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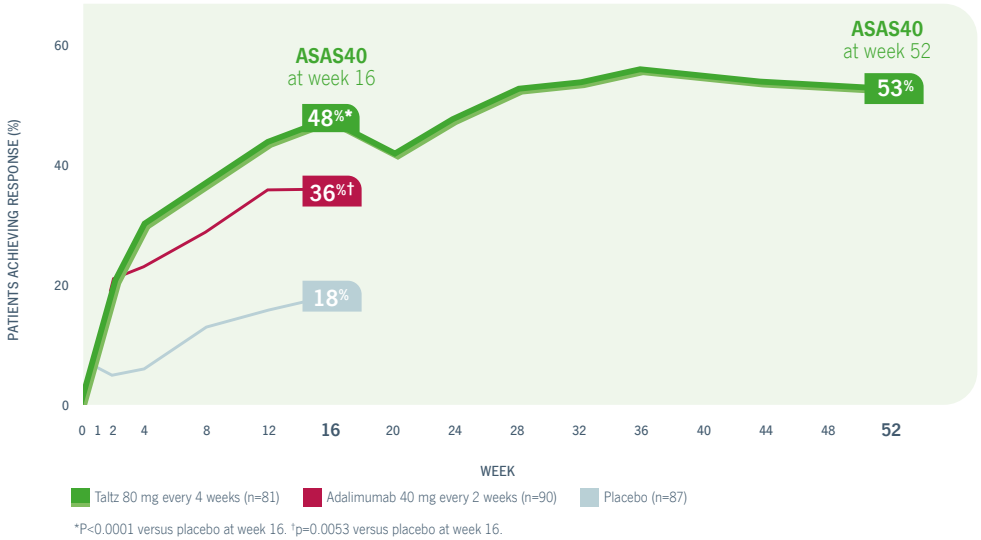
COAST-V (biologic-naïve): ASAS40 response rates through week 52 (ITT, NRI)



*P<0.0001 versus placebo at week 16. †p=0.0053 versus placebo at week 16.

Powerful and Consistent Efficacy Demonstrated by Taltz[1-3]:

- **Achieving ASDAS<2.1 (low disease activity)**
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  - LSM change from baseline in placebo group and Taltz group at week 16 : -1.4 and **-2.9** respectively (p<0.001)
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Study design[1]:
In this phase 3, randomized, double-blind and placebo-controlled study, patients with r-axSpA who have not previously been treated with bDMARDs were randomly assigned to receive 80 mg Taltz every 2 (n=83) or 4 weeks (n=81), 40 mg adalimumab every 2 weeks (active reference group; n=90), or placebo (n=87). The primary objective was to compare Taltz versus placebo at week 16 as measured by the proportion of patients achieving an ASAS40 response.

ASAS=Assessment of SpondyloArthritis international Society. ASDAS= Ankylosing Spondylitis Disease Activity Score. BASDAI=Bath Ankylosing Spondylitis Disease Activity Index. bDMARD=biological disease-modifying anti-rheumatic drug. IL-17=interleukin-17. ITT=intention to treat. LSM=least-squares mean. mBOCF=modified baseline observation carried forward. NRI=non-responder imputation. r-axSpA=radiographic axial spondyloarthritis.

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Indications: Plaque Psoriasis - Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Psoriatic Arthritis - Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more diseasemodifying anti-rheumatic drug (DMARD) therapies. Axial Spondyloarthritis - Ankylosing spondylitis (radiographic axial spondyloarthritis). Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy. Non-radiographic axial spondyloarthritis. Taltz is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs). Dosage: Plaque Psoriasis - Recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks. Psoriatic Arthritis - Recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis. Axial Spondyloarthritis (radiographic and non-radiographic) - Recommended dose is 160 mg (two 80 mg injections) by subcutaneous injection at week 0, followed by 80 mg every 4 weeks. Special Population: Elderly (≥ 65 years): No dose adjustment is required. There is limited information in subjects ≥ 75 years. Renal or hepatic impairment: No studies for renal and hepatic impairment patients. Contraindications: Serious hypersensitivity. Clinically important active infections. Special Precautions: Traceability, infections, hypersensitivity, inflammatory bowel disease, immunisations. Pregnancy, breast-feeding, fertility. Adverse Reactions: Injection site reactions, upper respiratory tract infections, tinea infection, oropharyngeal pain, nausea, herpes simplex (mucocutaneous). EUSPC14JAN2021

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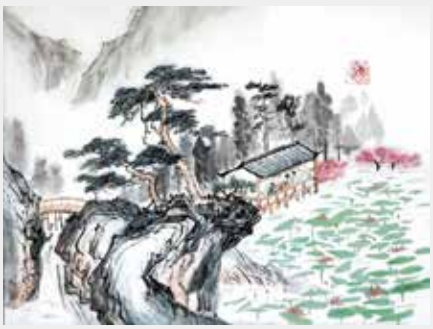

“松柏長春　山秀悠恬”

This is a painting by a local rheumatology patient Ms Ivy YIP, who has axial spondyloarthritis. She presented with back pain and ankle arthritis, complicated by uveitis and bowel inflammation. The painting was created when she was 40 years old, shortly after the flare-up of her back pain.

"Painting reduces my perception of the pain experience." Painting helps our patients better manage the symptoms of stress and anxiety accompanying the disease, thereby facilitating the recovery process and improving the quality of life.

Ms Ivy YIP kindly donated this art work of hers to the Hong Kong Society of Rheumatology to celebrate the Society's thirtieth anniversary. The painting was used as the design for the Society's tote bags.

Dr Carrel KL YU
Specialist in Rheumatology

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Advances in Rheumatology

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It is our pleasure to introduce this special issue on advances in the treatment of rheumatic diseases. The diagnosis and therapies of rheumatic diseases have undergone a major revolution in the past two decades. In the 1990s, only a few drugs were available for common rheumatic disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other inflammatory arthritis, namely corticosteroids, methotrexate, azathioprine, sulphasalazine, hydroxychloroquine and cyclophosphamide. There were very limited treatment options further straddled by safety concerns such as opportunistic infections, premature menopause and oncogenicity. The era of biological therapies in rheumatology ensued early in the new millennium when infliximab, the first anti-tumour necrosis factor (TNF) chimeric monoclonal antibody, was marketed in Hong Kong. Thereafter, a number of other anti-TNF, non-TNF biologics, targeted synthetic disease modifying anti-rheumatic drugs (DMARDs) and small molecules became available. These compounds target other cytokines, complements and cellular antigens such as interleukin (IL)-6, T-lymphocyte-associated protein 4 (CTLA-4) , IL-12, IL-17, IL-23, complement C5a, CD20, ICOS and IL-2. More recently, oral drugs that inhibit the downstream signalling of cytokine and other cellular receptors have been developed. Examples are the Janus kinase (Jak) and tyrosine kinase (Tyk) inhibitors, which have been tested in RA, spondyloarthritis and psoriatic arthritis. The Jak inhibitors offer the advantage of oral administration, lower cost and the lack of immunogenicity. Coupled with the development of these novel therapies, less costly biosimilar and generic compounds are increasingly available to benefit more patients in the public healthcare system.

In addition to therapeutics, advances in imaging techniques have helped earlier and better diagnosis of rheumatic diseases. Rheumatologists have increasingly gathered experience in bedside musculoskeletal ultrasound (MSUS) to document synovitis and bony erosion and to assist intra-articular, periarticular and soft tissue injections. Magnetic resonance imaging (MRI) and proton emission tomography (PET) are increasingly used for the diagnosis of certain rheumatic diseases such as spondyloarthritis, inflammatory myopathies and systemic vasculitides. In this issue of the Hong Kong Medical Diary, the concept of pre-clinical RA, the daily clinical use of MSUS, and advances in SLE, spondyloarthritis and psoriatic arthritis will be reviewed by our fellow rheumatology colleagues. We sincerely hope that you will enjoy reading the articles.

The year 2022 is very special to rheumatologists in Hong Kong. Apart from the third anniversary of the global COVID-19 pandemic, Hong Kong will host the Asia Pacific League of Rheumatology (APLAR) meeting for the second time on 6th-9th December 2022. We are expecting internationally renowned speakers to deliver their lectures in person or online. Pre-meeting workshops on ultrasonography and interchange with the mainland China/Macau rheumatologists in the Greater Bay Area will be organised. We welcome all of you to participate in this exceptional APLAR 2022 meeting.

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Who with Arthralgia will Develop Rheumatoid Arthritis?

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Dr Jacqueline SO

Rheumatoid arthritis (RA) is a chronic, debilitating, autoimmune disease typically presenting as symmetrical polyarthritis. It commonly affects females aged between 30 and 50 years old, with a female to male ratio of 3:1. The prevalence of RA in Hong Kong is 0.35%.[1] Inflammation of the synovial membrane, also known as synovitis, is the classical feature of the disease. Seropositive RA patients are those with the presence of autoantibodies either rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) and seronegative RA patients are those without these antibodies. The 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria of RA consists of four domains with point scores for each: joint involvement, serology (RF and/or anti-CCP), symptom duration (≥ 6 weeks) and acute phase reactants (ESR/CRP)[2], with sensitivity and specificity of 84% and 60% respectively for these classification criteria.[3]

The causative factors and pathophysiology of RA have remained unclear. Uncontrolled, persistent joint inflammation could lead to severe pain and irreversible joint destruction and deformity. Patients with RA have lower quality of life as compared to patients with other diseases. Early diagnosis and aggressive treatments are associated with less joint damage and higher chance of drug-free remission.[4] Are we able to identify patients at high risk of developing RA?

WHAT IS PRE-RA?

Pre-RA is a term used retrospectively after having diagnosed patients with RA. This is the preclinical period before RA, a period characterised by the complex interaction between genetics and environmental exposure, which in turn triggers immune activation and autoantibodies production.[5] EULAR study group for risk factors for RA agreed on six phases of RA development, including genetic risk factors, environmental risk factors, systemic autoimmunity, symptoms without clinical arthritis, unclassified arthritis and RA.[6] These phases occur in a continuum with genetic and environmental risk factors predisposing patients to the development of RA (Fig. 1). These risk factors may trigger abnormal local and systemic immune responses, leading to the development of symptomatic phases in pre-RA (symptoms without clinical arthritis and unclassified arthritis), and eventually the development of RA. Patients with subclinical synovitis detected by ultrasound or MRI are regarded as the phase between symptoms without clinical arthritis and unclassified arthritis.

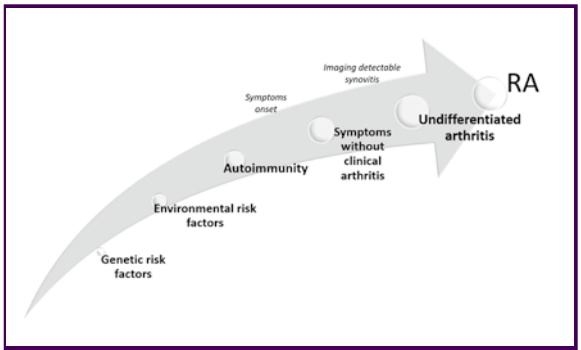

Fig. 1: Phases of RA development (Adapted from Gerlag DM, Raza K, van Baarsen LG, Brouwer E, Buckley CD, Burmester GR, et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. Ann Rheum Dis. 2012;71(5):638-41.6)

WHAT ARE THE CLINICAL FEATURES OF HIGH-RISK PATIENTS?

Polyarthritis is a common presentation of RA and other rheumatic diseases such as psoriatic arthritis, peripheral spondyloarthritis and crystal arthropathy.[7] The proportion of patients with undifferentiated arthritis who developed RA varies from 6%-55%.[8] Persistent polyarthritis was associated with increased risk of development of RA.[9] Patients with morning stiffness for at least 60 minutes, symptoms over metacarpophalangeal (MCP) joints, symptom duration less than 12 months, worst symptoms in the early morning, first-degree relative with RA, difficulty in masking a fit and positive squeeze test of MCP joints were more likely to develop RA.[10] On the other hand, chronic arthralgia for more than three years did not predict inflammatory arthritis but could be a presenting symptom of fibromyalgia.[11]

X-ray is a readily available tool commonly used to detect bony erosions. However, radiographic changes often lag behind disease progression in RA. Ultrasound could detect synovitis in patients without clinical synovitis. A combination of ultrasound power doppler signal and serology might predict the development of inflammatory arthritis in individuals with non-specific musculoskeletal symptoms.[12] Some studies also showed joint or bone inflammation on MRI may predict the development of RA.[13,14] Notably, these

imaging features are non-specific for RA and may be present in other conditions such as psoriatic arthritis. More studies are required to evaluate the use of these imaging modalities as adjunctive tools for the prediction of the development of RA. High-resolution peripheral quantitative computer tomography is a new imaging modality that could accurately measure volumetric bone mineral density and bone microstructure. Growing evidence showed its superiority compared to MRI in detecting bone erosion in patients with undifferentiated arthritis. However, currently its use is limited to research purposes.[15]

WHAT ARE THE RISK FACTORS FOR DEVELOPING RA?

Systemic Autoimmunity Associated with RA

RF and Anti-CCP Antibodies

Both RF and anti-CCP could precede the onset of disease symptoms by years.[16] RFs are antibodies directed against the Fc portion of immunoglobulin (Ig). RFs are present in about 60-80% of RA patients, with a specificity of ~70%. The low specificity of RF is due to the presence of RF in healthy elderly, infections and other autoimmune diseases[17] (Table 1). Persistent RF positivity, presence of > 1 RF Ig isotype and higher RF titre conferred a higher risk of RA.[18] Anti-CCP carries a high specificity up to 95% and a sensitivity similar to RF.[16] Patients with anti-CCP were associated with more severe radiological erosion and poorer outcomes.[16] Arthralgia patients with positive anti-CCP antibodies were strongly associated with the development of arthritis.[19] Higher anti-CCP level was also conferred to a higher risk of progression to RA.[20] Of note, the risk of developing RA within five years in the general population with positive anti-CCP was only 5.3%.[21]

Table 1: Conditions associated with RF positivity (Adapted from The major nonrheumatic diseases associated with rheumatoid factor positivity [Internet]. UpToDate.[17])

Rheumatoid arthritis		
Other rheumatic diseases eg. Sjogren syndrome, mixed connective tissue diseases, mixed cryoglobulinemia, systemic lupus erythematosus	Sarcoidosis, malignancies, primary sclerosing cholangitis	Chronic infections eg. hepatitis C, tuberculosis, and subacute infective endocarditis

Anti-carbamylated protein, anti-mutated citrullinated vimentin, anti-RA33 and anti-BiP are novel biomarkers that may be detected before the onset of RA. However, larger studies are required to validate their use.[22,23]

Cytokines

Biologic treatments targeting cytokines and their receptors, such as anti-tumour necrosis factor (TNF), anti-interleukin (IL) 6 and Jak kinase inhibitors are effective in treating RA. Upregulation of pro-inflammatory serum cytokines such as IL-1α, IL-1β, IL-4, IL-10 and TNF-α were observed before the onset of RA. Anti-IL-5, anti-IL15 and monocyte chemoattractant protein-1 level were also associated with the development of RA in high-risk patients.[23-26] However, more studies are required for the validation of their utility in predicting the development of RA.

GENETIC RISK FACTORS

RA has a complex genetic architecture with a heritability of around 60%. The prevalence of RA varies in different populations and affects as much as 5-6% of the population in the native American Indian. Twin studies showed the risk of concordance was 4-fold higher in monozygotic twins as compared to dizygotic twins, likely due to the interplay between genetic and environmental factors. Human Leukocyte Antigen (HLA)-DR is a Class II Major Histocompatibility Complex (MHC) molecule which has a strong genetic susceptibility to RA. HLA-DRB1 alleles are well known for their genetic predisposition to RA across different populations. HLA-DRB1*04 and HLA-DRB1*01 alleles confer the strongest genetic susceptibility to RA[27], while HLA-DR3 alleles are commonly associated with anti-CCP negative RA.[28] There are also some non-HLA risk loci for RA which account for around one-fourth of the genetic burden of RA. A recent study attempted to use DNA methylation profiling in undifferentiated arthritis patients for the prediction of the development of RA.[29] Currently, genetic testing in RA is mostly research-based.

ENVIRONMENTAL RISK FACTORS

Smoking

Smoking is a well-recognised risk factor in RA which is consistent among different gender and ethic variations.[30] The effect of smoking on the risk of RA is possibly related to epigenetic alterations.[31] Smoking and the number of pack-years are strongly associated with the risk of developing RA, regardless of the presence of RF or anti-CCP.[32] Furthermore, smokers with positive RF or anti-CCP were conferred a higher risk of RA than those without these antibodies.

Dysbiosis

The role of gut microbiota and risk of RA development was evidenced by the absence of arthritis in germ-free and antibiotic-treated mice but the development of severe arthritis after reconstitution of human RA faecal microbiota into these mice.[33,34] An imbalance of oral and gut microbiome composition was also observed in RA patients including a relative increase in abundance of Prevotella corpi and Collinsella in faecal samples and Lactobacillus salivarius and Atropobium spp in salivary samples of RA patients.[35-37] The microbiota diversity and richness were also lowered in RA patients, similar to other autoimmune diseases. Although different studies confirmed dysbiosis in patients with RA, the pattern of dysbiosis was erratic. More studies

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are required to identify disease-specific gut microbial profile in predicting the development of RA.

Periodontitis

The incidence of periodontal disease was significantly higher in RA patients compared to healthy controls. Periodontitis severity is also positively correlated with RA disease activity.[38] The oral microbe Porphyromonas gingivalis has been proposed as a major periodonotopathogen involved in triggering the production of anti-CCP.[39] However, some epidemiological studies showed conflicting results regarding the correlation between P. gingivalis and RA.[40]

Infections

Although microbial-specific antibodies and microbial contents could be found in serum or synovial tissues of RA patients, studies on the link between infectious antigenic stimuli and the risk of RA yielded inconclusive findings.[41] Nonetheless, multiple antibiotic use was associated with an increased risk of developing RA.[42]

Diet and Physical Activity

The risk of cardiovascular diseases preceded the onset of RA.[43] Obesity with high body mass index was associated with an increased risk of RA in women. High intake of red meat and salt and regular consumption of sugar-sweetened soda were risk factors of developing RA.[44] On the contrary, a healthier diet exerts a protective effect towards RA in young women.[45] The risk of RA was also 35% lower in women with regular physical exercise.[46]

WHAT CAN WE DO?

