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You can help prevent zoster, its associated pain, and postherpetic neuralgia (PHN)

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4. Study design for ZEST. In the ZOSTAVAX® Efficacy and Safety Trial, efficacy was evaluated in a placebo-controlled, double-blind study of ZOSTAVAX®, 2,483 subjects 50 to 59 years of age were randomized to receive a single dose of either ZOSTAVAX® (n=1,210) or placebo (n=1,212), and were monitored for the occurrence of zoster for an average of 3.3 years (range 0.6 to 3.5 years).

5. Measured by the ID pain burden of illness score.

6. The ID pain burden score is a composite score that incorporates the incidence, severity, and duration of acute and chronic zoster-associated pain over a 6-month follow-up period.

7. A clinically significant zoster-associated pain persisting or appearing at least 90 days after the onset of rash.

The control and outcome of rheumatoid arthritis (RA) and other connective tissue diseases have greatly improved with better understanding of disease pathophysiology, and availability of effective and safe treatments. In this issue of the Journal, five rheumatologists will be writing on five therapeutic areas of rheumatology. Dr Lucia Chau and Dr Gavin Lee will give an overview of the basic and clinical aspects of two groups of commonly used medications, glucocorticoids and NSAIDs. With the widespread use of biologic agents, you will encounter patients receiving these medications whether you are a rheumatologist or not. Dr Carrel Yu will highlight the risks and benefits of biologic use and Dr Temy Mok will summarize clinical use and toxicity monitoring of immunosuppressants in autoimmune disease for us in this issue. Last, but not least, Dr Samson Lee will review evidence for treatment options of a common symptom, ie, soft tissue pain. I hope you will find the articles of this issue both interesting and enjoyable to read.

Asclepius was so adept in the art of healing that he not only cured the sick, but could also raise people from the dead. In the picture, he can be seen reviving Hippolytus, another figure in Greek mythology, who died as he was thrown from his chariot in a man-made accident. (Eventually, Asclepius was killed by Zeus for upsetting the natural order of the Universe).

Asclepius reviving Hippolytus
Claude Lorraine, (1604–1682)
French Baroque Painter

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Editor
Glucocorticoid Use in Rheumatology: Mechanism of Action, Adverse Effects and Guidance on Monitoring

**Introduction**

Glucocorticoid has revolutionized the treatment of countless medical conditions since its first use in the 1950’s. It is particularly useful in rheumatology, for example, in the treatment of systemic lupus erythematosus, inflammatory myositis, systemic vasculitis and various arthritides. In this article, the mechanisms of the therapeutic effects, as well as side effects, of glucocorticoids will be reviewed. Guidance on monitoring patients for adverse events will be discussed.

**Mechanisms of anti-inflammatory actions of glucocorticoids**

The therapeutic effects of glucocorticoid result from its genomic and non-genomic effects. Genomic effects work through the glucocorticoid receptor (GR) and regulation of gene transcription, while in non-genomic pathways, gene transcription is not involved. The GR is present in the cytoplasm of virtually all cells as a hetero-oligomer consisting of the GR and heat-shock proteins. The binding of glucocorticoid to the GR leads to dissociation of the heat-shock proteins, resulting in transformational changes and activation of the GR (Figure 1). Subsequently, the activated GR-glucocorticoid complex passes through the nuclear membrane and forms homodimers. The homodimers regulate gene transcription via: (a) direct binding to glucocorticoid responsive elements of DNA, (b) interaction with other transcription factors, eg, nuclear factor, (NF)-κB and activating protein (AP)-1, and (c) modulation of stability of specific mRNA molecules. Examples of genes that are regulated by glucocorticoid are shown in Table 1, and the end result is down-regulation of inflammatory products.

In contrast to genomic effects, non-genomic effects are more rapid. An example is the activation of endothelial nitric oxide synthetase (eNOS). Glucocorticoid stimulates the activity of phosphatidylinositol-3-hydroxykinase (PI3K) via a transcription-independent pathway in endothelial cells. Activated PI3K in turn phosphorylates protein kinase B (Akt) which subsequently leads to phosphorylation and activation of eNOS.

**Adverse effects of glucocorticoid therapy**

Due to the pleiotropic effect of glucocorticoids, they have multiple potential

---

**Table 1. Genes regulated by glucocorticoid**

<table>
<thead>
<tr>
<th>Category</th>
<th>Genes Regulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines</td>
<td>IL-1β, IL-6, IL-11, TNF-α, GM-CSF</td>
</tr>
<tr>
<td>Chemokines</td>
<td>MCP-1, eotaxin, IL-8, RANTES, MIP-1α</td>
</tr>
<tr>
<td>Adhesion Molecules</td>
<td>ICAM-1</td>
</tr>
<tr>
<td>Enzymes</td>
<td>iNOS, COX-II, cPLA2α</td>
</tr>
<tr>
<td>Inhibitory Proteins</td>
<td>Lc-1, IL-1RA type I, SPLI</td>
</tr>
</tbody>
</table>

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**Figure 1. Genomic action of glucocorticoid receptor**

![Figure 1. Genomic action of glucocorticoid receptor](image)
adverse effects, for example, skin and muscle atrophy, glaucoma, Cushing’s syndrome, diabetes mellitus and hypertension. However, the likelihood of adverse effects varies between individuals; some can tolerate a moderate dose while others may have marked adverse effects on a minimal dose. In general, the duration, dosage, dosing regimen, specific glucocorticoid used, mode of application, and the individual’s susceptibility to adverse effects will determine the occurrence and severity of the adverse effects. Some of the adverse effects are discussed in detail below.

