Rheumatoid arthritis
early management guidelines for GPs

Rheumatoid arthritis is the commonest systemic autoimmune disease, affecting 1% of the population, with a high cardiovascular mortality and significant economic impact and morbidity. Aggressive treatment within the initial six months to two years of disease onset is needed to improve long term outcome.

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Rheumatoid arthritis afflicts 1% of the Australian population, predominantly affecting women, with an increasing incidence from the mid-twenties onwards. Over 80% of individuals will need lifelong medications to control symptoms and complications of the disease. Earlier and more aggressive treatment, rather than newer drugs, has improved the outlook of this disease over the last two decades. It is now clear that much of the erosive joint damage establishes itself within the initial six months to two years of disease onset, a time when management needs to be optimal.

The GP's role in managing rheumatoid arthritis

Shared management between GP and rheumatologist is the ideal scenario. Prompt liaison with a rheumatologist to confirm the diagnosis and initiate disease modifying antirheumatic drug (DMARD) therapy within three months of onset of rheumatoid arthritis is crucial for a favourable outcome. Once the disease is under control, close monitoring for drug toxicities, disease activity and extra-articular features by the GP and at least three-monthly follow up by the rheumatologist are the next steps. Ongoing disease activity after three months of active treatment warrants escalation of treatment and again needs liaison with the rheumatologist. Liaison with a physiotherapist and occupational therapist is also needed.

Diagnosis of early rheumatoid arthritis

Early treatment can occur only when an early diagnosis is made. On the other hand, premature

IN SUMMARY

- **Being familiar with the American College of Rheumatology classification criteria for rheumatoid arthritis and excluding common differential diagnoses (including viral arthropathies) will enable you to recognise rheumatoid arthritis among symmetrical inflammatory polyarthropathies of at least six weeks' duration.**
- **Early liaison with a rheumatologist may confirm the diagnosis and allow initiation of therapy. Ideally, disease modifying drugs should be started within three months of onset of disease, because joint damage occurs quickly. Biological agents targeting tumour necrosis factor, namely etanercept and infliximab, look promising but are currently reserved for patients who have failed first line therapies.**
- **Intra-articular injection of corticosteroid is a useful option for acutely inflamed joints. High dose systemic corticosteroids should not be used, except in specific situations such as vasculitis or interstitial lung disease.**
- **Patient education, monitoring for articular and extra-articular complications and toxicities of drugs, physiotherapy and occupational therapy are other cornerstones of the early management of rheumatoid arthritis.**

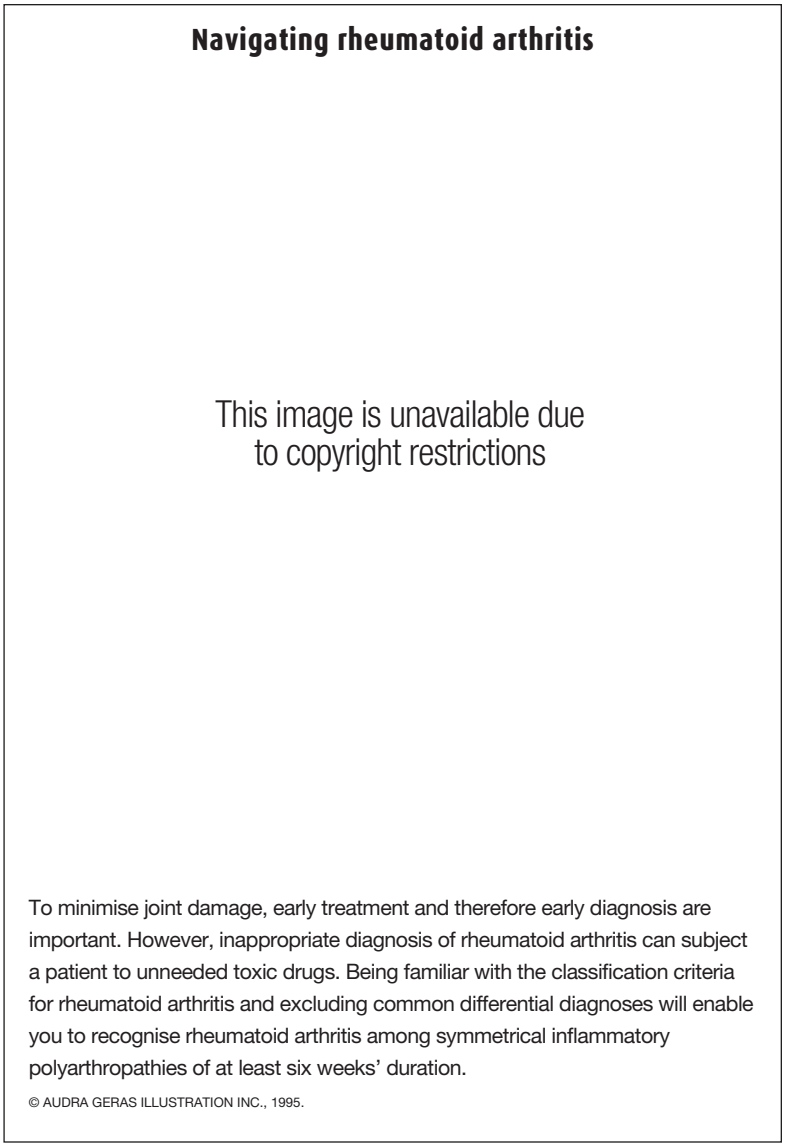
Table 1. Criteria for classifying rheumatoid arthritis*

