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References: 1. Marso SP, McGuire DK, Zinman B, et al. for the DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. New England Journal of Medicine 2017; 377:723–732. **2.** Wysham C, Bhargava A, Chaykin L, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. JAMA 2017; 318(1):45–56. **3.** Lane W, Bailey TS, Gerety G, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA 2017; 318(1):33–44. **4.** Tresiba® Packing Insert. **5.** Jonassen I, Havelund S, Hoeg-Jensen T, et al. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharmaceutical Research 2012;29(8):2104-14

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Contents

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The Cover Shot

One of the excitements of SCUBA diving is meeting the vast number of marine lives. This is a collage of four different marine creatures taken during my dives in Bali and Ishigaki island. From top left to the bottom right, they are the nudibranch, peacock mantis shrimp, green sea turtle, and a clownfish dancing in the anemone.

Spotting the peacock mantis shrimp under a rock in Tulamben was a gasping moment. It was beautiful but dangerous, being able to deliver a powerful punch equivalent to a bullet! The ocean never fails to amaze the divers and keep us humble.

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What is the Insight into Rheumatology in the 21st Century?

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Rheumatology is a subspecialty of general medicine that only became well recognised in the 1970s in Hong Kong. There were only a handful of physicians interested in this new specialty, and yet polyarthralgia as a symptom of many rheumatic diseases is one of the most commonly complained problems.

The 1950s brought corticosteroids to rheumatoid arthritis (RA) sufferers. It significantly reduced the inflammation, and this was the 'take up your bed and walk' drug. However, the long-term use of steroids also brings significant side effects to these patients. The next drug invention is non-steroid anti-inflammatory drugs like indomethacin and ibuprofen. They are the miraculous drugs to many people living with arthritis. However, they are the double-edged swords; some patients do not survive from severe gastrointestinal bleeding, and some die of renal failure. The history of using methotrexate to treat RA could be dated back to 1948. Aminopterin, an anti-folate agent, was used successfully to treat childhood leukaemia. Aminopterin was also studied in several RA patients in an observational study in 1951 by Gubner et al.[1]. Methotrexate, also an anti-folate agent, was subsequently manufactured to replace aminopterin. The rheumatology community was however not interested in methotrexate as corticosteroids were so efficacious in treating RA at that time.

Furthermore, there was concern about using an anti-cancer drug to treat a "benign disease," RA. Now we know RA is not a benign disease nor a disease limited to the joints only. It is a chronic autoimmune systemic disease that may lead to joint damage and functional loss if not treated promptly. Before the era of the biological agents, the conventional disease-modifying drugs (DMARDs), including methotrexate, sulfasalazine and hydroxychloroquine, can only provide modest efficacy, and clinical remission is very difficult, if not impossible, to achieve. With the success story of using biological agents, including both TNF inhibitors and non-TNF inhibitors in RA, the rheumatology community has finally come to the consensus of adopting the treat-to-target principle in managing RA. The target has changed from pain control previously to genuine clinical remission.

The introduction of biological agents substantially changes the landscape in Rheumatology. Over time, we have become more sophisticated in our ability to assess disease activity in various rheumatic diseases. Our improved understanding of disease pathogenesis and the development of drugs targeting key immunologic pathways have led to better outcomes for the patients. While we are celebrating the triumph of the RA story, it has become more and more essential to develop new drugs for other rheumatic diseases. Research and awareness of Rheumatology have expanded rapidly around the end of the 20th Century and are expected to continue to shine in the 21st Century.

This special issue of Rheumatology will take you through the current developments and changes in the treatment paradigm in some of the common and uncommon rheumatic diseases, including lupus nephritis, psoriatic arthritis, giant cell arteritis, and IgG4-related disease. Besides, an under-recognised but life-threatening immunological condition, known as hereditary angioedema (HAE), is also included to make it known to the readers of the Hong Kong Medical Diary.

References

1. Gubner R, August S, Ginsberg V. Therapeutic suppression of tissue reactivity. Effect of aminopterin in rheumatoid arthritis and psoriasis. Am J Med Sci. 1951;22:176–82.

NOW FOR ADULT **PSORIATIC ARTHRITIS (PsA)** AND **ANKYLOSING SPONDYLITIS (AS)**[1]

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1. Cosentyx® Hong Kong Product Insert (Ref: EMA Apr 2016)

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Powder for solution for subcutaneous injection, solution for subcutaneous injection in pre-filled syringe or pre-filled pen contain 150 mg of secukinumab. **Indications: Plaque psoriasis** Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. **Psoriatic arthritis** Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. **Ankylosing spondylitis** Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. **Dosage and administration:** ***Dosage*** **Plaque psoriasis:** The recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg. **Psoriatic arthritis:** The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. For patients who are anti-TNFα inadequate responders or patients with concomitant moderate to severe plaque psoriasis, the recommended dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg. **Ankylosing spondylitis:** The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. For all of the above indications, available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks. **♦Paediatric population (aged below 18 years):** The safety and efficacy of Cosentyx in children below the age of 18 years have not yet been established. No data are available. **♦Renal impairment / hepatic impairment:** Cosentyx has not been studied in these patient populations. No dose recommendations can be made. ***Administration*** Cosentyx is to be administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites. **Contraindications:** ♦Cosentyx is contraindicated in patients who have/had severe hypersensitivity reactions reaction to the active substance or to any of the excipients. ♦Clinically important, active infection (e.g., active tuberculosis) **Warnings and precautions: ♦Infections:** Cosentyx has the potential to increase the risk of infections. Caution in patients with chronic or history of recurrent infection. If a patient develops a serious infection, the patient should be closely monitored and Cosentyx should not be administered until the infection resolves. Anti-tuberculosis therapy should be considered prior to initiation of Cosentyx in patients with latent tuberculosis. Cosentyx should not be given to patients with active tuberculosis. **♦Crohn's disease:** Patients with active Crohn's disease treated with Cosentyx should be followed closely. **♦Hypersensitivity reactions:** In clinical studies, rare cases of anaphylactic reactions have been observed in patients receiving Cosentyx. Administration of Cosentyx should be discontinued immediately and appropriate therapy initiated if an anaphylactic or other serious allergic reaction occurs. **♦Latex-sensitive individuals:** The removable cap of the Cosentyx pre-filled syringes/pen contains a derivative of natural rubber latex. **♦Vaccinations:** Cosentyx should not be given concurrently with live vaccines. Patients receiving Cosentyx may receive concurrent inactivated or non-live vaccinations. **♦Concomitant immunosuppressive therapy:** In psoriasis studies, the safety and efficacy of Cosentyx in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. **Women of childbearing potential:** Effective method of contraception during treatment and for at least 20 weeks after treatment should be used. **Pregnancy:** There are no adequate data from the use of secukinumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Cosentyx in pregnancy. **Breast-feeding:** It is not known whether secukinumab is excreted in human milk. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Cosentyx must be made taking into account the benefit of breast-feeding to the child and the benefit of Cosentyx therapy to the woman. **Adverse drug reactions: Very common (≥10%):** Upper respiratory tract infections. **Common (1 to <10%):** Oral herpes, diarrhea, rhinorrhea. **Uncommon (0.1 to <1%):** Oral candidiasis, neutropenia, otitis externa, tinea pedis, conjunctivitis, urticaria. **Rare (0.01 to <0.1%):** Anaphylactic reactions. **Interactions:** Live vaccines should not be given concurrently with Cosentyx. Therapeutic monitoring should be considered when using Cosentyx with CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin). No interaction was seen when Cosentyx was administered concomitantly with methotrexate (MTX) and/or corticosteroids in arthritis studies (including in patients with psoriatic arthritis and ankylosing spondylitis). **Packs and prices:** Powder in Vial: 1's. Solution in pre-filled syringe: 1's or 2's. Solution in pre-filled pen; 1's or 2's. Not all pack sizes are marketed. **Legal classification:** P1S1S3

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The Current Management of Psoriatic Arthritis – Early Diagnosis, Monitoring of Disease Severity and Cutting-Edge Therapies

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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 30 April 2020.

BACKGROUND

Psoriatic arthritis (PsA) is a chronic immune-mediated disease with heterogeneous clinical manifestations including psoriasis, peripheral arthritis, axial disease, enthesitis, dactylitis and nail involvement. Up to 30% of patients with psoriasis will develop synovio-entheseal manifestations[1]. In the majority of patients, the musculoskeletal symptoms develop after the cutaneous manifestations, but can also coincide with or precede (15%) the diagnosis of psoriasis. PsA is an important disease to recognise as it carries significant morbidity and disability[2]. Furthermore, early diagnosis and prompt treatment are important as delay in treatment is associated with worse treatment outcomes[3].

SCREENING

Several screening tools have been developed to facilitate the early diagnosis of patients with psoriatic arthritis. These include the Toronto Psoriatic Arthritis Screening Questionnaire (ToPAS), Psoriasis Epidemiology Screening Tool (PEST), Psoriatic Arthritis Screening and Evaluation (PASE), and the Psoriasis and Arthritis Screening Questionnaire (PASQ) [4-6]. These screening tools have comparable sensitivity (82-97%) and specificity (73-93%) (Table 1). They can be used in the dermatology clinics or primary care offices to facilitate early identification of PsA patients.

Table 1. Screening tools for early diagnosis of psoriatic arthritis. (Adapted from Machado P.M, Raychaudhuri SP. Disease activity measurements andmonitoring in psoriatic arthritis and axial spondyloarthritis, Best Pract. Res.Clin. Rheumatol.28 (2014) 711e728.)

Screening tools	Description	Sensitivity/specificity
Topas	Self-administered 11 items + pictures/ diagrams Maximum score: NA	Sensitivity 87% Specificity 93%
PEST	Self-administered 5 items + joint diagram Maximum score: NA	Sensitivity 97% Specificity 79%
PASE	Self-administered 15 items Maximum score: 75	Sensitivity 82% Specificity 73%
PASQ	10 items + joint diagram Self report	

ToPAS, Toronto Psoriatic Arthritis Screening; PEST, Psoriasis Epidemiology Screening Tool; PASE, Psoriatic Arthritis Screening and Evaluation; PASQ, Psoriasis and Arthritis Screening Questionnaire; NA, not applicable.

CLINICAL CHARACTERISTICS

Clinical Features

Five clinical subtypes of PsA have been described by Moll and Wright in 1973[7]. The oligo-articular subtype involving no more than four joints is the most common. Others include the symmetrical polyarticular subtype, distal subtype, arthritis mutilans and axial subtype. Other extra-articular features include enthesitis (e.g. plantar fasciitis and Achilles tendonitis), dactylitis and nail disease (pitting and onycholysis).

Laboratory Test

The majority of patients (95%) with PsA have a negative test for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibody. Around 25% of patients are HLA-B27 positive. Acute phase reactants including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are used to assess disease activity.

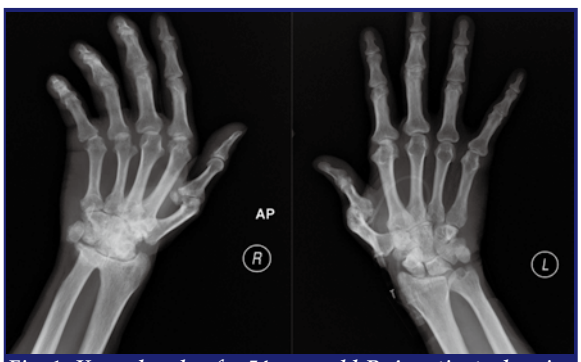

Fig. 1 X-ray hands of a 54-year-old PsA patient, showing asymmetrical involvement with erosion, new bone formation and ankyloses (With patient's permission).

Imaging Features

Radiographic imaging of the hands and feet may show joint erosion, joint resorption and new bone formation (Fig. 1). The pencil-in-cup deformities are observed in cases of arthritis mutilans. Ultrasonography can help to supplement diagnosis and disease activity assessment for arthritis, enthesitis and dactylitis.

In axial disease, radiographs of the spine and sacroiliac joints can be used to assess for sacroiliitis and para-marginal syndesmophytes, which are typically asymmetrical in PsA patients. Magnetic resonance imaging (MRI) can be used to evaluate disease activity and structural damage in the spine and sacroiliac joints.

DIAGNOSIS

The diagnosis of PsA is a clinical judgement based on clinical, laboratory and imaging assessment. There are no validated diagnostic criteria for PsA. The Classification Criteria for Psoriatic Arthritis (CASPAR) criteria (Table 2) published in 2006 has been designed to select patients for clinical trials[8] and provide guidance for the physician.

Table 2. The Classification Criteria for Psoriatic Arthritis (CASPAR) consist of established inflammatory articular disease (joint, entheseal or spine) plus ≥ 3 points from the following categories. (Adapted from Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classificationcriteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006; 54: 2665-73.)

- Current psoriasis (score of 2)
- History of psoriasis in the absence of current psoriasis (score of 1)
- Family history of psoriasis in the absence of current psoriasis or history of psoriasis (score of 1)
- Dactylitis (score of 1)
- Juxta-articular new bone formation (score of 1)
- RF negativity (score of 1)
- Nail dystrophy (score of 1)

MANAGEMENT

Disease Activity Assessment

In managing patients with PsA, a careful assessment of disease activity in the different symptom domains is important to guide treatment decision. Disease activity assessment includes assessing for the extent of skin involvement, peripheral arthritis, axial disease, enthesitis, dactylitis and nail disease. Different disease activity indices have been developed, including those that are specific to each domain or composite disease activity indices. Also, a treat-to-target approach aiming at low disease activity or remission is advocated guided by these disease activity indices (e.g. MDA and DAPSA) [9].