**Avascular necrosis**

Avascular necrosis (AVN, or osteonecrosis) is the most feared adverse effect of glucocorticoids among Hong Kong residents due to its publicity in the SARS era. The pathophysiology linking glucocorticoid use and AVN is not fully understood, but it is postulated that glucocorticoids lead to the deposition of lipids in the femoral head, causing femoral hypertension and ischaemia. Clinical studies have suggested a higher dose poses a higher risk for AVN than cumulative doses or duration of therapy. A dose of more than 20 mg/day of prednisolone is generally regarded as a threshold risk for AVN.

### Osteoporosis

In patients receiving long term glucocorticoids, 12% of bone is lost in the first few months, followed by a slower phase of 2–5% per year. A dose of as low as 6 mg/day prednisolone for 6 months may cause significant bone loss. Steroid induced osteoporotic fracture is most common in vertebral bodies and ribs due to the loss of cancellous bone. The risk of fracture is also related to race, age, body weight, female sex, menopausal status, smoking history and nature of underlying illness.

### Gastrointestinal bleeding

Glucocorticoids are shown to increase gastric acid secretion, reduce gastric mucus, induce hyperplasia of gastrin and parietal cells and delay healing of ulcers in animal studies. In meta-analyses, the pooled relative risk for peptic ulcers ranged from 1.3 to 2.3. The risk is higher in patients taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs). The risk of upper gastrointestinal bleeding is also higher in patients receiving anticoagulants and having a history of upper gastrointestinal bleeding.

### Guidance on the use of glucocorticoids

To promote a safer use of glucocorticoids, the EULAR has published recommendations on the use of low-dose glucocorticoids (<7.5 mg/day prednisolone equivalent) and medium- to high-dose glucocorticoids (75–100 mg/day prednisolone equivalent) in rheumatic diseases. When low-dose glucocorticoid is used, it is recommended that clinicians monitor blood pressure, blood glucose, body weight, oedema, symptom of ischaemic heart disease and peptic ulcer. Monitoring of bone mineral density (BMD) by dual energy X-ray absorptiometry (DEXA) scan should be done according to local guidelines. For patients at risk of glaucoma (eg, family history of glaucoma, high myopia or diabetes), ophthalmologic evaluation should be done at the start of therapy. The EULAR recommendations for management of medium- to high-dose glucocorticoid therapy are listed in detail in Table 2. In general, clinicians should monitor patients closely to ensure the lowest possible dose is used for the shortest duration, and carefully observe patients for adverse effects. Of note, clinicians should offer prophylaxis for osteoporosis and patients should be instructed on prevention of acute cortisol insufficiency, particularly during severe intercurrent illnesses.

### Conclusion

Glucocorticoids are useful and essential in the management of a broad variety of diseases. Its pleiotropic nature is linked to the wide variety of possible adverse effects. However, with judicious use and careful monitoring, the benefit of glucocorticoid therapy can be maximized with minimal increase in adverse outcomes.

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Table 2. The EULAR recommendations on the management of medium- to high-dose glucocorticoid therapy

| 1. Explain to patients (and their family and/or carers, including healthcare professionals) the aim of medium/high dose glucocorticoid treatment, and the potential risks associated with such therapy |
| 2. Discuss measures to mitigate such risks, including diet, regular exercise and appropriate wound care |
| 3. Patients with, or at risk of, glucocorticoid-induced osteoporosis should receive appropriate preventive/therapeutic interventions |
| 4. Patients and the patients’ treatment teams should receive appropriate, practical advice on how to manage glucocorticoid-induced hypothalamic-pituitary-adrenal axis suppression |
| 5. Provide an accessible resource to promote best practice in the management of patients using medium/high-dose glucocorticoids to general practitioners |
| 6. Before starting medium/high dose glucocorticoid treatment consider comorbidities predisposing to adverse effects. These include diabetes, glucose intolerance, cardiovascular disease, peptic ulcer disease, recurrent infections, immunosuppression, (risk factors of) glaucoma and osteoporosis |
| 7. Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of undertreatment |
| 8. Keep the requirement for continuing glucocorticoid treatment under constant review, and titrate the dose against therapeutic response, risk of undertreatment and development of adverse effects |
| 9. All patients should have appropriate monitoring for clinically significant adverse effects. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological adverse effects |

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Fibromyalgia

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Key words:
Fibromyalgia (纖維肌痛), diagnosis (診斷), management (治療)

Introduction

Fibromyalgia is a systemic disorder characterized by chronic widespread musculoskeletal pain, stiffness, fatigue and tenderness. It is often associated with somatic symptoms, eg, allodynia and hyperalgesia and psychological disturbances, for example, poor sleep, anxiety, depressive symptoms and cognitive impairment. Physical examination shows increased tenderness at muscle and tendon insertion sites; persistent pain and tenderness should continuously be present, for at least 3 months, above and below the waist on both sides of the body.

