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The 1st monthly SC anti-TNF designed with patients in mind

Monthly dosing for best-in-class comfort and tolerability

- Formulated for best-in-class comfort1,2,3

<table>
<thead>
<tr>
<th></th>
<th>Etanercept 50mg</th>
<th>Pre-filled syringe 25mg</th>
<th>Adalimumab 40mg</th>
<th>Monthly Simponi 50mg</th>
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</thead>
<tbody>
<tr>
<td>Citric acid-free formulation</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Low injection volume (≤0.5 ml)</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Number of injections per year</td>
<td>52</td>
<td>104</td>
<td>26</td>
<td>12</td>
</tr>
</tbody>
</table>

Tolerability

- Low level of injection site reactions (ISPs) including pain1,2,3

<table>
<thead>
<tr>
<th></th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Monthly Simponi Simponi 50mg and 100 mg doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9%</td>
<td>8%</td>
<td>2.2%</td>
</tr>
<tr>
<td>SC biologic</td>
<td>36%</td>
<td>14%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

Data taken from latest available SmPCs; not necessarily comparable

- Low discontinuation rate4
  - 2.2% patients on Simponi 50mg monthly + MTX discontinued therapy due to adverse events vs. 4.5% on placebo + MTX

References:
During the past decade, the debut of "biological agents" has transformed the practice of rheumatology. The use of these drugs has significantly improved the outcomes of patients with rheumatoid arthritis (RA). As a result, physicians are seeing fewer and fewer RA joint deformities nowadays. Although the true disease-modifying effects of biological agents in spondyloarthropathy (SpA) have not been well established, these drugs are effective in improving SpA patients’ quality of life, by significantly reducing their symptoms. Many new treatments for lupus have fallen short of expectations in clinical studies; however, belimumab recently met its primary endpoint in phase 3 trials and it has been approved for treating lupus. Major advances in the treatment of gout have also been made over the past few years, in terms of wider choices of therapeutic agents and treatment recommendations that are more evidence-based. We hope that you enjoy reading the articles of this issue, which have been prepared by a group of young and aspiring rheumatologists in Hong Kong.

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Gout is one of the most common rheumatic diseases in adults, affecting an estimated 6.1 million people in the United States of America (US). Over the last few decades, the prevalence of gout in many countries has risen, due to population aging, dietary changes, widespread prescription of diuretics for cardiovascular disease, and increased prevalence of comorbidities that promote hyperuricaemia, such as hypertension, obesity, type 2 diabetes mellitus, and chronic kidney disease.

Gout is associated with hyperuricaemia, which is defined as serum urate level >404 µmol/L – the limit of urate solubility at physiological temperature and pH. However, hyperuricaemia is not sufficient to cause gout. In one cohort, gout developed in 22% of subjects with urate concentrations >535 µmol/L during a 5-year period.¹

**Primary Principles of Management**

The approach to management of all gout cases should include patient education about the disease and its treatments, and initiation of diet and lifestyle modifications. The clinician should identify potential serum urate-elevating medications, such as thiazide and loop diuretics. Although low-dose aspirin (≤325 mg/day) elevates serum urate, most patients will have to continue taking it for cardiovascular disease prophylaxis. Clinicians should also consider causes of hyperuricaemia for all gout patients, and conduct an appropriate comorbidity checkup, such as urinalysis, renal ultrasound, and complete blood count, and blood chemistry. Urine uric acid measurement is useful to identify uric acid overproduction in gout patients with onset before age 25 years, or with a history of urolithiasis.

**Treat to serum urate target**

Target serum urate level should be lowered sufficiently to durably improve signs and symptoms of gout. The minimum serum uric acid concentration target for a gout patient is 356 µmol/L (6 mg/dL). Serum urate lowering below 297 µmol/L (5 mg/dL) may be needed in some patients, for example, patients with tophaceous gout.

