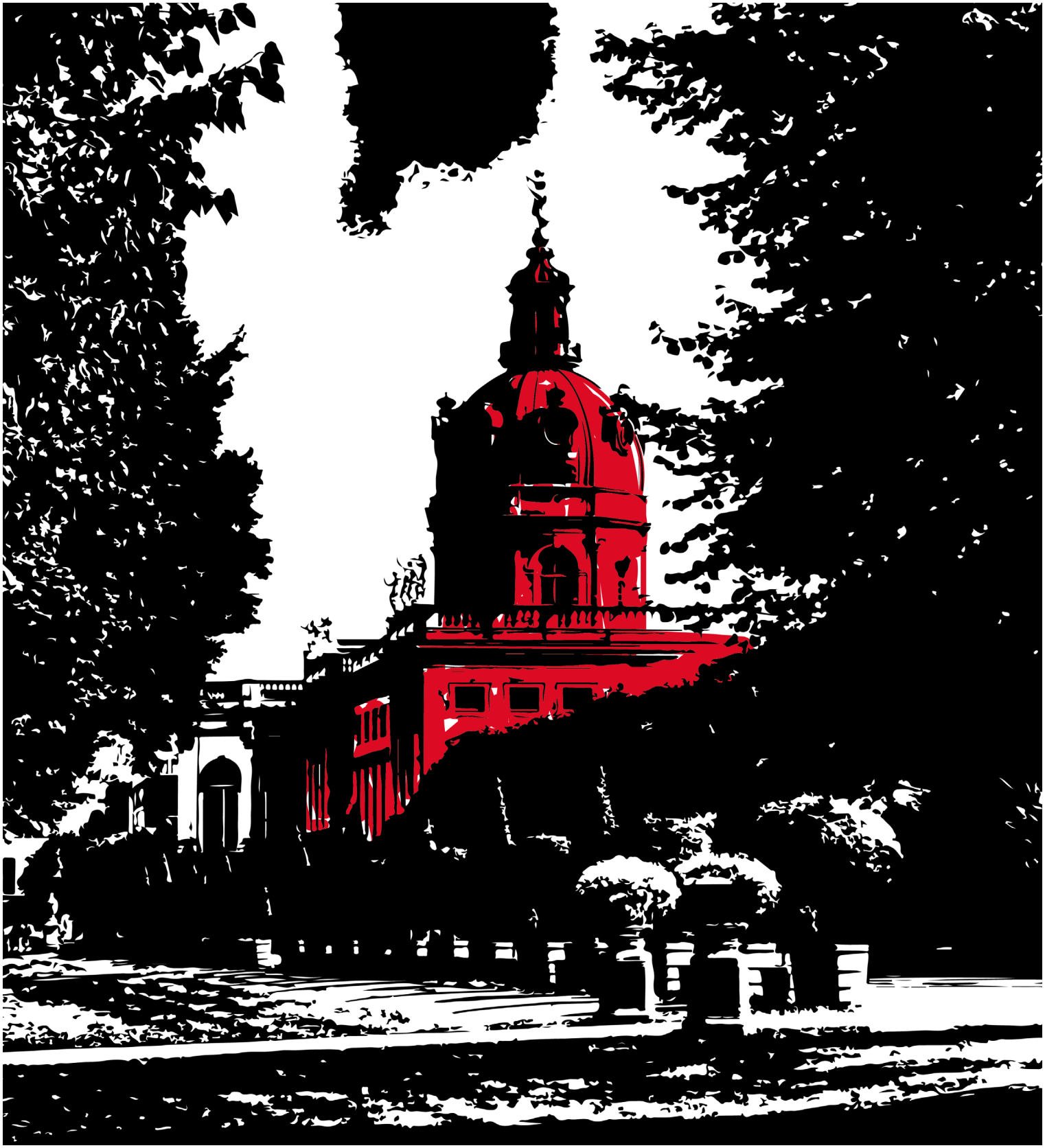
EMJ EUROPEAN MEDICAL JOURNAL

EUROPEAN MEDICAL JOURNAL

ISSN 2397-6764 Vol 3.1 • March 2018 • europeanmedical-journal.com



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Front cover and contents artwork: Stacey Rivers/EMJ

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EUROPEAN MEDICAL JOURNAL 3.1
MARCH 2018

Welcome

Dear readers,

A very warm welcome to the first edition of the European Medical Journal's flagship publication of 2018: *EMJ 3.1.* This issue brings you review and feature articles from key opinion leaders across a range of therapeutic areas, including allergy and immunology, reproductive health, neurology, and dermatology. *EMJ 3.1* is a truly diverse publication that offers something for everyone to enjoy and engage with.

The Editor's Pick for this issue is the captivating evidence-based review by Jain, describing the current status of intrauterine insemination as a first-line infertility management strategy, as well as the prognostic factors that may impact its success. Despite being developed >50 years ago, intrauterine insemination remains an excellent option for a variety of patients because it is relatively simple and patient-friendly. The review also highlights the critical importance of counselling and appropriate timing as integral parts of infertility management.

> "With these captivating articles, alongside many more, we are incredibly proud to present you with *EMJ 3.1* and the multidisciplinary viewpoint that the hand-selected peer-reviewed articles represent."

Moving towards gastroenterological insights, the fascinating literature review penned by Babikow et al. details the sensitivity and specificity of faecal DNA biomarker testing and stool DNA-based assays to detect abnormalities in the colon. With colorectal cancers causing the second largest number of cancer-related deaths in the USA, the authors draw some intriguing conclusions and suggest poignant areas for development to improve colorectal cancer screening and detection in the future.

The dermatologists among you will be delighted to learn that Starace et al. present a fascinating case study of longitudinal melanonychia in a teenager and consider the multifaceted effects of skin conditions. In addition, Boonpiyathad et al. discuss urticaria, outlining the aetiology of the disorder, diagnostic techniques, and potential disease exacerbants. Finally, Kelly and Ryan look beyond the surface of psoriasis and detail the immunological contributors behind the skin disease.

With these captivating articles, alongside many more, we are incredibly proud to present you with *EMJ 3.1* and the multidisciplinary viewpoint that the hand-selected peer-reviewed articles represent. We eagerly look forward to the scientific and medical advancements that are sure to be unveiled before the publication of *EMJ 3.2* this summer.

Kind regards,

Spencer Gore

Chief Executive Officer, European Medical Journal

The threat of relapse is always there.
Constantly playing on multiple myeloma patients' minds.[2]

Click here to visit **www.rethinkmyeloma.com** to find out more.

Fewer reminders for patients.
Prolonging remission is an important goal when treating multiple myeloma.[1,3]

Patient quote from a real-world study of face-to-face interviews with 50 patients with relapsed/refractory multiple myeloma across five countries. Person displayed is for illustrative purposes only, and does not reflect the identity of the patient quoted.

1. Hulin C et al. Leuk Res 2017; 59: 75-84.
2. Hauksdóttir B et al. Oncol Nurs Forum 2017; 44(2): E64-E81.
3. Liwing J et al. Br J Haematol 2014; 164(5): 684–693.

UK-MM180006 Date of preparation: February 2018

RETHINK
RELAPSE

Celgene

Foreword

Prof Mátyás Benyó

University of Debrecen, Hungary.

Dear colleagues,

I am delighted to invite you to 2018's first edition of the *European Medical Journal: EMJ 3.1*.

Nowadays, in this era of evidence-based medicine, it is essential to have scientifically well-supported studies and thorough reviews synthesising knowledge on specific diseases and their background. The optimal platform for such publications are scientific journals, which provide opportunities for practicing clinicians and research teams to obtain knowledge. One pearl among these journals is the *European Medical Journal*, which covers all current significant fields of medicine.

My Editor's Pick for this issue, by Jain, provides a useful overview of intrauterine insemination's role in infertility management. Considering the growing incidence of infertility worldwide, this is a significant paper. Although a wide range of diagnostic possibilities and different assisted reproductive techniques are available, their application still raises questions for many clinicians. Intrauterine insemination is a first-line treatment option in the management of non-tubal infertility because it is simpler and less invasive than other assisted reproductive techniques.

Naturally, it is essential to have effective screening tools for colorectal cancer, and it has been shown that the screening of DNA in stools can detect local and advanced malignancies. Addressing this topic, Babikow et al. provide an excellent review of recent publications on faecal DNA biomarkers.

In surgical intervention, minimally invasive operations are often favoured because they require less analgesics, shorter hospital stays, and the possibility of faster recovery both during and after the intervention. Non-resectional lung volume reduction surgery enables intervention under non-intubated anaesthesia and within this edition Ambrogi et al. outline their well-documented study of 108 patients undergoing this type of operation that was designed to measure both early and long-term outcomes.

EMJ 3.1 also contains a broad range of key articles from the field of dermatology. Starace el al. present an interesting case of longitudinal melanonychia in a teenager, while two fascinating reviews regarding psoriasis and urticaria are also presented. With psoriasis regarded as a complex systemic inflammatory disorder affecting multiple other systems, such as the cardiovascular and respiratory systems, its inclusion within this multidisciplinary journal is eminently suitable.

All papers featured within this edition were peer-reviewed, so accurate content is guaranteed.

The *EMJ* Editorial Board wishes you pleasant reading and encourages you to submit articles to European Medical Journal.

Kindest regards,

Mátyás Benyó

Assistant Professor, Department of Urology, Faculty of General Medicine, University of Debrecen, Debrecen, Hungary; Member of the executive committee of Hungarian Association of Andrology.

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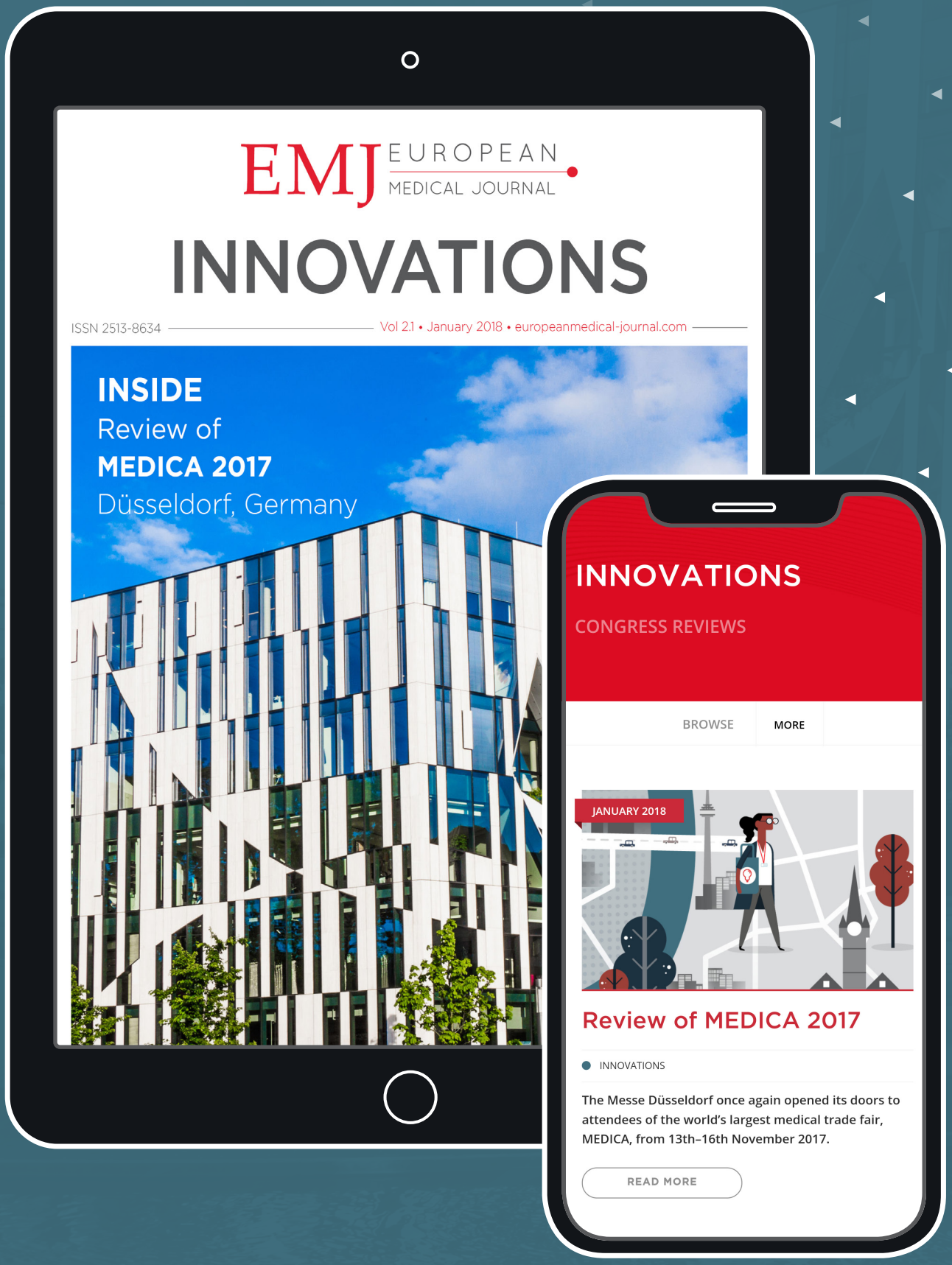

Featured inside:

Congress Review

+ Review of MEDICA 2017 Düsseldorf, Germany, 13th–16th November 2017

Feature

+ Patient–Physician Interaction on Social Media: The Physician's Point of View Elena Nikiphorou, Francis Berenbaum

Articles

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+ A Transition from Disease-Centred to Goal-Directed Individualised Care of Patients with Multiple Morbidities: A Journey to Goal-Orientated Patient Healthcare Katarzyna Rygiel

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EUROPEAN LEAGUE AGAINST RHEUMATISM RECOMMENDATIONS FOR EARLY ARTHRITIS: WHAT HAS CHANGED?

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Disclosure: The author has declared no conflicts of interests.
Received: 17.02.17 **Accepted:** 26.09.17
Citation: EMJ. 2018;3[1]:12-16.

CLINICAL PRACTICE GUIDELINES BEFORE BIOLOGICALS: 1996–2007

Rheumatoid arthritis (RA) is a chronic, disabling, inflammatory, autoimmune disease that affects approximatively 0.4–1.0% of the population. Immune dysregulations, synovial membrane hyperplasia, activation of proinflammatory cells, and release of cytokines, such as interleukin (IL)-1, IL-6, and tumour necrosis factor-alpha (TNF-α) are involved in the pathophysiological process. The first RA clinical practice guidelines were developed in 1996 by members of the American College of Rheumatology (ACR).[1] The authors underlined that optimal management requires early diagnosis and timely introduction of agents that reduce the probability of irreversible joint damage. The initial evaluation should document symptoms of active disease, functional status, objective evidence of disease activity, mechanical joint problems, the presence of extra-articular disease and comorbid conditions, as well as the presence of radiographic damage in selected involved joints. Baseline laboratory evaluations included complete blood cell count, platelet count, chemistry profile, immunoglobulin (Ig)M-rheumatoid factor (IgM-RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

The aggressiveness of the treatment was defined according to poor prognosis associated with early age at onset, high IgM-RF, active inflammation, and presence of extra-articular manifestations. The initial drug treatment involved non-steroidal anti-inflammatory drugs (NSAID), e.g., aspirin or ibuprofen, to reduce joint pain and swelling; however, NSAID do not alter the course of the disease nor prevent joint destruction. Patients whose disease remains active despite NSAID were candidates for disease-modifying antirheumatic drugs (DMARD), the most widely used being methotrexate (MTX). The timing was recognised as an important factor; i.e., the initiation of DMARD should not be delayed beyond 3 months for any patient with an established diagnosis. Early RA was not mentioned, but the goal was to intervene in the disease before joints are damaged. These guidelines were followed by an update in 2002;[2] the authors of the guidelines insisted that a specialised rheumatologist should estimate the progression of disease and determine a prognosis. The Arthritis Impact Measurement Scale and the Health Assessment Questionnaire were identified as valid evaluation tools for functional status. The ACR established a scale of improvement, depending whether there has been a 20–70% improvement. A scoring system was established as an outcome measure for radiographic progression. At that time, newly proposed therapies were infliximab (a chimeric IgG1 monoclonal antibody against TNF-α) and etanercept (a soluble TNF receptor protein, binding soluble TNF-α), in combination with MTX; both drugs were shown to be beneficial in improving clinical symptoms.[3,4] Anakinra (a human recombinant form of IL-1 receptor antagonist) also was evaluated.[5] Due to the new agents incurring higher costs, longitudinal studies were necessary to justify their use.

In 2006, guidelines were published by the British Society for Rheumatology (BSR) specifically focussing on early cases and the first 2 years of therapy.[6] Again, the authors recommended to establish patients with RA on DMARD therapy as soon as possible. DMARD therapies should be prescribed as part of an aggressive package of

care, incorporating escalating doses, intra-articular steroid injections, parenteral MTX, and combination therapy, rather than sequential monotherapy, progressing to biologic (e.g., anti-TNF-α) therapy, when required.

The European League Against Rheumatism (EULAR) recommendations for the management of early arthritis were published first in 2007,[7] with updates every 3 years.[8-10] In 2007, anti-cyclic citrullinated peptide/anti-citrullinated protein antibody (anti-CCP/ACPA) positivity was added to the diagnosis criteria. Simultaneously, the authors claimed that early diagnosis was complicated due to the absence of specific tests. Nowadays, we know that anti-CCP/ACPA precedes the clinical onset of RA by years and are initially produced at extra-articular sites.[11] The committee recommended that patients presenting with arthritis of more than one joint be referred to a rheumatologist, ideally within 6 weeks after the onset of symptoms.[7] Another recommendation was to use new techniques to detect synovitis, including magnetic resonance imaging (MRI). Factors predicting persistent and erosive disease should be measured, including the number of swollen and tender joints, inflammation parameters (CRP and ESR), levels of IgM-RF and anti-CCP/ACPA, and radiographic erosions. IgA-RF has also been mentioned as a sign of poor prognosis, but *HLA-DRB1* genotyping was regarded as less suitable. Most importantly, the authors recommended to begin aggressive DMARD therapies as early as possible, even if the patients did not yet fulfil established classification criteria for RA. This was an important paradigm change. Among patients with recent onset polyarthritis, those who received DMARD treatment early had a better outcome with regard to radiographic progression, function, and ability to work, than those in whom DMARD treatment was delayed by a few months.

CLINICAL PRACTICE GUIDELINES AFTER BIOLOGICALS: 2010–2016

The primary reason for discontinuation of traditional DMARD, such as MTX, were adverse effects. First clinical studies with biologicals (IL-1 receptor antagonist and anti-TNF-α therapies) emerged 1998–2003. However, as with traditional DMARD, many patients (20–40%) who were treated with TNF-α antagonists did not respond to treatment or were unable to sustain the response over time. Alternatives, such as abatacept (which inhibits macrophage/T cell interactions),[12] were developed and clinically tested from 2005–2006 in RA patients with an inadequate response to MTX and/or anti-TNF.[13] In 2010, 15 recommendations were developed by a EULAR committee, regarding patients in whom synthetic DMARD and anti-TNF-α therapies have failed.[8] Meanwhile, other alternative biological therapies came on the market, in particular tocilizumab, a humanised monoclonal antibody against the IL-6 receptor,[14] and rituximab, a monoclonal antibody that targets CD20+ B cells.[15] These biologicals are expensive; however, they may enable the lowering of short and long-term indirect costs of disease.[8] Again, the authors insisted that treatment with synthetic DMARD, such as MTX has to be started as soon as possible. Biologicals are kept in reserve for when patients present with poor prognosis factors and respond insufficiently to synthetic DMARD; at first, a TNF-α inhibitor in combination with MTX should be used. Patients with RA, for whom a first TNF-α inhibitor has failed, should receive another biological, such as tocilizumab, rituximab, or abatacept. In cases of refractory severe RA or contraindication to MTX and/or biological agents, the following synthetic DMARD were suggested: azathioprine, ciclosporin A, or, in exceptional circumstances, cyclophosphamide. Intensive medication strategies should be considered in every patient. Anti-malarial drugs (e.g., hydroxychloroquine) and anakinra were not recommended because, while effective in RA, their efficacy is lower than that of other agents in their class.

The 2010 ACR/EULAR classification criteria for RA included at least one joint with definite clinical synovitis (swelling), not better explained by another disease, and a scoring system with the number and type of joints, serology (IgM-RF and ACPA), acute-phase reactants (CRP and ESR), and duration of symptoms. In fact, these criteria were designed to be applied in early arthritis and possibly contributed to a certain degree of uncertainty in the diagnosis of RA.

A further update of these EULAR recommendations came out in 2013.[9] Briefly, the EULAR committee underlined that all TNF-α inhibitors, tocilizumab, abatacept, and, under certain circumstances, rituximab, were essentially considered to have similar efficacy and safety. If the first biological DMARD strategy fails, any other biological DMARD may be used. The recommendations also addressed tofacitinib (Janus kinase inhibitor)

as a targeted synthetic DMARD, which was recommended, where licensed, after use of at least one biological DMARD.[16]

THE 2016 UPDATE OF THE EULAR RECOMMENDATIONS

The most persuasive argument that RA has multiple pathways to the same phenotype is the diversity of responses to highly specific biological DMARD.[17] Thus, it will be important in future to better categorise patient subpopulations. The authors of the 2016 update of the EULAR recommendations mentioned that identifying the underlying disease is difficult, particularly at early stages.[10] The hypothetical subgroups of early arthritis are frequently clinically undifferentiated and can develop into established RA or another definite arthropathy, remain undifferentiated, or resolve spontaneously. The challenge with early arthritis is the difficulty in knowing what it might become, which produces some tension between the risks of over-treating and under-treating. In recent years, research on early arthritis has been a major focus. After defining the target population and formulating a definition of management, the 2016 committee selected research questions to serve as the basis for a systematic literature review. Clinical examination is still the method of choice for detecting synovitis, which may be confirmed by ultrasonography. The authors focussed on clinical examination and downplayed the role of MRI, as well as the use of biomarkers in making an appropriate diagnosis.

Multiple studies that claim greater sensitivity for MRI or ultrasound have not convinced the committee, since the drawback of using these diagnostic techniques is reduced specificity. In the opinion of the committee members, all evidence for drug treatment should be based on clinically detecting arthritis. In cases of undifferentiated arthritis, if a definite diagnosis cannot be reached, risks factors for persistent and/or erosive disease should be considered in management decisions. Compared with previous recommendations, the authors, even more so than before, focussed on early referral and early DMARD treatment for those who need it, since this may improve outcomes. A recent study validated this concept for anti-TNF-α therapies.[18] MTX remains the anchor drug and, unless contraindicated, should be part of the first line of treatment in patients at risk of persistent disease. NSAID should be used at the minimum effective dose for the shortest time possible, after evaluation of gastrointestinal, renal, and cardiovascular risks; this also includes the new specific cyclooxygenase-2 inhibitors. The authors put a warning on careless and unlimited glucocorticoid use, since new evidence points to side effects of long-term use. All these therapies are accompanied by some risk, particularly around infection or toxicity, and, as such, rheumatologists have to exercise caution in when to intercede and with which agent. Hydroxychloroquine, which is a drug rheumatologists often use when there is some degree of uncertainty,[19] remains excluded from the recommendations. The 2016 revision further enshrines treat-to-target as the principle that should guide clinical decisions, which is taken to mean treatment in spite of absence of inflammatory disease activity. The guidelines include additional emphasis on outcomes monitoring, which might mark a change in usual practice for some clinicians. Disease activity should be more tightly assessed, at least every 1–3 months, until the treatment target has been reached. Dynamic exercises and occupational therapy should be considered as adjuncts to drug treatment. Based on epidemiological evidence, the authors added words on prevention of arthritis: stop smoking,[20] good dental care,[21] and avoid obesity.[22] This last revision underlined that treatment is more than providing drugs; health professionals are key in providing education and, more than before, communication with the patient as a partner rather than as a recipient of care was emphasised. The updated recommendations are largely consistent with the standards of care for managing these patients in other parts of the world.

POINT OF VIEW OF A RESEARCHER

There are many positive points to take from these recommendations, such as treating early RA as aggressively and as soon as possible, tightly monitoring the disease activity, and avoiding detrimental environmental factors that also emphasise the relevance of epigenetic research in the field.[23] The aim for coming years, according to the 2016 updated EULAR recommendations,[10] is to cure the disease. This sounds very optimistic, but let us explore this possibility in the eyes of a researcher.

Many methods exist to induce arthritis in animals and RA can similarly also have multiple aetiologies, reflecting the concept that it is probably not a

single disease but a syndrome.[17] This predicts large, inter-individual variations in the response to therapies and limits the significance of large genetic studies with undifferentiated cohorts.[24] Thus, it will be essential to better define the patient subgroups, not only as early or established RA but also according to the pathological mechanisms. In the clinic, the use of biomarkers in the diagnosis of RA was reduced to a minimum.

From a clinician's point of view, this appears logical, since according to the 2010 ACR/EULAR classification criteria as mentioned above no more than the assessment of symmetric polyarthritis, signs of inflammation (CRP and/or ESR), and autoantibodies (IgM-RF and/or anti-CCP/ACPA) are needed; however, to achieve personalised medicine, this is insufficient. As mentioned previously, not all RA patients respond to current biologic therapies and responses are not always maintained.[25] The change from one biological DMARD to the others, as suggested in the recommendations, is time intensive and costly. To identify patient subgroups, large cohorts, specific biomarkers, and multicentre association studies, including responders and non-responders to given therapies, are needed. HLA genotyping and searches for defined polymorphisms have to be reconsidered. To be able to differentiate anti-TNF-α responders from non-responders, biomarkers, such as serum IgA-RF (associated with a poor prognosis)[26] and cartilage oligomeric matrix protein (associated with cartilage destruction),[27] have to be reintroduced. Other new markers, such as autoantibodies against carbamylated peptides, have to be evaluated in large clinical settings.[28] Early MRI erosion progression is a valid measure of structural damage that can be used in clinical trials, but is not routinely used outside of a clinical trial setting.[29] Simultaneously, the pathophysiological mechanisms have to be differentially identified. Certain disease forms are more driven by the adaptive immune system than others and respond better to abatacept and, as such, these patients better match the definition of autoimmunity than others in which a chronic inflammatory process is ongoing. The hallmarks of RA include not only inflammation and immune dysfunctions, but also synovial tissue hyperplasia and aggressive synovial fibroblasts, i.e., the effectors of joint destruction. The current DMARD mainly target inflammation and may relieve pain; the other components of the disease, however, are only dampened indirectly, if at all. MTX as a cytostatic agent might limit synovial hyperplasia, and anti-TNF-α therapies might reduce, but not abolish, the aggressive behaviour of RA synovial fibroblasts. No DMARD directly targets these cells, and, as long as this is the case, no real cure of the disease is possible. RA synovial fibroblasts are intrinsically activated due to biochemical and epigenetic modifications.[30] They slowly but persistently continue to destroy cartilage and bone, even in the absence of TNF-α. Indeed, hip and knee joints with moderate-to-advanced pre-existing damage resulted in radiographic progression, even after TNF-α-blocking therapies.[31] Conversely, other patients showed repair of their arthritic hip joints,[32] demonstrating again the disease's heterogeneity. In addition, for hands, the response to therapy could be different.[33]

Epigenetic therapies,[23,30,34] in addition to the proposed DMARD, need to be clinically evaluated. Again, it can be predicted that only a subgroup of patients will respond.[30] In fact, the chronicity of the disease might be related to positive feedback loops that allows biostability, i.e., a more stable cellular differentiation and memory. This can occur at different cellular levels and involves chromatin changes. To cure the disease, such feedback loops have to be disrupted. The aim will, therefore, be to interfere with the mechanisms that lead to chronicity and to offer patients a personalised therapy, thereby fulfilling the goal of the 2016 EULAR committee: curing the disease.

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CURRENT APPROACH TO THE TREATMENT OF CORONARY CHRONIC TOTAL OCCLUSIONS

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Disclosure: The authors have declared no conflicts of interest.
Received: 03.04.17 **Accepted:** 09.02.18
Citation: EMJ. 2018;3[1]:17-20.

Coronary chronic total occlusions (CTO), in spite of excellent progress in the field of medicine, remain a great challenge for interventional cardiologists. CTO is defined as the occlusion of a coronary artery with a thrombolysis in myocardial infarction (TIMI) score of 0 flow estimated for >3 months duration. CTO is observed in 15–30% of diagnostic coronary angiograms.[1]

Due to the low success rates of therapeutic intervention for CTO compared to regular coronary angioplasty, and the greater experience required to perform the associated procedures successfully, chronic occlusions are regarded as a separate type of cardiac lesion. Although revascularisation of CTO is associated with longer procedural times and increased exposure to radiation and contrast, the procedure's lower success rates can be improved by new CTO strategies. Prof Gerald Werner, CTO expert and former President of the Euro CTO Club, recommends considering chronic occlusions as a target for percutaneous coronary intervention (PCI), similar to any other lesion; however, the technique and experience of the operator must go beyond what is needed for performing PCI in non-occluded coronary arteries.[2]

In March 2017 at the American College of Cardiology (ACC) Scientific Session, the first randomised trial of stenting versus optimal medical therapy for coronary chronic occlusion was presented.[3] DECISION-CTO was a prospective, multicentre, open-label randomised trial comparing the optimal medical therapy with or without stenting for CTO in patients with silent ischaemia, stable angina, or acute coronary syndrome. The primary endpoint of the study was a composite of death, cardiac infarction, stroke, and repeat revascularisation.

During the study, patients were randomised to two groups: 398 to optimal medical therapy and 417 to optimal medical therapy plus PCI of CTO. The success rate of PCI was 90.6%. After 3 years of observation, 19.6% of the optimal medical treatment patients reached the primary endpoint versus 20.6% in the interventional group; this met the noninferiority margin (p=0.008) and the components of the composite endpoint did not differ significantly.[3] The second major finding from the trial was that no improvement in quality of life scores or angina occurrence was observed. Moreover, the authors carried out a per-protocol and an as-treated analysis; they observed that event rates did not significantly differ between the two groups.[3] DECISION-CTO had four major limitations: lack of clarity regarding how many patients had symptoms or ischaemia after revascularisation of non-CTO lesions; whether myocardial territories due to the CTO were viable at the outset of the study; an almost 20% rate of crossover from the medical therapy arm to the PCI arm; and that the trial was terminated. These limitations significantly decreased the power of the results.

Data from the CREDO-Kyoto AMI registry showed that CTO in a non-infarct-related artery was associated with an increased 5-year mortality in ST-elevation myocardial infarction patients with multivessel disease.[4] Similar results were observed in the SCAAR report: CTO was associated with increased mortality, and this correlation was most prominent not only in patients with acute coronary syndrome, but also in patients <60 years of age.[5] However, a meta-analysis including 28,486 patients in non-randomised trials confirmed that successful CTO PCI was associated with a lower risk of death, stroke, coronary artery bypass grafting,

and less recurrent angina pectoris, when compared with failed procedures.[6] Procedural success in the studies included in the meta-analysis was 71% (range: 51–87%). The increasing success rate of revascularisation observed in recent years is noteworthy, with many devices and techniques having been introduced to improve the effectiveness of PCI of CTO.[7]

Many of the current imaging methods have been developed to overcome the barriers to successful PCI of CTO. Coronary computed tomography angiography is used to predict the success rate of recanalisation and allows better visualisation of the anatomy of arteries, which is not always seen in coronary angiography. Many important predictors of procedure failure have been identified, including severe calcification, bending, blunt stump, the presence of many occlusions, and occlusion length. Coronary computed tomography angiography cannot be recommended for all CTO patients, but this imaging technique should be considered for patients with challenging or ambiguous lesions.

The most basic technique for starting the CTO procedure is via the antegrade approach. In some cases, the use of modern hydrophilic guidewires enables microchannels to be found in the occlusion, allowing access to the true lumen in the distal artery; however, this situation does not occur very often. Typically, other techniques must be used to reopen the artery and, in such cases, occlusion crossing can be achieved by entering the subintimal space, allowing re-entry into the true lumen. Dissection can be completed using a knuckle wire, made by forming a loop in a polymer-covered guidewire (usually of the Fielder variety [ASAHI Intecc Co., Ltd., Aichi, Japan] or the PILOT variety [Abbott Vascular, Santa Clara, California, USA]) and advancing it through the artery.

Re-entry can also be achieved by pushing the wire until it reaches the true lumen. This technique is called subintimal tracking and re-entry (STAR), which is used as the very last resort for crossing the occlusion. It is also possible to carry out a contrast injection into the subintimal space via a microcatheter at the proximal cap to perceive a dissection plane, a process termed contrast-guided STAR. However, access to the distal true lumen is most often achieved by either the mini-STAR technique or limited antegrade subintimal tracking. In the first case, the true lumen is found by advancing the loop of wire distal to the lesion to limit the dissection plane. In the limited antegrade subintimal tracking technique, re-entry is achieved using a stiffer wire (e.g., Confianza [ASAHI Intecc Co., Ltd., Aichi, Japan]).

To ensure better control of crossing the occlusion subintimally, the CROSSBOSS™ (Boston Scientific, Marlborough, Massachussets, USA) catheter was designed. Microdissections created by this fast-rotating catheter allow insertion of a STINGRAY™ (Boston Scientific) balloon and a guidewire into the subintimal space. The STINGRAY guidewire can be pushed towards one of the two side ports of the STINGRAY balloon to reach the true lumen of the artery. These techniques require more procedural and fluoroscopy time, as well as longer stent length, compared to intimal tracking.[8] Subintimal techniques can be supported by an intravascular ultrasound, which is useful for finding entry to the true lumen from the subintimal space.

In the case of failure of the aforementioned techniques, other options are available, including the retrograde approach, which was described for the first time in 1990.[9] The initial path of the retrograde procedure was via a venous bypass graft, but in 2006 the first paper describing retrograde crossing with the use of septal collateral vessels was published.[10] Since then, the retrograde approach has been used worldwide and can be used to treat the most complex CTO lesions. The European guidelines for revascularisation,[11] published in 2014, do not consider the retrograde approach as a primary therapeutic option for CTO; however, the Euro CTO Club recommendations[1] suggest this technique not only for the second attempt after antegrade failure, but also in cases of very complex CTO with an expected antegrade success rate of <50%.

Due to the fact that the distal cap of the occlusion is softer than the proximal cap, it allows for an easier crossing of the body of the occlusion without losing the true lumen of the artery. Moreover, a distal wire at the end of the occlusion can be used as a marker (marker wire technique), which can aid in the advancement of the antegrade microcatheter (kissing wire technique) and requires less contrast medium. Another successful technique is controlled antegrade and retrograde subintimal tracking (CART). The retrograde-advanced guidewire enters a false lumen, which is then enlarged by inflation of the balloon, allowing the antegrade wire to advance and reach the true lumen.

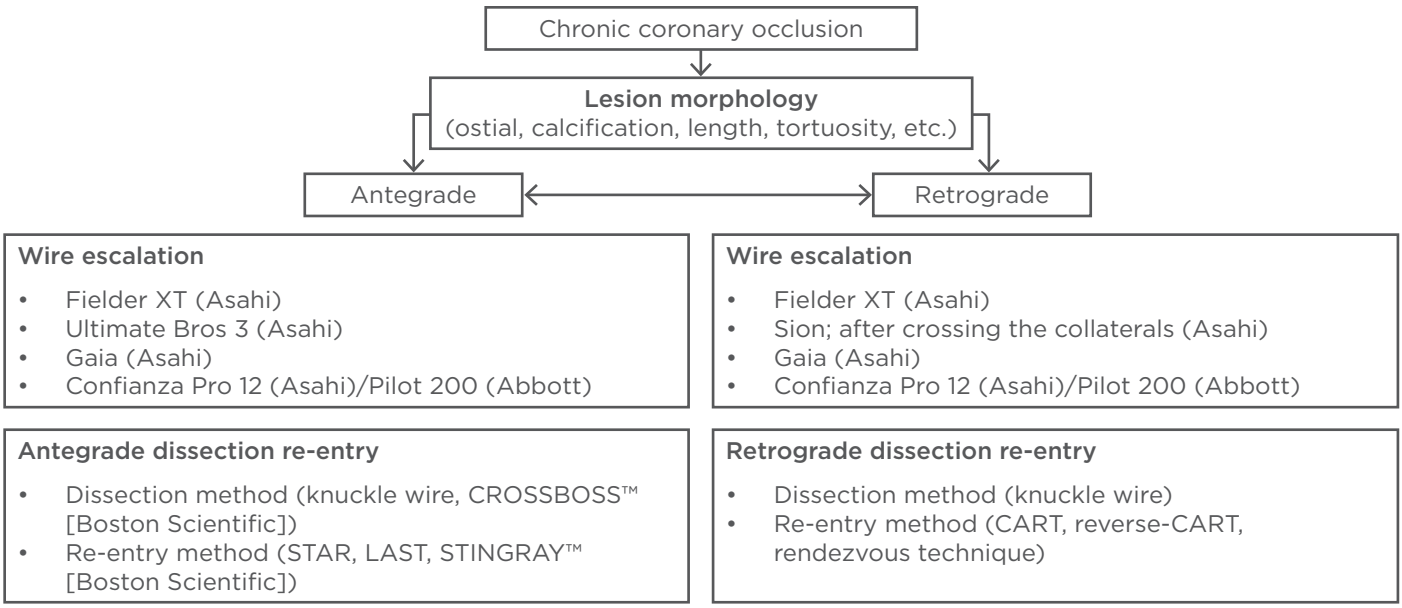

Figure 1: Strategic options for chronic total occlusion treatment.
CART: controlled antegrade and retrograde subintimal tracking; LAST: limited antegrade subintimal tracking; STAR: subintimal tracking and re-entry.

A more commonly used technique is the reverse-CART, a variant of the CART technique in which the antegrade wire reaches the false lumen and the balloon is advanced in an antegrade manner to enlarge the subintimal space where the retrograde wire is positioned. Another retrograde technique is the rendezvous method, which uses two microcatheters moved forward in an antegrade and retrograde manner, allowing the antegrade wire to advance to the distal part of the artery.[12] Although very useful, the retrograde approach should be reserved for very experienced operators. This approach can be used after antegrade crossing failure or as the initial approach to CTO therapy, particularly in patients with ambiguous proximal caps, ostial and long occlusions, occlusions with severe proximal tortuosity or calcification, CTO vessels that are difficult to engage, and occlusions with distal major bifurcation.

The successful revascularisation of CTO with PCI in centres with very experienced operators could occur in >90% of cases and complication rates have been shown to be comparable when using the retrograde technique and contemporary antegrade techniques.[13,14] The first step in PCI of CTO is careful selection of the collateral vessel because some patients have restricted collateral pathways.[15] To find a suitable route via a septal collateral, superselective injection through a microcatheter for better visualisation of the selected vessel is used. Another technique for advancing the wire is called septal surfing. During septal surfing, the operator will attempt to cross collaterals without clear visualisation of the pathway; appropriate guidewire selection during this process is crucial. The dedicated wires for collateral passage are wires from the Sion family (ASAHI Intecc Co., Ltd., Aichi, Japan) and excellent tip control gives even higher chances of a successful crossing. The SUOH3 wire (ASAHI Intecc Co., Ltd.) has a very low tip load (0.3 gram-force), which can be very useful in severely tortuous vessels.

The second step of PCI is the delivery of the microcatheter to the distal CTO and retrograde wiring in the lesion. Development of specialised microcatheters has significantly improved collateral channel crossing and the most commonly used microcatheters for the retrograde approach are Finecross® MG (Terumo, Somerset, New Jersey, USA) and Corsair and Caravel (ASAHI Intecc Co., Ltd.). Microcatheters, thanks to their crossing profile and good trackability, support cross collateral channels, saving procedure time and protecting the collaterals.

Data from 45 centres in Japan showed that predictors for PCI of CTO failures were in-stent occlusion, calcified lesions, and lesion tortuosity. Moreover, lesion calcification was an independent

predictor of PCI failure after successful collateral channel crossing.[16] In our opinion, supported by the studies discussed, the retrograde technique is effective and safe if performed by experienced operators in centres with a high volume of CTO patients. The long-term outcomes after a successful retrograde procedure have been noted as very good.[17] Modern medicine in the field of interventional cardiology offers patients with CTO lesions an interesting spectrum of treatment, and these patients should be given the opportunity to be relieved from ischaemic symptoms to the same extent as patients without CTO lesions. However, our own experiences have shown that non-invasive and invasive cardiologists alike have insufficient knowledge about CTO procedures, which makes them ineligible to properly perform PCI of CTO.[18] The available options for CTO treatment are shown in Figure 1.

The most challenging aspect for the interventional cardiologist, not a CTO operator, is gaining the proper qualification to perform the procedure and the knowledge of when to refer the patient to a specialised centre. It must be remembered that of all patients with total CTO diagnosed by angiography, only 10% underwent PCI for CTO and 7% were revascularised.[19] It is crucial to assemble the entire medical community, not just interventional cardiologists, to disseminate this knowledge about qualification and treatment of coronary CTO to improve the care of coronary patients.

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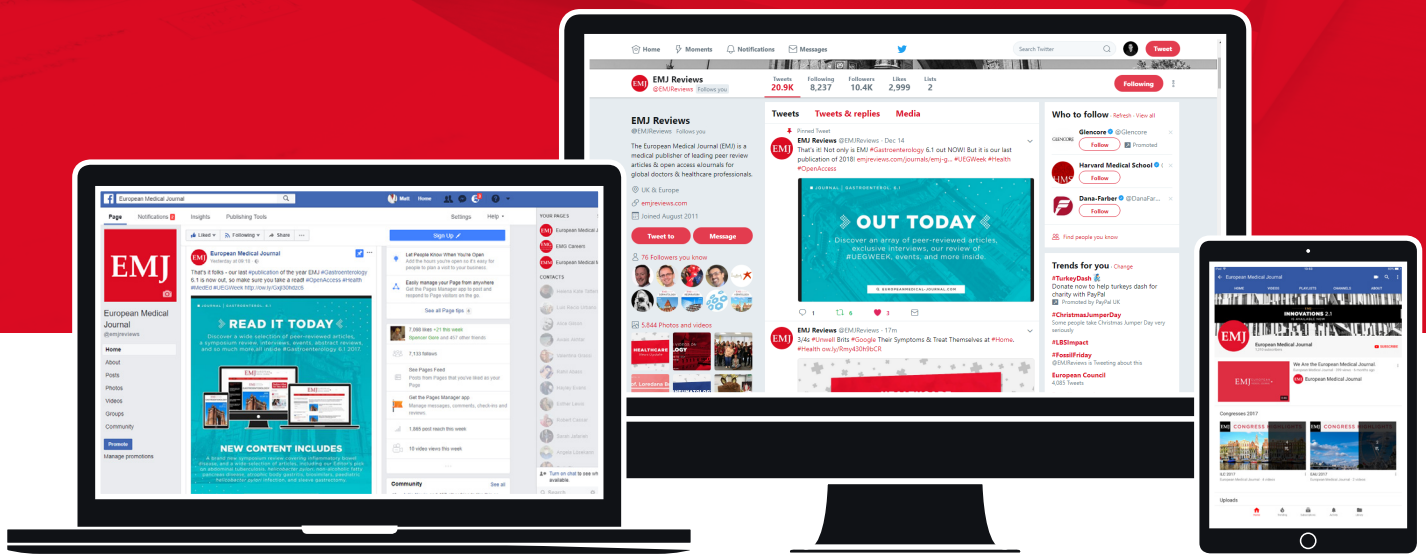

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INTERLEUKIN-23 IN PSORIASIS: INTEGRATING NEW THERAPIES IN THE CURRENT TREATMENT LANDSCAPE

This symposium took place on 14th September 2017 as a part of the 26th European Academy of Dermatology and Venereology (EADV) congress in Geneva, Switzerland

Chairperson

Kristian Reich[1]

Speakers

Kristian Reich,[1] Andrew Blauvelt,[2] Giampiero Girolomoni[3]

1. Dermatologikum Hamburg, Hamburg; Dermatologikum Berlin, Berlin; Georg-August-Universität Göttingen, Göttingen, Germany

2. Oregon Medical Research Center, Portland, Oregon, USA

3. University of Verona, Verona, Italy

Disclosure: Prof Reich has served as an advisor and/or paid speaker for, and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Eli Lilly and Company, Medac, Merck Sharp & Dohme Corp., Novartis, Ocean Pharma, Pfizer, Regeneron, Sanofi, Takeda, UCB Pharma, and Xenoport. Dr Blauvelt is a scientific advisor and clinical study investigator for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly and Company, Genentech/Roche, GlaxoSmithKline, Janssen, Leo, Merck, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac, and a paid speaker for Eli Lilly and Company, Janssen, Regeneron, and Sanofi Genzyme. Prof Girolomoni is a scientific advisor for AbbVie, Abiogen, Almirall, Amgen, Bioderma, Biogen, Boehringer Ingelheim, Celgene, Ducray, Eli Lilly and Company, Galderma, Genzyme, Janssen, Hospira, Insiderma, Leo Pharma, Menlo Therapeutics, Merck, MSD, Mundipharma, Novartis, Pfizer, Pierre Fabre, Regeneron, Samsung, Sanofi, Sandoz, and Sun Pharma.

Acknowledgements: Writing assistance was provided by Jane Grills, ApotheCom, London, UK.

Disclaimer: This report contains information on drug treatments that are not currently approved for use in Europe. Interleukin-23 (p19) inhibitors risankizumab and tildrakizumab are not approved for the treatment of psoriasis or psoriatic arthritis in Europe.

Support: The publication of this article was funded by Janssen. The views and opinions expressed are those of the authors and not necessarily of Janssen.

Citation: EMJ. 2018;3[1]:22-29.

MEETING SUMMARY

Prof Reich welcomed delegates to the satellite symposium and explained that the aims of the meeting were to introduce the clinical role of targeted interleukin (IL)-23 therapies in psoriasis, show why IL-23 therapy is effective against psoriasis, show how it works in patients by illustrating emerging clinical trial data, and, finally, describe how the IL-23 inhibitors can be used to address unmet clinical needs in patients with psoriasis. Dr Blauvelt started the meeting by providing an update on the current understanding of the immunology of cytokine pathways in psoriasis. Prof Reich then gave an overview of the clinical value of IL-23 inhibitors as novel targeted treatments for psoriasis, summarising data from pivotal clinical trials that have been carried out to support the introduction of these treatments into the clinical armamentarium. Finally, Prof Girolomoni reviewed the indications for biologic therapies and discussed how IL-23 inhibitors can be integrated into the current therapeutic environment. The satellite symposium concluded with a lively question and answer session.

An Immunologic Understanding of Cytokine Pathways in Psoriasis

Doctor Andrew Blauvelt

Psoriasis has a highly complex pathophysiology driven by increased T helper (Th) cell activity resulting in inflammation, overproduction and activation of keratinocytes, and the formation of psoriasis plaques. IL-23 is a key upstream regulatory cytokine in psoriasis pathogenesis. Produced by antigen-presenting dendritic cells, the normal function of IL-23 is to stimulate differentiation, activation, proliferation, and survival of Th17 cells. Specialised Th17 cells are normally involved in the adaptive response utilised in mucocutaneous defence against infection by extracellular organisms such as *Candida albicans* or *Staphylococcus aureus*, which may also play a role in pathogenesis of psoriasis (Figure 1).[1-4] IL-23 is composed of two molecular subunits, p19 and p40; blockade of IL-23 can be achieved by targeting either subunit, but only p19 subunit inhibition specifically blocks the IL-23 cytokine. Ustekinumab, a biologic therapy for psoriasis and psoriatic arthritis, is an inhibitor of p40, and results in the blockade of IL-12 as well as IL-23. The focus of current clinical research has been the specific inhibition of IL-23 via more targeted inhibition of the p19 subunit alone. In patients with psoriasis, overproduction of IL-23 occurs in the upper dermis, leading to excessive Th17 cell accumulation and overproduction of IL-17A and IL-22. This leads to keratinocyte proliferation and activation, pro-inflammatory cytokine production (e.g., tumour necrosis factor [TNF]-α), and neutrophil accumulation.