Diagnosis

Fibromyalgia presents a diagnostic challenge for physicians. Identification of fibromyalgia patients by the original 1990 American College of Rheumatology (ACR) classification criteria required a specialized physical examination to quantify tender point count. The criteria required tenderness on pressure (tender points) in at least 11 of 18 specified sites, together with the presence of widespread pain for diagnosis. Pain, on digital palpation, should be performed with an approximate force of 4 kg and must be present in at least 11 out of the following 18 tender point sites:

1. Occiput at the nuchal ridge: Bilateral, at the suboccipital muscle insertions
2. Low cervical: Bilateral, at the anterior aspects of the intertransverse spaces at C5–C7
3. Trapezius: Bilateral, at the midpoint of the upper border
4. Supraspinatus: Bilateral, at origins, above the scapula spine near the medial border
5. Second rib: Bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
6. Lateral epicondyle: Bilateral, 2 cm distal to the epicondyles
7. Gluteal: Bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
8. Greater trochanter: Bilateral, posterior to the trochanteric prominence
9. Knee: Bilateral, at the medial fat pad proximal to the joint line

Unfortunately, in clinical practice, not all fibromyalgia patients experience all symptoms and have tender points. Although fibromyalgia is classified based on the presence of chronic widespread pain, the symptoms may be localized to the shoulders, necks, back and hips. The utility of such diagnostic criteria is dependent on the clinical setting. The major obstacle in the diagnosis is the lack of objective physical or laboratory findings in fibromyalgia. It has not been widely adopted in primary care.

The 2010 ACR diagnostic criteria allow for diagnosis by history, without specialized training. They constitute a more complex evaluation of fibromyalgia in patients and assess patients based on scores from both a widespread pain index (WPI) and a symptom severity (SS) scale. The critical diagnostic variables are WPI and categorical SS scales for cognitive symptoms, unrefreshed sleep, fatigue, and number of somatic symptoms. The WPI quantifies the extent of bodily pain on a scale from 0–19 to measure pain or tenderness in 19 different body regions, including: shoulder girdle, hip, jaw, upper arm, upper leg, lower arm, lower leg, upper back, lower back, chest, neck and abdomen. The SS scale is comprised of two measurements, both the severity and the extent of symptoms. SS Scale measures problems with fatigue, cognitive dysfunction and unrefreshing sleep over the past week, each symptom is measured on a scale of 0–3 (0 = no problem, 1 = a slight or mild problem, 2 = a moderate or considerable problem and 3 = a severe, continuous, life-disturbing problem). The sum of these scores together with a measure of the physician’s impression of the number of somatic symptoms the patient has, on a scale of 0–3 (0 = no symptoms, 1 = a few symptoms, 2 = a moderate number of symptoms, and 3 = a great deal of symptoms), form an SS scale score of 0–12.

The SS scale and the WPI are combined to assess a case of fibromyalgia: WPI >7 and SS >5 or WPI 3–6 and SS >9 are predictive of fibromyalgia. The symptoms should have been present for at least 3 months and other causes have been excluded. Fibromyalgia is a diagnosis of exclusion and patients must be thoroughly evaluated for the presence of other disorders that could be the cause of symptoms before a diagnosis of fibromyalgia is made. The ACR classification criteria constitute a simple clinical case definition of fibromyalgia and correctly classify 88.1% of cases, it does not require a physical or tender point examination. They are useful in the longitudinal evaluation of patients with marked symptom variability.
Prevalence
Fibromyalgia is not uncommon; studies have estimated that the prevalence of fibromyalgia in the US general population was 2–6.4% (3.5–7.7% in women and 0.5–4.9% in men). Branco et al. estimated the prevalence of fibromyalgia in Europe at 4.7% and White et al. estimated the prevalence of fibromyalgia at 3.3% in Ontario, Canada (4.9% women vs. 1.6% men). In the general population of Brazil, the prevalence of fibromyalgia has been estimated at 4.5%. It is of note that fibromyalgia was rarely observed in China, with a prevalence of 0.05%, which was distinctly lower than in reports from other parts of the world. The prevalence of fibromyalgia in Hong Kong was estimated to be 0.82% (95% confidence interval (CI): 0.35%, 1.29%); the prevalence of fibromyalgia in the Chinese population of Hong Kong was low but was similar to that of some other Western countries.

Mortality does not appear to be increased in patients with fibromyalgia, but the risk of death from suicide and accidents was seen to be increased. A prospective study from Denmark followed patients with fibromyalgia for 16 years and there was a reported 10-fold increased risk of death from suicide. A Swedish study of patient perspectives confirmed that fibromyalgia has a significant negative impact on the quality of social and economic functions in patients’ lives and the average yearly cost for service utilization among fibromyalgia patients is $2,274.

Pathophysiology
The aetiology of fibromyalgia is multifactorial and includes both environmental and genetic factors. The identification of central sensitization and abnormal central nociceptive processing in affected patients suggested that fibromyalgia was driven primarily by central sensitization and possibly through changes in several neuronal systems but not necessarily reliant on peripheral processes. Investigators have investigated different mechanisms in fibromyalgia, including studies of muscle, sleep physiology, neurohormonal function and psychological status. Although the pathophysiology of fibromyalgia remains unknown, an increasing body of literature points towards central, rather than peripheral, mechanisms.

Management
Fibromyalgia treatment is often difficult for both clinicians and patients because of the lack of a universally effective treatment or cure. Multidisciplinary approaches involving both physicians and psychiatrists for management of fibromyalgia, include non-pharmacological approaches, for example, education, lifestyle changes and psychological treatment. Alongside pharmacological treatment, these can help the individual to achieve significant improvement. Models of pain behavior that interrelate biological, cognitive, emotional and behavioural variables form the basis for cognitive-behavioural and operant-behavioural approaches that have been seen to be effective in pain management. Evidence-based recommendations, including the European Congress of Rheumatology (EULAR) 2006 recommendations and the 2005 American Pain Society (APS) guidelines, have been developed in fibromyalgia management. Both guidelines recommend the use of acetaminophen, weak opiates, tricyclic antidepressants (TCAs) and other antidepressants as effective pharmacologic treatment options.

