Rheumatoid Arthritis – monitoring of DMARDs

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Key concepts

- Most people with rheumatoid arthritis require DMARD therapy to control symptoms and prevent joint damage. Treatment is initiated by a specialist as early as possible in the disease process.
- Treatment usually begins with methotrexate and then other DMARDs such as sulphasalazine, hydroxychloroquine or leflunomide are added when inflammation is not controlled.
- People prescribed DMARDs require close monitoring for adverse effects and drug interactions.

Rheumatoid arthritis is a chronic autoimmune disease characterised by inflammation of the synovial tissue in joints causing swelling, pain, stiffness and joint destruction.[1,2] Spontaneous remission is uncommon (<5%) and most affected individuals require long term disease modifying anti-rheumatic drug (DMARD) therapy to control symptoms and prevent joint damage.

A GPs role in the care of a patient with rheumatoid arthritis includes early referral for diagnosis and treatment, management of co-morbidities, co-ordination of secondary care and allied health care input and, in conjunction with the treating rheumatologist, monitoring of DMARD therapy.

This article covers important aspects of the care of patients taking DMARDs including monitoring requirements, adverse effects and drug interactions.

DMARDS are initiated in rheumatoid arthritis as soon as possible to prevent disease progression and reduce symptoms

The aim of treatment for rheumatoid arthritis is to achieve minimal joint inflammation (a therapeutic remission). Patients diagnosed with rheumatoid arthritis should start treatment with DMARDs as soon as possible, as early treatment has been shown to improve outcomes.[3] Joint damage occurs early in the course of rheumatoid arthritis and is largely irreversible.[1, 4] The degree of inflammation is closely related to joint damage therefore early control of inflammation should prevent joint damage. People with synovitis persisting for six weeks should be urgently referred to a rheumatologist.

Commonly used oral DMARDs include methotrexate, sulfasalazine, hydroxychloroquine, low-dose prednisone and a newer agent, leflunomide. Other less commonly used DMARDs include azathioprine, cyclosporin and sodium aurothiomalate (intramuscular gold). Biological DMARDS, tumour necrosis factor (TNF) inhibitors, are discussed on page 27.

Methotrexate is usually the first choice DMARD

Methotrexate is usually first line therapy in moderate to severe rheumatoid arthritis because it is effective, has a predictable adverse effect profile, is simple to administer and is inexpensive.[3] In individuals with highly active disease methotrexate may be commenced in combination with other DMARDs. Mild disease may be treated with sulfasalazine or hydroxychloroquine monotherapy.

If methotrexate is not tolerated an alternative DMARD may be used as monotherapy.[3]

Add another DMARD when inflammation is not controlled

If inflammation is not controlled, usually the next step is to add another DMARD such as sulfasalazine.

Triple therapy with methotrexate, sulfasalazine and hydroxychloroquine has been shown to be clinically effective and may also be used.[1, 2]

Other therapies include leflunomide, cyclosporin and azathioprine

Leflunomide is available on special authority* for the treatment of rheumatoid arthritis that has not adequately responded to methotrexate and sulfasalazine. Leflunomide can be used alone or in combination with methotrexate. In clinical trials leflunomide had similar efficacy to methotrexate but may be less well tolerated, with additional adverse effects such as hair loss and hypertension.[5]

Cyclosporin and azathioprine are usually reserved for patients who are unresponsive to other DMARDs, due to the increased risk of adverse effects. Azathioprine is less well tolerated than methotrexate and cyclosporin is associated with nephrotoxicity. They can control inflammation but there is less evidence of their effect for long term treatment of rheumatoid arthritis.[6]

* Special Authority requirement is to be removed on 1st November 2008

Biological DMARDs such as adalimumab and infliximab may be indicated if inflammation is uncontrolled by combination therapy (see page 27).[2]

Onset of action for DMARDs is between two to six months

The onset of action for DMARDs varies. Response is seen with methotrexate within one to two months while hydroxychloroquine can take up to six months for a response.[7]

DMARDs require regular monitoring for toxicity

DMARDs require regular laboratory monitoring for adverse effects. A management plan should be agreed between the patient, GP and Rheumatologist. It should state which doctor is primarily responsible for arranging and reviewing the laboratory investigations.