Psoriasis is associated with genetic polymorphisms in the *p19* and *p40* subunit genes of IL-23, as well as in *IL-23R*, a gene that encodes for a subunit of the IL-23 receptor present on the cell surface of Th17 cells.[5] A defect in *IL-23R* has been shown to be protective against the development of psoriasis by impairing IL-23-induced Th17 effector responses in humans.[6] Importantly, IL-17A, produced by Th17 cells and other cell types, is a downstream effector cytokine in psoriasis pathogenesis. There is evidence from animal studies, as well as human tissue studies, that blockade of IL-17 prevents the development of IL-23-mediated epidermal thickening and psoriasis-like disease.[7] In contrast, the inhibition of IL-23 provides upstream inhibition of pathologic processes.

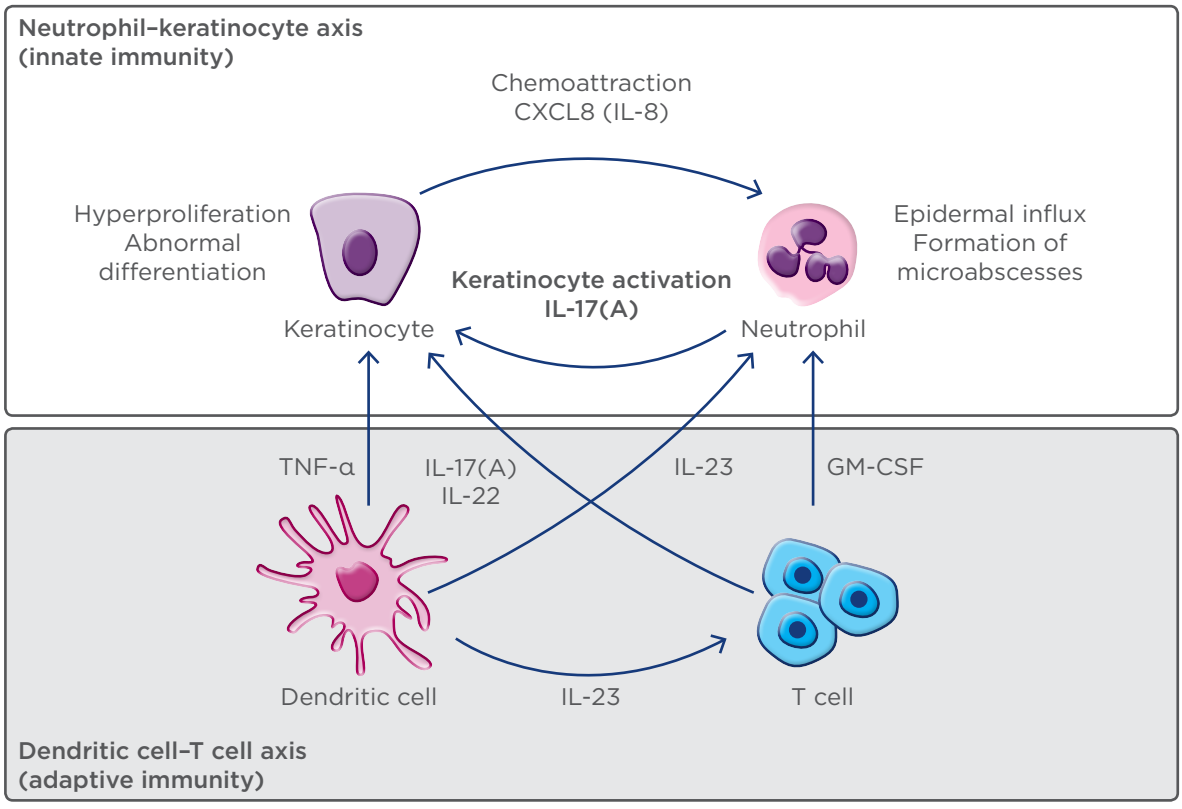

Figure 1: Model of psoriasis pathogenesis.[2]

GM-CSF: granulocyte-macrophage colony-stimulating factor; IL: interleukin; TNF: tumour necrosis factor.

Blocking different targets in the immunopathogenic pathways involved in psoriasis has varying effects. Inhibition of the pathologic process with a broad immunosuppressant drug, such as methotrexate, is associated with more safety concerns and is less effective than more targeted inhibition of key cytokines such as IL-23 and IL-17A. Similarly, the mechanism of action of targeted inhibition of cytokine pathways has implications for safety and dosing. For example, loss of IL-17A activity is associated with the development of chronic mucocutaneous candidiasis in both mice and humans. Although there are currently no supporting scientific studies, it has been hypothesised that IL-23 blockade does not block all downstream IL-17 production (i.e., some residual IL-17A production remains from non-Th17 cells in the skin and gut); therefore, this may explain why IL-23 blockade may not lead to candidiasis or inflammatory bowel disease. To date, clinical evidence from studies of IL-23 inhibitors has shown no increase in the incidence of serious infections, reactivation of tuberculosis infection, hepatitis B, candidiasis, or inflammatory bowel disease. Blocking upstream targets, such as IL-23, is also associated with a need for less frequent dosing, since clinical efficacy of IL-23 inhibitors in psoriasis persists longer than serum drug levels. It is possible that IL-23 inhibition may cause the death of Th17 cells, which are dependent on IL-23 for cell survival, and thus could lead to prolonged disease control. Such considerations are based upon the basic understanding of the IL-23/Th17 immunologic pathway but require detailed tissue studies in humans to confirm.

The Clinical Value of Interleukin-23 Inhibitors

Professor Kristian Reich

Several IL-23 inhibitors are in clinical development, including guselkumab. It is the first IL-23 inhibitor to be approved for the treatment of patients with moderate-to-severe plaque psoriasis in the USA and is in Phase II evaluation for use in psoriatic arthritis. Other IL-23 inhibitors in clinical development include tildrakizumab and risankizumab, which are in Phase III, and mirikizumab, in Phase II.

Clinical Evidence: Guselkumab

The efficacy and safety of guselkumab has been evaluated in two recently published pivotal randomised, double-blind, placebo and active-controlled Phase III trials: VOYAGE 1[8] and VOYAGE 2.[9] In VOYAGE 1, guselkumab was compared with adalimumab and placebo over a 1-year active comparator period, followed by a 4-year follow-up.[8] The study included 837 patients, of whom 174 were initially randomised to placebo, 329 to guselkumab, and 334 to adalimumab. Co-primary endpoints included the proportions of patients achieving an Investigator Global Assessment (IGA) score of cleared or minimal disease (IGA 0 or 1), and ≥90% improvement in Psoriasis Area Severity Index (PASI 90) at Week 16 in the guselkumab group compared with placebo. The baseline patient characteristics were those of a typical psoriasis population: mean BMI of 30, mean overall PASI of 22, mean dermatology quality of life (QoL) index of 14, and a long duration of disease (mean: 18 years). Compared with placebo, a significantly higher percentage of patients on guselkumab achieved an IGA 0 or 1 (85.1% versus 6.9%, respectively; $p<0.001$) and PASI 90 (73.3% versus 2.9%, respectively; $p<0.001$). The response to guselkumab was rapid and the proportion of patients achieving PASI 100 at Week 16 was significantly higher for guselkumab than placebo ($p<0.001$). Responses to guselkumab were also significantly better than to adalimumab in the proportion of patients achieving IGA 0 or 1, PASI 90, and PASI 100. High level clinical responses were sustained to Week 48 (Figure 2).[8] Guselkumab was effective in improving the scalp and nail manifestations of psoriasis, although the improvements compared with adalimumab were attenuated.[8] Unpublished long-term data show that responses to guselkumab were sustained for up to 2 years, demonstrating excellent longevity of the therapeutic response.

A high level of treatment response has been shown to correlate with improved patient QoL. The Phase III clinical data from VOYAGE 1 show that the higher level of clinical efficacy in terms of PASI 90/100 response reported for guselkumab compared with adalimumab translates into significant and sustained improvements in QoL, as evidenced by higher Dermatology Life Quality Index (DLQI) scores.[8]

VOYAGE 2 had a similar design to VOYAGE 1, but included a period of randomised withdrawal (Weeks 24–28) followed by re-treatment or treatment switch (PASI 90 non-responders) through to Week 48.[9] Co-primary endpoints were the same as in VOYAGE 1.

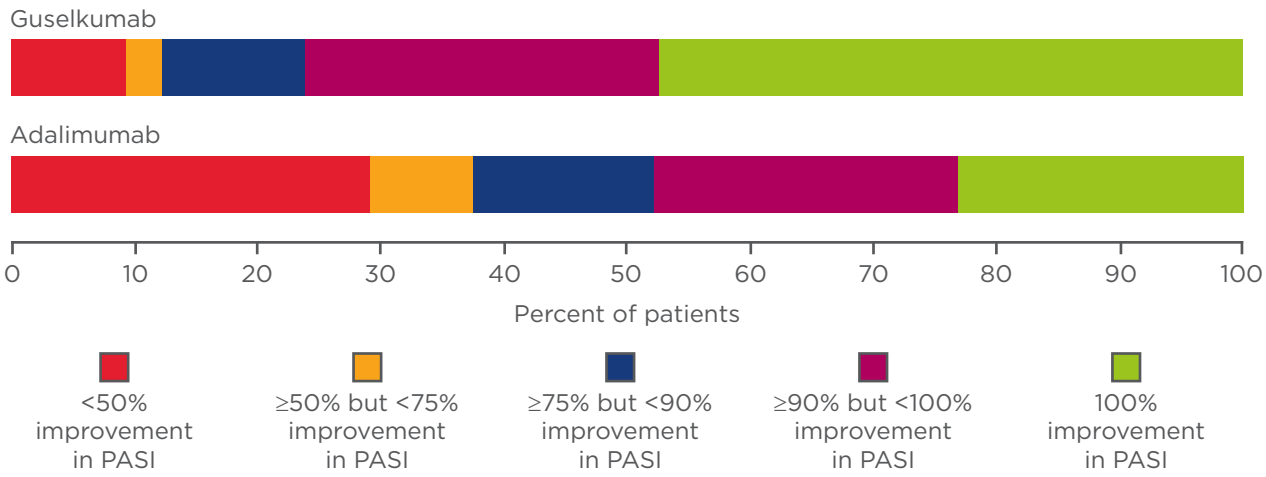

Figure 2: Distribution of psoriasis treatment responses (improvement in Psoriasis Area Severity Index) at Week 48 in the VOYAGE 1 trial.[8]
PASI: Psoriasis Area Severity Index.

A total of 992 patients were randomised in a 2:1:1 ratio to guselkumab (496 patients), placebo (248 patients), and adalimumab (248 patients). Efficacy results were very similar to those of VOYAGE 1; clinical responses were observed early in the treatment period and, at Week 16, significantly higher proportions of patients achieved IGA 0 or 1, PASI 90, and PASI 100 compared with either placebo or adalimumab ($p<0.001$ for all comparisons with guselkumab).[9] VOYAGE 2 also evaluated the effect of withdrawal of active treatment and demonstrated that the therapeutic efficacy of guselkumab was sustained after treatment was stopped. The mean time to loss of PASI 90 response was 15.0 weeks in the guselkumab-treated patients compared with 8.6 weeks in adalimumab-treated patients. In addition, 66% of patients who did not achieve a PASI 90 response to adalimumab achieved PASI 90 after switching to guselkumab at Week 28.[9]

The Phase III VOYAGE 1 and 2 safety data showed that guselkumab has a comparable safety profile to adalimumab with no new safety signals reported, resulting in a favourable risk:benefit profile. The incidence of overall infection, serious infections, and infections requiring antibiotic treatment were similar in guselkumab and adalimumab-treated patients.[8,9]

Clinical Experience with Other Interleukin-23 Inhibitors

Risankizumab is an IL-23 inhibitor that is in Phase II/III of clinical development. Data from a comparative clinical trial of risankizumab versus ustekinumab showed that in patients treated with risankizumab (dosed at Weeks 0, 4, and 16), 50% of patients maintained a PASI 90 response at Week 48; i.e., 32 weeks after the last risankizumab dose.[10] These data provide further evidence of the sustainable effect of IL-23 inhibition in psoriasis, as seen in VOYAGE 2 with guselkumab. The immunological impact of targeted upstream IL-23 inhibition in the immunopathology of psoriasis requires further study to better understand this effect on the underlying disease process.

Another IL-23 in Phase III development is tildrakizumab. Data from the placebo-controlled reSURFACE 1 Part 1 trial[11] show that although a significantly higher percentage of patients treated with tildrakizumab achieve PASI 75, PASI 90, and PASI 100 compared with placebo, the proportions of patients with PASI 90 and PASI 100 responses were lower than those reported for guselkumab or risankizumab.[8-11] However, the proportion of patients achieving PASI 90 and PASI 100 improved at 28 weeks,[11] suggesting that the time to treatment response may be longer with tildrakizumab; head-to-head comparisons are needed to better understand the efficacy of tildrakizumab.

IL-23 inhibitors also represent a promising new treatment option for patients with psoriatic arthritis. Guselkumab is the first anti-IL-23 biologic to demonstrate efficacy in psoriatic arthritis. Clinically significant effects on American College of Rheumatology (ACR) 20, ACR50, and ACR70 scores, enthesitis, and dactylitis at 24 weeks have

been reported in a Phase II trial.[12] In summary, in patients with moderate or severe psoriasis, IL-23 inhibitors are associated with high levels of clinical response, stable long-term responses that extend beyond serum drug levels, convenient injection intervals, and no safety concerns to date compared with other biologic treatments.

The Current Landscape of Psoriasis Treatments: When and Where to Embed Emerging Therapeutic Options

Professor Giampiero Girolomoni

Despite the introduction of new biologic treatments, there are a number of unmet needs in the clinical management of moderate-to-severe psoriasis, including late or inadequate use of systemic treatment, poor tolerability or effectiveness of conventional therapy in many patients, and effective treatment of psoriasis in difficult areas (scalp, genitalia, and palmoplantar areas).[13,14] In addition, many current therapies (including biologics) lose optimal efficacy over time in a substantial proportion of patients. Severe psoriasis has a very significant impact on QoL, affecting the emotional,[15] socio-familial,[16] financial,[17] work,[18] and leisure[19] aspects of patients' daily lives. The systemic inflammation associated with severe psoriasis also puts patients at increased risk of metabolic disorders, such as Type 2 diabetes mellitus, non-alcoholic fatty liver disease, hypertension, and, ultimately, atherosclerosis and cardiovascular disease.[20]

Appropriate use of systemic therapy is very important, and treatment success requires the complete, or almost complete, clearance of psoriasis. Systemic therapy is indicated for patients with a PASI ≥10 or those with a PASI <10 who have involvement of the hands, scalp, face, nails, or palmoplantar or genital areas.[21] Other indications include a body surface area (BSA) involvement of ≥5%, either where there is resistance to topical therapy or where patients are reluctant to use it; a BSA <5% with disseminated lesions; a patient's subjective perception of disease severity (e.g., DLQI ≥10); active psoriatic arthritis; and psoriasis associated with severe symptoms (e.g., itch or burning) that are not controlled by topical therapies. Treatment goals should be agreed with patients after an informed discussion and re-evaluated after 3–4 months during treatment initiation and every 3–6 months during maintenance. The treatment efficacy goal that best correlates with disease remission and good patient satisfaction is an improvement in BSA of ≥90% (PASI 90); the targets for the maintenance phase are a minimum PASI of <1 or a BSA <1%, and a DLQI of <5.[21,22] If treatment goals are not met, therapy may be changed or another drug may be added to the treatment regimen.

Box 1: Key factors to be considered when choosing a biologic treatment.[21]

Patient characteristics

- Patient age, sex, body weight.
- Patient expectations.
- Comorbidities that may contraindicate or raise a caution on the use of selected biologics (e.g., latent tuberculosis, severe heart failure, personal history or strong family history of demyelinating disease or alopecia areata for TNF-α blockers, Crohn's disease for IL-17A inhibitors).
- Presence of concomitant diseases that may benefit from the same treatment (e.g., psoriatic arthritis, Crohn's disease, ulcerative colitis, pyoderma gangrenosum, uveitis, sarcoidosis, Behçet's disease, hidradenitis suppurativa for anti-TNF-α monoclonal antibodies; Crohn's disease for ustekinumab).

Disease characteristics

- Disease severity, activity, and stability.
- Skin areas involved.
- Severity of symptoms (e.g., pruritus).
- Disease and treatment history, rapid relapse after treatment withdrawal, intermittent or continuous disease activity.

Treatment-related considerations

- Drug availability.
- Overall efficacy (short and long-term) and the need for a rapid response.
- Tolerability and safety (including patient concerns over side effects).
- Need for flexible treatment (e.g., need for easy interruption or restart).
- Administration modality (oral, subcutaneous, intravenous; frequency of injections).

IL: interleukin; TNF: tumour necrosis factor.

A survey of the use of biologic therapy recently reported that many physicians also adjust either the dose or dose interval as a strategy to improve treatment response or maintain remission, even though this is an off-label approach and cannot be recommended.[23] Important factors to be considered when selecting a systemic psoriasis treatment include age, body weight, treatment availability, disease severity, comorbidities, and concomitant diseases (Box 1).[21,22]

There is limited evidence to indicate which factors, if any, influence treatment outcomes. Age and body weight can have an impact on treatment efficacy, as well as disease severity and disease manifestations such as psoriatic arthritis. A multicentre study reported that patients who were genotyped positive for *HLA-C*6* (generally younger patients) had a faster and greater response to treatment with the IL-23/IL-12 inhibitor ustekinumab.[24] A French study[25] recently reported that patients were more likely to be prescribed adalimumab than either etanercept or ustekinumab if they had severe psoriasis or if they had psoriatic arthritis. Younger patients (<30 years of age) and those who had positive screening for latent tuberculosis were more likely to receive ustekinumab than adalimumab. Patients with chronic obstructive pulmonary disease were also more likely to receive ustekinumab or etanercept than adalimumab, and there was a trend toward increased etanercept use in patients with cardiovascular comorbidities, metabolic syndrome, or a history of cancer. Systemic psoriasis treatments have distinct efficacy and safety profiles. Conventional systemic treatments such as methotrexate, cyclosporine, and dimethyl fumarate are associated with significant metabolic toxicity resulting in side effects (e.g., nausea, fatigue, headache, diarrhoea) and poor tolerability. TNF-α inhibitors have demonstrated greater tolerability compared with conventional therapy and are associated with longer drug survival times.[26] Ustekinumab has also been reported to have higher drug persistence rates and longer drug survival than the TNF-α inhibitors etanercept, infliximab, and adalimumab.[27]

To conclude, the choice of treatment for a patient with moderate-to-severe psoriasis should involve a holistic decision-making approach, encompassing disease, patient, and treatment characteristics.

Question and Answer Session

Q: Why has candidiasis been noted in patients treated with IL-17 inhibitors but not in the clinical trials with IL-23 inhibitors?

A: Dr Blauvelt replied that an IL-17 inhibitor blocks all production of IL-17 from all cell types (Th17, neutrophils, innate lymphoid cells), and therefore, as IL-17 has a defensive role in the skin and gut, elimination of IL-17 would be expected to result in skin infections or gut inflammation. With IL-23 inhibition, a large proportion of IL-17 production will be removed, but a small amount (˜10%) of IL-17 production is not under IL-23 control, and it is hypothesised that this residual IL-17 is sufficient to protect the skin from *Candida* infection and the gut mucosa from inflammation.

Q: If you have a patient who is treated with adalimumab and does not achieve a PASI 90 response, what is the best treatment strategy?

A: Dr Blauvelt replied that if a patient is clearly not responding to treatment, the drug needs to be switched. In a patient with inadequate response, however, the situation is more difficult, and you can consider either switching or adding another drug to the regimen, such as methotrexate. Prof Reich added that dose adjustment is also an option; with adalimumab the normal dose is administered every 2 weeks but can be changed to weekly dosing on label, although this will double the cost of treatment.

Q: Can achieving and maintaining remission in psoriasis impact patients' risk of cardiovascular disease?

A: Dr Blauvelt replied that there is an almost linear correlation between the level of systemic inflammation and the severity of psoriasis, and a patient with severe psoriasis is likely to have an increased risk of atherosclerosis and cardiovascular disease. Therefore, clearing psoriasis should improve cardiovascular risk by reducing inflammation. Some evidence is emerging to support this in the case of TNF-α inhibitors, but studies need to be carried out for IL-17 and IL-23 inhibitors.

Prof Reich added that, because atherosclerosis is an inflammatory process, treatment with an anti-inflammatory agent could reduce cardiovascular risk. If a psoriasis treatment could block pro-inflammatory cytokines in the heart vessels in

addition to reducing the skin inflammation, it would have an impact on cardiovascular risk. The picture is not yet clear, but data are emerging showing that IL-17 inhibition may have positive effects on markers of cardiovascular risk.

Q: Why are we seeing differences in clinical responses with guselkumab, tildrakizumab, and risankizumab when they all target the same key cytokine, IL-23?

A: Prof Reich replied that there are also reported differences in the response to different TNF-α inhibitors. Blocking the same target does not mean the clinical response will be exactly the same; there will be differences in affinity, immunogenicity, and other aspects. Dr Blauvelt added that the mechanism of action is not the only consideration for treatment response; the drug must be dosed at the correct level and at the right frequency, because these factors also influence efficacy.

Q: Do you think that treatment with guselkumab is disease-modifying?

A: Prof Reich replied that, at present, only very preliminary observations can be made in this regard. IL-23 inhibitors, as a class, have a clear sustained efficacy that persists months beyond their pharmacokinetics and provides a lasting clinical response for a substantial subgroup of patients. More data from biopsy studies are required before this can be described as disease modification, but it seems likely that research is taking us closer to disease modification in the future. Prof Girolomoni and Dr Blauvelt agreed with Prof Reich's views.

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FROM REGISTRY DATA TO REAL-LIFE EXPERIENCES: A HOLISTIC PERSPECTIVE OF PSORIASIS TREATMENT

This symposium took place on 15th September 2017 as a part of the 26th European Academy of Dermatology and Venereology (EADV) congress in Geneva, Switzerland

Chairperson

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Speakers

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Disclosure: Prof Puig has received grants, research support, honoraria, or consultation fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo Pharma, Eli Lilly, Merck-Serono, MSD, Novartis, Pfizer, Sandoz, and VBL; Prof Puig has also participated in a company-sponsored speaker's bureau for Janssen. Dr Warren has acted as a speaker and/or received honoraria or consultation fees from AbbVie, Amgen, Almirall, Boehringer Ingelheim, Celgene, Janssen, Novartis, Eli Lilly, Pfizer, Medac, and Xenoport; Dr Warren has also received grants or research support from UCB, AbbVie, Novartis, and Eli Lilly. Prof Gniadecki has received grants, research support, honoraria, or consultation fees from AbbVie, Janssen, Amgen, Celgene, Therakos, Leo Pharma, Novartis, and Eli Lilly; Prof Gniadecki has also participated in company-sponsored speaker's bureaux for Therakos and Janssen.

Acknowledgements: Writing assistance was provided by Marta Lozano-Wilhelmi, ApotheCom, London, UK.

Support: The publication of this article was funded by Janssen Pharmaceutica NV. The views and opinions expressed are those of the authors and not necessarily of Janssen Pharmaceutica NV.

Citation: EMJ. 2018;3[1]:30-37.

MEETING SUMMARY

Registries provide very high-quality data on the persistence of different therapies in the real world and can be used to compare and guide therapeutic guidelines. Dr Warren gave an overview of the different types of registries that capture data on patients with psoriasis. Furthermore, he discussed findings from the British Association of Dermatologists Biological Interventions Register (BADBIR), the Psoriasis Longitudinal Assessment and Registry (PSOLAR), and the Danish Biologic Interventions Registry (DERMBIO) data that help to gain insight on how best to prescribe drugs in a clinical setting. Prof Puig and Prof Gniadecki presented cases encountered in clinical practice to illustrate how real-world data can support the clinical decision-making process. Throughout their presentations, Prof Puig and Prof Gniadecki engaged the audience in interactive discussion on how to improve patient monitoring and management of comorbidities, and addressed issues such as drug survival, safety, and economics.

Interpreting Long-Term Registry Data in the Treatment of Psoriasis

Doctor Richard Warren

The presentation compared registries used to capture data in patients with psoriasis, evaluated the differences between studies that use registry data, and provided insights into how registry data should be interpreted.

Real-world evidence (RWE) is used to evaluate the impact of treatments in a routine clinical setting. RWE can be obtained from various sources, including patient registries, existing electronic health records, routinely collected administrative

data, primary patient data collection, and/or population surveys. Registries can provide information about a disease and/or therapeutic strategies. Compared with randomised controlled trials (RCT), RWE offer many advantages. Of note, RCT are commonly driven by an efficacy endpoint and are seldom powered to look at safety either in detail or the long term. Furthermore, the professional support networks that exist within RCT are often not available in a real-world setting, which can impact outcomes including treatment adherence, persistence (the duration of time from initiation to discontinuation of therapy),[1] and efficacy.

There are currently three key styles of registries for psoriasis and psoriatic arthritis (PsA): pharmacovigilance registries, epidemiology or observational studies, and network registries. Examples of pharmacovigilance registries include BADBIR, the German Psoriasis Registry (PsoBest), DERMBIO, and PSOLAR. BADBIR is a prospective observational comparator registry for patients with moderate-to-severe psoriasis receiving biologics (n=8,424) or conventional systemic therapies (n=4,488) and collects data from 151 dermatology departments across the UK and Ireland. An early publication based on these data compared the baseline characteristics of the patients between two cohorts (biologics [n=5,065] and systemic therapies [n=3,334]).[2] The findings showed that patients who had psoriasis for a reasonable amount of time (mean disease duration: 23.0±12.6 years versus 19.0±13.4 years) and those receiving biologics compared with non-biologics were generally heavier (mean body weight: 90.3±21.5 kg versus 87.2±21.4 kg).[2] All patients demonstrated high Psoriasis Area Severity Index (PASI) scores (16.4±8.3 versus 15.5±7.9, respectively), which were reasonably well matched between the cohorts.[2] A 5-year follow-up allowed the assessment of treatment, disease activity, and adverse events (data not shown).[3]

PsoBest is a registry for patients with moderate-to-severe psoriasis, with and without arthritis, with a 5-year observation time and follow-up of every 3 months; patients from this registry were treatment-naïve receiving biologics or non-biologic systemic therapies. Patients receiving biologics in this registry had a significantly greater mean duration of disease compared with systemic therapy (21.9±14.1 years versus 16.9±0.0 years). All other baseline characteristics were well matched.[4,5] PsoBest provided additional value in that it collected data on the first-line systemic therapy Fumaderm®, and therefore may provide RWE on the use of fumerates in these patients.

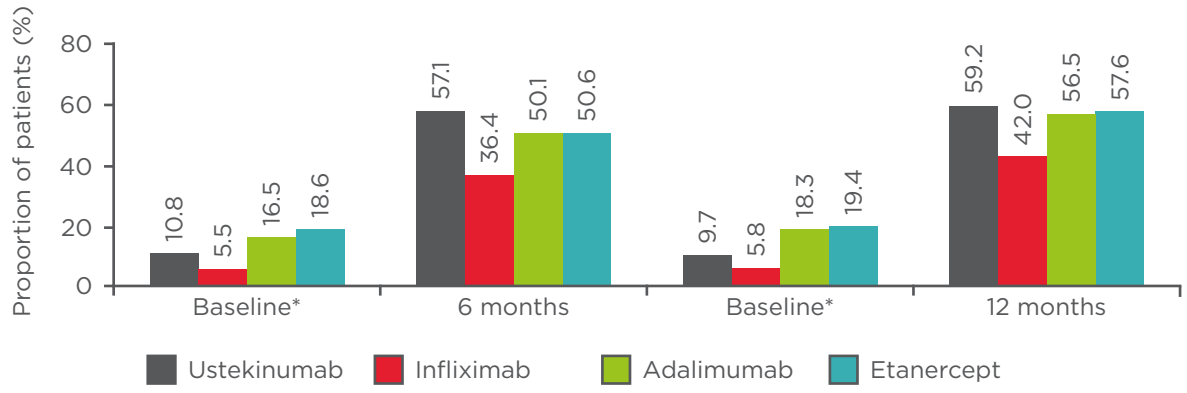

Figure 1: PSOLAR data. Proportion of patients with Physician's Global Assessment score of 0 (clear) or 1 (minimal) at 6 and 12 months.

Data were analysed from 2,076 users who initiated infliximab (n=116), adalimumab (n=662), etanercept (n=257), or ustekinumab (n=1,041) during PSOLAR participation. Only the first biologic started during registry participation was analysed. Of the participants, 80% had been exposed to a biologic prior to enrolment. Evaluations were limited to patients who had baseline data and continued their initiated therapy at their 6-month and/or 12-month visits.

*Baseline psoriasis severity was assessed at the closest visit before the first dose of the newly initiated biologic.

PGA: Physician's Global Assessment; PSOLAR: Psoriasis Longitudinal Assessment and Registry.

Adapted from Strober et al.[8]

DERMBIO is a registry for patients with psoriasis vulgaris receiving biologics (adalimumab [n=576]; etanercept [n=176]; infliximab [n=176]; ustekinumab [n=170]) with a 10-year data collection period.[6] Although this registry does not have a conventional therapy cohort, it provides other valuable RWE, for example, it shows that patients prescribed adalimumab, etanercept, or infliximab are more likely to have PsA compared with patients prescribed ustekinumab (38.1%, 39.6%, or 43.8% versus 14.1%, respectively).[6] Furthermore, patients prescribed the former three treatments are also more likely to be receiving concomitant methotrexate (21.9%, 22.5%, or 55.1% versus 12.4%, respectively).[6] Therefore, registries such as DERMBIO add value by helping to capture prescribing habits in a real-world setting.

PSOLAR is a registry for patients with moderate-to-severe psoriasis from 300 practices across North America, Latin America, and Europe. More patients in this registry receive biologics (ustekinumab, n=4,364; infliximab, n=1,394; or other biologics, n=4,251) compared with systemic therapies (n=2,804).[7] The value of this registry in providing RWE is highlighted in the vast patient numbers.

There are several key factors to consider when interpreting data obtained from registries: the size of the registry and/or whether the registry is powered to address the investigative question of interest. In addition, the external validity of the registry is important; for example, BADBIR collects data nationwide, indicating it is a reliable representation of the real-world setting in the UK and Ireland. Two other important factors of consideration are whether an *a priori* question was set and what adjustments have been performed.

Data from the PSOLAR registry in 2016 demonstrated that ustekinumab (n=1,041) was the most effective treatment compared with infliximab (n=116), adalimumab (n=662), and etanercept (n=257) over 12 months, measured by the proportion of patients with a Physician's Global Assessment (PGA) score of 0/1 (Figure 1).[8] Adjusted logistic regression analyses demonstrated that patients receiving tumour necrosis factor (TNF)-α inhibitors were significantly less likely to achieve a PGA score of 0/1 at 6 months compared with ustekinumab patients. Similar estimates were observed at 12 months, but only the infliximab versus ustekinumab data were significantly different.[8] In view of efficacy measures based on registry data, it is important to emphasise that PGA or PASI data are often missing. Accordingly, investigative efficacy questions may not always be possible or provide the full efficacy assessment. Consequently, drug persistence may be used.

Persistence is an important parameter in the measure of long-term therapeutic performance in a real-world setting[6] and arguably an appropriate surrogate for how successful a drug may be in a given population over time. Bio-CAPTURE,[9] a small registry based in the Netherlands collecting data across eight regional, non-academic centres, showed ustekinumab (n=66) to have the highest long-term drug survival compared with adalimumab (n=101; p=0.066) and etanercept (n=82; p=0.032) in 2011. A Japanese registry also demonstrated ustekinumab to have the highest long-term drug survival compared with infliximab (n=38) and adalimumab (n=59); both of which had a significance of $p<0.05$.[10] However, in view of earlier comments regarding registry size the small patient numbers in the registry would suggest these findings should be interpreted tentatively. Shortly after the Japanese and Dutch study data were released, data from the PSOLAR registry indicated ustekinumab to have the highest persistence compared with infliximab, etanercept, and adalimumab as a first, second, and third-line biologic.[11] Although taking into consideration that PSOLAR is a single company-sponsored registry, this conclusion may also be only tentatively accepted by the clinical community. BADBIR, however, corroborated these findings over a 3-year follow-up and overcomes concerns regarding patient numbers and single company-sponsored registries.[12] Altogether, the similar findings across different registries confirm the validity of the findings. Accordingly, these data support ustekinumab as the gold standard for psoriasis treatment in terms of persistence; however, recent RCT have indicated interleukin (IL)-17 inhibitors to be superior to ustekinumab.[13] If these findings translate into a real-world setting, IL-17 may be considered as a potential treatment over the coming years.

RWE from registry data have provided insights into the most common reasons for drug discontinuations. Data from BADBIR indicated ineffectiveness of therapy, particularly etanercept, and adverse events, particularly infliximab, to be the most common reasons for patients discontinuing biologics, while PSOLAR identified ineffectiveness to be the primary reason.[11] Data

from PsoBest suggest biologics to be associated with a high rate of serious infections compared with conventional systemic non-biologics.[5] In consideration of the factors discussed earlier when interpreting data from registries, PsoBest may not have been powered sufficiently to address investigative questions around serious infections. Both BADBIR and PSOLAR reported infections to be more common with infliximab use compared with other biologics. The current trend to use infliximab less often in real-world settings may be a reflection of the latter.

In conclusion, the data presented suggest that RWE based on registry data will be beneficial for long-term monitoring of adverse events and efficacy in psoriasis patients. Through future collaborations and publications of RWE, we will also continue to improve the wealth of information available in the field of dermatology.

Real-Life Experiences and Clinical Cases: An Interactive Discussion

Professor Lluís Puig and Professor Robert Gniadecki

As the need to provide a personalised treatment approach is becoming more important, the demand for real-world data to aid clinical decision-making in the treatment of psoriasis is increasing. Prof Puig and Prof Gniadecki presented patient cases to illustrate how real-world data can support clinical considerations such as patient adherence, comorbidities, drug survival, patient monitoring, safety, and economics.

Case 1: Association Between Psoriasis and Inflammatory Bowel Disease

A 25-year-old breastfeeding woman presented with mild psoriasis, which she had for the past 14 years, a PASI of 11.3 with no PsA, a history of intermittent abdominal pain, and occasional diarrhoea without blood in the stool. In light of these symptoms, clinical decision-making was centred around screening the patient for inflammatory bowel disease (IBD) or therapy with anti-IL-17 agents, which would likely exacerbate the IBD.

An analysis of data from DERMBIO, a Danish nationwide cohort study of 5.5 million patients,[14] found a psoriasis-associated increased risk of Crohn's disease and ulcerative colitis that was higher in severe psoriasis. Additionally, an increased risk of psoriasis in patients with IBD was also observed. However, of the 11,000 patients with Crohn's disease and the 30,000 patients with ulcerative colitis combined, only 82 had mild psoriasis and 54 had severe psoriasis, potentially explaining why clinicians rarely encounter this combination of conditions in practice.

Faecal calprotectin measurements are routinely used in the diagnosis and monitoring of patients with IBD; however, given the risk of obtaining false-positive results with this method,[15] the patient should ideally be referred to a gastroenterologist. The patient denied colonoscopy and referral to a gastroenterologist but noticed that her symptoms improved on a gluten-free diet. The patient was tested for coeliac disease and tested positive for anti-transglutaminase antibody. Although a meta-analysis comparing real-life data to registry data suggested an association between coeliac disease and psoriasis,[16] the link between a gluten-restricted diet and improvement in psoriasis is still lacking. Eventually, the patient was seen by a gastroenterologist who was unable to make a final diagnosis; after 3 months on a gluten-free diet, her psoriasis improved.

Case 2: Paradoxical Onset of Psoriatic Arthritis?

A 39-year-old man with psoriasis for the last 15 years, who was given methotrexate 15 mg on psoriasis flare, had to discontinue treatment after 2 months due to lack of efficacy and increased liver transaminases. The patient had a PASI of 10.6 before initiation of ustekinumab 90 mg (given at Week 0, Week 4, and then every 12 weeks). After 4 months of treatment, his PASI decreased to 1.2; however, after 11 months of treatment, the patient developed joint pain, three tender joints, one swollen joint, and occasional knee pain. No radiographic changes were detected and the patient was referred to a rheumatologist, who diagnosed possible PsA as a result of ustekinumab treatment. Clinical considerations for this patient included the potential for the joint pain being a treatment-related adverse event and impacted the decision to continue or discontinue treatment with ustekinumab.

A retrospective study assessing patients with psoriasis receiving biologic treatment found that 22 out of the 327 patients who met the inclusion criteria developed PsA during treatment: 6 (27.2%) patients who received etanercept therapy,

10 (45.4%) who received adalimumab, 4 (18.2%) who received ustekinumab, and 2 (9.2%) who received infliximab.[17] These results suggest that biologic therapy may not be sufficient to prevent the onset of articular involvement, and in most of the verified PsA cases, arthritis occurred in concomitance with severe cutaneous involvement.

Therefore, it is possible to develop PsA-like symptoms and signs on treatment with both TNF-blockers and ustekinumab, and a diagnosis of paradoxical arthritis was ruled out. In this instance, owing to a lack of history of joint pain, the inflammation status of the joint was determined, and the patient was given an intra-articular injection to allow the continuation of ustekinumab treatment, which ultimately improved the patient's skin.

Case 3: Dose Escalation

An obese 68-year-old man with a 30-year history of psoriasis, no PsA, mild hypertension, and a daily smoking habit, was previously treated with methotrexate and adalimumab but discontinued both due to lack of efficacy. The patient was started on adalimumab 40 mg every other week and had a good response (PASI 0–6) for 3 years. Upon psoriasis flaring up the dose was increased to 40 mg every week. As a result of these flare ups clinicians considered the options of continuing the patient on a higher dose, reverting to the standard dose of 40 mg every other week, or changing the biologic treatment entirely.

In an unpublished dose-escalation study by Gniadecki,[18] 1,256 patients receiving 40 mg adalimumab every other week achieved PASI ≥75 (64.1%), PASI ≥90 (40.3%), and PASI 100 (21.7%). The 349 (27.8%) patients who had a PASI <50 during Weeks 24 and 252 of the study were dose-escalated to 40 mg every week. Of these 349, 182 (52.1%) remained on every-week dosing and 167 (47.9%) achieved a PASI 75 response and were de-escalated to every other week. Later, 83 patients were re-escalated to every-week dosing, owing to a PASI <50 response (Figure 2).[18,19]

After escalation of adalimumab dosing to every week, approximately one-quarter of patients were able to successfully have their dose de-escalated and remained on every-other-week dosing for nearly 1 year without the need for dose re-escalation. Therefore, transient increase in the dosing frequency of adalimumab to every week improved responses to treatment and permitted long-term maintenance to be achieved.

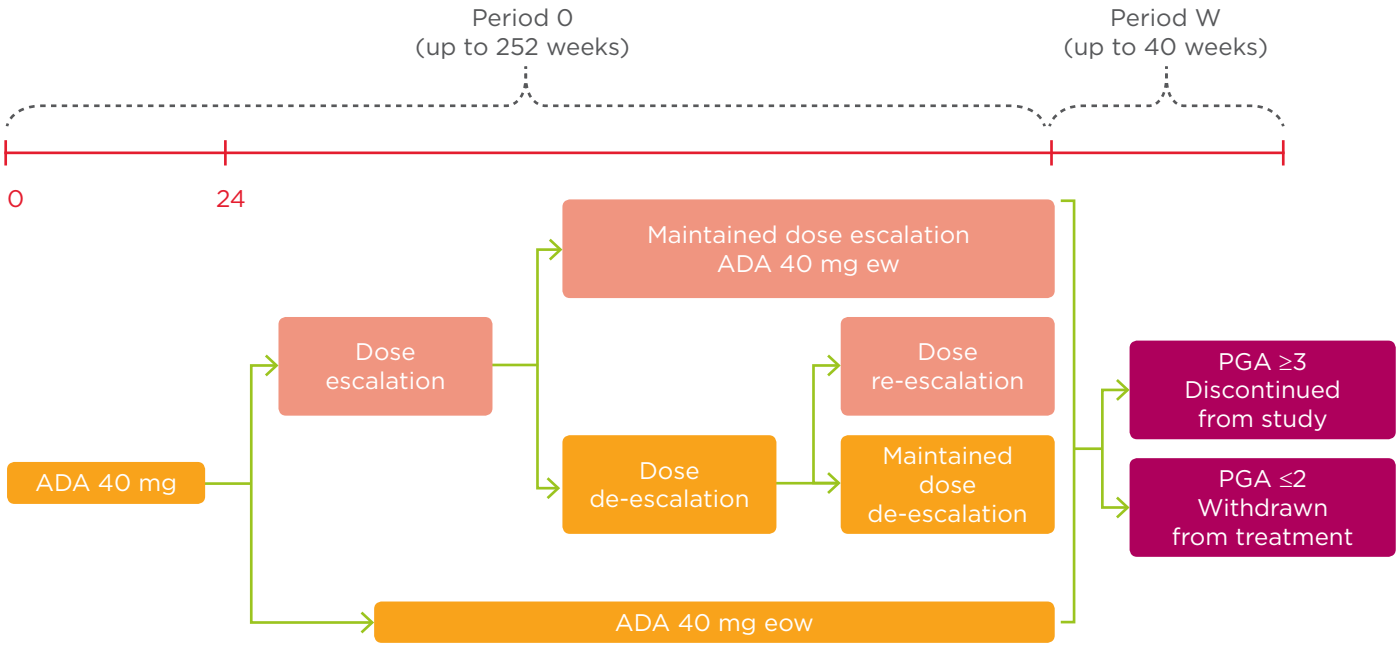

Figure 2: Dose escalation.
Adalimumab 40 mg every week can be considered in patients with inadequate response to adalimumab 40 mg every other week.
ADA: adalimumab; eow: every other week; ew: every week; PGA: Physician's Global Assessment.
Adapted from Gniadecki[18] and Gniadecki et al.[19]

Unmet Needs

There are a number of unmet needs in the clinical management of psoriasis. Focus on real-world practice needs to increase by moving away from population measures, such as PASI 75 and PASI 90, which are best suited to drug comparison in clinical trials, and moving towards individual measures (e.g., absolute PASI). Also, steps need to be taken to avoid inequality of care and ensure that access to treatment is improved for certain patient populations, such as elderly female patients with low educational and socioeconomic status.

PASI, the most frequently used clinical severity scale in clinical trials and drug approval, often depends on a 75% improvement in the baseline PASI score. In clinical trials, the mean baseline PASI is 20, whereas in real life it is closer to 12 or lower; therefore, the true success of psoriasis treatment seems to be under-represented. This discrepancy may relate to the way numerical values are assigned to the degree of body surface area involvement; thus, a better method to assess clinical improvement is needed.

Moreover, the relevance of baseline PASI diminishes with increasing duration of treatment, which implies that absolute PASI values are more appropriate to assess long-term response. Absolute PASI scores can be used where PASI 2 corresponds to a PASI 90, and a PASI 5 score, often considered the threshold for therapeutic adjustment or switching, corresponds to a PASI 75 or better response.[20]

Economics and Adherence

In the first year of treatment, some biologics carry a significant increase in their dose and, consequently, their cost. Therefore, it might be more sensible to switch to a drug that has a relatively small increment in the induction phase, rather than to others that might have a larger increment. Puig et al.[21] developed a decision tree with a 2-year time horizon to compare the cost consequence of biologic drugs for moderate-to-severe psoriasis from the perspective of the Spanish National Health System. Secukinumab monotherapy was found to be associated with the lowest cost per responder, followed by infliximab, and then ustekinumab.

Low adherence to therapies in psoriasis decreases treatment outcomes and increases total healthcare costs. Hsu and Gniadecki[22] surveyed patients' attitudes to treatment and measured adherence to biologics using the medication possession ratio index in a population of patients treated for psoriasis vulgaris. The medication possession ratio was calculated based on hospital records documenting the dispensing of biologics to patients, PASI, Dermatology Life Quality Index, presence of PsA, concomitant treatment, and cause for treatment discontinuation, all of which were obtained from DERMBIO. Patients' attitudes and beliefs were measured using the Medication Adherence Rating Scale. The authors found that adherence to biologics was very high, which is consistent with a positive attitude to treatment.

Factors Impacting Drug Survival

Biologic drug survival in psoriasis reflects long-term performance in real-life settings.[23] In economies where there is a need for sustainability, it is common practice to optimise the treatment dose by lengthening the dosing intervals for patients achieving PASI 90 and PASI 100. Sex, obesity, comorbidities, previous biologic exposure, and combination treatment are some of the variables that affect PASI response.[23] A retrospective, observational study on biologic drug survival in a real-life cohort of patients with moderate-to-severe chronic plaque psoriasis, found that cumulative probability of drug survival was lower in obese patients and significantly higher for ustekinumab than for any other biologic agent.[23] Multivariate analysis showed that obesity, etanercept treatment, and strict adherence to approved doses were associated with an increased probability of drug withdrawal, whereas ustekinumab treatment, and PASI 75 and PASI 90 responses at Week 16, prolonged drug survival.

Patients with Comorbidities

A 67-year-old male who has had psoriasis for 10 years, with no PsA, had a PASI of 16.4. The patient was obese, had unstable angina and hypertension, and eventually suffered a myocardial infarction. He had been subject to many treatments with no response; thus, the first treatment choice was an anti-TNF agent or methotrexate because both drugs are associated with a reduced rate of cardiovascular events. Cyclosporine should be avoided in this patient type due to the resulting increase in blood pressure and vascular resistance.

A 57-year-old woman with latent tuberculosis received adalimumab before starting on a efalizumab. After 22 months on adalimumab,

she presented with pneumonia. In elderly populations, and particularly vulnerable patients, a pneumococcal vaccine is prudent as these individuals are at a high risk of infection. A study by Dommasch et al.[24] examined the risks of infection and malignancy with the use of TNF antagonists in adult patients with psoriatic disease and found that there was a small increased risk of overall infection with the short-term use of TNF antagonists. Of reported infections, 97.6% were non-serious, and the large majority of these were upper respiratory tract infections.

A 67-year-old woman on infliximab acquired a left knee prosthesis infection, so her treatment was stopped. Following psoriasis relapse, she was started on ustekinumab and the infection was initially controlled with antibiotics. However, because her condition had become unstable and the prosthesis was replaced, a decision had to be made about the interruption of biologics prior to her operation. A study by Bakkour et al.[25] looked at the risk of postoperative complications in patients with psoriasis on biologic therapy undergoing surgical procedures. The authors reported that continuing biologic therapy in patients with psoriasis and PsA peri-operatively did not increase the risk of postoperative complications, and that interrupting biologic therapy peri-operatively significantly increased the risk of disease flare. There are currently very little data on the subject and for minor surgery. Some practitioners are stopping biologic therapy, which could have a detrimental effect on patients' psoriasis. However, for major surgery the risk of infection changes; therefore, stopping treatment should be considered and approached on a case-by-case basis.