Non-pharmacological Treatment

Non-pharmacological treatment includes patient education about the chronic nature of the disease and the importance of controlling inflammation and the prevention of joint damage. Lifestyle modification, such as weight reduction, smoking cessation, physical activity and stress management, is also crucial for the management of PsA. The screening and management of co-morbidities, especially metabolic syndrome and atherosclerotic cardiovascular diseases, are also important.

Pharmacological Treatment

Over the past decade, the option of pharmacological treatments for PsA has expanded from non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and conventional disease-modifying anti-rheumatic drugs (csDMARDs) to include biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) which target specific cytokines and intracellular signalling pathway involved in PsA. Their efficacy in controlling disease activity and preventing disease progression has been proven in randomised controlled trials.

Treatment guidelines and recommendations have been published by several international organisations to guide physicians' decisions in selecting the optimal treatment. These include the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in 2015, European League Against Rheumatism (EULAR) in 2015, and American Association of Rheumatology (ACR) in 2018[10-12].

In general, a stepwise approach with a treat-to-target principle is advocated. The choice of treatment remains a shared decision between patients and physicians, and should also take into account of patients' preferences, co-morbidities and costs.

TREATMENT OPTIONS

NSAIDs and Glucocorticoids

NSAIDs and local injection of glucocorticoids may be used to control symptoms of PsA. The physician should be cautious about the potential side effects of NSAIDs. The systemic steroid is generally avoided as it is associated with a risk of psoriatic flare upon steroid tapering and the risk of pustular psoriasis. When the systemic steroid is used, the lowest effective dose should be used (usually prednisolone < 7.5 mg per day).

Conventional DMARDs

Before the development of advanced therapies (bDMARDs and tsDMARDS), csDMARDs were used to treat PsA, including methotrexate, leflunomide, sulphasalazine and cyclosporin A. Their role has been increasingly challenged because of the scant evidence of their efficacy in peripheral PsA and because they do not affect radiological progression. csDMARDs are not useful in axial disease, enthesitis and nail disease.

Due to their low cost and universal availability, csDMARDs remain to be the first line of therapy for peripheral arthritis in the EULAR and GRAPPA guidelines, with the need for early escalation of therapy if adequate response cannot be achieved. On the contrary, the latest ACR guideline conditionally recommended TNF inhibitors as first-line therapy over csDMARDs except in patients with frequent serious infections or those who are contraindicated to TNF inhibitors. csDMARDs might also be considered as first-line in patients with mild disease, who prefer oral therapies and who want to avoid biologics.

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Abbreviations: GBM=glioblastoma multiforme; TMZ=temozolomide

References: 1. Data on file. Novocure. Last updated January 2019. **2.** Stupp, R. *et al.* JAMA 318, 2306–2316 (2017).

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HK-OPT-201910-02

Biological DMARDs and Other Advanced Therapies

Biological therapies targeting TNF, interleukin-17, interleukin 12/23 and the co-stimulatory pathways have been developed for use in PsA.

Anti-TNF agents (Infliximab, Adalimumab, Etanercept, Certolizumab and Golimumab) are recommended as the preferred first-line option when selecting a bDMARD based on long-term experience and well-established efficacy and safety balance. They are useful in both skin and peripheral joint involvement and can prevent radiographic damage[13]. Combining a csDMARD with TNFi may have a role. However, most studies show that compared to biologic monotherapy. Combination therapy is no better in improving clinical symptoms, although there may be a role in improving drug survival[14]. Based on the studies in axial spondyloarthritis, anti-TNF is also effective in treating enthesitis, dactylitis, and axial diseases[15].

Secukinumab and Ixekizumab are the two bDMARDs targeting the IL-17 pathways currently approved for the treatment of PsA and are effective in both skin and musculoskeletal features[16,17]. A recent head-to-head trial compared the efficacy of Ixekizumab with Adalimumab in biological-naïve patients showing the superiority of Ixekizumab[18]. Ustekinumab, an antibody targeting the shared p40 subunit of IL12 and IL23, is effective for both skin and musculoskeletal manifestations with a more impressive response in skin manifestations[19]. Abatacept, a molecule that blocks the T cell co-stimulation pathway, has a moderate effect in treating the joint manifestation but only a modest effect on the skin in PsA[20].

Targeted synthetic molecules acting against the JAK/ STAT pathway have been developed to treat autoimmune diseases, including PsA. Tofacitinib, an oraltsDMARDwith activity against JAK3 and JAK1, is approved for the treatment for PsA[21]. Other JAK inhibitors, including Filgotinib (JAK1 inhibitor) and Upadacitinib (JAK1 inhibitor) are being studied in clinical trials for the treatment of PsA[22].

CONCLUSION

Psoriatic arthritis is a disease with heterogeneous manifestations occurring in up to 30% of patients with psoriasis and is associated with significant morbidity. Early diagnosis is assisted by screening questionnaires, facilitating early treatment to control disease activity and structural progression. Emerging therapies provide an effective means to control inflammation and prevent long-term joint destruction.

References

1. Villani AP, Rouzaud M, Sevrain M, et al. Prevalence of undiagnosed psoriatic arthritis among psoriasis patients: systematic review and meta-analysis. J Am AcadDermatol 2015; 73: 242-8.
2. Tillett W, Shaddick G, Askari A, et al. Factors influencing work disability in psoriatic arthritis: first results from a large UK multicentre study. Rheumatology (Oxford) 2015; 54: 157-62.
3. Haroon, M., Gallagher, P. & FitzGerald, O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann. Rheum. Dis. 74, 1045–1050 (2015).
4. M.E. Husni, K.H. Meyer, D.S. Cohen, E. Mody, A.A. Qureshi, The PASE questionnaire: pilot-testing a psoriatic arthritis screening and evaluation tool, J. Am. Acad. Dermatol. 57 (2007) 581e587.
5. G.H. Ibrahim, M.H. Buch, C. Lawson, R. Waxman, P.S. Helliwell, Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire, Clin. Exp. Rheumatol. 27 (2009) 469e474. 34 S.P. Raychaudhuri et al. / Journal of Autoimmunity 76 (2017) 21e37
6. V. Chandran, D.D. Gladman, Toronto Psoriatic Arthritis Screening (ToPAS) questionnaire: a report from the GRAPPA 2009 annual meeting, J. Rheumatol. 38 (2011) 546e547.
7. 7. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973; 3: 55-78.
8. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006; 54: 2665-73.
9. Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2017; 0:1-15.
10. Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheum 2016; 68 (5): 1060-1071.
11. Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016; 75:499–510.
12. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthrit Care & Res 2019; 71 (1): 2–29.
13. Mease PJ. Biologic therapy for psoriatic arthritis. Rheum Dis Clin North Am 2015; 41: 723-38.
14. Acosta Felquer ML, Coates LC, Soriano ER, Ranza R, Espinoza LR, Helliwell PS, et al. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. J Rheumatol2014; 41:2277–85.
15. Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. N Engl J Med 2016; 374: 2563-74.
16. Mease P, van der Heijde D, Landewe R, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Ann Rheum Dis 2018; 77: 890-897.
17. Mease P, Roussou E, Burmester G, et al. Safety of Ixekizumab in patients with psoriatic arthritis: results from a pooled analysis of three clinical trials. Arthritis Care Res (Hoboken) 2019; 71(3): 367-378.
18. Mease P, Smolen JS, Behrens F, et al. A head-to-head comparison of the efficacy and safety of Ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis; 24-week results of a randomised, open-label, blinded assessor trial. Ann Rheum Dis 2019; 0:1–9
19. Weitz JE, Ritchlin CT. Ustekinumab: targeting the IL-17 pathway to improve outcomes in psoriatic arthritis. Expert OpinBiolTher 2014;14: 515-26.
20. Mease P, Genovese MC, Gladstein G, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomised, double- blind, placebo-controlled, phase II trial. Arthritis Rheum 2011; 63: 939-48.
21. Paik J, Deeks ED. Tofacitinib: a review in psoriatic arthritis. Drugs 2019; 79(6): 655-663.
22. Mease P, Coates KC, Helliwell PS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a ranodmised, placebo-controlled, phase 2 trial. Lancet 2018; 392 (10162): 2367-2377.
23. Machado P.M, Raychaudhuri SP. Disease activity measurements andmonitoring in psoriatic arthritis and axial spondyloarthritis, Best Pract. Res.Clin. Rheumatol. 28 (2014) 711e728.

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Abbreviations: ASAS 20/40, Assessment in SpondyloArthritis International Society 20%/40% improvement criteria; axSpA, axial spondyloarthritis; DAS28, disease activity score 28 joints; ESR, erythrocyte sedimentation rate; PASI75/90, 75% or 90% improvement in the Psoriasis Area and Severity Index; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF, tumor necrosis factor

References: 1. Keystone E, Ladewé R, van Vollenhoven R, *et al. Ann Rheum Dis*. 2014;73(12):2094-100. **2.** van der Heijde D, Dougados M, Landewé R, *et al. Rheumatology* (Oxford). 2017;56(9):1498-1509. **3.** van der Heijde D, Deodhar A, FitzGerald O, *et al. RMD Open*. 2018;4(1):e000582.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "The Current Management of Psoriatic Arthritis – Early Diagnosis, Monitoring of Disease Severity and Cutting-Edge Therapies" by Dr Shirley Chiu-wai CHAN & Dr Helen Hoi-lun TSANG 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 30 April 2020 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. **Musculoskeletal manifestations of psoriatic arthritis (PsA) occur only in patients with established psoriasis.**
2. **Screening of PsA is important, and several screening tools have been developed to be applied in dermatology clinics or primary care offices.**
3. **Enthesitis, dactylitis and nail disease are important extra-articular manifestations to assess in patients with PsA.**
4. **Most patients with psoriatic arthritis have a positive test for rheumatoid factor and/or anti-cyclic citrullinated peptide antibody.**
5. **The Classification Criteria for Psoriatic Arthritis (CASPAR) criteria is the ONLY gold standard for diagnosing patients with psoriatic arthritis.**
6. **The treatment of PsA follows a stepwise approach with a treat-to-target principle.**
7. **Conventional disease-modifying anti-rheumatic drugs (cDMARDs) are the first-line treatment for PsA because of their efficacy in controlling disease activity and halting radiographic progression.**
8. **Anti-TNF agents are recommended as the preferred option when selecting biological DMARDs based on long-term experience and well-established efficacy and safety balance.**
9. **There is a lack of head-to-head trial to directly compare the efficacy of different biological therapies in PsA.**
10. **Oral agents targeting small molecules such as PDE4 or the JAK/ STAT pathway are available for the treatment of PsA.**

ANSWER SHEET FOR APRIL 2020

Please return the completed answer sheet to the Federation Secretariat on or before 30 April 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

The Current Management of Psoriatic Arthritis – Early Diagnosis, Monitoring of Disease Severity and Cutting-Edge Therapies

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Answers to March 2020 Issue

Time to enhance our preparedness to handle trauma and stress-related disorders in Hong Kong

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

Immunoglobulin (Ig) G4-related Disease: What Do We Need to Know?

Dr Philip Hei LI

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MBBS, MRes(Med), PDipID, FHKCP, FHKAM(Medicine)

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INTRODUCTION

Immunoglobulin (Ig) G4 is the least abundant of the four subclasses of IgG and often considered an inhibitory or anti-inflammatory molecule found in patients with various autoimmune or allergic conditions. However, relatively little attention had been paid to this "minor" molecular until the discovery of its association with type I autoimmune pancreatitis in the early 2000s[1]. Since then, many clinical entities have been found to be related to IgG4, and the new entity of IgG4-related disease (IgG4-RD) was born.

IgG4-RD remains an increasingly recognised immune-mediated systemic disorder and involvement of almost every anatomical site has been reported. It is a fibro-inflammatory condition with characteristic histopathological features, and unifies what were previously thought to be unrelated individual organ disorders. Other examples of previous disease entities now under the diagnostic umbrella of IgG4-RD include Riedel's thyroiditis, Ormond's disease (idiopathic retroperitoneal fibrosis), Mikulicz disease (lymphoepithelial sialadenitis), Küttner's tumour (chronic sclerosing sialadenitis), and other "idiopathic" pseudotumours. Regardless of the organ involved, patients with IgG4-RD share similar clinical, serological and histopathological features that are key to its Diagnosis[2-4]. The exact disease pathogenesis and the role of IgG4 remains poorly understood. It has been hypothesised that IgG4 is only a surrogate marker or a down-regulatory response, rather than being a pathogenic molecule.

DIAGNOSIS AND PRESENTATION OF IgG4-RD

Various proposed diagnostic criteria and consensus papers on the pathology of IgG4-RD have been published[5,6]. In brief, the Diagnosis of IgG4-RD is usually considered "definite", "probable" or "possible" depending on the constellation of clinical, serological and, especially, histopathological findings (Fig. 1). The recommended cut-off value for serum IgG4 level is 135 mg/dL. The three characteristic histological findings include: 1) dense lymphoplasmacytic infiltrate, 2) "storiform" or swirling fibrosis, and 3) obliterative phlebitis. IgG4 immunostaining should show >10 IgG4+ plasma cells per high power field and an IgG4+/IgG+ plasma cell ratio >0.4. In addition, patients who fulfil other organ-specific criteria are also considered to have a "definite" diagnosis[7]. For example, organ-specific diagnostic criteria are available for conditions including IgG4-related–Mikulicz disease, sclerosing cholangitis and kidney disease. However, it is important to remember that elevated serum IgG4 levels are neither sensitive nor specific. Elevated serum IgG4 levels can be seen in a variety of other conditions such as malignancies, infections, or autoimmune disorders. Furthermore, IgG4+ plasma cells can be seen in a variety of other conditions and often masquerade various malignancies, infections or autoimmune disorders.