Low-dose TCAs have proven short-term efficacy for pain control, improved sleep, and improved sense of well-being in fibromyalgia patients. Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline also improve symptoms in fibromyalgia. Treatment by dual serotonin/norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, milnacipran and duloxetine were also effective. Patients taking either SSRIs or SNRIs should be carefully monitored for worsening depression or emergence of suicidal thoughts. Unfortunately, NSAIDs, including cyclo-oxygenase (COX-2) inhibitors, are ineffective against pain associated with fibromyalgia. The EULAR 2006 guidelines, recommended pregabalin as first-line pharmacologic treatment option for patients with fibromyalgia. Pregabalin was the first agent to receive a US Food and Drug Administration (FDA) approved indication for the treatment of fibromyalgia. EULAR guidelines also recommend the use of tropesitron, pramipexole and the APS guidelines specifically recommend anti-depressants as first-line treatment.

Conclusion
There is evidence in support of fibromyalgia as a dimensional, or continuum, disorder. Treatment is difficult but both non-pharmacological and pharmacological approaches would be of benefit to a patient with fibromyalgia. Further studies to elucidate the pathogenesis of fibromyalgia and evidence-based studies on treatment response are essential.

References

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**Immunosuppressants in Systemic Lupus Erythematosus – Treatment Options and Potential Toxicity**

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Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects young women of child-bearing age. This disease is characterized by immune-complex mediated vasculitis and inflammation, leading to damage in various internal organs of the body. SLE is more prevalent among the Chinese population compared with Caucasians. It is estimated that around 0.07% of the population in Hong Kong suffers from this disease. SLE is more prevalent among the Chinese population compared with Caucasians. It is estimated that around 0.07% of the population in Hong Kong suffers from this disease. SLE is a heterogeneous syndrome involving diverse organ manifestations and serological features, and the clinical course consists of exacerbations and remissions. Depending on the severity of organ involvement during the heightened disease activity at a "flare", different treatment options are considered.

Articular and cutaneous manifestations are the most frequent presentations of lupus and are found in over 80% of patients. In the absence of systemic involvement, anti-malarials such as hydroxychloroquine (HCQ) are effective therapy for skin and joint manifestations. The recommended daily dose of HCQ is 200–400 mg. This drug is generally well tolerated with uncommon adverse effects including hyperpigmentation of skin and bull’s eye retinopathy. Methotrexate (MTX), an immunosuppressive drug, better known as an anchor disease modifying anti-rheumatic drug (DMARD) in the treatment of rheumatoid arthritis, targets the metabolism of folic acid and is also efficacious for articular and cutaneous manifestations of SLE. The therapeutic dose of MTX ranges from 7.5–20 mg/week and it is often prescribed with folic acid to lessen its mucositis adverse effects. MTX may potentially cause leukopenia and deranged liver function and, therefore, requires frequent monitoring in early commencement. If patients remain refractory to these medications, low-dose corticosteroids may be required for treatment.

The treatment goals in SLE include induction of remission and prevention of future relapses. Corticosteroids and immunosuppressive drugs are the mainstay of therapy for moderate to severe presentations of lupus, such as profound haematological involvement, serositis, lupus nephritis and nervous system involvement. Prednisolone 0.5–1.0 mg/kg/day, or equivalent dose of other preparations of corticosteroids, are required at flares with moderate to severe manifestations. Pulse steroids, ie, methylprednisolone 500–1,000 mg daily for three consecutive days, are reserved for severe lupus presentations such as Class IV lupus nephritis with crescents, cerebritis and transverse myelitis. A number of immunosuppressive drugs have been used for many decades in lupus history, and more recently, some immunosuppressants, previously used in solid organ transplantation, have been shown to be efficacious in the treatment of active SLE. Table 1 highlights some common immunosuppressive drugs used in the treatment of SLE, their indications, recommended doses for local Chinese patients, and adverse effect profile.

Azathioprine is a common immunosuppressive drug that has a steroid-sparing effect, allowing gradual tapering of corticosteroids to a low maintenance dose for long-term use in the prevention of a flare. It is associated with bone marrow suppression presenting as megaloblastic anaemia and leukopenia. Thiopurinemethyltransferase (TPMT) genotyping or TPMT activity measurement may be useful for the prediction of patients at risk of significant myelosuppression, but is not cost-effective due to the low frequency of homozygous subjects who have very low TPMT activity.