Recommended investigations for commonly used DMARDs are listed in Table 1 (see centre pages 29–32. Note: these pages can be pulled out for future reference). This includes recommended frequency of monitoring, what to look for and what to do about it. The frequency of monitoring varies between agents based on their likelihood of causing toxicity.

The table also includes clinical signs which may suggest toxicity. These clinical signs should be enquired about at consultations and patients should be advised to report them if they occur.

Set up a reminder on your PMS for monitoring.

Prescribing points for DMARDs

Methotrexate

- Dosing — administered once a week orally or by injection. Starting dose is 5–10 mg ONCE a week, increase by 2.5–10 mg every four to six weeks to a maximum of 25 mg ONCE a week.
- Folic acid — 5mg folic acid, once per week (but not on the same day as methotrexate), should always be prescribed.
- Potential adverse effects — nausea, mouth ulcers, hair loss, cytopaenias, elevated liver enzymes, rarely pneumonitis.[3]
- Interactions — methotrexate accumulates in the presence of renal impairment. Although this seldom has any clinical effect, patients with renal impairment, whether caused by NSAIDs, diuretics, dehydration or kidney disease should take lower doses and should be monitored carefully for any deterioration in renal function. Trimethoprim and cotrimoxazole interact with methotrexate and significantly increase the risk of marrow aplasia; the combination should be avoided.[3]
- Alcohol — patients should be advised to limit alcohol consumption to no more than one (females) or one and a half (males) standard drinks per day. This is roughly half of the level recommended for the general population. Liver function should be vigilantly monitored in patients who consume alcohol.
- Flu vaccination — annual influenza vaccination should be given but live vaccines should be avoided.[8]
- Contraception — methotrexate is a known teratogen. Effective contraception is required for women of child bearing potential taking methotrexate, or men taking methotrexate whose partner is of child bearing potential. Effective contraception needs to be continued for three months after stopping methotrexate.[9]

Sulfasalazine

- Dosing — starting dose is 500 mg orally daily, increase by 500 mg a week to a maximum of 40 mg/kg or 3g daily in divided doses.
- Potential adverse effects — nausea, abdominal pain, hair loss, cytopaenias, agranulocytosis, elevated liver enzymes, skin rashes.[3]
- Interactions — potentially reduces the absorption of digoxin, however the combination does not need to be avoided. Patients should be observed for signs

of under-digitalisation and digoxin levels should be measured if response is not adequate.[10]

- Pregnancy — can be used in pregnancy but doses should not exceed 2 g/day. Folic acid supplementation should be given during pregnancy and to women trying to conceive.[8] Causes reversible oligospermia.[6]
- Yellow discolouration — causes a yellow discolouration of urine and tears; warn patients it may stain undergarments and soft contact lenses.[9]

Hydroxychloroquine

- Dosing — starting dose is 400mg orally daily in divided doses for one to three months (maximum 6mg/kg/day), then a maintenance dose of 200–400mg daily.
- Potential adverse effects — blurred vision, skin rash, photosensitivity, very rarely maculopathy. Blue-black discolouration of skin may occur with long-term use.[3, 9]
- Photosensitivity and photophobia — may increase the skin's sensitivity to sunlight and also cause photophobia. Sunscreen is advised and patients should wear sunglasses in bright light.[9]

Leflunomide

- Dosing — loading dose (optional) 100 mg orally once daily for three days, then 10–20 mg once daily.
- Potential adverse effects — GI disturbance, weight loss, hair loss, rash or itch, mouth ulcers, headache, raised liver enzymes, cytopaenias, hypertension, rarely peripheral neuropathy and pneumonitis.[3] There is an increased susceptibility to infections which should be treated promptly. With many of the adverse effects, discussion with the specialist team may result in dose reduction or trial of symptomatic treatment.
- Interactions — concurrent use with other drugs that have the potential to cause liver or marrow toxicity may increase the risk of these toxicities occurring.[9] For example, the risk of pneumonitis is increased when leflunomide is combined with methotrexate.[12]
- Alcohol — patients should be advised to limit alcohol consumption[8] to no more than one (females) or one and a half (males) standard drinks per day. This is roughly half of the level recommended for the general population. Liver function should be vigilantly monitored in patients who consume alcohol.
- Flu vaccination — annual influenza vaccination is recommended but live vaccines should be avoided.[8]
- Contraception — leflunomide is very teratogenic. Effective contraception is required for women for two years and men for three months after stopping leflunomide. Blood concentrations of its active metabolite should be measured before conception occurs.[9]
- Washout — leflunomide has an extremely long half life and can be retained in the body for up to two years. If toxicity occurs or for any other reason e.g. desire to conceive, a wash out procedure with cholestyramine may be considered.