Patients commonly present with painless subacute swelling, organomegaly or organ damage. Constitutional symptoms are infrequent, although weight loss can occur especially with multi-organ involvement. The disease can have a multitude of clinical manifestations depending on the organ system(s) involved, IgG4-RD is infamously a great masquerade of many infective, malignant or autoimmune disease. It is often initially misdiagnosed as malignancies (presenting as "pseudotumours") or may even be incidentally diagnosed during other radiological or histological examinations.

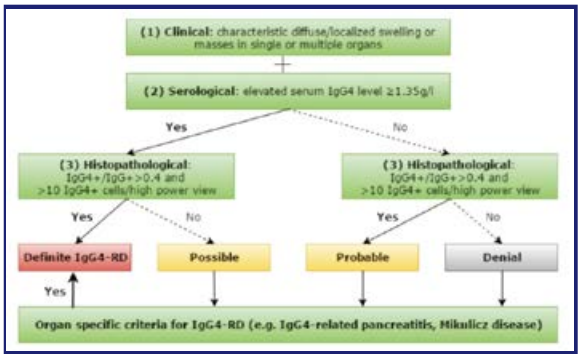

Fig. 1: Diagnostic algorithm for IgG4-RD (Adapted from Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012;22(1))

MANAGEMENT OF IgG4-RD

There is a lack of randomised controlled trials, and hence optimal treatment for IgG4-RD has not yet been established, although an international consensus guideline has been published[8]. Even subclinical disease can lead to irreversible organ damage, but not all patients require immediate treatment. Generally speaking, treatment is tailored for individual patients, and watchful waiting may be an appropriate option for

asymptomatic patients with mild disease involvement or following surgical debulking. When treatment is considered, glucocorticoids are used as first-line for remission induction; IgG4-RD characteristically responds promptly to therapy. Non-responders to glucocorticoid therapy are rare, although around half of IgG4-RD patients relapse during or after glucocorticoid tapering[9]. The use of steroid-sparing agents (either upfront or sequential) has been a matter of debate, but maintenance immunosuppression is often indicated for patients with a higher risk of recurrence – especially in patients with elevated serum IgG4, IgE, and eosinophils, patients with multi-organ involvement, and patients with a history of previous relapse[10]. Many experts now recommend rituximab, a monoclonal anti-CD20 antibody, as second-line treatment in IgG4-RD patients with recurrent or refractory disease.

IgG4 RD IN HONG KONG

Despite continued advances in the understanding of the disease and the various multinational guidelines available, few studies examined factors to predict disease severity or disease prognostication. Furthermore, local data for Hong Kong had been limited. To address this gap in knowledge, we performed an analysis of all IgG4-RD patients to elucidate the clinical features of IgG4-RD in Hong Kong (n=104) and factors predicting disease prognosis[11].

We reported that IgG4-RD patients in Hong Kong were predominantly older (mean age 62 years), and there was a male predominance (male-to-female ratio=3:1). These findings were consistent with other reported populations. Over 95% of patients had serum IgG4 level of >135 mg/dL and an IgG4:IgG ratio of >8%. Hepatobiliary and pancreatic, and ophthalmic systems, salivary gland and lymph node(s) were the most common organ systems involved (Fig. 2). Glucocorticoids were most frequently used, while local experience with other immunomodulatory agents was limited. We also identified that pre-treatment serum IgG4 levels (β=0.347; P=0.004) were associated with salivary gland involvement and multisystem disease. The reason for this particular association remains unclear. Nonetheless, based on this finding, we recommend that salivary gland involvement should be screened in patients with IgG4-RD, especially in the presence of higher levels of serum IgG4.

CONCLUSION

IgG4-RD is a complex and relatively new systemic immune-mediated disease. Despite rapid advances, the huge disease heterogeneity sometimes makes diagnosis and treatment decisions difficult. Data from Hong Kong remains scarce, but increased physician awareness will be required for early Diagnosis and optimal management of this masquerading disease. Further studies, especially focusing on treatment strategies within the contexts of different epidemiology and patient characteristics, warrant further pursuance.

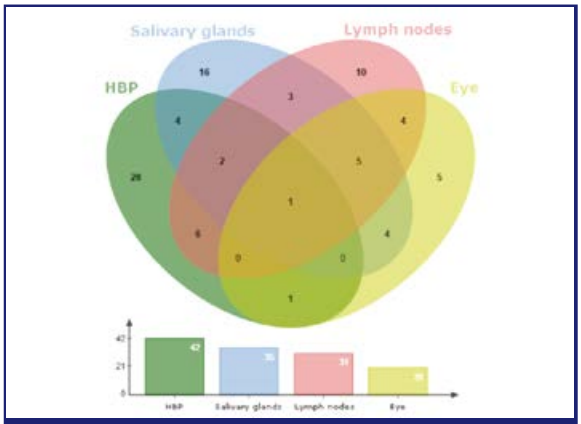

Fig. 2: Venn diagram of the four most commonly involved organ systems (n=89)
(Excerpted from Li PH, Ko KL, Ho CT, Lau LL, Tsang RK, Cheung TT, et al. Immunoglobulin G4-related disease in Hong Kong: clinical features, treatment practices, and its association with multisystem disease. Hong Kong Med J. 2017;23(5))

References

1. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344(10):732-8.
2. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366(6):539-51.
3. Carruthers MN, Stone JH, Khosroshahi A. The latest on IgG4-RD: a rapidly emerging disease. Curr Opin Rheumatol. 2012;24(1):60-9.
4. Stone JH, Khosroshahi A, Deshpande V, Chan JK, Heathcote JG, Aalberse R, et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum. 2012;64(10):3061-7.
5. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012;22(1):21-30.
6. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25(9):1181-92.
7. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol. 2006;4(8):1010-6.
8. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. Arthritis Rheumatol. 2015;67(7):1688-99.
9. Campochiaro C, Ramirez GA, Bozzolo EP, Lanzillotta M, Berti A, Baldissera E, et al. IgG4-related disease in Italy: clinical features and outcomes of a large cohort of patients. Scand J Rheumatol. 2016;45(2):135-45.
10. Wallace ZS, Mattoo H, Mahajan VS, Kulikova M, Lu L, Deshpande V, et al. Predictors of disease relapse in IgG4-related disease following rituximab. Rheumatology (Oxford). 2016;55(6):1000-8.
11. Li PH, Ko KL, Ho CT, Lau LL, Tsang RK, Cheung TT, et al. Immunoglobulin G4-related disease in Hong Kong: clinical features, treatment practices, and its association with multisystem disease. Hong Kong Med J. 2017;23(5):446-53.

Systemic Vasculitis: A New Era for Giant Cell Arteritis

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INTRODUCTION

Giant cell arteritis (GCA) is classified as one of the large vessel vasculitides, according to the Chapel Hill Consensus Conference in 2012[1]. It predominantly affects the branches of the aorta, especially the cranial arteries. It is an uncommonly recognised disease in the elderly population. The potential life-threatening complications such as irreversible loss of vision, as well as large vessel complications such as stenosis, aneurysm, and dissection of large arteries make early diagnosis and treatment of GCA crucial.

Recent advances include a better understanding of large vessel involvements, newer imaging modalities for diagnosis and the latest treatment using a biological agent targeting interleukin-6 (IL-6).

EPIDEMIOLOGY

GCA is a disease of the elderly. It rarely occurs in patients younger than 50 years of age. It is relatively rare in Asians, while it is the most common type of vasculitis in Europe and North America. The annual incidence in the prevalent regions can be as high as 17/100,000 population older than 50 years of age[2], while in Japan, the annual incidence is 1.47/100,000 population older than 50 years of age[3]. Women are affected two to three times more commonly than men in Northern Europe[4].

PATHOPHYSIOLOGY

Genetic factors play a role in the development of the disease. HLA-DRB1*04 carrier status has been reported to have a higher risk of developing GCA[5]. This allele is also reported more frequently in countries with a higher prevalence of GCA.

An understanding of the immunopathological pathway helps in developing novel treatments for this disease[6]. Dendritic cells located in the adventitia-media border of large and medium arteries play a pivotal role in the pathogenesis of GCA. An unknown trigger leads to abnormal maturation of vascular dendritic cells in the large vessel wall. These antigen-presenting cells recruit T cells, the latter proliferating to T helper-one cells and T helper-17 cells. Cytokines, including interferon-gamma, interleukin (IL)-2, IL-17, IL-22, are then secreted by these activated T cells. Macrophages are then recruited, and these macrophages produce pro-inflammatory cytokines, including IL-6 and IL-1, and secrete matrix metalloproteinases, all contributing to vessel wall damages. Interferon-gamma also enhances the formation of giant cells from macrophages. All these immunopathogenetic processes lead to the characteristic features seen in the biopsied vessel wall.

CLINICAL PRESENTATION

The symptoms of GCA arise from tissue ischemia related to vasculitis of the cranial vessels. Symptoms include temporal headache and scalp tenderness due to superficial temporal artery involvement, jaw claudication due to maxillary artery involvement, tongue pain or necrosis due to lingual artery involvement. Constitutional symptoms such as fever, weight loss, anorexia are also common due to the underlying systemic inflammation. At times fever of unknown origin can be the only presentation of large-vessel GCA. New-onset headache is one of the most common presentation, while jaw claudication is the most specific. On physical examination, one must try to palpate for abnormalities over the temporal artery region, which may show tenderness, absence of pulse, or swollen temporal artery.

The most worrying complication of GCA is an irreversible loss of vision. Therefore, visual symptoms upon presentation are essential to enquire for. Around 50% of GCA patients have ocular involvement. The most common ophthalmic presentation (up to 80-90%) is anterior ischemic optic neuropathy[7]. Patients complain of painless vision loss or amaurosis fugax. The examination will show pale or swollen optic disc but a normal retina. Central retinal artery occlusion and posterior ischemic optic neuropathy are other possible presentations. Patients may present with double vision when the blood supply of the extraocular muscles are affected.

In the absence of these classical clinical features, large vessel involvement is a previously underestimated presentation of GCA. Along with the advances in imaging techniques, including the availability of PET-CT and MRI scans, vasculitis of the thoracic or abdominal aorta is found in as high as 80% of patients with GCA[8]. These large vessel involvements may be asymptomatic and yet, if not discovered, will bear the risk of long term complications, including stenosis, dissection, and aneurysm.

Polymyalgia rheumatica (PMR) is well recognised to be associated with GCA. Up to 50% of biopsy-proven GCA carries PMR manifestations[9]. For PMR cases, around

Table 1. ACR classification criteria for GCA (Adapted from Hunder, G.G., et al., The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum, 1990. 33(8))

Criterion	Definition
1. Age at disease onset ≥50 years	Development of symptoms or findings beginning at age 50 or older.
2. New headache	New onset of or new type of localised pain in the head.
3. Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation unrelated to arteriosclerosis of cervical arteries.
4. Elevated ESR	Erythrocyte sedimentation rate ≥ 50 mm/h by the Westergren method.
5. Abnormal artery biopsy	Biopsy specimen with the artery showing vasculitis characterised by prominence of mononuclear cell infiltration or granulocyte inflammation, usually with multinucleated giant cells.

For purposes of classification, a patient with vasculitis shall be said to have giant cell (temporal arteritis) if at least three of these five criteria are present.

20% of patients had underlying GCA[10]. Therefore, one should ask about symptoms of polymyalgia rheumatica when facing a patient with suspected GCA. These symptoms include pain and stiffness in the proximal girdle, shoulder, and hip.

HOW TO DIAGNOSIS GCA?

The American College of Rheumatology (ACR) classification criteria (Table 1) for GCA was published in 2000[11]. The symptoms included are not diagnostic criteria, and they resemble those of other confounding conditions, such as central nervous system infection.

Initial investigations should include inflammatory markers such as ESR and CRP. Normochromic normocytic anaemia and thrombocytosis may be present due to the underlying inflammation. Imaging of the brain, as well as an attempt to rule out the possibility of central nervous system infection, should be pursued. If a patient already has presented with visual symptoms, an urgent ophthalmology referral is indicated.

The gold standard for diagnosis is temporal artery biopsy. However, the sensitivity can be as low as 40%[12] due to skipping lesions, an inadequate biopsy sample, and/or prior use of steroids before a biopsy. The time required to have a biopsy report is also another reason to look for a better diagnostic tool that can give an immediate result.

Newer modalities of imaging, i.e. an ultrasound with power Doppler and/or MRI scan offer a non-invasive way to diagnose GCA. Ultrasound of the temporal artery may show the "halo" sign, which is due to the inflamed temporal artery wall. The latest European Rheumatology guidelines on imaging for large vessel vasculitis recommends that for inpatients with classical clinical presentation and a positive ultrasound sign, temporal artery biopsy may not be necessary[13].

High-resolution MRI for the cranial arteries, black blood MR angiogram (MRA), or PET-CT scan are also useful in diagnosing GCA. MRI and MRA have the advantage over PET-CT because MRI does not use radiation.

TREATMENT

Irreversible vision loss in GCA is a rheumatological emergency. Prompt treatment is imperative. First-line treatment is systemic steroids. Studies have shown the benefits and effects of systemic steroids to control inflammation and to rapidly avert vision loss[14]. Small studies have shown that the administration within 24 hours from the onset of symptoms may lead to better visual outcome[15]. Steroid use can also prevent the contralateral eye from being involved. Systemic steroids should be given if GCA is highly suspected.