Cyclophosphamide (CTX) is a cytotoxic drug and has been the gold standard for induction therapy in active lupus nephritis for many decades. CTX is also indicated for major central or peripheral nervous system involvement by lupus. CTX induction therapy can be prescribed as daily oral tablets or can be delivered as a monthly intravenous pulse dose both for 6 months. CTX induction therapy is associated with bone marrow suppression and increased risk of infection and requires close monitoring of white blood cell counts.
IV lupus nephritis,2 this concern has been demonstrated to be an effective induction and maintenance therapy in active Class III and IV lupus nephritis. While concomitant diltiazem may cause haemorrhagic cystitis which can be prevented by ample fluid intake and application of mesna prior to pulse therapy. A key concern for patients with SLE receiving CTX is the potential for premature ovarian failure. However, with the introduction of mycophenolate acid (MPA), which clinical studies have demonstrated to be an effective induction and maintenance therapy in active Class III and IV lupus nephritis,3 this concern has been alleviated. MPA is an immunosuppressant with a suppressive effect on T and B lymphocytes implemented in the management of organ transplantation. Unlike CTX, MPA does not affect ovarian function, although its use during pregnancy is not recommended. Mycophenolate mofetil (MMF) is a pro-drug of MPA with increased bioavailability; however, it may be associated with gastrointestinal side effects, such as stomach upset and diarrhoea. Early clinical trials on the efficacy of MMF in patients with SLE excluded patients with active aggressive crescentic glomerulonephritis and did not include other major organ involvement as primary study endpoints. However, despite this, the clinical efficacy of MMF in other systemic manifestations of SLE has been widely reported. Cyclosporine (CSA) is an old-fashioned immunosuppressive drug in the treatment of SLE. It is a calcineurin inhibitor and targets T lymphocytes. CSA is not widely used in lupus therapy as it is associated with adverse effects including hypertension, impaired renal function and hypertrichosis. It is considered in patients with SLE who have active diseases refractory to conventional therapy, such as significant thrombocytopenia and lupus nephritis. While concomitant diltiazem may be used to potentiate the immunosuppressive effect of CSA, patients on CSA should avoid grapefruit juice as this inhibits its metabolism. Tacrolimus, another member of the calcineurin inhibitors class, has increasingly been reported to be useful in treating active lupus nephritis, but clinical data from randomized controlled trials are still pending.

Family planning is an important aspect in the management of patients with SLE and concerns have been raised by patients with regards to the safety of immunosuppressive drugs during pregnancy. The FDA category in terms of ‘risk for pregnancy’ for the discussed immunosuppressants are shown in Table 1. Overall, hydroxychloroquine, corticosteroids and azathioprine are generally safe during pregnancy but patients should be advised on contraception and postpone planning for pregnancy if they have recent history of active disease under treatment of other immunosuppressive drugs.3 While the use of prednisolone and azathioprine is not contraindicated in breastfeeding, the potential benefits of breastfeeding must be weighed against possible risk.

Although immunosuppressive agents are effective treatment for active SLE in most patients, there remain issues such as refractory diseases and drug compliance. A number of biologic agents that target specific immune cells or soluble factors are currently under evaluation in clinical trials and may offer better treatment outcomes in patients with refractory conditions. Explanation of the clinical effectiveness and adverse effect profile to patients would help improve compliance. Moreover, the choice of immunosuppressive agents and the dosage prescribed also largely depends on concomitant comorbidities such as infective complications and impaired renal function. Importantly, the risk of infection and necessary preventive measures should be emphasized when commencing patients on immunosuppressive drugs.

### Table 1. Common immunosuppressive drugs used in the treatment of SLE

<table>
<thead>
<tr>
<th>Medication (Route and dosage)</th>
<th>Indication</th>
<th>Common side effects</th>
<th>Compatibility with pregnancy</th>
<th>Compatibility with breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (p.o. 7.5–20 mg/week)</td>
<td>Articular and cutaneous manifestations</td>
<td>Leukopenia, nausea, vomiting, mucositis, deranged liver function, folate deficiency</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Azathioprine (p.o. 2 mg/kg/day)</td>
<td>Steroid-sparing drug in moderate to severe disease</td>
<td>Bone marrow suppression, liver function derangement</td>
<td>Yes</td>
<td>Yes (benefits may outweigh risks)</td>
</tr>
<tr>
<td>Cyclophosphamide (p.o. 100 mg daily for 6 months or monthly intravenous pulse 750 mg/m² for 6 months)</td>
<td>Induction therapy for severe lupus nephritis and major nervous system involvement</td>
<td>Nausea, vomiting, bone marrow suppression, haemorrhagic cystitis, premature ovarian failure</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Mycophenolate mofetil (Cellcept®) (p.o. 1 g BD as induction, 1 g/day as maintenance)</td>
<td>Induction and maintenance therapy for lupus nephritis</td>
<td>Nausea, vomiting, diarrhoea, bone marrow suppression</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Myophenate sodium (Myfortic) (720 mg BD as induction, 720 mg daily as maintenance)</td>
<td>Induction and maintenance therapy for lupus nephritis</td>
<td>Nausea, vomiting, diarrhoea, bone marrow suppression</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Cyclosporine (3–5 mg/kg/day)</td>
<td>Moderate to severe disease</td>
<td>Renal impairment; hyperuricaemia, hypertension, headache, gum hypertrophy, hypertrichosis</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

A complete list of references can be downloaded from [www.SOPHYSICIANSHK.org](http://www.SOPHYSICIANSHK.org)
Take the Enbrel® route in RA, AS and PsA
Risks and Benefits of Biologic Agents in Rheumatic Disease

Many rheumatic diseases manifest as joint inflammation, for example, rheumatoid arthritis (RA), a chronic systemic autoimmune arthritis which affects around 1% of the population. Without proper and timely treatment, persistent inflammation leads to cartilage damage, bone erosion and joint destruction. The introduction of synthetic DMARDs, such as methotrexate and sulphasalazine, has resulted in marked improvement in the control of arthritis. However, despite these medications, a significant proportion of patients continue to have persistent joint inflammation and progressive joint destruction.

