Rheumatoid arthritis

By Dr Luke Bereznicki

Introduction

Rheumatoid arthritis is the most common autoimmune disease in Australia, affecting approximately 2% of the population. It is more common in females, who tend to develop the condition at an earlier age. Disease onset most commonly occurs in people aged 35 to 64 years. Rheumatoid arthritis has led to a number of important changes to its management. These include recognition of the importance of early diagnosis and treatment, increasing use of DMARDs in combination, the development and increasing use of anti-cytokine medications, and recognition of the contribution of coexisting diseases (particularly cardiovascular disease) to the long-term outcomes for people with rheumatoid arthritis.

Pathophysiology

Rheumatoid arthritis is an inflammatory autoimmune disease with local and systemic manifestations. It usually affects the synovial joints initially, causing pain, swelling and stiffness. The inflammatory response involves a number of cells (e.g. T-lymphocytes, B-lymphocytes, macrophages) and cytokines (e.g. tumour necrosis factor (TNF), interleukin-1 (IL-1)). White blood cells invade the synovium...
A number of inflammatory mediators are released (including cytokines, chemokines and prostanoids) which damage surrounding bone, cartilage, tendons and ligaments and may cause systemic symptoms such as fatigue. This inflammatory process leads to functional limitations, and progresses to joint destruction (with both bony erosions and cartilage loss) and extra-articular disease (e.g. rheumatoid nodules, osteoporosis, lung fibrosis). Mortality rates are higher in people with rheumatoid arthritis compared to people without the disease, presumably as a result of chronic, systemic inflammation.

**Initial diagnosis**

In the past, the outcome of rheumatoid arthritis was progressive joint destruction with loss of joint function. However, the aims of treatment have shifted from palliation to early induction of disease remission to prevent joint damage. This is due to earlier diagnosis and treatment, new medications, and better monitoring of patients. Joint damage, largely irreversible, occurs early in rheumatoid arthritis. In one study, 30% of patients had evidence of bony erosions at the time of diagnosis, and 60% at two years following diagnosis. Research shows that early diagnosis and initiation of DMARDs within three months are critical. A delay of even 12 weeks in their introduction is associated with substantially greater joint damage at five years following diagnosis.

No single test or set of criteria is available to diagnose rheumatoid arthritis. A combination of clinical assessment, laboratory tests and x-rays are generally used. Joint swelling (synovitis) associated with pain or stiffness is a key diagnostic feature in early disease, along with the number of tender or swollen joint areas, and the pattern of joint involvement. The classic pattern is symmetrical involvement of the small joints of the hands and feet. Atypical joint involvement, which occurs in some patients, presents with only one large joint affected. General symptoms such as fatigue, fever, sweating and weight loss may also be present in early disease. A number of tests can be used to assist diagnosis, although the absence of positive results does not necessarily rule out rheumatoid arthritis. These include acute phase reactants (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)), full blood count and autoantibody tests (rheumatoid factor (RF), anticyclic citrullinated peptide antibodies (anti-CCP)).

**Initial therapy**

In the early stages of inflammatory arthritis, a definitive diagnosis of rheumatoid arthritis may be difficult to make. However, if rheumatoid arthritis is suspected initial therapy can be commenced. This consists of omega-3 fatty acids at a dose of at least 2.7 g daily in divided doses (equivalent to 9 standard dose fish oil capsules), with or without paracetamol and/or an NSAID. For those with severe symptoms and functional impairment or in patients at risk of NSAID adverse effects, low-dose prednisolone/prednisone is recommended. DMARDs may also be considered when there are several swollen joints, especially if autoantibody tests are positive (in conjunction with referral to a rheumatologist). Other recommended interventions include:

**Table 1. Conventional DMARDs.**

<table>
<thead>
<tr>
<th>DMARD</th>
<th>Efficacy*</th>
<th>Efficacy in combination with methotrexate*</th>
<th>Major toxicity frequency*</th>
<th>Selected adverse effects**</th>
<th>Recommended monitoring**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>+</td>
<td>Unknown</td>
<td>+</td>
<td>Myelosuppression, hepatotoxicity</td>
<td>FBE, U&amp;E, LFT baseline; repeat FBE every 2 weeks until dose stable, then FBE every 1–3 months</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>Renal insufficiency, anaemia, hypertension</td>
<td>FBE, U&amp;E, LFT, BP, urinalysis baseline, then U&amp;E, BP every 2 weeks until dose stable, then every 3 months</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>Infections, diarrhoea, alopecia, rash, raised liver enzymes, headache, paraesthesia</td>
<td>LFT, FBE, Cr, BP baseline; then every 2–4 weeks for 3 months, then every 3 months</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>Myelosuppression, pulmonary infiltrates, hepatic fibrosis and cirrhosis</td>
<td>FBE, Cr, LFT baseline and dose increase; then every 2–4 weeks for 3 months, then every 3 months. PFT, chest x-ray baseline</td>
</tr>
<tr>
<td>Gold salts</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>Rash, itch, diarrhoea (with oral gold), myelosuppression, proteinuria</td>
<td>FBE, urinalysis baseline; oral: repeat each month; IM: every 1–2 weeks for the first 5 months then before each injection</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>Rash, retinal damage, GI adverse effects</td>
<td>FBE, Cr, LFT baseline and dose increase; ophthalmic exam baseline, then annually</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>Myelosuppression, proteinuria, rash, stomatitis</td>
<td>FBE and urinalysis every 2 weeks until dose stable, then every 1–3 months</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>Myelosuppression, rash</td>
<td>FBE, Cr, LFT baseline and dose increase; then every 2–4 weeks for 3 months, then every 3 months</td>
</tr>
</tbody>
</table>

*Taken from Roberts et al. 2006. ± scoring is a clinical guide to relative effects representing the views of the authors based on published studies.

**Taken from the AMH 2011.**
The immune response is most effective when started early. The ‘window of opportunity’ where treatment is most effective is particularly important for people with more aggressive disease. This is particularly important for the management of rheumatoid arthritis. DMARDs prevent joint damage. A meta-analysis demonstrated that early introduction of DMARDs (e.g., methotrexate) may be beneficial in the management of rheumatoid arthritis. It can now be expected to have a drug well controlled and are likely to avoid long-term damage and disability. 

Ongoing management

The prognosis for people newly diagnosed with rheumatoid arthritis has improved as the importance of early diagnosis and treatment is increasingly recognised. Most people who develop rheumatoid arthritis can expect to have their disease well controlled and are likely to avoid long-term damage and disability.

The ultimate aim in treating rheumatoid arthritis is to induce complete remission. If remission cannot be achieved, treatment is aimed at controlling disease activity and slowing the rate of joint damage. Other treatment goals include alleviation of pain, maintenance of function for essential activities of daily living and work, and maximisation of quality of life.

DMARDs

The early use of DMARDs, their use in combination, and the development of new biological DMARDs (bDMARDs) are seen as major advances in the management of rheumatoid arthritis and are largely responsible for the positive changes in patient outcomes.

Conventional DMARDs

A number of conventional DMARDs are available (see Table 1 for a comparison of available agents). Methotrexate is regarded as first-line treatment, particularly for moderate to severe disease or where there is a high risk of erosive disease. Research has found that it improves clinical and radiological outcomes; has an acceptable long-term safety profile; is acceptable to patients, with good adherence rates; and is cost-effective. Leflunomide or sulfasalazine are recommended as alternatives where methotrexate is contraindicated. Hydroxychloroquine is considered an appropriate choice for mild disease. The most common adverse effects of methotrexate are gastrointestinal problems and hepatic toxicity. Folic acid is recommended to reduce the risk of gastrointestinal toxicity; the suggested regimen in the Therapeutic Guidelines (Rheumatology) is 5–10 mg once weekly.

There is increasing evidence that combination therapy is more effective than monotherapy for many patients. The balance between benefit and risk varies among combinations. A recent meta-analysis found that methotrexate plus sulfasalazine and/or hydroxychloroquine had particularly favourable benefit/risk ratios compared to other combinations of conventional DMARDs. Current Australian guidelines state that combination therapy appears to have no greater toxicity than monotherapy, although individual combinations vary in terms of toxicity.

