

Helping patients achieve remission of rheumatoid arthritis

Rheumatoid arthritis is the most common autoimmune disease in Australia. Over 400 000 people, mostly women, are affected.¹ It is a disabling condition that impacts on quality of life and increases mortality, mainly through cardiovascular disease.¹ Around 25% of people may stop working, or have a reduced capacity to work, 6 years after diagnosis.¹

Primary care practitioners have a role in early referral for treatment (which improves patient outcomes), monitoring disease-modifying antirheumatic drugs (DMARDs) and providing advice to patients on managing their disease.

Early referral for early treatment

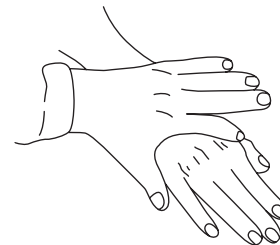
Consider referral to a rheumatologist, **within 6 weeks of the onset of symptoms**, for patients with:

- two or more swollen joints, and/or
- morning stiffness for > 30 minutes, and/or
- involvement of metacarpophalangeal and/or metatarsophalangeal joints.²

Joint damage occurs early in the disease and is progressive.²⁻⁴ Patients who are diagnosed and managed earlier have a better prognosis.²⁻⁵

Joint swelling (synovitis) associated with pain or stiffness is a feature of early arthritis.^{2,5} Tenderness of the joint line is insufficient to detect synovitis.⁵ Determine the total number of affected hand and foot joints by a 'squeeze test', involving gentle palpation of individual joints (Figure 1).^{4,6}

Figure 1: 'Squeeze test' for joints of the hands and feet⁴



Diagnosis may be established when there are at least 4 of 7 features (Box 1).⁷ This may be difficult in early arthritis, because the signs and symptoms vary and may develop over time.²⁻⁴ Referring patients with less severe symptoms may facilitate early intervention by a specialist before the disease progresses.⁴

Box 1: Features suggesting rheumatoid arthritis^{5,7}

- Morning stiffness for > 1 hour for > 6 weeks
- Three or more affected joints for > 6 weeks
- At least one affected hand joint for > 6 weeks
- Symmetrical arthritis in at least one area for > 6 weeks
- Presence of rheumatoid nodules
- Positive rheumatoid factor
- Bony erosions evident on X-rays of the hands, wrist or feet (uncommon in early disease)

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Conventional DMARDs
and biological DMARDs

Regular monitoring
essential

Involving patients

Case Study 45: DMARDs
in rheumatoid arthritis

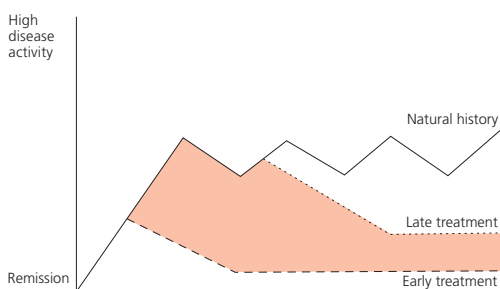
DMARDs — reduce symptoms and disease progression

Conventional disease-modifying antirheumatic drugs — or DMARDs — (e.g. methotrexate) and the newer, biological DMARDs are the only drug treatments that can minimise or prevent joint damage, preserve function and induce clinical remission (symptom relief, normal inflammatory markers and no joint swelling).⁵

Clinical remission is the treatment goal

Starting DMARDs early improves clinical remission (Figure 2).^{2–4} Patients at risk of persistent and/or erosive arthritis should be started on DMARDs as early as possible (Box 2).^{2,5}

Figure 2: Effect of early treatment with DMARDs³
(shaded area represents permanent joint damage)



Roberts LJ, et al. **Early combination disease modifying antirheumatic drug treatment for rheumatoid arthritis.** MJA 2006;184:122–5. © Copyright 2006. *The Medical Journal of Australia* — reproduced with permission.

Methotrexate — a first-choice DMARD

Use methotrexate in moderate to severe disease, or in patients at risk of persistent and/or erosive arthritis.^{2,5,9} Sulfasalazine or hydroxychloroquine may be considered in mild disease.⁵

Methotrexate has similar efficacy to other DMARDs, but has a better long-term benefit–harm profile.^{2,10,11} One review of observational and randomised controlled trials found that more patients continued treatment with methotrexate for 5 years than with either sulfasalazine or injectable gold.¹²

Methotrexate makes up over 20% of the medications for rheumatoid arthritis prescribed by GPs.¹³ It may be used with other conventional DMARDs. Combining treatment with biological DMARDs can lead to greater reductions in disease activity (see opposite).

Intensify treatment if clinical remission is not achieved

Combine sulfasalazine, hydroxychloroquine or both with methotrexate.^{3,5,11} Consider combination therapy as initial treatment for those with a poorer prognosis.⁵ In patients with severe disease, or who have not responded to monotherapy, combining two or more DMARDs improves clinical efficacy compared with a single DMARD.^{2,5,15–17}

If initial combination therapy is ineffective or not tolerated, leflunomide may be used alone or with methotrexate.^{5,8,11} Leflunomide is as effective as methotrexate in slowing progression of joint damage, but may be less tolerated.¹⁸ If clinical remission is still not achieved, biological DMARDs may be started.