Over the past decade, biologic therapies have revolutionized the treatment of rheumatic diseases like RA, ankylosing spondylitis, psoriatic arthritis and juvenile inflammatory arthritis. Blocking signaling by tumour necrosis factor (TNF), a proinflammatory cytokine, has been a major target in tackling the underlying pathology of autoimmune diseases with biological molecules. Etanercept, a fully humanized TNF antagonist, was approved in 1998 as the first biologic therapy for the treatment of RA. Infliximab and adalimumab swiftly followed, and certolizumab pegol and golimumab were approved more recently.

Although TNF inhibitors have proven to be effective treatments for RA and other rheumatic conditions, a proportion of patients with RA do not respond, or achieve an optimal response, to TNF inhibition. Therefore, biologic agents that target other inflammatory pathways have also been developed. To date, agents targeting IL-1 (anakinra) and IL-6 pathways (tocilizumab), T-cell co-stimulatory pathways (abatacept) and B cells (rituximab) have been approved for the treatment of moderate to severe RA, and other rheumatic conditions (Table 1).

As with any drug, safety concerns affect the choice and use of these agents. Several issues, such as the risk of infection, malignancy or infusion reactions, apply to all biological compounds in this class. Other safety concerns, such as demyelinating disease, congestive heart failure, leucopenia and hyperlipidaemia, are associated with individual biologic agents and there are some conditions that affect patient selection and management that are specific to certain biologic treatments.

Infections
It is well recognized that patients with RA are at an increased risk of infection, and while biologic therapies are effective in achieving disease control in RA, interference in the innate or adaptive immune system presents a further increased risk of infection and potential reactivation of latent infection. This remains one of the main safety concerns of these therapies.

TNF signaling is crucial in recognizing and responding to infection. As the use of the TNF inhibitors increases, data regarding serious bacterial infections have been collected in several large registries and databases. Analyses of these data have revealed an increased risk of infections with the three anti-TNF agents, particularly in the first 6 months of treatment (adjusted hazard ratio [HR]: 1.8; 95% CI: 1.3–2.6). In addition, increased rates of pneumonia have been noted within the first 6 months, suggesting the first 6 months is the period of greatest risk.

TNF inhibitors are not the only biologic agents to cause increased risk of infections; tocilizumab, a humanized antibody to the IL-6 receptor, disrupts IL-6 signaling. Infection rates in patients with RA treated with tocilizumab are similar to those in patients treated with TNF inhibitors. A meta-analysis of abatacept in RA has shown that the increase in serious infections following treatment was not statistically significant; this finding was supported by a Cochrane review of abatacept use for all indications.

Randomized controlled trials (RCTs) of rituximab in patients with RA have reported higher rates of serious infection with rituximab than with control, but the differences were not statistically significant. This was further demonstrated by a meta-analysis of three RCTs.

Tuberculosis reactivation
It is known that TNF plays an essential role in defence against Mycobacterium tuberculosis and other intracellular bacterial and fungal pathogens. Early
Hepatitis B reactivation

Immune suppression has been associated with hepatitis B virus (HBV) reactivation in chronic carriers. Patients with resolved hepatitis B infection may be at risk of reactivation if they receive TNF inhibitors. A meta-analysis of 257 patients receiving TNF inhibitors reported a reactivation rate of 39% in HBV carriers. However, in patients with active hepatitis B infection, reactivation is more likely to occur in those who are actively infected, rather than in chronic carriers. Therefore, the biologic agents should be carefully considered with careful counseling and intensive monitoring.

Table 1 Biologic agents for the treatment of RA

<table>
<thead>
<tr>
<th>Medications</th>
<th>Target</th>
<th>Route of administration</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>TNF-alpha</td>
<td>intravenous</td>
<td>3–10 mg/kg every 4–8 weeks</td>
</tr>
<tr>
<td>Etanercept</td>
<td>TNF-alpha</td>
<td>subcutaneous</td>
<td>50 mg weekly</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>TNF-alpha</td>
<td>subcutaneous</td>
<td>40 mg monthly</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>TNF-alpha</td>
<td>subcutaneous</td>
<td>200 mg fortnightly</td>
</tr>
<tr>
<td>Golimumab</td>
<td>TNF-alpha</td>
<td>subcutaneous</td>
<td>50 mg monthly</td>
</tr>
<tr>
<td>Abatacept</td>
<td>T-cell costimulation</td>
<td>intravenous</td>
<td>500–1,000 mg every 4 weeks</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD20+ B cells</td>
<td>intravenous</td>
<td>2 separate 1,000 mg doses 2 weeks apart every 6 months</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IL-6 receptor</td>
<td>intravenous</td>
<td>4–8 mg per kg every 4 weeks</td>
</tr>
<tr>
<td>Anakinra</td>
<td>IL-1 receptor</td>
<td>subcutaneous</td>
<td>100 mg daily</td>
</tr>
</tbody>
</table>

of clinical registries and prospective observational studies identified no increase in malignancies other than skin cancers, associated with the use of TNF inhibitors. Regardless of treatment, patients with RA, or other autoimmune diseases, are at higher risk of developing malignancies compared to the general population. For example, patients with RA have a higher risk of lung cancer and lymphoma; the risk of lymphoma seems to correlate with disease activity.