**General health, diet, and lifestyle measures**

Although certain diet and lifestyle measures have been advocated to

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**Table 1. General health, diet, and lifestyle measures for gout patients**¹

<table>
<thead>
<tr>
<th>Avoid</th>
<th>Limit</th>
<th>Encourage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ meats high in purine content (eg, liver, kidney, sweetbread)</td>
<td>Serving sizes of:</td>
<td>• Low-fat or non-fat dairy products</td>
</tr>
<tr>
<td></td>
<td>• Beef, lamb, pork</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Seafood with high purine content (eg, sardines, shellfish)</td>
<td></td>
</tr>
<tr>
<td>Soft drinks, other beverages or food sweetened with high-fructose</td>
<td>• Servings of naturally sweet fruit juices</td>
<td>• Vegetables</td>
</tr>
<tr>
<td>corn syrup</td>
<td>• Table sugar and sweetened beverages and desserts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Table salt, including in sauces and gravies</td>
<td></td>
</tr>
<tr>
<td>Alcohol overuse (defined as &gt;2 servings per day for a male and 1</td>
<td>• Alcohol (particularly beer, but also wine and spirits)</td>
<td></td>
</tr>
<tr>
<td>serving per day for a female) in all gout patients</td>
<td>in all gout patients</td>
<td></td>
</tr>
<tr>
<td>Any alcohol use in gout during periods of frequent gout attacks,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or advanced gout under poor control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
decrease the frequency of acute gout attacks and to lower serum urate levels, the emphasis of non-pharmacological management of gout should be on diet and lifestyle choices for promoting and maintaining ideal health and optimal management of serious comorbidities, including coronary heart disease, diabetes, hyperlipidaemia, and hypertension.

The American College of Rheumatology (ACR) has grouped dietary recommendations for gout into three simple qualitative categories, termed “avoid”, “limit”, or “encourage” (Table 1). Gout patients should be advised to limit consumption of purine-rich meat and seafood as well as sweetened soft drinks. Consumption of low-fat or non-fat dairy products and vegetables is to be encouraged. Consumption of alcohol (particularly beer, but also wine and spirits) should be reduced and alcohol overuse is to be avoided in all gout patients.2

Nevertheless, it is recognised that diet and lifestyle measures alone provide therapeutically-insufficient serum urate lowering effects for a large proportion of gout patients. Some clinical trials have demonstrated that diet and lifestyle modifications decrease serum urate by 10% to 18%.3

**Management of Acute Gout Attack**

Patients with a history of gout may be instructed to start treatment upon signs and symptoms of an acute gout attack (Table 2). Medications for treatment of acute gouty arthritis should be preferentially initiated within 24 hours of onset of symptoms, because early treatment leads to better patient-reported outcomes. Established urate-lowering drugs should be continued without interruption during an acute gout attack.

For mild to moderately-severe acute gout, monotherapy with oral nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, or oral colchicine are all acceptable treatment options (Table 2). The choice of the most appropriate medication should be based on the patient’s preference, prior response to pharmacologic therapy, and associated comorbidities.

**NSAIDs**

While the US Food and Drug Administration (FDA) has approved naproxen, indomethacin, and sulindac for the treatment of gout, other NSAIDs may be similarly effective. Randomised trials also support the efficacy of etoricoxib and high-dose celecoxib for acute gout.

**Colchicine**

Oral colchicine is also effective if it is initiated within 36 hours of symptoms onset. Colchicine at a dose of 1.2 mg at the onset of a flare, followed by 0.6 mg 1 hour later, has similar efficacy to that of a high-dose regimen, but with fewer gastrointestinal side effects. The use of colchicine is limited by the requirement for dose-reduction in patients with chronic kidney disease, and drug interactions with medications, for example, clarithromycin erythromycin, and cyclosporine.

**Corticosteroid**

Intra-articular corticosteroid is an effective treatment for acute gout of one or two large joints. Oral prednisolone at 0.5 mg/kg per day is an acceptable acute gout treatment for patients who cannot tolerate NSAIDs or colchicine. The oral steroid can be discontinued after the first 5–10 days.

**Initial combination therapy**

For patients with a severe gout attack or polyarticular involvement, the initial simultaneous use of two pharmacological modalities can be considered. Recommended combinations include colchicine and NSAIDs, oral prednisolone and colchicine, and intra-articular steroid with any of the other modalities. Combining NSAIDs and systemic corticosteroids should be avoided because of increased gastrointestinal adverse effects.

**Pharmacological Urate-Lowering Therapy**

Indications for pharmacological urate-lowering treatment include presence of tophus, urolithiasis, chronic kidney disease and frequent acute gout attacks. Xanthine oxidase inhibitors, uricosuric agents and uricase agents are approved for lowering the urate level. Xanthine oxidase inhibitors, either allopurinol or febuxostat, are the recommended first-line approach (Table 2).

**Allopurinol**

The starting dose should be ±100 mg/day, to be gradually titrated upwards every 2–5 weeks to the appropriate maintenance dose in order to achieve the target serum urate level (<356 μmol/L). The maintenance dose of allopurinol may be raised.