Proper evaluation and early recognition of high-risk individuals are crucial to preventing the development and progression of RA. Lifestyle modifications in high-risk patients include smoking cessation, weight reduction, regular exercise, a balanced diet and routine dental care (Fig. 2). Judicious use of antibiotics is also advocated in order to avoid dysbiosis. Blood tests for autoantibodies RF and anti-CCP should be considered in symptomatic individuals. Close monitoring for disease progression in seropositive patients are required as antibodies may precede the onset of RA. Ultrasound and MRI joints should only be considered in selective pre-RA patients.

CONCLUSION

In summary, the interplay among multiple factors including genetics, environment, microbiome and immune responses could trigger the development of RA. Early identification of patients in pre-RA phase and modification of risk factors may potentially delay the progression of RA.

Fig. 2: Management of patients at risk of RA development (Developed by the author)

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Ultrasound in Rheumatology

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INTRODUCTION

Ultrasound (US) is a safe, inexpensive, patient-friendly imaging technique that is free of ionising radiation and allows the detection of a broad spectrum of abnormalities in the joints and peri-articular soft tissues. US has continued to gather interest and popularity among rheumatologists because of its indisputable utility for assessing various abnormalities in rheumatic conditions. US has also transformed our understanding of the pathophysiology of different rheumatic diseases. The roles of ultrasound in rheumatology include diagnosis, identification of subclinical disease, assessment of response to therapy, prediction of disease remission and relapse, and guided interventions. In this article, the principal applications of ultrasound in rheumatology are reviewed.

APPLICATION OF ULTRASOUND IN RHEUMATOLOGY

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory joint disease which can cause cartilage destruction, bone damage, and disability. Early diagnosis is the key to optimising therapeutic success regarding radiological and functional outcomes. Many studies have confirmed the superiority of US over clinical examination in detecting synovitis.[1] This is mainly because US can visualise mildly thickened synovium which is not yet detectable by clinical palpation with the latter leading to missed diagnosis. Doppler US is a technique to evaluate the blood flow of vessels at a level of microvascularity. It improves the sensitivity and specificity of US in the assessment of inflammation by detecting and quantifying the vascularisation changes in the pannus, due to the abnormal blood flow that reflects in real-time the activity of the inflammatory process.[2,3] US has also demonstrated superior sensitivity comparing conventional radiography in detecting bone erosions in RA patients.[4] Since ultrasound can identify both subclinical synovitis and early erosive disease preceding changes seen on conventional radiography, it is frequently used as a diagnostic tool in an early arthritis clinic (Fig. 1).[4,5]

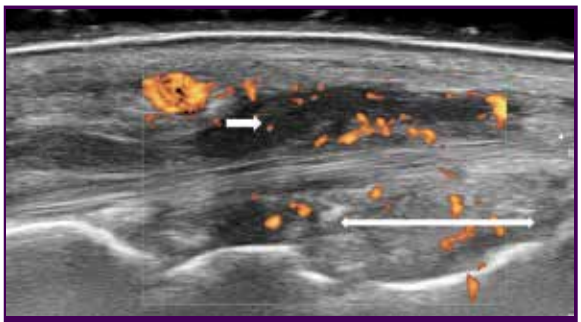

Fig. 1: US of the right wrist in a patient with early RA. Grey-scale image illustrated thickened synovium at the radio-carpal joint (left-right arrow) and within the tendon sheath of the extensor digitorium (arrow). The active power Doppler signal showed hyperaemia, indicating active arthritis and tenosynovitis. (Clinical photo from personal collection)

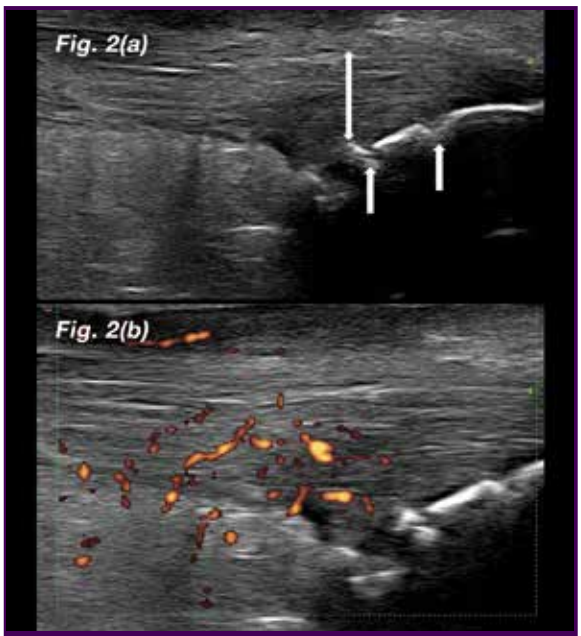

Fig. 2: Longitudinal views of the Achilles tendon in a patient with axial spondyloarthritis. (a) Grey-scale image showed the presence of a hypoechoic, thickened Achilles tendon (up-and-down arrow) at its bony attachment on the calcaneus as in enthesopathy. Discontinuity of the bone surface indicated bone erosion (arrow) as in chronic structural damage. (b) The presence of power Doppler signal indicated active enthesitis. (Clinical photo from personal collection)

Spondyloarthritis

Enthesis is the region where a tendon, ligament, joint capsule, fascia or muscle attaches to the bone. Enthesis

is the target tissue involvement in spondyloarthritis (SpA) and enthesitis, which is active inflammation of an enthesis, is the key pathogenesis of this group of diseases. The diagnosis of enthesitis has been underestimated, mainly due to the lack of sensitivity of the clinical examination for its detection. This situation is now improving with the increasing practice of ultrasound among rheumatologists. US is a tool with good sensitivity and specificity for assessing enthesitis.[6-7] It is proven superior in terms of sensitivity to clinical examination for detecting enthesitis and has revealed a high frequency of abnormalities in asymptomatic patients with subclinical enthesitis.[6] The grey scale assessment in US is employed to detect the structural components of enthesitis. The elementary lesions include thickening, hypoechogenicity, enthesophytes and erosions. Power Doppler signal is utilised to evaluate any hyperemia and neovascularisation in the entheses; such presence indicates active inflammation. Patients with SpA and active enthesitis will demonstrate active power Doppler signals at the enthesitic sites, a unique feature not usually found in other groups of inflammatory arthritis (Fig. 2).

CRYSTAL-RELATED ARTHROPATHIES

Crystal-related arthropathies are the result of crystal deposition in joints and peri-articular tissues. Identifying the crystals is mandatory to distinguish between gout and other crystalline arthropathies, such as calcium pyrophosphate deposition disease (CPPD). US allows direct visualisation of crystal deposition in the joint and the peri-articular tissues. Four elementary US lesions are identified in gout: double contour, tophus, aggregates and erosion.[8] Double contour, tophus and aggregates are demonstrated to be highly specific for the diagnosis of gout. The role of US was also highlighted in the European Alliance of Associations for Rheumatology (EULAR) evidence-based recommendations for gout as a potential tool for diagnosis and monitoring of gout.[9,10] US can also help differentiate gout from CPPD by the location of the crystal deposition in the cartilage. The existence of a hyperechoic band over the anechoic hyaline cartilage surface (the double contour sign) is a differentiating feature of the intra-cartilage deposit pattern of CPPD crystals. This sonographic feature carries good sensitivity for differentiating gout and CPPD.[11] Although important advances in the management of gout have been achieved in recent years, the patient's care is far from optimal in primary care or rheumatology practice. US is a helpful tool to improve the quality of assessment for gout patients.

OSTEOARTHRITIS

Conventional radiography is the most widely used imaging technique for diagnosing osteoarthritis (OA). It shows changes in bony structures, but it cannot demonstrate the early alterations of articular cartilage or the presence of joint effusion, nor can it evaluate the conditions of peri-articular soft tissues. US of the osteoarthritic joint can identify many features of OA that are often not apparent on physical exam or radiography: effusion, synovitis, articular cartilage wear, meniscal extrusion and popliteal cysts. In OA patients with synovitis, joint effusion with synovial hypertrophy can be detected by grayscale. In the presence of active inflammation, power Doppler can demonstrate increased local vascularisation within the synovial tissue. A higher grade of synovial hypertrophy, power Doppler signal and joint effusion was found in patients with radiographic erosive OA in comparison with patients with radiographic nonerosive OA.[12]

POLYMYALGIA RHEUMATICA

The main symptoms of polymyalgia rheumatica (PMR) are pain and stiffness of the shoulder and hip girdles, usually with an elevation of the inflammatory markers. Accurate PMR diagnosis is essential and challenging since many other musculoskeletal conditions can mimic the symptoms, some of which also respond initially to glucocorticoids. US was a valuable tool for detecting and assessing the inflammatory process. It allows direct visualisation of the intra-articular and extra-articular features of PMR, including subdeltoid bursitis, biceps tenosynovitis, trochanteric bursitis and synovitis of the shoulders and hips. US was introduced into the provisional classification criteria for PMR.[13] It improves the accuracy of diagnosis and provides guidance on needle placement for glucocorticoid injection to the inflamed bursa, tendon sheath and joint.

GIANT CELL ARTERITIS

Giant cell arteritis (GCA) is a medical emergency affecting the large and medium-sized arteries; prompt diagnosis of GCA together with prompt initiation of glucocorticoid treatment is the key to preventing irreversible ischemic complications, including vision loss and stroke. Historically, diagnosis has been based on clinical examination, raised inflammatory markers and temporal artery biopsy. However, the biopsy is invasive, and it lacks sensitivity. US is fast, non-invasive, more sensitive and more quickly available than temporal artery biopsy and conventional angiography in making the diagnosis. US of temporal and axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial GCA.[14] The most significant US abnormalities for GCA are the "halo" (a homogenous, hypoechoic thickening of the vessel wall) and the "compression" signs (thickened arterial wall remains incompressible upon application of pressure with the US probe). It is gratifying to see the progress of sonography of the cranial arteries, which may reduce the dependence on, or substitute the need for, temporal artery biopsy for diagnosis.

OTHER CONNECTIVE TISSUE DISEASES

Over the last decade, there has been an increasing interest in exploring the potential roles of US in evaluating the different target organs and tissues (salivary gland, lung, skin, muscle) other than the musculoskeletal systems in patients affected with various connective tissue diseases (CTD). US has been proposed as a new imaging modality for assessing salivary glands in primary Sjogren's syndrome, interstitial lung disease in patients with CTD, dermal thickness in systemic sclerosis, and inflamed muscles in autoimmune myositis.

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AMGEVITA (adalimumab)

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AMGEVITA™ (Adalimumab) Abbreviated Prescribing Information

AMGEVITA™ 40 mg solution for injection in pre-filled syringe/AMGEVITA™ 40 mg solution for injection in pre-filled pen

INDICATIONS Rheumatoid arthritis: AMGEVITA in combination with methotrexate, is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate; the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. AMGEVITA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. AMGEVITA reduces the rate of progression of joint damage as measured by x-ray and improves physical function, when given in combination with methotrexate. Polyarticular juvenile idiopathic arthritis: AMGEVITA in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in adolescents aged 13 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). AMGEVITA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years. Ankylosing spondylitis (AS): AMGEVITA is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy. Psoriatic arthritis: AMGEVITA is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. AMGEVITA reduces the rate of progression of peripheral joint damage as measured by x-ray in patients with polyarticular symmetrical subtypes of the disease and improves physical function. Psoriasis: AMGEVITA is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA. Crohn's disease: AMGEVITA is indicated for treatment of severe, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. **DOSAGE AND ADMINISTRATION** Rheumatoid arthritis: The recommended dose of AMGEVITA for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with AMGEVITA. Glucocorticoids, salicylates, non-steroidal anti-inflammatory drugs, or analgesics can be continued during treatment with AMGEVITA. In monotherapy, some patients who experience a decrease in their response to AMGEVITA 40 mg every other week may benefit from an increase in dosage to 40 mg adalimumab every week. There may be a need for dose interruption, for instance before surgery or if a serious infection occurs. Re-introduction of AMGEVITA after discontinuation for 70 days or longer should result in the same magnitudes of clinical response and similar safety profile as before dose interruption. Ankylosing spondylitis and psoriatic arthritis: The recommended dose of AMGEVITA for patients with ankylosing spondylitis and for patients with psoriatic arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Psoriasis: The recommended dose of AMGEVITA for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose. Crohn's disease: The recommended AMGEVITA induction dose regimen for adult patients with severe, active Crohn's disease is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), 80 mg at week 2 (given as two 40 mg injections in one day), can be used with the awareness that the risk for adverse events is higher during induction. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped AMGEVITA and signs and symptoms of disease recur, AMGEVITA may be re-administered. No dose adjustment is required in elderly. Adalimumab has not been studied in patients with renal and/or renal impairment. Polyarticular juvenile idiopathic arthritis from 13 to 17 years of age: The recommended dose of AMGEVITA for patients in adolescents aged 13 to 17 years (with ≥ 30 kg weight) with polyarticular juvenile idiopathic arthritis is 40 mg every other week. AMGEVITA is administered every other week via subcutaneous injection. There is no relevant use of adalimumab in patients aged less than 2 years for this indication. AMGEVITA is administered by subcutaneous injection. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. Active tuberculosis or other severe infections such as sepsis, and opportunistic infections. Moderate to severe heart failure (NYHA class III/IV). **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** Traceability: In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Infections: Patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, including tuberculosis, before, during and after treatment with AMGEVITA. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period. Hepatitis B reactivation: Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including adalimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with AMGEVITA. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Neurological events: TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Allergic reactions: Serious allergic reactions associated with adalimumab were rare during clinical trials. Non-serious allergic reactions associated with adalimumab were uncommon during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following adalimumab administration. Dry natural rubber: The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex), which may cause allergic reactions. Immunosuppression: In a study of 64 patients with rheumatoid arthritis that were treated with adalimumab, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B-, NK-cells, monocyte/macrophages, and neutrophils. Malignancies and lymphoproliferative disorders: With the current knowledge, a possible risk for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded. Haematologic reactions: Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with adalimumab. Vaccinations: No data are available on the secondary transmission of infection by live vaccines in patients receiving adalimumab. Patients on AMGEVITA may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to AMGEVITA in utero is not recommended for 5 months following the mother's last AMGEVITA injection during pregnancy. Congestive heart failure: AMGEVITA should be used with caution in patients with mild heart failure (NYHA class I/II). AMGEVITA is contraindicated in moderate to severe heart failure. Treatment with AMGEVITA must be discontinued in patients who develop new or worsening symptoms of congestive heart failure. Autoimmune processes: Treatment with AMGEVITA may result in the formation of autoimmune antibodies. The impact of long-term treatment with AMGEVITA on the development of autoimmune diseases is unknown. Concurrent administration of biologic DMARDS or TNF-antagonists: Serious infections were seen in clinical studies with concurrent use of anakinra and another TNFantagonist, etanercept, with no added clinical benefit compared to etanercept alone. Concomitant administration of AMGEVITA with other biologic DMARDS (e.g. anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions. Surgery: The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on AMGEVITA should be closely monitored for infections, and appropriate actions should be taken. Small bowel obstruction: Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that adalimumab does not worsen or cause strictures. Elderly: Particular attention regarding the risk for infection should be paid when treating the elderly. **INTERACTIONS** Adalimumab has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking adalimumab as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when adalimumab was given together with methotrexate in comparison with use as monotherapy. Administration of adalimumab without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab. The combination of AMGEVITA and anakinra and the combination of AMGEVITA and abatacept are not recommended. **PREGNANCY AND LACTATION** Women of childbearing potential: Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least five months after the last AMGEVITA treatment. Pregnancy: Due to its inhibition of TNF , adalimumab administered during pregnancy could affect normal immune responses in the newborn. AMGEVITA should only be used during pregnancy if clearly needed. Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. Breastfeeding: AMGEVITA can be used during breastfeeding. Fertility: Preclinical data on fertility effects of adalimumab are not available. **ADVERSE REACTIONS**The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain. Serious adverse reactions have been reported for adalimumab. TNF-antagonists, such as AMGEVITA affect the immune system and their use may affect the body's defence against infection and cancer. Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of adalimumab. Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome. In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients. **SPECIAL PRECAUTIONS FOR STORAGE, DISPOSAL AND OTHER HANDLING** Store in a refrigerator (2°C – 8°C). Do not freeze. Keep AMGEVITA in the outer carton in order to protect from light. The pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The pre-filled syringe or pre-filled pen must be protected from light, and discarded if not used within the 14-day period. Please read the full prescribing information prior to administration and full prescribing information is available upon request.

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Despite significant progress over the past decade, much work remains to be undertaken to confirm US as a useful outcome tool in the diagnosis, disease monitoring and treatment response in different CTDs.

ULTRASOUND-GUIDED INTERVENTIONS

Ultrasound guidance improves the precise identification of the target and the accuracy of the needle placement during interventional procedures to the joint cavity, tendon sheath, bursae and other soft tissues. It prevents injury to the neurovascular structures and decreases unwanted complications such as bleeding. Intra-articular placement of steroids is employed to treat different inflammatory arthritis. An incorrectly placed corticosteroid injection can potentially damage the cartilage and soft tissue structures. The use of ultrasound guidance increases the safety and efficacy of joint injections.[15,16]

CONCLUSION

The importance of ultrasound has been widely appreciated in evaluating various rheumatic diseases. In summary, ultrasound sheds excellent insights into the pathophysiology of rheumatic conditions and provides diagnostic, prognostic, and therapeutic implications in managing the diseases. It plays an important role, especially when other imaging modalities are either less appropriate or unavailable for various reasons. With the increasing validation of ultrasonography in various rheumatic diseases, the utility of ultrasound in daily rheumatological practice will continue to expand over time. In Hong Kong, most of the rheumatology departments in the public sector have established their own US service in their rheumatology clinics. Since 2021, musculoskeletal ultrasound has been incorporated into the curriculum training for rheumatology trainees. Each trainee must keep a logbook for the musculoskeletal ultrasound scan performed in various anatomical sites for various rheumatic diseases. The core members of a Special Interest Group of Ultrasound in the Hong Kong Society of Rheumatology have collaborated to organise hands-on ultrasound workshops at different levels (beginner, intermediate and advanced courses) around the year. The aim is to maximise the training opportunities of this clinical skill set for all local trainees and rheumatologists. US has become an extension of the right hand of rheumatologists, and it will continue to evolve in rheumatology to facilitate the best clinical care for our patients.