Conclusion

Biologic agents directed at TNF-alpha, T-cell co-stimulation, B-cells, and IL 6 are efficacious in clinical trials for the treatment of RA patients with an inadequate response to conventional DMARDs. Evidence has shown that these biologic agents can delay radiographic progression. That means, in addition to the reduction of short-term disability from symptoms of inflammatory arthritis, biologic agents are beneficial in preventing long-term disability from joint damage. Therefore, the biologic agents are important tools for the treatment of rheumatic diseases. When used judiciously, they are effective and relatively safe. However, patients being prescribed these agents should be carefully followed by physicians in view of possible serious adverse effects. By combining conventional DMARDs and biologic agents, the management of rheumatic diseases has been transformed over the past 10 years offering patients with rheumatic diseases great hope that they will experience clinical benefits and maintain functional and happy lives.

References

WHEN COMBINATION IS NOT AN OPTION

ONE BIOLOGIC MONOTHERAPY STANDS OUT

ACTEMRA®
tocilizumab
Selective COX-2 Inhibitors and Non-Selective NSAIDs: A Recap

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Director, Rheumatology Centre
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Key words:
Nonsteroidal anti-inflammatory drug
(非類固醇消炎止痛藥), COX-2 inhibitors
(環氧化酶-2抑制劑), NSAIDs
(非類固醇消炎止痛藥)

Introduction
Since the discovery of salicylate in 1763, over 250 years ago, there has been tremendous development which has resulted in a large family of medication, namely, NSAIDs. These have a wide spectrum of clinical indications, from treating short-term acute pain like dysmenorrhoea and acute dental pain to chronic conditions including degenerative and inflammatory joint diseases. It has been estimated that over 17 million Americans receive NSAIDs on a daily basis; this is not surprising as NSAIDs are commonly prescribed across many different specialties. This article will review this class of medication, with a particular focus on those areas that not commonly discussed.

Classification of NSAIDs
Over the past two decades, delineating and distinguishing COX selectivity to categorize different NSAIDs has been emphasized. The selectivity of COX-1 and COX-2 will be elaborated further, but it should be noted that there are different chemical classes within this large family (Table 1).

<table>
<thead>
<tr>
<th>Chemical class</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylate (acetylated)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Salicylate (non-acetylated)</td>
<td>Diflunisal, salsalate</td>
</tr>
<tr>
<td>Propionic acids</td>
<td>Ibuprofen, naproxen, ketoprofen</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>Diclofenac, etodolac, indomethacin, sulindac</td>
</tr>
<tr>
<td>Oxicams (enolic acid)</td>
<td>Piroxicam, meloxicam</td>
</tr>
<tr>
<td>Fenamates (antranilic acid)</td>
<td>Mefenamic acid, meclofenamate</td>
</tr>
<tr>
<td>Nonacidic (naphthylalkanone)</td>
<td>Nabumetone</td>
</tr>
<tr>
<td>Selective COX-2 inhibitor</td>
<td>Celecoxib, etoricoxib</td>
</tr>
</tbody>
</table>

Mechanism of action and efficacy

Inhibition of cyclo-oxygenase

The main mechanism of action that accounts for the clinical efficacy of NSAIDs is the inhibition of cyclo-oxygenases (COX-2 and COX-1); this in turn affects the conversion of arachidonic acid into various prostaglandin related products (PGG2, PGH2, PGD2, PGE2, PGI2 and TXA2).

COX-1, a constitutive form, maintains important physiologic functions, whereas, COX-2, an inducible form, is produced as a response to an inflammatory state. However, one should note that COX-2 is constitutively expressed in brain, kidney, bone and the female reproductive system. The anti-inflammatory mode of action of NSAIDs is due to the inhibition of COX-2.

Non-prostaglandin mediated effects

NSAIDs may be inserted into biological membranes and disrupt interactions, for example, NSAIDs decrease the expression of Lselectin which is critical for migration of neutrophils to sites of inflammation. An in vitro study has demonstrated that NSAIDs inhibit NF-kB and consequently inhibit TNF-alpha and inducible nitric oxide synthetase (iNOS).

Table 1
An impact on apoptosis and an anti-proliferative effect has been demonstrated by NSAIDs that cannot be entirely explained by the inhibition of prostaglandin synthesis. The anti-proliferative effect of NSAIDs provides the rationale for their use in reducing the development of colonic adenomas.

**Clinical indications (Table 2)**

NSAIDs have anti-inflammatory effects in various inflammatory musculoskeletal disorders, for example, in acute gout attack, persistent inflammatory arthritides (rheumatoid arthritis, arthritis spondylitis and psoriatic arthritis), and soft-tissue inflammation (bursitis, tendinitis). Some NSAIDs have an indication for ‘pain’, and trials have been conducted in the context of post-operative pain control, acute dental pain and dysmenorrhoea. NSAIDs may be used in combination with other modalities for the control of cancer pain.

**Adverse effects and precautions**

**Gastrointestinal:**
As COX-1 maintains gastrointestinal (GI) mucosal integrity, NSAIDs can cause GI adverse effects due to its inhibition. This can be avoided by using specific COX-2 inhibitors; the use of a proton pump inhibitor is an alternative measure but it cannot tackle the damage to small bowel and large intestinal mucosa.

**Cardiovascular:**
NSAIDs may cause water retention, increased hypertension and deterioration for patients with congestive heart failure. The association of a cardiovascular event, which was initially thought to be related to the use of a specific COX-2 inhibitor, has also been shown to occur when using non-naproxen non-selective NSAIDs.

**Renal:**
Water and electrolyte disturbance (hyponatraemia and hyperkalaemia) have been reported. Patients with pre-existing renal impairment should be monitored for acute deterioration of renal function. Other NSAIDs-related kidney problems include nephrotic syndrome, chronic interstitial nephritis and papillary necrosis.

