# Medical management of rheumatoid arthritis

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The management of rheumatoid arthritis has changed in the last 10 years. Back then, a patient who awoke with painful swollen joints in the hands, knees and feet, which persisted for a couple of months, might have been treated with NSAIDs for a while until, after a delay of perhaps a year or more, a disease-modifying anti-rheumatic drug (DMARD) would be started. When that was only partly helpful, several months would go by before switching to the next drug in line (sequential monotherapy). When all the drugs had been tried, combination therapy or prednisone would be considered. Drug doses were kept low, and there was a high level of anxiety about side effects. At the end of the line there were no more treatment options. Patients with rheumatoid arthritis lived with chronic inflammation and complained little, while their joints, sooner or later, crumbled away and the orthopaedic surgeon was consulted.

Ten years on there have been many changes. The fundamental difference is that the importance of controlling inflammation early and completely has been recognised. This means starting DMARD treatment as soon as the diagnosis is confirmed, and treating to the target of minimal joint activity. DMARDs are used in multiple combinations and a new range of 'biological drugs' has been developed that are better at controlling the inflammatory immune processes involved in RA. There are greater financial and social costs arising from more intense monitoring, frequent treatment changes, greater health risks from side effects of medication, and drug costs. In one study that showed improved outcomes with combination therapies, patients were seen every month in outpatients to have their treatment reviewed and changed. Current rheumatology services cannot provide that; there are implications for the organisation and funding of health services. For general practice this means identifying patients with suspected RA and making early referral – anyone with synovitis lasting more than six weeks should be referred. GPs can be involved in disease management, adjusting medication according to therapeutic targets, and managing patients on DMARDs using knowledge of the health risks they carry. It would be a mistake to think that everything has changed however. Access to rheumatology services remains poor in many areas of the country. There is still no cure for RA and there are many patients whose arthritis cannot be controlled adequately despite the new approaches. Although patients at the most severe end of the spectrum are able to use one of the new biological drugs, they are still waiting for others to be funded. And it is too early to know whether the new treatments will be cost-effective in reducing disability and the need for surgery.

## Improvements in diagnosis

Although it can be fairly obvious when a patient has rheumatoid arthritis, the classical presentation of an acute onset of symmetrical polysynovitis affecting the hands, wrists, shoulders, knees and feet occurs in only about 20% of cases. Making a diagnosis can be difficult; a rheumatologist can help. RA can start insidiously, be asymmetrical, affect only large joints such as the knee, and be rheumatoid factor negative. It needs to be distinguished from other causes of chronic inflammatory arthritis, such as gout, pseudogout, connective tissue diseases and spondyloarthritis. This is not always easy, and sometimes treatment needs to be started before the diagnosis is certain.

There are diagnostic criteria for RA (Table 1) that were developed for use in clinical trials. They do not work

well in early disease however, as rheumatoid factor is often negative, nodules and radiographic changes absent in the first few months, even in people who will eventually develop these features. Two commonly-used biomarkers for RA diagnosis and prognosis are IgM rheumatoid factor (RF) and anti-CCP antibody. Despite its name and availability on blood test forms, RF is not specific to RA, being found in many other conditions and in about 5% of the normal population. The new test, anti-CCP antibody, detects antibodies to cyclic citrullinated peptide, an amino acid derived from arginine and a component of filligrin, which is a protein found in epithelial cells. As with all autoantibodies, its utility is not as good as first hoped, as it may be negative in people with erosive RA and can be positive in other types of arthritis. Its sensitivity is lower than RF (between 40 and 60% vs 73%) and specificity higher (around 90%, vs 82%); combining RF and anti-CCP gives a specificity of 96%. Patients with early arthritis and who are positive for RF and anti-CCP are more likely to develop erosive disease, so these tests can be used to guide a treatment decision. Conversely, those who are negative for both of these markers have a better prognosis, and such a finding should prompt review of the diagnosis.