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INTERLEUKIN-23 INHIBITION AS A STRATEGY TO TREAT IMMUNE-MEDIATED INFLAMMATORY DISEASES

This symposium took place on 1st December 2017 as part of the Psoriasis Gene to Clinic, 8th International Congress in London, UK

Speakers

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Disclosure: Prof Prinz is or has served as a consultant for Novartis, Pfizer, Janssen-Cilag, and Amgen, and has participated in speakers' bureaux meetings for Novartis, Pfizer, Abbott, Janssen-Cilag, MSD, and Amgen. Prof Danese is or has been a consultant, provided research support, or been a principal investigator, and participated in speakers' bureaux meetings for Abbvie, Allergan, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer, Sandoz, Tigenix, UCB Pharma, and Vifor.

Acknowledgements: Writing assistance was provided by Jane Grills, ApotheCom, London, UK.

Support: The publication of this article was funded by Janssen. The views and opinions expressed are those of the authors and not necessarily Janssen.

Citation: EMJ. 2018;3[1]:38-44.

MEETING SUMMARY

The satellite symposium comprised two short presentations aimed at providing an overview of the rationale for the use of interleukin (IL)-23 inhibition as a targeted strategy to treat immune-mediated inflammatory diseases. Presentations by Prof Prinz and Prof Danese focussed on psoriasis and inflammatory bowel disease, respectively, as examples of clinical indications in which the gene-to-clinic approach has led to the development and approval of biologic IL-23 inhibitors. In psoriasis the introduction of targeted anti-IL-17/IL-17 receptor A-chain (RA) and anti-IL-23 biologic therapies has provided a paradigm shift in the management of the disease, making complete clearance of disease a realistic aim for the first time. The use of IL-12/IL-23 inhibitors, such as ustekinumab, is now also possible in Crohn's disease (CD), providing another example of the successful translation of immunological targeting into clinical practice.

Interleukin-23 Inhibition as a Strategy to Treat Immune-Mediated Inflammatory Diseases: A Focus on Psoriasis

Professor Jörg Christoph Prinz

Effector T cells have evolved into different functional subsets, each with distinct physiological roles and signature cytokine profiles.[1-3] T helper 17 (Th17) cells are a functional lymphocyte subset that has developed to co-ordinate the immune response against bacterial and fungal infections and are characterised by the production of IL-17, IL-22, and interferon (IFN)-γ. As well as providing a key protective role in host immunity, Th17 can also have a pathogenic role in various autoimmune diseases, including systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease (IBD).[3] Specific and targeted inhibition of Th17-mediated immune pathways has therefore emerged as a highly effective treatment approach for psoriasis and IBD, with a number of biologic agents being developed and licensed for these indications.

Differentiation of Th17 cells from naïve cluster of differentiation 4-positive (CD4+) T cells occurs in three distinct stages.[4] Upon activation of T cells, transforming growth factor-β and IL-6 establish early commitment to the Th17 lineage by activating signal transducer and activator of transcription 3 (STAT3), which induces the expression of IL-21.

Cytokines	Source of cytokine	Receptor complexes	Expression of receptors
IL-17A IL-17F IL-17A/F heterodimer	• Th17 cells • NK T cells • CD8+ T cells • LTi cells • γδ T cells • NK cells • PMN cells (low concentration)	IL-17RA IL-17RC	Ubiquitous (higher in haematopoietic tissues) Most human tissues (preferentially on nonhaematopoietic tissues)
IL-17C	Epithelial cells (trachea, colon, skin)	IL-17RA IL-17RE	Ubiquitous (higher in haematopoitic tissues) Selectively induced in epithelia by bacterial, inflammatory stimuli
IL-17E	• Th2 cells • NK T cells • Alveolar MΦ • PMN cells (lower concentration)	IL-17RA IL-17RB	Ubiquitous (higher in haematopoietic tissues) Th2 cells, Th9 cells, fibroblasts, basophils, endocrine cells, kidney cells, and liver cells

Figure 1: Spectrum of targets for interleukin-17A and interleukin-17RA antibodies.[5-8]
IL: interleukin; LTi: lymphoid tissue inducer; MΦ: macrophages; NK: natural killer; PMN: polymorphonuclear leukocyte; R: receptor; Th: T helper.

Autocrine signalling by IL-21 then promotes STAT3-dependent expression of the master transcription factor for Th17 differentiation, retinoic acid receptor-related orphan receptor gamma t (RORγt), leading to the production and expression of IL-17A and the IL-23 receptor. This allows IL-23 to bind to and exert its effects on previously committed Th17 cells, stabilising the phenotype and expansion of Th17 cells, which secrete the effector cytokines IL-17A, IL-17F, IL-21, IL-22, and IL-26. The development of biologic agents that target the Th17 pathways has used several approaches. One approach is to inhibit the Th17 effector response, either by inhibiting the production of IL-17A/IL-17F using anti-IL-17 antibodies or by inhibiting the signalling of IL-17A/F through the blockade of the IL-17 receptor alpha chain. More recently, an alternative strategy has emerged: the inhibition of IL-23 using anti-IL-23 antibodies to interfere with the stabilisation and expansion of Th17 cells.

The IL-17 family consists of six cytokines (IL-17A–F), which signal through a family of heterodimeric IL-17 receptor complexes, i.e., receptors composed of two different chains. Receptors for IL-17A, IL-17F, IL-17C, and IL-17E are composed of the IL-17RA chain and one of three different other chains to form a functional receptor unit. The IL-17RA chain combines with the IL-17-RC chain for binding of IL-17A and IL-17F, with the IL-17RE chain for binding of IL-17C, and with the IL-17RB chain for binding of IL-17E (Figure 1).[6] Antibodies directed against IL-17A selectively neutralise IL-17A and the IL-17A/F heterodimer.[5,7,8] However, as the IL-17RA chain is part of several heterodimeric IL-17 chain receptors, blocking IL-17RA interferes with the signalling of most members of the IL-17 cytokine family, including IL-17C and IL-17E, and therefore IL-17RA blocking has a much broader effect. This broader inhibitory activity may explain the greater efficacy that has been observed with antibodies directed against the IL-17RA chain compared with those against IL-17A. This improvement in efficacy is exemplified by the comparative efficacy of brodalumab (an anti-IL-17RA antibody) and secukinumab (an anti-IL-17A antibody) in the treatment of chronic plaque psoriasis. Although no head-to-head clinical trials have been conducted, Phase III clinical data from the AMAGINE-2 and AMAGINE-3 (both brodalumab) and ERASURE (secukinumab) studies show that both treatments are highly effective in patients with plaque psoriasis, with approximately 80% of brodalumab-treated patients and 65% of secukinumab-treated patients becoming clear or almost clear of psoriasis.[9,10] However, a greater proportion of patients treated with brodalumab attained ≥75% improvement in Psoriasis Area Severity Index (PASI) 75, PASI 90, and PASI 100 responses as compared with secukinumab.[9,10] Importantly, the response can be maintained over time, which has been shown in

recently published data showing that psoriasis treatment with secukinumab is associated with sustained PASI responses through 3 years of treatment.[11]

An alternative approach to blocking the Th17/IL-17 effector response is to block the upstream cytokine IL-23. As mentioned previously, inhibition of IL-23 interferes with the stabilisation and expansion of Th17 cells without affecting the differentiation of Th17 populations and consequently IL-23 inhibition has regulatory effects on memory effector T cells (i.e., those involved in the pathogenic response), but not on naïve or central memory T cells.[4] Currently, clinical data are available for three IL-23 inhibitors in the treatment of psoriasis: tildrakizumab, guselkumab, and risankizumab. Although differences in the overall response to each of the IL-23 antibodies have been observed in clinical trials, blocking IL-23 appears to be highly efficacious. An improvement of >90% in PASI is realistic and clinical trials have reported that, at Week 12 or 16 (depending on the study), 12–14% of patients treated with tildrakizumab, 34–37% of patients treated with guselkumab, and 48% of patients treated with risankizumab achieved complete clearance of psoriasis (i.e., PASI 100 response).[12,13] Tildrakizumab seems to be associated with a slower initial clinical response, but the efficacy appears to 'catch-up' with the other IL-23 inhibitors over time, and 67–69% of patients achieve a Physicians' Global Assessment of 0 or 1 (indicating clear or almost clear of psoriasis) by 28 weeks.[12,13] However, it is important to note that these data are not from head-to-head comparisons of the IL-23 inhibitors and the outcomes reported for risankizumab are from a Phase II clinical trial. Clinically, the effect of blocking IL-23 has been shown to be superior to blocking tumour necrosis factor (TNF)-α.[14] The VOYAGE 1 trial, which compared guselkumab with the anti-TNF-α inhibitor adalimumab in patients with moderate-to-severe psoriasis, reported that specific interference with the maintenance of activation of Th17 cells via IL-23 inhibition achieved PASI 75, PASI 90, and PASI 100 responses in a significantly higher percentage of patients than did TNF-α blockade.[14]

Although blocking either IL-17 or IL-23 targets the same Th17 effector pathway, there is a difference in the effects of each of these approaches on the immune response.[15-18] Blocking IL-23 has been shown to be very effective in both psoriasis and CD, whereas anti-IL-17A or IL-17RA antibodies are highly effective for the treatment of psoriasis but may exacerbate CD in a subset of patients. This effect has been reproduced in a mouse model of colitis, in which IL-17 inhibition weakened intestinal epithelial barrier function and increased inflammation, while IL-23 inhibition enhanced regulatory T cell accumulation and attenuated inflammation. It is therefore important to be aware of this possibility because psoriasis and IBD are associated and can develop concurrently in some patients.

Comparison of the dosing regimens of the targeted biologic agents used in psoriasis highlights another interesting issue. Blocking the effector cytokines TNF-α and IL-17 requires more frequent and potentially higher doses of inhibitory antibodies than upstream interference with the regulation of Th17 activation through the inhibition of IL-23. Antibodies against TNF-α (adalimumab), IL-17 (secukinumab), and IL-17RA (brodalumab) have dose intervals of 2 or 4 weeks, while for anti-IL-23 antibodies (guselkumab, risankizumab) dosing intervals of up to 12 weeks are sufficient to maintain clinical response.[13,19-23] Adalimumab and guselkumab have similar serum half-lives (approximately 10–20 days);[19,23] however, achieving a sufficient response with adalimumab requires much more frequent dosing than with guselkumab. A 5 mg dose of guselkumab given four times over 40 weeks was sufficient to achieve a Physicians' Global Assessment of 0 or 1 in up to 40% of patients.[24,25] The differences are even more intriguing when the pharmacokinetics of guselkumab are examined. Although the mean serum concentration of guselkumab is almost zero 50 days after a 5 mg dose, a treatment response is maintained;[25,26] in other words, clinical efficacy outlasts the presence of the biologic inhibitor. From an immunological perspective, these data indicate that blocking effector cytokines, such as TNF-α, is associated with a different mechanism of action than the inhibition of IL-23; IL-23 antibodies appear to downregulate ongoing Th17 responses and provide disease control beyond the actual presence of active substance. This may be the major difference between blocking effector cytokines and blocking IL-23.

In summary, the extremely high clinical efficacy of IL-23 and IL-17 pathway inhibition has set a new standard for the treatment of plaque psoriasis and, for the first time, achieving complete clearance of disease has become a realistic treatment goal for many patients. Importantly, blocking IL-23 interferes

with the maintained activation of Th17 cells and Th17 differentiation, and preferentially regulates the memory effector cells involved in the pathogenic immune response. This is a different therapeutic pathway to inhibition of IL-17 or IL-17RA and long-term follow-up of the clinical effects of sustained IL-23 inhibition is required to assess potential safety benefits of IL-23 inhibition compared with direct inhibition of the IL-17 effector response.

Interleukin-23 Inhibition as a Strategy to Treat Immune-Mediated Inflammatory Diseases: Evidence from the Treatment of Inflammatory Bowel Disease

Professor Silvio Danese

Although the exact cause of IBD is not entirely understood, it is believed to involve a complex interaction between genes, the immune system, and environmental factors. Genetic susceptibility, the composition of the gut microbiome and an inappropriate immune response can all play a role in the development of IBD.[27] Indeed, genome-wide association studies have revealed major genetic variations in the IL-23 receptor and the IL-12 p40 subunit, both of which are involved in the immune inflammatory response in patients with CD and ulcerative colitis (UC). However, although there is a strong genetic susceptibility for IBD and >163 genetic associations for IBD have been identified, these account for <30% of all cases of IBD.[27] An inappropriate immune response is responsible for the development of IBD in the majority of patients and a targeted inhibition of key immune-mediated inflammatory pathways has emerged as a leading new therapeutic strategy. Among the plethora of potential lymphocyte and effector cytokine targets, T cells are the key drivers of the pathophysiology of IBD from early to late disease.[28] Although the immune pathways associated with IBD have many similarities with other autoimmune inflammatory diseases, such as psoriasis, there are patterns of cytokine-mediated pathology that are specific to IBD. Firstly, it must be noted that inhibition of effector cytokines in the Th17 pathway (e.g., with anti-IL-17A antibodies) can exacerbate inflammation in some patients with CD, as Prof Prinz explained previously, and this is important to remember when using such biologics in the clinic. With regard to the immunopathology of IBD, there is clinical evidence that shows upregulation of IL-12 occurs in patients with early CD compared with those who have UC or healthy controls.[29,30] Upregulation of IL-23 then occurs once CD is established.[30,31] A study in mice has shown that IL-12 continues to contribute to chronic intestinal inflammation during established colitis and consequently IL-12 has been identified as a key therapeutic target.[32] Additionally, experimental colitis models have shown that treatment with anti-IL-23 antibodies attenuated extensive inflammation in both the caecum and colon, and reduced inflammatory infiltrates and epithelial hyperplasia.[33] IL-23 inhibition has therefore also been identified as a key target for targeted biologic treatment in CD.

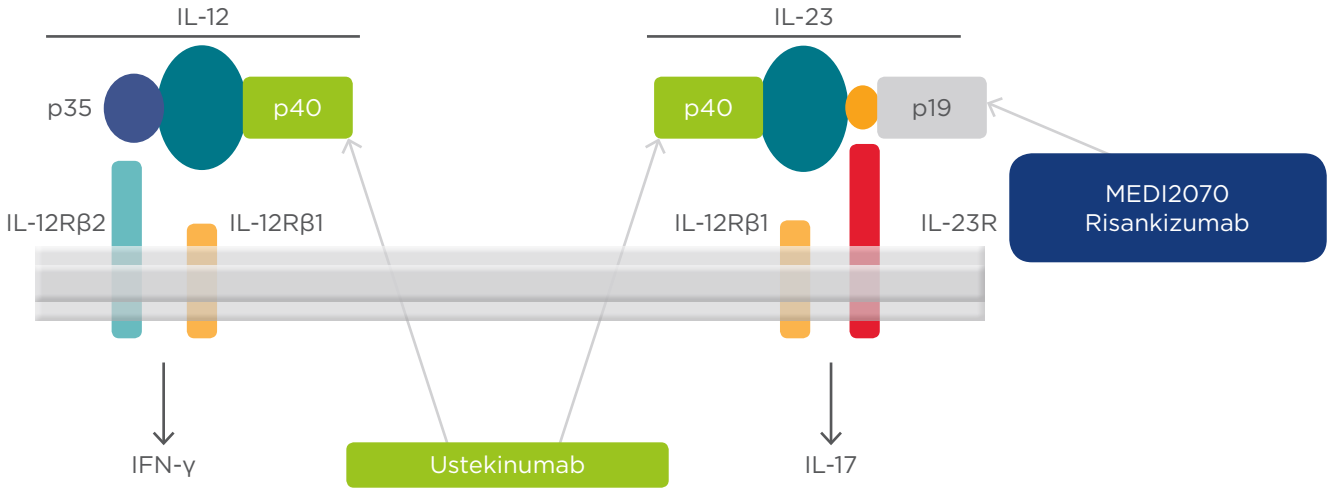

Figure 2: Targets for interleukin-12 and interleukin-23 inhibition in Crohn's disease.
IFN: interferon; IL: interleukin; R: receptor.

Table 1: Response to ustekinumab in patients with Crohn's disease who have previously failed anti-tumour necrosis factor-α or conventional treatment (Week 6).[34,35]

Treatment group	Proportion of patients (%)	p value versus placebo
UNITI-1 TNF antagonist failure		
Placebo (n=247)	21.5	NA
130 mg (n=245)	34.3	0.002
˜6 mg/kg (n=249)	33.7	0.003
Combined (n=494)	34.0	<0.001
UNITI-2 Failed conventional treatment		
Placebo (n=209)	28.7	NA
130 mg (n=209)	51.7	<0.001
˜6 mg/kg (n=209)	55.5	<0.001
Combined (n=418)	53.6	<0.001

NA: not applicable; TNF: tumour necrosis factor.

A number of biologic treatments are being developed for targeted inhibition of IL-12 and IL-23 in patients with CD (Figure 2). Ustekinumab, the first such biologic to be approved for the treatment of CD, targets the p40 subunit that is present on both IL-12 and IL-23. Risankizumab is another biologic that is in clinical development and targets the p19 subunit, which is present on IL-23 but not on IL-12 (Figure 2).

Phase III clinical data have shown that the approved dose of ustekinumab, 6 mg/kg, was associated with a clinical response in a significantly higher proportion of patients than placebo in both patients who had previously failed treatment with anti-TNF-α and those who had previously failed conventional treatment (Table 1).[34] Maintenance treatment with ustekinumab has also been shown to be effective in maintaining clinical remission in CD, administered as a subcutaneous dose of 90 mg either every 12 weeks or every 8 weeks.[35] Similar clinical data are emerging for risankizumab, which is currently in clinical development and awaiting approval for the treatment of CD.

To conclude, the development of IL-12 and IL-23 targeted inhibitors is a classic example of the gene-to-clinic approach, providing an effective, novel therapeutic strategy in CD. Clinical studies are ongoing to evaluate the efficacy of IL-12 and IL-23 inhibitors for the treatment of UC, and the publication of the clinical data is eagerly awaited.

Question and Answer Session

Q: In dermatology, when you clear a lesion with a systemic drug there is usually one lesion that stands out and recurs, and that recurrent lesion is frequently the very first lesion that the patient had. This could be a residual lesion that is somehow different to the rest of the skin lesions; do you see that in UC as well, or in IBD?

A: Prof Danese replied that this is a great point and is also seen in patients with CD. For example, when a patient with CD is given an anti-TNF-α drug, healing is observed in the ileum but not in the rectum, and treatment with two drugs is needed because the disease is driven by different mechanisms of action in the different sites. Currently, we have little understanding of zonal gene expression and the mechanisms that drive inflammation in the gut, and this should be the focus of research efforts to understand the differences between different disease sites and locations in order to determine effective drug treatment combinations. Prof Prinz also commented that in dermatologic indications there appears to be a residual scar or residual lesion that is characterised by a greater tendency to restart inflammation, potentially due to low levels of residual inflammation.

Q: As alluded to in the symposium, there are patients who have CD and develop paradoxical psoriasis, and patients with psoriasis who develop

CD. Do you have any insights into the genetics, the immunology, and the management of those patients?

A: Prof Danese replied that, at present, although the clinical characteristics of these patients have now been elucidated, as yet nothing is known about the underlying genetics in such cases. We only know that the disease is somehow driven, again, by IL-23 and that these patients respond very well to ustekinumab treatment.

Click here to view the full symposium.

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MISSION: RAPID ACTION AND LASTING REMISSION: A FOCUS ON DISEASE PROGRESSION IN ULCERATIVE COLITIS

This symposium took place on 29th October 2017, as part of the 25th United European Gastroenterology (UEG) Week in Barcelona, Spain

Chairperson

William J. Sandborn[1]

Speakers

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Disclosure: Dr Sandborn has received research grant support and consultation fees from Takeda, Genentech, Pfizer, Amgen, Janssen, AbbVie, and UCB Pharma. Dr D'Haens has received consultation fees and/or research grant support from AbbVie, Ablynx, Amakem, Amgen, AM Pharma, Avaxia, Biogen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene/Receptos, Celltrion, Cosmo, Covidien/Medtronics, Ferring, DrFALK Pharma, Eli Lilly and Company, Engene, Galapagos, Genentech/Roche, Gilead, GlaxoSmithKline, Immunic, Johnson & Johnson, Lycera, Medimetrics, Millenium/Takeda, Mitsubishi Pharma, MSD, Mundipharma, Nextbiotics, Norgine, Novo Nordisk, Otsuka, Pfizer/Hospira, Prometheus Laboratories/Nestlé, Protagonist, Robarts Clinical Trials, Salix, Samsung Bioepis, Shire, Sandoz, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant, and Vifor. Dr Panaccione has received research grant support and/or consultant fees from AbbVie, Abbott, Amgen, Aptalis, AstraZeneca, Baxter, Eisai, Ferring, Janssen, Merck, Schering-Plough, Shire, Centocor, Elan, GlaxoSmithKline, UCB, Pfizer, Bristol-Myers Squibb, Warner Chilcott, Cubist, Celgene, Gilead Sciences, and Takeda Pharmaceuticals, and fees for participating in a speaker's bureau or advisory board from Genentech, Proctor & Gamble, Prometheus, Millennium, and Salix.
Acknowledgements: Writing assistance was provided by Michela Siberry, ApotheCom, London, UK.
Disclaimer: The primary objective of the GEMINI LTS study was to evaluate the long-term safety profile of vedolizumab. Vedolizumab was administered every 4 weeks (Q4W) in the GEMINI long-term safety study as per study protocol. Please refer to full prescription information. Increases to Q4W dosing are recommended in patients who experience a decrease in their response.
Support: The publication of this article was funded by Takeda. The views and opinions expressed are those of the authors and not necessarily those of Takeda.
Citation: EMJ. 2018;3[1]:45-51.

MEETING SUMMARY

Do flares of ulcerative colitis (UC) cause long-term bowel damage? Dr Sandborn opened the symposium by challenging the audience to think about their mindset regarding this question, as this may significantly influence therapeutic decisions. He then presented data showing the chronic, progressive nature of UC and argued that early appropriate therapy may slow disease progression. Dr D'Haens followed by describing the hurdles in achieving early and long-lasting remission in UC, like the delayed or suboptimal use of biologics. He also introduced strategies to overcome these hurdles, such as early intervention and treat-to-target. Dr Panaccione reviewed clinical trial and real-world data from current treatment options, specifically gut selective treatment, in the context of which outcomes patients value most.

Mission Assigned: Rapid Onset and Lasting Remission in Ulcerative Colitis

Doctor William J. Sandborn

Does Ulcerative Colitis Cause Long-Term Bowel Damage?

UC is still considered by many physicians as a benign disease that does not lead to long-term damage. To refute this, Dr Sandborn presented accumulating data on the progressive nature of UC. Using the example of the IBSEN study,[1] a cohort of 423 patients with UC in Norway, diagnosed between 1990 and 1994 and systematically followed up for up to 10 years, he showed that an unfavourable disease course was observed in nearly 50% of patients: 37% followed a relapsing and remitting disease course, 6% had a chronic active disease course, and 1% experienced an increase in the intensity of their symptoms. He concluded that those patients who experienced an unfavourable disease course were, in his opinion, insufficiently treated.

Measures for the Progression of Ulcerative Colitis

The progression of UC has been measured in various studies against different outcomes, including proximal disease extension, colectomy, hospitalisation, colorectal cancer, and bowel damage. In a Swiss inflammatory bowel disease (IBD) cohort[2] of 918 patients with UC, proximal disease extension occurred in around 15% of patients over a median disease duration of 9 years. When measuring disease progression by the need for surgery, data from the IBSEN study[1] showed colectomy rates of around 10% in UC patients during the first 10 years following diagnosis. According to a review of various population-based cohort studies, hospitalisation occurs in around 50% of UC patients at some point during their disease course, which increases over time from 17–29% in the first year, to 29–54% within 5 years, and up to 66% in 10 years.[3] A Danish nationwide cohort study of patients with UC demonstrated that the relative risk of colorectal cancer is significantly increased after 8–9 years of disease compared with the general population.[4] Patients at significant risk are those who have failed to achieve endoscopic or histologic remission, those with extensive and long duration pancolonic disease, and those with concomitant primary sclerosing cholangitis.[4]

Although it is known that UC is progressive in nature, how to measure disease progression in individual patients remains an open question. In terms of morphological progression, unlike in Crohn's disease (CD), UC is not typically accompanied by strictures and fistulising complications.[5] In UC, mucosal appearance does not represent the total disease burden, since a disconnect occurs between endoscopic healing, resolution of acute inflammation, and the persistence of disabling symptoms.[6] In summary, further research is needed to better understand the long-term functional consequences of UC, including comparing effective with ineffective inflammation control over long periods of time.[5]

Early Improvements: Better Long-Term Outcomes

Studies show that early endoscopic improvements can predict better long-term outcomes for patients with UC. A study of 157 newly diagnosed patients with UC receiving their first course of steroids, followed up over 5 years, demonstrated that patients in complete clinical and endoscopic remission after 3 months had a very low colectomy rate or need for immunosuppressive therapy, as well as a significantly reduced risk of relapse and hospitalisation compared with patients not achieving complete remission.[7] Furthermore, a subanalysis of the infliximab ACT I and ACT II trials showed that a Week 8 Mayo endoscopy subscore of 0 or 1 (indicating mucosal healing) versus a score of 2 or 3 (indicating moderate or severe disease) predicted a significantly reduced rate of colectomy or need for rescue therapy.[8]

Early Intensive Treatment: Which Patients Can Profit?

Findings from CD studies show that early intensive treatment in some patients may be needed for optimal disease control. The CALM study[9] demonstrated that early, intensive control with treatment in response to predefined targets including biomarkers (a treat-to-target approach), rather than only clinical symptoms, resulted in more patients achieving remission. Early intensive treatment should be personalised in UC and may not be necessary for all patients. It is therefore necessary to identify patients who may benefit from early intensive treatment. To guide the initiation of appropriate treatment in the right patients at the right time, we need a global evaluation of overall disease severity. The International Organisation for the Study of Inflammatory Bowel Disease (IOIBD) recently proposed a UC disease severity index providing a global disease severity evaluation to guide appropriate treatment initiation.[10]

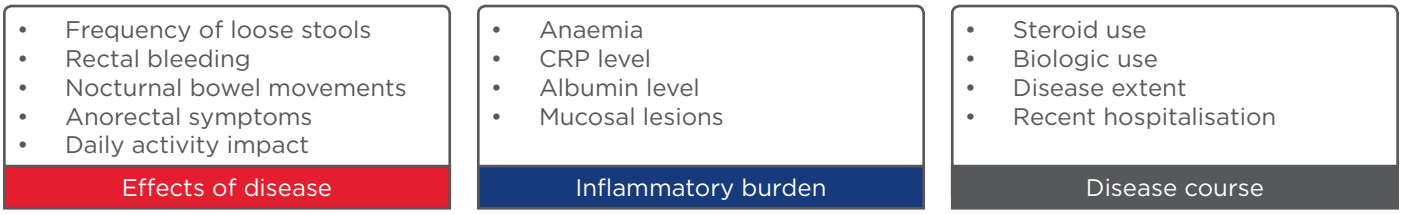

Figure 1: The International Organisation for the Study of Inflammatory Bowel Disease (IOIBD): Ulcerative colitis overall disease severity index.
CRP: C-reactive protein.
Adapted from Siegel et al.[10]

The disease course, effects of the disease on the patient, and inflammatory burden are taken into account to assess the overall disease severity (Figure 1).[10] A treatment strategy should also consider patients' perceptions of their disease and treatment preferences.[11]

Mission Assessed: Challenges and Strategies to Achieve Early, Lasting Remission

Doctor Geert D'Haens

Why Do We Not Achieve Long-Lasting Remission in all Ulcerative Colitis Patients?

Not all patients with UC achieve early and lasting remission. This may be due to patients underestimating their disease activity, the inappropriate use of conventional therapy, and the delayed or suboptimal use of biologic therapy. A small survey comparing clinical or endoscopic remission with patient perceptions showed that patients with UC may underestimate their disease activity.[12] A larger USA survey of 451 patients with UC and 300 gastroenterologists also showed discrepancies between patients' responses and physicians' assessments.[13] The UC CARES study[11] evaluated symptoms in 150 patients with moderate-to-severe UC receiving conventional therapies, and concluded unsatisfactory disease control (based on the number of daily stools and rectal bleeding) in over half of the patients. Patient quality of life was closely associated with unsatisfactory disease control, with overall work and activity impairment increasing with disease severity and even affecting patients in remission.[12]

An Inappropriate Treatment Choice?

The majority of patients with UC are still treated with conventional treatment (5-aminosalicyclic acid, corticosteroids, and immunosuppressants)[14] and only a minority will eventually receive a biologic. Compared with CD, in patients with UC, physicians may be waiting too long to initiate biologic therapies; at the end of the first year following diagnosis, around 5% of patients with UC have received biologic therapy compared with 10–15% of patients with CD, according to epidemiologic data published in 2015.[15]

More recent data from an American insurance database showed the use of biologics between 2008 and 2016 in 6% of patients with UC (n=28,120) and 19% of patients with CD (n=16,260).[16] Coupled with low uptake, biologics may also be used suboptimally. A USA insurance claims-based survey of 1,699 patients with UC receiving anti-tumour necrosis factor (TNF) treatment between 2005 and 2013 showed suboptimal use among 51% of patients within 6 months, and 91% of patients within 3 years. Drug switching, adding combination treatment, dose escalation, and discontinuations due to adverse events (AE) were used to identify suboptimal use of biologics.[17]

Strategies to Achieve Early, Lasting Remission

A number of strategies can be employed to achieve early, lasting remission (Figure 2);[18] these include early intervention, treating to target, tight control monitoring, and individualised treatment.

Early intervention

A meta-analysis of 2,073 patients with UC showed that early mucosal healing was associated with improved long-term outcomes. Mucosal healing at the first endoscopic evaluation after initiation of

therapy (compared with no mucosal healing) was 4.5-times more likely to lead to long-term clinical remission, and about 10-times more likely to lead to long-term steroid-free clinical remission.[19]

Further data supporting that early intervention may be associated with greater clinical response comes from the GEMINI 1 trial.[20] Patients with UC with ≥1 but <3 years disease duration were more likely to have a clinical response to vedolizumab at Week 6 than those with a disease duration of ≥3 but <7 years (difference from placebo: 30.1% versus 18.5%).[20]

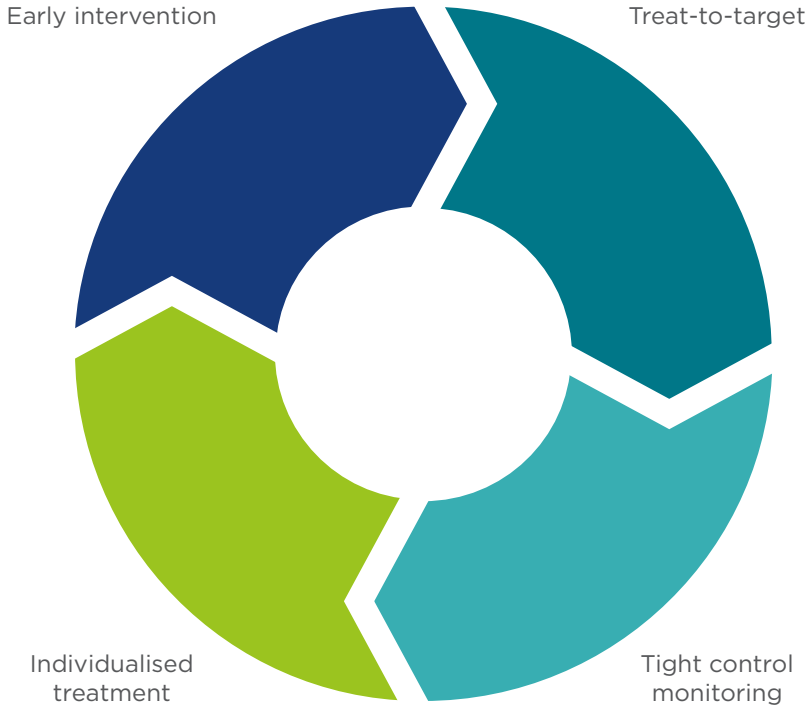

Figure 2: Clinical strategies associated with improved long-term outcomes.
Adapted from Colombel et al.[18]

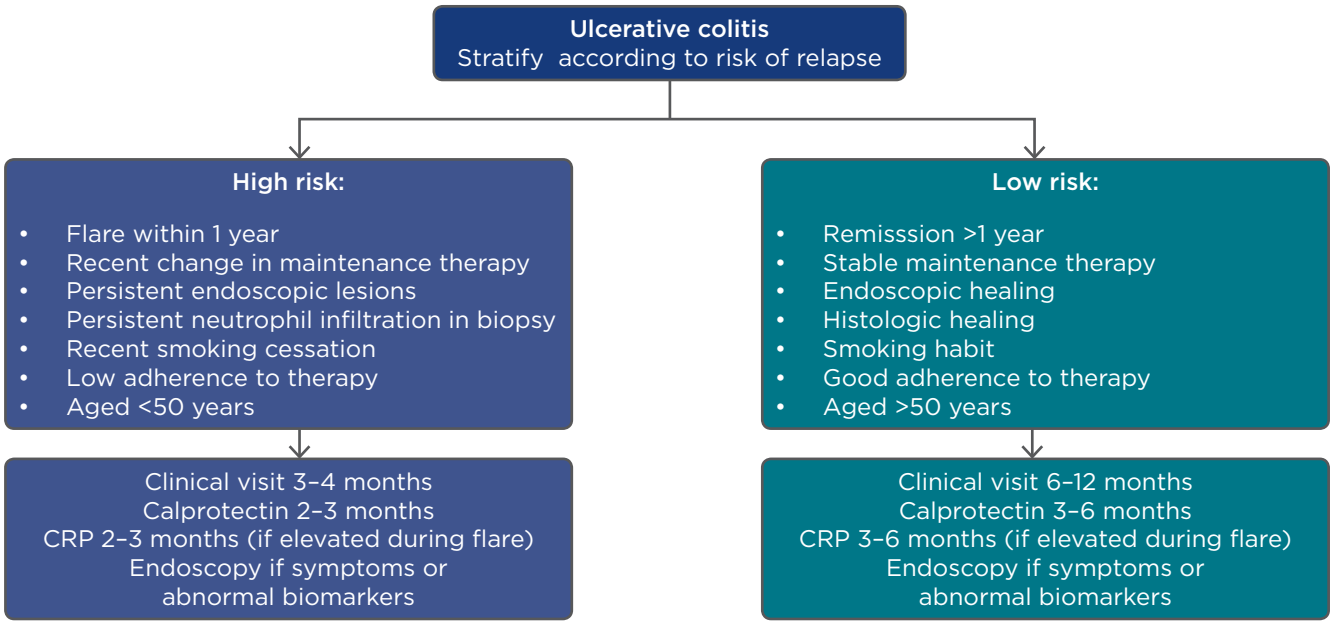

Figure 3: A proposed algorithm for individualising ulcerative colitis patient management.
CRP: C-reactive protein.
Adapted from Panes et al.[28]

Treat-to-target

Treat-to-target is a concept used widely in the management of chronic diseases, such as rheumatoid arthritis,[21] hypertension,[22] and diabetes.[23] The IOIBD concept, Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE), defines a composite of two targets for UC treatment: clinical remission, defined as resolution of rectal bleeding and normalisation of bowel habit, and endoscopic remission, defined as a Mayo endoscopic subscore of 0 or 1.[24] Clinical remission should be assessed every 3 months until symptom resolution and every 6–12 months thereafter. Endoscopic outcome should be assessed 3–6 months after the start of therapy for a patient with symptoms.[18,24]

The feasibility of a treat-to-target strategy in clinical practice was tested among UC patients at the University of California, Oakland, California, USA, from 2011 to 2012. Proactive interventions, such as adjustments to medical therapy performed continuously over 80 weeks, resulted in 80% of patients reaching the target, compared with 30% of patients who had few or no interventions.[25] Challenges with applying treat-to-target to clinical practice include a lack of data showing the effect on long-term disease modification, the evolution or inclusion of additional targets like histologic healing, potential overtreatment of low-risk patients, and proof of cost-effectiveness.[18] Patients may be reluctant to follow their physicians' advice and recommendations because they are fearful of complications, or they may be in denial about the severity of their disease. Patient education and a physician–patient shared decision is important when undertaking a treat-to-target approach.[26]

Tight control and monitoring

After achieving the target, tight control and monitoring are essential to obtain objective information on disease activity by monitoring symptoms, performing endoscopy, and measuring biomarkers to determine whether treatment adjustments are needed.[27] A proposed algorithm for monitoring UC stratifies patients according to high or low risk of relapse and, in conjunction with biological markers, helps support the most appropriate treatment choice (Figure 3).[28] Incorporating predictive tools into this algorithm, such as proteomics, genomics, or serologic markers that predict response to therapy, would enable further personalised treatment selection.[18]

Mission: Remission: Optimising Rapid Onset and Long-Term Outcomes with Gut-Selective Therapy

Doctor Remo Panaccione

Treatment Goals for Patients and Physicians

Physicians have different treatment goals to patients. For example, physicians aim to induce and maintain remission, and ultimately avoid complications, whereas patients want fast and sustained symptom relief with minimal side effects. Two commonly prescribed classes of biologic therapies approved for the treatment of moderate-to-severe UC are anti-TNF-α agents, which work systemically, and the gut-selective anti-α4β7 integrin, vedolizumab.[29-32] Anti-TNF-α agents revolutionised treatment of UC with early remission rates reaching up to around 40% and Week 54 rates up to 35%.[33-36] While generally safe, the TREAT registry of 5,394 patients with CD followed up over 5 years demonstrated an increased risk of serious infection in patients with moderate-to-severe disease and identified infliximab treatment as an independent risk factor.[37] The European Crohn's and Colitis Organisation (ECCO) consensus guidelines recommend particular care to be taken to consider serious infection as a complication of immunosuppressive therapy, including anti-TNF-α therapy.[38]

How Does Gut-Selective Treatment Meet the Goals?

A number of gut-selective biologics are in development.[39] Vedolizumab is currently the only gut-selective anti-α4β7 integrin biologic with marketing authorisation for the treatment of moderate-to-severe UC. Rapid onset of action with vedolizumab has been reported in a post-hoc analysis of the GEMINI 1 trial data. Within 2 weeks of starting therapy, 30.8% of anti-TNF-α naïve patients with moderate-to-severe UC achieved complete resolution of rectal bleeding (versus 18.4% with placebo), and 44.6% of patients achieved a stool frequency subscore of ≤1 (versus 22.4% with placebo).[40] The proportion of patients receiving vedolizumab who achieved these outcomes continued to increase between 2 and 6 weeks.[40] The same trend is seen in the overall population, including patients with previous anti-TNF-α experience.[40] Emerging evidence for early symptomatic improvement with the investigational anti-αEβ7 integrin, etrolizumab, showed rectal bleeding remission in approximately 20–25% of

patients with anti-TNF-α refractory UC by Week 2 and about 40% of patients by Week 4.[41]

A further important endpoint has been analysed in another GEMINI 1 post-hoc analysis; mucosal healing, measured as a Mayo endoscopic subscore of ≤1, was achieved in almost half of the anti-TNF-α naïve patients as early as Week 6 (versus 25% with placebo), increasing to 60% by Week 52 (versus 24.1% with placebo). Improvements were also observed in anti-TNF-α failure patients but not to the same extent.[42]

These study data are complemented by real-world data from the US VICTORY Consortium;[43] 12-month real-world data showed that 77% of patients with UC receiving vedolizumab treatment achieved a Mayo endoscopic subscore of 0 or 1 at 12 months, with 53% of patients achieving a score of 0. Mucosal healing was similar among patients who were anti-TNF-α naïve or had one prior anti-TNF-α therapy.[43] However, markedly fewer patients achieved either of these endpoints if they had previously received ≥2 anti-TNF-α therapies.[44]

Data on lasting clinical remission with vedolizumab can be derived from the GEMINI LTS cohort (see disclaimer). Of the patients who received vedolizumab induction and maintenance to Week 52 in GEMINI 1, followed by vedolizumab every 4 weeks in the open-label extension study, and had data available at around 5 years (n=63), 98% had a clinical response and 90% were in clinical remission.[45]

Vedolizumab Safety Profile

When considering long-term treatment, the safety profile of a drug is as important to the patient as its efficacy. The favourable safety and tolerability profile of vedolizumab has been confirmed by assessment of an integrated safety data analysis from >4,000 patient-years of vedolizumab exposure in IBD clinical trials.[46,47] Low exposure-adjusted incidence rates for infections and no cases of progressive multifocal leukoencephalopathy have been reported.[46-48] Real-world safety data from 2,857 vedolizumab-treated patients in 33 studies have been pooled and evaluated; the AE rate was consistent with that reported in the GEMINI programme, with low rates of serious AE, infections, and serious infections,[48] reassuring patients and physicians that real-world clinical practice reflects outcomes recorded in clinical trials. As of August 2017, vedolizumab has 143,127 patient-years of post-marketing exposure worldwide.

In summary, treatment options are continuing to improve for IBD and UC, allowing physicians to better gauge patient values when choosing a therapy. Optimal use of biologic therapy will help patients achieve treatment targets of early and lasting remission. Systemic anti-TNF medications are effective in some patients and generally safe, but disease control can be limited[33-36] and some safety issues remain.[37,38]

Early symptomatic improvement, long-lasting maintenance of clinical and endoscopic remission, and a favourable long-term safety profile make vedolizumab a suitable agent for both early and long-term treatment of UC.

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TARGETING MUCOSAL HEALING: OPTIMISING RESULTS WITH EARLY APPROPRIATE THERAPY IN CROHN'S DISEASE

This symposium took place on 30th October 2017, as part of the 25th United European Gastroenterology (UEG) Week in Barcelona, Spain

Chairperson

Julián Panés[1]

Speakers

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Disclosure: Prof Panés has received consulting fees from AbbVie, Amgen, Boehringer-Ingelheim, Genentech (Roche), Janssen, Oppilan, Pfizer, Robarts, Takeda, Theravance, and TiGenix, and speaker fees from AbbVie, Biogen, Celtrion, Ferring, Janssen, and MSD. Prof Peyrin-Biroulet has received consulting fees from Merck, AbbVie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor Pharma, Pharmacosmos, BMS, UCB, Hospira, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Eli Lilly and Company, Pfizer, HAC Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, and Samsung Bioepis, and lecture fees from Merck, AbbVie, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Mitsubishi, and HAC Pharma. Prof Lees has received research support from AbbVie and Shire, and has acted as a consultant to AbbVie, MSD, Hospira, Pharmacosmos, Takeda, Vifor Pharma, Dr Falk Pharma, he has also received speaking fees and travel support from Pfizer, AbbVie, MSD, Takeda, Shire, Ferring, Hospira, Warner-Chilcott, and Dr Falk Pharma.
Acknowledgements: Writing assistance was provided by Ellie Miller, ApotheCom, London, UK.
Support: The publication of this article was funded by Takeda. The views and opinions expressed are those of the authors and not necessarily those of Takeda.
Disclaimer: The primary objective of the GEMINI LTS study was to evaluate the long-term safety profile of vedolizumab. Vedolizumab was administered every 4 weeks in the GEMINI LTS study as per study protocol. Please refer to full prescription information. Increasing dose frequency to every 4 weeks is recommended in patients who experience a decrease in their response (Entyvio SmPC).[1]
Citation: EMJ. 2018;3[1]:52-57.

MEETING SUMMARY

Given the progressive nature of Crohn's disease (CD), Prof Panés made a case for timely intervention in at-risk patients to achieve the ultimate goal of slowing disease progression. Prof Peyrin-Biroulet looked at the more recent treatment target of endoscopic healing and reviewed the positives and negatives of the current endoscopic indices to measure disease activity. Prof Lees then provided an overview of the clinical trial programme and real-world data of vedolizumab, a gut-selective α4β7 integrin inhibitor.

The Case for Early Intervention in Crohn's Disease

Professor Julián Panés

Aiming to Stop Disease Progression: What is the Right Target?

CD is progressive in nature and so, to avoid irreversible damage and achieve the ultimate goal of slowing down disease advancement, timely intervention is considered essential.[2,3] Mucosal healing can be used as a surrogate target for slowing disease progression, as shown by evidence from a Norwegian population cohort of CD patients.[4] This study highlighted that mucosal

healing after 1 year of treatment was associated with a decreased risk of surgery in subsequent years, compared with patients who had not achieved mucosal healing after 1 year.[4] Therefore, once mucosal healing is achieved, the risk of disease progression and the requirement for surgery should be significantly reduced, resulting in a more benign disease course, as Prof Panés explained.

However, mucosal healing in CD may not always be sufficient in Prof Panés' opinion. A study in Barcelona, Spain, aimed to evaluate the use of colonoscopy compared to magnetic resonance imaging (MRI) as a predictor of the need for resection surgery in patients with CD.[5] The results showed that severe endoscopic lesions did not serve as a predictor of resection surgery, whereas transmural lesions in the form of stenosis or intra-abdominal fistulas at MRI were associated with an increased risk of surgery in patients with CD.[5] Therefore, transmural healing in CD might be more important than mucosal healing. The evidence from this study contributed to the evolution of therapeutic goals in CD, which, in Prof Panés' opinion, should include transmural healing.

Optimising Treatment with Current Therapies

Focussing on treatment options, early intervention in CD with biologic-based therapy has been shown to improve patient outcomes. The REACT study[6] demonstrated that patients who underwent earlier intervention with combined immunosuppression including an anti-tumour necrosis factor alpha (TNF-α) agent required less hospitalisation, less surgery, and had fewer complications than those who underwent conventional management. Prof Panés therefore emphasised that it is possible to optimise the use of current therapies to achieve better results for patients.

Treatment and therapeutic targets should also be individualised to the characteristics of the patient and the stage of the disease; in patients with milder forms of the disease who have not developed complications such as strictures or fistulas, a step-up approach may be the most appropriate to avoid intensive therapy and the adverse events associated with it. On the other hand, in patients with more progressive forms of the disease, early intensive therapy may be more effective in reducing complications and the need for surgical intervention.

Close-Up on Endoscopic Healing as a Treatment Goal: What Do We Need to Know?

Professor Laurent Peyrin-Biroulet

Target Definitions Used in Clinical Trials

To define appropriate treatment targets for CD, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative came to the evidence-based consensus that a combination of clinical remission and endoscopic remission should be the target. Clinical remission is defined as the resolution of abdominal pain and normalisation of bowel habits, while endoscopic remission is defined as the absence of ulceration at ileocolonoscopy. When endoscopy cannot adequately evaluate the inflammation, the resolution of inflammation as assessed by cross-sectional imaging is a target.[2,3]

The definition of endoscopic healing in CD trials has evolved in recent years. Until 2009, endoscopic healing was determined by a physician's assessment using empirical definitions describing ulcers, erythema, or pseudopolyps. The definition then evolved to the absence of ulceration. Although this is now widely used as a primary endpoint in randomised controlled trials,[7] there are limitations to this definition because it does not account for remaining lesions, such as erosion, erythema, or oedema, and it is not sensitive to degrees of change.[7]

Scores for Measuring Disease Activity

To standardise clinical practice, an objective scoring system is needed that is practical in the real world. Endoscopic scoring systems have been developed to evaluate disease activity, including the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's Disease (SES-CD); however, their usefulness has not been fully assessed.