### Table 2. Management of gout

- Patient education on diet and lifestyle measures
- Management of comorbidities, for example, hypertension, diabetes mellitus, hyperlipidaemia
- Acute gout attack should be treated with NSAID (or COX2 inhibitors), colchicine, or corticosteroid within 24 hours of onset
- Anti-inflammatory prophylaxis is recommended for all gout patients when urate-lowering therapy is commenced
- Oral colchicine or low-dose NSAID are appropriate gout prophylactic treatments. Dose adjustment is needed in patients with comorbidity, for example, chronic kidney disease
- Long-term urate-lowering therapy is indicated for gout patients with tophus, urolithiasis, chronic kidney disease, or frequent acute gout attacks
- A xanthine oxidase inhibitor with either allopurinol or febuxostat is the recommended first-line urate-lowering therapy in gout
- A combination of one xanthine oxidase inhibitor and one uricosuric agent is appropriate when serum urate target cannot be achieved by xanthine oxidase inhibitor monotherapy
- Target serum urate level for gout management is <356 μmol/L
The first new Urate-lowering gout drug for 40 years

A novel non-purine, selective xanthine oxidase inhibitor

Significantly superior to allopurinol 300 mg in lowering serum uric acid level

83% reduction in tophus area by week 52

References:

FEBURIC® (Febuxostat) Prescribing Information

Indications: Treatment of chronic hyperuricemia in conditions where urate deposition has already occurred (including a history, or presence of tophus and/or gouty arthritis). Dosage and administration: The recommended oral dose of FEBURIC is 80 mg once daily, regardless of food. Gout flare prophylaxis of at least 6 months is recommended. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Warnings and precautions: Patients with cardio-vascular disorders, acute gouty attacks, xanthine deposition, thyroid disorder, galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption and who are concomitantly treated with mercaptopurine, azathioprine and theophylline. Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgement. Un desirable effects: The most commonly reported ADRs are liver function abnormalities (3.5%), diarrhea (2.7%), headache (1.8%), nausea (1.7%), rash (1.5%). Full prescribing information is available upon request.

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above 300 mg/day, even in patients with renal impairment, provided there is regular monitoring for drug hypersensitivity and other adverse effects. The ACR has made a novel recommendation of testing HLA-B*5801 in subpopulations at high risk of severe allopurinol hypersensitivity, including patients of Han Chinese and Thai ethnicity (Table 3).

**Febuxostat**

Febuxostat is an alternative xanthine oxidase inhibitor that can be used as first-line urate-lowering therapy. In a 52-week trial, febuxostat at daily doses of 80 mg and 120 mg was 2.5 and 3.0 times respectively more likely than a daily dose of 300 mg of allopurinol to achieve serum level target.\(^4\) Daily 40–80 mg febuxostat is superior to 300 mg/day allopurinol for lowering serum urate level below target in patients with mild to moderate renal function impairment.\(^5\) However, published safety data on febuxostat in stage 4 chronic kidney disease or worse is lacking. Safety of febuxostat in persons with allopurinol hypersensitivity is unknown.

**Uricosuric therapy**

Probenecid is the recommended uricosuric agent for urate-lowering monotherapy. It is indicated in patients who cannot tolerate xanthine oxidase inhibitor. However, probenecid is not recommended for patients with creatinine clearance <59 mL/minute. Elevated urinary uric acid and history of urolithiasis contraindicate uricosuric therapy.

**Combination therapy**

The role of combination therapy with a xanthine oxidase inhibitor and a uricosuric drug has not been well studied in randomised trials. Combination therapy may be considered a second-line approach in refractory gout. Apart from probenecid, other medications with less marked uricosuric effect, such as losartan, may be considered.\(^2\)

**Uricase**

Uricase converts uric acid into the soluble purine degradation product, allantoin. Pegloticase, a porcine uricase, has demonstrated efficacy in randomised trials in lowering serum urate level in patients with chronic gout that is refractory to conventional treatment. Pegloticase should only be used under specialist supervision for patients with severe gout burden that is refractory to oral urate-lowering drugs. The duration of treatment of uricase is not well defined.