*Table 1. American Rheumatism Association Classification Criteria for Rheumatoid Arthritis.*

| Four features must be present – the first four for at least six weeks |
|---|
| **Morning stiffness:** Lasting at least an hour |
| **Arthritis of three joint areas:** (Out of right or left PIP, MCP, wrist, elbow, knee, ankle, MTP) |
| **Hand joint involved:** At least one area swollen out of wrist, MCP, or PIP joint |
| **Symmetric arthritis:** Simultaneous arthritis in joint areas on both sides of the body |
| **Rheumatoid nodules** |
| **Serum rheumatoid factor** |
| **Radiographic changes:** Typical of rheumatoid arthritis in the hand or wrist |

### Who should be treated, and when?

Patients diagnosed with rheumatoid arthritis should start treatment as soon as possible, as early treatment with DMARDs has been shown to improve outcome. If CRP measurements are plotted against time, the area under the curve (i.e. the cumulative burden of inflammation) correlates closely with joint damage scores. Good control of inflammation should therefore prevent joint damage. Several disease activity indices have been developed to give a therapeutic target, although uptake in the clinic has been slow because they can be time-consuming. They incorporate clinical measures (tender and swollen joint counts), biomarkers of inflammation (ESR or CRP) and functional measures (disability index). In making treatment decisions, the philosophy is to 'treat-to-target' using whatever means available. Sequential monotherapy has been replaced by a range of strategies, including combination therapy, more frequent changes in drugs and doses, and the use of newer and more powerful inhibitors of the inflammatory process. It has also led to a revision of previous predominantly negative ideas about the role of prednisone.

### Which drug, in which order?

The choice of initial drug is almost always methotrexate, owing to its high response rate (about 85%), predictable side effect profile, ease of administration and low cost. It is given as a once-weekly oral dose, starting at 7.5–10mg weekly, rapidly increased according to tolerability to the usual therapeutic dose of 15–25mg/week. Methotrexate may be dispensed as 2.5 or 10mg tablets. Subcutaneous administration can be more effective as oral bioavailability varies between patients, but is sometimes difficult to organise logistically. Folic acid (either 5mg weekly or 0.8mg daily) has been shown to reduce side effects (notably liver and cytopoenias) and is routinely prescribed. Folic acid probably reduces the effectiveness of methotrexate and can be taken at a different time of the week (e.g. Methotrexate on Monday, Folic acid on Friday).

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The common side effects of methotrexate are nausea and mouth ulcers. Nausea is probably mediated by a central effect and is not associated with gastrointestinal ulceration. It may settle with continued use, or else the dose can be divided. Antiacid preparations rarely help but some patients benefit from an antiemetic such as domperidone taken for a day or two around the time of dosing. Rarely, methotrexate can cause a pneumonitis characterised by acute onset of shortness of breath. It is due to alveolar oedema, which can be seen on CXR, and can progress rapidly over a few hours. It needs to be distinguished from infective causes and bronchiolitis associated with rheumatoid arthritis itself. Patients suspected of having methotrexate pneumonitis should be referred to the acute medical service as it is life-threatening. It is treated with high dose intravenous corticosteroids. A more insidious onset of respiratory involvement occurs characterised by a dry cough. Other rare side effects include photosensitivity, although it is not necessary to advise all patients to avoid sunlight. NSAIDs reduce

*Table 2. Dosing, side effects and monitoring of commonly used DMARDs. This table is intended as a guide and is not exhaustive nor intended to replace information in data sheets or given by local rheumatology services.*

| Drug | Dosing | Side effects | Cautions | Monitoring |
|---|---|---|---|---|
| **Methotrexate** | 7.5–25mg/week<br>Co-prescribe folic acid 5mg/week or 0.8mg/day | Nausea, mouth ulcers, hair loss, cytopoenias, elevated liver enzymes, rarely pneumonitis | Contraindicated in pregnancy, breastfeeding. Limit alcohol intake. Dose reductions in severe renal impairment | Baseline CXR, LFT, hepatitis screen, FBC, renal function; fortnightly LFT, FBC first 6 weeks then 1–3 monthly |
| **Sulphasalazine** | 1.5–3.0g/day in divided doses | Nausea, abdominal pain, cytopoenias, agranulocytosis, elevated liver enzymes, skin rashes, reversible oligospermia | Sulphonamide allergy. May colour urine yellow and stain soft contact lenses. | Baseline LFT, FBC; monthly for 6 months, 3-monthly thereafter |
| **Hydroxychloroquine** | 200mg–400mg daily | Blurred vision, skin rash, photosensitivity. Very rarely maculopathy | | Baseline eye screening if staying on treatment, then at 5 years, then annually |
| **Leflunomide** | Loading dose (optional) 100mg x 3, maintenance 10–20mg/day | Diarrhoea, hair loss, raised liver enzymes, cytopoenias, hypertension, peripheral neuropathy | Contraindicated in pregnancy and breastfeeding. Washout procedure available | Baseline CXR, LFT, hepatitis screen, FBC, renal function; fortnightly LFT, FBC first 6 weeks then monthly |
| **Adalimumab** | 40mg sc every 2 weeks, used with methotrexate | Injection site reactions, anaphylactoid reactions, cytopoenias, raised liver enzymes, reactivation of latent TB, increase risk of infection, demyelination | Safety in pregnancy not established – avoid. Withhold injection if systemic infection is present | Screen for infection and TB. Baseline FBC, LFT, hepatitis screen, CXR. Monthly LFT, FBC |