Four out of the seven criteria are needed for a classification of rheumatoid arthritis. Criteria 1 to 4 must be present for at least six weeks.

1. Morning stiffness in and around joints for at least one hour before maximal improvement
2. Arthritis (soft tissue swelling or fluid observed by a physician) of three or more of the 14 joint areas, namely bilateral proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle and metatarsophalangeal joints (all small joints in one side taken as one unit)
3. Arthritis of one out of three hand joints, namely wrists, metacarpophalangeal, proximal interphalangeal joints
4. Symmetrical arthritis (for the small joints, absolute symmetry is not needed)
5. Rheumatoid nodules
6. Serum rheumatoid factor demonstrated by any test that has had positive results in less than 5% of normal control subjects
7. Radiographic changes on posteroanterior view of the hands showing periarticular erosions apart from osteoarthritic changes

* American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis.[1]

Navigating rheumatoid arthritis



To minimise joint damage, early treatment and therefore early diagnosis are important. However, inappropriate diagnosis of rheumatoid arthritis can subject a patient to unneeded toxic drugs. Being familiar with the classification criteria for rheumatoid arthritis and excluding common differential diagnoses will enable you to recognise rheumatoid arthritis among symmetrical inflammatory polyarthropathies of at least six weeks' duration.

diagnosis or overdiagnosis of rheumatoid arthritis can subject a patient to unneeded toxic drugs, particularly because early diagnosis can be difficult at times. Systemic autoimmune diseases such as rheumatoid arthritis do not yet have a diagnostic test. For research purposes, patients can be classified as having rheumatoid arthritis by the presence of four out of the seven criteria of the American College of Rheumatology (Table 1).[1] These serve as a useful diagnostic *aide-mémoire* for rheumatoid arthritis, although they can be fulfilled by many other systemic autoimmune rheumatic diseases.

Clinically, a symmetrical inflammatory polyarthritis of large and small joints of both upper and lower limbs of more than six weeks' duration should arouse the suspicion of the diagnosis of rheumatoid arthritis. Early morning stiffness, usually of the hands, of more than half an hour suggests an inflammatory process and is an additional supportive point. Rheumatoid arthritis also typically involves metacarpophalangeal joints, metatarsophalangeal joints and then proximal interphalangeal joints, and tends to spare the distal interphalangeal and axial joints initially (Figure). In a small percentage of patients, rheumatoid nodules over bony prominences is a helpful finding at presentation.

The presence of serum rheumatoid factor also points to rheumatoid arthritis, but is not a diagnostic test. About 20 to 30% of adult rheumatoid arthritis patients are rheumatoid factor negative, and variable proportions of patients with most other autoimmune rheumatic diseases or chronic infections can be rheumatoid factor positive,

including up to 5% of the normal population and more in the elderly. Once the diagnosis is rheumatoid arthritis, high rheumatoid factor titres correlate with many extra-articular features, including nodules and vasculitis.