Most of the GCA patients are elderly with comorbidities that predispose them to steroid-induced side effects. Conventional steroid-sparing agents, including methotrexate, azathioprine, and mycophenolate, have been used. Small studies have proven the steroid-sparing effect of these agents[6].

The encouraging results of Tocilizumab in treating GCA patients shown in the prospective randomised controlled trial has been groundbreaking in the field of large vessel vasculitis[16]. Tocilizumab is an IL-6 inhibitor. Patients in the intervention group were given 26 weeks of biweekly subcutaneous tocilizumab, together with a standard protocol of systemic steroids. Patients in the placebo group were given comparable doses of systemic steroids only. The primary outcome was the rate of sustained steroid-free remission. This study showed that patients treated with Tocilizumab demonstrated a higher rate of steroid-free remission when compared to the placebo group. The cumulative steroid dose was lower in the Tocilizumab group, demonstrating the steroid-sparing effect of the drug. Neutropenia happened in around 4% of the tocilizumab-treated group; otherwise, the rate of adverse events was similar among the two treatment groups.

Further data from the long-term extension of this landmark trial will be published soon and was presented as an abstract in the latest international Rheumatology conference[17]. The initial result showed that, after two more years of follow-up, the remission rate was still higher in the Tocilizumab-treated group when compared with the placebo group. The steroid-sparing effect was also sustained.

CONCLUSION

With the advancements in both imaging technology and treatment, patients with GCA can now be better managed. The availability of ultrasound, MRI, and PET-CT may save patients from invasive temporal artery biopsy. Tocilizumab has recently been approved for the treatment of GCA; this new drug offers a more effective and safer alternative therapy to these patients when compared to the use of systemic steroids.

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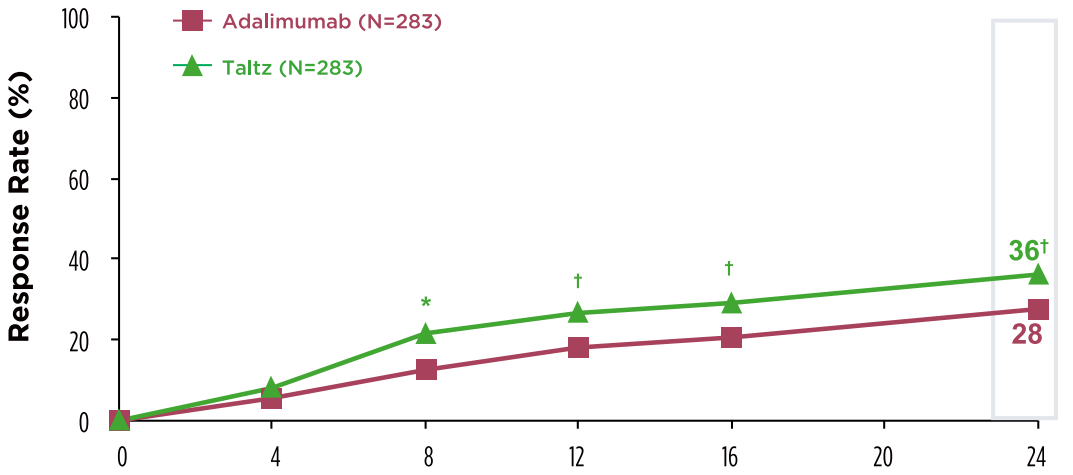
SPIRIT H2H (BIOLOGIC NAÏVE): PERCENTAGE OF PATIENTS SIMULTANEOUSLY ACHIEVING

ACR 50 AND | **PASI 100 At WEEK 24, NRI**



* P<0.01 vs adalimumab at week 24. Onset of response was statistically significant higher as early as week 8 through to week 24.

† P<0.05 vs adalimumab at week 24.

All patients had BSA ≥3%; patients with BSA ≥10%, PASI ≥12, sPGA ≥3 followed the approved dosing for moderate to severe plaque psoriasis.

ACR50 = American College of Rheumatology response criteria with 50% improvement; BSA = body surface area; IL = interleukin; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; sPGA = static Physician Global Assessment.

Reference: Mease PJ, et al. Ann Rheum Dis. 2019;78:261-262.

Taltz Abbreviated Prescribing Information

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 disease-modifying anti-rheumatic drug (DMARD) therapies. **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. No data are available in children and adolescent ≤ 18 years and limited information in subjects ≥ 75 years. **Contraindications:** Serious hypersensitivity. Clinically important active infections. **Special Precautions:** Infections, hypersensitivity, inflammatory bowel disease, immunization. Pregnancy, breast-feeding, fertility. **Adverse Reactions:** Injection site reactions, upper respiratory tract infections, tinea infection, oropharyngeal pain, nausea.

Please see Important Safety Information in the full prescribing information.
Please see Instructions for Use included with the device.

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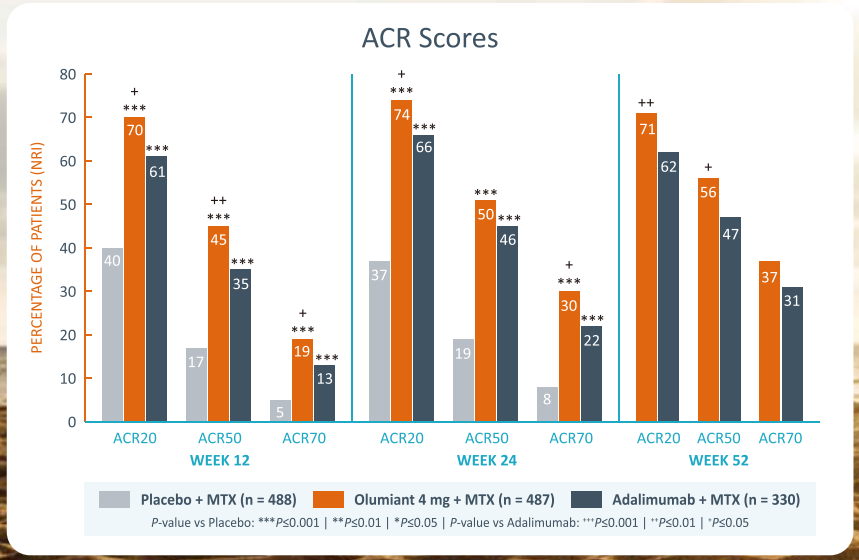
- Clinically significant improvement was seen as early as 1 week in a head-to-head trial of MTX-IR patients, as measured by ACR50.[1]



OLUMIANT® (baricitinib) Abbreviated Prescribing Information

Therapeutic indications: OLUMIANT is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. OLUMIANT may be used as monotherapy or in combination with methotrexate. **Recommended dose:** The recommended dose of OLUMIANT is 4 mg once daily. A dose of 2 mg once daily is appropriate for patients such as those aged ≥ 75 years and may be appropriate for patients with a history of chronic or recurrent infections. A dose of 2 mg once daily may also be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering. **Contraindications:** Known hypersensitivity to the baricitinib or any of the excipients. Pregnancy. **Special precaution:** Caution in patients with chronic, active or recurrent infections, monitor if infection develops; interrupt if not responding to treatment. Screen for tuberculosis, do not give if active; treat first if latent. Avoid or interrupt OLUMIANT with abnormal blood cell levels, lipids and liver enzymes. Use with live vaccines not recommended. The risk of malignancies including lymphoma is increased in patients with rheumatoid arthritis, OLUMIANT clinical data are insufficient to assess potential incidence of malignancies. Caution in patients with risk factors for deep venous thrombosis or pulmonary embolism, consider VTE prophylaxis. Use with bDMARD or other JAK is not recommended. **Adverse reaction:** The most commonly reported adverse drug reactions (ADRs) occurring in ≥ 2 % of patients treated with OLUMIANT monotherapy or in combination with conventional synthetic DMARDs were increased LDL cholesterol (33.6 %), upper respiratory tract infections (14.7 %) and nausea (2.8 %). Infections reported with OLUMIANT treatment included herpes zoster. **Drug interaction:** Combination with biologic DMARDs or other JAK inhibitors has not been studied. Use of baricitinib with potent immunosuppressive medicinal products such as azathioprine, tacrolimus, or ciclosporin was limited in clinical studies of baricitinib, and a risk of additive immunosuppression cannot be excluded.

Full prescribing information is available upon request.

Reference: 1. Taylor PC et al. *N Engl J Med* 2017; 376.652-62

cDMARD = conventional disease-modifying antirheumatic drug; JAK = Janus kinase; MTX = methotrexate; MTX-IR = Methotrexate-Inadequate Responder

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PP-BA-HK-0042 03/19

References

1. Jennette, J.C., et al., 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum, 2013. 65(1): p. 1-11.
2. Andersen, J.B., et al., Incidence Trends and Mortality of Giant Cell Arteritis in Southern Norway. Arthritis Care Res (Hoboken), 2020.
3. Kobayashi, S., et al., Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. Arthritis Rheum, 2003. 49(4): p. 594-8.
4. Gonzalez, E.B., et al., Giant-cell arteritis in the southern United States. An 11-year retrospective study from the Texas Gulf Coast. Arch Intern Med, 1989. 149(7): p. 1561-5.
5. Gonzalez-Gay, M.A., et al., Genetic markers of disease susceptibility and severity in giant cell arteritis and polymyalgia rheumatica. Semin Arthritis Rheum, 2003. 33(1): p. 38-48.
6. Al-Mousawi, A.Z., et al., Reviewing the Pathophysiology Behind the Advances in the Management of Giant Cell Arteritis. Ophthalmol Ther, 2019. 8(2): p. 177-193.
7. Hayreh, S.S., P.A. Podhajsky, and B. Zimmerman, Ocular manifestations of giant cell arteritis. Am J Ophthalmol, 1998. 125(4): p. 509-20.
8. Blockmans, D., et al., Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Rheum, 2006. 55(1): p. 131-7.
9. Gonzalez-Gay, M.A., Giant cell arteritis and polymyalgia rheumatica: two different but often overlapping conditions. Semin Arthritis Rheum, 2004. 33(5): p. 289-93.
10. Nesher, G. and G.S. Breuer, Giant Cell Arteritis and Polymyalgia Rheumatica: 2016 Update. Rambam Maimonides Med J, 2016. 7(4).
11. Hunder, G.G., et al., The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum, 1990. 33(8): p. 1122-8.
12. Luqmani, R., et al., The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technol Assess, 2016. 20(90): p. 1-238.
13. Dejaco, C., et al., EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis, 2018. 77(5): p. 636-643.
14. Hunder, G.G., et al., Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. Ann Intern Med, 1975. 82(5): p. 613-8.
15. Gonzalez-Gay, M.A., et al., Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum, 1998. 41(8): p. 1497-504.
16. Stone, J.H., et al., Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med, 2017. 377(4): p. 317-328.
17. Long-Term Outcome of Tocilizumab for Patients with Giant Cell Arteritis: Results from Part 2 of a Randomized Controlled Phase 3 Trial. Abstract, ACR 2019.

Radiology Quiz

Dr Leanne Han-qing CHIN

MBBS, FRCR

Dr Leanne Han-qing CHIN

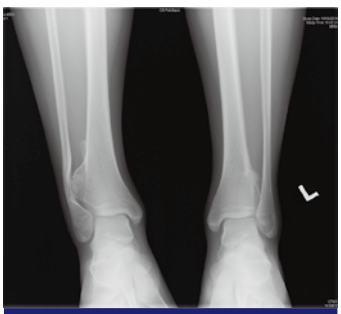

Fig 1. X-ray bilateral ankles (frontal views)

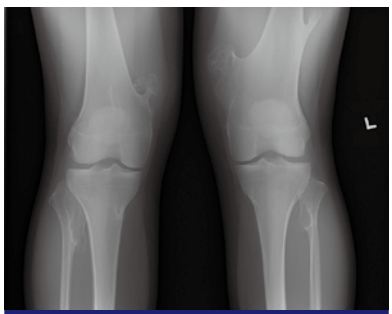

Fig 2. X-ray bilateral knees (frontal views)

An 11-year-old girl with good past health presented to Accident & Emergency Department with symptoms of right ankle swelling and pain. Multiple areas of hard swelling were also palpated at the bilateral distal thighs. Limb power, sensation, and range of motion, and overlying skin were otherwise unremarkable. There was no history of trauma. X-rays of the ankles and knees were performed.

Questions

1. What are the plain film findings?
2. What are the alternative names for this condition?
3. What is the inheritance pattern?
4. What are the important complications to be aware of?
5. What are the red flags for malignant transformation?
6. What is the next step of management?

(See P.28 for answers)

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... more than 300 clinical trial publications[4]

... more than 180 open label extension publications[4]

Reference: 1. Burmester GR, Mease P, Dijkmans BA, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory d iseases. Ann Rheum Dis. 2009;68(12):1863-1869. 2. Data on file, AbbVie Inc. Humira patients currently treated worldwide Q2 2018. 3. Hong Kong Humira Prescribing Information, version May 2018 4. A literature search strategy was designed to find Adalimumab publications parsed out by study type: Open Label Extensions (OLE), Meta-analysis, Observational / Registry Studies, and Randomized Controlled Trial (RCTs). Four databases in the ACS STN command language platform were used: Medline: 1946 to 17 Jul 18, Embase: 1947 to 17 Jul 18, Biosis: 1926 to 18 Jul 18 and HCAPLUS (Chemical Abstracts Plus): 1907 – 17 Jul 18.