renal clearance of methotrexate and therefore have a theoretical interaction, but this is not a clinical problem with once weekly drug dosing. Liver and bone marrow toxicity occur and are usually managed by dose reduction in the first instance. Intake of alcohol and other liver toxins should be limited.

When methotrexate fails to control the inflammation, there are many possible strategies, and not a lot of evidence as to which is best. Guidelines have been produced by various authorities (for the American College of Rheumatology guideline see reading list). The next step is usually a methotrexate combination therapy, although if methotrexate has been stopped because of toxicity then a different DMARD (usually sulphasalazine) may be given as monotherapy. There are many permutations and combinations of DMARDs. The choice of a combination is a matter of clinical judgment, but is influenced to some extent by PHARMAC funding restrictions on leflunomide and adalimumab. Hydroxychloroquine and sulphasalazine are commonly used with methotrexate, a triple therapy that has been shown to be effective in clinical trials. Other combinations may include intramuscular gold, azathioprine, and low-dose prednisone.

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Leflunomide is available on special authority (rheumatologist) to people who have tried both methotrexate and sulphasalazine (alone or in combination), and can be used either by itself or in combination with methotrexate. It has a similar side effect profile to methotrexate, with the addition of diarrhoea, hair loss and hypertension. It can be retained in the body for up to two years due to enterohepatic circulation, but blood levels and a washout procedure can be done. This should be considered for women who wish to conceive as leflunomide is teratogenic. Cyclosporin can also be useful, although it has a narrow therapeutic window and has not found an established place in therapy. It is quite well tolerated but renal toxicity (increased creatinine and hypertension) limits the doses that can be used.

### Biological agents

Studies identifying pro-inflammatory cytokines in the 1980s led directly to the development of biologi-

cal DMARDs, introduced in 1998. These are antibodies directed at specific cytokines. The most widely used, and the only type funded in NZ, are anti-Tumour Necrosis Factor alpha (TNFα) agents. At present, adalimumab is the only TNF inhibitor funded for rheumatoid arthritis in New Zealand, although both etanercept and infliximab have this indication. The special authority requires patients to have tried three months' treatment with each of methotrexate, combination (triple) therapy, leflunomide or cyclosporin, and disease activity criteria. It is more effective when used with methotrexate. Clinical trial results have been impressive, particularly in stopping and in some cases reversing the progression of joint damage. Although TNF inhibitors are highly effective at controlling inflammation, there are concerns about serious infections, the reactivation of latent tuberculosis, and a possible increased risk of malignancy. Before starting, patients are screened for TB by CXR and Mantoux test; serological tests are also used but not widely available. Patients with active or latent TB are treated according to NZ guidelines. Hepatitis B and C, and HIV screening where appropriate, should also be done.

Adalimumab is given subcutaneously. Injection site reactions are the commonest side effect (redness, itching and swelling) and if not infected can be managed with application of ice or a local corticosteroid cream. Anaphylactoid reactions can occur and may need treatment with antihistamine and steroid. Most patients are taught to self-inject. The drug should be withheld if there is any sign of systemic infection. Patients whose arthritis does not respond to an anti-TNF drug, or where they have had to stop because of side effects, may respond to a second TNF inhibitor, or a biological drug with a different target. These options are not yet funded for use in RA patients in New Zealand.

### B cell therapies

Therapies aimed at depleting B cells have been developed with the idea that removing B cell clones that make pathogenic autoantibodies would lead to long-lasting improvement in a range of autoimmune conditions. Rituximab is a biological drug that targets a B cell surface marker, CD20. It is given as two intravenous infusions spaced two weeks apart. Although rituximab has been shown to be an effective treatment for RA, there are questions about how long the improvements last, which affects cost-effectiveness. It is in routine use in rheumatology clinics worldwide but is usually reserved for those whose disease has proved refractory to anti-TNF therapy. Rituximab is not currently on the pharmaceutical schedule for use in RA.