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CIMZIA® offers improved quality of life in patients with axSpA

TREATMENT WITH CIMZIA® HAS SHOWN:

Long-term symptom relief over 4 years:[1]

Morning stiffness

Numeric rating scale

Baseline	Week 24	Week 204
6.6	>>> 3.0	>>> 2.7

Nocturnal back pain

Numeric rating scale

Baseline	Week 24	Week 204
6.9	>>> 3.3	>>> 3.0

High retention-rate:[1]

At 204 weeks

67%	63%
in AS patients	in nr-axSpA patients

Abbreviations: AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; nr-axSpA: non-radiographic axial spondyloarthritis

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Abbreviated Hong Kong Prescribing Information

NAME OF THE MEDICINAL PRODUCT: Cimzia 200 mg solution for injection. Each pre-filled syringe contains 200mg certolizumab pegol in 1 ml. **THERAPEUTIC INDICATIONS:** ***Rheumatoid arthritis:*** In combination with methotrexate (MTX) for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including MTX, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. In combination with MTX, Cimzia is also indicated for the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs. Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with MTX. ***Axial spondyloarthritis:*** Treatment of adult patients with severe active axial spondyloarthritis, comprising: *Ankylosing spondylitis (AS)* - Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs). *Axial spondyloarthritis without radiographic evidence of AS* - Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs. ***Psoriatic arthritis:*** In combination with MTX for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. **POSOLOGY AND METHOD OF ADMINISTRATION:** ***Loading dose:*** The recommended starting dose for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. For rheumatoid arthritis and psoriatic arthritis, MTX should be continued during treatment with Cimzia where appropriate. ***Maintenance dose:*** *Rheumatoid arthritis:* 200 mg every 2 weeks for adult patients. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate. *Axial spondyloarthritis:* 200 mg every 2 weeks or 400 mg every 4 weeks for adult patients. *Psoriatic arthritis:* 200 mg every 2 weeks for adult patients. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate. For the above indications, available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment. *Paediatric population (< 18 years old):* The safety and efficacy of Cimzia in children and adolescents below age of 18 years have not yet been established. *Elderly (≥65 years old):* No dose adjustment is required. Renal and hepatic impairment: Cimzia has not been studied in these patient populations. No dose recommendations can be made. *Method of administration:* The total content (1 ml) of the pre-filled syringe should be administered as a subcutaneous injection only. Suitable sites for injection would include the thigh or abdomen. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Active tuberculosis or other severe infections such as sepsis or opportunistic infections. Moderate to severe heart failure (NYHA classes III/IV). **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** Infections (including serious infections), Tuberculosis, Hepatitis B Virus (HBV) reactivation, Malignancies and lymphoproliferative disorders, Skin cancers, Paediatric malignancy, Chronic obstructive pulmonary disease (COPD), Congestive heart failure, Haematological reactions, Neurological events, Hypersensitivity, Immunosuppression, Autoimmunity, Vaccinations, Concomitant use with other biologics, Surgery, Activated partial thromboplastin time (aPTT) assay, Elderly patients. **INTERACTIONS:** The combination of certolizumab pegol and anakinra or abatacept is not recommended. **FERTILITY, PREGNANCY AND LACTATION:** Women of childbearing potential The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last Cimzia dose due to its elimination rate, but the need for treatment of the woman should also be taken into account. Pregnancy Data from prospectively collected pregnancies exposed to Cimzia with known pregnancy outcomes, does not indicate a malformative effect of Cimzia. However, the available clinical experience is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with Cimzia administration during pregnancy. Animal studies using a rodent anti-rat TNFα did not reveal evidence of impaired fertility or harm to the foetus. However, these are insufficient with respect to human reproductive toxicity. Due to its inhibition of TNFα, Cimzia administered during pregnancy could affect normal immune response in the newborn. Cimzia should only be used during pregnancy if clinically needed. Breast-feeding: Cimzia can be used during breastfeeding. Fertility Effects on sperm motility measures and a trend of reduced sperm count in male rodents have been observed with no apparent effect on fertility. **UNDESIRABLE EFFECTS:** bacterial infections, viral infections, eosinophilic disorders, leukopaenia, headaches, sensory abnormalities, hypertension, nausea, hepatitis, rash, pyrexia, pain, asthaenia, pruritus, injection site reactions. **DATE OF REVISION OF THE TEXT:** February 2018. Please refer to full prescribing information before prescribing.

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Axial Spondyloarthritis: Diagnosis, Assessment, and Management

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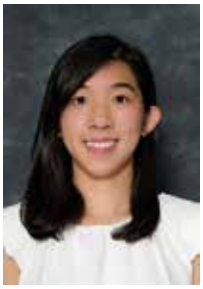

Dr Karen CY HO Dr Ho-yin CHUNG

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 October 2022.

ABSTRACT

Axial spondyloarthritis (SpA) refers to a spectrum of rheumatic diseases characterised by spondylitis, sacroiliitis, peripheral arthritis, and enthesis. The optimal management of patients with SpA consists of a combination of pharmacologic and non-pharmacologic approaches. In addition to conventional synthetic DMARDS (csDMARDs), advances in biologic DMARDs (bDMARDs) and targeted synthetic DMARDS (tsDMARDs) have greatly improved the prognosis of SpA. Traditional methods of monitoring rely on a self-rated assessment tool, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which is prone to confounders. Magnetic resonance imaging (MRI) of axial joints, which consists of the SI joint and spine, now plays an important role in both clinical management and research. The extent of inflammation on MRI has been demonstrated to correlate with clinical disease activity scores, inflammatory cytokines, and with inflammatory cellularity on tissue biopsy. Hence, axial joint MRI is a more objective measure of disease activity in axial SpA. In addition to the established diagnostic utility of SI joint MRI, emerging research in spinal MRI is heading in similar directions. Advancement in imaging techniques paves the way for personalised medicine, allowing quantitative assessment of therapeutic response.

INTRODUCTION

Axial spondyloarthritis (SpA) refers to a spectrum of rheumatic diseases characterised by spondylitis, sacroiliitis, peripheral arthritis, and enthesis. Axial SpA is also associated with a number of extra-articular features, including anterior uveitis, pulmonary fibrosis, and aortitis. The usual age of onset is in the 20s. Although this disease entity was first described as early as the 2nd century AD, distinct clinical subtypes have emerged over time, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-related SpA, reactive arthritis (ReA), and undifferentiated spondyloarthritis (unSpA). Chronic inflammation in axial SpA is associated with increased mortality due to cardiovascular complications[1] and infection.[2]

Diagnosis of SpA relies on imaging of the SI joint or the presence on serology of human leukocyte antigen (HLA) B27, a class I surface antigen. AS, the prototype of axial SpA, is also known as radiographic axial SpA, being defined by the presence of radiographic sacroiliitis. In contrast, non-radiographic SpA is defined by its absence. Anti-CD 74 is a potential disease marker recently proposed to aid in the diagnosis of axial SpA.[3]

ASSESSMENT AND MONITORING OF DISEASE ACTIVITY

Assessment of active inflammation and monitoring of disease activity is important to guide treatment. Pharmacologic advancements have improved the prognosis, functional status, symptoms[4-7] and long-term cardiovascular complications.[1,8] However, novel biologic drugs may be expensive,[9] not without risks[2,10], and may induce immunogenicity. A more accurate assessment of active inflammation allows for fine-tuning of the threshold for initiating biological therapies. A treat-to-target (T-to-T) approach minimises irreversible damage from chronic inflammation and other complications.

The self-rated Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[11] is the most utilised tool for the assessment of disease activity in axial SpA. However, it is prone to confounders such as depression[12] and fibromyalgia[13], and correlates poorly with spinal inflammation[14,15]; both of these limitations potentially reduce the accuracy of the BASDAI. Other commonly used proinflammatory markers c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) offer poor discriminatory value for sacroiliitis.[16] The Ankylosing Spondylitis Disease Activity Score (ASDAS)[17], a newer composite index, is a more objective tool, and correlates well with axial SpA-related spinal inflammation on magnetic resonance imaging (MRI).[18] In particular, the short tau inversion recovery (STIR) sequence allows visualisation of inflammation; the latter correlates with inflammatory cellularity on tissue biopsy[19], and is useful for screening and exclusion of other pathologies.

Currently in clinical practice, BASDAI and ASDAS are the recommended assessment tools, and CRP and ESR are routinely used. The Assessment of SpondyloArthritis International Society (ASAS) identified a number of updated criteria for use in clinical practice and research. The four domains include: patient global, pain, functional (assessed by Bath Ankylosing Spondylitis Functional Index [BASFI])[20],

and inflammation (assessed by the mean of BASDAI questions 5 and 6). Partial remission or low disease activity is defined when each domain gives a value of 2 (on a scale of 0 to 10) or less. The inactive disease is defined by an ASDAS score of 1.3 or less. Based on the International classification of functioning, disability, and health (ICF) core set for AS, the ASAS health index (ASAS HI) is developed to capture the whole range of functioning and disability in axial SpA.[21]

CONVENTIONAL MRI SEQUENCES AND FUTURE DEVELOPMENTS

MRI of the axial joints plays an increasingly central role in both clinical management and research (Fig. 1). In addition to the diagnostic utility of SI joint MRI, emerging evidence finds spinal MRI heading in similar directions (Fig. 2).[22-25] Inflammatory lesions such as the corner inflammatory lesion (CIL) and fatty corner lesion (FCL) in a specific pattern or of sufficient quantity are specific to axial SpA.[22-25] The extent of inflammation has been demonstrated to correlate with clinical disease activity scores[18,26], inflammatory cytokines[26], and with inflammatory cellularity on tissue biopsy[19]. Hence, axial joint MRI offers utility for the assessment of disease activity[27], but there are insufficient data for the cost-effectiveness of its use in monitoring. MRI scoring systems such as the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI indices[28,29] are used extensively in research.

Conventionally, STIR or fat-saturation MRI is used to identify inflammation, while T1 MRI is used to detect structural changes. Newer techniques such as whole body MRI[30,31] and diffusion weighted imaging (DWI)[26] have been respectively proposed for identification of generalised inflammation and quantification of inflammation. In addition, artificial intelligence (AI) is recently being developed for the detection of inflammatory sacroiliitis in axial SpA.[32] Advancement in imaging techniques paves the way for personalised medicine, allowing quantitative assessment of therapeutic response in the future.

MANAGEMENT AND TREATMENT

Optimal management consists of a combination of pharmacologic and non-pharmacologic approaches. Drug treatments include non-steroid anti-inflammatory drugs, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDS (tsDMARDs).

Common csDMARDs include sulfasalazine (SSZ) and methotrexate (MTX). SSZ is recommended for the treatment of peripheral SpA with few or no axial symptoms, with significantly improved peripheral pain scores on BASDAI after three months of treatment.[33] In contrast, MTX monotherapy offers limited efficacy. Three trials of MTX compared with placebo showed no statistically significant difference in BASDAI, CRP and patient global assessment. No additional efficacy was conferred when MTX was added to infliximab monotherapy in two trials.[35] SSZ and MTX should only be considered in predominantly peripheral arthritis, or as second-line agents for axial symptoms.[34]

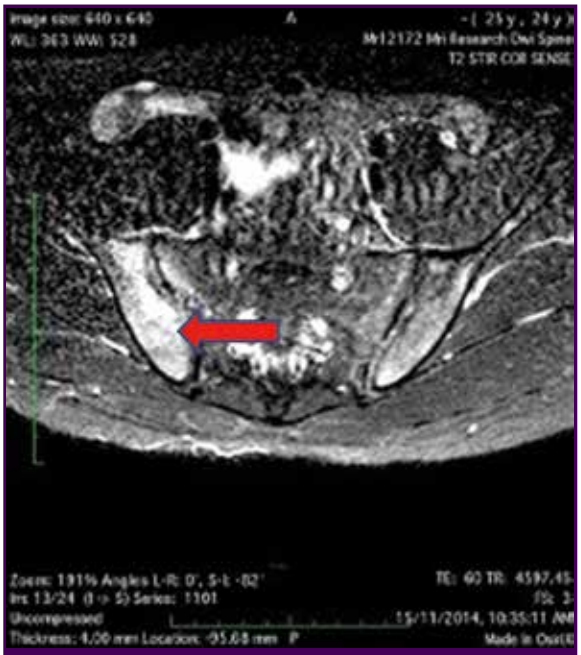

Fig. 1: Active sacroiliitis on MRI sacroiliac joint (Clinical photo from personal collection)

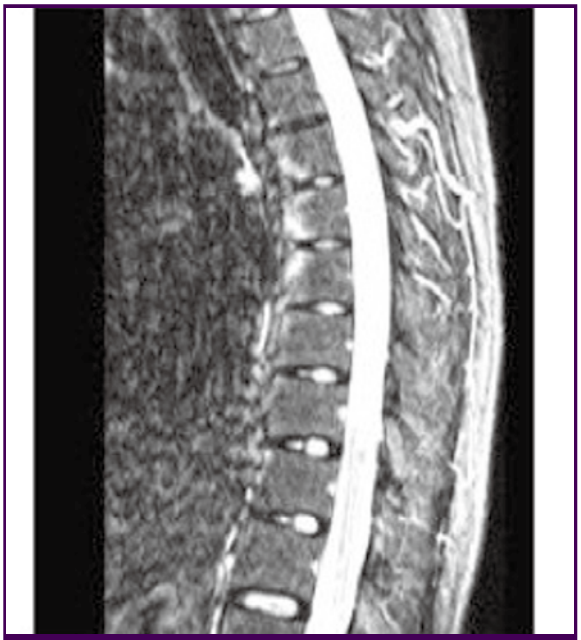

Fig. 2: Active spondylitis on MRI spine (Clinical photo from personal collection)

The bDMARDs target specific pathways in the immune system. These drugs include tumour necrosis factor inhibitor (TNFi) , interleukin (IL)-17 inhibitors (IL-17i) and IL-23 inhibitors (IL-23i). TNFi carries established efficacy in axial disease and is recommended by the American College of Rheumatology (ACR). ASAS guidelines recommend consideration of bDMARDs for cases of persistently high disease activity (BASDAI score ≥ 4 despite conventional treatments). The efficacy of TNFi in active SpA has been demonstrated in many controlled trials, showing improvements in patient-reported outcomes, composite response criteria, and

spine and sacroiliac inflammation on MRI.[36] Five TNFi drugs (adalimumab, certolizumab, etanercept, golimumab and infliximab) are licensed for use in SpA, and four (adalimumab, etanercept, certolizumab and golimumab) for non-radiographic axial SpA.

The inflammatory cytokines IL-23 and IL−17 were found in higher serum concentrations in patients with SpA compared to healthy controls.[37] IL-23 positive cells within the subchondral bone marrow were also significantly elevated compared to osteoarthritis. Inhibitors of IL-17 and IL-23 can theoretically be used to treat SpA.

Secukinumab and ixekizumab are IL-17i with demonstrated efficacy in phase III randomised controlled trials (RCT) in both TNFi-naive and TNFi-experienced patients with radiographic axial SpA.[38] A systematic review of RCTs showed when compared to placebo, IL-17i increased the ASAS20 response (an improvement of >/= 20% from baseline in at least three of the four above-mentioned domains) in SpA.[39] IL-17i therapy should be considered for active SpA where TNFi is contraindicated, such as comorbid heart failure or demyelinating disease, and for primary poor responders to TNFi. IBD is a contraindication for IL-17i therapy.

However, clinical studies with IL-23i, ustekinumab, showed a lack of efficacy in axial SpA despite its efficacy in PsA.[40] The PSUMMIT 1/2 phase III study evaluating the efficacy of ustekinumab in PsA found that at week 24, the primary endpoint of the American College of Rheumatology 20 response (ACR20) of at least 20% improvement in pain, physical functioning, and acute-phase reactant levels, was achieved in 42-50% in the ustekinumab group. Radiographic progression of the disease was also significantly reduced through 52 weeks.[41] Similarly, risankizumab also showed no clinically meaningful improvement in disease activity in AS.[42] The efficacy of IL-23i in treating PsA is believed to be due to the overexpression of IL-23 and IL-23-induced T helper 17 cytokines (IL-17 and IL-22) in the pathogenesis of psoriatic plaques, synovitis, joint erosion, enthesitis and new bone formation. However, most studies failed to show any evidence for clinically significant improvement of the primary and secondary endpoints of IL-23i in axial SpA.

The tsDMARDs target specific molecular structures. The two major types of tsDMARDs used in SpA are phosphodiesterase inhibitors and kinase inhibitors. Phosphodiesterase-4 inhibitors (PDE4i) act on immune cells by inhibiting the degradation of cyclic adenosine monophosphate, and hence decreasing pro-inflammatory cytokines. Apremilast is a PDE4i found in phase II and phase III trials to have efficacy in both skin psoriasis and PsA[43], and in poor responders to csDMARDs and TNFi. However, results in axial SpA are less promising. A prospective controlled trial (POSTURE) comparing two dosages of apremilast versus placebo showed no statistical difference at week 16.[44]

Kinase inhibitors act on specific targets in the Janus Kinase and Signal Transducer and Activator of Transcription (JAK-STAT) pathway that transduces signals from a variety of cytokines. This pathway is the pathogenic mechanism of many rheumatic diseases such as rheumatoid arthritis and SpA. Tofacitinib is an example of JAK inhibitor with efficacy in both axSpA and PsA. A phase III, randomised, double-blind, placebo-controlled study from 2018 to 2020 of active axial SpA found that tofacitinib 5 mg twice daily had a significantly greater ASAS20 response rate.[45] Similarly, a randomised controlled trial of two dosages of tofacitinib versus adalimumab (TNFi) versus placebo found an ACR20 response of 61%, 52%, and 33% in the respective groups. Clinical response was maintained over a one-year period of treatment, without radiographic structural damage progression in more than 90% of the patients.[46]

It is interesting to note that apremilast and IL23i demonstrated efficacy on PsA but not in axial SpA, suggesting the presence of multiple inflammatory pathways that vary with the subtypes of SpA. This divergence of immunopathological mechanisms fuels further research into target-oriented approaches to drug development.