**Prophylaxis of Acute Gout**

Acute gout attack is a frequent complication of urate-lowering therapy. Prophylactic anti-inflammatory medication should be given when urate-lowering therapy is initiated. Low dose oral colchicine (0.5 mg once or twice daily) is a safe and effective prophylaxis. However, the dose has to be adjusted in patients with renal function impairment. Alternatively, low dose NSAID (such as naproxen 250 mg twice daily) with proton pump inhibitor (where indicated) can be used as prophylaxis. In patients with intolerance or contraindication to both colchicine and NSAID, low dose prednisolone (≤10 mg/day) is the second-line choice of gout prophylaxis. In view of the known risks of prolonged corticosteroid use, clinicians should evaluate the risk/benefit ratio of steroid prophylaxis frequently and adjust the treatment regimen accordingly.\(^6\)

Acute gout prophylaxis should be continued for as long as there is evidence of continued gout disease activity (such as presence of tophus, recent acute gout attacks, or chronic gout arthritis), and/or the serum urate target (<356 µmol/L) has not yet been achieved. It has been recommended that the duration of acute gout prophylaxis should be at least 6 months, or 3 months after achieving target serum urate level. Anti-inflammatory gout prophylaxis should be continued for at least 6 months after achieving target serum urate in a patient who has had resolved tophi.

**Summary**

There is some evidence that the prevalence of gout is increasing. All gout patients should receive education about diet and lifestyle modifications to decrease their risk of acute gout attacks and lower their serum urate level. Acute gout can usually be managed with NSAID, colchicine, or corticosteroid, supplemented with topical ice. All patients planning for long-term uric-acid-lowering therapy, should receive adequate anti-inflammatory prophylaxis for acute gout. Low dose colchicine or low dose NSAID are the preferred choices for most patients. Xanthine oxidase inhibitors, such as allopurinol and febuxostat, are the recommended first-line urate-lowering therapy. The starting dose of allopurinol should be 100 mg/day or less, gradually titrated upwards. The target serum urate level for urate-lowering therapy is <356 µmol/L.

**Table 3. Use of allopurinol in gout**

- Starting dose should be <100 mg/day for any patient, and <50 mg/day in patients with chronic kidney disease.
- Gradually titrate dose upwards every 2–5 weeks to appropriate maximum dose.
- Target serum urate level is <356 µmol/L.
- Dose can be raised to >300 mg/day, even with renal impairment, provided that the clinician monitors the clinical response and adverse reactions closely. Consider checking HLA-B*5801 in selected patients at risk of severe allopurinol hypersensitivity, including Han Chinese and Thai ancestry.

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References

Update on Novel Therapies for Systemic Lupus Erythematosus

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Key words:  
SLE (系統性紅斑狼瘡), treatment (治療), biological (生物製劑), B-cells (B細胞)

Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease that mainly affects women of childbearing age; it is more prevalent in certain ethnic groups such as Asians, Africans and Hispanics. Despite improvements in the medical care and survival of SLE patients, the disease still causes significant morbidity and mortality, due to disease manifestations affecting major organs and treatment-related complications/toxicity. While this chronic and disabling disease remains incurable, researchers are pursuing more efficacious therapies with fewer adverse effects by modifying conventional regimens and developing new targeted therapies.

In the past two decades, the United States (US) Food and Drug Administration approved only three drugs for treating SLE, namely corticosteroids, hydroxychloroquine and aspirin. There remain unmet needs for the development of alternative therapies that are safer and more effective and might induce long-lasting remission in SLE patients. Thanks to advances in basic science and biotechnology, several targeted therapies for SLE have been developed during the past few years.

Conventional Therapies

The choice of SLE therapy depends on the organs involved. Moreover, a number of factors have to be considered in the treatment plan; these include disease severity, reversibility of the manifestations, underlying pathology, presence of medical comorbidities, and expected tolerability and adverse effects of the therapies.

Skin and joint disease are the most common manifestations of SLE; arthritis is the cardinal feature. In Hong Kong, 82% of patients with SLE present with arthritis or arthralgia at disease onset; however, only a minority develop joint erosion. Mild arthritis usually responds to non-steroidal anti-inflammatory drugs (NSAIDs). Some anti-malarial agents are also effective drugs for arthritis, and corticosteroids may be necessary in serious cases. For treating persistently-active lupus arthritis, methotrexate and other disease-modifying antirheumatic drugs used for rheumatoid arthritis may be necessary.

Mucocutaneous manifestations are also commonly encountered in SLE; 61% of patients have facial rash at presentation. Since ultraviolet light may trigger cutaneous lupus, preventive measures such as sunscreens are mandatory. Skin lesions of SLE commonly respond to topical corticosteroids and anti-malarials. In patients with refractory lupus skin disease, other medications such as dapsone, thalidomide and mycophenolate mofetil (MMF) may be considered.