The CDEIS score was the first validated endoscopic score for CD. Preselected lesions were recorded on a standard form in different segments of the colon. Stepwise multiple regression was then performed to create an index that correlated with the endoscopist's estimate of lesion severity. This index was shown to be valid in subsequent studies and is therefore useful for those endoscopists who are aware of the data collection procedure in the follow-up of patients, especially in clinical trials.[8]

The SES-CD was developed later to be a more practical and simple alternative to the CDEIS score,

and included only characteristics that contribute to symptomatology, such as scores for ulcer size, ulcerated surface, affected surface, and luminal narrowing.[9] The CDEIS score is still regarded as the gold standard and is moderately responsive to changes in endoscopic disease activity;[10] however, the SES-CD is simpler than CDEIS[10] and may have a greater responsiveness to change in disease activity.[11] Both CDEIS and SES-CD are suitable for central reading in clinical trials.[7]

What is the Right Target to Predict Patient Outcome?

Today, many CD trials use different arbitrary and unvalidated definitions of endoscopic healing and/or response. A French study found that when the strict definition of mucosal healing (CDEIS=0) was achieved, it was associated with better clinical outcomes, including a lower risk of relapse and intestinal resection.[12] However, it is hard to achieve a CDEIS score of zero with drugs that are currently available. This was highlighted by the CALM study,[13] an open-label, multicentre study that evaluated two different treatment algorithms in patients with moderate-to-severe CD, with one tight control treat-to-target arm and one conventional clinical management arm that mirrored the treatment in clinical practice at the time the study was designed. The results showed that the percentage of patients on the treat-to-target approach who achieved complete endoscopic remission, defined as CDEIS=0, was lower (18%) than those who achieved endoscopic remission (46%), defined as CDEIS <4.[13]

During the induction phase of treatment, endoscopic response as a treatment goal is a valid predictor for patient outcomes, whereas the goal of endoscopic remission is more important during follow-up with the patient. A post-hoc analysis of the SONIC study[14] of biologic and immunomodulator-naïve patients in CD aimed to determine the best definition for endoscopic response on the SES-CD and CDEIS indices. It was found that endoscopic response, defined by a decrease from baseline in SES-CD or CDEIS of ≥50% at Week 26, was useful to predict the number of patients in corticosteroid-free clinical remission at Week 50.[14]

To standardise the practice, the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) recommend an endoscopic response definition of >50% decrease in SES-CD or CDEIS, and an endoscopic remission definition of a SES-CD score of 0–2.[7] However, both the endoscopic response and endoscopic remission definitions require prospective testing in CD trials.[7]

Usage of Scores and Targets in Clinical Practice

In contrast to randomised controlled trials, in clinical practice endoscopy scores are often not used for patients with CD because clinical activity is regarded as more relevant for gastroenterologists to base their therapeutic decisions on.[15] This was confirmed by the results from a survey that gathered data on the management of inflammatory bowel disease (IBD) and showed that endoscopic scores are only used in 11% of patients with CD.[16] In conclusion, it is important to establish an objective scoring system to measure endoscopic healing. The CDEIS or SES-CD indices have enabled results to be compared across studies and the effort should be continued to standardise the practice using clear definitions of endoscopic response and mucosal healing. For real-world practice, disease management needs to be based on an objective scoring system and, by improving endoscopic reports and using the CDEIS score or the SES-CD, this could be achieved in the future.

Meeting Evolving Treatment Goals with Gut-Selective Therapy

Professor Charlie Lees

How to Meet the Targets with Current Therapeutic Options

Following the previous talk on how to define and measure treatment targets, Prof Lees focussed on how these targets could be met with currently available therapies. He reminded the audience that CD is characterised by periods of flares and periods of remission, and that the periods of flares can result in accumulation of bowel damage as the disease evolves over time.[17] This leaves a window of opportunity to achieve the best results for patients when treating early in the disease course. When treating patients to the predefined targets, it is important to keep value-based healthcare in mind to achieve cost-effective solutions. Prof Lees argued that the only way to control rising costs is to strive to improve patient outcomes efficiently, which requires investment in quality of care that is safe, appropriate, and effective.[18]

Important data showing the benefit of a treat-to-target algorithm came from the CALM trial.[13]

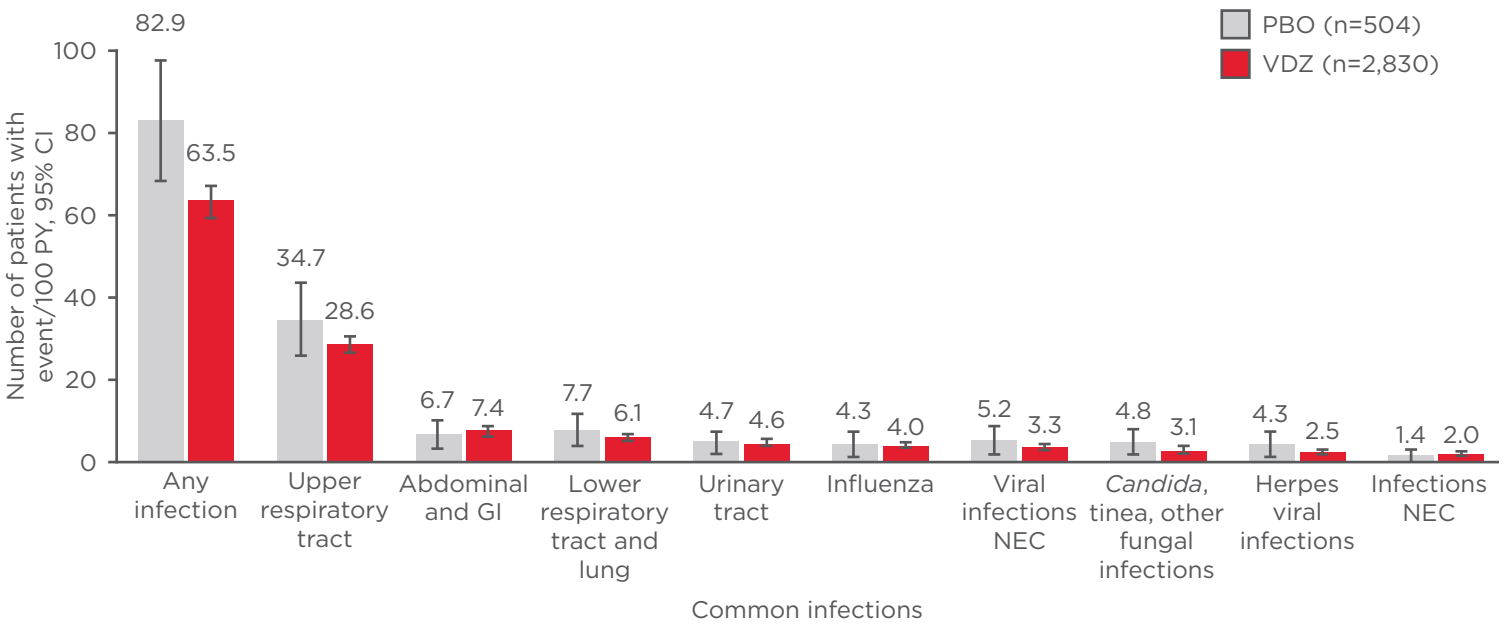

Figure 1: Data pooled from six trials (total exposure: 4,811 patient-years) show that there was no increase in adverse events in those patients treated with vedolizumab versus placebo in a 5-year safety analysis.

A common infection was defined as ≥2 patient events/100 PY in the VDZ group.

CI: confidence interval; GI: gastrointestinal; NEC: not elsewhere classified; PBO: placebo; PY: patient-years; VDZ: vedolizumab.

Adapted from Colombel et al.[35]

The results showed that when applying intensive, highly controlled treat-to-target treatment with an anti-TNF-α-based strategy, mucosal healing (defined as CDEIS <4 and no deep ulcers) was achieved in around 46% of patients at Week 48 of treatment; in the conventional clinical management arm, around 30% of the patients achieved mucosal healing.[13] However, this still leaves over half the patients requiring alternative drugs to help them reach remission, as Prof Lees stated. Currently approved biologic therapies for moderate-to-severe CD comprise TNF-α inhibitors (infliximab,[19] adalimumab[20]), interleukin-12/23 inhibitors (ustekinumab[21]), and the gut-selective anti-α4β7 integrin (vedolizumab[1]). Thus, there is a variety of biologics that can be used to treat patients with moderate-to-severe CD and it is important to choose the right timepoint to assess if the biologic is working for the patient.

Gut-Selective Treatment: Short-Term and Long-Term Goals

Looking at how the gut-selective vedolizumab can be used to achieve the STRIDE targets, relevant evidence is available from a post-hoc analysis of GEMINI 2 and 3 pooled data. Results showed that in an anti-TNF-α-naïve population, 48.9% of patients treated with vedolizumab achieved clinical remission (CD Activity Index ≤150) at 52 weeks (versus 26.8% with placebo), and in the overall population, including patients with failed anti-TNF-α treatment, 37.7% of patients achieved this (versus 21.6% with placebo).[22] In a GEMINI 2 post-hoc analysis looking at the onset of symptomatic improvement, vedolizumab showed a significant response in a composite score of reduction in abdominal pain and liquid or soft stools compared with placebo at Weeks 2, 4, and 6. This demonstrates the relatively fast alleviation of symptoms in some patients treated with vedolizumab, notably those without prior exposure to anti-TNF-α agents.[23] The same trend was seen in the overall population, but less markedly.[23]

However, there are patients whose response will take longer, and thus further assessments will be necessary, including endoscopic assessment of mucosal healing, as the STRIDE targets suggest. Long-term data on mucosal healing with vedolizumab came from the GEMINI LTS cohort where the primary objective was to evaluate the long-term safety profile of vedolizumab. A retrospective chart review of anti-TNF-α refractory CD patients (n=24) with a median

vedolizumab treatment duration of 3.2 years showed that 29% of patients had complete mucosal healing (no ulcers as recorded by a physician's assessment), 38% had partial healing (marked improvement), and 33% showed no healing.[24]

Real-world data provide further evidence on mucosal healing with vedolizumab; in a study by Vivio et al.,[25] 30% of CD patients showed complete mucosal healing, defined as an SES-CD of zero, and 52% showed endoscopic improvement at 22 weeks. This was also observed by the Amiot et al.[26] study, which showed that 30% of CD patients treated with vedolizumab had no ulcers between 30 and 54 weeks of treatment duration, and the US VICTORY consortium, where 58% of patients had no ulcers or erosions at 52 weeks.[27] Currently, there is ongoing research that will provide more breadth to the available data on mucosal healing with vedolizumab.[28]

The Goal of Maintaining Remission

The current data show that it is possible to achieve remission and mucosal healing with vedolizumab, but a focus on maintaining remission is also paramount. With anti-TNF-α therapy, a loss of response over time can be expected by ≥50% of patients at 12 and 24 months.[29-31] Additionally, there remains a safety signal with anti-TNF-α therapy, albeit relatively modest, when looking at predictors of serious infection. For example, in the TREAT registry,[32] infliximab treatment was identified as an independent predictor of serious infection, although prednisone, narcotic analgesic therapy, and ongoing moderate-to-severe disease activity were identified as higher risk factors.

Data on lasting clinical remission with vedolizumab can be derived from the GEMINI LTS cohort; participants in this long-term safety study included patients who completed the maintenance phase of the GEMINI 2 trial and continued to be treated with vedolizumab every 4 weeks (see disclaimer). Of them, 74% were in clinical remission at 52 weeks and 89% (n=54/61 observed cases) of patients achieved clinical remission after approximately 5 years of cumulative exposure. Thirty-seven percent of patients were in remission when the stricter analysis was applied, where all patients without available 5-year-data were counted as non-responders.[33,34]

The Safety Profile: Of High Importance for Long-Term Treatment

For a long-term treatment, the safety profile is of special importance. With a total exposure of 4,811 patient-years, a significant amount of safety data is accumulating for vedolizumab. Data pooled from six clinical trials showed that there was no increase in adverse events in patients treated with vedolizumab versus placebo in a 5-year safety analysis and no cases of progressive multifocal leukoencephalopathy were reported (Figure 1).[35] This was confirmed by a meta-analysis of real-world safety data, which evaluated 2,857 vedolizumab-treated patients and reported adverse event rates consistent with the data from the clinical trials.[36] As of August 2017, vedolizumab has 143,127 patient-years of post-marketing exposure worldwide, a number that has doubled from the previous year.

In conclusion, the treatment goals for CD are evolving to a composite target of clinical and endoscopic remission, with the main aim of slowing disease progression. By optimally using the current drugs on the market, the aim is to avoid long-term complications. This involves identifying high-risk patients early in their disease course and treating them with an appropriate biologic that can achieve and maintain clinical remission. Vedolizumab, a gut-selective biologic, has been shown to achieve and maintain clinical remission in the long-term, with early symptomatic improvements and mucosal healing shown by exploratory/real-world data. Vedolizumab also has a favourable safety profile, as demonstrated in 5-year pooled clinical and real-world studies.

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EDITOR'S PICK

My Editor's Pick for this issue, by Jain, provides a thorough review into intrauterine insemination's role in infertility management. It is essential to clarify the range of indications for each assisted reproduction technique, since the efficacy and outcome is significantly determined by the proper patient selection, which requires close co-operation between gynaecologists and andrologists. The paper reviews the current status of intrauterine insemination in infertility management, providing an excellent guideline for all clinicians.

Prof Mátyás Benyó

INTRAUTERINE INSEMINATION: CURRENT PLACE IN INFERTILITY MANAGEMENT

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Disclosure: The author has declared no conflicts of interest.
Acknowledgements: The author is grateful to her teachers, patients, and family for their patience and support. Without their encouragement and stimulus this work would not have come into place.
Received: 10.05.17 **Accepted:** 30.08.17
Citation: EMJ. 2018;3[1]:58-66.

ABSTRACT

Infertility has become a significant problem worldwide. Multiple management options are available nowadays, which include intrauterine insemination (IUI), *in vitro* fertilisation (IVF), and intracytoplasmic sperm injection. IUI is one of the oldest and most popular methods. After >50 years since it was first used, IUI has evolved through various innovations but still struggles to find its place in infertility management. After the introduction of revised guidelines from the National Institute for Health and Care Excellence (NICE) in 2013, there has been a surge in the use of IVF as a primary treatment modality. The aim of this evidence-based review is to highlight the factors associated with success of IUI and to find out whether IUI can be offered as a first-line treatment option for infertile couples.

Keywords: Clinical pregnancy, infertility, intrauterine insemination (IUI), live birth, prognostic factors.

INTRODUCTION

Infertility is a disease of the reproductive system and is defined by the failure to achieve a clinical pregnancy after ≥12 months of regular unprotected sexual intercourse.[1] It has become a significant global problem with a considerable physical, psychological, and social impact. According to a systematic analysis of 277 health surveys, there were around 48.5 million couples suffering from infertility worldwide in 2010. Among women 20–44 years of age, 1.9% (95% confidence interval [CI]: 1.7–2.2%) had primary infertility and 10.5% (95% CI: 9.5–11.7%) had secondary infertility.[2] Assisted reproductive techniques are now considered the established treatment option for couples suffering from infertility; they embrace a wide scope of techniques of which intrauterine insemination (IUI), *in vitro* fertilisation (IVF), and intracytoplasmic sperm injection (ICSI) are most popular.

INTRAUTERINE INSEMINATION

IUI involves the deposition of processed semen (partner/donor) in the uterine cavity close to the

time of ovulation. The rationale behind IUI is to increase the gamete density at the site of fertilisation.[3] The first report of IUI was published by Cohen[4] in 1962, and since then this technique has evolved through various innovations. Though the basic procedure remains the same, success rates in IUI cycles have grown from 5% to >20% per cycle with advances in stimulation protocols, cycle monitoring, timing of ovulation, semen preparation methods, and luteal phase support. IUI is a simple and easy procedure, with a short learning curve and minimal equipment requirements. Being less invasive, cheaper, and accompanied by a reduced chance of complications like multiple pregnancy and ovarian hyperstimulation syndrome in comparison to IVF/ICSI, IUI is considered the first-line treatment option. It offers less psychological burden for couples and hence has a lower dropout rate and good compliance with treatment.

Prerequisites

IUI is a Level I assisted reproduction procedure where only semen handling takes place outside of the body, and the rest of the processes involved in human conception, like ovulation, fertilisation, embryogenesis, and implantation, take place naturally. Hence, it can be considered as an extension of natural conception. The prerequisites for a couple to undergo an IUI cycle are:

- Ovulatory cycle (natural or stimulated)
- At least one patent functional fallopian tube (preferably both)
- Total motile sperm count >10 million/mL

Indications and Contraindications

IUI can be offered for a wide range of indications (Table 1).

Table 1: Indications for intrauterine insemination.

Homologous insemination		Donor insemination
Physical or psychosexual dysfunction	Infertility	
• Hypospadias • Retrograde ejaculation • Erectile dysfunction • Vaginismus • HIV serodiscordant couple	• Unexplained infertility • Mild-to-moderate male factor • Minimal to mild endometriosis • Anovulatory infertility • Unilateral tubal disease • Cervical factor	• Azoospermia • Severe OATS when IVF-ICSI is not affordable • Inheritable genetic disease in male • Lesbian • Single women

IVF-ICSI: *in vitro* fertilisation with intra-cytoplasmic sperm injection; OATS: oligoasthenoteratozoospermia.

Table 2: Prognostic factors for intrauterine insemination.

Pre-cycle (non-modifiable)	During IUI cycle	Post-IUI
• Age of female • BMI • Duration of infertility • Infertility aetiology • Single or multiple factors • Number of IUI cycles	• Stimulated or natural • Ovarian stimulation: CC/letrozole/Gn • Type of Gn: recombinant versus urinary • Prevention of premature LH surge: use of GnRH analogues • Mono-follicular/multi-follicular • Endometrial thickness • Ovulatory trigger • Timing of IUI: ovulation, semen collection, preparation, and insemination • Semen parameters • Semen preparation method • Number of inseminations • Easy or difficult IUI • Type of catheter	• Abstinence • Immobilisation • Luteal phase support

CC: clomiphene citrate; Gn: gonadotropin; GnRH: gonadotropin-releasing hormone; IUI: intrauterine insemination; LH: luteinising hormone.

IUI should be avoided in a few conditions, either because it is not possible, it is less successful, or moving directly to IVF is a better option. These conditions include:

- Active pelvic infection: cervicitis, endometritis.
- Cervical stenosis, atresia.
- Blocked fallopian tubes.
- Severe oligoasthenoteratozoospermia where IVF-ICSI is the treatment of choice.
- Stage III/IV endometriosis.
- Dense pelvic adhesions.
- Poor ovarian reserve.

Prognostic Factors

The success of IUI depends upon a wide range of parameters (Table 2). In the next few sections, these parameters are discussed in light of the current evidence.

Age of female

Female age is the most important determinant of human conception. It is well established that clinical pregnancy and live birth rates are higher in females <35 years of age, in cases of both natural as well as assisted conception.[5,6] The limited success of stimulated IUI over immediate IVF in older women was shown in the FORT-T trial.[7] Hence we recommend judicious use of IUI in women >35 years of age, as declining ovarian reserve and oocyte quality may not lead to the desired results in IUI in women of advanced age.

BMI

Female obesity is an established cause for poor reproductive performance, but to date there is insufficient evidence that female obesity has an adverse effect on IUI outcomes. Further well-designed trials are therefore needed.

Duration of infertility

Most of the studies published so far have been heterogeneous in subject inclusion on the basis of infertility duration, which has typically ranged from 3–10 years. However, available evidence suggests that the longer the duration of infertility, the lower the likelihood of success with IUI.[5,6]

Infertility aetiology

Women with secondary infertility score better than women with primary infertility during IUI (21.4% versus 7.9%).[5,8] Couples with multiple infertility factors have fewer chances of conception with IUI than couples with a single infertility factor.

Unexplained infertility

IUI in unexplained infertility has been compared in many ways. In a recent meta-analysis of 14 trials with 1,867 women, there was no difference in live birth rates between IUI and timed intercourse (TI) both in natural or stimulated cycles. However, there was an increase in live birth rate in stimulated cycle IUI in comparison to natural cycle IUI (odds ratio [OR]: 0.48; 95% CI: 0.29–0.82) without an increase in multiple pregnancy rate.[9]

In the FASTT trial,[10] three cycles of clomiphene citrate (CC)/IUI followed by three cycles of follicle stimulating hormone (FSH)/IUI were compared with up to six cycles of IVF. In the IVF arm, there was an increase in pregnancy rate, a reduced time to conception, and lower costs per delivery.[10] Similarly, the current National Institute for Health and Care Excellence (NICE) guidelines recommend IVF over IUI in unexplained infertility.[11] In the recent Cochrane review,[12] IVF was associated with higher live birth rates than unstimulated IUI (OR: 2.47; 95% CI: 1.19–5.12). In women pre-treated with CC/IUI, IVF appears to be associated with higher birth rates than gonadotropin plus IUI (OR: 3.90; 95% CI: 2.32–6.57). However, in treatment-naïve women there is no conclusive evidence of a difference in live birth rates between IVF and IUI with CC or gonadotropins.[12]

Male factor infertility

Infertility due to suboptimal semen parameters can be overcome by IUI in males in whom sperm count, motility, or morphology is affected moderately, while IVF-ICSI is the treatment of choice in cases where a severe defect or a combination of defects is present. In the two Cochrane reviews conducted on male subfertility, IUI was not better than TI in a natural cycle or stimulated cycle.[13,14] Also, there was no difference in live birth and pregnancy rates between controlled ovarian stimulation (COS)-IUI and IUI.[13,14] Recently, sperm DNA fragmentation has also been taken into account while managing male sub-fertility, with it stated that a higher (>30%) DNA fragmentation index may lead to poor chances of success in an IUI cycle. However, there is insufficient evidence (Level C) to recommend the use of DNA integrity tests to predict pregnancy with IUI.[15]

Endometriosis

Level II evidence suggests that COS with IUI is a viable treatment option in women with American Fertility Society (AFS)/American Society for Reproductive Medicine (ASRM) Stage I and II

endometriosis after laparoscopic correction of the disease.[16] Although tubes are patent in endometriosis, adhesions and altered pelvic anatomy do not give encouraging results in IUI. In women with minimal to mild endometriosis, IUI with controlled ovarian stimulation may be effective in increasing live birth rate (OR: 5.6; 95% CI: 1.18–17.4) compared with expectant management. Furthermore, IUI with COS may be more effective at increasing pregnancy rates (OR: 5.1; 95% CI: 1.1–22.5) than IUI alone and may be as effective in women within 6 months of surgical treatment as in women with unexplained infertility.[17] IVF is a better choice in Stage III and IV endometriosis, after 2–3 failed IUI cycles in early stage disease, or if associated factors are present, such as diminished ovarian reserve, advanced female age, compromised tubal function, or poor semen parameters.

Anovulatory infertility

In principle, IUI is not an indication in anovulatory infertility, yet most ovulation induction cycles are combined with IUI to obtain better results. IUI can be considered in women with polycystic ovarian syndrome if there is an associated male factor or in women who failed to conceive despite successful induction of ovulation. The clinical pregnancy rates per cycle ranged from 11–20% and the multiple pregnancy rates ranged from 11–36%. Current recommendations suggest IUI should not be first-line therapy in anovulatory women.[18]

Cervical factor subfertility

Abnormalities of cervical-mucus production or sperm-mucus interaction might impair fertility. The diagnosis is established by a negative post-coital test despite normal semen parameters and coital function, although nowadays the routine use of post-coital test is not recommended while evaluating an infertile female.[11,19] Though a higher pregnancy rate was found following IUI in comparison to expectant management (51% versus 33%) in couples with isolated cervical factor,[20] IUI was found to be an ineffective treatment for cervical hostility in a systematic review of five trials.[21]

Tubal factor infertility

Laparoscopic assessment or IVF is suggested for women with bilateral tubal disease or distal tubal occlusion on hysteron-salpingography. COS-IUI can be suggested as initial treatment in isolated unilateral proximal tubal occlusion. However, the cumulative pregnancy rate after three cycles was lower in couples with unilateral tubal disease in comparison to couples with unexplained infertility (30.9% versus 42.6%).[22]

Number of intrauterine insemination cycles

There is a general consensus in the literature that between four and six IUI cycles may be performed in appropriately selected patients with reasonable pregnancy rates before resorting to alternative treatments. In a retrospective analysis of 15,303 IUI cycles, it was found that the ongoing pregnancy rate (OPR)/cycle decreased from 7.4% in the first cycle to 4.7% and 4.6% in the sixth and ninth cycle, respectively, but the cumulative OPR was 18.3%, 30.3%, and 41.2% after three, six, and nine cycles, respectively.[23] We recommend careful evaluation of the patient's age, duration of infertility, ovarian reserve, pelvic factors, and semen parameters before continuing with IUI treatment beyond three to four cycles.

Ovarian stimulation protocols

Apart from male factors and physical or psychosexual dysfunction where natural cycle IUI can be offered, COS is an integral part of IUI. The rationale of ovarian stimulation is to increase the number of fertilisable oocytes to increase the chances of conception. CC, letrozole, tamoxifen, gonadotropins (human menopausal gonadotropin urinary highly purified FSH, recombinant FSH), combination protocol, and gonadotropin-releasing hormone (GnRH) analogues are used for COS-IUI. In the largest review of 43 trials, involving 3,957 women, the following conclusions were made:[24]

- Significantly higher pregnancy rates with gonadotropins (OR: 1.8; 95% CI: 1.2–2.7) in comparison to anti-oestrogens.
- No significant difference between anti-oestrogens and aromatase inhibitors (OR: 1.2; 95% CI: 0.64–2.1).
- No significant difference between different types of gonadotropins.
- Gonadotropins alone are more effective than with the addition of a GnRH agonist (OR: 1.8; 95% CI: 1.1–3.0).
- No benefit of adding a GnRH antagonist to gonadotropins (OR: 1.5; 95% CI: 0.83–2.8).
- No evidence of the benefit in doubling the dose of gonadotropins (OR: 1.2; 95% CI: 0.67–1.9), although the multiple pregnancy rates and ovarian hyperstimulation rates were increased.

There are numerous studies demonstrating the effectiveness of one protocol over another; at present, we would recommend a cost effective individualised stimulation protocol for IUI cycles. The approach of mild ovarian stimulation with the aim of two to three follicles with close ultrasound monitoring of the cycle and strict cancellation criteria is optimal.

Mono-follicular versus multi-follicular cycles

Multi-follicular growth is associated with higher pregnancy rates in COS-IUI. In a meta-analysis, the chance of pregnancy was 5% higher with two follicles and 8% higher with three or four follicles. At the same time, the risk of multiple pregnancy was increased by 6%, 10%, and 14% with two, three, and four follicles, respectively.[25] In our previous study, we found a cumulative pregnancy rate (CPR) of 19.7% in mono-follicular cycles and 29.4% in multi-follicular cycles.[26] Hence, we strongly recommend mono-follicular or bi-follicular cycles, and cancellation should be considered if there are >3 follicles of ≥16 mm on the day of human chorionic gonadotropin (HCG) administration.

Endometrial thickness

Optimal endometrial thickness is essential for conception. There are scarce data regarding the influence of endometrial thickness and pattern on the success of IUI cycles.[27] Still, a trilaminar endometrium with thickness ≥8 mm is considered favourable and a thin (<6 mm) or hyperechoic endometrium on the day of HCG administration is not suitable for successful IUI outcome.

Endometrial injury

Intentional endometrial injury is currently being proposed as a technique to improve the probability of pregnancy in women undergoing IVF; however, the effectiveness of this procedure in women attempting to conceive via IUI, expectant management, or TI remains unclear. In a systematic review of nine trials, there was low-quality evidence that endometrial injury may improve clinical pregnancy rates (relative risk [RR]: 1.98; 95% CI: 1.51–2.58). Further high-quality trials are required to confirm these findings.[28]

Timing of intrauterine insemination

To achieve optimal success, IUI should be done as close to ovulation as possible; hence, the timing of IUI in relation to ovulation is very important.

Ovulatory trigger

According to the analysis of the natural cycle by the World Health Organization (WHO), ovulation occurs 24–56 hours after onset of luteinising hormone (LH) surge (mean time: 32 hours), and after HCG injection ovulation starts 32–38 hours later and is sequential thereafter.[29] A mature oocyte is fertilisable for 12–24 hours after release.[30] There are multiple methods for synchronisation, like detection of LH surge in urine or blood, administration of urinary (5,000–10,000 international units intramusculatory) or recombinant HCG (250 mcg subcutaneously) or GnRH agonist (leuprolide 1 mg/decapeptyl 0.1 mg/buserelin 0.5 mg subcutaneously), or a combination of them. According to a Cochrane review[31] of 14 randomised control trials (RCT) there was no difference in live birth rate (LBR) between HCG versus LH surge or urinary HCG versus recombinant HCG, and HCG versus GnRH agonist. Also, there was no optimal time interval from HCG injection to IUI.[31] Documentation of ovulation on ultrasound before IUI is also reported to yield higher pregnancy rates (23.5% versus 8.8%).[32]

Timing of semen collection, preparation, and insemination

Semen collection for IUI should preferably be done at the clinic. There should be no delay from collection to processing of semen, because prolonged exposure of sperm to seminal plasma results in a marked decline in both motility and viability, hence they must be separated as soon as possible after ejaculation. After semen washing, there are certain changes in the acrosome of the sperm, which initiates capacitation and a progressive decrease in sperm motility due to exhaustion of energy sources.[33] Hence, a prolonged sperm wash to IUI interval may lead to a reduced number of fertilisable sperms reaching the fallopian tubes.[34] We recommend semen processing within 30 minutes of ejaculation and IUI within 1–2 hours of semen processing to get the best results in terms of clinical pregnancy.

Semen parameters

Volume of inseminate varied between 0.2–1.0 mL in most of the studies. Inseminate volume <0.2 mL would not be sufficient for IUI as it may not compensate for the dead space of an IUI catheter. Similarly, higher volumes of inseminate increases the chances of back-spill and there is no evidence that increasing inseminate volume can increase the

chances of conception; hence, the optimal volume of inseminate should be between 0.3 mL and 0.5 mL.

There is wide variation in the literature regarding semen quality and IUI success rates, with a huge difference in the values of various semen parameters. Ombelet et al.[35] suggested that the following cut-off values can be taken while considering IUI:

- Inseminating motile count: >1 million.
- Sperm morphology using strict criteria: >4% normal morphology.
- Total motile sperm count in native sample: 5–10 million.
- Total motility in native sample: >30%.

While using these cut-offs, the sensitivity (ability to predict pregnancy) was limited but the specificity (ability to predict failure to conceive) was much better.

Semen preparation techniques

Insemination with unprocessed semen is associated with pelvic infection and it is necessary to remove seminal plasma to avoid prostaglandin-induced uterine contractions. The rationale behind semen preparation in IUI is the separation of motile, morphologically normal, spermatozoa from infectious agents, antigenic proteins, dead sperm, leukocytes, and immature germ cells, which may lead to the production of free oxygen radicals. The most popular methods are simple wash and centrifugation, double density gradient, or swim up. In a systematic review of five RCT, there was insufficient evidence to recommend any specific method of semen preparation.[36] The choice of semen preparation method should be decided on the basis of quality of the native sample. The time of centrifugation is more important than the g-force for inducing formation of reactive oxygen species, which may lead to sperm membrane injury; hence, the time of centrifugation should be kept at minimum.[37] There are also certain advanced methods for sperm preparation, like hyaluronic-mediated sperm selection, filtration method, and magnetic-activated cell sorting, which are reported to give a higher fraction of motile, viable, and non-apoptotic sperm with high DNA integrity and better cryo-survival rates, but their use in IUI is limited.

Number of inseminations

Insemination is timed around ovulation and can be done once or twice. There is controversy in the literature regarding the number of inseminations for male factor and non-male factor infertility. The rationale of double IUI in a multi-follicular cycle and in male factor subfertility is to widen the fertilisation window so as to deliver more sperm for fertilisation of multiple oocytes released sequentially. In most of the published studies, a single well-timed insemination was done between 34 and 36 hours post HCG administration. Some authors found a benefit of conducting two inseminations, where one was preovulation (around 12–24 hours post-HCG) and the second insemination was conducted post ovulation (between 34 and 48 hours post-HCG).[38,39] However, in a meta-analysis by Polyzos et al.[40] there was no benefit of double IUI in terms of clinical pregnancy rate in couples with unexplained infertility. In a separate meta-analysis by Zavos et al.,[41] there was a trend towards higher pregnancy rates (OR: 2.0; 95% CI: 1.07–3.75; p<0.03) in male factor infertility. In a retrospective study, there was no difference in clinical pregnancy rates in donor insemination with double IUI (single 16.4% versus double 13.6%).[42] Therefore, we do not recommend double IUI, as it increases the cost and psychological burden to the couple without increasing the pregnancy rates.

Easy versus difficult intrauterine insemination

Use of tenaculum, uterine sound, or touching the fundus while doing an IUI, back-spillage of semen, blood on the tip of an IUI cannula, and abdominal cramps or spotting post-IUI indicates a difficult IUI. In all these cases, the chances of conception are lower compared to an easy IUI. Studies on IUI under ultrasound guidance are also inconclusive.[43,44]

Type of catheter

Various types of catheters are available commercially, such as soft or rigid, disposable or metal, with or without stylet. A Cochrane review of nine trials suggested that there was no evidence of significant difference in CPR or LBR with the choice of catheter type.[45] We recommend an IUI catheter should be atraumatic, non-toxic, and easy to use.

Abstinence

In natural intercourse, cervical crypts act as a sperm reservoir, providing a supply of sperms for up to 72 hours, but in IUI there is no such reservoir. The fertilisable life span of washed sperms is only 2–3 hours, while it is 12–24 hours for a mature oocyte. Hence, we recommend sexual intercourse around the time of IUI in couples with non-male factor infertility.

Table 3: Complications of intrauterine insemination.

Related to IUI procedure	Related to COS	Remote
• Trauma • Infection • Bleeding • Pain/cramping	• Multiple pregnancy • Monitoring • Cost • OHSS	• Ectopic pregnancy • Abortion • Pelvic inflammatory disease • Psychological

COS: controlled ovarian stimulation; IUI: intrauterine insemination; OHSS: ovarian hyperstimulation syndrome.

Immobilisation post-intrauterine insemination

Sperm may reach the fallopian tubes within 5 minutes of insemination.[46] The rationale of immobilisation after IUI is to prevent any leakage of semen and to compensate for the absence of sperm reservoir in cervical mucus that forms after natural intercourse. Significant improvements in cumulative OPR (27% versus 18%) and LBR (27% versus 18%) were reported after 15 minutes of immobilisation versus immediate mobilisation post IUI.[47]

Luteal phase support

Progesterone is essential for the establishment and maintenance of pregnancy. There is no need for luteal phase support in natural cycle IUI. In cycles stimulated with CC, letrozole, or combined protocols of CC or letrozole with gonadotropins, there is sufficient endogenous LH level that stimulates development of the corpus luteum. On the other hand, in gonadotropin stimulated IUI cycles, supraphysiologic oestradiol levels lead to negative feedback at the hypothalamus, which leads to lower luteal LH levels and therefore to defective implantation. In an updated systematic review and meta-analysis of 11 trials with 2,842 patients, the CPR (RR: 1.56; 95% CI: 1.21–2.02) and LBR (RR: 1.77; 95% CI: 1.30–2.42) were significantly higher with vaginal progesterone supplementation in patients undergoing gonadotropin IUI cycles. The number of treated patients needed to have one additional live birth totals 11.[48] In view of the low-cost, ease of administration, and side effects, we recommend the use of vaginal natural micronised progesterone over HCG or dydrogesterone or progesterone gel in gonadotropin-stimulated IUI cycles. At present, there is insufficient evidence regarding use of GnRH agonists at the time of implantation in IUI cycles.[49]

Complications

Although IUI is a simple minimally invasive procedure, it is not without complications (Table 3). If done properly, the chances of infection are negligible (0.01–0.20%). The most feared complication of IUI is multiple pregnancy, which is related to COS. Most of the studies in the past have reported very high rates of multiple pregnancy with COS IUI (10–40%).[25] However, if stimulation is milder and a strict cancellation policy is adopted, it is comparable to IVF single embryo transfer (7% versus 5%).[50] The chances of ectopic pregnancy and spontaneous abortion are similar to other infertility treatments.

WHY DOES INTRAUTERINE INSEMINATION FAIL?

IUI is a simple technique that gives reasonable pregnancy rates in selected sets of patients, though it is not without limitations. The main reasons for failure of IUI treatment are:

- Poor patient selection.
- Improper timing of IUI in relation to ovulation.
- Poor semen preparation technique or triple sperm defects.
- Faulty technique or difficult IUI.
- Subtle tubal dysfunction or peritubal adhesions.
- Poor oocyte quality.
- Non-receptive endometrium.

INTRAUTERINE INSEMINATION VERSUS EXPECTANT MANAGEMENT/TIMED INTERCOURSE/INTRACERVICAL INSEMINATION/FALLOPIAN TUBE SPERM PERFUSION/*IN VITRO* FERTILISATION

There is insufficient evidence for superiority of IUI over expectant management or TI. IUI with frozen semen is superior to intracervical insemination.[51]

Fallopian tube sperm perfusion was not found to be better than IUI.[52] In a recent RCT of 602 couples, COS-IUI was found to be noninferior to IVF single embryo transfer and IVF in a modified natural cycle in terms of time to achieve pregnancy (8.39, 8.04, and 8.32 months, respectively) and LBR (47%, 52%, and 43%, respectively) and was found to be more cost effective.[50] The treatment dropout rates were significantly lower with the IUI group. In another study, the cost per pregnancy resulting in at least one live birth was three times higher with IVF compared to IUI.[53]

COUNSELLING

Counselling is an integral part of any assisted reproductive technique programme. It should be incorporated in the treatment cycle from the beginning, either by the treating fertility specialist themselves or by a psychological counsellor. As we know, infertility and undergoing fertility treatment is stressful for the couple with lots of expectations from every cycle; therefore, they should be informed about the available options, treatment process, prognosis, and cost analysis. Couples should be given an informed choice and assisted at every step so that there are fewer treatment dropouts.

CONCLUSION

This review highlights the current status of IUI in infertility management. IUI should be considered as a first-line treatment option in the management of infertility, considering its simple, patient friendly, non-invasive nature, and cost effectiveness over IVF. The approach of mild ovarian stimulation while minimising the risk of multiple pregnancy, proper timing to enhance success, and with thorough counselling, should be adopted.

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EARLY AND LONG-TERM OUTCOMES AFTER NON-INTUBATED, NON-RESECTIONAL LUNG VOLUME REDUCTION SURGERY

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Disclosure: The authors have declared no conflicts of interest.
Received: 29.11.16 **Accepted:** 27.11.17
Citation: EMJ. 2018;3[1]:68-75.

ABSTRACT

Objective: In 2001, the introduction of non-resectional lung volume reduction surgery (LVRS) enabled surgery under non-intubated anaesthesia. This study compares this combined technique to a group of patients with a similar disorder who refused non-intubated anaesthesia.

Methods: Between January 2001 and October 2015, 108 patients with severe emphysema underwent non-resectional LVRS under non-intubated anaesthesia. During the same period, another 15 patients scheduled for LVRS refused non-intubated surgery and underwent the same procedure under traditional intubated modality. Respiratory and functional parameters were evaluated. Time to residual volume recurrence and overall survival were analysed with the Kaplan–Meier method.

Results: Thirteen cases (12%) required intubation due to tenacious pleuropulmonary adhesions (n=7) or intolerance (n=6). Compared with the intubated group, the non-intubated group were found to have significantly better results in post-operative partial pressure of carbon dioxide in arterial blood ($PaCO_2$) (45±8 versus 52±8 mmHg; p=0.04), global operative time (41±24 versus 72±31 minutes; p=0.01), non-fatal complication rate (13.6% versus 33.3%; p=0.029), and especially postoperative pneumonia rate (3.1% versus 33.3%; p=0.004); patient satisfaction for anaesthesia was also improved in the non-intubated group (3.6±1.2 versus 2.8±1.7; p=0.03). Mean air leakage (5.3±3.5 versus 6.1±4.6 days), hospital stay (6.3±4.8 versus 8.0±6.1 days), and 90 days postoperative mortality rate (1.0% versus 6.6%) were lower, yet not significantly, in the non-intubated cohort. All mean respiratory and symptomatic parameters significantly improved in both groups, with no intergroup significant difference, and persisted for 4 years after surgery. Mean follow-up for the non-intubated group was 78±30 months. Analysis of time to residual volume recurrence and overall survival showed no statistically significant intergroup difference.

Conclusion: Non-intubated, non-resectional LVRS presents a 90-day postoperative non-fatal complication rate and patient satisfaction for non-intubated anaesthesia that are significantly better than intubated procedures. The long-term outcomes were similar between both groups.

Keywords: Emphysema, lung volume reduction surgery (LVRS), minimally invasive thoracic surgery, non-intubated thoracic surgery, video-assisted thoracic surgery (VATS).

INTRODUCTION

Lung volume reduction surgery (LVRS) has proved an effective treatment in palliating emphysematous symptoms in selected patients.[1] This procedure was primarily performed as a trans-sternal anatomical bilateral resection on the most severely emphysematous target area.[2] Subsequently, resectional LVRS was proposed in either a unilateral or bilateral (one stage or two stages, respectively) video-assisted thoracoscopic (VATS) approach, giving preference to the most damaged side,

which similarly achieved satisfying results.[3] In the same period, fold plications without resection, i.e., non-resectional, were carried out for the treatment of bullous emphysema through either thoracotomy[4] or VATS[5] approaches.

On the basis of the two procedures aforementioned, Mineo et al.[6] successfully proposed a variant of the original LVRS technique, which consisted of the simple non-resectional plication of target areas. This procedure proved to be suitable for conscious patients, without the need for a single-lung ventilation, although the procedure was equally effective as resectional LVRS.[7] The operation was primarily conducted under thoracic epidural anaesthesia[8] and via a multiportal approach;[6] however, more recently a uniportal access under intercostal local block was adopted.[7]

In this observational study, the outcomes of a cohort of patients undergoing non-intubated, non-resectional LVRS are reviewed and compared with the long-term outcomes of similar patients who refused non-intubated operation.

MATERIALS AND METHODS

Patient Setting and Population

Between January 2001 and October 2015, a total of 108 consecutive patients with moderate-to-severe emphysema underwent non-resectional LVRS under non-intubated anaesthesia. In 77 patients, the procedure was accomplished through a conventional multiport VATS approach under epidural anaesthesia. The final 31 patients were operated on using a uniportal technique under intercostal block. The Tor Vergata University's (Rome, Italy) Institutional Review Board allowed the retrieval of all patient data regarding patient follow-up. The retrospective study was approved by the ethics committee of Tor Vergata University. During the same period, another 15 patients scheduled for LVRS refused non-intubated surgery and therefore underwent the same non-resectional procedure under general anaesthesia with one-lung ventilation; these patients were subsequently used as the control group.

All patients gave written informed consent after reading a written explanation of the main characteristics and theoretical advantages and disadvantages of non-resectional LVRS performed either by sole epidural anaesthesia, intercostal nerve block, or through general anaesthesia and one-lung ventilation. The form stressed specifically that during an awake operation, some surgical manoeuvres might be found more technically demanding, and that the procedure might be less comfortably tolerated due to risks of hypercapnia and panic attacks; the immediate postoperative course, however, was expected to be smoother than after general anaesthesia, due to the lack of weaning-related adverse effects. Conversely, general anaesthesia may have allowed achievement of an immobile operative field, and avoided the risk of panic attacks, although a longer stay in the recovery room and early postoperative respiratory discomfort were likely to be more common.

Preoperative Assessment

All patients underwent radiologic studies, including digital inspiratory and expiratory chest X-ray, and high-resolution chest computed tomography (CT). Dynamic and static pulmonary function tests were performed before and after inhalation with two puffs of aerosolised β_2-agonists. Exercise tolerance was tested by both a 6-minute walking test and using maximum increments on a treadmill. The degree of dyspnoea was scored according to the modified Medical Research Council Score.[9] Quality of life was quantified using the St. George's Respiratory Questionnaire.[10]

Indications

Indications towards LVRS originated from panel discussions among surgeons, pulmonologists, anaesthesiologists, intensive care specialists, physiotherapists, and psychologists. The main inclusion criteria included severe respiratory impairment characterised by the triad of bronchial obstruction, defined as when forced expiratory volume in 1 second is ≤40% than predicted, despite a bronchodilator; hyperinflation, when residual volume is ≥180% than predicted; and upper lobe targeted disease with compressed adjacent parenchyma. These patients must quit smoking and show determination and the capability to sustain a structured preoperative respiratory rehabilitation programme. With the introduction of non-resectional, non-intubated procedures, both old age and comorbidities have progressively become less strict exclusion criteria.

In addition, other exclusion criteria were clinical obesity (BMI ≥30 kg/m^2), imaging or clinical suspect for an obliterated pleural cavity, refusal of an awake procedure and an extreme anxious attitude, haemodynamic instability, inability to co-operate, and any contraindication to the planned regional

anaesthetic technique (e.g., coagulopathy). In the case of asymmetric emphysema, the procedure was initially only performed on the most damaged side, subsequently determining the clinical, functional, and anatomical postoperative evolution of the opposite, less damaged side. Conversely, in the presence of a symmetric distribution of disease and damage within the lungs, LVRS was performed as a staged bilateral procedure with an interval of no longer than 4–6 weeks between surgeries.

Anaesthesia

Epidural anaesthesia

The anaesthetic was administrated through a thoracic epidural catheter inserted at T4 after premedication of 7.5 mg midazolam. In the operating room, patients received a continuous infusion of 0.5% ropivacaine and sufentanil 1.66 µg/mL into the epidural space. In some instances, a topical vagal blockade was also performed. The anaesthetic was administrated using multiportal VATS.

Intercostal block anaesthesia

After insertion of venous and radial artery catheters, an aerosolised 5 mL solution of 2% lidocaine hydrochloride was administered for 5 minutes to avoid a cough reflex. The intercostal block was accomplished by a local injection of a 20–30 mL solution of 2% lidocaine and 7.5% ropivacaine to achieve a rapid onset with a long-lasting analgesic effect. The inoculation was performed along the surface area selected for uniportal VATS, and included subcutaneous layers, intercostal nerves, and parietal pleura. The grade of local anaesthesia was always adequate. In a few cases, benzodiazepine (midazolam 0.03–0.1 mg/kg) or opioids (remifentanil 15 µg/kg/min) were intravenously supplemented during lung manipulation. The employment of a bispectral index to monitor the level of sedation during the operation allowed the regulation of the sedation level through a real-time measurement.

General anaesthesia

Patients undergoing non-resectional LVRS through general anaesthesia received a thoracic epidural catheter insert between T5 and T8, and a continuous infusion of ropivacaine. General anaesthesia was induced with intravenous propofol (1.5–2.0 mg/kg), fentanyl (0.1 mg), and vecuronium (0.1 mg/kg), and maintained using a continuous infusion of these drugs.