HUMIRA® abbreviated prescribing information

Presentation: For pre-filled syringe and pre-filled pen presentation adalimumab 40mg/0.4mL solution for injection. **Indications and Dosage:** *Adult Rheumatoid Arthritis* 40 mg SC as a single dose EOW, use with MTX. In monotherapy patient who experience decrease in response may benefit from an increase in dose to 40 mg every week. *Adult Ankylosing Spondylitis, Axial Spondyloarthritis without radiographic evidence of AS and Psoriatic Arthritis* 40 mg SC as a single dose EOW. *Adult Crohn's Disease* 80 mg at week 0, followed by 40 mg at week 2 as induction , then 40 mg SC EOW; if need for a more rapid response, the regimen 160 mg at week 0, 80 mg at week 2, can be used with the awareness of the higher risk for adverse events during induction. *Adult Ulcerative Colitis* 160 mg at week 0 and 80 mg at week 2 as induction treatment, then 40 mg SC EOW. *Adult Psoriasis* initially 80 mg SC, followed by 40 mg SC given EOW starting 1 week after the initial dose; if experience insufficient response beyond 16 weeks, may benefit from an increase to 40mg Every Week. *Adult Hidradenitis Suppurativa* 160mg SC on day 1 and 80mg SC on day 15, followed by 40mg SC on day 29 and subsequent 40mg SC Every Week. *Adult Uveitis* 80mg SC at week 0, followed by 40mg SC EOW from week 1. *Paediatric Polyarticular Juvenile Idiopathic Arthritis, adolescent and children 2-12 yr* 24mg/m² body surface area SC EOW up to a maximum single dose of 20mg adalimumab (for aged 2-4) and a maximum single dose of 40mg (for aged 4-12); *13-17 yr* 40 mg SC as a single dose EOW. *Paediatric Enthesitis- Related Arthritis children 6 yr and older* 24mg/m² body surface area SC EOW up to a maximum single dose of 40mg. *Paediatric Crohn's Disease adolescent and children 6-17 yr, <40kg* initially 40mg SC at week 0, followed by 20mg at week 2 as induction; if need for a more rapid response, the regimen 80mg SC at week 0 and 40mg at week 2, can be used with the awareness of the higher risk for adverse event during induction, then 20mg SC EOW; if experience insufficient response, may benefit from an increase to 20mg Every Week; *≥40kg* initially 80mg SC at week 0, followed by 40mg at week 2 as induction; if need for a more rapid response, the regimen 160mg SC at week 0 and 80mg at week 2, can be used with the awareness of the higher risk for adverse event during induction, then 40mg SC EOW; if experience insufficient response, may benefit from an increase to 40mg Every Week. *Paediatric Plaque Psoriasis children 4 yr and older* 0.8mg/kg body weight initially SC at week 0 and 1, followed by 0.8mg/kg SC EOW up to a maximum single dose of 40mg. *Adolescent Hidradenitis Suppurativa 12 yr and older >30kg* 80mg SC at week 0 and 40mg EOW from week 1; if experience insufficient response, an increase to 40mg Every Week may be considered; *Paediatric Uveitis children 2 yr and older <30kg* 20mg SC as a single dose EOW, use with MTX; a loading dose of 40mg may be considered 1 week before start of maintenance therapy; *≥30kg* 40mg SC as a single dose EOW, use with MTX; a loading dose of 80mg may be considered 1 week before start of maintenance therapy. **Contraindications:** Patients with known hypersensitivity to adalimumab or any of its excipients. Patients with active tuberculosis or other severe infections. Patients with moderate to severe heart failure (NYHA class III/IV) **Precautions:** As with other TNF-α inhibitor, monitoring closely for infections including tuberculosis before, during and after treatment; Carriers of HBV as reactivation; Pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; History of lymphoma or malignancy; Worsening of CHF; Women of child-bearing potential; Pregnancy & lactation; Elderly > 65 yr; Vaccinations. **Interactions:** other biologic DMARDs or TNF antagonists, live vaccines. **Undesirable effects:** Respiratory tract, systemic, intestinal, skin and soft tissue, ear, oral, reproductive tract, urinary tract, fungal and joint infections; benign neoplasm; skin cancer excluding melanoma; leukopenia; anemia; thrombocytopenia; leucocytosis; hypersensitivity, allergies; increased lipids; hypokalaemia; increased uric acid; blood sodium abnormal; hypocalcaemia; hyperglycemia; hypophosphatemia; dehydration; mood alterations; anxiety; anxiety, insomnia; headache; paraesthesias; migraine; nerve root compression; visual impairment; conjunctivitis; blepharitis; eye swelling; vertigo; tachycardia; hypertension; flushing; haematoma; cough; asthma; dyspnoea; abdominal pain; nausea & vomiting; GI hemorrhage; dyspepsia; gastroesophageal reflux disease; sicca syndrome; elevated liver enzymes; rash; pruritus; urticarial; bruising; dermatitis; onychoclasis; hyperhidrosis; musculoskeletal pain; muscle spasms; haematuria, renal impairment; injection site reaction; chest pain; edema; coagulation and bleeding disorders; autoantibody tests positive; increased blood lactate dehydrogenase; impaired healing. **Full local prescribing information is available upon request.**

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SLE: The Management of Lupus Nephritis

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterised by multi-organ involvement and presence of antibodies to components of the cell nucleus. Clinical manifestations are heterogeneous. It frequently involves the kidneys, in up to 60% of patients. If left untreated, it may result in significant morbidity and mortality. Around 5-20% of lupus nephritis (LN) patients developed end-stage renal disease at ten years.[1] Patients seldom report specific symptoms related to the kidneys until there is nephrotic syndrome or renal failure. The clinical renal disease is marked by more than 3+ on a dipstick, the presence of proteinuria of more than 0.5 g/24 hours, the presence of red cell casts or white cell casts, and/or elevated serum creatinine. Renal biopsy is frequently performed to delineate the specific histological features, which are stratified to different classes of lupus nephritis based on the International Society of Nephrology and Renal Pathology Society criteria (Table 1).

Table 1. Summary on Proposed treatment option according to the International Society of Nephrology / Renal Pathology Society (ISN/RPS) histological classes (Table 1:Adapted from reference 1-12)

Class	Description	Induction therapy	Maintenance therapy
I	Minimal mesangial	Variable dose of prednisolone depending on the severity	Aza
II	Mesangial proliferative	Variable dose of prednisolone depending on the severity	Aza
III	Focal proliferative	P + MMF or P + IV CYC or P + TAC	MMF or Aza or TAC
IV	Diffuse proliferative	P + MMF or P + IV CYC or P + TAC	MMF or Aza or TAC
V	Membraneous	P + Aza + ACEI/ARB or P + MMF/CSA/TAC	Aza or MMF/ CSA/TAC
VI	Advanced sclerosing involving >90% glomueruli	Active GN is not usually present.	
V+III or V+IV		Treat as class III or IV	Treat as class II or IV

Footnotes: ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, AZA=azathioprine, CSA= cyclosporine A, MMF=mycofenolatemofetil, P= prednisolone, TAC=tacrolimus. GN= glomerulonephritis

TREATMENT GOALS OF LUPUS NEPHRITIS

The goals of treatment are to induce remission in the short term and maintain remission in the long run. The immunosuppressive therapy of LN consists of the induction phase, which takes about six months; and the maintenance phase, which takes more than three years. Induction therapy involves intensive immunosuppressive therapy in combination, and maintenance therapy involves a prolonged period of less intensive immunosuppressive therapy to prevent relapse and progression of the renal disease.

MANAGEMENT OF LUPUS NEPHRITIS

A. Class I and Class II Lupus Nephritis

Class I and Class II LN usually respond to moderate doses of corticosteroid. Choices of immunosuppressive therapy are mainly determined by the severity of the extra-renal manifestation of the disease. Azathioprine (AZA) can be used as a steroid-sparing agent. Kidney Disease Improving Global Outcome (KDIGO) guideline[2] recommends that management should be based on concomitant extra-renal lupus manifestations if present. Corticosteroid is warranted for those with nephrotic syndrome. Immunosuppressive therapy may be necessary when the response is unsatisfactory and if relapses are frequent.

B. Class III / IV Lupus Nephritis

It is crucial to start treatment early. Delay in effective treatment implies continuous damage to nephrons, reduces renal reserve and poses negative impact on renal survival. Early aggressive treatment with high-dose corticosteroids in combination with IV cyclophosphamide (CTX) or oral mycophenolate mofetil (MMF) is recommended.

Asian Lupus Nephritis Network (ALNN) consensus[3] recommends intravenous pulse corticosteroids at a dose of 250-1,000 mg methylprednisolone daily for three days to patients with crescentic involvement of 10% or more of the glomeruli on renal biopsy, or those with deterioration in renal function. Following the pulse corticosteroid therapy, oral prednisolone is given at lower maintenance and tapering doses. The alternative treatment is high initial dose of oral prednisolone 0.8-1 mg/kg daily. ALNN suggests the dose of the oral corticosteroids to be tapered down to a target dose of prednisolone below 20 mg daily after three months and below 10 mg daily at six months.

Mycophenolate Mofetil vs Cyclophosphamideas Induction Therapy in Class III/IV

Ginzler EM et al. compared the efficacy and toxicity of MMF (up to 3 g/day) against National Institute of Health (NIH) IV CTX (0.5-1 g/m^2) monthly for six months in 140 patients with Class III, IV or V LN. Concomitant oral prednisolone (1 mg/kg/day) was given in both groups. Of this cohort, 76% were African and Hispanic Americans, 54% had Class IV LN, and 44% were with a nephrotic range of proteinuria at >3.5 g/day. At the end of six months, there were significantly more patients in MMF arm who achieved complete remission (22.5%) than in the CTX arm (5.8%). There was no difference in the rates of renal relapse, end-stage renal disease, nor death on follow-up. Pyogenic infections, alopecia, and menstrual disturbances were less common, but diarrhoea was more common in MMF arm. This study thus demonstrated evidence that MMF may be more effective and is a less toxic alternative to pulse CTX in mild to moderate LN.

No superiority of MMF over CTX was found during the induction phase of the Aspreva Lupus Management Study (ALMS).[5] The study was a 24-week remission-induction randomised open-labeled trial comparing MMF (target dose 3 g/day) with NIH IV CTX (0.5-1 g/m^2 monthly for six months).

Based on the existing data, ALNN recommends MMF as the standard-of-care treatment option. For the target dosing of MMF in the induction phase, international guidelines recommend MMF up to 3 g/day. ALNN recommends 1.5-2 g daily for Asians because side effects are more common among Asians.

CTX induction may be associated with more sustained remission and more favourable renal outcome in the long term. For severe active LN with high risk of disease progression into end-stage renal disease (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy and interstitial fibrosis), monthly pulse CTX for total six or seven doses is preferred.

C. Pure Class V Lupus Nephritis

Risk of renal function deterioration is much lower in pure membranous LN, and the choice of immunosuppression is mainly guided by the degree of proteinuria. Patients with a low degree of proteinuria and stable renal function can be managed with blood pressure control and ACEI or ARB. For patients with nephrotic range proteinuria or worsening proteinuria, prednisolone plus MMF (2-3 g/day) is used followed by MMF (1-2 g/day) or AZA (2 mg/kg/day) as maintenance therapy.

D. Class VI Advanced SclerosingLupus Nephritis

This class is included because it represents the last stage of lupus nephritis. Over 90% of glomeruli are sclerosed, which is the sequelae of healing following prior inflammation. Active glomerulonephritis is not usually present. Response to immunosuppressants is usually poor. This stage is characterised by gradual renal function decline and progression into end-stage renal failure.

LONG TERM MAINTENANCE THERAPY

Azathioprine (AZA, usually at 2 mg/kg/day) or MMF (1-2 g/day) in combination with low-dose oral corticosteroids is recommended by ACR[6] and EULAR[7] for maintenance therapy to consolidate LN remission and to prevent relapse. For patients treated with MMF for induction, it is preferrable to continue MMF for maintenance based on data on a Chinese cohort[8]; substituting MMF with AZA before 24 months was associated with an increased risk of renal flare. There is little evidence as to when to stop immunosuppression; EULAR recommends at least three years of MMF treatment in patients given MMF (3 g daily for 6 months) as induction therapy, then followed by lower dose of MMF (0.5-1.5 g daily) as maintenance. Asian Lupus Nephritis Network (ALNN) recommends not to reduce MMF dose below 1 g daily within the second year.

ROLE OF CALCINEURIN INHIBITORS IN LUPUS NEPHRITIS

Calcineurin inhibitors (CNIs) inhibit T-cell mediated immune responses and exert anti-proteinuric effect by stabilising the podocytes in the kidneys. An RCT compared tacrolimus (TAC) (0.06-0.1 mg/kg/day) with MMF (2-3 g/day) in combination with high-dose prednisolone in 150 Chinese patients with class III, IV or V active LN and suggested a comparable rate of complete renal responses (62% and 59% respectively)[9]. However, there was a trend of more renal relapses in the TAC-treated group after switching to azathioprine for maintenance at five years. CNIs are currently recommended for refractory cases of proliferative LN.