**Haematology:**
Anti-platelet action has been seen to occur with non-selective NSAIDs (this, however, does not occur with COX-2 inhibitors, as there is an absence of COX-2 activity in platelets). Therefore, one may consider withholding NSAIDs pre-operatively for approximately 3 days (four to five times the drug half-life) prior to surgery (some studies have shown that 1 day is sufficient for an ibuprofen user). Neutropenia is an uncommon (<1%) adverse effect of NSAIDs use.

**Pulmonary:**
Bronchospasm (in some case due to inhibition of COX-1) and pulmonary infiltrates with eosinophilia have been described, though the incidence of these events is not known.

**Hepatic dysfunction:**
A few years ago, the media reported the extremely rare occurrence of using topical NSAIDs resulting in hepatic damage. This caused major concern for patients and, as a result, there are currently patients declining the appropriate use of NSAIDs. The biochemical elevation of transaminase without clinical hepatitis has been seen to occur; in a large retrospective study of 625,000 patients, the incidence of acute liver injury was 3.7 per 100,000. Treatment with sulindac increased the incidence to 27 per 100,000, which is still very rare. Transient minor increases in transaminase have not been useful for predicting the subsequent occurrence of acute liver damage. Therefore, patients should be properly advised on this issue.

**Central nervous system:**
Cognitive impairment and psychosis have been found, especially in geriatric patients using indomethacin. There is an association of aseptic meningitis among patients with lupus using NSAIDs from the phenyl propionic acid group (ibuprofen and naproxen). Patients using non-salicylate NSAIDs occasionally suffer from tinnitus.

**Cutaneous reaction:**
Both morbilliform rash and urticaria can be related to the use of NSAIDs. Toxic epidermal necrolysis and Steven-Johnson syndrome are severe but rare complications also associated with the use of NSAIDs, particularly the oxicam class; the estimated risk is very low at 1 per 100,000 patients over 8 weeks of therapy.

**Prescribing NSAIDs in clinical practice**
A comprehensive patient assessment should be undertaken to minimize the risk when prescribing NSAIDs. Risk factors for NSAIDs-induced gastropathy (Table 3) or those factors that may predispose patients toward acute renal impairment (Table 4) should be assessed. Comorbidities, such as congestive heart failure, hypertension, and asthma with suboptimal control, are factors that should encourage the consideration of another therapeutic class before using NSAIDs.
Old age is related to a higher risk of various NSAID-related complications, for example, gastropathy, renal impairment and cognitive changes. Therefore, the American Geriatric Society has recommended avoidance of NSAIDs use in pain management for patients over 75 years of age.

The possibility of combining different therapeutic classes of analgesics should be considered rather than prescribing patients high-dose NSAIDs. It is good practice to keep the dosage of NSAID at the lowest possible effective dosage and for a limited duration (the shorter the better).

Patients should be properly educated regarding the use of NSAIDs, as with all medications. Clinicians and other healthcare professionals should not alarm patients by using examples of rare complications or special clinical case scenarios, instead, patients should be properly guided by well-balanced information.

Patients should be educated that different painful conditions can arise from various mechanisms, such as angina due to underlying myocardial ischaemia, or epigastric pain due to peptic ulcer disease. Patients should be made aware that although NSAIDs can be used as an analgesic, it will not be an appropriate treatment for all painful medical conditions.

**Conclusion**

NSAIDs are commonly prescribed, as both an effective anti-inflammatory agent and an analgesic option; they play an important role in managing patients on a daily basis. Although NSAIDs are known to be associated with various adverse effects, the risks can be minimized if a proper patient assessment has been conducted. As a medication that has been used in the medical field for over 250 years, we still need to better understand their mechanism of action in order to achieve a better and safer outcome for our patients.

<table>
<thead>
<tr>
<th>Table 3 Risk factors for NSAIDs-related gastropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age &gt;65</td>
</tr>
<tr>
<td>• History of peptic ulcer</td>
</tr>
<tr>
<td>• High dose of NSAIDs used</td>
</tr>
<tr>
<td>• Co-administering medications: moderate-to high dose steroid, anticoagulant, aspirin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4 Risk factors for NSAIDs-related acute kidney injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Old age</td>
</tr>
<tr>
<td>• Pre-existing renal impairment</td>
</tr>
<tr>
<td>• Renal artery stenosis</td>
</tr>
<tr>
<td>• Nephrotic syndrome</td>
</tr>
<tr>
<td>• Dehydration and volume depletion</td>
</tr>
<tr>
<td>• Congestive heart failure</td>
</tr>
<tr>
<td>• Cirrhosis</td>
</tr>
<tr>
<td>• Co-administered medications: diuretics, ACE-I, angiotensin receptor blocker, calcineurin inhibitors</td>
</tr>
</tbody>
</table>

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**THE SOCIETY OF PHYSICIANS OF HONG KONG**

**UPCOMING EVENTS**

- **May 18, 2014**  Sunday Symposium  The Langham Hotel, TST
- **June 13, 2014**  Friday Lunch and lecture at HKMA in Central
- **July 6, 2014**  Sunday Symposium  The Langham Hotel, TST
- **July 20, 2014**  Sunday Symposium  The Langham Hotel, TST

Programme subject to change

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- The treatment of severe active and progressive RA in adults not previously treated with methotrexate.
HUMIRA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.
HUMIRA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

³ As of June 2012.


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