Surgical Technique

The operation was performed in full lateral decubitus with multiportal VATS associated with epidural anaesthesia or in the last period with uniportal VATS associated with intercostal block. When the operations were performed with multiportal VATS, four flexible thoracoscopic trocars were used; one for the operative thoracoscope, usually placed in the sixth intercostal space along the midaxillary line, and the others placed in the third and fifth intercostal space along anterior axillary lines, and in the fourth intercostal space along the posterior axillary line. When the operations were performed with uniportal VATS, the single port of 30–40 mm was carried out along the space judged to be the most suitable to reach the foreseen area. However, most of the time the port was placed in the fourth intercostal space because the upper lobe of the lung is the area most affected. The operation aimed to reduce 20–30% of the lung volume by removing functionally ineffective hyperinflated lung tissue through plication without resection.

A 10 mm camera, angled at 30°, was used to facilitate oblique vision of the lung in spite of spontaneous ventilation. The most emphysematous target areas were visualised and pushed down with a cotton swab, while anelastic lung edges were grasped with ring forceps to create two parallel ridges of non-functional, redundant tissue. After this, a 45 mm 'no knife' endostapler with 3.5 mm cartridges was applied on the placated lung region. Following this, the two folds were distally sutured apart from each other by a supplementary no knife stapler in order to buttress the plication structure and protect the previous stapling lines. The plication cyanoacrylate application (Glubran 2®, GEM SRL, Viareggio, Italy) was used on the lung tissue to minimise the risk of air leak.

At the end of the procedure, one 28 Ch chest tube was collocated through the posterior end of the incision. The insertion of one transintercostal suture that significantly reduced the onset of subcutaneous emphysema was found to be useful. Muscle sutures were tightened after asking the patient to breathe deeply or cough to achieve maximal lung re-expansion. Unilateral LVRS was performed in patients with distinct radiologic evidence of between-lung heterogeneity of emphysema (asymmetric emphysema), while a symmetric distribution of disease within the lungs was considered an indication for a staged bilateral

treatment (no longer than 4–6 weeks from the first procedure).

Follow-Up

Respiratory and functional results were initially evaluated every 6 months for the first 2 years, and discussed within the aforementioned panel group. Thereafter, control groups were assessed yearly. Further LVRS was reconsidered in cases of functional or spirometric decline to the preoperative status. In such instances, contralateral or ipsilateral re-do procedures were proposed, with CT showing evident lung destruction or hyperinflation in a defined targeted area with relative conservation of the underlying parenchyma.

Statistical Evaluation

Descriptive statistics were presented as mean ± standard deviation, while post-treatment changes were indicated as the mean percentage of the baseline value. Due to the relatively small sample size, non-parametric tests for paired and unpaired comparisons were used (Wilcoxon rank-sum test and Mann–Whitney U test, respectively). Analysis was conducted using SPSS® 19.0 version (SPSS Inc., Chicago, Illinois, USA). The significance was set at $p<0.05$. Survivals and time-to-event evaluations were performed by the Kaplan–Meier method.[11] The day of operation was used as the starting point and the day of residual volume returned equal to baseline value as the endpoint. The significance test was assessed according to the Mantel log-rank test.

RESULTS

The two groups (non-intubated versus intubated) were homogeneous for anagraphic and clinical data. The non-intubated group showed a higher average age (65±6.1 versus 60±9.6 years). It was demonstrated that the overall stay in operatory theatre for the non-intubated group was significantly shorter than the intubated group (41±24 minutes versus 72±31 minutes; p=0.01). Global conversion rate to general anaesthesia was 12.0% (13 of 108), and this was equally due to surgical reasons, such as tenacious adherences (n=7) and intolerance to sustain non-intubated anaesthesia (n=6).

Early Outcomes

Early outcomes are documented in Table 1. It was noted that all measured oxygenation parameters were similar between groups, except arterial pressure of carbon dioxide, measured 1 hour postoperatively, which was significantly lower in the non-intubated group (45±8 versus 52±8 mmHg; p=0.04). There was no perioperative mortality in either groups. Compared to the intubated group, 90 days postoperative mortality was lower in the non-intubated group, with 1.0% versus 6.6%. Only one death was experienced within 90 days due to acute pneumonia. The non-fatal complications rate was significantly lower than that experienced after intubated LVRS (13.6% versus 33.3%; p=0.029). Among these, only three patients developed early postoperative pneumonia, compared with three patients in the intubated group (p=0.004). Persistent air leakage (>7 days) was experienced in 24 patients (25.2%); only three of which required restapling of the suture.

Mean air leakage period (5.3±3.5 versus 6.1±4.6 days) and hospital stay (6.3±4.8 versus 8.0±6.1 days) were shorter in the non-intubated group; however, these results are not significantly different (Table 1). Patient satisfaction for anaesthesia 90 days after surgery (0=minimal satisfaction, 4=maximal satisfaction) was significantly greater in the non-intubated group (3.6±1.2 versus 2.8±1.7; p=0.03) (Table 1).

Long-Term Outcomes

Mean follow-up of the non-intubated group was 78±30 months and 85±13 months for the intubated group. No patients (except those who died) were lost at follow-up over the first 4 years after procedure. Thereafter, 11 patients in the non-intubated group and 2 patients in the intubated group were lost. Mean values of all respiratory and symptomatic parameters significantly improved in both groups, with no intergroup significant difference. All the mean values persisted better than the preoperative baseline for 4 years after surgery (Table 2). In 71 patients, LVRS was repeated on the other side of the body after a mean period of 36±18 months. Namely, residual volume persisted higher than preoperative values for more than 36 months in 24 patients. This evolution was not significantly different from that documented after the intubated procedure (Figure 1A and 1B). Analysis of long-term survival showed no statistically significant difference between non-intubated and intubated groups, in terms of both time to residual recurrence (p=0.4) (Figure 1A) and overall survival (p=0.7) (Figure 1B).

Table 1: Baseline, intraoperative, and immediate postoperative comparisons between study groups.

Variables	Non-intubated group (n=108)	Intubated group (n=15)	p value
Age (years)	65.00±6.10	60.00±9.60	NS
Cigarette pack/year (number of packs smoked per day multiplied by the number of years as a smoker) (n)	32.00±10.00	34.00±12.00	NS
1-second forced expiratory volume predicted (mL)	0.85±0.40	0.88±0.30	NS
Forced vital capacity (mL)	2.38±0.60	2.41±0.80	NS
Residual volume predicted (mL)	5.30±0.80	5.10±0.60	NS
Diffusing capacity carbon monoxide (mmol/KPa*min)	3.80±0.80	3.90±0.70	NS
PaO_2 (mmHg)	73.02±6.40	74.05±5.40	NS
6-minute walking test (m)	385.00±50.00	390.00±66.00	NS
Dyspnoea Index (MRC Breathlessness Scale)	3.15±0.70	3.00±0.90	NS
Quality of life (St. George's Respiratory Questionnaire Manual; best: 0; worst: 100)	26.00±17.50	23.50±18.90	NS
Oral methylprednisolone users, n (%)	84.00 (78.00)	11.00 (73.00)	NS
Oxygen dependent, n (%)	71.00 (66.00)	10.00 (66.00)	NS
Global-operatory theatre time (min)	41.00±24.00*	72.00±31.00	0.01
PaO_2/FiO_2 end procedure (mmHg)	191.00±45.00*	210.00±50.00	NS
PaO_2/FiO_2 1-hour postoperative (mmHg)	154.00±30.00*	145.00±50.00	NS
$PaCO_2$ end procedure (mmHg)	55.00±10.00*	42.00±5.00	NS
$PaCO_2$ 1-hour postoperative (mmHg)	45.00±8.00*	52.00±8.00	0.04
24-hour postoperative basal pain (VAS 1–10)	4.30*	4.50	NS
Air leakage period (days)	5.30±3.50*	6.10±4.60	NS
Persistent air leak (>7 days), n (%)	24.00 (25.20)*	5.00 (33.30)	NS
Hospital stay (days)	5.60±4.80*	8.00±6.10	NS
90-day postoperative mortality, n (%)	1.00 (1.00)*	1.00 (6.60)	NS
Postoperative non-fatal complications, n (%)	13.0 (13.60)*	5.00 (33.30)	0.029
Postoperative pneumonia, n (%)	3.00 (3.10)*	3.00 (33.30)	0.004
90-day patient satisfaction score (0–4)	3.60±1.20*	2.80±1.70	0.030

*Limited to 95 patients, after excluding those converted to open access or intubated anaesthesia.
FiO_2: fractional inspired oxygen; MRC: Medical Research Council; NS: not significant; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen; VAS: visual analogue scale.

DISCUSSION

Pulmonary emphysema is a very common disease and is still characterised by a significant mortality rate.[12] LVRS proved effective in improving symptoms for a variable and yet significant period in patients with upper lobe predominant emphysema.[13-17] Pulmonary hyperinflation causes loss of lung elastic recoil and an unfavourable length–tension relationship of the diaphragm, limiting its capacity to produce effective airflow.[18] Accessory respiratory muscles are activated and work against a high load, which is worsened by loss of muscle efficiency.[19] The physiological basis of the procedure lies on the reduction of hyperinflation, and the restoration of normal parenchyma elasticity with improvement of respiratory muscle dynamics, increase in oxygen availability, and less energy expenditure.[20]

All these steps can be surgically accomplished by resecting the most damaged lung area. Nevertheless, according to previous experiences, even the non-resectional lung plication technique may achieve similar results.[6] The procedure proved simpler and quicker than resectional LVRS and avoided interruption of bronchovascular structures.

Table 2: Postoperative mean ± standard deviation values and p values compared to baseline value.

Variables	12 months (n=93)		24 months (n=90)		36 months (n=89)		48 months (n=86)	
	mean±SD (p value versus baseline)	p value versus intubated	mean±SD (p value versus baseline)	p value versus intubated	mean±SD (p value versus baseline)	p value versus intubated	mean±SD (p value versus baseline)	p value versus intubated
1-second forced expiratory volume predicted (mL)	1.22±0.40 ***	NS	1.12±0.40 ***	NS	1.08±0.40 **	NS	0.98±0.40 *	NS
Forced vital capacity (mL)	2.85±0.50 ***	NS	2.70±0.50 ***	NS	2.70±0.50 ***	NS	2.65±0.50 **	NS
Residual volume predicted (mL)	4.00±0.80 ***	NS	4.20±0.80 ***	NS	4.30±0.60 ***	NS	4.50±0.90 ***	NS
Residual volume recurrence, n (%)	0.00 (0)	NS	6.00 (6.00)	NS	30.00 (29.00)	NS	49.00 (49.00)	NS
Diffusion capacity carbon monoxide (% n predicted)	47.00±6.50 *	NS	45.00±7.10 *	NS	44.00±5.80 *	NS	39.00±6.60 *	NS
PaO_2 (mmHg)	77.25±5.20 **	NS	75.00±5.20 *	NS	74.25±6.00 (NS)	NS	73.50±5.20 (NS)	NS
6-minute walking test (m)	471.00±71.00 ***	NS	445.00±61.00 **	NS	425.00±75.00 *	NS	410.00±66.00 (NS)	NS
Dyspnoea Index (MRC Breathlessness Scale)	1.78±0.70 ***	NS	2.00±0.70 ***	NS	2.20±0.70 **	NS	2.50±0.70 *	NS
Quality of life (St. George's Questionnaire Manual; best: 0 worst: 100)	16.30±11.50 ***	NS	18.50±10.70 ***	NS	19.10±10.10 ***	NS	20.50±9.80 **	NS

*p<0.05; **p<0.01; ***p<0.001 and control group.
MRC: Medical Research Council; NS: not significant; PaO_2: partial pressure of oxygen; SD: standard deviation.

These evident advantages were weakened by the significant postoperative impairment due to general anaesthesia with one-lung ventilation, which had still remained significantly elevated, hindering the acceptance of the treatment among both patients and physicians.[21]

In the present study, non-intubated LVRS was safely and easily performed under thoracic epidural anaesthesia[7] or local anaesthesia.[8] This procedure was promptly accepted by the patients, while also meeting the compliance of the deputed physician and referred pulmonologists. This renewed confidence implies that many patients are referred to the surgeon and operated on earlier than in other centres. The evolution of early postoperative gas exchanges documents that hypoxia and hypercapnia worsening during non-intubated anaesthesia can be rapidly resolved. Avoidance of general anaesthesia, reflected in satisfactory perioperative respiratory performance, allowed a more rapid recovery with shorter hospitalisation, and immediate return to many day-to-day activities, including drinking, eating, and walking. As a matter of fact, this study experienced a significantly lower 90-day postoperative non-fatal complications rate, especially with regard to postoperative pneumonia incidence. This is a major benefit of non-intubated procedures because they allow constant ventilation during the operation with better postoperative ventilation.[6]

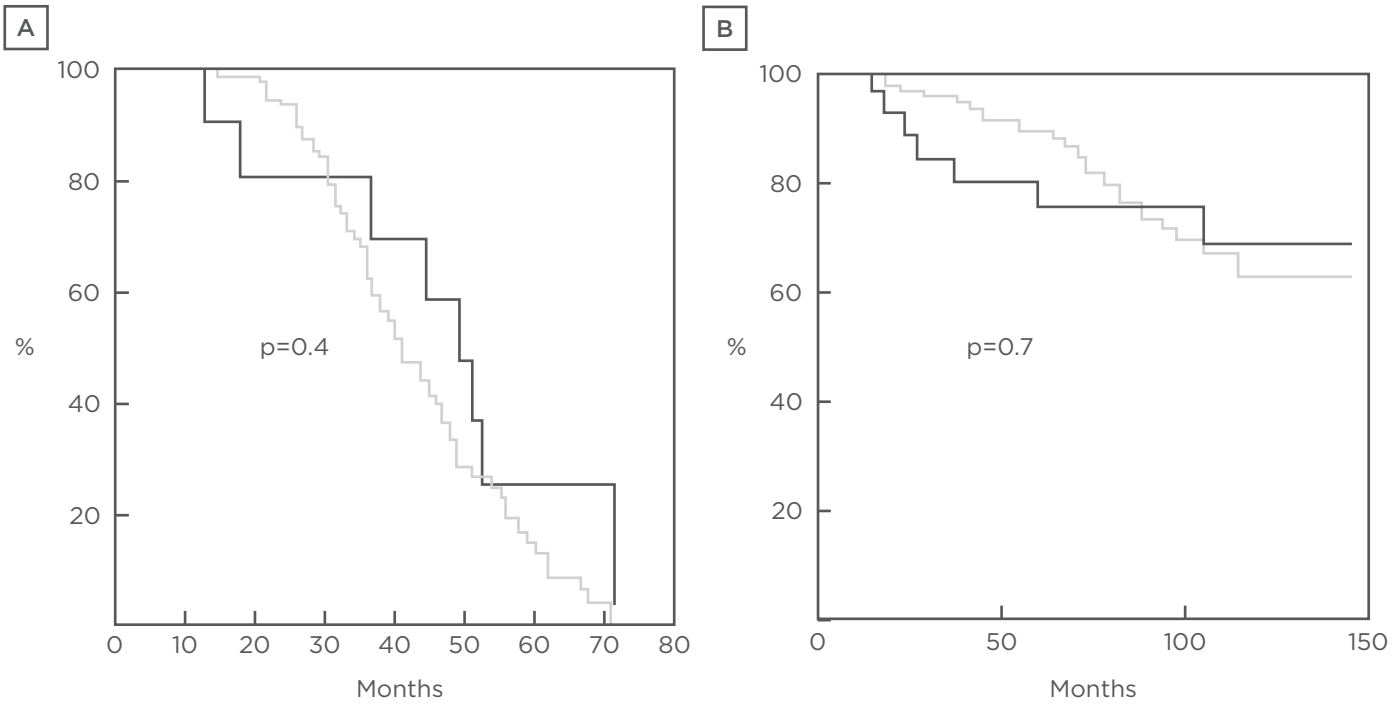

Figure 1: Kaplan–Meier curve results.

A) Time to residual volume recurrence between non-intubated (grey) and intubated (black) lung volume reduction surgery; B) overall survival between non-intubated (grey) and intubated (black) lung volume reduction surgery. The curves are similar throughout the study period. No statistically significant differences were found at the log-rank test.

As a consequence, non-intubated techniques allow shorter hospital stays without affecting incremental improvements incurred in clinical and respiratory function measurements.

No differences were found in long-term outcomes between non-intubated and intubated anaesthesia. In more than three-quarters of the patients from both groups, the residual volume persisted below the preoperative value for >36 months. The majority of the early recurrences of the residual volume were due to the small postoperative increase in the value, despite the postoperative amelioration of the flows and the subjective symptomatic improvement. In another subset of patients, the rapid worsening of residual volume value was unpredictable, which could potentially signify a different genetic base.

In the final period of the study, a uniportal approach was initiated that was found to be efficacious and safe.[8] These early results must be evaluated after a longer follow-up to provide more reliable data. The authors acknowledge limitations of the study, which are partially mitigated by the observational nature of the study. The major limitation of the study is the retrospective non-randomised nature of the investigation, but this evident flaw can be counterbalanced by the consistent sample size collected in one single institution. The results suggest that non-intubated, non-resectional LVRS is safe and reliable. Compared to intubated similar procedures, this technique can achieve a significantly shorter global operative time, lower rate of 90-day postoperative non-fatal complication rate, and improved patient satisfaction for anaesthesia without affecting long-term outcomes.

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IMMUNOPATHOLOGY OF ALLERGIC CONJUNCTIVITIS

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Disclosure: The authors have declared no conflicts of interest.
Received: 29.03.17 **Accepted:** 02.01.18
Citation: EMJ. 2018;3[1]:76-83.

ABSTRACT

Allergic conjunctivitis is predominantly an immunoglobulin E-mediated hypersensitivity reaction to environmental allergens. Allergic diseases affect >30% of the world's population, of which 40% report associated ocular manifestations. Cellular and soluble mediators play a major role in the pathophysiology of allergic conjunctivitis. Mast cells, which are major effector cells of allergic conjunctivitis, undergo activation and degranulation to release histamine, tryptase, prostaglandins, leukotrienes, and cytokines. These mediators play important roles in immunopathological mechanisms that generate the clinical manifestations of allergic conjunctivitis. These clinical features include conjunctival hyperaemia, chemosis, tearing, itching, papillae, mucus discharge, and eyelid oedema. Histamine mediates the early phase of the allergic immune response, whereas lipid mediators and cytokines are involved in the late phase of the immunopathology of allergic conjunctivitis. Current management of allergic conjunctivitis includes non-pharmacological approaches such as allergen avoidance and palliative therapy, whereas pharmacological therapeutic modalities may include antihistamine–mast cell stabiliser combination ophthalmic formulations and allergen-specific immunotherapy. Furthermore, as cellular and soluble mediators play a pivotal role in the immunopathogenesis and immunopathology of allergic conjunctivitis, development of immunotherapeutic and pharmacotherapeutic agents specific to these mediators can enhance the therapeutic index and safety profile of anti-allergy treatment.

Keywords: Allergic conjunctivitis, immunopathogenesis, immunopathology, immunotherapy.

INTRODUCTION

Allergic hypersensitivity reaction affecting the ocular surface is either immunoglobulin (Ig)E and/or T cell mediated, with allergic conjunctivitis being predominantly an IgE-mediated hypersensitivity immune reaction to environmental allergens.[1] The two forms of allergic conjunctivitis are seasonal allergic conjunctivitis and perennial allergic conjunctivitis. Seasonal allergic conjunctivitis is due to outdoor airborne allergens. The common aeroallergens are tree and grass pollen, which are common during the spring and summer months. Perennial allergic conjunctivitis is a year-round variant of allergic conjunctivitis, which is associated with dust mites, mould, and pet dander.[2,3] Allergic disease affects more than a third of the world's population and >40% of these individuals have ocular involvement associated with their allergic condition.[4] The quality of life of individuals with allergic conjunctivitis is affected, with a significant impact on work productivity and school performance.[5] This review focusses on the immunopathogenesis, immunopathology, clinical manifestations, and immunotherapeutic modalities of allergic conjunctivitis.

CONJUNCTIVA: AN IMMUNOLOGIC ACTIVE BARRIER

Conjunctiva is an immunologically active mucous membrane that consists of epithelial and subepithelial layers.[6,7] The conjunctival subepithelial layer is a fibrovascular connective tissue consisting of blood vessels, immune cells, and non-immune cells. Goblet cells, intraepithelial lymphocytes, and Langerhans cells are found in the conjunctival epithelial layer.[7,8] Macrophages and connective tissue-type mast cells are found only in the subepithelial layer (conjunctival stroma) of the conjunctiva, whereas eosinophils are not present in the normal conjunctiva.[7,9] The distribution

of immune cells in the conjunctiva constitutes the mucosal immune system of the conjunctiva known as the conjunctiva-associated lymphoid tissue (CALT).[10] It is biased toward inducing anti-inflammatory immunity that favours the generation of IgA-producing plasma cells, regulatory T cells, and immunosuppressive cytokines (e.g., interleukin 10), which provide immunological protection for the cornea. Diffuse lymphoid effector tissue is the efferent arm of CALT and consists mainly of effector lymphocytes. Follicle-organised inductive lymphoid tissue is the afferent arm of CALT and consists of B cells, T cells, and apical follicle-associated epithelium with microfold cells. It serves as a site of localised immune processing of antigens that pass through the conjunctival epithelium.[11]

Mast cells are major effector cells of allergic inflammation of the conjunctiva, of which the connective tissue type that contains tryptase and chymase are found in the conjunctiva stroma.[1,12] Histamine is a low molecular weight biogenic amine secreted by degranulated conjunctival mast cells and plays an important role in the immune and pathological mechanisms of allergic conjunctivitis via interaction with histamine receptors. It is noteworthy that histamine receptors are members of the G protein-coupled receptors.[3,13,14] Histamine is produced by L-histidine decarboxylate-mediated decarboxylation of histidine and it is degraded by histamine N-methyl transferase and diamine oxidase.[14-17] Histamine 1 receptor (H1R) and histamine 2 receptor are expressed on nerve cells, vascular smooth muscles, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, macrophages, dendritic cells (DC), goblet cells, T cells, and B cells.[18,19] Histamine 3 receptors are expressed on nerve cells and goblet cells.[8] Histamine 4 receptors are expressed on mast cells, goblet cells, basophils, eosinophils, monocytes, macrophages, T cells, basophils, and DC.[17,19] The healthy conjunctiva epithelium has intercellular junctions that help maintain its barrier function of preventing allergens from gaining access to the subepithelial layer;[20] however, in allergic conjunctivitis, disruption of the conjunctival epithelial barrier function through the activation of the protease-activating receptor is likely to play a role in the pathogenesis of allergic conjunctivitis.[21] Furthermore, epithelial cells have an active role in allergen-induced conjunctival inflammation through the action of cytokines, chemokines, thymic stromal lymphopoietin (TSLP), and adhesion molecules they release during the allergic response. These mediators promote the influx of immune cells into the site of allergic inflammation.[22-24]

Toll-like receptors (TLR) are pattern recognition receptors expressed on both non-immune (epithelial, fibroblast) and immune cells (macrophages, DC, lymphocytes, mast cells) of the conjunctiva.[25,26] Interaction between an appropriate TLR ligand and a TLR initiates a signalling cascade that leads to the generation of cytokines.[8] Activation of TLR-2 and TLR-4 expressed on mast cells is associated with degranulation of activated mast cells and release of cytokines, and, as such, it is most likely that increased expression of TLR on the conjunctiva occurs during ocular allergic conditions.[26] The conjunctiva expresses transient receptor potential (TRP) channels, such as TRPV1, found on sensory nerve fibres, epithelial cells, and mast cells.[27] Activation of TRPV1 on conjunctival epithelial cells and mast cells is associated with ocular itch.[28]

Fibroblasts are cells that produce compounds that make up the extracellular matrix and provide structural support to the conjunctiva.[29] Additionally, conjunctival fibroblasts can act as immune modulators in allergic conjunctivitis by expressing chemokines (e.g., thymus and activation-regulated chemokine or chemokine [C-C motif] ligand 17 [CCL17]), matrix metalloproteinase, and adhesion molecules (e.g., intercellular adhesion molecule 1) in response to stimulation by IL-4 released by degranulated mast cells. It is noteworthy that thymus and activation-regulated chemokines are potent chemoattractants for Type 2 helper (Th2) cells.[30,31]

IMMUNOPATHOGENESIS: THE SENSITISATION PHASE OF ALLERGIC CONJUNCTIVITIS

Exposure of the conjunctiva to allergens initiates the immunopathogenesis of allergic conjunctivitis, which is initially characterised by the sensitisation of conjunctival mast cells by allergen-specific IgE. Protease produced by environmental allergens activate protease-activated receptor-2 in the conjunctiva, culminating in a breakdown of the tight junction between conjunctival epithelial cells and subsequent entry of the allergen into the subepithelial layer, where they have access to immune cells.[32] Conjunctival DC engulf and process these allergens, changing them into peptides

that are complexed to major histocompatibility complex Class II molecules on the mature DC. Additionally, to ensure activation of naïve T cells in the regional secondary lymphoid organs, there is upregulation of CD80 and CD86, costimulatory molecules required for providing the costimulatory signal during the activation of naïve T cells. In the regional lymph node, the interaction of peptide–major histocompatibility complex Class II on the mature DC with T cell receptor on naïve CD4 T cells results in activation, proliferation, and differentiation of CD4 T cells into allergen-specific Th2 cells. Allergen-specific Th2 cells release IL-4, a cytokine that induces the proliferation and differentiation of allergen-specific B cells into plasma cells that produce allergen-specific IgE. The interaction between CD40 on allergen-specific B cell and CD40 ligand on allergen-specific Th2 cell is associated with allergen-specific Th2 cells releasing IL-4, which induces the proliferation and differentiation of allergen-specific B cells into plasma cells that produce allergen-specific IgE.[33] Conjunctival mast cells become primed when allergen-specific IgE binds via its Fc region to the Ig-like domain of the alpha chain of Fc Epsilon Receptor I (FcεRI) on the surface of conjunctival mast cells.[34,35]

Environmental allergens possess proteolytic capabilities that cause damage to the epithelium; subsequently, damaged epithelial cells release pro-allergic cytokines, such as IL-33.[36] Additionally, TSLP is a pro-allergic cytokine released by allergen-activated conjunctival epithelium. Li et al.[37] demonstrated that short ragweed pollen, an agonist for TLR4, is capable of inducing conjunctival epithelial cells to produce TSLP via the TLR4-dependent innate immunity pathway. TSLP interact with TSLP receptors on conjunctival DC, leading to upregulation of OX40 ligand expression. TSLP-activated conjunctival DC expressing OX40 ligand migrates to the regional lymph node to promote Th2 differentiation via OX40 ligand and OX40 interactions.[38,39] It is noteworthy that TSLP inhibit IL-12p40 expression in DC, allowing for conjunctival DC to activate naïve CD4 T cells to differentiate into Th2 cells.[40] Furthermore, Li et al.[41] demonstrated that pollen interacts with TLR4 on ocular surface epithelium in innate immunity to induce the conjunctival epithelium to secrete IL-33, a pro-allergic epithelial cytokine that promotes Th2 cell differentiation. Thus, Th2 cells and conjunctival epithelial cells participate in initiating priming of conjunctival mast cells in the sensitisation phase of allergic conjunctivitis (Figure 1).[1,33,39]

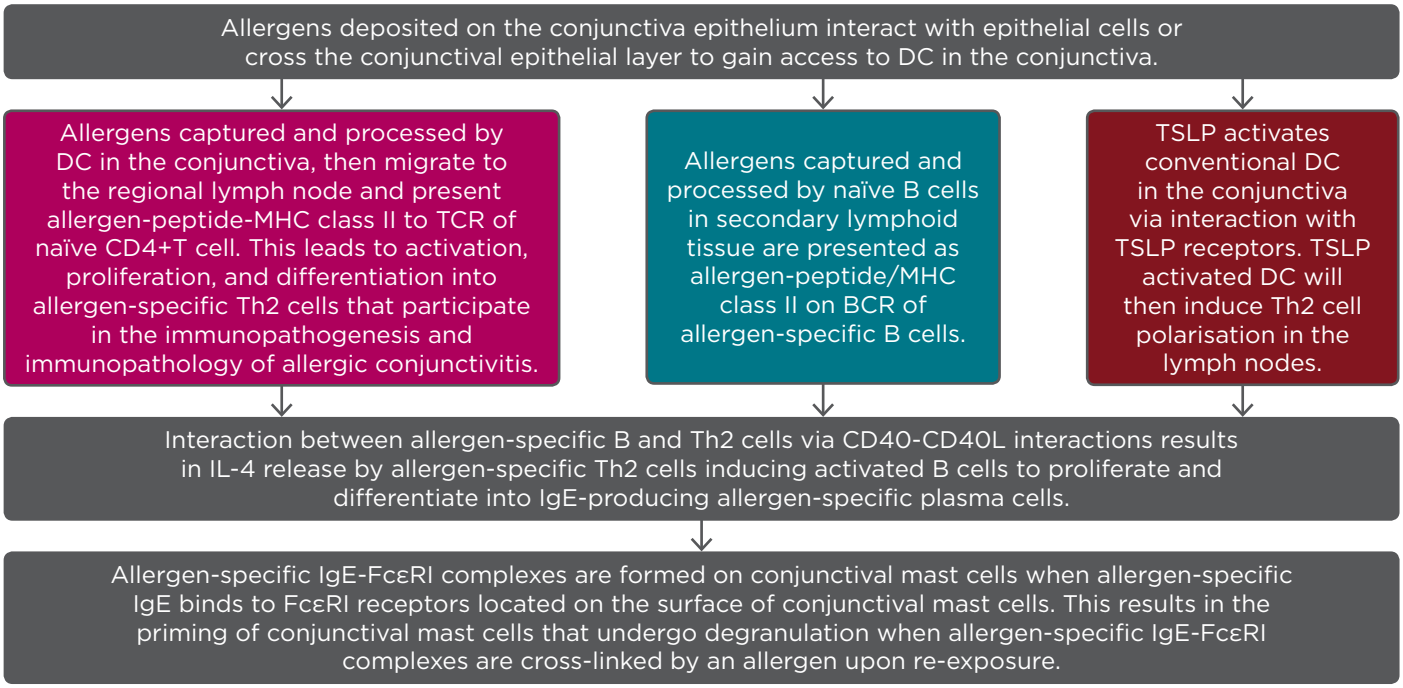

Figure 1: Sensitisation phase of allergic immune response is associated with generation of allergen-specific immunoglobulin E antibodies that bind to FcεRI receptors on the surfaces of conjunctival mast cells.

Note: The three colours depicted represent three routes of Th2 polarisation.

BCR: B cell receptor; DC: dendritic cells; IgE: immunoglobulin E; IL-4: interleukin 4; MHC: major histocompatibility complex; TCR: T cell receptor; Th2: Type 2 helper; TSLP: thymic stromal lymphopoietin.

Innate lymphoid cells (ILC), grouped into three cell types on the basis of cytokine and transcription factor profile, may have a role in allergic eye disease. ILC2 has similar lymphoid morphology and phenotype to Th2 cells, but lacks an antigen receptor. Epithelial cell and myeloid cell-derived IL-25, IL-33, and TSLP can activate and recruit ILC2, which, in turn, releases IL-4 that plays a role in Th2 cell differentiation.[36] Innate T cells, such as γδT cells and natural killer T cells, have been shown to maximise the expression of allergic conjunctivitis. Both natural killer T cells and γδT cells can secrete IL-4, which promotes the differentiation of CD4 T cells into allergen-specific Th2 cells.[42,43] Furthermore, though Th2 cells are the predominant mediators in ocular allergy, evidence exists of other Th cell subsets participating in allergic eye disease. Th1, Th2, Th17, and regulatory T cells are other subsets of CD4 T helper cells, of which Th1 and Th17 cells, in addition to Th2 cells, play a role in severe chronic forms of ocular allergy, such as atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC).[40]

IMMUNOPATHOLOGICAL MECHANISMS: THE EARLY PHASE OF ALLERGIC CONJUNCTIVITIS

Re-exposure of the conjunctiva to allergens that induced the priming of conjunctival mast cells leads to early and late phase immunopathological responses characteristic of allergic conjunctivitis. The early phase allergic response is initiated by the binding of multivalent allergens to the IgE–FcεRI complex on primed conjunctival mast cells. This is followed by crosslinking of IgE–FcεRI complexes on primed conjunctival mast cells causing activation and subsequent degranulation of primed conjunctival mast cells.[4,33,44,45] Degranulation of mast cells results in immunobiological reactions that occur in response to the release of preformed mediators, such as biogenic amines (e.g., histamine) and neutral proteases (e.g., tryptase). Release of preformed mediators is followed by synthesis and release of lipid mediators (e.g., prostaglandins, leukotrienes) and cytokines (e.g., IL-4).[4,33] This outlines the activation phase of allergic response in allergic conjunctivitis. The signs and symptoms of the early phase of allergic conjunctivitis include hyperaemia, chemosis, tearing, itching, and eyelid oedema. The clinical manifestations of the early phase allergic reaction are attributed to the action of histamine on the vascular endothelium of conjunctival blood vessels, conjunctival sensory nerve fibres, immune cells, and resident cells in the conjunctiva and conjunctival epithelium. When histamine interacts with H1R and histamine 2 receptor on conjunctival blood vessels, it induces conjunctival vasodilation and increased capillary leakage, which cause conjunctival hyperaemia and chemosis, respectively. Interaction between histamine and H1R on conjunctival sensory nerve fibres is associated with the patient's complaint of ocular itch. Histamine interacts with histamine receptors on DC leading to maturation of dendritic cells. Histamine-activated DC are capable of activating naïve CD4 T cells to differentiate into allergen-specific Th2 cells that secrete IL-4, a cytokine that activates conjunctival fibroblasts to undergo proliferation and increased collagen synthesis, which manifests as papillae on the palpebral conjunctiva (Figure 2). Additionally, Ahadome et al.[46] demonstrated that conjunctival conventional DC-derived aldehyde dehydrogenase mediates the inflammation-induced conjunctival fibroproliferative pathological changes in a mouse model of severe allergic disease via its synthesis of retinoic acid, following interaction between DC and conjunctival fibroblasts.

Furthermore, the binding of histamine with its receptors on the conjunctival epithelium is associated with breach of the barrier function of the conjunctival epithelium and expression of adhesion molecules, chemokines, and cytokines from histamine-activated conjunctival epithelial cells.[4,8,15,16,33,45,47] Interaction between histamine and H4R on mast cells and Th2 cells is associated with recruitment of these cells to the site of allergen-induced conjunctival inflammation to potentiate the histamine-induced allergic inflammation with remodelling of the conjunctiva.[19,48] In addition to the role of IL-4 in remodelling the palpebral conjunctiva, tryptase released along with histamine during the early phase is known to trigger the proliferation of conjunctival fibroblasts, which results in papillary hypertrophy of the palpebral conjunctiva. It is notable that histamine and tryptase are biomarkers of IgE-mediated mast cell activation and degranulation in the early phase of allergic conjunctivitis.[4] Thus, conjunctival fibroblasts promote allergen-induced conjunctival inflammation and tissue remodelling in allergic conjunctivitis.[49] It is also noteworthy that patients with AKC and VKC present with significant papillary hypertrophy of the lower and superior palpebral conjunctiva, respectively. Furthermore, limbal gelatinous hyperplasia is another conjunctival fibroproliferative lesion in VKC and AKC.[1,50]

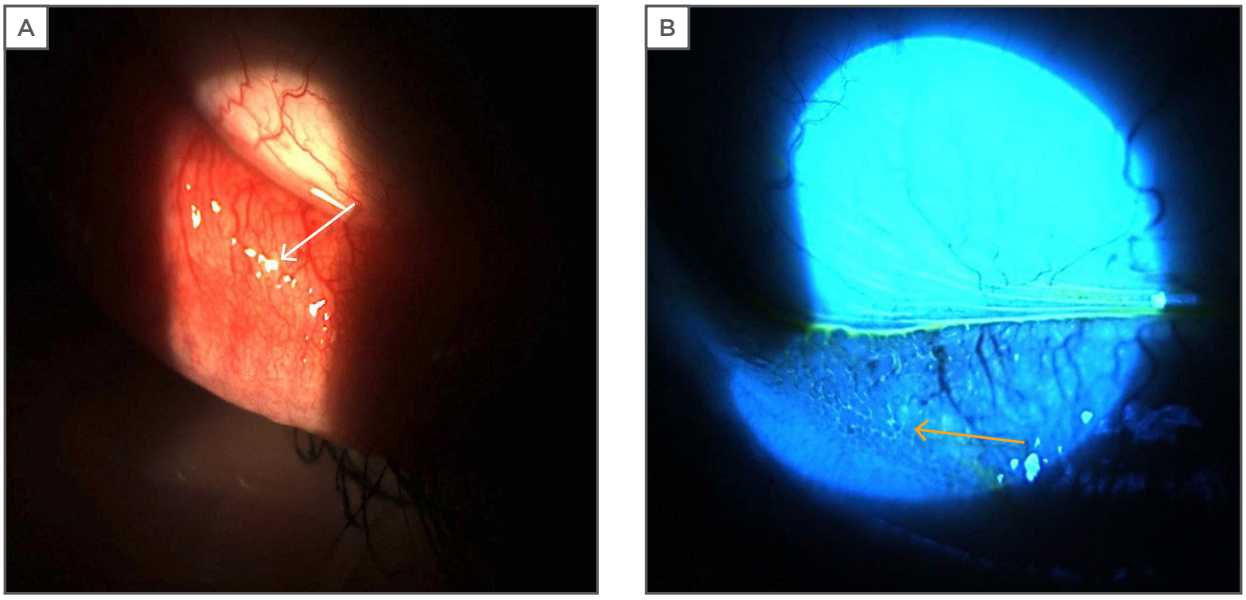

Figure 2: Photographs of inferior palpebral conjunctiva papillae in a patient with seasonal allergic conjunctivitis.

A: white light on inferior palpebral conjunctiva with reflections off of papillae (white arrow); B: blue light on inferior palpebral conjunctiva with fluorescein dye pooling between papillae (yellow arrow).

IMMUNOPATHOLOGICAL MECHANISMS: THE LATE PHASE OF ALLERGIC CONJUNCTIVITIS

Additionally, degranulated mast cells release lipid mediators, such as prostaglandins and leukotrienes, which play a role in the early stages of the late phase allergic response and potentiate the histamine-mediated clinical expression of allergic conjunctivitis. Prostaglandin causes conjunctival hyperaemia by inducing vasodilation of conjunctival blood vessels. It also intensifies the histamine-mediated ocular pruritus. Leukotrienes induce vasodilation and increased permeability of conjunctival blood vessels, which manifest as conjunctival hyperaemia and chemosis, respectively.[33] Additionally, prostaglandin D2 and leukotriene D4 may induce the recruitment and activation of ILC2.[36] Cytokines (e.g., IL-4, IL-5, and IL-13) and chemokines (e.g., CCL17) are released from degranulated conjunctival mast cells. Cytokines play a role in activating conjunctival epithelial cells and fibroblasts, as well as recruiting and activating eosinophils in the late phase. These cytokine-activated conjunctival cells release chemokines and adhesion molecules that recruit inflammatory cells to the site of allergic inflammation. IL-5 recruits and activates eosinophils, a type of immune cell that participates in the late phase of allergic conjunctivitis, where it plays a role in tissue damage and ocular surface remodelling, particularly in perennial allergic conjunctivitis and chronic forms of ocular allergy. Intercellular adhesion molecule 1 plays a role in the recruitment of immune cells, including lymphocytes into the conjunctiva, which leads to the persistence and exacerbation of chronic allergen-induced conjunctival inflammation.[2,33,50] IL-4 and IL-13 stimulate conjunctival fibroblasts to produce vascular endothelial growth factor, which plays a role in remodelling the palpebral conjunctiva, resulting in papillary hypertrophy of the palpebral conjunctiva.[51] As such, conjunctival mast cell-derived cytokines and chemokines in conjunction with prostaglandins and leukotrienes contribute to the immunopathology of the late phase of allergic conjunctival inflammatory reaction.[1]

Conjunctival hyperaemia and chemosis are ocular findings attributed to the action of histamine and leukotrienes (Figure 3).[2,4,33] The hallmark symptom of ocular itch is mediated by the interaction between histamine and its receptor on conjunctival sensory fibres. TRPV1 activation by leukotriene B4 is associated with ocular itching via interaction with LTB4 and its receptors on sensory nerve fibres; histamine-induced itching requires the activation of TRPV1 on sensory nerve fibers.[52] Mucoid secretion in allergic conjunctivitis is associated with oversecretion of mucus by histamine-activated

goblet cells in the conjunctiva[8] and leukotriene (C4 and D4)-activated goblet cells.[2,4,33] Conjunctival fibroproliferative lesions in allergic conjunctivitis are due to infiltration of the conjunctiva with immune cells recruited by chemokines and adhesion molecules,[1,2,33,50] as well as the action of conjunctival DC-derived aldehyde dehydrogenase.[46]

CURRENT AND EMERGING TREATMENTS IN OCULAR ALLERGY

Management of allergic conjunctivitis should include allergen avoidance, pharmacotherapy, immunotherapy, and patient education. Specifically, topical medications cover a wide range of pharmacological classes, including vasoconstrictors, antihistamines, mast cell stabilisers, dual action antihistamines/mast cell stabilisers, and corticosteroids. Although topical corticosteroids are highly effective in relieving the signs and symptoms of acute flare up of allergic conjunctivitis, their prolonged use can result in unwanted and serious sequelae. As such, the use of immunomodulators, such as calcineurin inhibitors, would provide comparable treatment efficacy without the side-effect profile associated with chronic corticosteroids in recalcitrant cases or chronic forms of ocular allergy, such as AKC and VKC. Cyclosporine is a calcineurin inhibitor that blocks the IL-2-induced proliferation of Th2 cells and inhibits histamine release from mast cells. Immunosuppressive effects of cyclosporine would be effective in controlling allergic conjunctival inflammation.[50,53] Similarly, tacrolimus is a calcineurin inhibitor with a similar mechanism of action to cyclosporine but greater immunosuppressive potency. Attas-Fox et al.[54] reported that tacrolimus 0.03% dermatologic ointment was safe and well-tolerated in providing therapeutic benefit for patients with intractable allergic conjunctivitis. In chronic forms of allergic conjunctivitis, both cyclosporine and tacrolimus, by virtue of their mechanism of action, can be helpful in intractable cases.

Another potential therapy for treating allergic rhinoconjunctivitis is omalizumab, a recombinant humanised monoclonal antibody that binds to the Fc portion of IgE to reduce the availability of free IgE for binding to FcεRI. Another mechanism of action of omalizumab is to dissociate IgE from the IgE–FcεRI complex on primed mast cells.[55] Because allergic conjunctivitis is an IgE-mediated conjunctival inflammatory disease, there is a potential clinical use for omalizumab in the management of allergic conjunctivitis. Allergen-specific immunotherapy reduces the clinical expression and prevents recurrence of allergic diseases by inducing immunological tolerance to allergens. Allergen-specific immunotherapy for treating allergic conjunctivitis involves the administration of allergens into the conjunctiva, which then results in the induction of increased immune tolerance to the inciting allergen.

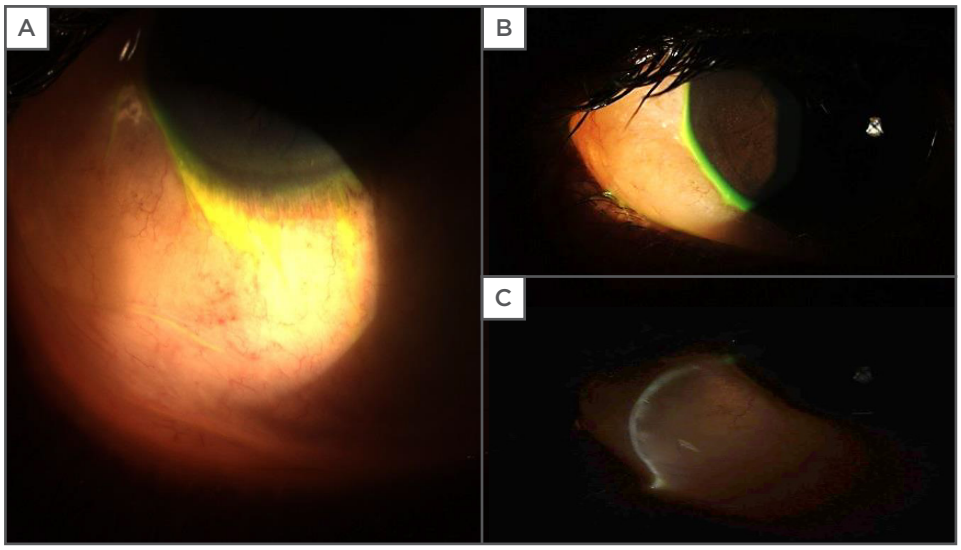

Figure 3: Photographs of severe bulbar conjunctival chemosis secondary to allergy.
A and B: severe conjunctival chemosis of temporal conjunctiva with marked elevation and billowing over lower eyelid and extending to corneal limbus; C: optic section through conjunctival chemosis indicates substantial underlying oedema causing striking elevation.

This mode of allergen-specific immunotherapy would be beneficial for patients with perennial allergic conjunctivitis.[56] Future consideration for targeted immunotherapy may include the blocking of TSLP signalling via a soluble TSLP receptor–Ig to decrease downstream signalling. This has been shown to be effective in pulmonary DC and may prove effective as an agent in attenuating TSLP-induced activation of DC that leads to the generation of allergen-specific Th2 cells.[57] Schlereth et al.[58] reported that blockade of C-C chemokine receptor Type 7 (CCR7) in immunised mice resulted in inhibition of allergic conjunctivitis. Because CCR7 is pivotal for chemokine-mediated trafficking of mature allergen-ladened DC to the lymph node, blockade of CCR7 may be therapeutically beneficial in individuals with allergic conjunctivitis. As such, most of the cells and mediators that participate in the immune and pathological mechanism of allergic conjunctivitis could be potential therapeutic targets for allergic conjunctivitis.

CONCLUSION

Allergic conjunctivitis is predominantly an IgE-mediated hypersensitivity reaction to environmental allergens. Cellular and soluble mediators play a major role in the immunopathogenesis and immunopathology of allergic conjunctivitis. Allergen-induced degranulated conjunctival mast cells release histamine, tryptase, prostaglandins, leukotrienes, and cytokines. Soluble mediators are also released by activated epithelial cells and fibroblasts in the conjunctiva. These mediators play important roles in immune and pathological mechanisms that generate the clinical manifestations of allergic conjunctivitis. Current management of allergic conjunctivitis includes non-pharmacological and pharmacological therapeutic modalities. Research into the emerging role of pattern recognition receptors in the immunopathogenesis of allergic conjunctivitis, as well as further studies on immune mechanisms of molecules derived from allergen-activated conjunctival epithelial cells and myeloid cells, would provide a clear understanding of their role in the immunopathogenesis and immunopathology of allergic conjunctivitis. Furthermore, it will be imperative for current and future research to broaden our understanding of the role of conjunctival macrophages in the immunopathogenesis and immunopathology of allergic conjunctivitis. Such knowledge is required for developing immunotherapeutic and pharmacotherapeutic agents with an enhanced safety profile and anti-allergic therapeutic index.

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ADVANCES IN FAECAL DNA TESTING FOR COLORECTAL CANCER SCREENING: A LITERATURE REVIEW FOR PRIMARY CARE PROVIDERS

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Disclosure: The authors have declared no conflicts of interest.
Received: 19.06.17 **Accepted:** 13.11.17
Citation: EMJ. 2018;3[1]:84-89.