Radiographs of the hands and feet in early disease may be normal, but they often show soft tissue swelling around the joints, juxta-articular osteopenia and, possibly, joint space narrowing. The presence of classic 'marginal erosions' provides strong support for the diagnosis of rheumatoid arthritis. However, plain radiography is relatively insensitive in detecting these erosions, with research groups identifying them by MRI or ultrasound within the first few months of disease activity.

Many viral arthropathies (e.g. parvovirus B19, Ross River virus, Barmah Forest virus and rubella) can mimic rheumatoid arthritis, but most of them resolve fully in a few weeks, although occasional cases last up to a year. Serological exclusion of these viruses may be needed if there has been possible exposure.

Table 2. Important extra-articular presentations of rheumatoid arthritis

Skin
Rheumatoid nodule
Vasculitic rash
Eyes
Secondary Sjögren's syndrome
Scleritis
Episcleritis
Central nervous system
Atlantoaxial dislocation and occasional cord compression
Carpal tunnel syndrome
Mononeuritis multiplex with vasculitis
Respiratory
Pleuritis
Pulmonary nodule
Interstitial lung disease
Bronchiolitis obliterans and late bronchiectasis
Cardiovascular
Premature coronary artery disease
Pericarditis
Conduction abnormalities
Myocarditis and endocarditis with mitral regurgitation
Haematological
Anaemia of chronic disease
Felty's syndrome with cytopenia
Hepatosplenomegaly and lymphadenopathy
Renal
Amyloidosis
Renal failure

Clinical evaluation

Clinical evaluation of patients with rheumatoid arthritis is needed not only for diagnosis but also to assess disease activity, functional status and extra-articular complications (Table 2). Duration of morning stiffness, number of swollen and tender joints, limitation of motion and deformities should also be noted.

Relevant investigations

Initial investigations should include the acute phase reactants erythrocyte sedimentation rate and C-reactive protein, full blood counts, rheumatoid factor, and x-ray of both hands and feet. Synovial fluid analysis is important for a 'rogue' joint when infection and crystal arthropathies need to be excluded. It is essential to perform renal function tests before commencing nonsteroidal anti-inflammatory drug (NSAID) therapy and during follow up. Liver function tests are needed initially, as well as before starting disease modifying agents, particularly methotrexate, leflunomide and sulfasalazine. Blood counts are relevant because rheumatoid arthritis patients can have anaemia of chronic disease, or occult gastrointestinal blood loss due to NSAIDs. More rarely, the cytopenia of Felty's syndrome may be detected.

Platelet counts can also act as an acute phase reactant, becoming elevated with active chronic inflammation. As a marker of acute inflammation, C-reactive protein is more sensitive than erythrocyte

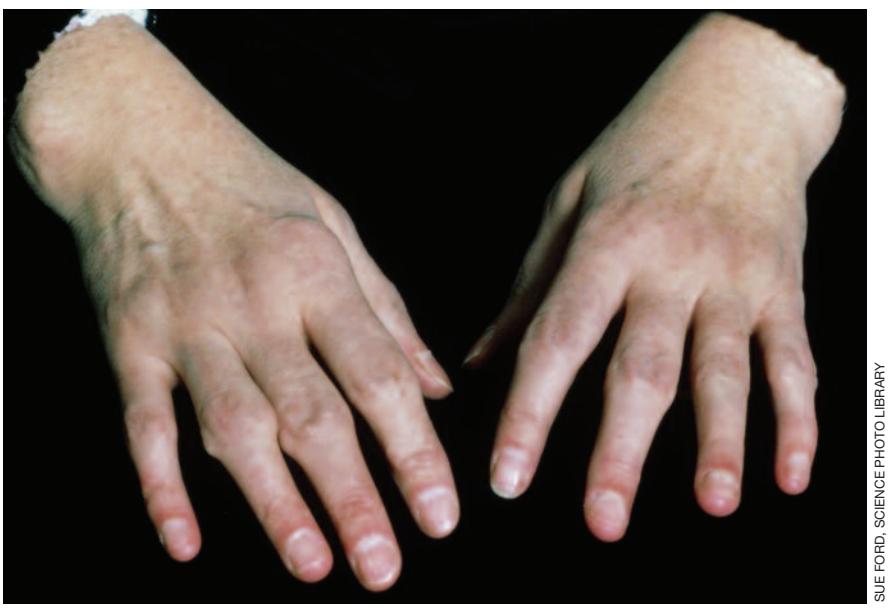


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Figure. Moderately severe, symmetrical, inflammatory synovitis affecting the metacarpophalangeal and proximal interphalangeal joints in a woman. This pattern present for longer than six weeks is highly suggestive of rheumatoid arthritis.

sedimentation rate and reflects a more recent state of inflammation.