Box 2: Indicators of poorer outcome in rheumatoid arthritis^{2,4,5,8}

Clinical presentation

- High disease activity at onset
- Long duration of disease
- Large number of swollen joints (> 20)*
- Involvement of small joints of hands and feet
- Early involvement of large joints
- Extra-articular features (e.g. nodules)
- Impaired functional status

Laboratory tests at onset

- Positive rheumatoid factor*
- Elevated erythrocyte sedimentation rate (ESR)* or C-reactive protein (CRP)*
- Anti-cyclic citrullinated peptide (anti-CCP) antibodies
- Early radiological erosions

Sociodemographic status

- Female
- Onset in early adulthood
- Onset in elderly males
- Smoking
- Low socioeconomic status
- Low educational level

*Major indicators



Prescribing pointers for methotrexate^{5,14}

- Prescribe methotrexate **once a week**
- Overdose is an uncommon but potentially serious error — provide written instructions about weekly, rather than daily, dosing and specify the day and time of dosing
- Use with folic acid to reduce the risk of gastrointestinal adverse effects
- Split the **once-a-week** dose into 2 or 3 divided doses (over 24 hours) if gastrointestinal adverse effects occur
- Explain to patients why methotrexate has been prescribed — they may be aware of its use as a cancer treatment
- Set up a reminder system for monitoring

Biological DMARDs

Biological DMARDs target pro-inflammatory cytokines that are involved in joint destruction, in particular tumour necrosis factor alpha (TNF-alpha) and interleukin-1 (IL-1).⁵ There are 4 biological DMARDs available in Australia — etanercept, infliximab and adalimumab (TNF-alpha inhibitors), and anakinra (IL-1 receptor antagonist).

Where do they fit?

Systematic reviews of randomised controlled trials have shown a large effect of biological DMARDs on disease activity compared with placebo.^{19–23} This is mainly in patients with severe disease who have not responded to at least one conventional DMARD.^{19–23} Combining treatment with methotrexate provides greater efficacy compared with methotrexate alone.^{19–23}

There is no direct evidence from randomised controlled trials that biological DMARDs differ in their efficacy. Indirect comparisons suggest that etanercept, infliximab and adalimumab have similar effectiveness, while anakinra may be less effective.^{19,23} Choice of treatment depends on patient preference.²⁴

Biological DMARDs are generally well tolerated^{19–23}, but some patients may stop treatment due to adverse effects (e.g. injection site reactions).

PBS eligibility

The PBS listing for biological DMARDs reflects their place in therapy. Patients are only subsidised if they have severe disease (e.g. at least 20 affected joints) and do not respond to, or cannot tolerate, conventional DMARDs.



Prescribing biological DMARDs on the PBS

- Only 1 biological DMARD is subsidised per patient at any one time
 - 4 drug choices are available to be prescribed in each treatment cycle
 - Patients receive subsidised treatment while they continue to show a response (defined in the PBS restriction)
- Patients may switch to another drug (e.g. because of adverse effects) without having to experience disease flare to re-qualify for treatment
 - If there is an inadequate response to 1 drug, it cannot be re-prescribed within the same treatment cycle
 - If there is an inadequate response to 3 drugs, patients may not enter another treatment cycle for 5 years

Regular monitoring is essential — for all DMARDs

Monitor disease activity and drug toxicity to guide choice of and changes in treatment.^{2,5} Review patients every 1–3 months, until clinical remission is achieved, for measures of disease activity including:

- number of tender and swollen joints
- duration of morning stiffness
- elevated ESR and CRP levels
- functional status (e.g. activities of daily living).^{2,5,9}

Joint damage may be assessed by X-ray every 6–12 months during the first few years.²

Maximal response to conventional DMARDs usually occurs within 3 months, but varies depending on the drug (e.g. methotrexate: 1–2 months).^{5,14} Biological DMARDs can have a more rapid onset of effect.¹⁴ Drug toxicity is specific for each DMARD (see insert). Most conventional DMARDs have an established toxicity

profile, but biological DMARDs are new drugs and their long-term risks are unknown. Reports of serious adverse effects are emerging, such as tuberculosis (reactivation and community-acquired), lymphoproliferative disease (e.g. lymphoma), blood dyscrasias, demyelinating disease (e.g. multiple sclerosis, Guillain–Barré syndrome), lupus-like autoimmune disease and precipitation of heart failure.^{25–28}

Specific steps to monitor for rare but serious adverse effects are important, because rheumatoid arthritis already predisposes to infection, lymphoma and cardiovascular disease.^{8,27}

In rural areas, access to specialists may be limited, so the primary care practitioner may play a greater role in monitoring patients. A management plan should be agreed between the patient, primary care practitioner and specialist.⁵

Involving patients in their management

Rheumatoid arthritis impacts on quality of life and self-management is important for patients.⁵ Educational programs, such as the arthritis self-management course (ASMC) reduce pain, fatigue and distress about the disease.⁵ The Arthritis Foundation delivers the ASMC in every Australian State and Territory.⁵

Provide an opportunity for patients to ask questions about their disease, and involve them in decisions about choice of treatment.⁵ Offer advice on non-pharmacological management, such as exercise and occupational therapy. Information for patients about lifestyle measures and managing rheumatoid arthritis is available from the Arthritis Australia website at www.arthritisaustralia.com.au.

NEW — *Therapeutic Guidelines: Rheumatology*

The first version of *Therapeutic Guidelines: Rheumatology* was published in 2006. It provides more information about diagnosis and treatment of rheumatoid arthritis, as well as patient education and advice on lifestyle changes. *Therapeutic Guidelines* is an independent, evidence-based resource developed by Australia's leading experts. It is available in print and electronically. For more information, refer to the Therapeutic Guidelines website at www.tg.com.au.

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Online citations available at:
www.nps.org.au/healthpro

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



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