**Table 2. Biological DMARDs.**

<table>
<thead>
<tr>
<th>bDMARD</th>
<th>Description</th>
<th>Selected adverse effects*</th>
<th>Recommended monitoring*</th>
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</thead>
<tbody>
<tr>
<td><strong>TNF-alpha inhibitors</strong></td>
<td></td>
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<tr>
<td>Adalimumab</td>
<td>Humanised monoclonal antibody against TBF-alpha</td>
<td>Infections, worsening heart failure, blood dyscrasias, (infliximab also hypersensitivity, infusion-related reactions)</td>
<td>FBE, Cr, LFT baseline (also at dose increase for adalimumab and infliximab)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Fab fragment of a humanised TNF-alpha inhibitor monoclonal antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>Humanised soluble recombinant TNG-alpha type II receptor-lgG1 fusion protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>Human monoclonal antibody against TNF-alpha</td>
<td></td>
<td></td>
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<tr>
<td>Infliximab</td>
<td>Chimeric mouse-human monoclonal antibody against TNF-alpha</td>
<td></td>
<td></td>
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<tr>
<td><strong>Cytokine modulators</strong></td>
<td></td>
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<tr>
<td>Abatacept</td>
<td>An immunoglobulin and extracellular CTLA4 domain fusion protein that selectively inhibits T-cell co-stimulation</td>
<td>Infections, infusion-related reactions</td>
<td>FBE, Cr, LFT baseline</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Human recombinant interleukin 1 receptor antagonist</td>
<td>Infections, neutropenia</td>
<td>FBE baseline</td>
</tr>
<tr>
<td>Rituiximab</td>
<td>Chimeric monoclonal anti-CD20 antibody that depletes B-cells</td>
<td>Infections, infusion-related reactions</td>
<td>FBE, Cr, LFT baseline</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Humanised monoclonal anti-interleukin 6 receptor antibody</td>
<td>Infections, neutropenia, thrombocytopenia, hyperlipidaemia, infusion-related reactions</td>
<td>FBE, lipids, LFT baseline, then platelets and neutrophils every 4–8 weeks; LFT every 4–8 weeks for 6 months, then 3 monthly; lipids at 4–8 weeks</td>
</tr>
</tbody>
</table>

*Taken from the AMH 2011.20
Cr = creatinine, FBE = full blood examination, LFT = liver function tests.
therapy should be considered for those who do not respond adequately to monotherapy or may be used initially for those with a poor prognosis (e.g. high disease activity, large number of swollen joints).\textsuperscript{5,10}

**Corticosteroids**

A low to moderate dose (7.5 mg to 15 mg) of prednisolone/prednisone is effective in reducing symptoms of rheumatoid arthritis and progression to joint destruction.\textsuperscript{16} Intra-articular or intramuscular corticosteroids are also effective for rapid symptomatic relief.\textsuperscript{10} Because they have a rapid onset, corticosteroids are useful as ‘bridging therapy’ when DMARDs or other combination therapy are commenced.\textsuperscript{5,10} However, they are not recommended for long-term use due to their well-known adverse effect profile (including increased cardiovascular risk, mood disturbances and osteoporosis).\textsuperscript{5,10}

**Biological DMARDs**

The bDMARDs target cytokines and cells of the immune system that are involved in joint destruction (see Table 2 for a comparison of available agents). The available evidence demonstrates that the combination of methotrexate and a bDMARD is superior to either drug alone at reducing symptoms and progression of joint damage in patients with early disease and those who do not respond to conventional DMARDs.\textsuperscript{17} In Australia, their use is reserved for the treatment of rheumatoid arthritis if remission is not achieved with the appropriate use of conventional DMARDs.\textsuperscript{5} They are all more effective when used in combination with methotrexate.\textsuperscript{5,17} People taking bDMARDs are at increased risk of bacterial infection, and patients should be asked to report symptoms suggestive of infection, including fever or persistent cough.\textsuperscript{5,18}

**Analgesics**

The use of paracetamol is recommended for managing pain in early rheumatoid arthritis, although many patients are unlikely to receive sufficient pain relief when used alone.\textsuperscript{10} Patients should be encouraged to take paracetamol ‘around the clock’ to maximise its effectiveness. If possible, paracetamol should be used instead of NSAIDs, although NSAIDs are more effective in established disease.\textsuperscript{18} The use of regular paracetamol and fish oil (see below) is a useful way to limit the need for NSAIDs. Opioid analgesics (e.g. codeine, tramadol, oxycodone) may also be recommended when pain is interfering with patients’ ability to function.\textsuperscript{20} Other options, such as amitriptyline, may also be recommended.\textsuperscript{20}

Because of their adverse effect profile (e.g. increased cardiovascular risk, gastrointestinal toxicity, hypertension) and the fact that they do not reduce joint damage, NSAIDs are not regarded as first-line treatment for rheumatoid arthritis. Their role is to reduce symptoms prior to the commencement of a DMARD.\textsuperscript{5,21} An important practical consideration is a patient’s need for chronic use of NSAIDs in rheumatoid arthritis. This can be used as a prompt to initiate more intensive therapies.\textsuperscript{21} They should be used for the shortest duration possible at the lowest effective dose and avoided in people taking corticosteroids and/or anticoagulants.\textsuperscript{10}