The role of CNIs in maintenance therapy was evaluated in several studies. A study in 70 Chinese patients who received TAC or AZA for maintenance found no significant difference in the rates of renal relapses.[10]

Using CNIs in conjunction with other immunosuppressants as a multi-target approach to achieve synergism and to facilitate a lower dosage of individual drugs had been investigated. An RCT involving 368 Chinese patients with active LN demonstrated that combination of low dose MMF (1 g/day) with TAC (4 mg/day) was superior to intravenous CTX pulses for induction of complete renal responses at 24 weeks (46% versus 26%).[11] Withdrawal due to serious infections, herpes zoster infections, and pneumonia was more common in the multi-target group. Despite an apparent benefit in the induction phase, the role of multi-target therapy for maintenance is less clear. In the long-term extension study, the renal relapse rates were similar between patients who continued multi-target therapy and patients who received AZA after IV CTX induction.[12]

The side effects of CNIs, including hypertension, hyperlipidemia, hirsutism, and gingival hyperplasia, are less frequently seen with TAC than with CSA. The

narrow therapeutic window, risks of nephrotoxicity and the need for therapeutic drug monitoring with TAC or CSA limit their widespread use in the treatment of LN. Voclosporin, a new analogue of CSA, has increased potency and less plasma variability than CSA and is currently under phase 3 trial after promising phase 2b trial results.

BIOLOGICAL AGENTS FOR LUPUS NEPHRITIS

Belimumab is a human monoclonal antibody that inhibits B-cell activating factor. It is approved in the United States and Europe to treat SLE.Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody to deplete B cells. It is currently off-label used in the treatment of LN due to controversial results among clinical studies. The LUNAR trial failed to demonstrate a superiority of RTX over MMF plus prednisolone in proliferative LN patients.[13] In a meta-analysis of 10 studies involving over 200 RTX-treated LN patients, the pooled proportion of complete remission was 51%.[14] Data from well-designed clinical trials on the efficacy of RTX is lacking. In the latest EULAR recommendation, RTX can be used to treat severe renal or non-renal manifestations that failed first-line immunosuppressants.

ADJUNCTIVE MEASURES

All LN patients should be treated with a background of hydroxychloroquine unless there is contraindication. Optimal blood pressure control is essential, and the target blood pressure should be below 130/85 mmHg. High-risk patients warrant a more aggressive control of blood pressure to below 120/80 mmHg. Proteinuria should be minimised by adding ACEI or ARB, these drugs being well-proven renoprotective agents and can retard or halt the deterioration of the renal function in chronic kidney disease. Aggressive treatment of the atherosclerosis risk factors such as the use of statins and aspirin in selected patients is essential.

CONCLUSIONS

The initial choices of treatment should be based on the risk stratification of individual patients. MMF should be regarded as the first-line therapy for proliferative LN. CTX should be reserved for high-risk patients such as those with crescentic glomerulonephritis, rapidly deteriorating renal function, or refractory disease. TAC can be considered an alternative to MMF for induction therapy when MMF is not tolerated or when MMF is contraindicated. Low-dose combination of MMF and TAC should be further explored in high-risk patients. Early response to immunosuppressive therapy was shown to be the best prognostic factor for good long-term renal outcome. Patients who fail to achieve a satisfactory response by six months should be switched to an alternative treatment regimen.

References

1. Houssiau FA, Ginzler EM. Current treatment of LN. Lupus 2008;17:426-30.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGOClinical Practice Guidelines for Glomerulonephritis.Kidney Int. Suppl. 2012;2:139-274.
3. Mok CC, Yap DYH, Navarra SV, et al. for the Asian Lupus Nephritis Network (ALNN). Nephrology 2014;19:11-20
4. Ginzler EM, Dooley MA, Aranow C, et al. MMF or IV CTX for LN.New Eng J Med 2005;353:2219-28.
5. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am SocNephrol. 2009;20(5):1103–1112.
6. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment and management of lupus nephritis. Arthritis Care Res. 2012;64:797-808.
7. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis.2012;71:1771-82
8. Yap DY, Ma MK, Mok MM, et al. Long-term data on corticosteroids and mycophenolate mofetil treatment in lupus nephritis. Rheumatology 2013;52:480-6.
9. Mok CC, Ying KY, Yim CW, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis. 2016; 75:30e6
10. Chen W, Liu Q, et al. Outcomes of maintenance therapy with tacrolimus versus azathioprine for active lupus nephritis: a multicenter randomized clinical trial. Lupus 2012; 21:944e52
11. Liu Z, Zhang H, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med. 2015; 162:18e26
12. Zhang H, et al. Multitarget Therapy for Maintenance Treatment of Lupus Nephritis. Journal of the American Society of Nephrology: JASN. 2017; 28:3671-3678.
13. Rovin BH, Furie R, Latinis, K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The lupus nephritis assessment with rituximab study.Arthritis & Rheumatism 2012, 64: 1215-1226
14. Alshaiki F, Obaid E, Almuallim A, et al. Outcomes of rituximab therapy in refractory lupus: A meta-analysis. Eur J Rheumatol. 2018;5(2):118–126.

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References: 1. Strand V *et al.* Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs. *Arthritis Research & Therapy.* 2015;17(1):307. **2.** Wollenhaupt J *et al.* Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. *Arthritis Res Ther.* 2019;21(1):89. **3.** Lee EB *et al.* Tofacitinib versus Methotrexate in Rheumatoid Arthritis. *New England Journal of Medicine.* 2014;370(25):2377-2386. **4.** Fleischmann R *et al.* Placebo-Controlled Trial of Tofacitinib Monotherapy in Rheumatoid Arthritis. *New England Journal of Medicine.* 2012;367(6):495-507. **5.** Wan R, Mok cc. The Hong Kong Society of Rheumatology Biologics Registry: Updated Report (Nov 2018). *Hong Kong Bulletin on Rheumatic Diseases.* 2019;18. **6.** Pfizer Inc.Data on file; HKPI of Xeljanz XR version13-MAR-2018

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Hereditary Angioedema in Hong Kong: Early Beginnings and Hope for the Future

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INTRODUCTION

Hereditary angioedema (HAE) is a rare primary immunodeficiency disease caused by a deficiency in C1-esterase inhibitor protein (C1-INH). It is an autosomal dominant condition affecting around 1 in 50,000 individuals. Epidemiological studies vary across different geographical regions, but the prevalence of HAE in the Chinese population remains unknown. HAE is characterised by recurrent episodes of non-pruritic angioedema, which most commonly affects the extremities, face, and bowels. The most feared manifestation is laryngeal oedema, which can be complicated by life-threatening asphyxiation[1]. Without treatment, angioedema typically lasts for 3-5 days. Psychologically, it can result in extreme anxiety and depression for patients and their families, cause significant embarrassment, limit work productivity, and pose devastating effects on the patients' quality of life[2]. Primarily due to the lack of awareness, HAE is often misdiagnosed or mistaken as allergy, "idiopathic" or "functional" conditions. Delay or misdiagnosis of this condition results in unnecessary investigations, intervention, and ineffective treatment. Early recognition of symptoms is paramount for early diagnosis, treatment, prevention, development of patient-centred action plans, and early family screening.

According to the World Allergy Organization/ European Academy of Allergy and Clinical Immunology guidelines, there are two major forms of hereditary angioedema; HAE type I due to a C1-INH deficiency and HAE type II due to a C1-INH dysfunction[1]. The diagnosis of HAE with a normal C1-INH level (sometimes referred to "type III") is extremely rare and should only be contemplated in exceptional cases such as the worldwide reported cases of rare mutations in factor XII, angiopoietin-1 gene and the plasminogen genes, etc. HAE type I and II are caused by different mutations on the SERPING[1] gene, which codes for C1-INH; C1-INH is a major serine protease inhibitor responsible for blocking proteases within the complement pathway, contact system and the fibrinolytic system[1]. Bradykinin is the primary mediator for angioedema resulting in increased vascular permeability and angioedema; precursors of bradykinin, such as kallikrein and factor XII, are normally inhibited by C1-INH. In patients with HAE, a deficiency in the C1-INH will result in the dysregulation of these pathways thus precipitating bradykinin-mediated angioedema.

APPROACH TO DIAGNOSIS

In clinical practice, a detailed history-taking can often help to delineate the aetiologies of angioedema (Fig. 1). More often, patients present with both wheals and angioedema, which points more towards a histamine-mediated type of angioedema – often caused by an IgE dependent or type I hypersensitivity reactions[3]. On the contrary, bradykinin-mediated angioedema is characterised by the lack of wheals, slower progression, longer duration, lack of pruritus, and failure to respond to antihistamines and steroids. A therapeutic trial of antihistamines is sometimes warranted to guide diagnosis in cases of unclear aetiology.

Bradykinin-mediated angioedema can be further classified into hereditary and acquired causes. Foremost, we should clarify whether the patient is taking angiotensin-converting enzyme inhibitors (ACEI), and if so, the medication should be withheld to observe for the resolution of symptoms. Complete cessation of further angioedema episodes may take weeks following cessation of ACEI. Older patients without a positive family history of angioedema should prompt the possibility of acquired C1-INH deficiency, and underlying diseases should be sought, especially B-cell lymphoproliferative disease and autoimmune diseases[4].

Complement C4 level, C1-INH antigen levels, and CI-INH functional levels can be measured to make the diagnosis of HAE. The C4 level is a good screening test for HAE and can, in 95% of the time, be depressed while the patient is asymptomatic[1]. The test sensitivity increases to more than 99.5% during an attack of HAE likely due to the formation of factor XIIf and its disinhibited activation of C1r, a subunit that cleaves C4, which in turn causes cleavage of C4.

The diagnosis of type I HAE can be confirmed with a low C1-INH level. If the C4 level and C1-INH level are both normal, but a diagnosis of HAE is highly suspected, we may proceed with a C1-INH functional level, which will be low in type II HAE. In acquired C1-INH deficiency, C1-INH levels will be low, but unlike type I HAE, measurement of the complement C1q subunit will be low. Sequencing of the SERPING1 gene can support the diagnostic workup of type I and II HAE and can be relevant in cases of mosaicism.

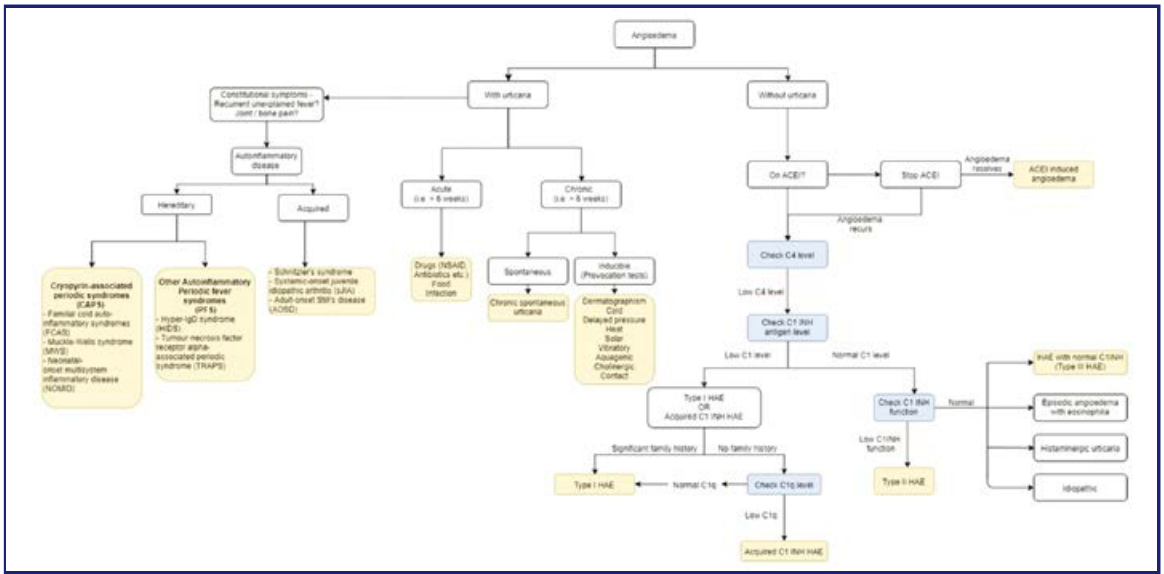

Fig 1: Suggested diagnostic algorithm for angioedema (Developed Dr Jane WONG & Dr Philip LI)

MANAGEMENT AND TREATMENT OF HAE

Treatment of HAE falls into two main categories - on-demand therapy and prophylactic treatment. Patient-centred treatment plans, or action plans, should be clearly explained to patients in anticipation of an acute attack. We recommend that all patients with HAE receive on-demand therapy to stop symptoms to rapidly prevent morbidity and mortality[5]. Treatment options for acute treatment include plasma-derived or recombinant C1-IN, icatibant, a β2 bradykinin receptor antagonist, and ecallantide, a plasma kallikrein inhibitor[6,7]. They have all been shown to be efficacious against HAE attacks, and choice among these options depends on the mode of administration, cost, convenience, safety profile, and availability of the drugs. Standard treatment against histaminergic angioedema, such as adrenaline, corticosteroids, and antihistamines are not useful in the treatment of HAE. Fresh frozen plasma should be used with caution as it may cause a paradoxical exacerbation of symptoms, likely related to the additional bradykinergic components in the pooled plasma, and should not be used if there are safer alternative medications.

It is also essential to educate patients to avoid triggers such as stress, physical trauma, alcohol, and medications, including ACEI and oestrogen-containing medications. Attenuated androgens and antifibrinolytic drugs are not shown to be efficacious for acute attacks of angioedema. If patients anticipate that there will be upcoming surgeries, or invasive medical or dental procedures, short term prophylaxis should be considered in high-risk patients. Treatment options include C1-INH replacement and attenuated androgens. Prophylaxis should be considered if the patient experiences frequent and severe attacks, and when on-demand therapy fails to improve the quality of life of HAE patients. Medications include the use of androgens, antifibrinolytics, kallikrein inhibitors, or C1-INH replacement, and use should be weighed against efficacy, costs, and side effects.