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### Prednisone

Low-dose prednisone has a DMARD action in limiting disability and progression of erosive disease, particularly in the first two years. Evidence suggests that there is no lower dose devoid of side effects however. In the average rheumatology clinic, about 50% of RA patients will be long-term users of steroids. The use of low-dose (5mg/day) prednisone is recommended at diagnosis by some rheumatologists, with the aim of withdrawing them after two years or once good disease control has been achieved with DMARDs. Others reserve prednisone as an add-in treatment when DMARDs are not achieving adequate disease control. Prednisone should be used before an anti-TNF inhibitor however. To cover acute flares of arthritis, intra-articular corticosteroid or a course of medium dose prednisone (up to 20mg daily) can be useful. High initial dose rapid tapering such as is used in asthma treatment is not a good strategy, as side effects are common on the high doses, and arthritis flares rapidly as the dose is reduced. The need for courses of oral prednisone or joint injections indicates poor disease control and should prompt a review of DMARD treatment. Those on low-dose prednisone require a bone density scan and be offered appropriate treatment for steroid related bone loss; cardiovascular risks need to be managed.

Rheumatoid arthritis is a systemic illness that also involves the joints. Medical management therefore entails managing problems in other organ systems. There is an excess mortality from RA, due largely to an increase in cardiovascular death, infections and lymphoreticular system malignancy. GPs have an important role to play, especially in managing cardiovascular risks and infections.

### Future prospects

The evolving knowledge of the basic science of the complex processes involved in RA reveals new potential therapeutic targets for intervention with biological drugs almost every month. Treatment options will increase and much better disease control and outcome will become the normal expectation. Remission and cure are even being talked about. Health care systems that already struggle to resource the costs of existing technologies will be stressed further. There will be an increasing need for much of the disease and drug monitoring to be done by rheumatology specialist nurses, with much better co-ordination and communication between primary and secondary care. There is in this a danger that rheumatology services will be consumed by the activity of intense treatment of a relatively small

number of patients with serious inflammatory arthritis. Patients with less treatable conditions or with non-inflammatory arthritis are likely to find access is restricted unless health care resources are enhanced and better organised.

### Managing symptoms

This article is focused on drug treatment approaches to disease modification in RA. Symptom control with NSAIDs and analgesics remain necessary for most patients, although they can more often be stopped than in the past, as disease control is improving. Drug treatment remains an important, but sometimes a small part of the overall management plan. Physiotherapy, occupational therapy, counselling, orthotics, and orthopaedic surgery all retain a place. As with all chronic diseases, patients need to understand the condition and its treatment; education is the key to disease management. Without it, the increasingly successful but complex and potentially hazardous treatment approaches are likely to fail. Education is an important role for rheumatology nurses, but all members of the health care team can contribute.

### Competing interests

None declared.

*List of further reading and resources*

***Websites***

| Organisation | Web address | Features |
|---|---|---|
| **New Zealand Rheumatology Association** | www.rheumatology.org.nz | Directory of NZ Rheumatologists and Rheumatology Centres. Disease and Drug information sheets (local) |
| **American College of Rheumatology** | www.rheumatology.org | Extensive patient information about various forms of arthritis and their treatment |
| **National Institutes of Health (US site)** | www.nlm.nih/govt/healthtopics | A good source of patient information about arthritis and many other health topics |

***Reading***

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# Alcohol and cardiovascular risk

*'An extensive body of data shows concordant J-shaped associations between alcohol intake and a variety of adverse health outcomes, including coronary heart disease, diabetes, hypertension, congestive heart failure, stroke, dementia, Raynaud's phenomenon, and all-cause mortality. Light to moderate alcohol consumption (up to 1 drink daily for women and 1 or 2 drinks daily for men) is associated with cardioprotective benefits, whereas increasingly excessive consumption results in proportional worsening of outcomes. Alcohol consumption confers cardiovascular protection predominately through improvements in insulin sensitivity and high-density lipoprotein cholesterol. The ethanol itself, rather than specific components of various alcoholic beverages, appears to be the major factor in conferring health benefits. Low-dose daily alcohol is associated with better health than less frequent consumption. Binge drinking, even among otherwise light drinkers, increases cardiovascular events and mortality. Alcohol should not be universally prescribed for health enhancement to nondrinking individuals owing to the lack of randomized outcome data and the potential for problem drinking.'*

*O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and Cardiovascular Health: The Razor-Sharp Double-Edged Sword. J Am Coll Cardiol 2007;50:1009-1014.*