**Omega-3 fatty acid supplements**

Current guidelines recommend omega-3 fatty acid supplementation as an adjunct for pain management and relief of joint stiffness in rheumatoid arthritis.\textsuperscript{5,10} At relatively high doses (> 2.7g per day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), they have been shown to reduce symptoms and the need for NSAIDs, and may also provide some cardiovascular protection.\textsuperscript{21} The benefits may take eight to 12 weeks to become fully apparent.\textsuperscript{5}

**Complementary medicines**

There is currently insufficient evidence to support the use of complementary and alternative medicines for the management of rheumatoid arthritis, with the exception of fatty acid supplementation.\textsuperscript{10} The Chinese herb Tripterygium wilfordii has been shown to be effective in improving the symptoms of rheumatoid arthritis. However, it is associated with significantly higher rates of serious adverse effects than placebo (e.g. impaired renal function, haematotoxicity, immunosuppressive effects).\textsuperscript{23} Current guidelines advise against its use.\textsuperscript{10}

**Non-pharmacological interventions**

Current Australian guidelines highlight the importance of patient knowledge and self-efficacy in the management of rheumatoid arthritis.\textsuperscript{5,10} Patients who feel helpless regarding their condition tend to have poorer outcomes. Arthritis self-management courses are offered by Arthritis Australia and have demonstrated improved disease outcomes.\textsuperscript{5} There is limited evidence of a beneficial effect of specific diets (e.g. gluten free, vegan, vegetarian) on patient outcomes.\textsuperscript{24} However, it is accepted that weight reduction in patients who are overweight or obese reduces impact on weight-bearing joints and the risk of cardiovascular disease.\textsuperscript{10} Maintaining BMI within the normal range is important, as there is evidence that patients with low BMI have poorer functional status.\textsuperscript{25} The available evidence suggests that low to moderate intensity exercise is effective in increasing aerobic capacity and muscle strength in people with rheumatoid arthritis, with no adverse effects on pain or disease activity.\textsuperscript{26} Cigarette smoking, in addition to increasing patients’ cardiovascular risk, may predispose to rheumatoid arthritis and increase disease severity.\textsuperscript{27} An active approach to assist rheumatoid arthritis sufferers to quit is therefore important for a number of reasons.

**Cardiovascular risk**

People with rheumatoid arthritis have a higher risk of cardiovascular disease, principally due to the presence of chronic systemic inflammation.\textsuperscript{28} The available evidence suggests that effective and sustained control of joint and systemic inflammation will reduce this excess cardiovascular risk.\textsuperscript{26} Prevention of cardiovascular disease in rheumatoid arthritis should involve a comprehensive approach including cardiovascular risk factor screening and management, effective control of disease activity, and prompt investigation of suspected cardiac disease.\textsuperscript{5,28}

**Summary**

There have been a number of important changes to the management of rheumatoid arthritis...
over the past 10 to 15 years. Early diagnosis and treatment are critical in slowing disease progression. Early use of DMARDs, combined use of disease-modifying agents, and the use of bDMARDs have been critical in improving patient outcomes. Pharmacists can assist patients with rheumatoid arthritis by encouraging them to learn more about their condition; educating them about their medications (e.g., benefits and risks); assisting with monitoring for adverse effects of treatment; and providing advice on disease management using both pharmacological and non-pharmacological strategies.

References
5. Therapeutic Guidelines Ltd. eTG Complete: Rheumatology, 2011.

Questions
1. The prevalence of rheumatoid arthritis in Australia is estimated to be:
   a) 1%.
   b) 2%.
   c) 3%.
   d) 4%.
2. The prognosis of rheumatoid arthritis has been improved by all of the following, EXCEPT:
   a) early diagnosis.
   b) early initiation of DMARDs.
   c) increased use of DMARDs in combination.
   d) increased use of NSAIDs.
3. The ‘window of opportunity’ for initiation of DMARD treatment for rheumatoid arthritis where the immune response is most responsive to therapy and the course of the disease can be altered is thought to be:
   a) 4 weeks.
   b) 8 weeks.
   c) 12 weeks.
   d) 16 weeks.
4. Which ONE of the following DMARDs is generally regarded as the preferred first-line treatment for moderate-severe rheumatoid arthritis?
   a) Methotrexate.
   b) Leflunomide.
   c) Cyclosporin.
   d) Sulphasalazine.
5. Beneficial strategies to limit the long-term use of NSAIDs in the treatment of rheumatoid arthritis include all of the following, EXCEPT:
   a) regular use of paracetamol.
   b) fish oil supplementation.
   c) early initiation of DMARD therapy.
   d) regular use of prednisolone.