CONCLUSION

MRI plays an increasingly important role in the diagnosis and assessment of disease activity in axial SpA. In addition to csDMARDs and bDMARDs, newer tsDMARDs provide more treatment options. These innovations pave the way for precision and personalised medicine in the future.

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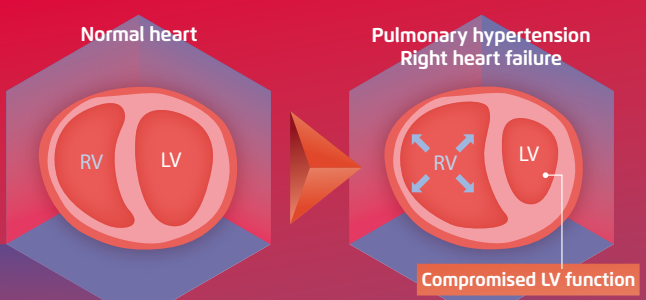
- PAH can occur in 8-12% of Sc patients, accounting for **75% of all CTD-PAH cases**[3]
- Estimated prevalence of PAH amongst SLE patients **ranges from 0.5% to 17.5%**[4]
- CTD-PAH is a leading cause of death in SSc patients and has **poorer 5-year survival rates** than other forms of PAH among intermediate-risk (37.8% vs. 56.1%) and high-risk patients (15.1% vs. 35.5%)[3,5]

RV function deterioration in PAH patients upon disease progression[2]



Adapted from Rosenkranz S, et al. 2020[1]

RV function deterioration precedes symptom progression in PAH patients[2]

A significant number of PAH patients could die from sudden cardiac death[1]

Early detection of RV function deterioration with ECHO parameters is urgently needed[6]

Early recognition of disease progression allows timely intervention to **prevent right heart failure**[2]

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Abbreviations: CTD: Connective tissue disorders; ECHO: Echocardiography; ERA: Endothelin receptor antagonist; IPAH: Idiopathic pulmonary arterial hypertension; LV: Left ventricle; PAH: Pulmonary arterial hypertension; PDE-5i: Phosphodiesterase-5 inhibitors; RV: Right ventricle; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis

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OPSUMIT® TABLETS 10MG ABBREVIATED PRESCRIBING INFORMATION ACTIVE INGREDIENT(S): macitentan **INDICATION(S):** Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. **DOSAGE & ADMINISTRATION:** Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH. Posology: The recommended dose is 10 mg once daily. Elderly: No dose adjustment is required in patients over the age of 65 years. There is limited clinical experience in patients over the age of 75 years. Opsumit should be used with caution in this population. Hepatic impairment: Based on pharmacokinetic (PK) data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment. However, there is no clinical experience with the use of macitentan in PAH patients with moderate or severe hepatic impairment. Opsumit must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (= 3 × ULN). Renal impairment: Based on PK data, no dose adjustment is required in patients with renal impairment. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. The use of Opsumit is not recommended in patients undergoing dialysis. Paediatric population: The safety and efficacy of macitentan in children and adolescents below 18 years have not yet been established. No data are available. Method of administration: The filmcoated tablets are not breakable and are to be swallowed whole, with water. They may be taken with or without food. Opsumit should be taken every day at about the same time. If the patient misses a dose of Opsumit, the patient should be told to take it as soon as possible and then take the next dose at the regularly scheduled time. The patient should be told not to take two doses at the same time if a dose has been missed. **CONTRAINDICATIONS:** Hypersensitivity to the active substance, soya or to any of the excipients listed in the full prescribing information. Pregnancy. Women of childbearing potential who are not using reliable contraception. Breastfeeding. Patients with severe hepatic impairment (with or without cirrhosis). Baseline values of hepatic aminotransferases (separate aminotransferases (AST) and/or alanine aminotransferases (ALT) > 3 × ULN). **SPECIAL WARNINGS & PRECAUTIONS:** The beneficial balance of macitentan has not been established in patients with WHO class I functional status of pulmonary arterial hypertension. Liver function: Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with endothelin receptor antagonists (ERAs). Opsumit is not to be initiated in patients with severe hepatic impairment or elevated aminotransferases (> 3 × ULN) and is not recommended in patients with moderate hepatic impairment. Liver enzyme tests should be obtained prior to initiation of Opsumit. Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin > 2 × ULN, or by clinical symptoms of liver injury (e.g., jaundice), Opsumit treatment should be discontinued. Reinitiation of Opsumit may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury. The advice of a hepatologist is recommended. Haemoglobin concentration: Decrease in haemoglobin concentrations has been associated with endothelin receptor antagonists (ERAs) including macitentan. Initiation of Opsumit is not recommended in patients with severe anaemia. It is recommended that haemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated. Pulmonary veno-occlusive disease: Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when macitentan is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. Use in women of childbearing potential: Opsumit treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised. Women should not become pregnant for 1 month after discontinuation of Opsumit. Monthly pregnancy tests during treatment with Opsumit are recommended to allow the early detection of pregnancy. Concomitant use with strong CYP3A4 inducers: In the presence of strong CYP3A4 inducers reduced efficacy of macitentan could occur. The combination of macitentan with strong CYP3A4 inducers (e.g., rifampicin, St. John's wort, carbamazepine, and phenytoin) should be avoided. Concomitant use with strong CYP3A4 inhibitors: Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nelfinavir, ritonavir, and saquinavir). Renal impairment: Patients with renal impairment may run a higher risk of experiencing hypotension and anaemia during treatment with macitentan. Therefore, monitoring of blood pressure and haemoglobin should be considered. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. Caution is recommended in this population. There is no experience with the use of macitentan in patients undergoing dialysis, therefore Opsumit is not recommended in this population. Elderly: There is limited clinical experience with macitentan in patients over the age of 75 years, therefore Opsumit should be used with caution in this population. Excipients: Opsumit contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Opsumit contains lecithin (soya). If a patient is hypersensitive to soya, Opsumit must not be used. This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'. **SIDE EFFECTS:** Very Common adverse reaction: Nasopharyngitis, Bronchitis, Anaemia, haemoglobin decrease, Headache, Oedema, fluid retention, Common adverse reaction: Pharyngitis, Influenza, Urinary tract infection, Leukopenia, Thrombocytopenia, Aminotransferase elevations, Hypotension, Nasal congestion, Uncommon adverse reaction: Hypersensitivity reactions (e.g., angioedema; pruritus; rash) Refer to the full prescribing information for other side effects. **PREGNANCY & LACTATION:** Use in women of childbearing potential/Contraception in males and females: Opsumit treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised. Women should not become pregnant for 1 month after discontinuation of Opsumit. Monthly pregnancy tests during treatment with Opsumit are recommended to allow the early detection of pregnancy. Pregnancy: There are no data from the use of macitentan in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is still unknown. Opsumit is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception. Breastfeeding: It is unknown whether macitentan is excreted in human milk. In rats, macitentan and its metabolites are excreted into milk during lactation. A risk to the breastfeeding child cannot be excluded. Opsumit is contraindicated during breastfeeding. Male fertility: The development of testicular tubular atrophy in male animals was observed after treatment with macitentan. The relevance of this finding to humans is unknown, but a deterioration of spermatogenesis cannot be excluded. **INTERACTIONS:** Cytochrome P450 enzymes CYP3A4, CYP2C8, CYP2C9, and CYP2C19. Strong CYP3A4 inducers. Ketoconazole. Sildenafil. Interaction studies have only been performed in adults. **PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.**

UPTRAVI® Tab 200mcg, 400mcg, 600mcg, 800mcg, 1000mcg, 1200mcg, 1400mcg, 1600mcg ABBREVIATED PRESCRIBING INFORMATION ACTIVE INGREDIENT(S): selexipag **INDICATION(S):** Uptravi is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. **DOSAGE & ADMINISTRATION:** Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH. Posology - *Individualised dose titration:* Each patient should be up-titrated to the highest individually tolerated dose, which can range from 200 micrograms given twice daily to 1,600 micrograms given twice daily. *Individualised maintenance dose:* The highest tolerated dose reached during dose titration should be maintained. If the therapy over time is less tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next lower dose should be considered. Dosage Adjustment with Co-administration of Moderate CYP2C8 Inhibitors: When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), reduce the dosing of Uptravi to once daily. If the therapy is not tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next lower dose should be considered. Revert to twice daily dosing frequency of Uptravi when co-administration of moderate CYP2C8 inhibitor is stopped. *Elderly:* No adjustment to the dose regimen is needed. *Hepatic impairment:* Uptravi should not be administered in patients with severe liver impairment (Child-Pugh class C). For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of Uptravi should be 200 micrograms once daily, and increased at weekly intervals by increments of 200 micrograms given once daily until adverse reactions, reflecting the mode of action of selexipag, that cannot be tolerated or medically managed are experienced. No adjustment to the dose regimen is needed in patients with mild hepatic impairment (Child-Pugh class A). *Renal impairment:* No adjustment to the dose regimen is needed in patients with mild or moderate renal impairment. No change in starting dose is required in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2); dose titration should be done with caution in these patients. *Paediatric population (< 18 years):* No data are available. Administration of selexipag in the paediatric population is not recommended. Method of administration - Oral use. The film-coated tablets are to be taken orally in the morning and in the evening. To improve tolerability, it is recommended to take Uptravi with food and, at the beginning of each up-titration phase, to take the first increased dose in the evening. The tablets should not be split, crushed or chewed, and are to be swallowed with water. Patients who have poor vision or are blind must be instructed to get assistance from another person when taking Uptravi during the titration period. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients listed in the full Prescribing information. Severe coronary heart disease or unstable angina. Myocardial infarction within the last 6 months. Decompensated cardiac failure if not under close medical supervision. Severe arrhythmias. Cerebrovascular events (e.g., transient ischaemic attack, stroke) within the last 3 months. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension. Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil). **SPECIAL WARNINGS & PRECAUTIONS:** Hypotension: Uptravi has vasodilatory properties that may result in lowering of blood pressure. Before prescribing Uptravi, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction). Hyperthyroidism: Hyperthyroidism has been observed with Uptravi. Thyroid function tests are recommended as clinically indicated in the presence of signs or symptoms of hyperthyroidism. Pulmonary veno-occlusive disease: Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when Uptravi is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. If confirmed, treatment with Uptravi should be discontinued. Elderly (≥ 65 years): There is limited clinical experience with selexipag in patients over the age of 75 years, therefore Uptravi should be used with caution in this population. Hepatic impairment: There is no clinical experience with selexipag in patients with severe liver impairment (Child-Pugh class C), therefore Uptravi should not be administered in these patients. The exposure to selexipag and its active metabolite is increased in subjects with moderate hepatic impairment (Child-Pugh class B). Renal impairment: In patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2), caution should be exercised during dose titration. There is no experience with Uptravi in patients undergoing dialysis, therefore Uptravi should not be used in these patients. Women of childbearing potential: Women of childbearing potential should practise effective contraception while taking selexipag. **SIDE EFFECTS:** The most commonly reported adverse reactions are headache, diarrhoea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing. These reactions are more frequent during the up-titration phase. The majority of these reactions are of mild to moderate intensity. Refer to the full prescribing information for other side effects. **PREGNANCY & LACTATION:** Women of childbearing potential: Women of childbearing potential should practise effective contraception while taking selexipag. Pregnancy: There are no data from the use of selexipag in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Selexipag and its main metabolite showed 20- to 80-times lower prostacyclin (IP) receptor potency in vitro for animal species used in reproductive toxicity testing compared to humans. Therefore, safety margins for potential IP receptor-mediated effects on reproduction are accordingly lower than for non-IP-related effects. Uptravi is not recommended during pregnancy and in women of childbearing potential not using contraception. Breast-feeding: It is unknown whether selexipag or its metabolites are excreted in milk. A risk to the suckling child cannot be excluded. Uptravi should not be used during breast-feeding. Fertility: There are no clinical data available. **INTERACTIONS:** Inhibitors of CYP2C8. Inducers of CYP2C8. Inhibitors of UGT1A3 and UGT2B7. Inhibitors and inducers of CYP3A4. PAH-specific therapies. Transporter inhibitors (rifampicin/rifampin). Anticoagulants or inhibitors of platelet aggregation. Midazolam. Hormonal contraceptives. **PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.**

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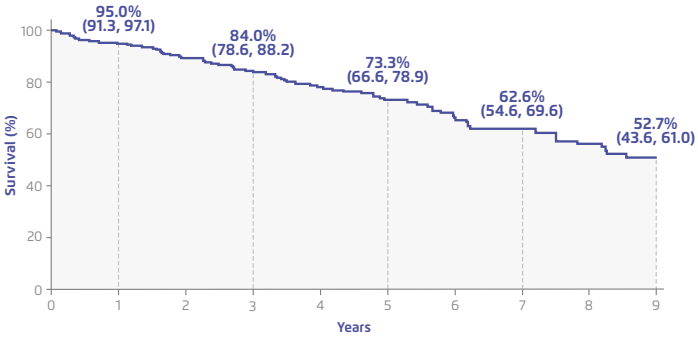
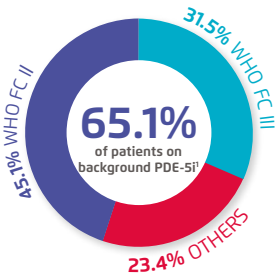
REAPING THE LONG-TERM SURVIVAL BENEFITS OF OPSUMIT® AND UPTRAVI® FOR YOUR PAH PATIENTS

Opsumit® macitentan

Kaplan-Meier survival curve for patients randomized to OPSUMIT® in SERAPHIN-OLE*



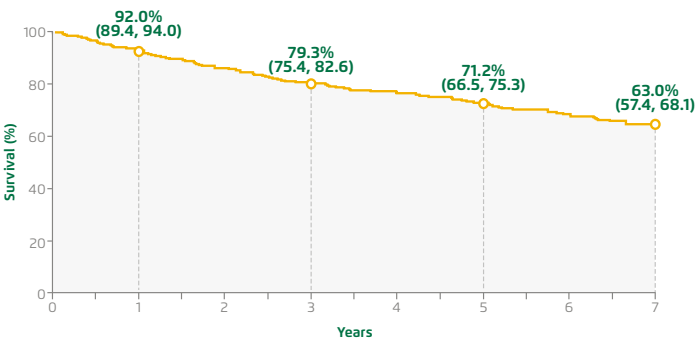
Patients at risk	242	225	210	171	145	105	79	69	49	22
Number of events	0	12	26	37	48	56	65	69	74	78



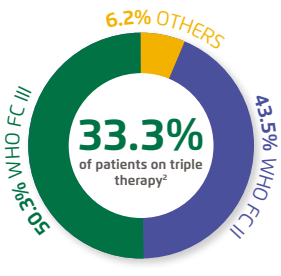
With OPSUMIT®, 52.7% of patients were kept alive after **9 years** of treatment[1]

Uptravi® selexipag

Kaplan-Meier survival curve for patients randomized to UPTRAVI® in GRIPHON-OLE**



Patients at risk	574	500	397	305	235	177	139	85
Number of events	0	45	79	105	119	130	140	147



With UPTRAVI®, patients were offered a **7-year** survival rate of **63%**[2]

** SERAPHIN-OLE was a long-term, multicentre, single-arm, non-comparative open-label study that evaluated long-term safety and tolerability of OPSUMIT® 10 mg in patients with symptomatic PAH.[1] Patients enrolled in SERAPHIN could enter SERAPHIN-OLE either after completing the double-blind treatment period of SERAPHIN without experiencing a primary endpoint event or after experiencing a morbidity event during SERAPHIN.[1] In this analysis, **most patients (65.1%) were on double combination therapy of OPSUMIT® + a PDE-5i. About 45.1% of patients were WHO FC II and 31.5% were WHO FC III.**[1]

** Patients enrolled into the GRIPHON were eligible to enter the corresponding long-term OLE study[2] in long-term follow-up of patients who were treated with UPTRAVI® in the placebo-controlled study (N=574) and the OLE study (N=330, of 574). Kaplan-Meier estimates of survival at 1, 3, 5, and 7 years were 92%, 79%, 71%, and 63%, respectively.[2] **The median exposure of UPTRAVI® was 3.0 years.[2] 33.3% of patients were treated with combination therapy of an ERA and PDE-5i at baseline.[2] 43.5% of patients were WHO FC II, and 50.3% were WHO FC III.**[2]

Abbreviations: ERA: Endothelin receptor antagonist; FC: Functional class; OLE: Open-label extension; PAH: Pulmonary arterial hypertension; PDE-5i: Phosphodiesterase-5 inhibitors; WHO: World Health Organisation

References: 1. Souza R, et al. Long-term safety, tolerability and survival in patients with pulmonary arterial hypertension treated with macitentan: Results from the SERAPHIN Open-Label Extension. Adv Ther. 2022. **2.** Galiè N, et al. Long-Term Survival, Safety and Tolerability with Selexipag in Patients with Pulmonary Arterial Hypertension: Results from GRIPHON and its Open-Label Extension. Adv Ther. 2022 Jan;39(1):796-810.