Recent trends in the treatment of early rheumatoid arthritis

The treatment principles include control of pain and inflammation, preservation of joint function, and early recognition and treatment of extra-articular features. This is achieved with a team including the patient, GP, rheumatologist/local physician, physiotherapist, occupational therapist, nurse, counsellor/psychologist and, at times, orthopaedic surgeon. The steps in managing newly diagnosed rheumatoid arthritis are summarised in the box on this page.

Patient education is an important early step, to apprise the patient of the long term nature of the disease, available treatment modalities, side effects and cost of therapy, extra-articular features and importance of follow up (see also the box on page 18). A holistic approach should include weight reduction, joint protection and advice regarding smoking. Cigarette smoking has been increasingly shown in epidemiological studies to be a risk factor for both the development and severity of rheumatoid arthritis.

We have also moved away from the older approach in which specific DMARDs were started much later and initial treatment was mostly restricted to NSAIDs. Delaying specific antirheumatic treatment until the development of radiographic erosions or clinical deformity caused considerable suffering and irreversible joint damage. The current approach is commencement of specific treatment alone or in combination at the time of rheumatoid arthritis diagnosis.[2]

The following sections will briefly discuss the various categories of drugs and their optimal use in rheumatoid arthritis.

Disease modifying antirheumatic drugs

The mainstays of currently used DMARD therapy include low dose methotrexate,

Steps in managing newly diagnosed rheumatoid arthritis

Step 1

Early inflammatory polyarthritis should be evaluated fully, with a full personal history, family history and clinical examination to exclude viral arthritis, other autoimmune connective tissue diseases (such as systemic lupus erythematosus and Sjögren's syndrome) and psoriatic and enteropathic arthritis related to inflammatory bowel diseases. Baseline laboratory tests are undertaken. Liaise early with a rheumatologist for co-ordinated investigations, assistance with diagnosis and shared care.

Step 2

Once the diagnosis of rheumatoid arthritis is considered, liaison with a rheumatologist is indicated. It is important to evaluate the disease activity in terms of pain, impact on activities of daily living, duration of morning stiffness, number of tender and swollen/hot joints, and objective markers of inflammation such as erythrocyte sedimentation rate and C-reactive protein.

Step 3

The patient should be educated about the nature of the disease, complications, outcome and available therapy. This information can be provided by the GP and reinforced by referral to the relevant local branch of the Arthritis Foundation of Australia. Advice on the symptomatic use of simple analgesics and NSAIDs should be given as part of the education package.

Step 4

For any particularly actively painful swollen joint, consider intra-articular corticosteroids. DMARDs should be started at the time of confirmed diagnosis, after appropriate patient education. Single or combination therapies will depend on factors such as rheumatoid arthritis severity, patient age and requirements, alcohol intake, and contraception and family planning.

Step 5

A team approach needs to be followed by the GP and rheumatologist, with inclusion of allied health professionals as indicated:

- physiotherapist to develop a home exercise program for stretching and strengthening of involved areas once acute pain has subsided
- occupational therapist for education on joint protection, and provision of splints for work and rest to both aid function and reduce deformities
- podiatrist for advice on appropriate footwear for correct distribution of weight bearing
- psychologist for cognitive behavioural approaches to pain management and disease self-management.

Step 6

Carry out regular clinical and investigative monitoring for drug toxicities and disease activities, initially every three weeks, and then every six to 12 weeks once control of inflammation is achieved. Regular (every three to six months) liaison with a rheumatologist is desirable.

Note

In the event of any unusual or unexpected presentations, a rheumatologist should be consulted.

sulfasalazine, leflunomide, hydroxychloroquine and intramuscular gold. Oral gold and penicillamine are not used much these days.

Methotrexate

Low dose methotrexate (Ledertrexate, Methoblastin) is the most popular and efficacious DMARD. These days one hardly considers treating rheumatoid arthritis without methotrexate either on its own or in combination. The dose starts at 7.5 mg (but it may be increased to a maximum of 25 mg) taken as a single dose once a week, on the same day. It is usually taken orally, but the same dose may be administered by intramuscular or subcutaneous injection if nausea is experienced. It takes about six weeks to start acting, its effect plateauing at around 12 weeks.