Additional prescribing points

- Azathioprine. Dosing - 1 mg/kg orally daily, increasing after four to six weeks to 2-3 mg/kg/day. Some rheumatology teams measure TPMT (Thiopurine Methyl Tranferase) at baseline. Low levels of this enzyme involved in the metabolism of azathioprine are an indication for reducing the dose. It is also possible to measure levels of azathioprine metabolites such as 6 Thioguanine (6 TGN). This may help guide treatment.
- Gold injections (sodium aurothiomalate). Dosing - 10 mg test dose (given in a clinic followed by 30 minutes observation), followed by weekly injections of 50 mg until significant response. Thereafter the interval between doses is increased in stages from 50 mg per week to 50 mg every four weeks. Nitritoid reactions (where the blood pressure falls) after injection of gold can occur. This should be checked after the first 10 mg dose of gold and thereafter. Concurrent use of ACE inhibitors may increase the incidence of nitritoid reactions. If a nitroid reaction occurs, gold injections should be withheld and discuss immediately with the Rheumatologist.

References:

1. National Prescribing Centre. Current issues in the drug treatment of rheumatoid arthritis. MeRec Bulletin 2007; 17(5). Available from: www.npc.co.uk/merec_index.htm (Accessed September 2008).
2. National Prescribing Service. Helping patients achieve remission of rheumatoid arthritis. NPS News 2006; 48. Available from: www.nps.org.au (Accessed September 2008).
3. Jones P. Medical management of rheumatoid arthritis. N Z Fam Physician 2007; 34(6): 427-31.
4. O'Dell J. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004; 350: 2591-602.
5. Osiri M, Shea B, Robinson V, et al. Leflunomide for treating rheumatoid arthritis. Cochrane Database Syst Rev 2003; 1: CD002047.
6. Walker-Bone K, Fallow S. Rheumatoid arthritis. BMJ Clin Evid 2007;12: 1124.
7. Australian Medicines Handbook 2007.
8. Chakravarty K, McDonald H, Pullar T, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology 2008; 47(6): 924-5.
9. White CE, Cooper RG. Prescribing and monitoring of disease-modifying anti-rheumatic drugs (DMARDs) for inflammatory arthritis. Collected reports on the rheumatic diseases 2005. Available from: www.arc.org.uk (Accessed September 2008).
10. Baxter K (ed). Stockley's Drug Interactions. [online] London: Pharmaceutical Press. Available from: www.medicinescomplete.com (Accessed on September 2008).
11. Savage RL, Highton J, Boyd IW, Chapman P. Pneumonitis associated with leflunomide: a profile of New Zealand and Australian reports. Intern Med J 2006; 36(3):162-9.

References for Table 1

1. Chakravarty K, McDonald H, Pullar T, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology 2008; 47(6): 924-5
2. White CE, Cooper RG. Prescribing and monitoring of disease-modifying anti-rheumatic drugs (DMARDs) for inflammatory arthritis. Collected reports on the rheumatic diseases 2005. Available from: www.arc.org.uk (Accessed September 2008).
3. Jones P. Medical management of rheumatoid arthritis. N Z Fam Physician 2007; 34(6): 427-31.
4. Harrison A. Disease-modifying anti-rheumatic drugs (DMARDs) for rheumatoid arthritis: benefits and risks. Medsafe Prescriber Update 1999; 18: 4-12.
5. National Prescribing Service. Disease-modifying anti-rheumatic drugs (DMARDs) for rheumatoid arthritis. Available from: www.nps.org.au (Accessed September 2008).
6. Clinical Knowledge Summaries. DMARDs. Available from: http://cks.library.nhs.uk/dmards# (Accessed September 2008).