OPSUMIT® TABLETS 10MG ABBREVIATED PRESCRIBING INFORMATION ACTIVE INGREDIENT(S): macitentan **INDICATION(S):** Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) I to III. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. **DOSAGE & ADMINISTRATION:** Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH. Posology: The recommended dose is 10 mg once daily. Elderly: No dose adjustment is required in patients over the age of 65 years. There is limited clinical experience in patients over the age of 75 years. Opsumit should be used with caution in this population. Hepatic impairment: Based on pharmacokinetic (PK) data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment. However, there is no clinical experience with the use of macitentan in PAH patients with moderate or severe hepatic impairment. Opsumit must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (> 3 × ULN). Renal impairment: Based on PK data, no dose adjustment is required in patients with renal impairment. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. The use of Opsumit is not recommended in patients undergoing dialysis. Paediatric population: The safety and efficacy of macitentan in children and adolescents below 18 years have not yet been established. No data are available. Method of administration: The filmcoated tablets are not breakable and are to be swallowed whole, with water. They may be taken with or without food. Opsumit should be taken every day at about the same time. If the patient misses a dose of Opsumit, the patient should be told to take it as soon as possible and then take the next dose at the regularly scheduled time. The patient should be told not to take two doses at the same time if a dose has been missed. **CONTRAINDICATIONS:** Hypersensitivity to the active substance, soya or to any of the excipients listed in the full prescribing information. Pregnancy. Women of childbearing potential who are not using reliable contraception. Breastfeeding. Patients with severe hepatic impairment (with or without cirrhosis). Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT) > 3 × ULN). **SPECIAL WARNINGS & PRECAUTIONS:** The beneficial balance of macitentan has not been established in patients with WHO class I functional status of pulmonary arterial hypertension. Liver function: Elevations of liver aminotransferases (AST/ ALT) have been associated with PAH and with endothelin receptor antagonists (ERAs). Opsumit is not to be initiated in patients with severe hepatic impairment or elevated aminotransferases (> 3 × ULN) and is not recommended in patients with moderate hepatic impairment. Liver enzyme tests should be obtained prior to initiation of Opsumit. Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin > 2 × ULN, or by clinical symptoms of liver injury (e.g., jaundice), Opsumit treatment should be discontinued. Reinitiation of Opsumit may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury. The advice of a hepatologist is recommended. Haemoglobin concentration: Decrease in haemoglobin concentrations has been associated with endothelin receptor antagonists (ERAs) including macitentan. Initiation of Opsumit is not recommended in patients with severe anaemia. It is recommended that haemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated. Pulmonary veno-occlusive disease: Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when macitentan is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. Use in women of childbearing potential: Opsumit treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception in practised. Women should not become pregnant for 1 month after discontinuation of Opsumit. Monthly pregnancy tests during treatment with Opsumit are recommended to allow the early detection of pregnancy. Concomitant use with strong CYP3A4 inducers: In the presence of strong CYP3A4 inducers reduced efficacy of macitentan could occur. The combination of macitentan with strong CYP3A4 inducers (e.g., rifampicin, St. John's wort, carbamazepine, and phenytoin) should be avoided. Concomitant use with strong CYP3A4 inhibitors: Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir). Renal impairment: Patients with renal impairment may run a higher risk of experiencing hypotension and anaemia during treatment with macitentan. Therefore, monitoring of blood pressure and haemoglobin should be considered. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. Caution is recommended in this population. There is no experience with the use of macitentan in patients undergoing dialysis, therefore Opsumit is not recommended in this population. Elderly: There is limited clinical experience with the use of macitentan in patients over the age of 75 years, therefore Opsumit should be used with caution in this population. Excipients: Opsumit contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Opsumit contains lecithin (soya). If a patient is hypersensitive to soya, Opsumit must not be used. This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'. **SIDE EFFECTS:** Very Common adverse reaction: Nasopharyngitis, Bronchitis, Anaemia, haemoglobin decrease, Headache, Oedema, fluid retention. Common adverse reaction: Thrombocytopenia, Aminotransferase elevations, Hypotension, Nasal congestion. Uncommon adverse reaction: Hypersensitivity reactions (e.g., angioedema, pruritus, rash) Refer to the full prescribing information for other side effects. **PREGNANCY & LACTATION:** Use in women of childbearing potential/Contraception in males and females: Opsumit treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised. Women should not become pregnant for 1 month after discontinuation of Opsumit. Monthly pregnancy tests during treatment with Opsumit are recommended to allow the early detection of pregnancy. Pregnancy: There are no data from the use of macitentan in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is still unknown. Opsumit is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception. Breastfeeding: It is unknown whether macitentan is excreted in human milk. In rats, macitentan and its metabolites are excreted into milk during lactation. A risk to the breastfeeding child cannot be excluded. Opsumit is contraindicated during breastfeeding. Male fertility: The development of testicular tubular atrophy in male animals was observed after treatment with macitentan. The relevance of this finding to humans is unknown, but a deterioration of spermatogenesis cannot be excluded. **INTERACTIONS:** Cytochrome P450 enzymes CYP3A4, CYP2C8, CYP2C9, and CYP2C19. Strong CYP3A4 inducers. Ketoconazole. Sildenafil. Interaction studies have only been performed in adults. **PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.**

UPTRAVI® Tab 200mcg, 400mcg, 600mcg, 800mcg, 1000mcg, 1200mcg, 1400mcg, 1600mcg ABBREVIATED PRESCRIBING INFORMATION ACTIVE INGREDIENT(S): selexipag **INDICATION(S):** Uptravi is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. **DOSAGE & ADMINISTRATION:** Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH. Posology - *Individualised dose titration*: Each patient should be up-titrated to the highest individually tolerated dose, which can range from 200 micrograms given twice daily to 1,600 micrograms given twice daily. *Individualised maintenance dose*: The highest tolerated dose reached during dose titration should be maintained. If the therapy over time is less tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next lower dose should be considered. Dosage Adjustment with Co-administration of Moderate CYP2C8 Inhibitors: When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and fenfluramicle), reduce the dosing of Uptravi to once daily. If the therapy is not tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next lower dose should be considered. Revert to twice daily dosing frequency of Uptravi when co-administration of moderate CYP2C8 inhibitor is stopped. *Elderly*: No adjustment to the dose regimen is needed. *Hepatic impairment*: Uptravi should not be administered in patients with severe liver impairment (Child-Pugh class C). For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of Uptravi should be 200 micrograms once daily, and increased at weekly intervals by increments of 200 micrograms given once daily until adverse reactions, reflecting the mode of action of selexipag, that cannot be tolerated or medically managed are experienced. No adjustment to the dose regimen is needed in patients with mild hepatic impairment (Child-Pugh class A). *Renal impairment*: No adjustment to the dose regimen is needed in patients with mild or moderate renal impairment. No change in starting dose is required in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2), dose titration should be done with caution in these patients. *Paediatric population (< 18 years)*: No data are available. Administration of selexipag in the paediatric population is not recommended. Method of administration - Oral use. The film-coated tablets are to be taken orally in the morning and in the evening. To improve tolerability, it is recommended to take Uptravi with food and, at the beginning of each up-titration phase, to take the first increased dose in the evening. The tablets should not be split, crushed or chewed, and are to be swallowed with water. Patients who have poor vision or are blind must be instructed to get assistance from another person when taking Uptravi during the titration period. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients listed in the full Prescribing Information. Severe coronary heart disease or unstable angina. Myocardial infarction within the last 6 months. Decompensated cardiac failure if not under close medical supervision. Severe arrhythmias. Cerebrovascular events (e.g., transient ischaemic attack, stroke) within the last 3 months. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension. Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil). **SPECIAL WARNINGS & PRECAUTIONS:** Hypotension: Uptravi has vasodilatory properties that may result in lowering of blood pressure. Before prescribing Uptravi, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction). Hyperthyroidism: Hyperthyroidism has been observed with Uptravi. Thyroid function tests are recommended as clinically indicated in the presence of signs or symptoms of hyperthyroidism. Pulmonary veno-occlusive disease: Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when Uptravi is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. If confirmed, treatment with Uptravi should be discontinued. Elderly (≥ 65 years): There is limited clinical experience with selexipag in patients over the age of 75 years, therefore Uptravi should be used with caution in this population. Hepatic impairment: There is no clinical experience with selexipag in patients with severe liver impairment (Child-Pugh class C), therefore Uptravi should not be administered in these patients. The exposure to selexipag and its active metabolite is increased in subjects with moderate hepatic impairment (Child-Pugh class B). Renal impairment: In patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2), caution should be exercised during dose titration. There is no experience with Uptravi in patients undergoing dialysis, therefore Uptravi should not be used in these patients. Women of childbearing potential: Women of childbearing potential should practise effective contraception while taking selexipag. Pregnancy: There are no data from the use of selexipag in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Selexipag and its main metabolite showed 20- to 80-times lower prostacyclin (IP) receptor potency in vitro for animal species used in reproductive toxicity testing compared to humans. Therefore, safety margins for potential IP receptor-mediated effects on reproduction are accordingly lower than for non-IP-related effects. Uptravi is not recommended during pregnancy and in women of childbearing potential not using contraception. Breast-feeding: It is unknown whether selexipag or its metabolites are excreted in human milk. In rats, selexipag or its metabolites are excreted in milk. A risk to the suckling child cannot be excluded. Uptravi should not be used during breast-feeding. Fertility: There are no clinical data available. **INTERACTIONS:** Inhibitors of CYP2C8. Inducers of CYP2C8. Inhibitors of UGT1A3 and UGT2B7. Inhibitors and inducers of CYP3A4. PAH-specific therapies. Transporter inhibitors (lopinavir/ritonavir). Anticoagulants or inhibitors of platelet aggregation. Midazolam. Hormonal contraceptives. **PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.**

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Axial Spondyloarthritis: Diagnosis, Assessment, and Management" by Dr Karen CY HO and Dr Ho-yin CHUNG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 October 2022. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **Radiograph of the lumbosacral spine is the diagnostic test for ankylosing spondylitis.**
2. **High ESR is a poor prognostic factor in spondyloarthritis.**
3. **Spine MRI could be used to make an earlier diagnosis of spondyloarthritis.**
4. **Methotrexate is used to treat peripheral arthritis in ankylosing spondylitis.**
5. **Sulphalazine cannot be used to treat sacroiliitis in ankylosing spondylitis.**
6. **NSAIDs is the first line treatment for axial spondyloarthritis.**
7. **MRI could be used to assess disease activity in axial spondyloarthritis.**
8. **Anti-TNF therapy is associated with increased fungal infection.**
9. **Anti-IL-6 could be used to treat axial spondyloarthritis.**
10. **Diffusion-weighted imaging and whole-body MRI are novel MR modalities in axial spondyloarthritis.**

ANSWER SHEET FOR OCTOBER 2022

Please return the completed answer sheet to the Federation Secretariat on or before 31 October 2022 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Axial Spondyloarthritis: Diagnosis, Assessment, and Management

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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

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Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to September 2022 Issue

Antiplatelet Therapy for Coronary Artery Disease: Evolution in Three Decades

1. T 2. F 3. T 4. T 5. F 6. T 7. T 8. T 9. F 10. F

Psoriatic Arthritis - A Multi-dimensional Disease

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Dr Tin-lok LAI

INTRODUCTION

Psoriatic arthritis (PsA), one of the most prevalent spondyloarthropathies worldwide, is characterised by arthritis and skin psoriasis.[1,2] The estimated global prevalence of psoriasis is about 2%, while in Hong Kong (HK) it is approximately 0.3%.[1,2] Although the local incidence of PsA in psoriasis is currently unknown, international data have reported that 7 to 40% of cases with psoriasis will develop PsA in their lifetime, and these figures are believed to be an under-estimation.[3,4]

PsA is one of the most complex rheumatic diseases that not only is confined to the joints and skin only but also affects various body organs and tissues.[1-4] The multiple dimensions of PsA are described below.[1-4]

MULTIPLE DIMENSIONS OF PsA

Various External Features of PsA

The presentation of PsA is highly heterogenous even within the skin and joints.[2,3] Psoriasis may present with variable lesions, including plaque, pustular, flexural, erythroderma, guttate, etc, which appear highly similar to some common dermatological conditions, such as eczema and fungal infection, thus often resulting in diagnostic delay.[3,4]

As the nail is considered a skin appendage, nail involvements are extremely common (approximately 40%), and yet are always under-emphasised and under-recognised.[3,5,6] Indeed, it is one of the major diagnostic criteria (ClASsification criteria for Psoriatic ARthritis - CASPAR) for PsA.[6] Nail features that have been described include pitting, onycholysis, leukonychia, crumbling, subungual hyperkeratosis and splinter haemorrhage, etc.[4,5] Nail involvements induce nail disfigurement and can cause digital pain leading to hand dysfunction and immobility.[5] In addition, nail psoriasis was found to have a role in predicting arthritis of the distal-interphalangeal (DIP) joints.[5]

There are five phenotypes of PsA. (1) The polyarticular type (>= 5 joints affected) can mimic rheumatoid arthritis (RA), while (2) the oligoarticular type (< 5 joints affected) looks like osteoarthritis (OA). Involvement of (3) lumbosacral spine or sacroiliac joints resembles ankylosing spondylitis (AS). (4) Predominantly involvement of the DIP joints of hands may resemble OA and gout, and (5) occasionally, rapid progression may cause the marked bone resorption and debilitating joint destruction of arthritis mutilans. Indeed, it can be confused with osteomyelitis or acute infection.[2,3] The many variations of articular presentations can make the diagnosis of PsA onerous, even to rheumatologists.[2,3,4] Moreover, the tendon and its insertion-point over digits and limbs are always inflamed, leading to tender enthesitis and dactylitis.[2,3,4] However, distinguishing features of PsA are mobility-limiting enthesitis and dactylitis which are absent in RA and OA.[2,3,4] Fig. 1 shows various characteristics of PsA.

Fig. 1: Various features of psoriatic arthritis (PsA) (Fig. 1a) psoriatic nail dystrophy (hyperkeratosis and crumbling) with distal interphalangeal joint arthritis (Fig. 1b) polyarticular type of PsA (Fig. 1c) arthritis multilans - shortening of right thumb, middle and little finger (Fig. 1d) arthritis multilans - shortening of left ring and little finger (Fig. 1e) Skin psoriasis with predominant distal-interphalangeal joint swelling (Fig. 1f) psoriatic toe-nail dystrophy with distal interphalangeal joint swelling (Clinical photos from personal collection)

UNLOCKING LUPUS

SLE has a pathophysiology that involves B, T, and dendritic cells, as well as inflammatory cytokines such as IFN-1, IL-6, and BAFF. By understanding the central role IFN-1 plays in that cascade, we can begin to further unlock the complex nature of this challenging disease.[1-6]

BAFF = B-cell activating factor; IFN-1 = type I interferon; IL-6 = interleukin 6; SLE = systemic lupus erythematosus.

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EXTRA-ARTICULAR INVOLVEMENT OF PsA

Physical Comorbidities

Extra-articular manifestations are common, particularly uveitis and inflammatory bowel disease (IBD).[7] The lifetime prevalence of uveitis exceeds 40% and increases with the duration of PsA.[7] Similarly, the risk of developing IBD in PsA was significantly elevated (1-4 fold) compared to the general population. Vice versa, the risk of having skin psoriasis or PsA in IBD was also significantly increased compared to matched controls, with a hazard ratio of 2.95 (95% confidence interval (CI) 2.6-3.3).[7,8] Although the exact pathophysiology of the extra-articular disease is not clearly understood, it is thought to be human leucocyte antigen (HLA) related, i.e. HLA-B27.[2,7] HLA-B27 positivity triggers a cytotoxic T-cell response which results in cross-inflammation in tissues and organs that share the same antigen i.e. synovium, eye, bowel and skin.[2,7] PsA is a polygenic and multifactorial disease, in which other HLA alleles and non-HLA alleles, such as HLA-DR7, HLA-B39, JAK2, PRDX5, and environmental factors also play crucial roles in the pathogenesis.[2,7,8]

Recently, comorbid metabolic syndrome (MetS) was found to be highly prevalent in PsA.[4] MetS is a strong predictor of subclinical atherosclerosis, which may progress to fatal cardiovascular complications in the later stages.[4] MetS in Asians is defined by the International Diabetes Federation (IDF) criteria as central obesity (abdominal circumference being >= 80 cm in women and 90 cm in men) plus any two of the following four metabolic components: (1) high triglyceride (>= 1.7 mmol/L) or on any lipid-lowering agent (2) low HDL cholesterol (< 1.03 mmol/L in males and < 1.29 mmol/L in females) or on any lipid-lowering agent, (3) systolic blood pressure (BP) >= 130 mm Hg or diastolic BP >= 85 mm Hg or on any anti-hypertensive agent and (4) raised fasting plasma glucose (>= 5.6 mmol/L) or current diagnosis of type 2 DM.[4,9]

In Hong Kong, Mok et al. found that 38% of 109 patients with PsA had comorbid MetS, which was significantly higher than the general population and other arthropathies including RA and AS.[10] These findings suggest that MetS has a strong correlation with PsA that is not merely coincidental.[10] Some researchers proposed that PsA triggers a generalised body inflammation and the production of cytokines i.e. interleukin (IL)-17, IL-22 and tumour necrosis factor-α (TNF-α).[11] These cytokines further enhance the release of insulin-like growth factor (IGF-1) and adipocytokines, resulting in glucose intolerance and obesity. Others proposed a reverse mechanism.[11] Angiotensin-converting enzyme (ACE) overactivity in PsA, especially those with MetS, increases blood pressure which further accelerates atherosclerosis.[12] Chronic MetS is also associated with non-alcoholic fatty liver disease.[4,11]

A Danish national cohort study demonstrated that psoriatic patients had an elevated crude hazard ratio of 1.49 (95% CI 1.21-1.85) of coronary artery calcification, using computed tomography angiography to determine a coronary artery calcium score.[13] Serial measurements of carotid intima-media thickness (C-IMT) and plaques using high-resolution ultrasonography found that the extent of arterial stiffness was directly associated with PsA disease activity. Achieving sustained minimal disease activity (MDA) in PsA can hamper plaque formation and arterial calcification.[14] Subclinical atherosclerosis may be due to both metabolic syndrome and its components, and the high inflammatory burden in psoriatic conditions.[10-14]

PSYCHOLOGICAL COMORBIDITIES

Emotional distress may be significant and burdensome, in addition to physical symptoms.[15,16] Indeed, it is an unmet need in the management of PsA, partly due to the physicians' unawareness and lack of knowledge in assessment tools.[15,16] Chronic anxiety and depression may lead to social withdrawal and isolation, which make the patients inaccessible to medical treatment. As a consequence, it worsens both psychological and physical distress.[15,16] The suicidality risk is substantially higher among them.[15,16]

Using the Hospital Anxiety and Depression scale (HADS), McDonough et al. reported significant anxiety and depression in respectively 36.6% and 22.2% of patients with PsA in Canada.[17] Data from Hong Kong showed a similar prevalence of depression (26.9%) in ethnic Chinese patients with PsA.[18] Furthermore, depression was associated with disease activity and functional status, using the Disease Activity in PsA (DAPSA) and the Health Assessment Questionnaire Disability Index (HAQ-DI), but no association was found with socio-demographics and the comorbidities.[18] Prevailing theories posit that the hypothalamus-pituitary-adrenal (HPA) axis and monoaminergic system in the brain is stimulated by multiple inflammatory signal molecules such as interleukins, TNF-α and acute phase protein, which were excessively released during the inflammatory process.[15-18] As a result, overexpression of corticotrophic-releasing hormone and cortisol affects the mood states of patients with PsA.[15-18]

Fatigue is generally defined as the feeling of lack of energy or extreme weakness, and is classified into three types: cognitive, motivational and physical.[19] Chronic fatigue is a known phenomenon among patients with rheumatic diseases; the side-effect(s) of the medications used may also be a culprit for the fatigue symptom.[19] Increasing evidence demonstrated that fatigue is driven by the immune-inflammatory mechanisms rather than psychological distress to potentially stigmatising skin and joint conditions.[19,20] In active PsA, energy is diverted to the production of numerous pro-inflammatory cytokines that further disrupt the uptake and breakdown of neurotransmitters in the brain which aggravates fatigue.[19,20] Psychological distress should not be underestimated and regular screening should be promoted.