Systemic corticosteroids and other immunosuppressive drugs are indicated for major-organ diseases of SLE, such as glomerulonephritis and neuropsychiatric disease. Renal involvement is one of the most serious manifestations. Milder forms of lupus nephritis can be managed with corticosteroids, in combination with azathioprine (AZA) as a corticosteroid-sparing agent. More serious lupus nephritis requires more intensive regimens that consist of corticosteroids and cyclophosphamide (CYC), MMF or the calcineurin inhibitors. CYC has long been used to treat severe organ manifestations of SLE including nephritis. MMF is the pro-drug of mycophenolic acid and is a selective and reversible inhibitor of inosine monophosphate dehydrogenase, which is the rate-limiting enzyme in the de novo synthesis of guanosine nucleotides that are essential for DNA polymerase activity and DNA production. A pilot randomised controlled trial and subsequent larger-scale multi-center randomised controlled trials conducted in the US confirmed similar efficacy of MMF compared with intravenous pulsed CYC for induction therapy of lupus nephritis. MMF is associated with less toxicity to the ovaries, which is important for patients of reproductive age. MMF is now the preferred...
first-line treatment for induction and maintenance therapy of lupus nephritis. AZA and cyclosporine A are alternative options for patients who are intolerant to MMF or plan to become pregnant.

Neuropsychiatric manifestations of SLE are more heterogeneous than renal disease. The American College of Rheumatology has defined 19 neuropsychiatric syndromes in SLE. Some manifestations, such as seizure, headache, anxiety, depression, can be treated with symptomatic treatment alone. However, more serious manifestations such as acute confusional state, psychosis, myelitis, optic neuritis, neuropathies and myasthenia gravis warrant more aggressive immunosuppressive therapy. Most rheumatologists use a combination of high-dose corticosteroids and an extended course of intravenous pulsed CYC. A recent randomised controlled trial demonstrated that intravenous pulsed CYC is more effective than pulsed methylprednisolone in treating severe neuropsychiatric SLE. Prednisolone combined with sequential daily oral CYC and AZA has also been used with success in lupus psychosis. For patients who are intolerant or refractory to conventional therapies, there have been anecdotal reports of success with other modalities such as intravenous immunoglobulin, rituximab, immunoadsorption, MMF, cyclosporine A and non-myeloablative CYC.

**B-cell Depletion Therapies**

B-cells may play important roles in the pathogenesis of autoimmune diseases through antigen presentation to T-cells, regulation of autoreactive T-cells, and the production of pro-inflammatory cytokines, immunoglobulins and autoantibodies. As B-cell hyperactivity is one of the major pathophysiological mechanisms of SLE, B-cell depletion has been studied as a therapeutic target.

Rituximab is a chimeric monoclonal antibody specific to the CD20 surface molecule on precursor and mature B-cells. Open-label series have reported efficacy of rituximab in various refractory SLE manifestations that include renal, haematological and neuropsychiatric disease, in both adult and paediatric patients. However, two recent randomised controlled trials, the EXPLORER and the LUNAR studies, did not confirm the efficacy of B-cell depletion in extra-renal and renal SLE. Ocrelizumab is a fully-humanised anti-CD20 monoclonal antibody with a similar action to rituximab. Despite favorable preliminary data, ocrelizumab studies were called-off because of the high incidence of severe infective complications reported in the trials, especially among Asian patients.

B-lymphocyte stimulator (BlyS) is an essential factor for B-cell survival and development. Belimumab is a fully-humanised monoclonal antibody against BlyS. A randomised trial showed belimumab to be effective in further reducing SLE disease activity on top of standard care, and delaying the time to lupus flares. It should be noted that BlyS blockade is not indicated in serious active lupus nephritis and neuropsychiatric manifestations. Anti-BlyS agents are not recommended in combination with CYC and other biological agents.

**Other Biological Therapies**

Blockade of co-stimulation of T-cells has been studied. Abatacept (CTLA4-Ig) inhibits this co-stimulatory pathway and has been shown to reduce auto-antibody production, ameliorate glomerulonephritis and prolong survival in murine lupus. A combination of CYC and abatacept was more effective than either agent alone in treating murine lupus nephritis. A study of abatacept in patients with non-life-threatening SLE manifestations suggested some clinical efficacy such as fatigue and physician-assessed flare, but the primary/secondary endpoints were not met. Atacicept (TACI-Ig), which blocks the activity of BlyS and APRIL (a proliferation-inducing ligand), is undergoing clinical evaluation in B-cell-mediated diseases including SLE. Anti-cytokine therapies, such as anti-interleukin-10, anti-interleukin-6 and anti-tumour necrosis factor, may play a role in the pathogenesis of SLE by stimulating autoantibody production. The clinical effect of these agents on SLE remains unconfirmed.