ABSTRACT

Recent epidemiological data gathered by the Centers for Disease Control and Prevention (CDC) suggest that colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the USA. Clinicians currently use five types of test to screen for CRC. Two of these five types, the DNA stool test and the faecal occult blood test, are non-invasive. The DNA stool test successfully detects both advanced neoplasias and non-advanced adenomas with more sensitivity than the faecal occult blood test. However, data suggest that it also generates more false-positive results. There is only one DNA stool test that has been approved by the U.S. Food and Drug Administration (FDA): the approved Cologuard® (Exact Sciences, Madison, Wisconsin, USA) test. This test screens for nine different DNA biomarkers, one haemoglobin biomarker, and one β-actin. This article is a literature review of research on faecal DNA biomarkers conducted in the past 5 years from four large databases. Key findings include the ability to reach a sensitivity as high as 98% to detect abnormalities in the colon using a multi-target stool DNA-based assay. In comparison, the Cologuard offers 92% sensitivity and 87% specificity for all stages of CRC. Testing DNA biomarkers can serve as an adequate screen for cancer and adenomas in average-risk adults. Areas for further research include implementing studies to compare long-term health consequences for patients who receive colonoscopies versus DNA stool tests, finding ways to improve both the sensitivity and specificity of screening tests, and finding ways to improve the detection of those biomarkers most associated with CRC, including microRNA detection in the marking panel.

Keywords: Colorectal cancer (CRC), early markers, faecal immunochemical test, screening test, stool DNA (sDNA).

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), colorectal cancer (CRC) is currently the second leading cause of cancer-related deaths in the USA.[1] In 2013, approximately 71,000 men and 65,000 women were diagnosed with CRC.[1] Primary care providers use five types of test to screen for CRC: two faecal occult blood tests (the guaiac faecal occult blood test and the faecal immunochemical test [FIT]), a DNA stool test (also referred to as the FIT-DNA), sigmoidoscopy, colonoscopy, and virtual colonoscopy.[2] Unfortunately, many symptoms of CRC, such as a change in bowel habits, blood in the stool, narrow stools, weight loss, fatigue, and vomiting, only manifest once the cancer has approached late stages. Almost half of CRC incidences are detected at late stages.[3] Therefore, early screening, accurate detection, and early intervention are all key to improved outcomes and decreased mortality.

Early detection of CRC is crucial to treatment and survival. The most reliable way to detect early CRC is through colonoscopy.[4] Colonoscopy offers high accuracy and allows for longer time between screening but also has numerous disadvantages, including an extensive bowel preparation process, risks due to general anaesthesia, risk of bowel perforation, and length of the procedure.[4] The U.S. Preventive Services Task Force

recommends that all adults have a colonoscopy for screening purposes, beginning at 50 years old, and that they undergo a repeat colonoscopy every 10 years if the results are normal, until the age of 75 years.[4]

In contrast, faecal occult blood tests and DNA stool tests offer a non-invasive screening alternative that involves no preparation and can be completed at home.[4] The development of CRC is a multistep process that begins with the normal mucosa of the large intestine mutating into abnormal lesions.[5] This causes a continuous shedding of mutated cells that are then excreted into the faeces.[5] Since human DNA is stable in faeces, it can be separated out and analysed for tumour-associated alterations.[5] Many tests have been conducted to identify the mutations most associated with CRC; however, there is currently just one DNA stool test approved by the U.S. Food and Drug Administration (FDA): the Cologuard® (Exact Sciences, Madison, Wisconsin, USA). The National Cancer Institute determined that Cologuard can discern microscopic blood as well as nine DNA biomarkers that code for three different genes (*NDRG4*, *BMP3*, and *KRAS*). These genes have been linked to both CRC and adenomas, which are precancerous but advanced growths found in the gut. As cells pass through a patient's colon and rectum, DNA from these cells shed and bind together in the stool. A specialised computer program can successfully analyse these cells and categorise them into positive or negative findings. Patients who are given a positive result are recommended to proceed with a colonoscopy.[5]

In a substantial study, it was demonstrated that in patients at average risk of developing CRC with no cancer-suggestive symptoms at the time, Cologuard could detect both more adenomas and more cancerous lesions than the FIT test.[5] In other words, Cologuard was more sensitive than the FIT test. It should be noted, however, that Cologuard produced more false-positive results than the FIT test.[5] Cologuard tests for seven DNA mutation biomarkers (*KRAS*) and two DNA methylation biomarkers (*NDRG4* and *BMP3*), as well as one haemoglobin biomarker and one β-actin marker.[6] Cologuard is currently covered under Traditional Medicare and Medicare Advantage plans for patients between the ages of 50 and 85 years who show no signs or symptoms of CRC and are at an average risk of developing CRC.[7] Medicaid coverage varies by state, and private insurance policies vary greatly. The out-of-pocket cost for one kit is $649.[6]

While the future for DNA stool tests is promising, there is a strong need for further research into DNA biomarkers beyond the nine currently used in Cologuard, as well as for research that validates the sensitivity and specificity of these biomarkers, particularly in detecting adenomas. In the current article, the authors investigated the following population, intervention, control, and outcomes (PICO) clinical question: Is faecal DNA testing accurate in screening for CRC? The following four online databases were used: PubMed, Scopus, Web of Science, and Cumulative Index to Nursing and Allied Health Literature. A review was conducted of the literature spanning the past 5 years from 2012 to January 2017.

METHODS

Search Strategies and Key Term Definitions

PubMed was the first database searched. The search began with 'colorectal cancer screening' and results were further narrowed by adding the additional keywords 'fecal DNA biomarkers' and 'noninvasive'. This yielded a total of 17 suitable articles from the PubMed database. Secondly, those same search terms were used in Scopus, which resulted in 11 articles. Thirdly, a search was conducted in Web of Science using the same key terms, which yielded 10 articles. Finally, a search search of the Cumulative Index to Nursing and Allied Health Literature resulted in no further articles after all the key terms were entered. This review of the literature was conducted on 11th February 2017.

The authors maintained the following inclusion criteria: articles published in English, published within the past 5 years, articles must pertain to faecal DNA biomarker testing rather than serum DNA, and articles must pertain to DNA testing rather than RNA. The terms 'faecal DNA biomarkers' and 'non-invasive' can be defined as follows: a faecal DNA biomarker is a biological DNA molecule found in faecal matter that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Biomarkers are also called molecular markers and signature molecules.[8] Non-invasive is defined as: "A procedure that does not require inserting an instrument through the skin or into a body opening."[9]

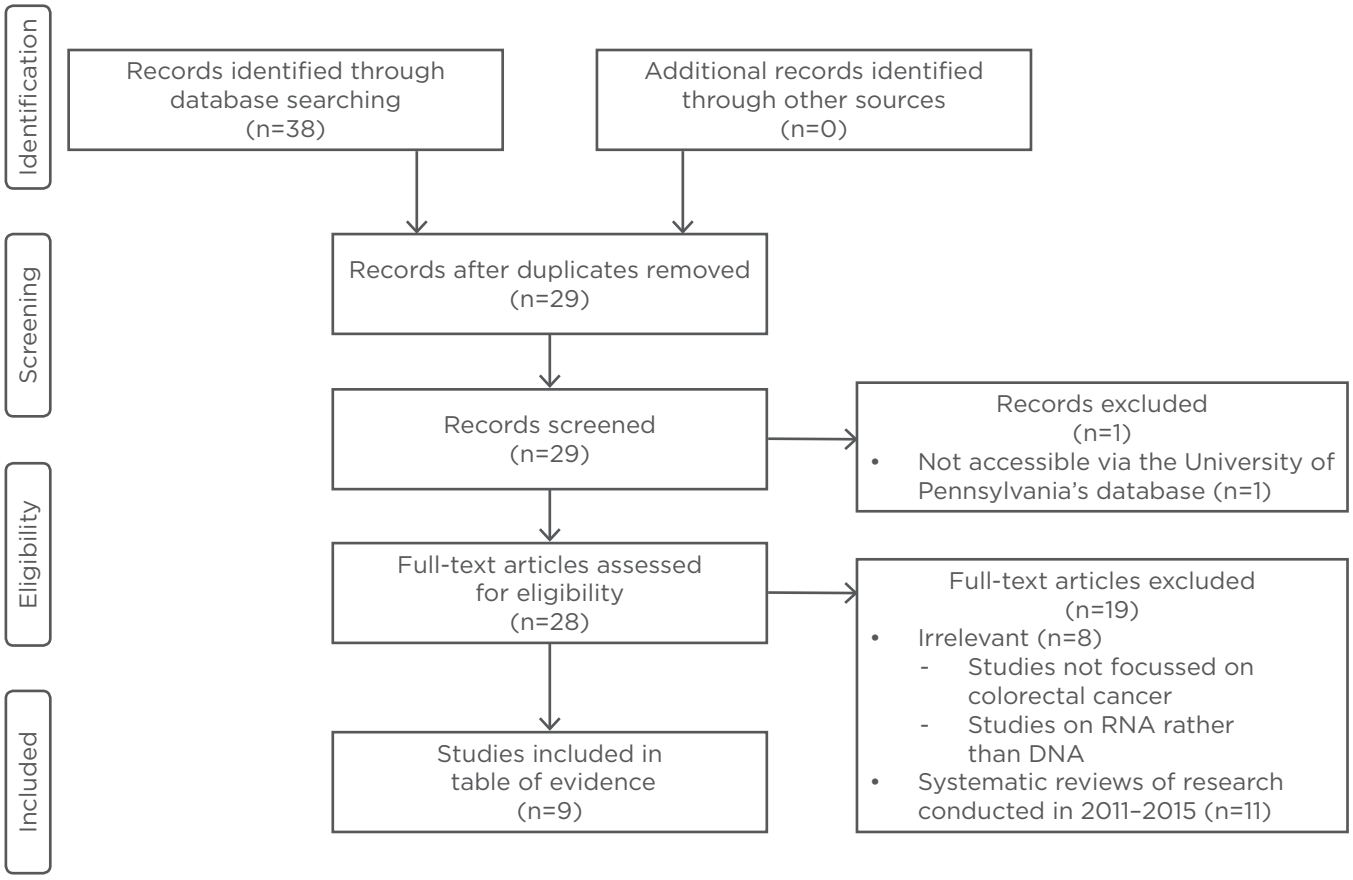

Figure 1: Preferred reporting items for systematic reviews and meta-analyses.

Organising the Evidence and Assessing Evidence Quality

To organise these articles, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram was used (Figure 1). This tool illustrates the stages of research conducted in a systematic review.[10] At the end of the searches from all four databases, 38 articles were identified. Nine articles were removed because they were duplicates (Figure 1). One article was not accessible through electronic means and was therefore excluded. Nineteen articles were removed due to irrelevance; many articles in this group were investigating other types of cancers, blood screening tests, and RNA testing. The nine articles that remained focussed specifically on the effectiveness of faecal DNA testing in the screening of CRC. These nine articles were evaluated using the Grading of Recommendations Assessment, Development, and Evaluation method. This is a system used for rating the quality of research evidence and considers the study design and magnitude of effect, along with the risk and presence of bias, imprecision, inconsistency, and indirectness. It assigns one of four levels of quality: high, medium, low, and very low (Table 1).[11]

RESULTS AND COMMON THEMES

Summary of Studies found in the Literature Review

Given the vast range of possibilities in the field of genetics and epigenetics, the studies analysed each focussed on different DNA markers (Table 1). Many focussed on determining the specificity of a single DNA mutation in detecting CRC.[12-14] Lu et al.[12] and Babaei et al.[13] both studied the *SFRP2*. Carmona et al.[15] looked at three genes: *AGTR1*, *WNT2*, and *SLIT2*, while Baxter et al.[16] conducted a study that isolated the 16S ribosomal RNA gene. Other studies focussed on epigenetics, specifically the methylation of promoter genes, which causes the potential for the hyperexpression or silencing of genes.[17,18] Several hypermethylated genes have been linked with CRC; Wu et al.[17] specifically looked at microRNA promoters in this context. Lastly, two articles tested stools for both genetic and epigenetic mutations, which is how Cologuard screens for CRC;[19,20] Lidgard et al.[19] and Imperiale et al.[20] both

used a multi-target stool DNA (sDNA) assay to measure sDNA markers as well as methylation. All studies differed regarding sample size, DNA markers, control groups, and findings. However, analysing the sensitivity and specificity of different biomarkers is beneficial in drawing conclusions about the usefulness of these tests relative to one another.

Table 1: Grading of recommendations assessment, development, and evaluation system applied to articles pertaining to faecal DNA testing in colorectal cancer screening.

Author	Type of study	Method	Sample or setting	Biomarker or detection method used	Sensitivity and specificity	GRADE[11]
Lu et al.,[12] 2014	Case-control	Quantitative	N=96 Outpatient university research institute	*SFRP2*, *GATA5*	*SFRP2*: Sensitivity: 57.0% Specificity: 70.0% *GATA5*: Sensitivity: 83.9% Specificity: 82.5%	Very low
Babaei et al.,[13] 2016	Cross-sectional	Quantitative	N=50 Outpatient university research institute	*SFRP2*	Sensitivity: 60.0% Specificity: 92.0%	Very low
Guo et al.,[14] 2013	Case-control	Quantitative	N=105 Outpatient university research institute	*FBN1*	Sensitivity: 72.0% Specificity: 93.3%	Low
Carmona et al.,[15] 2013	Case-control	Quantitative	N=151 Outpatient hospital office, public data sets	*AGTR1*, *WNT2*, *SLIT2*	Specificity: *AGTR1*: 21.0% *WNT2*: 40.0% *SLIT2*: 52.0%	Low
Baxter et al.,[16] 2016	Cross-sectional	Quantitative	N=404 Outpatient medical offices (4)	Detection of microbiota in FIT test	-	Low
Wu et al.,[17] 2014	Case-control	Quantitative	N=122 Outpatient university research institute	miR-34a and miR-34b/c miRNA methylation	miR-34a: Sensitivity: 76.8% Specificity: 93.6% miR-34b/c: Sensitivity: 95.0% Specificity: 100.0%	Low
Ghanbari et al.,[18] 2016	Observational	Quantitative	N=77 Outpatient university research institute	Let-7a-5p and Let-7f-5p miRNA	"Significant to discriminate between CRC subjects and healthy subjects."	Very low
Lidgard et al.,[19] 2013	Case-control	Quantitative	N=1,003 Outpatient medical offices (21)	Multi-target sDNA assay	Sensitivity: 98.0% Specificity: 90.0%	Low
Imperiale et al.,[20] 2014	Cross-sectional	Quantitative	N=9,989 Outpatient university research institute, medical offices (90)	Multi-target sDNA (Fit-DNA / Cologuard)	Sensitivity: 92.3% Specificity: 86.6%	Moderate

AGTR1: angiotensin II receptor type 1; *FBN1*: fibrillin 1; FIT: faecal immunochemical test; *GATA5*: GATA binding protein 5; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; miRNA: microRNA; sDNA: stool DNA; *SFRP2*: secreted frizzled-related protein 2 gene; *SLIT2*: Slit homolog 2 protein; WNT2: *WNT* family member 2.

Sensitivity and Specificity of Biomarkers

Of the nine studies found through the literature search, seven studies researched the sensitivity and specificity of stool biomarkers. Sensitivity is the extent to which a test can correctly identify a positive result (true-positive) and specificity is the extent to which a test can correctly identify a negative result (true-negative). A test with low sensitivity would produce more false-negatives and a test with low specificity would produce more false-positives. The sensitivities of the tests in the studies identified ranged from 57–98% (Table 1). Lidgard et al.[19] found the highest sensitivity (98%) using a multi-target sDNA assay to measure β-actin (a marker of total human DNA), mutant *KRAS*, aberrantly methylated *BMP3* and *NDRG4*, and faecal haemoglobin. It is possible that the high sensitivity was due to their test being an assay of multiple biomarkers for CRC. The study with the lowest sensitivity was Lu et al.,[12] which tested the biomarker *SFRP2* (57%). Babaei et al.[13] also studied *SFRP2* in stool samples and found a similar specificity of 60%. For specificity, the tests ranged from 21–100% (Table 1). Wu et al.[17] studied the methylation status of miR-34a and miR-34b/c promoter in CRC patients' stool samples and found the specificity of miR-34b/c was 100%. Carmona et al.[15] studied three genes in relation to detecting CRC in patients' stool: *AGTR1*, which had a specificity of 21%; *WNT2*, which had a specificity of 40%; and *SLIT2*, with a specificity of 52%.

CONCLUSION

This research is extremely relevant to many healthcare providers since it pertains to common screening tools. While providers currently just have one FDA-approved option (Cologuard), genetic detection of cancer risk continues to be an area of research and development. The Cologuard test is indicated in the screening of all adults ≥50 years old who are at an average risk for developing CRC. It is contraindicated in patients with a history of any form of cancer, if they had a previous positive result from any CRC screening method, have a family history of CRC, or have an inflammatory bowel disease.[6] Although this is an approved screening method that offers convenience and no direct risks to the colon, not all providers have embraced this new recommendation and the CDC continues to advise adults to have colonoscopies.[2] Hopefully, with continued research and improvements in the testing methods, this screening option will become more available and accurate in detecting CRC in adults.

Need for Further Research

There is still a great need for research in this area. To date, there have been no randomised controlled trials that compare different screening tests, such as colonoscopy and DNA stool-based tests, to one another; only studies that test the reliability, sensitivity, and specificity of specific screening tests have been performed. Because of this, it is difficult to know which tests are the most effective. Analysing long-term outcomes, including morbidity and mortality, is necessary to assess the role of multi-target sDNA testing. Another area for future research is on issues related to testing intervals, patient acceptance, compliance of screening guidelines, and barriers that prevent individuals from being screened for CRC. It is unclear if patient preference for non-invasive screening tools along with more effective methods of non-invasive screening will one day diminish the importance of the use of colonoscopies in the average-risk adult. Additionally, mRNA and microRNA are areas of current research that offer potential for highly specific and sensitive CRC screening. While more research is needed in several areas, the role of multi-target sDNA testing is continuously advancing and offers an affordable, convenient, and safe option for adults who are at an average risk for developing CRC.

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PSORIASIS: BEYOND THE SKIN

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Disclosure: Dr Ryan has acted as a consultant, advisor, or speaker for AbbVie, Dermira, Dr Reddy's, Janssen, Lilly, Medimetriks, Novartis, Regeneron-Sanofi, and UCB. Dr Kelly has declared no conflicts of interest.
Received: 27.07.17 **Accepted:** 19.12.17
Citation: EMJ. 2018;3[1]:90-95.

ABSTRACT

Previously considered as just a skin condition, psoriasis has come to be regarded as a complex, systemic inflammatory disorder that affects multiple other systems. The association of psoriasis with cardiovascular disease and the increased prevalence of cardiovascular risk factors in psoriasis patients is increasingly recognised. Psoriasis is also associated with sleep apnoea, chronic obstructive pulmonary disease, chronic kidney disease, and liver disease. Increased awareness by both patients and physicians of these associations is vital to maximise optimal health outcomes in psoriasis patients. Screening for associated comorbidities and implementation of appropriate interventions is necessary. Furthermore, there is a considerably increased prevalence of depression and anxiety in psoriasis patients that is often not detected by physicians. Patients should be opportunistically assessed and treated, or referred appropriately, for psychological and mental health issues. Further studies are required to expand our knowledge of the systemic manifestations of psoriatic disease, and to allow us to further improve the health outcomes of psoriasis patients.

Keywords: Cardiovascular risk, comorbidities, psoriasis, psoriatic arthritis (PsA).

INTRODUCTION

There is growing evidence that psoriasis is much more than just a disease of the skin, with several important systemic manifestations similar to those of other chronic inflammatory diseases. Psoriatic arthritis (PsA), an inflammatory arthritis, is a well-known extracutaneous manifestation of psoriasis. Other systemic manifestations of psoriasis have emerged over the last two decades. Psoriasis patients have a clinically significant increased risk of cardiovascular disease (CVD) and cardiovascular risk factors when compared with the general population.[1] There is also an increased prevalence of depression and anxiety among psoriasis patients.[2] Associations of psoriasis with chronic kidney disease (CKD), chronic liver disease, chronic obstructive pulmonary disease (COPD), and sleep apnoea have also been described.[3] Dermatologists should work in tandem with other specialists and primary care physicians to screen for these risk factors and treat them according to national and international guidelines.

An electronic search via PubMed and Google Scholar was undertaken for all studies regarding psoriasis-associated comorbidities. All randomised controlled trials, systematic reviews, meta-analyses, observational cohort studies, and case series were included; however, individual case reports were excluded. The results of the electronic search were analysed and are described below.

PSORIATIC ARTHRITIS

The most common extracutaneous manifestation of psoriasis is PsA. There is wide variation in the reported prevalence of PsA in psoriasis patients, varying from 6–42%.[4,5] Certain clinical features may suggest a slightly higher predisposition to PsA in patients, including scalp psoriasis, nail psoriasis (nail changes including pitting, onycholysis, onychoschizia, subungual hyperkeratosis, and oil spots), and a family history of PsA. Patterns of PsA include distal arthritis, asymmetric oligoarthritis, symmetric polyarthritis, arthritis mutilans, and spondyloarthritis. The average time from the manifestation of psoriasis to the onset of joint

disease is 7–12 years.[6-8] A delay in the diagnosis of PsA can impact on a patient's long-term outcome. Irreversible changes in the joint can occur within the first year of disease development in 40–60% of patients,[9] and therefore screening of psoriasis patients for PsA is pertinent at every visit. Patients should be asked about joint pain or back stiffness, particularly early in the morning or after a long journey. Morning stiffness lasting >30 minutes is a strong indicator of PsA.[10] Ideally a Psoriasis Epidemiology Screening Tool (PEST) questionnaire should be completed by psoriasis patients annually. There are no specific serological tests to confirm a diagnosis of PsA; however, radiography of joints can be useful to delineate the presence, extent, and pattern of joint damage. Radiographs, along with serology (rheumatoid factor and anti-cyclic citrullinated peptide), can also help to distinguish PsA from osteoarthritis or rheumatoid arthritis. All clinicians treating patients with psoriasis should not hesitate to refer them to a specialist.

CARDIOVASCULAR COMORBIDITIES

Beyond its association with PsA, the association between psoriasis and CVD has now been established and is an area of intensive research. There is considerable evidence that patients with moderate-to-severe psoriasis have an increased risk of conditions such as CVD, hypertension, hyperlipidaemia, obesity, diabetes, and metabolic syndrome.[1] Patients with psoriasis have higher rates of mortality when compared to the general population.[11] A seminal cohort study using the UK General Practice Research Database (GPRD) reported that patients with psoriasis had an increased adjusted relative risk for myocardial infarction after controlling for other cardiovascular risk factors, particularly in those with more severe psoriasis and in younger patients.[12] A similar study using the GPRD found the incidence of CVD risk factors, such as hypertension, diabetes, obesity, and hyperlipidaemia, was increased in psoriasis patients compared with the general population.[13] Recent studies examining the association of psoriasis and these cardiovascular risk factors have supported these findings.[14,15]

Studies have demonstrated that psoriasis patients are more likely to be obese; however, it is unclear whether obesity predates or is a consequence of psoriasis. A prospective study that followed 78,626 women for 14 years showed a positive correlation between increasing BMI and risk of incident psoriasis,[16] suggesting obesity may precede the development of the disease. A recent study examining children and adolescents with psoriasis showed that they are more obese compared to age and sex-matched controls. There was also a tendency towards central adiposity in psoriatic patients in this study.[17] Psoriasis patients have an increased incidence of dyslipidaemia, and important differences have been observed in lipoprotein size, particle composition, and cholesterol efflux mechanisms. These patients also have a lower level of high-density lipoprotein and an increased level of low-density lipoprotein; the proportion of these lipoproteins in psoriasis patients is similar to that of diabetic patients.[17] In psoriatic patients with an adverse lipid profile, statin therapy should be considered. Physicians should be vigilant to observe for liver toxicity in those patients prescribed both methotrexate and a statin.

A meta-analysis and systemic review suggested that the prevalence of diabetes was increased in psoriasis patients, with an odds ratio of 1.53 for mild disease and 1.97 for severe disease.[18] Percutaneous absorption of topical steroid treatments can lead to worsening of blood sugar control and diabetes. In rare cases, patients can develop iatrogenic Cushing's syndrome.[19] In a large meta-analysis looking at the prevalence of hypertension in 309,469 psoriasis patients, the odds ratio for hypertension in patients with mild psoriasis was 1.30, and 1.49 in those with severe psoriasis compared with healthy controls.[15]

Excess alcohol consumption and smoking are independent risk factors for the development of CVD and both are increased in psoriasis. A meta-analysis of 28 studies showed an association between psoriasis and current or former smoking, and suggested that smoking is an independent risk factor for the development of psoriasis.[20] Biochemically, cigarette smoking has been shown to increase the number of circulating T helper (Th)17 cells in the peripheral blood of psoriasis patients compared to non-smokers. Th17 cells are proposed to be one of the main drivers of psoriasis.[21]

All psoriatic patients require an annual lipid profile and glycated haemoglobin (HbA1c) or fasting glucose assessment for dyslipidaemia and diabetes or insulin resistance. They should have opportunistic blood pressure monitoring when attending appointments. There should be a low threshold to start cardioprotective medications; notably, beta blocker therapy for CVD can lead to

flares in psoriasis and is therefore best avoided. There are no dedicated guidelines for the management of coronary risk in patients with psoriasis and physicians should be mindful that scoring systems, such as the 10-year Framingham risk score, could significantly underestimate cardiovascular risk in these patients.[22]

There is debate as to the ability of biologic therapies to treat psoriatic comorbidities other than PsA. Some psoriatic registries have shown a reduced hazard ratio (0.26; 95% confidence interval: 0.12–0.56) for myocardial infarction for those patients treated with anti-tumour necrosis factor-α inhibitors compared with those not treated.[23] This was believed to be related to a reduction in inflammation and subsequent atherosclerosis. Following this, a double-blind placebo-controlled psoriasis trial of adalimumab that used positron emission tomography and computed tomography combined to measure vascular inflammation, did not show reduced vascular inflammation in adalimumab-treated patients.[24] Further studies are required to delineate the association of reduced cardiovascular risk in psoriasis patients treated with biologic therapies.

OTHER COMORBIDITIES

Psoriasis and Sleep Apnoea

There is increasing evidence showing an association between psoriasis and obstructive sleep apnoea (OSA). The association of OSA and psoriasis was first described in 1999.[25] Shalom et al.[26] looked at the prevalence of OSA in 12,336 patients with psoriasis and compared them to 24,008 age and sex-matched controls. The study found a significant association between psoriasis and OSA, which was still present following multivariate analysis adjusting for sex, ethnicity, BMI, COPD, hypothyroidism, hyperlipidaemia, and peptic ulcer disease.[26] A Danish study also looking at a population of psoriasis patients found that patients with more severe psoriasis and those with PsA had a greater incidence of OSA.[27] Karaca et al.[28] performed sleep studies on 33 patients with psoriasis and detected an increased frequency of OSA in psoriasis patients compared to that of the normal population.

Psoriasis and Chronic Obstructive Pulmonary Disease

A meta-analysis and systemic review identified four observational studies, with a total of 13,418 patients, looking at the association of COPD and psoriasis.[29] They found that psoriasis patients were at a much greater risk of developing COPD than the general population. This association was stronger among patients with more severe psoriasis.[29] The high prevalence of smoking among psoriasis patients further increases their risk of COPD.[20]

Psoriasis and Chronic Kidney Disease

Patients with moderate-to-severe psoriasis have an increased risk of moderate-to-advanced CKD independent of traditional risk factors. An epidemiological study using a UK primary care electronic medical records database identified 143,883 psoriatic patients and compared them to 689,702 patient controls. Patients who had received phototherapy, systemic, or biologic therapy were defined as having severe psoriasis. Patients with psoriasis were found to be more likely to develop CKD compared to controls. This increased risk was significant even after controlling for traditional risk factors for kidney disease (age, sex, diabetes, high blood pressure, high cholesterol levels, and use of non-steroidal anti-inflammatory drugs). Patients with severe psoriasis were almost twice as likely to develop CKD and were >4-times more likely to develop end-stage renal disease requiring dialysis.[30] PsA patients have a higher risk of CKD and end-stage renal disease compared to that of psoriasis patients.[31] Many systemic medications for psoriasis are excreted via the renal system, e.g., methotrexate. A lowered glomerular filtration rate can lead to decreased drug metabolism and drug toxicity. Renal function should be monitored via routine blood tests, blood pressure measurements, and urinalysis in all psoriasis patients, particularly those prescribed systemic treatments. Early detection is critical because once kidney disease develops it cannot always be reversed.

Psoriasis and Liver Disease

Liver fibrosis, like kidney disease, is generally asymptomatic and can go undetected until the condition becomes advanced. Non-alcoholic fatty liver disease (NAFLD) is the most common form of liver disease in developed countries. This form of liver disease denotes the presence of fat in the liver cells in the absence of excess alcohol consumption, which then leads to significant inflammation and liver fibrosis. The condition is closely linked to obesity and metabolic syndrome. Among a series of 130 psoriasis patients matched for BMI, age, and

sex with 260 healthy controls, psoriasis patients were found to have a higher rate of NAFLD following a liver ultrasound examination.[32] The psoriasis patients also had higher levels of C-reactive protein than controls.[32] Those psoriasis patients who had NAFLD also had higher interleukin-6 and adiponectin levels than those without disease.[32] A Dutch observational study of 2,292 people found 46.2% of psoriasis patients had a diagnosis of NAFLD compared to 33.3% of healthy controls.[33] This study did not control for BMI or metabolic disease. A study looking at the clinical features of NAFLD in psoriasis patients found NAFLD to be strongly associated with PsA.[34] Given that patients with PsA have higher levels of inflammatory cytokines than psoriasis patients without joint involvement, this is a credible association. The association between psoriasis and excessive alcohol intake is well-described. This confounds the already higher propensity of psoriasis patients to develop liver disease. Methotrexate, one of the first-line systemic treatments for psoriasis globally, is known for its propensity to cause liver fibrosis. In patients with no risk factors for hepatotoxicity, a cumulative dose of 3.5–4.0 g of methotrexate is acceptable. Beyond this dose, liver biopsy or possibly a switch of medications should be considered.[35] A systematic review of methotrexate and liver fibrosis in psoriasis patients found a 22% increased risk of any type of fibrosis on biopsy following the use of methotrexate.[36] There was also a trend towards methotrexate use and progression towards significant fibrosis, but this was not statistically significant. Duration and cumulative dose of methotrexate was not associated with fibrosis on biopsy. Psoriasis patients should have regular serum liver function tests, particularly those on systemic medication. All psoriasis patients on methotrexate should have regular procollagen-3 level tests, in addition to their regular liver function tests.[30]

THE PSYCHOSOCIAL BURDEN OF DISEASE

Patients with psoriasis may experience significant psychological and social disability. This varies among patients and does not always correlate with psoriasis severity; for example, a small patch of psoriasis on a young person's face compared to a large plaque on the back of an older person can have disproportionate effects on quality of life. Psoriasis patients may avoid some social situations, such as swimming, and can be restricted in their clothing choices, for example, avoiding wearing dark colours to minimise the appearance of skin flakes, wearing short sleeves, or shorts. Psoriasis patients also have a high risk of sexual dysfunction; patients with genital psoriasis report a lower frequency of intercourse, higher incidence of dyspareunia, and a worsening of their psoriasis following intercourse.[37] Unemployment levels are high among psoriasis patients; in a study of 5,604 psoriasis patients, 12% were unemployed. Of these, 92% cited psoriasis and/or PsA as the sole reason for not working.[38] A recent meta-analysis of 98 studies showed that the prevalence of depressive symptoms among psoriasis patients was 28%. The prevalence of clinical depression in this analysis was 12% using the International Classification of Diseases code.[39] Furthermore, psychological distress is also known to exacerbate psoriasis disease. A significant portion of patients report stress and distress as triggers for their psoriasis. In a review of 928,194 patients from 15 papers, the prevalence of anxiety was 48%, which was significantly higher than in healthy controls. Dermatology centres should screen patients for anxiety and depression at each clinic visit. Patients who may be suffering from depression should be referred to a specialist. Notably, fluoxetine, lithium, and some benzodiazepines used in the treatment of some mental illnesses can make psoriasis flare. Recent studies in mindfulness and cognitive behavioural therapy in psoriasis patients have shown significant improvements in mental health status and the clinical severity of their psoriasis.[40-42]

Up to 30% of psoriasis patients abuse alcohol. This can lead to a wide spectrum of health and social problems, including liver cirrhosis, ischaemic heart disease, atrial fibrillation, sudden death, cerebrovascular disease and stroke, acute and chronic kidney injury, peptic ulcers, depression, suicide, and anxiety. A large objective study found that mortality from alcohol-related causes was significantly higher in psoriasis patients than in the general population.[43] As previously noted, there is an increased incidence of NAFLD in psoriasis patients, which increases the adverse effects of excess consumption of alcohol on liver inflammation.[44] Excessive alcohol consumption can thus limit treatment options in these patients. Self-reported alcohol consumption often underestimates actual intake in psoriasis patients. Physicians should be aware that patients who abuse alcohol often evade detection until medical, legal, or social problems arise. Alcohol biomarkers,

such as erythrocyte mean cell volume, gamma-glutamyltransferase, and carbohydrate-deficient transferrin can assist in the detection of alcohol abuse. Screening questionnaires, such as AUDIT and CAGE, can also be helpful.[44] Alcohol excess in psoriasis is thought to be due to the psychological distress associated with the disease.[45] Studies have shown psoriasis patients who consume alcohol in excess have higher levels of anxiety.[39] Both smoking and alcohol consumption in excess have been shown to worsen psoriasis and decrease the efficacy of treatments.[46] Social behaviours, such as cigarette smoking and excessive alcohol consumption, are modifiable risk factors for both psoriasis and CVD. Psoriasis patients should be opportunistically counselled and supported to modify their behaviours.

CONCLUSION

Once thought of as merely a skin condition, psoriasis has come to be regarded as a complex systemic inflammatory disorder that affects multiple other systems, as described in this article. In recent years, the association of psoriasis with CVD is becoming increasingly recognised. There is also an association between psoriasis and sleep apnoea, COPD, CKD, and liver disease; thus, screening of psoriasis patients for these comorbidities and the implementation of appropriate interventions is necessary. Furthermore, depression and anxiety are very prevalent in psoriasis patients and often not detected by physicians; mental illnesses can be more difficult to assess and diagnose than systemic illnesses during a routine consultation. The use of validated questionnaires for depression and anxiety can be a useful screening method in the outpatient setting. It is vital that patients who are having mental health issues are treated and referred to appropriate specialists. Further studies are warranted to expand our knowledge of the systemic manifestations of psoriatic disease and to allow us to improve health outcomes in our psoriasis patients.

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URTICARIA DIAGNOSIS

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Disclosure: The authors have declared no conflicts of interest.
Received: 16.01.17 **Accepted:** 21.11.17
Citation: EMJ. 2018;3[1]:98-105.

ABSTRACT

Urticaria is a common skin condition that, though rarely fatal, can seriously impair a patient's quality of life. Urticaria is caused by cutaneous mast cell activation and degranulation disease triggered by numerous stimuli. The condition is defined as chronic if it persists for >6 weeks. Self-remission is common in acute urticaria, but in chronic cases less than half of patients achieve remission within 1 year. Diagnosis is typically reached using the patient's history along with a physical examination. Laboratory workup is based on clinical suspicion and is used to exclude underlying causes, although most cases constitute unknown or spontaneous causes. Extensive routine testing for an exogenous cause is not necessary and does not change the management. This review details the pathophysiology, aetiology, diagnosis, investigation, prognosis, differential diagnosis, and assessment of disease severity, highlighting the potential diagnosis of urticaria and enabling clinicians to make informed assessment decisions.

Keywords: Acute, aetiology, chronic, diagnosis, investigation, pathogenesis, urticaria.

INTRODUCTION

Urticaria, or hives, is a skin lesion generally described as the pruritic 'wheal-and-flare' reaction.[1] The wheal is a localised intracutaneous oedema surrounded by a flare, an area of redness or erythema produced as a result of dilated blood vessels. Individual hives can last from 30 minutes to 36 hours and vary in diameter from 1 mm to 20 cm. The central pallor of the hives occurs because the dilated blood vessels in the wheal are compressed. The pathology that characterises urticaria is present in the superficial dermis and includes regional alterations to the venular plexus. The prevalence of urticaria varies according to the population under investigation and the sampling method used. According to a German study, up to 20% of the population will experience an episode of urticaria at some point in their lifetime.[2] Overall lifetime prevalence rates of urticaria have been reported as 8.8% of the population.[2,3] At any given time, chronic urticaria affects up to 1% of the general population. Both children and adults can acquire urticaria but it appears to be more common among adults, with women affected more often than men. The average age of patients suggests that the condition typically begins in the third to fifth decade of life. No reliable evidence is available regarding the difference in prevalence between race or ethnic groups.[2]

PATHOPHYSIOLOGY

The wheal-and-flare reaction, which is characteristic of urticaria, occurs as a result of the effects of mediators released from mast cell granules, primarily histamine. Only two of the four types of histamine receptors, H1 and H2, are involved in urticaria. Activation of H1 receptors in the skin induces itching, flaring, erythema, and whealing, whereas activation of H2 receptors contributes only to erythema and whealing.[4]

The mechanism that stimulates mast cell degranulation is key to the pathophysiology of urticaria. Mast cells express a number of surface receptors, which, upon binding to various molecules, are able to initiate a signal to trigger degranulation; the stimuli that triggers degranulation may be exogenous or endogenous. Cross-linking of mast cell receptors bound to

specific immunoglobulin (Ig)E by exogenous allergens, also known as a Type I hypersensitivity reaction, may be relevant to acute urticaria but may not be relevant to chronic spontaneous disease. Other possible exogenous stimuli are pathogen-associated molecular patterns on microbes, which are able to bind to toll-like receptors on mast cells and trigger degranulation.[5] This is more often linked to acute viral or bacterial infections than other types of pathogens. Nonimmunologic stimuli include certain drugs, for example opiates, aspirin, and other nonsteroidal anti-inflammatory drugs; neuromuscular blocking agents, such as atracurium; antibiotics, such as polymyxin and vancomycin; and iodinated radiocontrast dyes. In addition, other stimuli, including complements, such as C5a anaphylatoxin, stem cell factor, and some neuropeptides, including substance P, can also trigger mast cell degranulation by binding to their respective receptors available on mast cell surface, independent of the involvement of IgE or IgE receptors.[6] Some foods, such as strawberries, also contain histamine-releasing substances. Moreover, direct exogenous histamine intake might occur following consumption of a number of food types, such as cheese, underprocessed scombroid fish, processed meat, tomatoes, pineapple, and avocados.[7] Endogenous stimuli that can trigger mast cell degranulation include immune complexes, such as autoantibodies and some autoantigens, for example vasculitis or immune complex from anti-IgE autoantibody, autoantibodies against mast cell IgE receptors (anti-FcεRI-autoantibody), and psychological stress.[8,9]

Mast cells, which are hypersensitive to physical stimulation, and IgE have been implicated in the pathogenesis of dermographism, cold urticaria, and solar urticaria, without certain mechanisms. In these conditions, physical stimuli induce a neoantigen, specific to IgE antibody, that binds to mast cells. Release of neuropeptides may also initiate or potentiate mast cell activation. Localised platelet clumping has been demonstrated in cold urticaria and, as such, platelet mediators, for example platelet-activating factor and factor IV, may be involved in disease pathogenesis.[10] Cholinergic urticaria, another type of physical urticaria, occurs in response to cholinergic sympathetic stimulation. The mechanism causing mast cell activation and histamine release involving cholinergic nerve endings remains unknown.[11] For delayed-pressure urticaria, pressure-induced wheals may result from a late-phase reaction, but the initial antigen is still yet to be identified.[12] Heat or pressure may cause autoantibody-containing plasma to leak into the extravascular tissue, leading to mast cell activation and degranulation. A non-autoantibody mechanism may also be involved because functional autoantibodies have been detected in approximately 60% of chronic urticaria sera.[13] Activation of an extrinsic coagulation cascade was found in chronic urticaria. Increased plasma levels of prothrombin fragments 1 and 2 and D-dimer, a measure of fibrinolysis, have been demonstrated and relate to disease severity, but the contribution of coagulation abnormalities to the pathogenesis of the disease remains unclear.[14]

Basophils from half of patients with chronic urticaria have been shown to be hyporesponsive to *ex vivo* anti-IgE stimulation and appear to be associated with basopenia.[15] This basophil hyporesponsiveness is caused by elevated levels of the IgE-receptor regulating inhibitory phosphatases, SH2 domain-containing inositol-5-phosphatase 1 and 2, which limits phosphorylation reactions critical for histamine secretion.[15] This abnormality appears to reverse with disease remission; therefore, it should be considered a marker of disease activity.[15]

CLASSIFICATION OF URTICARIA ON THE BASIS OF DURATION

Urticaria is classified as either acute or chronic.[1] Acute urticaria is defined by a symptom duration of <6 weeks. Chronic urticaria is generally defined by the presence of urticaria on >3 days of the week, for a period of 6 weeks or longer.

AETIOLOGY OF URTICARIA

The potential causes of new onset urticaria vary, although no specific aetiology can be identified among many patients. Acute urticaria is more likely to have an identifiable aetiology compared with chronic urticaria. Different aetiologies can activate mast cells through many different mechanisms, which are described hereafter.

Infections

Viral, bacterial, and parasitic infections are associated with new onset urticaria. Immune activation, involving immune complex formation and/or complement activation, is one proposed mechanism of urticaria development. Common bacterial infections, such as urinary tract infections, dental infections, *Helicobacter pylori*, and

Mycoplasma pneumonia have also been attributed to the onset of urticaria. Viral illnesses, the most common being picornavirus, as well as coronavirus, respiratory syncytial virus, hepatitis B or C, and HIV infection, have been reported among urticaria patients. Parasitic infections, such as *Ancylostoma*, *Strongyloides*, *Schistosoma mansoni*, *Anisakis simplex*, and *Blastocystis hominis,* have been associated with urticaria.

Allergic Reactions

IgE-mediated reactions are associated with urticaria. Antibiotics most frequently implicated in causing IgE-mediated urticaria include beta-lactams, such as penicillins and cephalosporins. Stinging and biting by insects, for example bees, wasps, hornets, fire ants, and kissing bugs, are associated with acute urticaria and are sometimes linked to anaphylaxis. Latex allergy, stimulated by inflation of balloons and use of latex gloves, has also been associated with urticaria. Allergy to foods and food additives is also associated with generalised urticaria, with milk, eggs, peanuts, tree nuts, soybeans, and wheat being the most common foods associated with the condition in children. In adults, fish, shellfish, tree nuts, and peanuts are most often implicated.

Blood product-related urticaria may arise from several mechanisms, including IgE-mediated allergic reactions, complement-mediated reactions, and other immunologic events.

Pseudoallergens

Pseudoallergens include artificial preservatives and dyes in modern processed foods, and aromatic compounds in some natural foods. One in three patients with chronic urticaria undergo a beneficial pseudoallergen-free diet for 3 weeks.[16]

Mast Cell Degranulation

Drugs, foods, and plants can cause urticaria due to mast cell degranulation through a non-IgE-mediated mechanism. The most frequently implicated substances are narcotics, muscle relaxants, vancomycin, and radiocontrast agents. Opiate analgesics, such as morphine and codeine, cause direct mast cell activation; additionally, opiate derivative ingredients in cough suppressant syrups can also cause urticaria. Moreover, anaesthetic muscle relaxants, including atracurium, vecuronium, succinylcholine, and curare, may cause urticaria. Nonsteroidal anti-inflammatory drugs, such as aspirin, ibuprofen, and naproxen, have been identified as common causes of urticaria.

Physical Factors

Physical urticarial syndromes are forms of chronic urticaria that are triggered by a wide range of specific physical factors. Aquagenic urticaria wheals generally affect the upper part of the body and are induced by water. Cold-induced urticaria is characterised by localised or diffused urticaria that can be accompanied by angioedema within minutes after exposure to a cold object, air, or liquid. Cold urticaria is usually idiopathic, but may occur among patients with cold-dependent antibodies, such as cryoglobulins or cold agglutinins. Delayed pressure urticaria is characterised by wheals or angioedema that develop 4–6 hours after applying any type of pressure, such as wearing tight clothing, hammering, walking, or sitting down. Dermatographism presents as wheals at sites of trauma, friction with clothing, or scratching. Heat contact urticaria is diagnosed when wheals develop 10 minutes after contact with a heat source. Solar urticaria is a less common form of urticaria and occurs following exposure to natural or artificial light sources. Vibratory urticaria is defined by the presence of skin swellings and itching after exposure to vibration at the contact site. Cholinergic urticaria is triggered by elevated core body temperatures, such as during a warm bath, prolonged exercise, or episodes of fever. Exercise-induced urticaria causes wheals during or after exercise.

Causal Agents

Exposure to causal agents for contact urticaria can be classified as nonimmunologic, such as benzoic acid, dimethyl sulfoxide, cobalt chloride, trafuril, polyaminopropyl biguanide (found in wet wipes), melon peel, levofloxacin hydrate ophthalmic solution, and cosmetics, or as immunologic, such as latex, raw meat, fish, potato, phenylmercuric propionate, hair dye, manufacturing facilities, and animal dander.[17]

Menstruation

Urticaria may worsen premenstrually; however, cases of urticaria that occur predominantly or only premenstrually have been attributed to progesterone sensitivity.

Autoimmune Diseases

Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and coeliac disease are associated with urticaria. Other autoimmune diseases, such as thyroid autoantibodies, specifically thyroid peroxidase antibodies or antimicrosomal antibodies, are more prevalent among patients with chronic urticaria.

Autoinflammatory Syndromes

Acquired autoinflammatory syndromes, including Schnitzler syndrome, systemic-onset juvenile idiopathic arthritis, and adult onset Still's disease, have been associated with the onset of urticaria, along with hereditary autoinflammatory syndromes, including cryopyrin-associated periodic syndromes such as familial cold autoinflammatory syndromes, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease; more rarely, hyper-IgD syndrome and tumour necrosis factor receptor-associated periodic syndrome.[1]

Psychological Factors

Psychological factors, including depression and anxiety, appear to play a contributory role in a proportion of patients suffering from urticaria. Flare-ups of urticaria have been shown to occur at times of psychological stress; however, psychological stress alone is unlikely to be the cause of urticaria.

Malignancy

Chronic urticaria is associated with an increased risk of haematological cancer, for example non-Hodgkin's lymphoma, and non-haematological cancers, such as brain, retroperitoneal, vulva, kidney, and other urinary systems.[18]

Unknown Cause

As part of the urticaria diagnosis and management guideline in 2013,[1] the term chronic idiopathic urticaria changed to chronic spontaneous urticaria (CSU). In the majority of cases, no cause can be found and hence a CSU diagnosis is made.