CONCLUSION

PsA is a heterogenous disease that affects physical and psychological wellbeing and interferes with daily activities. A better understanding of the diverse clinical

presentation, its comorbidities, and early treatment is the key to achieving clinical remission or minimal disease activity, thus improving the patients' quality of life.

A famous quote from Mencius <孟子> summarises the heterogeneity of PsA.

天降大任于斯人也
必先苦其心志 - Atherosclerosis, hypertension, cardiovascular events
勞其筋骨 - Arthritis, dactylitis, enthesitis
餓其體膚 - Skin and nail psoriasis, uveitis, IBD
空乏其身 - Metabolic syndrome, non-alcoholic fatty liver disease
行指亂其所為 - Anxiety, depression, fatigue

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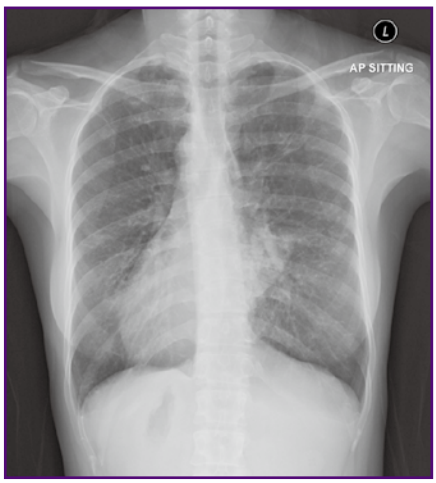
Radiology Quiz

Dr Sonia HY LAM
MBBS, FRCR, FHKCR, FHKAM (Radiology)

Dr Sonia HY LAM



A 39-year-old woman was admitted for on and off haemoptysis with a recent increase.

Questions

1. What are the CXR abnormalities?
2. What is the next step of investigation?
3. What is the next step of management?

(See P.36 for answers)

THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG
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Annual Scientific Meeting 2022

Innovations in Disease Diagnosis and Management

Date: 16 October 2022 (Sunday) **Time:** 09:30 - 17:00
Format: Hybrid
1) Online: Zoom Webinar
2) Onsite: 3/F & 4/F, Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Tsim Sha Tsui, Kowloon
(Pending COVID situation, only 180 seats available)

09:00-09:30 **Onsite and Online Reception**
09:30-10:00 **Opening Ceremony**

10:00-11:00 Session I A (AstraZeneca Session)

- **SGLT2 Inhibitors on Cardio-Renal Disease Management**
  Dr. Enoch WU *Specialist in Endocrinology, Diabetes & Metabolism*
- **An Update of Inhaled Therapies for Mild Asthma in Adults**
  Dr. Jamie Chung-Mei LAM *Specialist in Respiratory Medicine*

Session I B

- **Breakthroughs in the Treatment of Heart Failure**
  Dr. Michael Ka-Lam WONG *Consultant, Cardiac Medical Unit, Granthan Hospital*
- **Local Clinical Updates on Ketoanalogues Therapy with CKD Patients**
  Dr. Achilles Hoi-Kan LEE
  Consultant Physician, Department of Medicine & Geriatrics, Tuen Mun Hospital

11:20-12:20 Session II A (GlaxoSmithKline Session)

- **Treatable Trait in COPD**
  Dr. Terence Chi-Chun TAM *Honorary Clinical Associate Professor, HKU*
- **Starting Treatment Early for the Right Patients with Lower Urinary Tract Symptoms: 4 Things We Need to Know**
  Dr. Raymond Wai-Man KAN *Specialist in Urology*

Session II B

- **Burden of Antibody Deficiency & Feasibility of Subcutaneous Immunoglobulin Replacement in Hong Kong**
  Dr. Philip Hei LI *Clinical Assistant Professor, HKU*
- **New Opportunities to Treat Cognitive Impairment**
  Dr. Alexander Yuk-Lun LAU *Clinical Associate Professor (Honorary), CUHK*

12:20-13:15 Luncheon Symposium

- **Long COVID: Brain Fog and Other Psychiatric Sequelae**
  Prof. Ki-Yan MAK *Honorary Professor, HKU*

13:15-14:15 Session III A (Sanofi Session)

- **The Importance of Early Insulinisation in Glycemic Control**
  Dr. Rose Zhao-Wei TING *Specialist in Endocrinology, Diabetes & Metabolism*
- **Novel Therapeutics of Biologics in Management of Chronic Rhinosinusitis with Nasal Polyp**
  Dr. Joseph Chun-Kit CHUNG
  Consultant, Department of Ear, Nose & Throat, Queen Mary Hospital

Session III B

- **Medication and Cognitive Behavioral Training of ADHD**
  Dr. Fanny Wai-Fan LAM *Specialist in Developmental-Behavioural Paediatrics*
- **Management of COVID-19 Infection in Renal Failure Patients**
  Dr. Desmond Yat-Hin YAP *Clinical Associate Professor, HKU*

14:15-15:15 Session IV A

- **Suspecting, Diagnosing & Managing ATTR-Cardiomyopathy**
  Dr. Kevin Ka-Ho KAM *Honorary Clinical Associate Professor, CUHK*
- **Management of Severe Asthma - From Triple Inhalers Therapy to Biologics**
  Dr. David Chi-Leung LAM
  Clinical Associate Professor, Department of Medicine, HKU

Session IV B

- **Latest Update on Hyperuricemia Management - When and How?**
  Dr. Priscilla Ching-Han WONG *Specialist in Rheumatology*
- **Osteoporosis in Primary Care Clinic Settings**
  Dr. David Tak-Wai LUI *Clinical Assistant Professor, HKU*

15:35-16:35 Session V A

- **CAR-T Cell Therapy: New Hope for Patients with Haematological Malignancy**
  Dr. Thomas Sau-Yan CHAN
  Consultant, Division of Hematology, Queen Mary Hospital
- **The Use of Top Graft (Decalcified Tooth Tissue) in Modified Khoury's Technique with Autologous Concentrated Growth Factor (CGF) Preparation in Alveolar Augmentation**
  Dr. Spencer Chiu-Yee CHAN *Vice-President, Hong Kong Dental Association*

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Practical Tips in the Management of SLE

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Dr Shirley CW CHAN

BACKGROUND

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterised by loss of immune tolerance to nuclear antigen, autoantibody production and immune complex deposition. Immune dysregulation results in uncontrolled inflammation in various organ systems and subsequent organ damage. The prevalence of SLE varies across races and ethnicities, and it is more common in non-Europeans, including Asians, Hispanics and African Americans.[1] In Hong Kong, the prevalence of SLE was estimated to be around 0.1%.[2] The pathogenesis of SLE remains unknown, but it is believed to be contributed by genetic and environmental factors. Rapid scientific advances have led to a better understanding of disease mechanisms and consequently a rapidly evolving treatment landscape and management approach. This article serves to provide recent updates and offers practical tips for the management of SLE.

DISEASE CLASSIFICATION AND DIAGNOSIS

Patients with SLE demonstrate vast heterogeneity in clinical manifestation and disease severity. While some patients endure a stormy disease course, other patients have relatively mild disease with the absence of major organ involvements. Currently, there is no specific blood tests for SLE diagnosis. The specificity of antibody tests, such as anti-nuclear antibody (ANA) and anti-dsDNA, depends on the methods of detection and cut-off values.[3] Different sets of classification criteria have been developed to help identify homogenous SLE patients for comparison in different cohorts and recruitment into clinical trials (Table 1).[3-6]

Recently, a new set of criteria was developed jointly by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR), with the objective of achieving a better specificity than the former Systemic Lupus Collaborating Clinics (SLICC) criteria while maintaining the high sensitivity. Anti-nuclear antibodies (ANA) test was used as an entry criterion.[3] Patients with positive ANA will be assessed for the fulfilment of additive criteria. The additive criteria require patients to accumulate 10 points or more in seven clinical and three immunological domains. Only the highest-weighted criterion in each domain is counted (in the absence of a more likely explanation than SLE), the occurrence of a criterion at least once is sufficient, and the criteria need not occur simultaneously. The EULAR/ACR criteria are the first SLE criteria to incorporate a numeric cut-off score rather than the number of criteria fulfilled. A validation study using data of 1,533 Chinese patients with SLE demonstrated that the EULAR/ACR and the SLICC criteria performed equally well, and the specificity of the EULAR/ACR criteria could be improved by applying a higher cut-off score in this population while maintaining high sensitivity.[7]

Practical tips: The diagnosis of SLE relies on the physician's clinical judgement. Compatible clinical disease manifestations and serological evidence of autoimmunity form the cornerstone for disease diagnosis.

INTERPRETATION OF IMMUNOLOGICAL TESTS

Anti-nuclear Antibodies (ANA)

ANA refer to autoantibodies directed at antigens within the cell nucleus. ANA is an excellent screening test for SLE. However, positive ANA can also be also detected in healthy individuals and other chronic diseases. Therefore, interpretation of ANA results should take into account of the clinical contexts. Indirect immunofluorescence (IIF) with human epidermoid carcinoma cell line (Hep-2) cell substrate and solid phase assays are two commonly used detection methods.

The IIF test is the gold-standard test for ANA. Patient serum is incubated with Hep-2 cells fixed on glass slides. A fluorescein-conjugated antibody binds to human antibodies. Patient serum are tested at different dilutions, and an endpoint is reached when less than half of the cells on the slide show detectable fluorescence. ANA titre is reported as the dilution prior to this endpoint. The sensitivity and specificity of the ANA test vary at different titres. For example, ANA is detected in approximately 30% of healthy individuals at 1:40 dilution and 5% at 1:160 dilution respectively.[8] A higher ANA titre therefore confers better specificity for SLE and other autoimmune rheumatic diseases (AIRD), such as Sjogren's syndrome, systemic sclerosis, and mixed connective tissue diseases. The ANA titre does not correlate with disease activity, and therefore not a useful parameter for disease monitoring. The nuclear staining pattern is also reported in IIF test, including homogenous, speckled, nucleolar and centromere. ANA patterns provide suggestions of the underlying autoantibodies. Dense fine speckled (DFS) pattern and

Table 1: SLE classification criteria (Adapted from Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol.[3] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum.[4] Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum.[5]

	ACR 1997 criteria	2012 SLICC/ACR criteria	2019 SLICC criteria	
	Fulfil ≥ 4/11 criteria	Fulfil ≥ 4/17 criteria (≥ clinical and ≥1 immunologic criterion) **OR** Biopsy-proven LN with positive ANA/ anti-dsDNA	Entry criterion: ANA of at least 1:80 ever (Hep2 cells or equivalent) → If present, apply additive criteria Additive criteria* → Count the highest criterion in each domain. → Classified as SLE if total score ≥ 10 (≥ 1 clinical criterion)	
Clinical criteria/ domains	**Clinical criteria**		**Clinical domains [weighted score]**	
Mucocutaneous	1. Malar rash 2. Photosensitivity 3. Discoid rash 4. Oral/nasal ulcers	1. Acute or subacute cutaneous lupus 2. Chronic cutaneous lupus 3. Oral/nasal ulcers 4. Non-scarring diffuse alopecia (excluding alopecia areata, androgenic alopecia, or other causes e.g. drugs)	1. Mucocutaneous	Acute cutaneous lupus [6] Subacute cutaneous or discoid lupus [4] Ora ulcers [2] Non-scarring alopecia [2]
Musculoskeletal	5. Non-erosive arthritis in ≥ 2 hand joints (tender, swollen or effusion)	5. Synovitis ≥ 2 joints (swelling or effusion) OR tenderness ≥ 2 joints and ≥ 30 minutes of morning stiffness	2. Musculoskeletal	Joint involvement [6]: Synovitis ≥ 2 joints (swelling or effusion) OR tenderness ≥ 2 joints and ≥ 30 minutes of morning stiffness
Serositis	6. Pleurisy OR pericarditis	6. Typical pleurisy > 1 day OR pleural effusion OR pleural rub; Typical pericardial pain >1 day OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography	3. Serosal	Pleural or pericardial effusion [5]: imaging evidence Acute pericarditis [6]: ≥ 2 out of 4 features (Pericardial chest pain, pericardial rub, typical electrocardiography change, new or worsened pericardial effusion on imaging)
Haematological	7. Haemolytic anaemia with reticulocytotic OR leukopenia (< 4,000/mm^3 at least twice) OR lymphopenia (< 1,500/mm^3 at least twice) OR thrombocytopenia (< 100/cm^3)	7. Haemolytic anaemia 8. Leukopenia (< 4,000/mm^3 at least once) OR lymphopenia (< 1,000/mm^3 at least once) 9. Thrombocytopenia (< 100/cm^3 at least once)	4. Haematological	Leukopenia (< 4000/ mm^3) [3] Thrombocytopenia (< 100/cm^3) [4] Autoimmune haemolysis [4]
Renal	8. Proteinuria >500 mg/day or > 3+ by dipstick OR cellular cast (RBC, haemoglobin, granular, tubular or mixed)	10. Urine protein-to-creatinine ratio (or 24-hour urine protein) > 500 mg protein/24 hours OR RBC casts	5. Renal	Proteinuria > 0.5g/24h [4] Renal biopsy class II/V [8] Renal biopsy class III/IV [10]
Neuropsychiatric	9. Seizure OR psychosis	11. Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral OR cranial neuropathy	6. Neuropsychiatric	Delirium [2] Psychosis [3] Seizure [5]
			7. Constitutional	Fever (temperature >38.3 Celsius)[2]
Immunological criteria			**Immunological domains**	
Immunological/ serological	1. Positive ANA (not induced by drug) 2. Positive anti-dsDNA/ anti-Sm/ antiphospholipid antibodies (anticardiolipin IgG/IgM; lupus anticoagulant; or a false positive serological test for syphilis known to be positive for ≥ 6 months)	1. Positive ANA (above laboratory reference range) 2. Anti-dsDNA (above laboratory reference range or > 2-fold the reference range if tested by ELISA) 3. Anti-Sm positivity 4. Antiphospholipid antibody positivity: positive lupus anticoagulant, false positive result for rapid plasma regain, medium-/high-titre anticardiolipin (IgG/A/M), or anti-β2 glycoprotein I (IgG/A/M) 5. Low complements (C3/C4/ CH50) 6. Positive direct Coombs' test (in the absence of haemolytic anaemia)	1. Anti-phospholipid antibodies	Anti-cardiolipin antibodies OR Anti- β2 glycoprotein I antibodies OR Lupus anticoagulant [2]
			2. Complement proteins	Low C3 or low C4 [3] Low C3 and low C4 [4]
			3. SLE-specific antibodies	Anti-dsDNA antibody OR Anti-Smith antibody [6]

ACR = American College of Rheumatology; ANA = anti-nuclear antibody; C3 = complement component 3; C4 = complement component 4; ELISA = enzyme-linked immunosorbent assay; LN = lupus nephritis; RBC = red blood cell; SLE – systemic lupus erythematosus; SLICC = Systemic Lupus Collaborating Clinics.

anti-DFS70 antibodies are negatively associated with AIRD. Present in less than 1% of patients with AIRD, isolated anti-DFS70 positivity is useful to exclude AIRD diagnosis in patients with positive ANA.[9] Enzyme-linked immunosorbent assay (ELISA) utilises animal-derived or recombinant autoantigens for ANA detection. ELISA is less labour-intensive, but the different commercially available kits have various sensitivity and specificity.[10]

Practical tips: ANA should be interpreted in clinical contexts. A diagnosis of SLE should not be solely based on a positive ANA result. Higher ANA titres are more specific for SLE and other AIRDs.

Additional Immunological Tests

Although ANA patterns may provide some suggestions of the underlying autoantibodies, the interpretation is subjective. Additional testing for specific autoantibodies is useful to confirm the presence of disease-associated autoantibodies. Extractable nuclear antigen antibodies panel (or anti-ENA) can be detected using ELISA or immunoblot. The frequency and clinical associations of different autoantibodies are summarised in Table 2.[11]

Table 2: Common autoantibodies in SLE (Adapted from von Muhlen CA, Tan EM. Autoantibodies in the diagnosis of systemic rheumatic diseases. Semin Arthritis Rheum. 1995;24(5):323-58. [11])

Autoantibodies	Prevalence in SLE	Clinical associations
Anti-dsDNA	40-70%	Renal involvement; CNS involvement; correlates with SLE disease activity
Anti-Sm	15-30%	Renal involvement; CNS involvement; specific for SLE
Anti-RNP	30-40%	Raynaud's phenomenon; associated with mixed connective tissue disease
Anti-Ro	25-60%	Photosensitivity; subacute cutaneous lupus; neonatal lupus; Sjogren syndrome
Anti-La	9-35%	Neonatal lupus; Sjogren syndrome
Anti-phospholipid	30-40%	Thrombotic and obstetric complications

Since ANA titre does not correlate with disease activity, additional tests are usually performed for disease monitoring. A low level of serum complements (C3 and C4) and high level of anti-dsDNA titre reflect active disease in SLE. Other immunological tests such as anti-phospholipid autoantibodies and direct Coomb's test are helpful to support SLE diagnosis and to assess for associated conditions.