A chest radiograph is recommended before commencing the drug, and hepatitis serology for those at risk.

Regular monitoring, every four to six weeks, of cell counts and liver function is mandatory. Dosage adjustment may be required to maintain normal values, and methotrexate should be stopped if this cannot be achieved.

Common side effects include stomatitis and gastrointestinal intolerance (which may be ameliorated with folic acid supplementation 1 mg/day). Methotrexate pneumonitis, vasculitis and increased nodulosis are rare side effects.

Methotrexate is contraindicated in women of child-bearing potential who are unwilling to use reliable contraception and in people unable to restrict their alcohol intake to a minimum.

Sulfasalazine

Sulfasalazine (Pyralin EN, Salazopyrin EN-tabs) is also an efficacious drug, and there is over 60 years' experience of its use. The dose ranges from 2 to 3 g/day orally in two divided doses. It is usually started at 500 mg/day, and every week it is increased by 500 mg until it reaches 2 g/day. Sulfasalazine takes about two to three months to start acting.

Side effects include gastrointestinal intolerance, bone marrow suppression and occasional sulfa drug allergy. Monthly monitoring similar to that for methotrexate is needed for the first three months, and then testing can be spaced to three-monthly. Sulfasalazine may be continued during pregnancy.

Leflunomide

Leflunomide (Arava) has been used increasingly in the western world over the past five years. In Australia, it can be initiated only by a rheumatologist when a patient has not responded to methotrexate or if it is inappropriate to continue methotrexate because of toxicity. Once leflunomide has been commenced, GPs have an important role in its ongoing supply and the monitoring of both efficacy and toxicity. Leflunomide takes about two months to start acting and its efficacy is comparable to that of methotrexate (or even better, according to some studies). The daily dose is 10 to 20 mg/day. Because

Patient education

Patient education is the first step in the management of rheumatoid arthritis before drug therapy is initiated. Failure to explain the long term and mostly incurable and fluctuating nature of this autoimmune disease, the reasoning behind the prescribed therapies and the importance of regular follow up may lead to noncompliance.

The local branches of the Arthritis Foundation of Australia are reputable sources of well presented patient education. Contact details are available from the Foundation's national office (visit www.arthritisfoundation.com.au or telephone 02 9552 6085).

Questions frequently asked by patients

Q: *Is rheumatoid arthritis curable?*

A: No, but it is controllable. If intensive treatment is started early, joint functions can be preserved to a large extent.

Q: *Is it hereditary?*

A: Although it can be seen in families, it does not follow any inheritance pattern.

Q: *What is the long term outcome?*

A: Fewer than 20% of rheumatoid arthritis patients can stop taking the antirheumatoid drugs for ever after achieving full remission. Sixty per cent of patients manage well by taking disease modifying drugs on a lifelong basis, and the remaining 20% of patients tend to have very aggressive disease requiring immunomodulators, immunosuppressants and the newer biological agents.

Q: *Will it shorten my life expectancy?*

A: Several studies show the average life expectancy to be shorter by two to five years, mostly related to cardiovascular disease.

Q: *What about alternative or complementary medicine?*

A: Most of the alternative or complementary medicines are unproven, and they can be costly. However, omega-3 fatty acid supplements (e.g. cod liver oil) have been shown to be helpful and may also offer a cardiovascular benefit.

Q: *Can or should I receive flu and pneumococcal vaccinations while on treatment for rheumatoid arthritis?*

A: Overall it is recommended that immunosuppressed patients receive flu and pneumococcal vaccinations; they are safe because these vaccines do not contain live organisms.

of the drug's long half-life, and hence the delay in reaching steady plasma concentrations, an initial loading dose of 100 mg/day for three days has been recommended; however, the loading dose is now used less often because of the risk of diarrhoea, which can reduce compliance significantly.

Common side effects can include diarrhoea, skin rashes, stomatitis and hair thinning. Because of a possible risk of hepatitis and bone marrow suppression, the same blood and liver monitoring is required as for methotrexate. Similarly, leflunomide is contraindicated in pregnant women or women of child-bearing potential who are not using reliable contraception, and in persons unable to restrict their alcohol intake to a minimum. In the event of toxicity, cholestyramine can mop the drug from its abundant presence in the enterohepatic circulation.