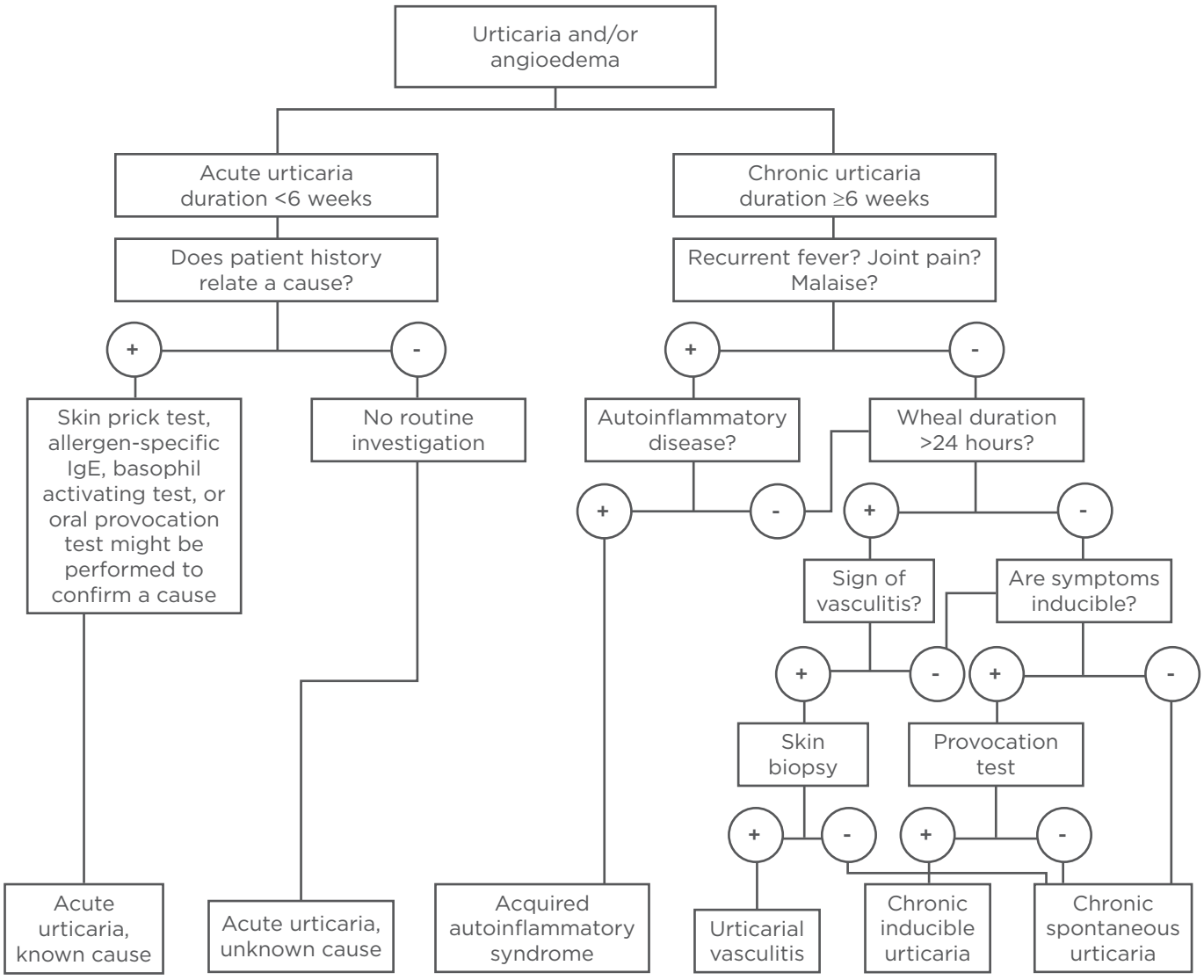

Figure 1: Algorithm for diagnosis and investigation of subtypes of urticaria.
IgE: immunoglobulin E.

Table 1: Urticaria aetiologies and investigations based on patient history and physical examination.

Clinical clue	Aetiology	Investigation
Food or drug ingestion immediately before symptoms	Food or drug allergy	Skin prick test, allergen-specific IgE, oral challenge test
Insect sting	Venom allergy	Skin prick test, allergen-specific IgE
Underlying allergic disease, related to allergen exposure	Aeroallergen allergy	Skin prick test, allergen-specific IgE
Dermatographia (lightly scratching)	Dermatographism	Pressure of a hand or a ballpoint pen tip
Smaller wheals (1–3 mm), burning or itching, brought on by heat, exercise or sweating, or by a hot bath	Cholinergic urticaria	Exercise or hot bath provocation
Provocation by any source of water	Aquagenic urticaria	Challenge with water at 35°C for 30 minutes
Cold stimulus	Cold urticaria	Cold provocation, for example, an ice cube on the forearm for 5 minutes
Heat stimulus	Heat urticaria	Heat source (45°C) for 5 minutes
Pressure stimulus, delay 4–6 hours after stimulus	Delayed pressure urticaria	Pressure test, for example, challenge with 15 pounds of weight suspended on a patient's shoulder for 15 minutes
Provocation by exercise	Exercise-induced urticaria	Exercise challenge in a controlled environment
Provocation by sunlight, 1–3 minutes after exposure	Solar urticaria	Phototesting with different wavelengths
Hives after direct contact	Contact urticaria	Cutaneous provocation test
Vibratory stimulus	Vibratory urticaria	Test with vortex mixer
Related to menstrual cycle	Cyclical urticaria (progesterone urticaria)	Progesterone challenge test
Painful or burning sensation, hives lasting >24 hours	Urticarial vasculitis	Skin biopsy
Fever, bone pain, malaise	Autoinflammatory disease	C-reactive protein test, test for paraproteinaemia, and carry out a skin biopsy
Gastric or abdominal pain, dental caries, travel to tropical country, eat uncooked food	Infection	*Helicobacter pylori* test, hepatitis virus B or C test, stool examination for parasite
Sudden loss of weight, elderly	Malignancy	Screening for malignancies
Unknown	Chronic spontaneous urticaria	Differential blood count, erythrocyte sediment rate, liver function test, thyroid autoantibodies, and autologous skin test

IgE: immunoglobulin E.

However, a subset of patients with CSU shows evidence of autoantibodies (chronic autoimmune urticaria), including antibodies to the high-affinity IgE receptor (FcεRI) and/or anti-IgE antibodies.[19] Autoimmune urticaria is associated with the IgG anti-IgE receptor (FcεRI) in 35–40% of patients and IgG anti-IgE in 5–10% of patients.[20] These autoantibodies can activate blood basophils and cutaneous mast cells.

DIAGNOSIS

The goal of a diagnostic measure is to identify the type of urticaria and the underlying cause. Urticaria is usually diagnosed by taking the patient's history alongside physical examination, with no investigation required to confirm the diagnosis. The first approach is a thorough exploration of the patient's history, covering a variety of topics: time

of onset, weekly frequency, duration of wheals, provoking factors, diurnal variation, occurrence in relation to workday or weekends, character and distribution of wheals, associated angioedema, itchiness or pain of wheals, systemic symptoms, personal and family history regarding urticaria and allergy, psychiatric diseases, gastrointestinal problems, induction by physical agents or exercise, use of drugs, observed correlation to food, relation to the menstrual cycle, type of work, hobbies, stress, quality of life and sleep, previous diagnosis, previous treatment and response to treatment, and previous investigations and results. Knowing the patient's history helps to exclude major comorbid disorders and physical urticaria. The approach of urticaria is presented in Figure 1.

The second step of diagnosis is a physical examination. A patient can visit a physician without skin lesions or after the lesions have healed. Skin lesion photographs taken by the patient can aid the diagnosis. The wheal is characterised by central swelling of variable size and the surrounding reflex erythema; the wheals will often dissolve and the skin will return to its normal appearance. Small size wheals (1–3 mm) are usually seen in physical urticaria. Urticarial vasculitis lesions are non-blanching and may be resolved with post-inflammatory hyperpigmentation. Angioedema typically appears as nonpruritic, brawny, nonpitting oedema, with neither well-defined margins nor erythema; swelling usually occurs around the eyes and lips and is also found on the hands, feet, and throat.

INVESTIGATIONS

Following a thorough discussion of the patient's history and a physical examination, diagnostic provocation tests, including drug, food, and physical tests, are performed as indicated by history and physical examination; moreover, laboratory testing based on related suspicions may also be appropriate. Diagnostic investigation concerning clinical clues and aetiology is summarised in Table 1. If urticaria is suspected to be caused by physical stimuli, a ballpoint pen test for dermatographism, ice cube test for cold urticarial, and pressure tests for delayed pressure urticaria are used to definitively diagnose the disease. IgE-mediated reactions from foods, drugs, or other allergens only rarely result in chronic urticaria; the skin prick test for aeroallergens, food, or serum allergen-specific IgE is used but is not a routine diagnostic test for patients with chronic urticaria.

There are a number of patients with CSU showing sensitivity to house dust mites, but those changing disease management remains unclear;[21-23] however, most cases of CSU do not have an identifiable cause. Routine laboratory testing can be performed to exclude underlying causes; a high eosinophil blood count can lead to allergy, parasitic disease, autoimmune disease, or tumour. Mildly elevated erythrocyte sedimentation rate can occur in CSU; on the other hand, high erythrocyte sedimentation rate levels are usually linked to urticarial vasculitis and autoimmune disease. Antinuclear antibody is indicated when urticarial vasculitis and autoimmune disease are suspected; however, positive low antinuclear antibody titre (1:80) can detect CSU. Skin biopsy is used when urticarial vasculitis is suspected. Hepatitis B and C titre may be associated with cryoglobulinaemia and some forms of cold-induced urticaria. Thyroid autoantibodies (antithyroid microsomal and peroxidase antibody) are low yield among patients without thyroid-related symptoms. Increased thyroid autoantibodies in titre may be associated with disease duration.[24] However, treatment with thyroid hormone among patients with positive autoantibodies presents little evidence to support a low rate of remission.

The autologous serum skin test (ASST) and the autologous plasma skin test (APST) indicating CSU are useful to diagnose autoimmune chronic urticaria. Testing for autoantibodies to anti-IgE and anti-FcεRI is not a routine laboratory measurement. The basophil histamine release test is the gold standard to detect functional autoantibodies, but the diagnosis does not need to be confirmed. ASST or APST are easy to use in practice and demonstrate relevance *in vivo* to mast cell degranulation and vasopermeability.[25] Moreover, ASST and APST can be used to predict remission rate in CSU.[26-28] The negative result of ASST and APST before treatment served as a predictor of good prognosis treatment and urticaria remission during a 2-year observational study.[26] In addition, negative ASST and negative basophil histamine release test are predictive of fast response to omalizumab;[29] oral corticosteroids and antihistamines should be ceased at least 7 days before performing ASST to avoid false-negative results. Serum vitamin D level is not indicated to determine the causes of CSU; however, vitamin D insufficiency is commonly found among patients with CSU and serum vitamin D level is associated with disease severity.[30,31] Vitamin D supplements may improve symptoms and quality of life among

CSU patients.[32-36] Monitoring serum 25-hydroxy vitamin D at baseline is suggested when possible, but is a weak recommendation.

Proteomic technology is used to identify novel autoantigens in chronic urticaria. Testis-specific protein 1 and the macropapain iota subunit of the proteasome multicatalytic endopeptidase complex were identified by proteomic technology as proteins that may be the trigger for urticaria.[37] Microarrays and quantitative real-time polymerase chain reaction were used to analyse differentially expressed genes in the phenomenon of wheal development, such as epidermal differentiation, intracellular signal function, transcriptional factors, cell cycle differentiation, inflammation, or coagulation.[38]

PROGNOSIS

Acute urticaria patients usually develop self-remission within 3 weeks;[39] however, approximately 20% of patients with acute urticaria progress to develop chronic conditions.[40] The duration of chronic urticaria is typically 1–5 years but may last >5 years in 14% of patients.[24] The prognosis of chronic urticaria patients with reported autoimmune urticaria being symptom-free after 1.2 years was 56.5%, while the percentage of CSU patients being symptom-free after 1 year was 34.5%.[41] Half of adults with chronic urticaria without expressing angioedema had spontaneous remission within 1 year, whereas 75% of patients with angioedema had persistent disease for >1 year.[42] It was also reported that 64.4% of patients with chronic urticaria achieved remission over 2 years.[26]

DIFFERENTIAL DIAGNOSIS

Other conditions may be confused with urticaria but can be distinguished based on the difference in presentation. Such conditions include urticaria pigmentosa, urticarial vasculitis, atopic dermatitis, contact dermatitis, drug eruptions, erythema multiforme, Henoch–Schonlein purpura, scabies, and viral exanthema. Urticaria pigmentosa presents an orange to brown hyperpigmentation of the lesions and positive Darier's sign: a wheal-and-flare reaction produced after stroking the lesions.[43]

ASSESSMENT OF DISEASE ACTIVITY

No specific laboratory test can be used to monitor urticaria activity. Disease activity in CSU can be accessed by an urticaria activity score for 7 days or an urticarial control test.[44,45] The urticarial control test can be done by the patient and shows the level of disease activity over the last 4 weeks.

CONCLUSION

Urticaria is a common skin condition and can be diagnosed in the primary care setting. The diagnosis is typically based on noting the patient's history and performing a physical examination; however, the cause of urticaria is difficult to determine. Investigations should be carried out with a specific test selected based on the patient's history. As each case differs, extensive laboratory testing is expensive and does not change the prognosis or management. Advances in the understanding of the pathophysiology and causes have helped clinicians to improve diagnosis and management of patients with urticaria.

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WHEN THE NAIL APPEARANCE PLAYS TRICKS: A CASE OF LONGITUDINAL MELANONYCHIA

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Disclosure: The authors have declared no conflicts of interest.
Received: 22.06.17 **Accepted:** 02.10.17
Citation: EMJ. 2018;3[1]:106-110.

ABSTRACT

A paediatric nail consultation is often required to reduce parents' concerns regarding their child's abnormal nail appearance. Nail pigmentation in children is a dermatological challenge because guidelines are not standardised, causing many doubts for dermatologists. In general, the majority of cases of melanonychia are benign in children and nail melanoma cases are very rare. However, alarming clinical and dermoscopic features can be observed, requiring nail surgery to confirm a diagnosis. Here, we present a case of longitudinal melanonychia in a teenager with atypical signs and a good prognosis.

Keywords: Children, management, melanonychia, nevus, pigmentation.

INTRODUCTION

Nail pigmentation represents a dermatological challenge, even for nail experts. The clinical and dermoscopic features of nail pigmentation are different in adults and children, and this aspect is very important for a better evaluation of melanonychia. In children, the majority of melanonychia cases are benign due to a melanocytic nevus or lentigo affecting the nail matrix; nail melanoma cases are very rare. Nevertheless, dermoscopy is a non-invasive method that can be very useful in the evaluation of nail pigmentation. The gold standard for the diagnosis remains histopathology,[1,2] which requires an accurate bioptic technique and a trained pathologist in nail diseases. Here, we present a case of longitudinal melanonychia (LM) with a worrying appearance in a young female patient.

CASE REPORT

We report a case of a 17-year-old Caucasian female patient who attended the skin cancer and nail diseases outpatient consultations of the Dermatology Unit of the University of Bologna, Bologna, Italy, for assessment of a band of LM on the first digit of her left hand. She explained that the nail pigmentation had been present since she was 1 year old and her parents, concerned by the atypical appearance of it, decided to escalate the problem and asked for an investigative biopsy. Histopathologic examination revealed that the nature of the lesion was benign. An onychodystrophy remains, with a small erosion of the proximal nail fold.

At time of investigation the patient denied experiencing any kind of pain or other symptoms, but her parents requested an urgent evaluation for the nail band changes, even though they were very slow over time. At clinical examination, we observed the pigmented band of the first digit of the left hand; the band was brown in colour, with longitudinal fissures, a small erosion at the proximal nail fold, and with an interrupted distal margin (Figure 1). The other fingernails were normal. We performed onychoscopy with an ultrasound gel for immersion, using a FotoFinder® dermatoscope (Teachscreen Software GmbH, Bad Birnbach, Germany) for a better visualisation of the band. Specifically, we observed a rectangular form of the band, proximally to distally, which varied in colour from brown to grey-pink, with irregular lines in thickness, spacing, and borders. We magnified the lesion to better observe the proximal nail fold and distal margin.

Figure 1: Longitudinal melanonychia of the first digit of the left hand.

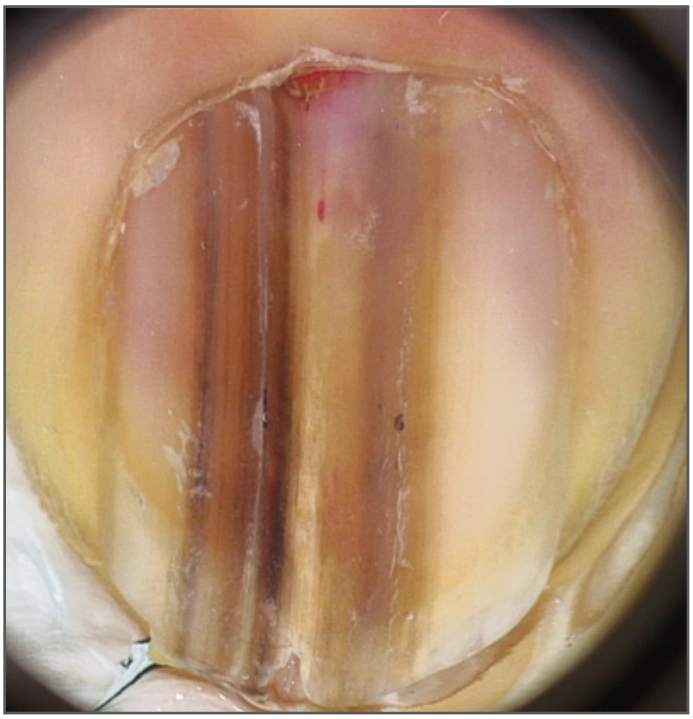

Figure 2: Dermoscopy performed with ultrasound gel. Investigation showed the presence of a longitudinal band that varied in colour from brown to grey-pink, with irregular lines in thickness and colour, irregular borders, and an interrupted distal margin.

By performing onychoscopy at the proximal nail fold, the lesion showed a small subungual red mass, while the distal margin revealed an interrupted border. No type of pigmentation was present at the hyponychium (Figure 2).

The patient's parents described how the appearance of the nail slowly changed over time, but they insisted on a new histological examination. We performed a longitudinal nail biopsy, which allowed observation of all nail components; histopathological observation confirmed the presence of individual melanocytes, without atypical features, at the dermoepidermal junction. Melanocytes have the tendency to aggregate in 'nests', which is typical of a junctional melanocytic nevus (Figure 3). We suggested a periodic follow-up of the lesion to reassure the parents.

DISCUSSION

Melanonychia in children is less common than in adults and it is burdened by less well-defined criteria concerning diagnosis and management. According to the literature, almost all cases of LM seen in children are benign and nail melanoma is rare. The need for biopsies in childhood melanonychia is under debate because LM in children can show some worrying signs, mimicking the aspect of nail melanoma in adults, such as colour changes with ageing, periungual pigmentation, and variation of the degree of the pigmentation.

Epidemiology

The epidemiology of melanonychia in children is described as more prevalent among races with higher skin pigmentation than Caucasians, with a mean age of onset of 3 years and no difference in sex.

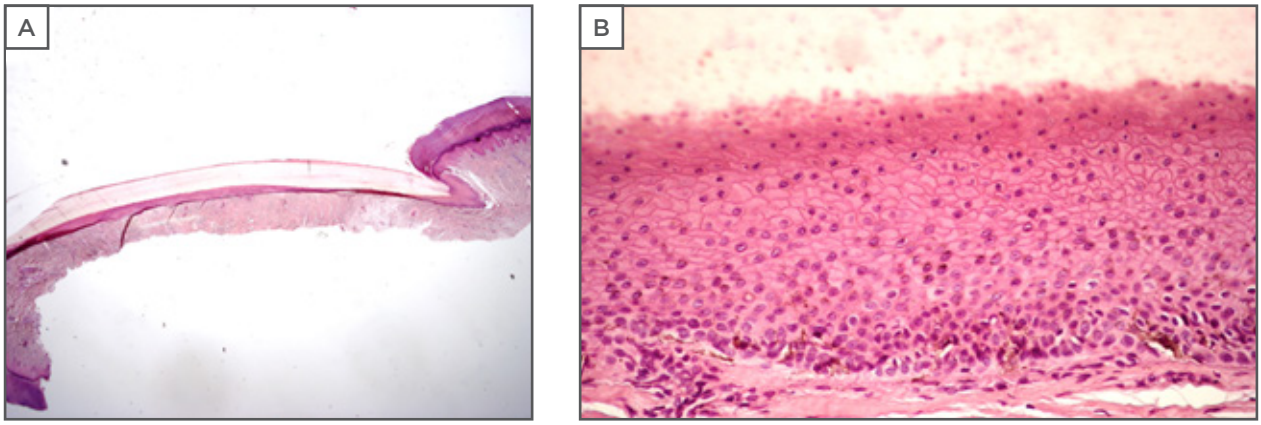

Figure 3: Longitudinal biopsy of the lesion with A) haematoxylin and B) eosin stain.
Individual melanocytes, without atypical features, at the dermoepidermal junction have the tendency to aggregate forming 'nests', which are characterised by a junctional melanocytic nevus.

The fingernails are more commonly affected than the toenails, and in the fingernails the most affected digit is the first, with a longitudinal pigmented band typically seen within the nail plate, running from the proximal to distal nail plate. In populations with melanin-rich skin, such as African-Americans, 77% of children with LM have a melanonychia caused by melanocytic activation, which is a process that displays racial variation.[3] In contrast, in Caucasians and populations with lower levels of melanin in the skin, the presence of pigmented streaks in children is typically caused by melanocytic proliferation. Benign melanocytic hyperplasia is diagnosed in 30% of children with LM and nevus of the nail matrix in 48%;[3,4] no cases are reported in Chinese children,[5] while 2.5% of black children aged <4 years present with melanonychia.[6] An interesting study of melanonychia in childhood was recently published, including a series of 30 children who showed 20 cases of lentigo, 5 of subungual nevus, and 5 of melanocytic hyperplasia, all histologically confirmed.[7]

Clinical and Dermoscopic Aspects

Clinical presentation of childhood melanonychia consists of a longitudinal band, which can be both transversal or total, involve one or more digit, and appear at any age. The clinical appearance of a melanonychia varies due to the underlying process, based on the concept that in children, as in adults, nail matrix melanocytes are inactivated, and, when triggered, undergo activation or proliferation. If one digit is affected, we can assume a proliferative process. Usually, the clinical appearance is a longitudinal pigmented band. The aspect of the band can be very different; for example, the colour may be pronounced and homogeneous, the borders can be well defined or less sharp, and the width can range from a few millimetres to the entire nail plate. The corresponding nail plate can show some changes or be normal. A brown-black periungual pigmentation, known as Hutchinson's sign, can be either present or not. When multiple nails are involved in melanonychia, we can consider this due to a normal racial genetic variant, particularly in populations with melanin-rich skin, or we can classify it as a complex syndrome, such as Peutz–Jeghers syndrome and Laugier–Hunziker syndrome.

In Peutz–Jeghers syndrome, pigmented macules on the oral mucosa, lips, fingers, and toes, and melanonychia are associated with intestinal polyposis with a possible malignant degeneration. In Laugier–Hunziker syndrome, LM affects several nails and is associated with pigmented macules of the lips, mouth, oesophageal mucosa, and genitalia. Other causes of melanocytic activation in children are trauma, irradiation, or drugs, and this type of melanonychia is usually located on the thumbs and index fingers. In terms of medications for this condition, we have reported doxorubicin or hydroxyurea use,[8,9] as well as minocycline, zidovudine for antiretroviral therapy in HIV patients, antimalarials, or cancer chemotherapeutics.[10,11]

A dermoscopic pattern that suggests a melanocytic activation is a grey background of the band, with thin, grey-coloured, regular, and parallel lines. When considering conditions in a child other than a melanonychia of a single nail, a nail matrix

nevus, which can be congenital or acquired, is the most likely diagnosis. Nail matrix nevi occur more frequently in fingernails than in toenails, most often in the thumb, and they present with one or more longitudinal heavily pigmented band. The width of the band may vary in size and colour; in particular, the pigmentation may be homogeneous and dark.[2] In addition, >50% of cases of nail matrix nevi measure >3 mm.[1,3] Dark bands are associated with pseudo-Hutchinson's sign because the dark nail plate pigmentation is visible through the transparent nail fold.

As previously discussed, there are a lot of clinical and dermoscopic aspects in children that can be alarming for the clinician, such as in our reported case. For example, a periungual pigmentation, Hutchinson's sign, is typical in congenital nevi, and a gradual enlargement of the band can also be observed. The band can become darker and spread throughout the nail, or thinning and fissuring can occur. In children, it is also common to observe a gradual fading of the band;[12] fading of the pigmentation, called 'regressing nevoid nail melanosis in childhood', is unique to children and is not always indicative of regression of the nevus, but can indicate decreased melanocytic activity from nevus cells.[13]

The presence of dots on onychoscopy, distributed along melanocytic lines, is a new sign indicating regression of the LM. In an interesting study analysing this indication,[14] the authors suggested that the dots are an accumulation of melanin derived from a cluster of nevus cells that migrate upward from the dermoepidermal junction. Dermoscopically, they are black in colour with a regular size and shape from round to oval (<0.1 mm) and are regularly distributed along the lines or within the pigmented lines until they interrupt the lines. In most young patients, the dots disappear over time, together with the fading of melanonychia. According to the authors, these dots represent a sign of regression of a nevus and are not a warning sign of melanoma.[14] However, the dermoscopic pattern of a nevus shows the presence of a brown background with longitudinal brown-to-black regular and parallel lines, with regular spacing and thickness. Pathologically, most of the nevi in children are junctional nevi with regular nests and typical melanocytes, but the features between the lesions can be different and the differential diagnosis by a dermatologist requires more experience in nail histopathology.

As mentioned, nail melanoma in children has been described in only 12 cases. Of these, 8 reports were in Japanese children,[15,16] 2 were from South America (one from Argentina and one from Brazil),[14] and 2 cases were in Caucasians.[17] LM is the most frequent manifestation, with a dark-brown-coloured band and the presence of Hutchinson's sign.[18] In general, these cases of melanoma were *in situ* of the nail apparatus. In all these pigmented nails, there was either a process of evolution or regression.

Management

The real challenge for nail experts remains whether a benign lesion appearing in childhood can become a malignant lesion in adulthood. Dermoscopic patterns that suggest a melanoma in children can also be seen in LM, and their specificity in a young age is very low; a brown background with longitudinal brown-to-black lines, with an irregular degree of colour pigmentation, spacing, or varying thickness and ending abruptly, or a parallelism disruption, can be observed.

We recommend the examination of all aspects of a melanonychia in children when involving a single digit.[1] In our experience, the clinical features of melanonychia in children are the same as in adults, but the most important difference is the extreme variability of the dimensions, degree of the pigmentation, and distribution of the pigment, which evolve differently over time. All these characteristics should not cause concern for the clinician when the patient is a child.

CONCLUSION

The consensus of melanonychia management in children is still under debate and a standardised process is required. After reviewing the literature, the risk of melanoma is remote, while the risk of a permanent nail dystrophy due to nail biopsy can occur;[19] thus, a decision should be made that considers both the anxiety of the parents and the experience of the clinician. In fact, it is important to emphasise that paediatric nail consultation is mostly used to reassure worried parents about the aspects of their child's nail and also to manage the condition using personal experience of melanonychia in children, or refer the patient to nail experts in doubtful cases.

Criteria suggesting biopsy requirement in children should include the speed at which the band grows and the colour of the band; longitudinal excision is the best surgical option in biopsy cases.[20]

However, these features can also be seen in nail matrix nevi in children; therefore, their specificity to a particular condition is low. According to the literature, dermoscopy enhances the clinical evaluation of LM, improving the management and allowing a follow-up consultation due to electronic storage of the clinical and dermoscopical images. Moreover, dermoscopy allows clinicians to visualise the site of the pigment production, with the observation of the distal margin and the presence of the melanic deposition within the nail plate. In conclusion, we recommend periodic follow-up of the patient and management using clinical and dermoscopic pictures to inform the decision as to whether a nail biopsy should be performed after puberty.[13]

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POSITIVE VESSEL REMODELLING

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Disclosure: The authors have declared no conflicts of interest.
Received: 10.04.17 **Accepted:** 02.02.18
Citation: EMJ. 2018;3[1]:111-115.

ABSTRACT

Since its introduction, the success of percutaneous transluminal coronary angioplasty (PTCA) has been jeopardised by recoil, neointima proliferation, and luminal renarrowing; however, the benefit of positive remodelling has not gained widespread attention. While vessels will remodel positively up to a certain stage in the development of atherosclerosis, the therapeutic application of this process remains low. The prevention of vessel shrinkage during the healing process, which represents the predominant mechanism of restenosis after PTCA, is a prerequisite of long-term success in PTCA. The antiproliferative drugs that are currently used mainly on stents are known to be capable of this. Primary clinical studies have reported that positive remodelling leads to beneficial effects in coronary and peripheral angioplasty if no foreign body is inserted, and a paradigm change in percutaneous coronary intervention towards far fewer implants is within reach.

Keywords: Drug-coated balloon (DCB), percutaneous coronary intervention, vessel remodelling.

INTRODUCTION

The success rate of percutaneous peripheral and coronary angioplasty has been hindered by restenosis since its introduction by Dotter and Judkins,[1] and Grüntzig.[2] Initially, the main obstacles faced were elastic recoil and neointima proliferation, which contributed to luminal renarrowing. Bare-metal stenting was the initial solution; however, it was revealed to have only a marginal benefit due to the exaggerated neointima hyperplasia initiated by the insertion of a foreign body.[3] Drug-eluting stents (ES) have therefore been implemented to counteract the foreign body reaction, and this has proved especially successful in reducing reinterventions.[4] Drug-ES have therefore evolved as the current default solution.

There has not been as much research on the external size and the consecutive internal lumen changes of blood vessels, both during the development of atherosclerosis and after angioplasty. The stenting of most lesions restricts the ability of blood vessels to expand as part of the healing process, which is now sometimes referred to as vascular restoration. Both the positive remodelling effects in the natural disease process, as well as the antiproliferative drug-induced vessel enlargement, are greatly counterbalanced by neointima proliferation and a rigid stent-fortified vessel wall. Even with the use of bioresorbable scaffolds, the net effect, in spite of all methodological measurement flaws in the first year, is negative remodelling (luminal narrowing), while it is only later that part of the early narrowing is counteracted by vessel enlargement.[5] Other foreign body-associated problems, such as an enhanced thrombosis rate, remain.[6] Thus, by stenting or scaffolding most lesions, the ability of blood vessels to expand as part of the healing process or induction of vessel size increase by antiproliferative agents has not been recognised as a therapeutic option.

VESSEL REMODELLING

Though under-recognised, positive vessel remodelling is a commonly observed phenomenon

in vascular medicine. Most cardiologists are familiar with remodelling of the internal mammary artery after connecting it to the left anterior descending coronary artery: it grows to meet the blood flow demand. Similarly, arteriovenous shunts for dialysis patients will grow after the arteriovenous connection is established. In their seminal work, Glagov et al.[7] describe how vessels will enlarge (positive remodelling) during the development of atherosclerosis, as long as plaque material does not comprise more than 40% of the cross-sectional vessel area. In this process, compensatory positive remodelling will prevent luminal narrowing until the later stages of the atherosclerotic process. In addition, a dilative form of atherosclerosis occurs in some patients.

Unwanted positive vascular remodelling occurs after application of drug-ES and can cause secondary stent malapposition if the neointimal proliferation, caused by the foreign body reaction, does not compensate the luminal change.[8] This is thought to be one of the leading causes of late and very late stent thrombosis,[9-11] and is also thought to differ in magnitude between different antiproliferative drugs, excipients, and stent designs.[12,13] Paclitaxel-ES and sirolimus-ES seem to cause more vascular remodelling than everolimus-ES and zatarolimus-ES; the pharmacologic reason for this difference is not entirely clear. The drug effect leading to positive remodelling in this setting is counteracted by neointimal hyperplasia covering the stent mashes. Without a foreign body reaction, the expected net effect would be luminal enlargement.

More than 20 years ago, before the use of stents was widespread, Currier and Faxon[14] studied restenosis after percutaneous transluminal coronary angioplasty (PTCA), questioning whether therapy was aimed at the wrong target for addressing predominantly neointimal hyperplasia. He pointed to a PTCA-induced decrease in vessel size, measured as the area comprised by the internal elastic membrane, and suggested a therapy directed at arterial remodelling, which was not available at this time.

After plain old balloon angioplasty, most vessels heal with negative vessel remodelling. This means that the healing process causes an overall shrinkage of the cross-sectional area in the treated vessel segment, leading to luminal narrowing.[15,16] This vessel shrinkage is the predominant mechanism of restenosis after PTCA, while neointimal proliferation is the predominant mechanism after stenting, proven both experimentally and clinically through intravascular ultrasound.[17-19]

THERAPEUTIC UNDERESTIMATION OF VESSEL REMODELLING

With regard to the aforementioned, it is not surprising that the potential of positive remodelling to increase the lumen of atherosclerotic vessels as an interventional therapy has been underestimated. Paclitaxel is the best-evaluated drug in this context. Once absorbed, its hydrophilic nature allows the drug to stay in the arterial vascular wall for a prolonged period of time. Its inhibitory action on smooth muscle cell proliferation is caused by modulation of the microtubule formation and by upregulation of proapoptotic factors.[20,21] The mechanism of positive remodelling is thought to be the apoptosis of smooth muscle cells. Thus, the pathophysiology of spontaneous increased vessel size in the early stages of atherosclerosis is mimicked by the pharmacological effects induced by paclitaxel.

The effect of paclitaxel was found to be clinically unfavourable when, in the TAXUS II trial,[22] it was reported that it led to increased vessel size in stented areas. It also induces the increase of carotid vessel size after balloon injury if applied locally,[23] and the effect on vessel size is far greater than the effect on the reduction of neointimal proliferation.[24] Locally applied paclitaxel (applied during contrast injection,[25] by local application on a balloon using an appropriate excipient,[26] or by injection of paclitaxel into the pericardial sack[27]) leads to sufficient vascular tissue concentration to induce a sizable increase in vessel diameter. Unlike siromilus, paclitaxel is thereby able to induce apoptosis of smooth muscle cells. This leads to a decrease in medial and intimal smooth muscle cells, and in collagen content.[21] While this induces a theoretical risk of coronary artery aneurysm formation, the study of a large number of patients has not found an excess rate of coronary artery aneurysms after drug-coated balloon (DCB) angioplasty.[28]

The Effect of Alternative Drugs

Several limus-based drug balloons are currently in clinical development and some have even earned the Conformité Européenne safety mark. So far, these have only been tested in in-stent

restenosis settings; however, a clinical proof of positive remodelling with these compounds is still pending. While neointimal thickening seems to be better suppressed by sirolimus than by paclitaxel,[29] and sirolimus still has more effect on the vessel size than zatarolimus does, animal data suggest that sirolimus has a somewhat weaker effect on vessel size increase than paclitaxel.[29-31]

Preliminary Clinical Evidence

Primary clinical studies have provided evidence that positive remodelling leads to beneficial effects in coronary[32,33] and peripheral[34] angioplasty if no foreign body is implanted. A sizable percentage of cases exhibited a luminal increase of the coronary arteries from end of procedure to 4 months after, obviating the need to end angioplasty without residual stenosis (Figure 1). The average luminal diameters after DCB angioplasty either increased or showed no luminal renarrowing in >80% of treated lesions.[32,33] Since the initial report using quantitative angiography, these data have been confirmed by intravascular ultrasound and optical coherence tomography in various trials and by various groups.[35-37] It has been found that even side-branch ostia benefit from main vessel drug application. Using optical coherence tomography, Her et al.[38] described an increase of the ostial side branch area from 1.0–1.4 mm^2 (40%) without even touching the side branch during intervention, with insightful optical coherence tomography images available in the publication.[38]

Peripheral Vessels

Positive remodelling after application of paclitaxel was found angiographically in peripheral vessels as well. More patients exhibited a late lumen gain in the DCB group when compared to the regular balloon group, and a small average late lumen gain (0.01 mm) was found in the PACIFIER trial,[34] while there was an unexpected small average late lumen loss of 0.30 mm in the THUNDER trial.[39] Although the clinical importance of positive remodelling in peripheral vessels may be less well-established and of minor importance in the large conduit vessels, the use of DCB in peripheral arterial disease is generally very well accepted as an anti-renarrowing strategy.

Drug-Coated Balloons in *De Novo* Trials

This review does not intend to summarise the clinical trials performed in *de novo* vessels with DCB. Despite a large number of patients in three small randomised trials, and in a number of large registries on mostly small vessels and bifurcations in >3,500 patients, there is a need for more data comparing DCB in *de novo* lesions to modern drug-ES. A large trial, however, is expected to be presented for the first time this year (BASKET small trial).[40]

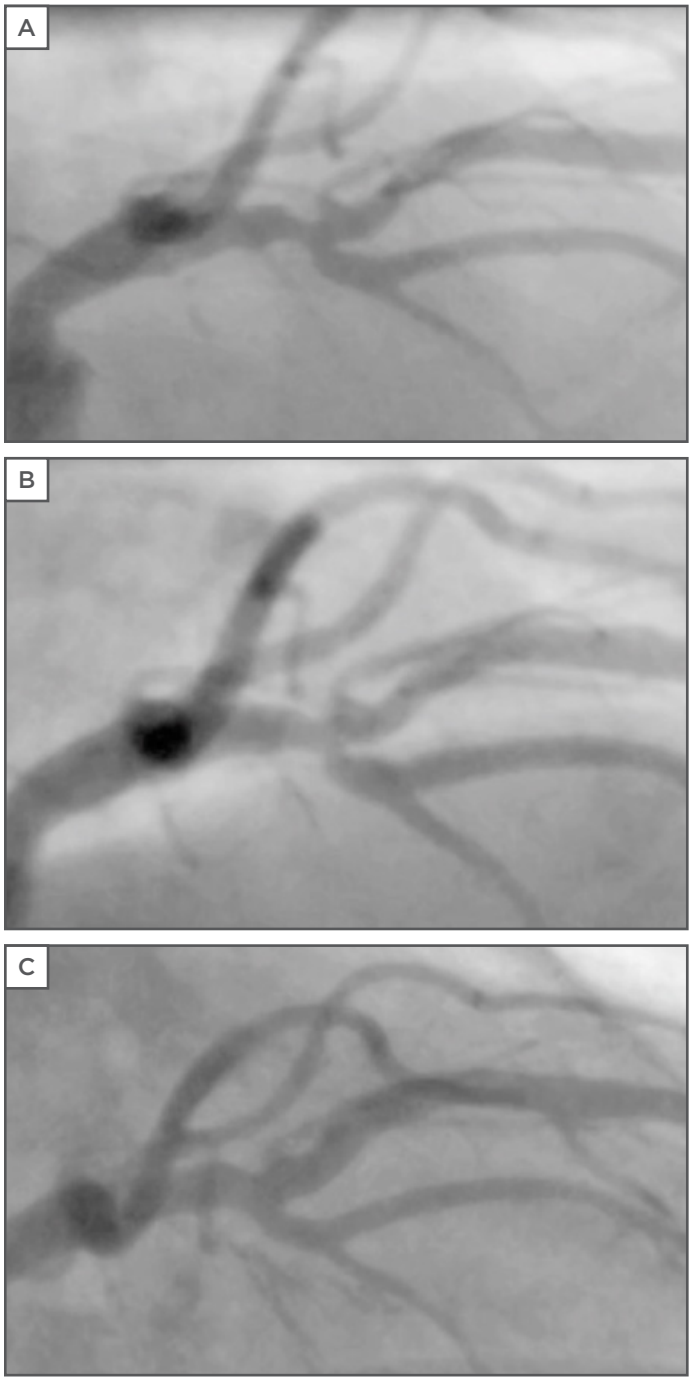

Figure 1: Proximal left anterior descending stenosis in bifurcation.
A) before, B) directly after, and C) 4 months after, showing late lumen enlargement. The bifurcation has been dilated and treated with the drug-coated balloon in both directions.

LIMITATIONS

Dissections

One might consider the above observation as less relevant against the background of other reasons beyond restenosis necessitating stents, such as dissection and elastic recoil. While these considerations are worthwhile and valid, dissections are not a predictor of restenosis after PTCA and late lumen loss is less in B dissections than in A dissections.[41] In addition, the overall number of PTCA cases that urgently require a stent is considered to be low. In the BENESTENT study,[42] the rate of dissection ≥C according to National Heart, Lung, and Blood Institute (NHLBI) classification was <5%, and >70% of all cases could be randomised successfully to DCB versus stenting in the ongoing Basel small vessel study (Scheller, Nov 2017, personal communication).[40] Therefore, a majority of percutaneous coronary intervention cases can benefit from the positive remodelling mechanism, while a subgroup, to be further defined, requires stents.

Thrombosis Rate

Another common claim is that stents are needed to prevent acute occlusion. However, *de novo* lesions treated only with DCB and achieving a result with residual stenosis ≤30% without major dissection and TIMI III flow exhibit no increased thrombosis rate. The criteria, achieved by an optimal PTCA result and considered to be safe, have been proposed by the Cadillac study[43] and by the German Drug-Coated Balloon Consensus Group.[44] Indeed, neither early nor late cases with acute or sub-acute thrombosis can be found among the >3,500 published cases in studies and registries using DCB as a stand-alone procedure. Therefore, this point of view also reveals a clinically significant option to achieve positive vessel remodelling in a large subgroup of patients, probably even in the majority of cases, by not using stents.

Bias by Patient Selection

The reported incidence of positive remodelling is limited to the patients that were suitable for DCB angioplasty. Thus, patients with major dissections (Class ≥C according to the NHLBI classification) were excluded, as were patients with major elastic recoil. The reported results can therefore only be applied to patients with a decent predilatation result. Since this is a large subgroup, and may represent the majority of patients, the observation is nevertheless meaningful and clinically relevant.

SUMMARY

There is strong evidence that positive vessel remodelling can serve as a good basis for a paradigm change in percutaneous coronary intervention towards fewer foreign body implants, obviating long-term problems with drug-ES, such as stent fracture, late malapposition, and late and very late thrombosis, as well as neoatherosclerosis in patients that have a decent acute PTCA result. A further and sustained benefit seems achievable in a large subgroup of patients. Some questions remain as to the potential benefit of this approach in various subgroups of patients and lesions, in severely diffuse disease and in milder disease stages, as well as in regard to the sustainability of long-term results after 5–10 years.

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OSTEOARTHRITIS AND AGEING

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Disclosure: The authors have declared no conflicts of interest
Acknowledgements: This work was supported by the Arthritis Research UK Pain Centre, University of Nottingham, Nottingham, UK. The study was also funded by the National Institutes for Health and Research, Nottingham Biomedical Research Centre, Nottingham.
Received: 12.04.17 **Accepted:** 31.07.17
Citation: EMJ. 2018;3[1]:116-123.

ABSTRACT

Ageing is a complex process of accumulation of molecular, cellular, and organ damage, leading to loss of function and increased vulnerability to disease and death, the rate and extent of which varies among individuals. Osteoarthritis (OA) is not only the most common joint disease, but is also one of the major causes of disability in people aged >65 years and is accompanied by comorbid conditions, increased mortality, and decreased quality of life. One of the major risk factors for OA is ageing. However, OA itself may be involved in the biological ageing process. This is likely to be in part a direct involvement, by contributing levels of systemic inflammation and sharing molecular pathways with biological ageing, such as mitochondrial damage leading to cell senescence. Although OA is not considered an inflammatory form of arthritis, there is evidence of subclinical low-grade inflammation in the whole joint and inflammatory processes play a key role in the disease pathogenesis. For instance, there is synovial inflammation (e.g., following injury), mechanically derived inflammation present due to biomechanical overloading of a joint, and systemic inflammation resulting from obesity. Systemic inflammation is often associated with frailty, and having a high concentration of inflammatory markers is predictive of incident frailty, some of which are known to increase with age and correlate with pain. In addition, OA may also contribute indirectly to biological ageing via the disability and pain resulting from it. Further research into the exact process linking OA and biological ageing, including frailty, is needed.

Keywords: Ageing, frailty, inflammation, osteoarthritis (OA), pain, sarcopenia.

INTRODUCTION

Osteoarthritis (OA) is the most common global chronic joint disease. The disease may affect single or multiple joints and even be generalised. OA is a chronic arthropathy affecting the entire joint, involving the cartilage, joint lining, ligaments, and underlying bone. In OA, cartilage loss, osteophyte formation (bone spurs), and subchondral bone sclerosis leads to pain, disability, and a reduction in quality of life.[1] Structural changes, visible by radiography, include narrowing of the joint space, osteophyte formation, and bone remodelling around the joints. OA can arise in any synovial joint in the body but is most common in the large joints (knees and hips), hands, and spine.[1]

OA is believed to result from both biomechanical and molecular changes in the joint brought about by injury, joint malalignment, obesity, ageing, and inflammation. OA is classified as idiopathic or secondary to anatomic abnormalities, trauma, or inflammatory arthritis. The American College of Rheumatology (ACR) criteria developed for hand, hip, and knee OA are intended to distinguish OA from other causes of symptoms and are best suited to clinical settings in which a high prevalence of other forms of arthritis and joint pain is expected. This is different from the definition used for epidemiological studies given the poor correlation between radiographic disease severity (joint damage) and the joint pain and functional impairment presented by a patient. Thus, OA can be

defined pathologically, radiographically, or clinically, but most epidemiological studies have relied upon radiographic features to characterise the disease.[2]

EPIDEMIOLOGY OF OSTEOARTHRITIS

OA is one of the most disabling diseases in developed countries. Global estimates are that 9.6% of men and 18.0% of women >60 years of age have symptomatic (painful) OA. Eighty percent of patients with OA have limitations in movement and 25% cannot perform their major daily activities.[3] World Health Organization (WHO) data also demonstrated that OA moved from the 12th to the 6th leading cause of years lost to disability or morbidity between 2002 and 2007. Increases in life expectancy and ageing populations are expected to make OA the fourth leading cause of disability by the year 2020.[3]

Individuals with OA (defined both symptomatically and radiographically) at the knee or the hip show a 55% excess in all-cause mortality. Diabetes (95% increased risk), cancer (128% increased risk), cardiovascular disease (38% increased risk), and the presence of walking disability at baseline (48% increased risk) are independently associated with the excess in all-cause mortality.[4] Importantly, deaths from cardiovascular causes are higher in patients with walking disability due to OA (72% higher), even after adjustment for baseline covariates, indicating that there is an interplay between the underlying OA and the additional comorbid conditions, which result in a higher risk of mortality. Thus, although the main clinical symptoms of OA are pain and disability, the consequences of the disease are much more far reaching.

Several risk factors that have been recognised to affect hip and knee OA are body weight, age, female sex, occupational activity and injury,[2] congenital abnormalities and joint shape, meniscal tears, presence of OA at other joints (Heberden's and Bouchard's nodes), and foot and knee alignment, in addition to genetic predisposition. Furthermore, specific inter and intra-articular patterns of OA may represent subsets that have different risk factor profiles and disease courses.