Practical tips: Additional testing for specific autoantibodies can be performed. These have different prevalence and clinical associations in patients with SLE. Serum complement levels and anti-dsDNA titres are useful for disease monitoring.

TREATMENT APPROACH

The goal of treatment in SLE is to improve short-term and long-term patient outcomes. Management of SLE aims at disease remission or low disease activity, prevention of flares and damage accrual, and minimising drug side effects.

Disease Activity Assessment

Disease activity assessment in SLE is complex, and various global and organ-specific disease activity indices have been developed. Systemic lupus erythematosus disease activity index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) are two of the commonly used global indices, especially in research settings.[12] SLEDAI consists of 24 weighted clinical and laboratory variables in nine organ systems. Variables are documented as present or absent, and the total score falls between 0 to 105. SLEDAI is easy to administer but does not capture improvement or worsening of each organ system. The BILAG index provides disease activity scoring across eight organ systems on an ordinal scale based on the physician's intention-to-treat premise. Physician global assessment (PGA) is a visual analogue scale based on clinician's judgement of overall disease activity ranging from 0 to 3. PGA is a simple and easy-to-use measure and plays an important role in assessing treatment response and remission. Training in scoring is useful to optimise test reliability.[13]

TREATMENT OF SLE

Treatment of SLE depends on disease severity, disease manifestations, patient's age and childbearing potential, cost and potential side effects.[14] Hydroxychloroquine (HCQ) is associated with a reduced frequency of disease flare, reduced risk of complications, and a good overall tolerability profile. HCQ is therefore recommended for all patients with SLE unless contraindicated. Contraindications include drug hypersensitivity to HCQ or underlying maculopathy. Corticosteroids are effective treatment with rapid onset of action, but are associated with different side effects, including infection, osteoporosis, avascular necrosis, metabolic disturbances and mood changes. During active disease, the dose of corticosteroid induction depends on disease severity and organ involvement. In chronic maintenance therapy, corticosteroid should be tapered to less than 5-7.5 mg/day (prednisolone equivalent). Immunomodulatory agents are effective for controlling disease activity, steroid tapering, and the prevention of disease flare. Commonly used immunomodulatory agents include azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), calcineurin inhibitors (CNI) and cyclophosphamide (CTX). AZA and MTX are considered in mild to moderate diseases, including cutaneous, musculoskeletal, serosal, or haematological involvement.[14-15] MMF is effective in renal and extra-renal manifestations, while CTX is considered an organ-threatening disease. MMF and CTX are teratogenic, whereas AZA and CNI are compatible with pregnancy.

Biological agents are considered when patients have persistently active disease despite standard of care treatment. B cell and interferon pathways have been targeted for the treatment of SLE. Belimumab (monoclonal antibody targeting B-cell-activating-factor) and Anifrolumab (monoclonal antibody targeting subunit 1 of type 1 interferon receptor) are approved

as add-on therapy in SLE.[16-18] Rituximab (chimeric antibody targeting CD20) is considered in patients with organ-threatening disease refractory to standard treatment. Other novel agents targeting various components of the immune and adaptative immune pathways are being developed.

REMISSION AND LOW DISEASE ACTIVITY STATE

Remission refers to the absence of clinical disease activity and has been endorsed as the long-treatment target in SLE.[14] Complete remission (absence of clinical activity and no use of corticosteroids and immunomodulatory drugs) is infrequent. The Definition Of Remission In SLE (DORIS) definition of remission includes clinical SLEDAI = 0, PGA < 0.5, prednisolone 5 mg/day or less, and stable antimalarials, immunosuppressive and biologics.[19] Another treatment target, Lupus Low Disease Activity State (LLDAS), was developed by the Asia-Pacific Lupus Collaboration (APLC).[20] Compared with DORIS definition or remission, LLDAS allows a SLEDAI score up to four points, PGA up to one, and a higher dose of corticosteroid ≤ 7.5 mg/day. Both definitions include a stable dose of antimalarials, immunosuppressives and biologics. Durable remission is rare in SLE, whereas LLDAS has been shown to be an attainable and achievable target.[21] Attainment of LLDAS for at least 50% of the observation period is associated with reduced flare, reduced damage accrual and better quality of life.[22]

Practical tips: Treatment of SLE depends on disease severity, organ manifestations, comorbidities, cost and potential side effects. Various indices are used to assess disease activity. Remission (or low disease activity state) and prevention of damage accrual form the long-term treatment targets in SLE.

CONCLUSION

Management of SLE is complex. SLE should be diagnosed by compatible clinical features and serological tests, after exclusion of mimics. Classification criteria were developed to help identify a more homogenous group of SLE patients for comparison among different cohorts and recruitment into clinical trials. Remission should be targeted, and the lowest disease activity state should be aimed at if remission cannot be achieved. Prevention of organ damage from uncontrolled disease activity or treatment side effects is equally important.

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What I Talk about When I Talk about Running: Running-related Soft Tissue Rheumatism

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Dr Ho SO

RUNNING AND RHEUMATOLOGY

Running is one of the most popular sports. Although running can lead to many health benefits, it carries a considerable risk of injury. While some of these injuries are traumatic, most are related to overuse or misuse. Importantly, many of them are amenable to nonsurgical management.

COMMON RUNNING-RELATED SOFT TISSUE RHEUMATISM

Patellofemoral Pain ("Runner's Knee")

Knee pain is one of the commonest complaints from runners and patellofemoral pain (PFP) is the most frequent diagnosis.[1] Women, second and third decades of life, high BMI, high mileage, decreased strength in hip abduction and biomechanical malalignment are the risk factors.[2] It is a clinical diagnosis. Individuals with PFP often complain of anterior knee pain that worsens with squatting, running, prolonged sitting, or when ascending or descending stairs. Pain is poorly localised "under" or "around" the patella. Acute phase treatment includes ice and NSAID. Rehabilitation involves knee and hip exercise to increase lower extremity strength, mobility, and overall function; foot orthoses (help control excessive foot overpronation or supination) and patellar taping (reducing pain and improving functional capacity). There is little evidence to support the use of intraarticular corticosteroid injection.[3]

Iliotibial Band Syndrome

The iliotibial band (ITB) is a long fascia that runs from the ilium to the anterolateral aspect of the proximal tibia; the ITB helps to stabilise the knee during running. ITB syndrome occurs primarily in runners, and is characterised by an insidious onset of aching or burning pain during running or when ascending/descending stairs over the lateral femoral condyle; the pain may radiate up the thigh towards the hip occasionally. Excessive hip pain can also be due to dysfunctional tensor fasciae latae (TFL), which is a common contributor to ITB syndrome. Precipitating factors include overuse, weak hip abductors leading to increased hip adduction ("knock-knees") and running on a surface with horizontal or vertical gradients.[4] Diagnosis of ITB syndrome is clinical, though musculoskeletal ultrasound can help to exclude sub-ITB bursitis. Focal tenderness at the distal ITB over the lateral femoral epicondyle is typical. Treatments are to relieve pain and to correct strength or mobility deficits (hip abduction weakness; flexibility of the ITB-stretching/foam roller to break up adhesions that restrict ITB motion). Some runners can reduce their symptoms by increasing their pace. For runners who tend to run in-toe, using a wider gait may decrease symptoms. Limited evidence suggests corticosteroid injection may provide short-term pain relief, although the long-term benefit is unlikely.[5]

Medial Tibial Stress Syndrome (Shin Splints)

Medial tibial stress syndrome (MTSS) is more common in overweight runners or military runners carrying heavy loads. It must be distinguished from stress fractures of the tibia in runners complaining of shin pain. While tenderness is diffuse in MTSS, a localised palpable area of tenderness is typical of stress fracture. Imaging may be necessary in some cases. Runners with MTSS can continue running but should reduce the total mileage. Shock-absorbing insoles may reduce symptoms and prevent a recurrence. Risk factors include obesity and limited mobility of the ankle and hip.[6]

Achilles Tendinopathy

Achilles tendinopathy occurs in up to 10 per cent of elite runners annually and seasoned runners are at particular risk.[7] Other risk factors include poor flexibility of the Achilles tendon, pes planus with tight calf muscle, and structural abnormality of the calcaneus. Typically, individuals will complain of pain or stiffness proximal to the posterior calcaneus. The pain is exertional and is relieved by rest. Runners often have recently increased their training intensity or have been training rigorously for a long time. A history of increased speed work or hill training, or improper or worn-out footwear are common. Treatment includes supporting the Achilles with a heel lift or elastic bandage or taping. Corticosteroid injection, either intratendinous or peritendinous, may provide short-term symptom relief, but there are case reports of tendon rupture after injection in patients with chronic tendinopathy.[8] Rehabilitation using resistance exercise is helpful.

CONTROVERCIES IN INJURY PREVENTION

Stretching

There is insufficient evidence to support or refute the

use of stretching to prevent injury.[9] It is helpful in rehabilitation for symptomatic relief of muscle spasms and lengthening of functionally shortened muscle-tendon units in tendinopathy. It should preferably be done following activity, when muscles are warm. The gains persist longer if one stretches regularly (3-5 days per week).

Barefoot Running

Compared to the heel strike used by runners wearing well-cushioned shoes, runners who go barefoot or wear minimalist shoes typically adopt a midfoot or forefoot strike with a shorter stride length. The reduced impact as a result of gait adjustment may be potentially beneficial. Barefoot running also improves proprioception and strengthens intrinsic foot muscles. It has been shown that barefoot runners had lower knee and hip injuries but more plantar surface and calf injuries.[10] Injury risk may also increase among runners with increased BMI and in those who often run on hard surfaces.

High Shoe Drop

The "drop" of the running shoe is the change in height from heel to toes. It has been shown that regular recreational runners using low-drop shoes sustained injuries at a significantly higher rate than those using high-drop shoes.[11] It is suggested that many recreational runners, who tend to use more heel strikes, may be less prone to impact-related injury with a higher shoe drop.

Personality

There is evidence that psychological factors may play a role in running injuries. One study found that although runners with type A personality traits did not have an increased rate of injury, they had a higher chance of multiple injuries.[12]

TIPS TO RUN FASTER AND INJURY-FREE

- Start low and go slow (10% increment rule)
- Cross-train
- Ease into training with a dynamic warm-up
- Run on a treadmill or a soft surface
- Fartlek run (running at a faster pace at random times of variable duration)
- Avoid fast downhill run
- Comfortable shoes
- Core strengthening
- Keep smiling

Individuals active enough to sustain a running-related injury are often reluctant to reduce their physical activity to any significant degree! Therefore, the concept of "relative rest" is important in the management of running-related injuries. Runners can maintain fitness by performing non-impact exercises such as swimming, rowing or biking, while the injury heals. (e.g. rowing machine).

Running is:
"One foot in front of the other, repeat as often as necessary to finish." *- Haruki Murakami*

Fig. 1: Run with the masters (Personal collection)

Fig. 2: Run fast alone, run far together! (Personal collection)

References

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8. Kearney RS, Parsons N, Metcalfe D, Costa ML. Injection therapies for Achilles tendinopathy. Cochrane Database Syst Rev. 2015(5):Cd010960.
9. Thacker SB, Gilchrist J, Stroup DF, Kimsey CD, Jr. The impact of stretching on sports injury risk: a systematic review of the literature. Med Sci Sports Exerc. 2004;36(3):371-8.
10. Lieberman DE. What we can learn about running from barefoot running: an evolutionary medical perspective. Exerc Sport Sci Rev. 2012;40(2):63-72.
11. Malisoux L, Chambon N, Urhausen A, Theisen D. Influence of the Heel-to-Toe Drop of Standard Cushioned Running Shoes on Injury Risk in Leisure-Time Runners: A Randomized Controlled Trial With 6-Month Follow-up. Am J Sports Med. 2016;44(11):2933-40.
12. Fields KB, Delaney M, Hinkle JS. A prospective study of type A behavior and running injuries. J Fam Pract. 1990;30(4):425-9.

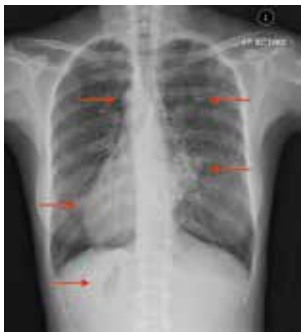
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2	3	4	★Zoom Live Recent updates on the Management of Ankylosing Spondylitis – Online 5	★Zoom Live Adult Pertussis Prevention in Influenza Season – Online 6	★Zoom Live A Synopsis Of Nasopharyngeal Carcinoma – Online 7	8
9	10	★Short Course on Clinical Toxicology (Video Lectures) 11	★The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed 12	★Zoom Live Polycystic Ovary Syndrome (PCOS)–Online ★Certificate Course in Cardiology (Video Lectures) 13	★Zoom Live Update on Management of Acne Vulgaris–Online 14	15
16	★Zoom live Practical Tips on Medical-legal Protection 17	★Zoom Live Approach to Urticaria and Angioedema in Hong Kong–Online ★Short Course on Clinical Toxicology (Video Lectures) 18	★Certificate Course on Difficult Communications in Healthcare 2022 (Video Lectures) 19	★Zoom live Practical Tips on Medical-legal Protection ★Zoom Live The Challenge of Anxiety Symptom Treatment in Major Depressive Disorder–Online ★Certificate Course in Cardiology (Video Lectures) ★FMSHK Foundation Meeting ★FMSHK Executive Committee Meeting 20	★Zoom Live Asthma in Children Revisit – Online 21	22
23	★Zoom Live COVID-19 Variant-Specific Vaccine and Boosters – Online 24	★Short Course on Clinical Toxicology (Video Lectures) 25	★Certificate Course on Difficult Communications in Healthcare 2022 (Video Lectures) 26	★Certificate Course in Cardiology (Video Lectures) 27	★Zoom Live Personalized Angina Management - A Review of Evidence–Online 28	29
30	★Zoom Live Latest Atopic Dermatitis management - What is achievable today? – Online 31					

Date / Time	Function	Enquiry / Remarks
5 WED 2:00 PM	**Zoom Live** **Recent updates on the Management of Ankylosing Spondylitis – Online** Organiser: Hong Kong Medical Association Speaker: Dr Carrel YU Ka-lung	HKMA CME Dept. 3108 2507 1 CME Point
6 THU 2:00 PM	**Zoom Live** **Adult Pertussis Prevention in Influenza Season – Online** Organiser: HKMA-HK East Community Network Speaker: Dr Raymond TSO	Ms Candice TONG 3108 2513 1 CME Point
7 FRI 2:00 PM	**Zoom Live** **A Synopsis Of Nasopharyngeal Carcinoma – Online** Organiser: Hong Kong Medical Association Speaker: Dr LEE Chi-chung	HKMA CME Dept. 3108 2507 1 CME Point
11 TUE 7:00 PM	**Short Course in Clinical Toxicology (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr NG Hon-wah	Ms Vienna LAM Tel: 2527 8898
12 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organiser: Hong Kong Neurosurgical Society Speaker: Dr Florence CHAN	Dr Calvin MAK 2595 6456 1.5 points CME Point
13 THU 2:00 PM	**Zoom Live** **Polycystic Ovary Syndrome (PCOS)–Online** Organiser: HKMA-KLN East Community Network Speaker: Dr Clement CHAN Leung-kwok	Ms Daphne LO 3108 2514 1 CME Point
7:00 PM	**Certificate Course in Cardiology (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Prof Harry George Mond	Ms Vienna LAM Tel: 2527 8898
14 FRI 2:00 PM	**Zoom Live** **Update on Management of Acne Vulgaris–Online** Organiser: HKMA-Shatin Community Network Speaker: Dr David LUK Chi-kong	Ms Candice TONG 3108 2513 1 CME Point
17 MON 2:00 PM	**Zoom live** **Practical Tips on Medical-legal Protection** Organiser: Hong Kong Chinese Medical Association Ltd Speakers: Mr David KAN, Mr Kevin WONG & Mr Jonathan CHEN	Ms Katrina LI Tel: 2250 2807
18 TUE 2:00 PM	**Zoom Live** **Approach to Urticaria and Angioedema in Hong Kong–Online** Organiser: HKMA-KLN West Community Network Speaker: Dr Philip Hei LI	Ms Daphne LO 3108 2514 1 CME Point
7:00 PM	**Short Course in Clinical Toxicology (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr FUNG Hin-tat	Ms Vienna LAM Tel: 2527 8898
19 WED 7:00 PM	**Certificate Course on Difficult Communications in Healthcare 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Peter Chi-wang PANG	Ms Vienna LAM Tel: 2527 8898
20 THU 2:00 PM	**Zoom live** **Practical Tips on Medical-legal Protection** Organiser: Hong Kong Chinese Medical Association Ltd Speakers: Mr David KAN, Mr Kevin WONG & Mr Jonathan CHEN	Ms Katrina LI Tel: 2250 2807
2:00 PM	**Zoom Live** **The Challenge of Anxiety Symptom Treatment in Major Depressive Disorder–Online** Organiser: HKMA-New Territories West Community Network Speaker: Dr CHEUNG Ngo	Ms Daphne LO 3108 2514 1 CME Point
7:00 PM	**Certificate Course in Cardiology (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: LAW Kwan-kin	Ms Vienna LAM Tel: 2527 8898
7:00 PM	**FMSHK Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong Venue: Council Chamber, 4/F,Duke Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong Venue: Council Chamber, 4/F,Duke Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
21 FRI 2:00 PM	**Zoom Live** **Asthma in Children Revisit – Online** Organiser: HKMA-YTM Community Network Speaker: Dr CHOW Siu-ngan	Ms Candice TONG 3108 2513 1 CME Point
24 MON 2:00 PM	**Zoom Live** **COVID-19 Variant-Specific Vaccine and Boosters – Online** Organiser: Hong Kong Medical Association Speaker: Dr Joseph TSANG Kay-yan	HKMA CME Dept. 3108 2507 1 CME Point
25 TUE 7:00 PM	**Short Course in Clinical Toxicology (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Patrick LEUNG Siu-chung	Ms Vienna LAM Tel: 2527 8898
26 WED 7:00 PM	**Certificate Course on Difficult Communications in Healthcare 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr CHOW Kai-ming	Ms Vienna LAM Tel: 2527 8898
27 THU 7:00 PM	**Certificate Course in Cardiology (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr CHENG Yue-hong	Ms Vienna LAM Tel: 2527 8898
28 FRI 2:00 PM	**Zoom Live** **Personalized Angina Management - A Review of Evidence–Online** Organiser: HKMA-KLN City Community Network Speaker: Prof Kelvin YIU Kai-hang	Ms Candice TONG 3108 2513 1 CME Point
31 MON 2:00 PM	**Zoom Live** **Latest Atopic Dermatitis management - What is achievable today? – Online** Organiser: Hong Kong Medical Association Speaker: Dr Mimi CHANG Mee	HKMA CME Dept. 3108 2507 1 CME Point

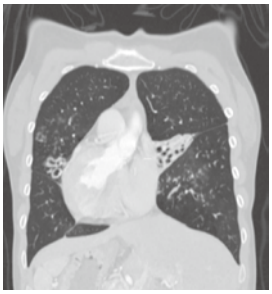
Answers to Radiology Quiz

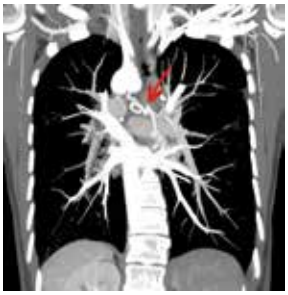
Answers:

1. (a) Medial left mid-lower zone triangular shaped opacity, bronchiectasis
   (b) Dextrocardia, right-sided aortic arch
   (c) Gastric bubble on the right



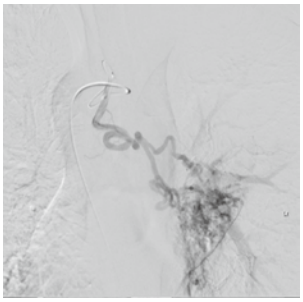
2. Contrast CT thorax





The contrast CT thorax showed collapsed left lingular segment, bronchiectasis in both lungs, hypertrophied bronchial arteries and situs inversus. The combination of situs inversus and bronchiectasis is in keeping with clinically biopsy proven Kartegener's Syndrome.