Family screening is recommended for all patients to screen for both symptomatic and asymptomatic individuals using a simple blood test checking the C4 level. In HAE type I and II, penetrance is high, but expressivity is variable, i.e., patients with diagnosed HAE may present with different symptom spectrums, severity, and frequency. Earlier diagnosis leads to more rapid recognition, avoiding unnecessary investigation and treatment. An accurate and timely diagnosis of HAE also translates to proper patient counselling and access to appropriate life-saving treatment

HAE IN HONG KONG

Due to a lack of awareness and deficiency of clinical immunology services, HAE had remained largely unheard of in Hong Kong until recent years. Despite repeated hospital admissions and life-threatening attacks, many patients remained undiagnosed (some for more than 60 years!), and there are still no registered medications available for HAE locally. However, much progress in the diagnosis and management of HAE in Hong Kong has been made in recent years.

Since the establishment of the territory's first public adult clinical immunology service at Queen Mary Hospital (QMH) in 2018, more than 35 genetically-confirmed HAE patients have now been identified. Facilities for C1-INH level, function, and genetic testing are now readily available. Prior to diagnosis, more than 20% of Hong Kong patients had a history of laryngeal attacks, and 64% of patients had been hospitalised (at least once) for acute angioedema attacks[8]. Since 2019, all HAE patients now have access to on-demand C1-INH replacement (registered on a named-patient basis) and personalised treatment plans. Applications for novel treatments such as bradykinin and kallikrein inhibitors are also underway. Furthermore, all potentially affected family members are actively invited for counselling and screening to identify asymptomatic or undiagnosed individuals.

To promote physician awareness, an approach to diagnosing HAE has been added as a chapter in the latest edition of the Hospital Authority's Handbook of Internal Medicine[9]. QMH has also been recognised as an "HAE Knowledgeable Hospital" by HAE International, and our Division has presented our findings of the first Chinese HAE registry at international conferences.

Hong Kong's first patient support group, "hae hk" (haehk.haei.org), was also formed in 2019 to create awareness, provide education to patients/families and gain access to treatments (Fig. 2). With the combined efforts of physicians, patients, family members and volunteers, it is hoped that more undiagnosed HAE patients can be identified and access to their much-deserved treatment and higher quality of life can be established.

Fig 2:Photo of the "hae hk" patient support group (Photo from HAE Group Collection)

References

1. W.R. Lumry, A.J. Castaldo, M.K. Vernon, M.B. Blaustein, D.A. Wilson, P.T.Horn. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression; Allergy Asthma Proc. 2010 Sep-Oct;31(5):407-14. doi: 10.2500/aap.2010.31.3394.
2. Maurer, M., Magerl, M., Ansotegui, I. et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. World Allergy Organ J 11, 5 (2018) doi:10.1186/s40413-017-0180-1
3. Zuraw, B. L., Bernstein, J. A., Lang, D. M., Craig, T., Dreyfus, D., Hsieh, F., ... Wallace, D. (2013). A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. Journal of Allergy and Clinical Immunology, 131(6). https://doi.org/10.1016/j.jaci.2013.03.034
4. Zuberbier, T, Aberer, W, Asero, R, et al. Endorsed by the following societies: AAAAI, AAD, AAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKI, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GA²LEN, IAACI, IADVL, JDA, NVvA, MSAI, ÖGDV, PSA, RAACI, SBD, SFD, SGAI, SGDV, SIAAIC, SIDeMaST, SPDV, TSD, UNBB, UNEV and WAO. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018; 73: 1393- 1414. https://doi.org/10.1111/all.13397
5. Cicardi, M., Bork, K., Caballero, T., Craig, T., Li, H.H., Longhurst, H., Reshef, A., Zuraw, B. and (2012), Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy, 67: 147-157. doi:10.1111/j.1398-9995.2011.02751.x
6. Craig, Timothy J. et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. Journal of Allergy and Clinical Immunology, Volume 124, Issue 4, 801 - 808
7. Riedl, Marc A et al. Recombinant human C1 esterase inhibitor for prophylaxis of hereditary angio-oedema: a phase 2, multicentre, randomised, double-blind, placebo-controlled crossover trial. The Lancet, Volume 390, Issue 10102, 1595 – 1602
8 P.H. Li, J. Wong, K. Lam, V. Chiang, E. Au. The first hereditary angioedema registry in Hong Kong Chinese. Poster session presented at: 2019 Focused Meeting of the European Society for Immunodeficiencies; 2019 Sep 18-21; Brussels, Belgium.
9. Hospital Authority (2019) Handbook of Internal Medicine 8th Edition.

SCUBA Diving: An Imaginary "Aquaman"

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Aquaman is a superhero in a Marvel movie. Aquaman, the human-born heir to the underwater kingdom of Atlantis, goes on a quest to prevent a war between the worlds of ocean and land.

In real life, we the human beings can only go underwater with a piece of equipment called SCUBA. SCUBA stands for Self-Contained Underwater Breathing Apparatus. It has been developed to enable man to stay underwater for a certain period of time, usually around 45-60 minutes. Air is compressed into a metal tank made of either steel or aluminium. Direct breathing of compressed air will damage the lungs (barotrauma), leading to pneumothorax. Pneumothorax underwater kills.

HOW CAN THE COMPRESSED AIR BE MADE SAFE TO BREATHE?

The purpose of a SCUBA diving regulator is to reduce the high-pressure in the air tank to a breathable ambient pressure on demand. Let's begin with some terminology and concepts.

First Stage: The first stage of a SCUBA diving regulator is the part of the regulator that attaches to the tank valve.

Second Stage: The second stage of a diving regulator is the part that the diver puts into his mouth.

The air inside a tank is compressed to a very high pressure to increase the air supply for a diver. A full SCUBA tank is often pressurised to 3,000 psi or 200 bars. Air pressure at sea level is 1 bar. The pressure surrounding the diver changes according to the depth of water. The genius design of the diving regulator is that the second stage automatically adjusts to the diver's depth and creates ambient pressure. This smart design allows man to enjoy and explore the wonders of the underwater world.

CERTIFICATION OF A SCUBA DIVER

A diver is certified when a person has completed a course of training as required by the agency issuing the card. The certificate card represents a defined level of skill and knowledge in underwater diving. The origin of the certification comes from a tragic accident in 1952 after two divers died while using university-owned equipment. Recreational certifications are issued by various agencies, such as NAUI and PADI.

WHAT IS SO GOOD ABOUT SCUBA DIVING?

Explore a New World

The ocean is a new world to land animals like us. Your eyes will access a whole new dimension filled with marine life and biodiversity. Bright coral reefs, flashy invertebrates, curious marine mammals like whales and an unbelievable array of colourful fishes. Diving brings you closer to nature, and it always gives you surprises.

Weightlessness

There are two ways to go weightlessness on earth. The first but expensive way is flying with the Zero-G plane, which is a modified Boeing 727 plane. You can experience zero gravity, flip and soar inside this special plane. The second choice is to go SCUBA diving. The feeling of weightlessness kicks in when one is descending into the deep blue sea. You would feel like you are flying in the sea, another dimension on earth. All the city noises are gone; you can only hear your breathing sound. All the chaos, troubles, and worries of everyday life vanish in those minutes underwater. The experience is tranquilising and addictive. Some divers would go straight into Zen mode.

Socialising and Making New Friends

When we are kids, we make new friends all the time. You meet people in a class, in church and even in sports competitions. When we grow up, meeting new people at times brings apprehension for some people. The buddy system in SCUBA diving provides a platform for making new friends or even having a buddy for life. Divers with different cultural backgrounds can share their own sea stories. There's always something interesting to share, such as finning over fantastic coral reef, watching big schools of fishes, drifting over the edges of dramatic drop-offs, diving in ancient wrecks, or exploring the incredible underwater landscape. But perhaps the best thing of all is sharing the adventure with like-minded friends, family, and buddies.

Redefine Your Limits

From time to time, we lose sight of a bigger picture of ourselves. We get caught up with our busy schedules, running errands, family stuff, etc. Sometimes, we forget we can live our lives outside these daily routines.

Sometimes we give too many excuses to ourselves, "I am not capable of", "I don't have time," "do it later," "I am afraid of trying new things," "I don't think I am good at," or even "I am too old for this". SCUBA diving can energise you by taking you out of your comfort zone. It provides you with a sense of accomplishment once you have mastered the skill. The deep-water exploration stretches your unthinkable area. Each dive is a new challenge that reshapes your limits.

Increase Your Confidence and Self-esteem

A return to the water after a break can give the diver a pre-dive apprehension. In order to tackle all the challenges underwater, a well-planned and well-executed dive is imperative to all divers. Keeping fit is an excellent way to improve confidence in dealing with any psychological or physical stress one may face during diving. Aerobic exercise program with regular cardiovascular boost-up training is of paramount importance. Having a good physique increases your self-esteem and confidence. This confidence can extrapolate your confidence in dealing with adversities in work and life.

In a nutshell, SCUBA diving brings many good things to your life. It is never too late to start reinventing yourself!

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			*NIL 1	*NIL 2	*NIL 3	*NIL 4
*NIL 5	*NIL 6	*NIL 7	*NIL 8	*NIL 9	*NIL 10	*NIL 11
*NIL 12	*NIL 13	*NIL 14	*NIL 15	*NIL 16	*NIL 17	*NIL 18
*NIL 19	*NIL 20	*NIL 21	*NIL 22	*NIL 23	*NIL 24	*NIL 25
*NIL 26	*NIL 27	*NIL 28	*NIL 29	*NIL 30		

Answers to Radiology Quiz

Answers:

1. Multiple bony outgrowths of sessile and pedunculated configurations are seen arising from metaphyseal regions of the long bones. They project away from the epiphysis. Broadening of the metaphysis, especially at right distal tibia is evident with mild ankle deformity. There are no aggressive bony features such as cortical destruction or large soft tissue component. No pathological fractures are evident.

2. - Hereditary multiple exostoses
   - Diaphyseal aclasis (due to association with broadening of the shaft at the end of long bones)
   - Osteochondromatosis

3. Autosomal dominant inheritance, with incomplete penetrance in females.

4. - Neurovascular impingement
   - Pathological fracture (especially pedunculated exostosis)
   - Bursitis
   - Deformity, limb-length discrepancy
   - Malignant transformation

5. The mnemonic "GLAD PAST" is useful for memorising features of malignant (sarcomatous) transformation:
   - G: Growth after skeletal maturity
   - L: Lucency (new)
   - A: Additional scintigraphic activity
   - D: Destruction (bony cortical)
   - P: Pain after puberty
   - A: and
   - S: Soft tissue mass
   - T: Thickened cartilage cap >1.5cm (detected on MRI)

6. - No further active management is required as osteochondromas on its own are benign
   - Regular follow-up is recommended to observe for complications as mentioned above, especially malignant transformation (with reported rates as high as 25%).

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*From a post-hoc analysis of the FOCUS trial, maintenance of sUA at <6.0mg/dL for 5 years led to overall stabilization of renal function as reflected in mean eGFR and sCr[1].

Reference :
1. *Whelton A*, et al. *J Clin Rheumatol*. 2011;17:7-13.