Hydroxychloroquine

Hydroxychloroquine (Plaquenil) is one of the mildest and safest DMARDs. It is often preferred as the starting DMARD in clinically mild rheumatoid arthritis or seronegative rheumatoid arthritis. It takes about three months to act. The dose ranges from 200 to 400 mg/day.

Common side effects include gastrointestinal intolerance, pigmentation and photosensitivity, pruritus, anorexia, insomnia, occasional seizurogenicity and flare up of psoriatic skin lesions. The much feared 'bull's eye retinopathy' is extremely rare, and regular 12-monthly ophthalmological review of colour fields and retina can help prevent it.

Intramuscular gold

Intramuscular gold is another efficacious agent that has been around for a long time, its place in the pecking order having been usurped by the above agents because of their better efficacy and side effect profiles. It is now available only as sodium aurothiomalate (Myocrisin) – a totally different salt to that of oral gold (auranofin), which is the least efficacious of the DMARDs.

Injectable gold takes about three months to start acting. It is usually started with incremental test doses of 5, 10 and 25 mg by deep intramuscular injection given 24 to 48 hours apart. Very occasionally, there can be a reaction in the form of peripheral circulatory shock, known as 'nitritoid reaction'. In the absence of that or any other form of reaction, an initial dose of 50 mg intramuscularly every week is started. This frequency is continued for at least 20 doses, and subsequently it can be reduced to fortnightly, three-weekly and monthly in a gradual manner depending on response.

Regular blood counts and urine protein testing at the frequency of injection is commenced initially. If there is proteinuria, a 24-hour urine protein collection should be tested because nephrotic syndrome with membranous glomerulonephritis can occur with gold. Another side effect is 'gold dermatitis', which does not often warrant permanent withdrawal of the drug.

Rational use of corticosteroids

The use of corticosteroids in rheumatoid arthritis has changed over the years because of a better understanding of rheumatoid arthritis, newer DMARDs and concerns about the toxicity of corticosteroids. Steroids are now used in very specific situations and manners in rheumatoid arthritis, some of which are mentioned below.

Intra-articular corticosteroid

Intra-articular injection of corticosteroid is ideal for symptomatic benefit, but it is usually a temporary measure that lasts for only a few weeks. However, it starts acting very quickly, often within 24 hours, and it creates confidence in the treatment process while waiting for the DMARDs to act.

Almost any joint can be injected, but large actively inflamed joints are the usual targets. Any one joint may be injected up to three to four times in any one year. The usual injection is with long acting agents, such as methylprednisolone acetate (Depo-Medrol, Depo-Nisolone), triamcinolone (Kenacort) or betamethasone (Celestone Chronodose), which can be mixed with local anaesthetic agents like lignocaine.

Low dose systemic corticosteroid

Doses of 5 to 10 mg/day of systemic corticosteroid can be used as bridge therapy before DMARDs start acting, to tide over for a short period – for example, prior to an important social or professional engagement. A dose of less than 10 mg/day does not usually cause hypothalamic suppression. Some studies suggest that in this dose systemic corticosteroid has disease modifying potential.

High dose corticosteroid

There are very few indications nowadays for sustained high dose corticosteroids in the management of rheumatoid arthritis, and these drugs should be initiated only by the patient's rheumatologist. Extra-articular complications such as interstitial lung disease and vasculitis are two definite indications requiring doses around 1 mg/kg bodyweight per day for six weeks or longer before any tapering process is started. Some people use intravenous methylprednisolone pulse 1 g as a single dose to tide over the crisis of a flare of disease activity while on full treatment.

Nonsteroidal anti-inflammatory drugs

NSAIDs are needed only when there is active inflammation and should not be used as analgesics for mechanical pain. Conventional NSAIDs do not differ in terms of efficacy, but they do in terms of half-life and toxicity. The maximum tolerated dose should not be exceeded, and combinations of NSAIDs should be avoided. At least three weeks of trial with an NSAID is needed before considering it as ineffective.