3. Left bronchial artery embolisation



The subsequent angiography of the hypertrophied bronchial artery demonstrated significant bronchial-pulmonary arterial shunting, which is not suitable for embolisation. The possibility of surgical management will therefore be further discussed with the clinician in-charge.

Dr Sonia HY LAM
MBBS, FRCR, FHKCR, FHKAM (Radiology)

Tremfya® (guselkumab)

Start a New Era of PsA Management with First-in-class IL-23i Tremfya®[1] An IL-23i with both PsO and PsA Indications[2]

RAPID AND SUSTAINED JOINT EFFICACY[3,6,7]

ACR20:

- At Week 4: ACR20 was achieved in 20% of PsA patients
- Long term: 74% ACR20 response rate was seen at 1 year and sustained out to 2 years in PsA patients treated with Tremfya®‖

ACR50:

- ACR50 response was maintained in 1 in 2 patients at 2 years

ACR70:

- Nearly 40% of patients maintained ACR70 response at 2 years

Demonstrated sustained relief in PsA at 2 years*[3]

COMPLETE SKIN CLEARANCE[3-5]

PASI 90:

- Greater proportion of patients on Tremfya® achieved PASI 90 versus those treated with secukinumab at Week 48†

PASI 100:

- At Week 24: PASI 100 was achieved in 45% of PsA patients treated with Tremfya®‡
- Long term: 53% of PsA patients treated with Tremfya® achieved PASI 100 out to 2 years§

PROVEN DURABILITY[3,8]

- Most patients who started on Tremfya® remained on Tremfya®
  - Around 9 out of 10 patients completed treatment through week 100

A well-tolerated safety profile with no unexpected safety signals[3]

(Based on Week 112 data from phase III DISCOVER-2 trial)

- No reported case of IBD throughout 2-year Tremfya® PsA treatment
- No patients on Tremfya® developed active tuberculosis
- No Tremfya®-related death case was reported

Convenient q8w maintenance dosing with high patient retention

- q8w maintenance dosing with a single administration[2¶]
- Most patients who started on Tremfya® remained on Tremfya®
  - Around 9 out of 10 patients completed Tremfya® treatment through week 100[3]

Please scan the QR code for the latest updates on Tremfya®

JanssenPro

*Sustained improvements in PsA severity (as measured by ACR scores, IGA scores and resolution of enthesitis and dactylitis). †Among patients with PsA, the primary endpoint of PASI 90 response at Week 48 was achieved by 82.5% of patients treated with Tremfya® versus 63.3% of patients treated with secukinumab. ‡45% (n=176) of biologic-naïve patients treated with Tremfya® q8w achieved PASI 100 at Week 24 versus 3% of patients treated with placebo (n=183; p<0.0001). §In patients randomized to Tremfya® at baseline and treated with Tremfya® q8w. Patients achieving PASI 100 at Week 100 (NRI): 53% (n=176). ‖In patients treated with Tremfya® q8w. 74.6% (n=248) of Tremfya® q8w patients achieved ACR20 at 1 year, and 74% (n=248) of Tremfya® q8w patients achieved ACR20 at 2 years in DISCOVER-2 (NRI). ¶The recommended dose of Tremfya® for PsO and PsA is 100 mg by SC injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks.

Study designs:
Mease PJ, et al., 2020*: DISCOVER-2 was a phase 3, double-blind, placebo-controlled study which enrolled biologic-naïve patients with active PsA (at least 5 swollen joints, at least 5 tender joints, and C-reactive protein ≥0.6 mg/dL) despite standard therapies. Patients were randomly assigned to SC injections of Tremfya® 100 mg every 4 weeks; Tremfya® 100 mg at weeks 0, 4, and then every 8 weeks; or placebo. The primary endpoint was ACR20 response at week 24 in all patients per assigned treatment group. Safety was assessed in all patients per treatment received.
Merola JF, et al., 2019†: ECLIPSE was a randomized, double-blind trial of adults with moderate-to-severe PsO who received Tremfya® 100 mg at Weeks 0, 4, then q8w, or secukinumab 300 mg at Weeks 0, 1, 2, 3, and 4, then q4w, both through Week 44. In the subset of patients with self-reported PsA in the ECLIPSE study, proportions of patients who achieved PASI 90 in both arms were also evaluated.
Griffiths CEM, et al. 2021‡: To assess the efficacy and safety through 5 years of continuous Tremfya® treatment, patients were included in VOYAGE 1 trial and randomized to Tremfya® 100 mg at Weeks 0, 4, 12, then q8w; placebo at Weeks 0, 4, 12 followed by Tremfya® 100 mg at Weeks 16, 20 then q8w; or adalimumab 80 mg at Week 0, 40 mg at Week 1, then 40 mg q2w through Week 47. At Week 52, all patients continued open-label Tremfya® through Week 252.

ACR=American College of Rheumatology. ACR20=improvement of at least 20% in the American College of Rheumatology core criteria. ACR50=improvement of at least 50% in the American College of Rheumatology core criteria. ACR70=improvement of at least 70% in the American College of Rheumatology core criteria. IBD=inflammatory bowel disease. IGA=Investigator's Global Assessment. IL-23i=interleukin-23 inhibitor. NRI=non-responder imputation. PASI=Psoriasis Area Severity Index. PASI 90=90% improvement or more from baseline on PASI score. PASI 100=100% improvement from baseline on PASI score. PsA=psoriatic arthritis. PsO=plaque psoriasis. q2w=every 2 weeks. q4w=every 4 weeks. q8w=every 8 weeks. SC=subcutaneous.

References:
1. Ritchlin CT, Helliwell PS, Boehncke WH, et al. Guselkumab, an inhibitor of the IL-23p19 subunit, provides sustained improvement in signs and symptoms of active psoriatic arthritis: 1 year results of a phase III randomised study of patients who were biologic-naïve or TNFα inhibitor-experienced. RMD Open. 2021;7(1):e001457. 2. Tremfya® Hong Kong prescribing information P03. 3. McInnes IB, Rahman P, Gottlieb AB, et al. Long-Term Efficacy and Safety of Guselkumab, a Monoclonal Antibody Specific to the p19 Subunit of Interleukin-23, Through Two Years: Results From a Phase III, Randomized, Double-Blind, Placebo-Controlled Study Conducted in Biologic-Naive Patients With Active Psoriatic Arthritis. Arthritis Rheumatol. 2022;74:475-485. 4. Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial [published correction appears in Lancet. 2020 Apr 4;395(10230):1114]. Lancet. 2020;395:1126-1136. 5. Merola JF, Li S, Hsu MC, et al. GUSELKUMAB WAS MORE EFFECTIVE THAN SECUKINUMAB IN PATIENTS WITH PLAQUE PSORIASIS AND THE SUBSET OF PATIENTS WITH SELFREPORTED PSORIATIC ARTHRITIS IN THE RANDOMIZED, DOUBLE BLIND, HEAD-TO-HEAD COMPARISON STUDY ECLIPSE OVER 1 YEAR. SAT0390. Annals of the Rheumatic Diseases 2019;78:1280-1282. 6. Nash P, McInnes I , Ritchlin CT, et al. GUSELKUMAB TREATMENT SHOWS RAPID ONSET OF EFFECT ON COMPONENTS OF AMERICAN COLLEGE OF RHEUMATOLOGY RESPONSE CRITERIA: RESULTS OF 2 RANDOMIZED PHASE 3 TRIALS. Abstract 0525. Annals of the Rheumatic Diseases 2021;80:1290-1291. 7. McInnes IB, Rahman P, Gottlieb AB, et al. Efficacy and Safety of Guselkumab, an Interleukin-23p19-Specific Monoclonal Antibody, Through One Year in Biologic-Naive Patients With Psoriatic Arthritis. Arthritis Rheumatol. 2021;73:604-616. 8. Griffiths CEM, Papp K, Song M, et al. MAINTENANCE OF RESPONSE THROUGH 5 YEARS OF CONTINUOUS GUSELKUMAB TREATMENT: RESULTS FROM THE PHASE-3 VOYAGE 1 TRIAL. Abstract 0532. Annals of the Rheumatic Diseases 2021;80:1297-1298.

Tremfya® 100mg/1ml solution for injection
ABBREVIATED PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): Guselkumab **INDICATION(S):** Plaque psoriasis - Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Psoriatic arthritis - Tremfya, alone or in combination with methotrexate, for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug therapy. **DOSAGE & ADMINISTRATION:** Plaque psoriasis - 100 mg by subcutaneous injection at weeks 0 and 4, followed by maintenance dose every 8 weeks. Consider discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Psoriatic arthritis - 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered. Consider discontinuing treatment in patients who have shown no response after 24 weeks of treatment. Safety and efficacy in children and adolescents below 18 years old have not yet been established. If possible, areas of skin that show psoriasis should be avoided as injection sites. **CONTRAINDICATIONS:** Serious hypersensitivity to the active substance or to any of the excipients. Clinically important active infections (e.g., active tuberculosis(TB)). **SPECIAL WARNINGS & PRECAUTIONS:** Infections: Tremfya may increase risk of infection. Do not initiate Tremfya in patients with any clinically important active infection until the infection resolves or is adequately treated. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and discontinue Tremfya until the infection resolves. Pre-treatment evaluation for TB: Prior to initiating Tremfya, evaluate patients for TB infection. Monitor patients receiving Tremfya for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating Tremfya in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Hypersensitivity: Serious hypersensitivity reactions, including anaphylaxis, have been reported in the post-marketing setting. Some serious hypersensitivity reactions occurred several days after treatment with guselkumab, including cases with urticaria and dyspnoea. If a serious hypersensitivity reaction occurs, discontinue Tremfya immediately and initiate appropriate therapy. Hepatic transaminase elevations: In psoriatic arthritis clinical studies, an increased incidence of liver enzyme elevations was observed in patients treated with Tremfya q4w compared to patients treated with Tremfya q8w or placebo. When prescribing Tremfya q4w in psoriatic arthritis, it is recommended to evaluate liver enzymes at baseline and thereafter. If increases in ALT or AST are observed and drug-induced liver injury is suspected, temporarily interrupt Tremfya until this diagnosis is excluded. Immunisations: Prior to initiating Tremfya, consider completion of all appropriate immunisations. Do not use live vaccines concurrently in patients treated with Tremfya. Before live viral or live bacterial vaccination, Tremfya should be withheld for at least 12 weeks after the last dose and can be resumed at least 2 weeks after vaccination. **SIDE EFFECTS:** Respiratory tract infection. Refer to the full prescribing information for other side effects. **PREGNANCY & LACTATION:** It is preferable to avoid use of Tremfya in pregnancy. A decision should be made whether to discontinue, or abstain from initiating treatment with Tremfya, taking into account the benefit of breast-feeding to the child and the benefit of Tremfya therapy to the woman. **INTERACTIONS:** No need for dose adjustment when co-administering guselkumab and CYP450 substrates. Safety and efficacy of Tremfya in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated in psoriasis studies.
PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.
API version to be quoted on promotional material: Tremfya aPI ver 3.0

CP-330933 Jul 2022

Janssen, a division of Johnson & Johnson (HK) Ltd.
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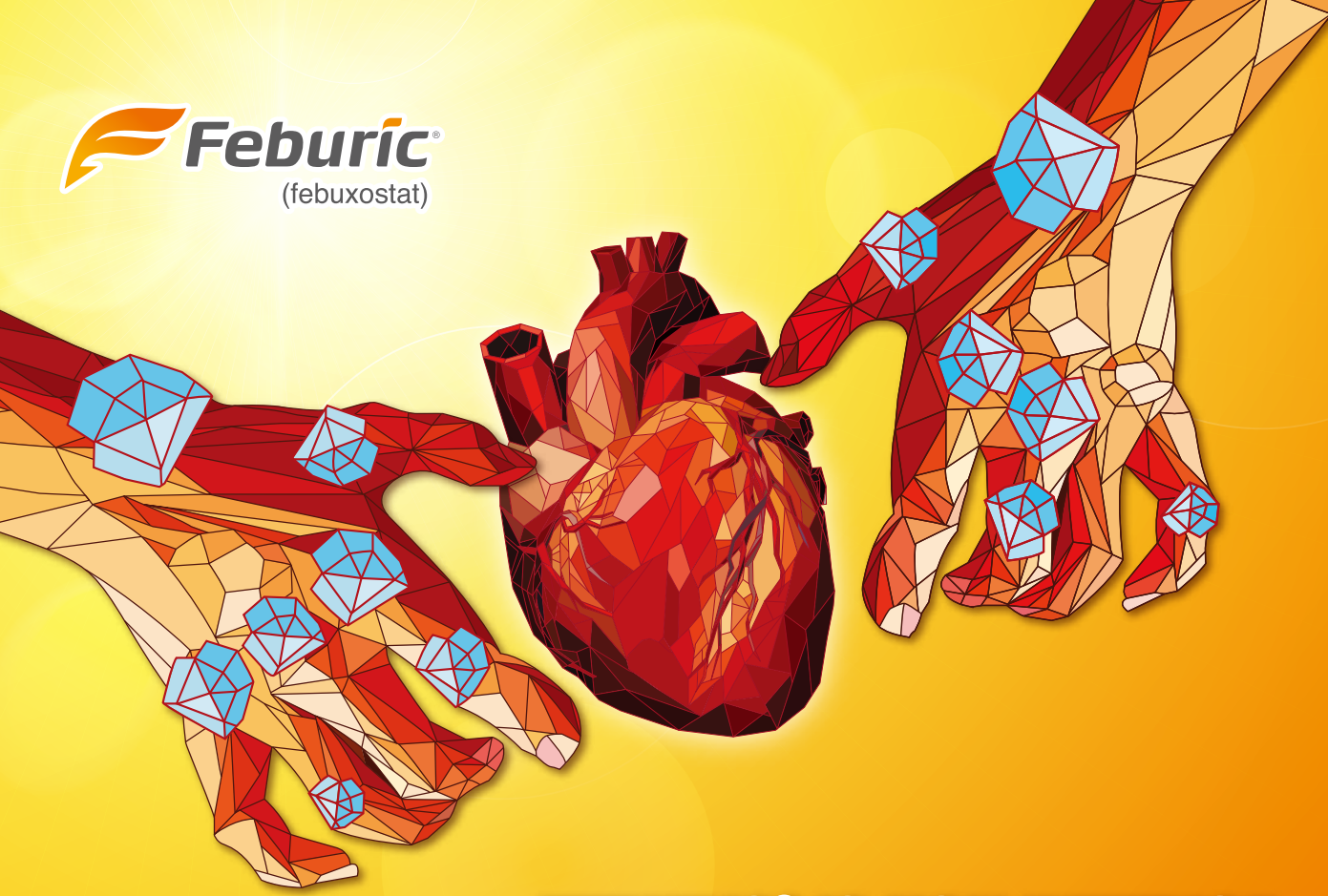
Tel: 2736 1711 Fax: 2736 1926

Janssen Immunology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Feburic®
(febuxostat)



FEBURIC® IS NON-INFERIOR TO ALLOPURINOL FOR CV ADVERSE EVENTS IN GOUT PATIENTS ≥60 YEARS WITH 1 CV RISK FACTOR[1]

Study Design:[1] The FAST trial was a prospective, randomised, open-label, non-inferiority trial investigating febuxostat versus allopurinol in patients with gout in the UK, Denmark and Sweden. A total of 6128 patients aged ≥60, already receiving allopurinol, and with at least one cardiovascular risk factor were randomly assigned 1:1 to continue allopurinol (n=3065) or start febuxostat at 80mg/day (n=3063), increasing to 120mg/day if necessary to achieve target serum urate concentration. The primary outcome was a composite of hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome, non-fatal stroke, or cardiovascular death. Median follow-up time in the study was 1467 days, and median on-treatment follow-up period was 1324 days. In the primary on-treatment analysis, febuxostat was found non-inferior to allopurinol with regards to the primary endpoint (HR=0.85; 95% CI: 0.70-1.03; p<0.0001). Cardiovascular death occurred in 2.0% and 2.7% of febuxostat and allopurinol patients, respectively, and also showed non-inferiority (HR=0.91; 95% CI: 0.66-1.27; p=0.018).

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; UK, United Kingdom

Reference: 1. Mackenzie IS et al. The Lancet. 2020;396 (10264):1745-1757.

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