Abbreviated prescribing information of Feburic© film-coated tablets

Version: 005 PI version: Nov 2018 **Composition:** Febuxostat **Indications:** FEBURIC is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). FEBURIC 120 mg is also indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). FEBURIC is indicated in adults. **Dosage: Gout** 80 mg once daily, **TLS** 120mg once daily; start 2 days before the beginning of cytotoxic therapy and continue for a minimum of 7 days. **Administration:** May be taken by mouth w/o regard to food. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** *Cardio-vascular disorders Treatment of chronic hyperuricaemia* Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended. A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study. The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure. *Prevention and treatment of hyperuricaemia in patients at risk of TLS* Patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome treated with FEBURIC should be under cardiac monitoring as clinically appropriate. *Medicinal product allergy/hypersensitivity* Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some, but not all of these patients reported renal impairment and/or previous hypersensitivity to allopurinol. Severe hypersensitivity reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were associated with fever, haematological, renal or hepatic involvement in some cases. Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions. Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens-Johnson Syndrome, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/hypersensitivity reactions including Stevens-Johnson Syndrome and acute anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time. *Acute gouty attacks (gout flare)* Febuxostat treatment should not be started until an acute attack of gout has completely subsided. Gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended. If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares. *Xanthine deposition* In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This has not been observed in the pivotal clinical study with FEBURIC in the Tumor Lysis Syndrome. As there has been no experience with febuxostat, its use in patients with Lesch-Nyhan Syndrome is not recommended. *Mercaptopurine/azathioprine* Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine as inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity. No interaction studies have been performed in humans. Where the combination cannot be avoided, a reduction of the dose of mercaptopurine/azathioprine is recommended. Based on modelling and simulation analysis of data from a pre-clinical study in rats, when coadministered with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to the 20% or less of the previously prescribed dose in order to avoid possible haematological effects. The patients should be closely monitored and the dose of mercaptopurine/azathioprine should be subsequently adjusted based on the evaluation of the therapeutic response and the onset of eventual toxic effects. *Organ transplant recipients* As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended. *Theophylline* Co-administration of febuxostat 80 mg and theophylline 400 mg single dose in healthy subjects showed absence of any pharmacokinetic interaction. Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels. No data is available for febuxostat 120 mg. *Liver disorders* During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment. *Thyroid disorders* Increased TSH values (> 5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (5.5%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function. *Lactose* Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. **Undesirable effects:** *Summary of the safety profile* The most commonly reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg) and post-marketing experience in gout patients are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, have occurred in the post-marketing experience. *List of adverse reactions* Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000) adverse reactions occurring in patients treated with febuxostat are listed below. The frequencies are based on studies and post-marketing experience in gout patients. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Adverse reactions in combined phase 3, long-term extension studies and post-marketing experience in gout patients. **Blood and lymphatic system disorders:** Rare: Pancytopenia, thrombocytopenia, agranulocytosis*. **Immune system disorders:** Rare: Anaphylactic reaction*, drug hypersensitivity*. **Endocrine disorders:** Uncommon: Blood thyroid stimulating hormone increased. **Eye disorders:** Rare: Blurred vision. **Metabolism and nutrition disorders:** Common***: Gout flares. Uncommon: Diabetes mellitus, hyperlipidemia, decrease appetite, weight increase. Rare: Weight decrease, increase appetite, anorexia. **Psychiatric disorders:** Uncommon: Libido decreased, insomnia. Rare: Nervousness. **Nervous system disorders:** Common: Headache. Uncommon: Dizziness, paraesthesia, hemiparesis, somnolence, altered taste, hypoaesthesia, hyposmia. **Ear and labyrinth disorders:** Rare: Tinnitus. **Cardiac disorders:** Uncommon: Atrial fibrillation, palpitations, ECG abnormal, left bundle branch block (see section Tumor Lysis Syndrome), sinus tachycardia (see section Tumor Lysis Syndrome). **Vascular disorders:** Uncommon: Hypertension, flushing, hot flush, haemorrhage (see section Tumor Lysis Syndrome). **Respiratory system disorders:** Uncommon: Dyspnoea, bronchitis, upper respiratory tract infection, cough. **Gastrointestinal disorders:** Common: Diarrhoea**, nausea. Uncommon: Abdominal pain, abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort. Rare: Pancreatitis, mouth ulceration. **Hepato-biliary disorders:** Common: Liver function abnormalities**. Uncommon: Cholelithiasis. Rare: Hepatitis, jaundice*, liver injury*. **Skin and subcutaneous tissue disorders:** Common: Rash (including various types of rash reported with lower frequencies, see below). Uncommon: Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash popular. Rare: Toxic epidermal necrolysis*, Stevens-Johnson Syndrome*, angioedema*, drug reaction with eosinophilia and systemic symptoms*, generalized rash (serious)*, erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic*, rash erythematous, rash morbilliform, alopecia, hyperhidrosis. **Musculoskeletal and connective tissue disorders:** Uncommon: Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis. Rare: Rhabdomyolysis*, joint stiffness, musculoskeletal stiffness. **Renal and urinary disorders:** Uncommon: Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria. Rare: Tubulointerstitial nephritis*, micturition urgency. **Reproductive system and breast disorder:** Uncommon: Erectile dysfunction. **General disorders and administration site conditions:** Common: Oedema. Uncommon: Fatigue, chest pain, chest discomfort. Rare: Thirst. **Investigations:** Uncommon: Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase. Rare: Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase*. * Adverse reactions coming from post-marketing experience ** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine. *** See full prescribing information for incidences of gout flares in the individual Phase 3 randomized controlled studies. *Description of selected adverse reactions* Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome and Toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated to the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis). Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended. Tumor Lysis Syndrome *Summary of the safety profile* In the randomized, double-blind, Phase 3 pivotal FLORENCE (FLO-01) study comparing febuxostat with allopurinol (346 patients undergoing chemotherapy for haematologic malignancies and at intermediate-to-high risk of TLS), only 22 (6.4%) patients overall experienced adverse reactions, namely 11 (6.4%) patients in each treatment group. The majority of adverse reactions were either mild or moderate. Overall, the FLORENCE trial did not highlight any particular safety concern in addition to the previous experience with FEBURIC in gout, with the exception of the following three adverse reactions. Cardiac disorders:Uncommon: Left bundle branch block, sinus tachycardia. Vascular disorders: Uncommon: haemorrhage. **Full prescribing information is available upon request.**

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Benlysta (belimumab)
Subcutaneous Use 200 mg/mL

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The ONE & ONLY
approved biologic for SLE treatment
New autoinjector for your patients

When standard therapy is not enough, why not choose BENLYSTA?

- Superior disease activity reduction at week 52[1*†‡]
- Reduced risk of severe SLE flares over 52 weeks[1§]
- Reduction in cumulative steroid dose over weeks 52[2¶]
- Rate of adverse events were similar between BENLYSTA and placebo[1]
- Emerging evidence on organ damage progression[3#]
- Fewer patients experienced renal flares vs standard therapy alone in patients with baseline proteinuria >0.5g/24 hrs[1^]

Physicians should exercise caution when considering the use of BENLYSTA in patients with chronic infections or a history of recurrent infection. Live vaccines should not be given for 30 days before, or concurrently with BENLYSTA[1].

BENLYSTA (belimumab)

Integrated Safety Information

Contraindications:
· Hypersensitivity to the active substance (belimumab) or to any of the excipients of the captioned product.

Warnings and Precautions:
· Not recommended in patients with severe active central nervous system lupus, severe active lupus nephritis, HIV, history of/current hepatitis B or C, hypogammaglobulinaemia (IgG <400mg/dl) or IgA deficiency (IgA <10mg/dl) and patients with a history of major organ transplant or hematopoietic stem/cell/marrow transplant or renal transplant.
· Caution in patients receiving other B cell targeted therapy or cyclophosphamide.
· Administration of BENLYSTA may result in hypersensitivity reactions and infusion reactions which can be severe, and fatal. In the event of a severe reaction, BENLYSTA administration must be interrupted and appropriate medical therapy administered.
· Physicians should exercise caution when considering the use of BENLYSTA in patients with severe or chronic infections or a history of recurrent infection Patients who develop an infection while undergoing treatment with BENLYSTA should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including belimumab until the infection is resolved.
· Patients should be monitored for any of these new or worsening symptoms or signs suggestive of progressive multifocal leukoencephalopathy (PML), and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.
· Live vaccines should not be given for 30 days before, or concurrently with BENLYSTA
· Caution should be exercised when considering belimumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

The following adverse events have been reported with a frequency of –
Very common (≥1/10): Bacterial infections, e.g. bronchitis, cystitis, Diarrhoea, Nausea
Common (≥1/100 to <1/10): Gastroenteritis viral, Pharyngitis, Nasopharyngitis, Leucopenia, Hypersensitivity reactions, Depression, Insomnia, Migraine, Pain in extremity, Infusion-related reactions, Pyrexia

Abbreviated Prescribing Information

BENLYSTA is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). **Indication:** As add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy. **Dosage and Administration:** BENLYSTA treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. BENLYSTA Solution for injection Recommended dose is 200mg once weekly, administrated subcutaneously. Dosing is not based on weight. If a patient is being transitioned from BENLYSTA intravenous to subcutaneous administration, the first subcutaneous injection should be administrated 1 to 4 weeks after the last intravenous dose. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions. A patient may self-inject or the patient caregiver may administrate BENLYSTA after the healthcare professional determines that it is appropriate. BENLYSTA Powder for concentrate for infusion Administered intravenously by infusion; must be reconstituted and diluted before administration. BENLYSTA infusions should be administered by a qualified healthcare professional trained to give infusion therapy. Administration of BENLYSTA may result in severe or life-threatening hypersensitivity reactions and infusion reactions several hours after the infusion has been administered. BENLYSTA should be administered in an environment where resources for managing such reactions are immediately available. Patients should remain under clinical supervision for a prolonged period of time (for several hours), following at least the first 2 infusions, taking into account the possibility of a late onset reaction. BENLYSTA should be infused over a 1-hour period. BENLYSTA must not be administered as an intravenous bolus. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction. **Contraindications:** Hypersensitivity to active substance (belimumab) or any excipients. **Special warnings & Precautions:** Not recommended in patients with severe active central nervous system lupus, severe active lupus nephritis, HIV, history of/current hepatitis B or C, hypogammaglobulinaemia (IgG <400mg/dl) or IgA deficiency (IgA <10mg/dl) and patients with a history of major organ transplant or hematopoietic stem/cellmarrow transplant or renal transplant. Caution in patients receiving other B cell targeted therapy or cyclophosphamide and patients with a history of malignancy or who develop malignancy whilst receiving treatment. Administration of BENLYSTA may result in hypersensitivity reactions and infusion reactions which can be severe, and fatal. In the event of a severe reaction, BENLYSTA administration must be interrupted and appropriate medical therapy administered. Risk of hypersensitivity reactions is greatest with the first two infusions or with the first two subcutaneous injections; however the risk should be considered for every administration. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. Premedication including an antihistamine, with or without antipyretic, may be administered before infusion of BENLYSTA. There is insufficient knowledge to determine whether premedication could diminish the frequency or severity of infusion reactions. In clinical studies, serious infusion and hypersensitivity reactions affected approximately 0.9% of patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Infusion reactions occurred more frequently during the first two infusions and tended to decrease with subsequent infusions. Patients should be advised that hypersensitivity reactions are possible on the day of, or the day after infusion, and be informed of potential signs and symptoms and the possibility of recurrence. Patients should be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet should be provided to the patient each time BENLYSTA is administered. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema. The mechanism of action of BENLYSTA could increase the risk for the development of infections, including opportunistic infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including belimumab. Physicians should exercise caution when considering the use of BENLYSTA in patients with severe or chronic infections or a history of recurrent infection. Patients who develop an infection while undergoing treatment with BENLYSTA should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including belimumab until the infection is resolved. The risk of using BENLYSTA in patients with active or latent tuberculosis is unknown. Progressive multifocal leukoencephalopathy (PML) has been reported with BENLYSTA treatment for SLE. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded. Live vaccines should not be given for 30 days before, or concurrently with BENLYSTA, as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA. Because of its mechanism of action, belimumab may interfere with the response to immunisations. However, in a small study evaluating the response to a 23-valent pneumococcal vaccine, overall immune responses to the different serotypes were similar in SLE patients receiving BENLYSTA compared with those receiving standard immunosuppressive treatment at the time of vaccination. Limited data suggest that BENLYSTA does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of BENLYSTA. In a substudy, a small group of patients who had previously received either tetanus, pneumococcal or influenza vaccinations were found to maintain protective titres after treatment with BENLYSTA. Immunomodulatory medicinal products, including belimumab, may increase the risk of malignancy. Caution should be exercised when considering belimumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. Patients with malignant neoplasm within the last 5 years have not been studied, with the exception of those with basal or squamous cell cancers of the skin, or cancer of the uterine cervix, that has been fully excised or adequately treated. **Interactions**: No interaction studies have been performed. **Pregnancy and lactation**: Limited data on use in pregnant women. Not to be used unless the potential benefit justifies the potential risk to the foetus. Not known whether BENLYSTA is excreted in human milk or absorbed after ingestion. Maternal IgG is secreted in breast milk so recommended to either discontinue BENLYSTA or breast feeding, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. **Undesirable effects**: See PI for full details. Very common: Bacterial infections, e.g. bronchitis, cystitis, urinary tract infection, Diarrhoea, Nausea. Common: Gastroenteritis viral, Pharyngitis, Nasopharyngitis, Viral upper respiratory tract infection, Leucopenia, Hypersensitivity reactions, Depression, Insomnia, Migraine, Injection site reactions, Pain in extremity, Infusion or injection related systemic reactions, Pyrexia. Uncommon: Anaphylactic reaction, Suicidal ideation, Suicidal behavior, Angioedema, Urticaria, Rash. Rare: Delayed-type, non-acute hypersensitivity reactions. **Overdose**: Limited clinical experience with overdose of BENLYSTA. In case of inadvertent overdose, patients should be carefully observed and supportive care administered, as appropriate. Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Abbreviated Prescribing Information based on PI version: BENLYSTA for infusion -GDS13v2/EMA2016091S and BENLYSTA for injection – GDS15/EMEA/H/C/002015/II/0065.

References: 1. Benlysta SC Prescribing Information version GDS15v5. **2.** Zhang F, Bae SC, Bass D, et al. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. Ann Rheum Dis. 2018;77:355-63. **3.** Urowitz MB, Ohsfeldt RL, Wielage RC, et al. Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis. Ann Rheum Dis. 2019;78(3):372-9. **4.** Stohl W, Schwarting A, Okada M, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. Arthritis Rheumatol. 2017;69(5):1016-27.

Remarks: * Defined as positive anti-dsDNA (-30 IU/mL) and low C3 and/or C4 complement. † Standard therapies permitted, alone or in combination: corticosteroids, immunosuppressants, antimalarials, and NSAIDs. ‡ SRI4 improvement at Week 52: 61.4% vs 48.4% (p=0.0006). § 10.6% of patients on BENLYSTA + standard therapy vs 18.2% of patients on placebo + standard therapy had a severe flare over 52 weeks (p<0.0061). ¶ cumulative prednisone dose (or equivalent) over 52 weeks was significantly lower in the BENLYSTA group (4758.1mg) versus placebo (4190.0mg) (P=0.0005). # Patients receiving BENLYSTA were 61% less likely to progress to a higher SDI score over any given year of follow-up compared with patients treated with SoC (HR 0.391; 95% CI 0.253 to 0.605; p<0.001). ^ Fewer patients with baseline proteinuria >0.5 gm/24 hours in the BENLYSTA group (11 of 99) had a renal flare compared with those in the placebo group (13 of 48) (11.1% vs 27.1%; HR 0.40 [95% CI 0.18–0.90]; P=0.0272).

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