Some of the newer selective COX-2 inhibitors – such as celecoxib (Celebrex) and rofecoxib (Vioxx) – appear safer than the other NSAIDs in terms of major gastrointestinal events in the short term, but theoretical and observed concerns about their cardiac, renal and prothrombotic complications need to be kept in mind in patients with cardiovascular risk factors.

Immunomodulators

Immunomodulators act in a targeted manner towards the basic pathophysiological autoimmune process.

Cyclosporin (Cicloral, Cysporin, Neoral, Sandimmun) is a cytokine modulator. Its dose in rheumatoid arthritis is much smaller than that used for prevention of graft rejection, averaging 3 mg/kg bodyweight per day in rheumatoid arthritis subjects. Regular monitoring of blood pressure and renal function is important because irreversible reduction in glomerular filtration rate can occur if serum creatinine is allowed to increase 30% from baseline, even if that value is still 'normal'. Side effects include hypertrichosis, nausea and tremors.

Biological response modifiers

Tumour necrosis factor (TNF) is currently believed to be an early and major cytokine driving the inflammatory cascade in rheumatoid arthritis. Two agents that target TNF are currently indicated for the treatment of rheumatoid arthritis in Australia. Both etanercept (Enbrel) and infliximab (Remicade) are currently available under PBS funding, with strict regulation on initiation only to patients with severe and treatment-resistant seropositive rheumatoid arthritis, under the care of a rheumatologist.

Etanercept is a receptor antagonist acting as a decoy to the body's TNF. The dose is 25 mg twice weekly by subcutaneous injection. Infliximab is a chimeric monoclonal antibody to TNF, administered as a 5 mg/kg intravenous infusion at zero, two and six weeks and thereafter eight-weekly. It must be administered with concomitant methotrexate.

Both agents are effective at reducing the signs and symptoms of rheumatoid arthritis compared with placebo, and are marginally better than traditional agents such as methotrexate. Early reports suggest they may have the particular benefit of retarding early joint damage on x-ray.

The toxicities of these two agents include predisposition to opportunistic infections (including reactivation of tuberculosis), acceleration of common infections, worsening of severe heart failure, onset or exacerbation of demyelinating disease and the development of lymphoma. Current projected costings will see these agents restricted to severe disease in those who have failed standard pharmacological therapy.

A fully humanised anti-TNF antibody, adalimumab (Humira) may be available in Australia in the near future. It can be self-administered fortnightly by subcutaneous injection.

Combination therapy

Analogous to oncology therapy, combination therapy targets different sites within the rheumatoid arthritis pathophysiological process. Several studies have shown that combinations of DMARDs produce the same or greater responses compared with the serial use of the individual agents. One of the best studied and efficacious combinations is sulfasalazine, methotrexate and hydroxychloroquine. Other combinations include cyclosporin and methotrexate, and leflunomide with methotrexate. The latter combination, however, combines two potentially hepatotoxic and bone marrow suppressant drugs and requires careful patient education and monitoring. A combination of methotrexate, sulfasalazine and initially high dose oral prednisolone (tapering over six weeks to 7 mg/day) was shown to be more effective than sulfasalazine alone, but the prednisolone may have been the key ingredient here.

Dietary supplementation

Omega-3 fatty acids, such as eicosapentaenoic acid and docosahexaenoic acid, are potentially anti-inflammatory. The anti-inflammatory dose of cod liver oil is 10 to 20 mL/day. It can spare the patient from taking an NSAID and also offer cardiovascular protection in elderly rheumatoid arthritis patients. Cod liver oil costs about 20 cents a day, whereas the equivalent dose of fish oil capsules (14 to 20 capsules per day) would cost about $5 a day.

Conclusion

Early recognition of rheumatoid arthritis, based on American College of Rheumatology criteria, should prompt patient education and initiation of DMARD treatment as the first line of management. Intensive treatment followed by a 'step down' approach (rather than the older, slower, build up of treatment) is the current strategy because joint damage occurs quickly. Examples of efficacious combinations include hydroxychloroquine, low dose methotrexate plus sulfasalazine, cyclosporine plus methotrexate, and leflunomide plus methotrexate. Opportunities for using intra-articular corticosteroids should be exploited for inflamed swollen joints. Ongoing monitoring for disease activity, extra-articular features and drug toxicities is important, in liaison with a rheumatologist. The biological response modifiers appear promising, but they are expensive and are currently reserved for the more severe forms of disease. MT

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