**Stem Cell Transplantation**

Although targeted SLE therapies are emerging, their long-term efficacy remains unclear. Curative therapy remains the ultimate management goal in autoimmune diseases. In the past decade, autologous haematopoietic stem cell transplantation has been studied in refractory and life-threatening SLE manifestations, with the aim at overcoming treatment resistance by intensifying the dosage of CYC, and eradicating autoreactive cells and dysregulated immune circuits.

**Preventing Complications**

Judicious use of glucocorticoids and preventing and managing cardiovascular risk factors and osteoporosis are equally important to minimising complications during SLE treatment. Vaccinations against common infections such as influenza, pneumococcus and human papilloma virus are safe and recommended. It is hoped that medical advances and emerging new agents will help lupus patients to survive even longer, and with better quality of life, in the future.

**Conclusion**

The treatment of SLE has undergone a major revolution in the past decade. The emergence of newer immunosuppressive agents, such as MMF, has helped to reduce treatment-related toxicities. Novel biological agents such as belimumab and epratuzumab have also been shown to provide additional clinical benefit on top of standard SLE therapies. These agents are important options for SLE patients with persistently-active disease manifestations despite conventional therapies. Data regarding the efficacy of the novel biological agents in SLE are eagerly awaited.

A complete list of references can be downloaded from www.SOPHYSICIANSHK.org
Spondyloarthritis (SpA) is a recently-introduced term to describe a group of chronic rheumatic diseases that are characterised by inflammation of axial and peripheral joints and associated with the human leucocyte antigen B27 (HLA-B27) and extra-articular features. SpA comprises ankylosing spondylitis (AS), axial psoriatic arthritis (PsA), SpA associated with inflammatory bowel disease and reactive arthritis. AS represents the advanced stage of the disease and is considered to be the prototype. Despite differences between these subtypes, their clinical features overlap and treatment responses are similar.

**Physical Therapy**

Physical therapy remains the cornerstone of SpA treatment. In order to obtain the greatest benefit, physicians should control the disease activity before starting appropriate exercise programs. Studies have shown that exercise programs can improve spinal mobility/flexibility,\(^1\)\(^{-}\)\(^5\) cardiorespiratory fitness,\(^6\)\(^{-}\)\(^8\) and endurance.\(^8\)

Although two clinical trials reported deterioration of cardiorespiratory fitness in unsupervised AS patients, SpA patients should be encouraged to take regular exercise throughout their lives.

**Axial Spondyloarthritis**

The traditional treatment goals for SpA are to improve spinal mobility, preserve functional status, and reduce pain and stiffness. Advances in SpA imaging have enabled accurate detection of spinal inflammation and structural changes; therefore, suppressing spinal inflammation and preventing syndesmophytes formation/ankylosis have become the new management goals. Unlike rheumatoid arthritis (RA), conventional disease modifying antirheumatic drugs (DMARDs) have no proven value for axial manifestations of SpA.\(^9\)\(^{-}\)\(^{12}\) TNF-\(\alpha\) blocking agents (without anchoring agent) are effective in improving spondylitis symptoms, and suppressing spinal inflammation on magnetic resonance imaging (MRI).\(^{11,13}\)\(^{-}\)\(^{15}\) In our territory, infliximab, etanercept, adalimumab and golimumab are the TNF-\(\alpha\) blockers available for SpA treatment. Despite their effectiveness, no data has demonstrated that TNF-\(\alpha\) blockers have structural modifying effects in axial disease,\(^{16,17}\) and it remains uncertain whether their use prior to any structural damage can prevent future ankylosis. Furthermore, this treatment carries significant risks including serious systemic infection. Careful screening and monitoring before and during treatment are necessary.

Intra-articular corticosteroid injection
into the sacroiliac joints is another effective treatment for axial SpA. A study showed the treatment to be effective in relieving symptoms as well as reducing inflammation on MRI. In contrast, systemic oral steroids have failed to demonstrate any long-term efficacy on axial disease control.

Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (COX-2) selective inhibitors have been shown to be effective in relieving symptoms. In addition, NSAIDs are also used to differentiate between inflammatory back pain and back pain due to other causes. Studies have shown that both NSAIDs and COX-2 inhibitors can retard the radiological progression of spinal disease when prescribed continuously, and they are considered to be potentially disease-modifying.

Other drugs that have been studied in axial SpA include thalidomide and pamidronate; however, their effectiveness is controversial. In addition, the toxicity of thalidomide makes it unsuitable for widespread use.

Peripheral Spondyloarthritis

Similar to RA, NSAIDs are considered to be useful as symptom-modifying treatment. In general, conventional DMARDs have limited efficacy for peripheral manifestations. Unlike RA, methotrexate (MTX) has no demonstrable effect on peripheral arthritis in SpA. Sulphasalazine (SSZ) is the only DMARD that has been shown to be effective, and should be considered as the first-line DMARD for peripheral arthritis in SpA patients. In PsA, DMARDs including SSZ, MTX, leflunomide, ciclosporin and azathioprine have been shown to have some effect, albeit small, on peripheral arthritis.

Similar to axial disease, TNF-α blocking agents have shown promising effects in treating peripheral joint disease. Ustekinumab and abatacept have also been shown to be effective in the management of PsA. The Assessment of SpondyloArthritis international Society recommends using TNF-α blocking agents in patients with refractory disease (ie, failed at least two NSAIDs; failed SSZ; and failed local steroid injections).

Surgical Intervention

Hip replacement surgery is indicated in 5% of all AS patients and is associated with good long-term outcomes. Spinal fusion is indicated for spinal instability with pain and neurological involvement. Atlanto-axial, atlanto-occipital and spinal stenosis are other indications for surgical intervention.

Extra-rheumatic Manifestation

Extra-rheumatic manifestations of SpA including anterior uveitis, aortic regurgitation, upper lobe pulmonary fibrosis and others, are managed conventionally. Infliximab and adalimumab could be used to treat inflammatory bowel disease. Recurrent uveitis can be treated with SSZ, infliximab and etanercept.

Enthesitis

Options in the treatment of enthesitis are limited. NSAIDs, steroid injection and physiotherapy play major roles in treatment. TNF-α blocking agents have been shown effective in treating enthesitis, as well as dactylitis.

Early Diagnosis and Management

The current concept of SpA management is for early-stage diagnosis and treatment. Starting physical exercise at an earlier stage can potentially improve spinal mobility. SpA patients should be encouraged to stop smoking at the earliest stage, as a recent study showed that smokers have higher rates of both spinal inflammation and structural changes. Early use of NSAIDs also yields better disease-modifying effects. Although it remains unclear whether early use of TNF-α blocking agents can retard spinal radiological progression, early and adequate suppression of inflammation may be essential as studies have shown persistent inflammation in SpA to be associated with cardiovascular morbidity.

Conclusion

SpA presents in a spectrum of manifestations, which requires rheumatologists to treat on an individualised basis. Frequent evaluation and monitoring of both disease and its treatments is necessary to obtain the best outcomes.

References:

Introduction
In the past, patients with rheumatoid arthritis (RA) had few treatment options and the treatment strategy tended to be conservative. Consequent inadequately-controlled disease activity led to joint damage and disability, and considerably impaired quality of life for RA patients.

Over the last two decades, there have been major advances in the management of RA. In particular, the emergence of biological therapies has revolutionised the goals of treatment. Rheumatologists now aim for early diagnosis and introducing early intensive treatment, in order to halt disease progression and irreversible structural joint damage. Disease remission, or at least low disease activity, has become the modern treatment target.

Update on RA Classification Criteria
The widely-used 1987 classification criteria for RA include seven items concerning: morning stiffness; arthritis of three or more joint areas; arthritis of hand joints; symmetric arthritis; rheumatoid nodules; serum rheumatoid factor; and radiographic changes (Table 1).1 Fulfilling any four of these criteria suggests a diagnosis of RA. These classification criteria, however, have low sensitivity for early RA. With the unmet demand for controlling earlier disease, revised classification criteria were developed in 2010. The new criteria distinguish RA based on the presence of synovitis in at least one joint and the achievement of a total score of six out of 10, which is calculated from individual scores in four domains: number and site of involved joints; serology, including both rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP); acute-phase reactants; and symptom duration (Table 2).2 Most importantly, even if these criteria are fulfilled, there should not be an alternative diagnosis that better explains the presence of...
synovitis. However, this new classification was developed primarily for classifying patients with RA in clinical trials and epidemiology studies.