PAIN AND DISABILITY IN OSTEOARTHRITIS

In general, the main symptom of OA is joint pain exacerbated by exercise and relieved by rest, although pain at rest or during the night is not uncommon in advanced disease. Knee pain due to OA is usually bilateral and is experienced in and around the knee. Hip pain due to OA is felt in the groin and anterior or lateral thigh. Hip OA pain can also be referred to the knee. Signs of OA include reduced range of joint movement, joint swelling/synovitis (warmth, effusion, synovial thickening), crepitus, periarticular tenderness, bony swelling, and deformity due to osteophytes.[1]

OA patients report with a diminished ability to perform the basic activities of daily living, such as climbing stairs or changing from a sitting to standing position.[5] In the UK, a recent survey, 'OA Nation', found that 81% of people with OA experience constant pain and face limitations in performing certain tasks.[4]

OSTEOARTHRITIS AND AGEING, MOLECULAR MECHANISMS OF CARTILAGE DEGENERATION

Although late-onset articular cartilage degeneration is common and age is one of the most important risk factors for the disease, the relationship between old age and OA is not fully understood.[6] In the past, it was believed that the link with age was due to 'wear and tear' of articular cartilage by continuous mechanical stress; we now know, however, that OA involves an active response to injury comprising remodelling of articular cartilage and subchondral bone, in addition to synovial inflammation and damage to other joint structures, such as ligaments and menisci.[7]

Biological ageing is a complex process and it is now widely accepted that ageing starts with molecular damage, leading to cell, tissue, and, ultimately, organ dysfunction.[8] Extensive evidence from animal models and *in vitro* studies has shown that mitochondria contributes to specific aspects of the ageing process, including cellular senescence, chronic inflammation, and the age-dependent decline in stem cell activity.[9]

Perhaps the best known and most long-standing hypothesis to explain ageing is the free radical theory, which proposes a central role for the mitochondrion as the principle source of intracellular reactive oxygen species (ROS) leading to mitochondrial DNA (mtDNA) mutations (Figure 1).[8,9]

Over the past 10 years, substantial evidence has accumulated showing that differences in mtDNA haplogroups correspond to variations

in prevalence and progression of cartilage loss in large joint OA.[10] The mtDNA haplotypes T, J, and the JT cluster, on the other hand, are significantly associated in populations from the USA, the Netherlands, and Spain, with radiographic incidence and progression of the disease.[11] Fernandez-Moreno et al.[11] report that the mtDNA haplogroup J, the same haplogroup associated with lower OA prevalence, lower disease progression, and lower cartilage loss, is also associated with a significantly lower risk of incident knee OA.

The functional relevance of these mitochondrial haplotypes has been recently shown, using cytoplasmic hybrid (cybrid) cell lines.[10] Cybrids incorporate mitochondria from human subjects and perpetuate the mtDNA-encoded components while maintaining the nuclear background of different cybrid lines as constant;[12] thus, allowing investigators to assess the influence of mtDNA variation on cell function.

The cybrids carrying the haplogroup H produce higher adenosine triphosphate levels than those with the haplogroup J, but this higher energetic efficiency was accompanied by higher production of ROS and the proportion of cells that survived in the presence of hydrogen peroxide was almost half the number of cybrids with haplogroup J. In chondrocytes during OA, oxidative stress may act together with inflammatory and/or mechanical stress to accentuate catabolic processes by increasing the levels of ROS relative to antioxidants.[13] The increased levels of ROS also contribute to the senescence secretory phenotype, in which the age-related decline in the responses of chondrocytes to anabolic growth factors is related to increased oxidative stress.[14] The depletion of antioxidants promotes mitochondrial dysfunction in chondrocytes,[15] which, in turn, can amplify the stress responses through increased production of nitric oxide and ROS and NF-κB signalling.[15,16]

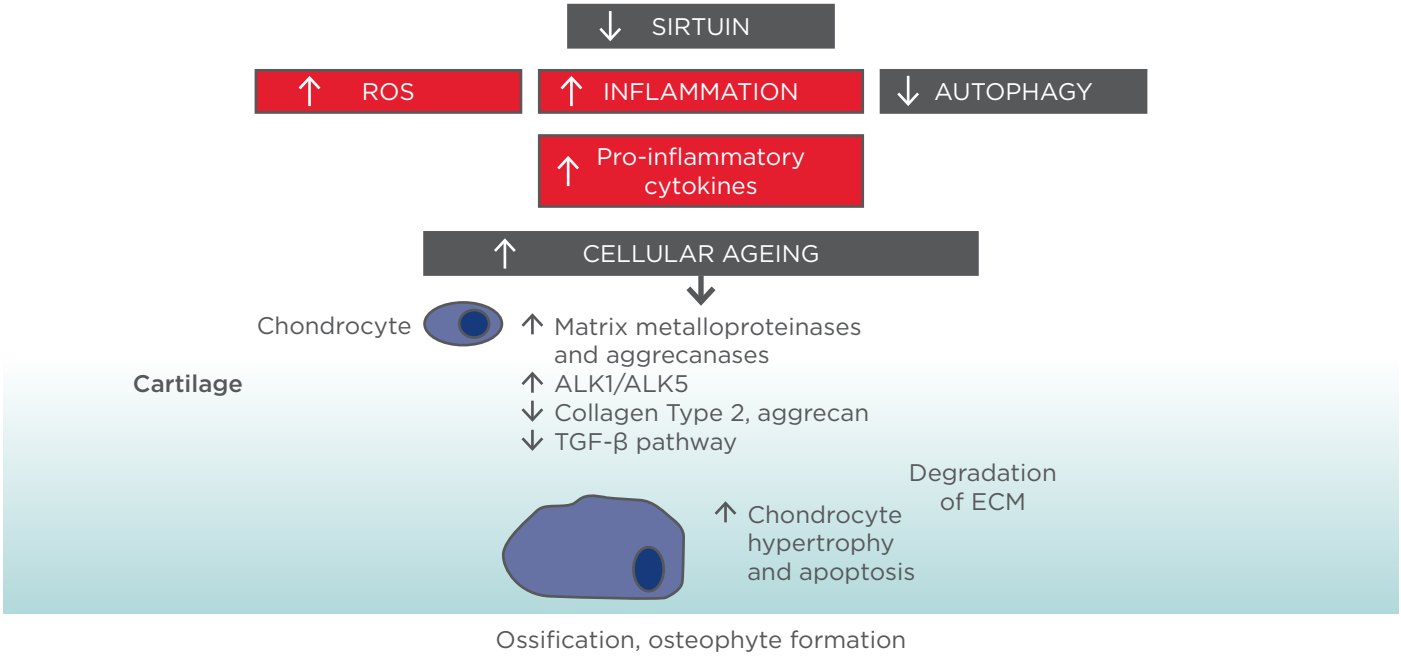

Figure 1: Molecular ageing mechanisms and risk of osteoarthritis.
Various cellular signalling mechanisms, including a decrease in the action of sirtuins in mitochondria, are involved in the process of cellular ageing, resulting in an increase in reactive oxygen species and inflammation, and a decrease in autophagy (lysosome-mediated degradation of damaged proteins and organelles).[56-58] These changes influence the expression of catabolic factors resulting in increased production of matrix metalloproteinases, aggrecanases, and pro-inflammatory cytokines, reduced TGF-β signalling, increase in TGF-β receptors ALK1/ALK5 ratio (a cause for elevated metalloproteinases-13 expression in osteoarthritis), and reduced levels of collagen Type 2 and aggrecan synthesis.[59] Mitochondrial dysfunction, inflammation, chondrocyte hypertrophy, and apoptosis all contribute to the development of osteoarthritis, with the resulting formation of osteophytes.
ALK: activin receptor-like kinase; ECM: extracellular matrix; ROS: reactive oxygen species; TGF: transforming growth factor.

These data, therefore, prove the functional relevance of mtDNA variation linked to risk of OA on cell function and survival and is in agreement with recent work by the same group showing that OA cartilage presents signs of early molecular ageing compared to healthy age-matched cartilage.[6]

This increase in cartilage ageing may also reflect overall higher ageing in other organ systems and may be related to the higher rate of comorbidities seen in OA patients.[17] Indeed, OA is also linked to biological ageing overall and strong links have been found between OA and frailty. An overview of some of the molecular mechanisms underlying the connection between cellular ageing and cartilage damage is presented in Figure 1.

OSTEOARTHRITIS AND SYSTEMIC INFLAMMATION

Although OA is not considered an inflammatory form of arthritis, there is evidence of subclinical low-grade inflammation in the whole joint and inflammatory processes play a key role in the disease pathogenesis.[18] Synovitis (inflammation of the synovium) is a critical characteristic of OA and is often considered the driver of the OA process. However, inflammatory processes are initiated via mediators that are released not just by the synovium but by bone and cartilage too.[18]

The drivers of this inflammation are varied and several sources of inflammation are involved in OA pathogenesis. In the first instance, there is synovial inflammation, which also affects cartilage and bone. Following a traumatic injury or a repetitive micro trauma to a joint, fragmented cartilage within a joint space provokes a reaction from synovial cells. As the fragments are considered foreign bodies, the synovial cells release inflammatory mediators. These mediators activate chondrocytes and produce metalloproteinases (MMP), which promote cartilage destruction. These mediators also induce inflammatory cytokines and MMP by the synovium itself that perpetuates further destruction of the synovium. Altered rates of osteophyte remodelling in OA are due to increased or decreased osteoclastic bone resorption.[19] There is evidence in the literature of chemical communication between chondrocytes and osteophytes.[20] Inflammatory mediators such as cytokines can move between these tissues, consistent with the fact that OA is a disease of the whole joint. Moreover, mechanical inflammation is also present due to biomechanical overloading of a joint that is detected by mechanoreceptors located at the joint surface. An abnormal increase in joint loading increases the expression and release of inflammatory cytokines, chemokines, and prostaglandins.[21] At an intracellular level, the mechanical forces are translated into chemical signals, also known as mechanotransduction, that trigger inflammation and gradual onset of OA. The presence of atherosclerosis-related inflammation and altered levels of adipokines offer a further contribution to systemic inflammatory processes in addition to joint-localised ones in OA.

It is known that obesity induces an inflammatory environment, because adipose tissues express cytokines and adipocytokines that have been identified in the plasma and synovial fluid of OA patients.[22-24] Obesity can also accelerate the OA process by inducing ischaemia at the subchondral level. The direct ischaemic effects on the bone are known to reduce cartilage nutrition and inflict multiple bone infarcts that are characteristic of advanced OA. Bone and cartilage remnants can be identified in the synovial and capsule space, with marked eburnation of bone surrounding the infarct. Adipokines also induce insulin resistance, endothelial dysfunction, and a systemic inflammation, which are implicated in atherosclerosis and could explain why OA patients have an almost 40% increased risk of cardiovascular disease.[22] Adipokines play an important role in the pathogenesis of OA and have been shown to contribute to the formation of osteophytes.[23,24] To date, the best-studied adipokines are adiponectin, leptin, visfatin, and resistin,[25] and in animal models it has been shown that a local knee injection of visfatin inhibitor protects mice from developing mechanical OA.[26]

Inflammation in OA is also involved when an increase of inflammatory mediators means that a increased concentration of oxidised proteins accumulate within the joint. These ROS cause oxidative damage, which can trigger inflammation, promote cell senescence or ageing, and in particular, chondrocyte ageing (Figure 1). In ageing, there is a loss in the ability of cells and tissues to maintain homeostasis, particularly when placed under abnormal stresses such as oxidative stress or biomechanical overloading of a joint. This promotes stress-induced senescence of chondrocytes. Ageing also involves the formation of advanced glycation end-products (AGE), which are produced in ageing tissues. These end-products alter the mechanical properties of cartilage, which leads to more brittle tissue with an increased fatigue failure, and stimulate the

overproduction of pro-inflammatory cytokines and MMP.[27] Overall, the integrity of the joint structure is compromised internally by inflammatory processes and externally by the systemic effects of ageing and mechanical loading.[18] Therefore, while there appears to be a complex interplay between mediators and inflammatory processes affecting different joint structures, the overall effect over time is one of gradual degradation of tissues, loss of optimal joint integrity and function, and the onset of pain (Figure 2).

OSTEOARTHRITIS AND FRAILTY

Knee OA is not only a leading cause of functional limitation and disability in ageing adults, as described above,[28] it is also strongly associated with another geriatric condition: frailty.[29-31] Clinical frailty is considered highly prevalent in old age and predictive of a high risk of falls, worsening mobility, disability, hospitalisation, and death.[32,33] It is an increasing global public health burden with the reported prevalence of frailty in older people varying from between 5.6% in Germany[29] to 42.6% in Chile.[34]

Knee OA and frailty are reported to share common risk factors such as obesity,[35,36] with knee OA also associated with greater prevalence of developing frailty.[30] Fried et al.[32] proposed the definition of frailty as being when ≥3 of the following criteria were present: unintentional weight loss, self-reported exhaustion, grip strength muscle weakness, slow walking speed, and low physical activity.

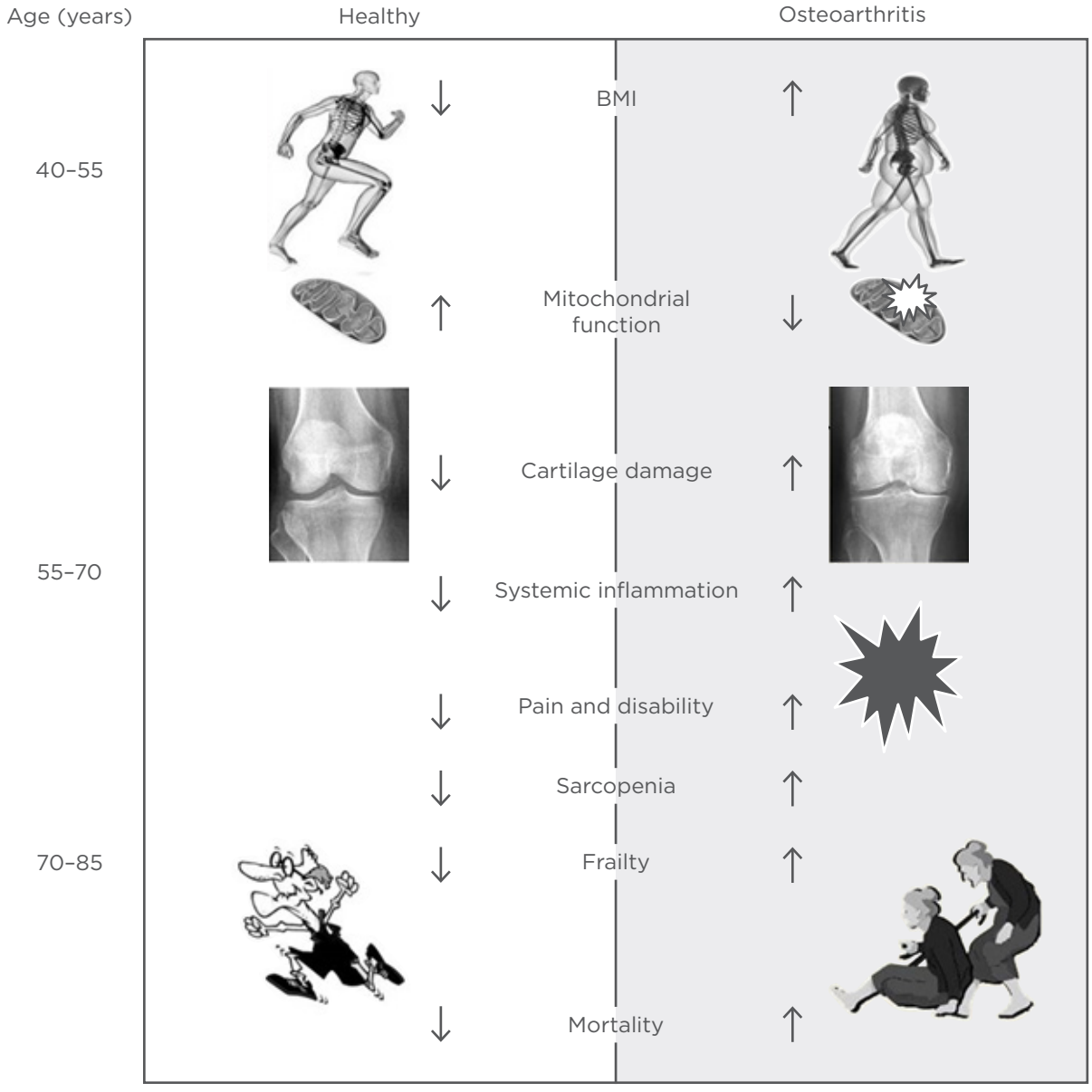

Figure 2: Schematic representation of the link between osteoarthritis and biological ageing.

Patients with the presence of one or two frailty criteria are categorised as being in a pre-frail state. Castell et al.[29] analysed older adults in six European countries and found the odds of pre-frailty and frailty were 1.54 and 2.96-times higher among OA than non-OA patients, respectively.

Patients with knee OA have been reported to have slow walking speed,[37] fatigue,[38] low physical activity,[39] whilst patients with hip OA have been reported to display all frailty criteria,[40] suggesting that patients with OA often display frailty criteria. Unintentional weight loss is often not a characteristic of knee OA; on the contrary a large proportion of severe knee OA is attributable to obesity.[41] The underlying mechanisms associating knee OA and frailty are not yet understood, but their identification would provide novel targets for the management and prevention of frailty in adults.

INFLAMMATION AS A POTENTIAL MECHANISM LINKING OSTEOARTHRITIS, FRAILTY, AND SARCOPENIA

In older patients with OA there are positive relationships between pain, frailty, and sarcopenia (Figure 2), although the mechanisms behind the associations are not yet fully understood. In these aged patients, quadriceps muscle weakness has been reported to be present without knee pain, suggesting that the quadriceps weakness is a possible primary risk factor for knee pain and progression of joint damage in people with knee OA.[42]

OA-related knee pain, along with quadriceps muscle weakness, can lead to a decrease in physical activity.[43] This inactivity may lead to the loss of muscle mass; however, systemic inflammation has also been suggested as a potential mechanism that associates OA and frailty.[30] Pain itself is a risk factor for the development of frailty. A recent prospective analysis, of 1,152 non-frail subjects at baseline, has demonstrated that lower limb OA-related pain was associated with an increased risk of developing frailty over 4.4 years, compared with people with OA and no pain.[44]

Age-related inflammation may not directly cause OA (as presented above) but is likely to act as contributing factors to its development and progression, as well as to increased pain and reduced physical function.[45] Obesity associated with OA and ageing further contributes to the inflammatory environment, leading to muscle atrophy and sarcopenia through the production of high levels of inflammatory markers and cytokines, such as C-reactive protein (CRP), tumour necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1-β.[46] TNF also contributes indirectly to sarcopenia by causing insulin resistance.

Both sarcopenia and obesity are independently associated with physical disability in elderly people. Sarcopenic obesity (age-related muscle atrophy in obese individuals) results in more physical limitations than sarcopenia or obesity alone, and has been strongly implicated in both risk of OA and frailty.[47,48] Systemic inflammation is often associated with frailty; for example, having a high concentration of the inflammatory markers CRP and fibrinogen were predictive of incident frailty in women.[49] Higher levels of CRP have also been reported in women with early knee OA, as well as predicting those whose disease will progress over 4 years.[50]

There have been further systemic markers of inflammation, whose levels in the blood have been demonstrated to increase with age and correlate with pain. TNF-α, along with CRP, has been reported to be positively associated with knee pain over a 5-year study of older adults with OA,[51] whilst higher serum levels of IL-6 are also considered to be associated with pain in early-stage knee OA.[52] Significant positive relationships have previously been identified between frailty and IL-6,[53] with a link also being reported between elevated IL-6 and the loss of bone and muscle.[54]

The exact mechanism driving the relationship between inflammatory mediators, pain, OA, frailty, and sarcopenia is currently unknown. Inflammatory cytokines involved in frailty, including IL-1, IL-6, and TNF-α, are also increased in OA cartilage as opposed to normal cartilage.[55] It is thought that a complex network of inflammatory cytokines including TNF-α, IL-1-β, and IL-10 are involved in the regulation of IL-6 and inflammation.[54] Further research into the exact process is needed.

CONCLUSION

OA is the most common joint disease and is highly prevalent after 60 years of age. However, the presence of OA appears to also influence the risk of unhealthy ageing, both as the presence of cardiometabolic comorbidities and as a risk factor for the development of frailty and sarcopenia later in life (summarised in Figure 2). In this article, we have covered some of the evidence linking OA

and OA pain to systemic inflammation, development frailty, and sarcopenia. Prospective studies directly linking the systemic inflammation that accompanies OA and pain in OA to the development of frailty and sarcopenia are not yet available. However, the evidence in the literature strongly suggests a functional link, and studies investigating the causal relationship between the two, the molecular mechanisms underlying them, and potential interventions, deserve careful consideration.

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INSOMNIA IN THE AGEING POPULATION: CHARACTERISATION AND NON-PHARMACOLOGICAL TREATMENT STRATEGIES

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Disclosure: The author has declared no conflicts of interest.
Received: 18.04.17 **Accepted:** 02.02.18
Citation: EMJ. 2018;3[1]:124-129.

ABSTRACT

Sleep problems represent a worldwide health concern among older adults, with an increasing prevalence of multimorbid conditions and a decreased quality of life. However, most elderly patients are not correctly diagnosed due to numerous confounding variables (e.g., medical and psychiatric disorders, polypharmacy, and psychosocial factors) affecting sleep and the confusion regarding the differential diagnosis in older adults between normal changes in sleep pattern as a result of ageing and sleep disorders. There are normal changes to the sleep architecture throughout the lifespan, and sleep disorders are not part of the ageing process; however, there are several sleep disorders that affect older adults. The most prevalent sleep disorder is insomnia, which is found in different forms and affects approximately 30–50% of the older adult population. The treatment strategies for sleep disorders are multivariate, with prescriptions of pharmacological treatments being the most common method among healthcare professionals; however, there is strong evidence that non-pharmacological treatments have better long-term effects. The aim of this review is to explain the difference between sleep disorders and sleep alterations as a result of ageing, to characterise insomnia in older adults, and, finally, to present the different effective non-pharmacological possibilities, accompanied by evidence, for the treatment of insomnia in older adults.

Keywords: Ageing, cognitive behavioural therapy (CBT), insomnia, older adults, sleep disorders.

INTRODUCTION

Across all the primary, secondary, and tertiary healthcare levels of both public and private healthcare systems, one of the major complaints that older adults seek medical advice for is changes in sleep behaviour. These subjective complaints are based on changes to the structure, quality, and quantity of sleep. Evidence for sleep alteration is confirmed through measuring objective polysomnographic and electroencephalographic data.

From the age of 60 years, there is a reduction in total sleep duration, with a redistribution of sleep episodes (naps) throughout the day and reduction of nocturnal sleep.[1,2] The sleep pattern of older adults is characterised by frequently disrupted sleep, with periods of being awake lasting >30 minutes, and individuals reporting a tendency to spend 15–20% of their time in bed being awake.[2,3] A meta-analysis conducted by Ohayon et al.[4] sampled 3,577 individuals aged 5–102 years. The study demonstrated that with increasing age, cycles of non-rapid eye movement sleep (NREM) 1 and NREM2 increase in duration, and there is less time spent in NREM3 and a decrease in the percentage of rapid eye movement sleep, impairing sleep efficiency. These data were corroborated by Dijk et al.[5] These changes in sleep pattern are explained by a set of anatomical and physiological modifications related to the circadian timing system and homeostatic regulatory mechanisms, as well as the contribution of social factors.[3,6]

The suprachiasmatic nucleus (SCN), the master pacemaker that adapts behaviour and physiology to recurring changes in environmental conditions, shows deterioration during the ageing process, whereby the ability to respond to information is

lost. The decreased expression of SCN genes that serve as the body's clock function indicators also interferes with the circadian rhythm by modifying the capacity of the SCN to generate rhythms or respond to external stimuli.[7]

In addition to these alterations, the quality of the optical transmission of the external temporal cues (day and night) from the retina to the SCN also undergoes deterioration with age, thus affecting the synchronisation of the rhythms, especially the sleep and wakefulness rhythm.[7] These altered sleep patterns are also reinforced by changes in light exposure time (exposure to early morning light, for example) by shifting the phase of sleep to earlier.[8]

The amplitude of rhythms also decreases with age, resulting in difficulty falling asleep and consequently encouraging naps during the day.[9] The amplitude of rhythms contributes to internal desynchronisation; an example is the effect of amplitude on the relationship between increased sleep propensity and melatonin. Melatonin, a hormone secreted at night by the pineal gland, enhances sleep propensity; however, its levels decrease with age, resulting in reduced sleep efficiency,[2] marked by the reduction of homeostatic pressure to sleep.[8] In addition, cortisol levels increase during the circadian phase of sleep (darkness), leading to increased sleep fragmentation;[10] this is because cortisol is associated with increased activity and low sleep propensity. Morgan et al.[11] showed that there was an association between sleep disorders and high levels of cortisol among the older population (aged 60–90 years).

In older adults, the changes observed in circadian regulatory mechanisms of sleep promote phase advances that influence homeostasis. An increased sleep requirement, reflected by going to bed earlier, occurs due to reduced sleep efficiency or sleep fragmentation; a decreased sleep requirement results in waking up earlier. Moreover, a lower circadian amplitude results in night-time insomnia and increased susceptibility for day-time napping, while a lower homeostatic sleep drive also results in sleep fragmentation.[6]

It is important to mention that social synchronisers, such as working hours and social activities, are not as relevant in the elderly population and are replaced by other social and temporal cues. Most of the older adult population are retired and do not have a regular daily routine. Sedentary behaviours and the lack of work and/or social activities can contribute to temporary disorganisation.

INSOMNIA: THE MOST PREVALENT SLEEP DISORDER

Considering that sleep patterns present alterations, as previously mentioned, it is imperative that a differential diagnosis be made between sleep disorders and sleep alterations in order to determine the most appropriate therapy. Sleep alterations are related to personal changes in the ageing process, whereas sleep disorders are disturbances that affect the diurnal functioning of the individual, seriously affecting their biopsychosocial range and quality of life, since sleep is fundamental for the maintenance of several physiological, psychological, cognitive, and social processes.

The sleep complaints of older adults most often lead to sleep disorders. The most prevalent complaint is the difficulty of initiating or maintaining sleep, which is seen in 30–50% of older adults.[3,12-15] Precipitating and perpetuating factors for sleep disorders include those that are also related to sleep pattern, such as inadequate behavioural sleep habits, age, and the use of medications. Invariably, insomnia is the most prevalent of all sleep disorders, with studies finding a wide range of insomnia rates. For instance, one study found rates of up to 40%, others found rates of around 20%, and other studies found lower rates.[2,12,16,17] Furthermore, insomnia rates have also been found to be on the rise, with Gamaldo et al.[12] reporting that insomnia rates among the elderly (≥60 years old) in the USA increased from 0.27% in 2002 to 1.29% in 2012.

Women are reportedly more commonly affected by insomnia than men, despite research data showing that there is a contrast between objective and subjective data.[13,18] This difference between subjective and objective sleep quality raises the question of whether standard objective sleep measures are appropriate for measuring women's experiences of poor sleep quality.[18] Additionally, it shows there is currently a lower demand from men for specialised healthcare services.

Insomnia is a sleep disorder and can also be a symptom of a medical and/or psychiatric condition. It is defined as a difficulty falling asleep or staying asleep, or waking earlier than expected and not

being able to return to sleep, even with adequate opportunity and the circumstances for sleep. There is also a poor quality of sleep and sleep tends to be non-restorative. It results in significant clinical distress and impairment in important areas of day-time functioning.[19,20]

Insomnia in older adults is more likely to be comorbid with other medical and/or psychiatric disorders, such as:

- Cardiovascular problems,
- Respiratory problems,
- Diabetes,
- Menopause,
- Cancer,
- Fibromyalgia,
- Parkinson's disease,
- Alzheimer's disease,
- Depression,
- Other sleep disorders such as obstructive sleep apnoea.[21-23]

Literature data have shown that insomnia in older adults is associated with falls and mood disorders and therefore may result in an increased risk of morbidity and mortality.[24-26] Alterations associated with cognitive performance are also observed, especially in relation to attention and concentration, memory problems, and executive functioning.[27,28] Furthermore, insomnia has been shown to be a predictor of cognitive decline, being considered an early sign and independent risk factor for dementia.[29]

Insomnia can be classified according to duration:

- Episodic insomnia (symptoms last between 1 and 3 months).
- Recurrent insomnia (when ≥2 episodes occur within 1 year).
- Acute insomnia (duration <3 months).[20]

Increasing age is not only associated with greater prevalence of insomnia,[12] but also with a decline in remission rates and greater persistence of the problem.[30] With ageing, there is also an increase in chronic insomnia, with many older people complaining of having had insomnia for years and some presenting with the condition for their entire lives.

In order to understand the chronic insomnia of older adults, Spielman et al.[31] explained how there are predisposing factors (a set of individual characteristics that increase the probability of developing insomnia, such as sex, age, neurotransmitter systems associated with sleep and wakefulness, and personality traits); precipitating factors (stressful events that precipitate the onset of the symptom, such as the death of a relative or unemployment); and perpetuating factors (behaviours that perpetuate sleep problems caused by attempts to compensate for poor sleep, even after the precipitating factors have been solved. Factors that maintain the condition include inadequate sleep habits, anxiety, medication, and many more).

TREATMENT

Pharmacological

Older adults make great use of both prescribed and non-prescribed hypnotic medications to improve their sleep problems and continue to use these medications over extended periods of time. It is well known that many risks associated with the use of medications in this age group exist. Due to altered pharmacokinetics, there is increased central nervous system sensitivity to the effects of these medications, as well as interactions with additional drugs taken for comorbid conditions. Use of benzodiazepines, non-benzodiazepine hypnotics, and diphenhydramine for treating insomnia results in an increased risk of cognitive impairment, acute respiratory insufficiency, vehicle accidents, dependence symptoms, and falls and fractures.[32-34] In addition, a review by McCall et al.,[35] based on retrospective and prospective cohort studies of suicide victims within the USA and other countries, showed that hypnotic medications are associated with suicidal thoughts. However, none of these studies were adequately controlled for factors such as depression, or other psychiatric disorders that may be linked to insomnia. It is important to mention that the adverse effects depend on the type of medication administered.[36-38] Frequent use of sleeping medications has also been found to be associated with a significantly increased mortality risk.[39]

There has been an effort to analyse appropriate pharmacological approaches. Recently, Edmonds and Swanoski[34] and Schroeck et al.[40] reviewed the safety and efficacy data associated with new therapeutic pharmacological alternatives approved by the U.S. Food and Drug Administration (FDA) for treating insomnia in the geriatric population (suvorexant, doxepin, ramelteon, and tasimelteon); however, these medications were demonstrated to have limitations and adverse effects.

Organisations such as the American Geriatrics Society (AGS)[41] do not recommend using benzodiazepines or non-benzodiazepine hypnotics in older adults. Despite these recommendations, benzodiazepines continue to be widely prescribed to older groups who are at the highest risk of developing serious adverse effects from these medications.[42]

Non-Pharmacological

There are several alternatives for treating insomnia in primary and secondary care settings, including non-pharmacological approaches such as cognitive behavioural therapy (CBT). The main advantages of CBT for insomnia are the lack of adverse effects and its long-lasting efficacy, with the changes in behaviour and beliefs allowing the benefits from this therapy to remain for a longer period of time. This is particularly relevant in the treatment of older adults due to the chronic nature and comorbidity of insomnia at this age; behavioural techniques have therefore been the proposed treatment approach.[43,44]

Several researchers have concluded that CBT should always be the first-line treatment for older adults.[17,44-46] For instance, Schroeck et al.[40] commented that "CBTI [chronic behavioural therapy for insomnia] is considered a first-line therapy approach for all forms of insomnia." An example of a case where researchers have argued for discontinuation of a pharmacological approach is Airagnes et al.,[33] who stated that, contrary to the belief of most clinicians, benzodiazepine can feasibly be discontinued with the use of psychotherapeutic or pharmacological strategies, and this can lead to long-term abstinence. They also commented that significant risk factors in the use of benzodiazepine include polypharmacy and the presence of comorbidities.

CBT for treating insomnia in older adults involves sleep hygiene (aims to change habits with an impact on sleep quality through psychoeducation); stimulus control (aims to associate sleep with relaxing activities only and avoid those that excite the individual and keep them awake); sleep restriction (limiting time in bed to sleeping time, thus increasing sleep efficiency); relaxation techniques (reduce somatic tension and intrusive thoughts that impair sleep); and cognitive therapy (disrupts dysfunctional beliefs and attitudes about sleep that lead to emotional distress and further sleep problems).[45,46]

Brasure et al.[47] demonstrated through a systematic review of >180 studies that CBT for insomnia improved global outcomes and nearly all sleep parameters in the general adult population, older adults, and adults who experienced chronic pain. These data were corroborated by the meta-analyses performed by van Straten et al.[48] and Vitiello,[49] who stated: "CBT for insomnia is effective, safe, and highly deployable". Studies show that using CBT is effective, with significant effects on the severity of insomnia, sleep efficiency, sleep quality, and sleep fragmentation.[17]

Digital forms of CBT for insomnia are also demonstrating promise as a therapeutic option, with some studies showing evidence of validity. For example, Chen et al.[50] demonstrated that a patient who successfully discontinued hypnotic treatment experienced restored sleep quality after intervention with a CBT mobile app, despite several limitations. Alessi et al.[51] studied community-dwelling veterans aged ≥60 years who met the diagnostic criteria of insomnia for ≥3 months. The researchers used stimulus control, sleep restriction, sleep hygiene, and cognitive therapy (individually or in small groups), in addition to weekly telephone behavioural sleep medicine supervision. The results showed significant improvements in sleep onset, sleep efficiency, and sleep quality in older adults with chronic insomnia.[52,53]

A complementary therapeutic measure involves social strategies and phototherapy. Diagnostic evaluation protocols should be investigated to indicate a requirement for this therapy. It should be determined whether the individual has decreased physical activity, social isolation, or reduced exposure to light, especially for residents of long-term institutions and those with dementia, including Alzheimer's disease. Therefore, one of the coadjuvant and effective therapeutic possibilities includes decreasing time spent in bed during the day, increasing physical activity and social activation, increasing daily exposure to sunlight (or artificial light), provision of structured sleep routines associated with night-time, decreased exposure to nocturnal light and noise, and, lastly, increased vigilance associated with the times of exposure to sunlight and/or artificial daylight (due to the circadian, homeostatic, and psychosocial changes, as previously explained).[46,54] Fiorentino and Martin[55] explained the efficacy and benefits of this technique in older adults, although there is no consensus about

the results.[56-58] Evidence regarding the efficacy of these protocols for dementia patients is still scarce.[59,60]

In addition to phototherapy, research shows that the introduction of structured social activities improves the parameters of sleep and sleep quality[54,61] and increases slow-wave sleep, with an impact on memory.[62] Literature data have demonstrated that low-impact aerobic activity, walking, and tai chi improve sleep in sedentary older adults with sleep disorders.[63]

CONCLUSION

The progress observed with the use of CBT is clear and has been proven in short, medium, and long-term periods of time. However, there is still a shortage of professionals trained to develop this type of therapy, especially with older adults. This perhaps is part of the explanation for the existing predominance of pharmacological treatments for insomnia in this population. An important issue is that, because many older adults have several contributing factors from different domains in their sleep, these complaints are best managed with a multifaceted treatment approach, that is, with a combination of pharmacological treatment and CBT.

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Fully Mature, Laboratory-Grown Human Eggs

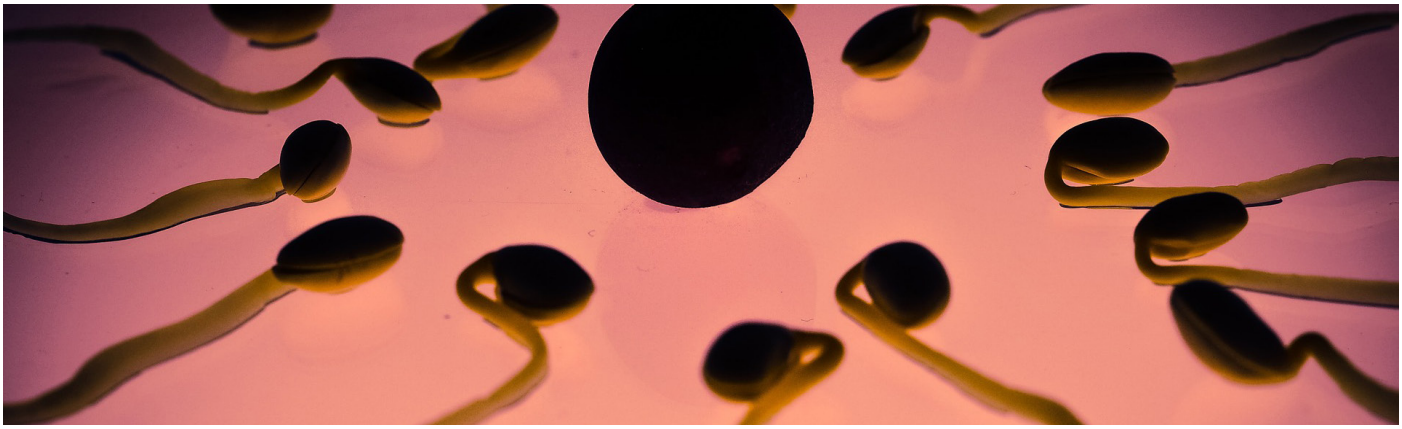
HUMAN OOCYTES have been grown to full maturity for the first time under tightly controlled laboratory conditions by a team based at the University of Edinburgh, Edinburgh, UK. Scientists have been attempting to grow human oocytes and sperm cells under laboratory conditions for decades. Therefore, this achievement by the laboratory team led by Prof Evelyn Telfer, School of Biological Sciences, University of Edinburgh, represents ground-breaking progress after decades of work. It is hoped that this technique will revolutionise infertility treatment.

The process involved the removal of 310 primordial follicles from ovarian tissue samples obtained during caesarean section surgery from 10 donor women. These primordial follicles were grown in a stringently controlled liquid medium. The researchers then extracted individual oocytes from the 87 remaining follicles and grew them, resulting in 32 fully mature eggs that were ready to be fertilised.

Growing oocytes to maturity within the laboratory will open new avenues to improve the currently available infertility treatment. For example, chemotherapy has long been associated with a negative impact on patient fertility. Currently, female patients have the option to freeze unfertilised oocytes, but this is not an option for paediatric patients. Therefore, this new technique offers an option for fertility preservation in paediatric cases. Additionally, it is speculated that this method could be used to develop immature eggs obtained through *in vitro* fertilisation (IVF), which would improve IVF's efficacy.

> "Growing oocytes to maturity within the laboratory will open new avenues to improve the currently available infertility treatment."

This new technique has exciting potential, but it is yet to be seen if the procedure can produce oocytes that can result in an embryo, fetus, and eventually a healthy baby, especially as the eggs produced are not identical to those released by the ovaries, with one difference being the significantly larger polar bodies in the eggs grown in the laboratory. For the time being, the eggs could prove to be enormously useful in understanding how oocytes grow and develop, enabling the progression of reproductive science.



Regulating Blood Vessel Growth Due to Inadequate Flow

THE DETECTION of inadequate blood flow to tissues during injury and consequent growth of new blood vessels is facilitated by a newly discovered gene. Researchers set out to better understand how blood and nutrient delivery to tissues is regulated and discovered insights that may greatly enhance the management of diseases of limited blood flow, including heart disease and stroke.

Dr Philip Marsden, Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Canada, and his team studied the recently discovered long non-coding RNA molecules (lncRNA), which are known to be involved in determining the final function of cells within an organism. As well as being the first study to identify the lncRNA that are most associated with endothelial cells, the results show that one lncRNA, known as STEEL (spliced-transcript endothelial-enriched lncRNA), was actively involved in sensing and correcting inadequate flow in the blood vessels by promoting vascular growth.

> "What is really interesting is that STEEL helps our body respond to inadequate blood flow by growing more blood vessels."

Dr Jeffrey Man, who works alongside Dr Marsden at the Keenan Research Centre for Biomedical Science, explained: "What is really interesting is that STEEL helps our body respond to inadequate blood flow by growing more blood vessels." He added: "These results show that our bodies are really finely tuned to perform, just as we need them to, and also demonstrates that disruptions to this fine balance can cause problems." The study authors concluded that by investigating these disruptions, we can improve the methods of healing and recovery following injury, particularly regarding blood vessel disorders. These data may also allow scientists to begin to uncover ways of blocking blood vessel flow as a method of tumour treatment and enhance efforts toward growing replacement organs for a number of conditions.

Finally, this study may also pave the way for further general investigations using lncRNA and provides an example of the number of proteins that can be related to a single lncRNA molecule. The authors noted that they plan to make the full list of lncRNA enriched with endothelial cells public for other researchers to use in the future, which will provide opportunities to find new tests and markers to better diagnose blood vessel disease patients.

Promising New Therapy Option for Adult Acute Lymphoblastic Leukaemia Patients

CHIMERIC ANTIGEN RECEPTOR (CAR) T cells are a key focus for the immunotherapy of B cell malignancies, with the greatest success seen to date involving the treatment of children with acute lymphoblastic leukaemia. Now, results from the ZUMA-3 trials have also shown promise for the treatment of adults.

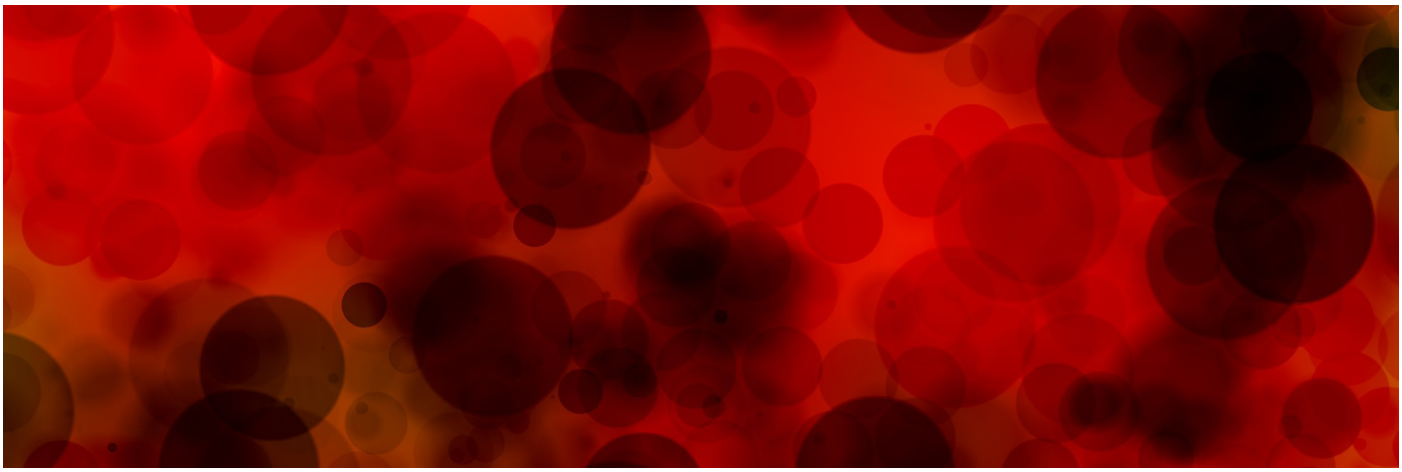
> "...This may not be a stand-alone therapy, but it may be a bridge to allogeneic transplantation, which can be curative for a substantial fraction of these patients."

The trial, which is still recruiting further patients, aimed to test the safety of KTE-C19, an anti-CD19 CAR T cell, as well as the rates of remission in adult patients with acute lymphoblastic leukaemia. The primary endpoint of the trial was the incidence of dose-limited toxicities, and the secondary endpoints observed the incidence of adverse events, duration of remission, relapse-free survival, overall survival, and minimal residual disease-negative responses.

A total of 22 patients were included in the initial study, with 16 receiving KTE-C19. Ten patients received a $1x10^6$ CAR T cells/kg dose, and 6 received a $2x10^6$ CAR T cells/kg dose, after undergoing lymphodepletion for 3 days. The patients did not experience any dose-limiting toxicities at these dose levels. Of the 16 patients, 11 were eligible for an efficacy analysis, which found an objective response rate of 82%. In addition, eight of these patients experienced complete disease remission, with one having total blast-free bone marrow. All of the remissions were negative for minimal residual disease, as observed via flow cytometry.

Despite the success of these initial results, four of the patients relapsed between Day 63 and 168 after KTE-C19 treatment. Dr Amelia Langsten, Medical director and section chief of the Bone Marrow and Stem Cell Transplant Program, Winship Cancer Institute, Atlanta, Georgia, USA, still holds hope for the novel treatment and commented: "...This may not be a stand-alone therapy, but it may be a bridge to allogeneic transplantation, which can be curative for a substantial fraction of these patients."

The results have shown that the use of KTE-C19 is clearly beneficial to adult acute lymphoblastic leukaemia patients, with a good safety profile. The trial continues, with the aim of improving the technique, focussing on second, third, and fourth-generation CAR T cells; the development of an improved benefit:risk ratio; and the ability to involve multiple targets.



Ulcerative Colitis Remission Reached with Apremilast

CLINICAL remission has been shown to drastically improve in patients taking apremilast for the treatment of ulcerative colitis, suggests a study performed at the Inflammatory Bowel Disease Clinical and Research Center, Humanitas Research Hospital, Milan, Italy. Previously approved for the treatment of psoriasis and psoriatic arthritis, apremilast was given orphan drug status in January 2018 for the treatment of paediatric ulcerative colitis.

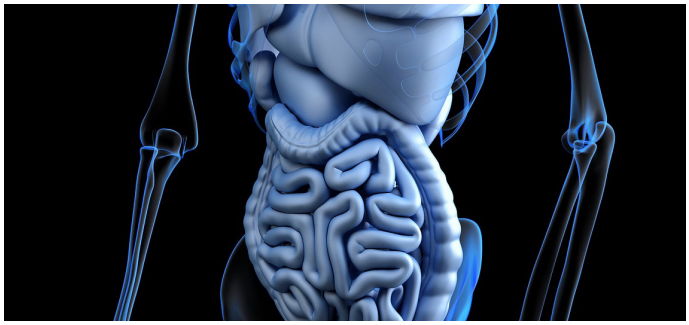
> “The achievement of clinical remission, which requires endoscopic improvement of the mucosa, is a meaningful goal in the treatments of ulcerative colitis. These findings suggest apremilast, which improved the likelihood of achieving remission in this 12-week study, merits further study in a larger trial...”

The Phase II, randomised, placebo-controlled, multicentre clinical trial assessed the efficacy of apremilast in treating patients with ulcerative colitis who had failed at least one conventional therapy but were naïve to biologic therapy. At the onset of the study, 170 patients were randomly divided into three groups: apremilast 40 mg (APR40; n=55), 30 mg (APR30; n=57), and placebo (n=58). The study’s primary endpoint was remission at Week 12, as measured by Total Mayo Score (TMS). By the end of the study, 21.8%, 31.6%, and 13.8% of patients had achieved TMS remission in the APR40, APR30, and placebo groups, respectively. When measuring clinical remission using the Partial Mayo Score, these percentages improved to 59.6% for APR30, 52.5% for APR40, and 36.2% for the placebo group.

Secondary endpoints, such as endoscopic remission, TMS clinical response, serum biomarkers, and mucosal healing were also measured, showing clinically meaningful improvements in the APR30 group compared to placebo.

“The achievement of clinical remission, which requires endoscopic improvement of the mucosa, is a meaningful goal in the treatments of ulcerative colitis. These findings suggest apremilast, which improved the likelihood of achieving remission in this 12-week study, merits further study in a larger trial,” explained Prof Silvio Danese, Inflammatory Bowel Disease Clinical and Research Center, Humanitas Research Hospital.

The researchers hope that their data will direct further research into developing oral immunomodulatory treatment options for patients with inflammatory bowel diseases. Indeed, plans are already underway to initiate a Phase III trial for apremilast 30 mg treatment for patients with ulcerative colitis.



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