**Treat-to-target**

Since progression of RA inevitably results in irreversible joint damage and functional impairment, having identified early disease, intensive treatment should begin immediately, before any structural progression or disability occur. Studies have shown that adequate disease control with sustained remission or low disease activity has less radiographic destruction, more favorable functional outcomes and even improves mortality. Consequently, the ultimate goal of treatment is disease remission. Although this may be difficult to achieve, especially for patients with long-standing disease, the aim, aided by new medications, is attaining at least low disease activity. There has been heated debate about how to define remission. Based on the various disease activity assessment core sets, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) concluded that to be considered in remission, a person with RA should have a tender joint count, swollen joint count, C-reactive protein, and patient global assessment scores all less than or equal to one, or Simplified Disease Activity Index less than or equal to 3.3. This is based on the fact that these clinical parameters are better predictors of good radiographic and functional outcomes. Based on both evidence and expert opinions an international task force has made 10 recommendations for treating RA to target, in order to guide treatment, (Table 3).7

**Table 2. 2010 ACR/EULAR classification criteria for RA**

<table>
<thead>
<tr>
<th>Joint Involvement (0–5)</th>
<th>Scores*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2–10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1–3 small joints (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4–10 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serology (0–3)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF and negative anti-CCP</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF/ low positive anti-CCP</td>
<td>2</td>
</tr>
<tr>
<td>High positive/ high positive anti-CCP</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute phase reactants (0–1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP/ abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of symptoms (0–1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

* A score of ≥6/10 is needed to classify patient as having definite RA

RA, rheumatoid arthritis; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

**Table 3. Ten recommendations on treating RA to target**

1. The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.
2. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
3. While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.
4. Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.
5. Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.
6. The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.
7. Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.
8. The desired treatment target should be maintained throughout the remaining course of the disease.
9. The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of co-morbidities, patient factors and drug-related risks.
10. The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.

**“Disease remission, or at least low disease activity, has become the modern treatment target”**

Breakthrough in RA

To satisfy the increasing demand for stringent disease control, biological agents have been rapidly developed. Anti-tumor necrosis factor (anti-TNF) inhibitors have been commercially available for almost 10 years and were the first biological therapy introduced in Hong Kong. Anti-TNF inhibitors available to treat RA in our territory are infliximab, etanercept, adalimumab and golimumab;
their clinical efficacy is well-established. Other biological disease-modifying anti-rheumatic drugs (DMARDs) include interleukin-6 receptor inhibitor (tocilizumab), anti-CD20 (rituximab) and the selective co-stimulation modulator (abatacept), which inhibits T-cell activation by binding to CD80 and CD86. All of these agents have proven efficacy, both clinically and radiologically. The latest agent being approved by the United States Food and Drug Administration for treatment of RA is tocitofinib. It is a janus kinase inhibitor and is the first in this new class of medications to be approved for use in RA. Last, but not least, traditional DMARDs still play an important role in treating RA; methotrexate (MTX), in particular, is considered the anchor drug in RA treatment regimens, both as monotherapy or combined with other non-biological DMARDs or biologicals.

### Consensus Recommendations from the Hong Kong Society of Rheumatology

Complete remission, or at least low disease activity, is undoubtedly our ultimate treatment target. However, regions differ in their treatment choice or practices according to the safety profile of the drugs and their affordability or acceptance by local patients. In 2010, the Hong Kong Society of Rheumatology developed local consensus recommendations based on the EULAR guidelines, for managing RA (Table 4). The key message is to initiate therapy as soon as RA is diagnosed, and to treat intensively for patients with serious disease or poor prognostic factors. MTX is recommended as the first-line DMARD for treatment-naive RA patients, unless contraindicated or the patient is intolerant to MTX. Treatment should be escalated for those who have suboptimal response to MTX by combining it with either synthetic or biological DMARDs.

### References

ORENCIA® Safety and tolerability profiles supported by up to 7 years of data1

Indications2

Adult Rheumatoid Arthritis (RA)
ORENCIA® is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. ORENCIA® may be used as monotherapy or concomitantly with disease-modifying anti-rheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

Juvenile Idiopathic Arthritis
ORENCIA® is indicated for reducing signs and symptoms in pediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis. ORENCIA® may be used as monotherapy or concomitantly with methotrexate (MTX).


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WHEN COMBINATION IS NOT AN OPTION

ONE BIOLOGIC MONOTHERAPY STANDS OUT
References:


