Disease modifying drugs in adult rheumatoid arthritis

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SYNOPSIS

Effective treatment of rheumatoid arthritis now involves starting disease-modifying antirheumatic drugs at the time of diagnosis. This aims to slow development of the irreversible joint damage that leads to long-term disability. Many patients are treated with methotrexate. This is effective, but like other disease modifying drugs it has serious adverse effects. Monitoring patients is important particularly if they are taking a combination of drugs for their arthritis.

Index words: sulfasalazine, methotrexate, leflunomide.

(Aust Prescr 2003;26:36–40)

Introduction

Rheumatoid arthritis affects 1% of the Australian population. It is characterised by symmetrical polyarthritis involving the small joints of the hands and feet. Despite treatment, rheumatoid arthritis patients may still have progressive joint destruction, deformity and disability and a reduced life expectancy.

Rheumatoid arthritis should be suspected when there are three or more swollen joints, half an hour or more of morning stiffness and metacarpophalangeal or metatarsophalangeal joint involvement.[1] Early referral to a rheumatologist is recommended for a shared care approach. This allows accurate early diagnosis, and determination of baseline damage and disease activity with clinical, laboratory and radiographic markers. Markers of a poor prognosis include early bone erosions, a positive rheumatoid factor, genetic markers (HLA-DR4 subgroups), functional status and inflammatory markers.

General approach to drug therapy

Drug therapy is just one component in the treatment of rheumatoid arthritis, which also includes non-pharmacological treatments such as physiotherapy and exercises. All patients should be instructed in the self-adjustment of simple analgesics and anti-inflammatory drugs as these complement therapy with slow-acting disease-modifying antirheumatic drugs (DMARDs). The DMARDs are no longer withheld until radiographic joint erosions develop. They are now introduced at the diagnosis of rheumatoid arthritis, aiming at quick eradication of inflammation. It is important as their efficacy is greatest early in the course of the disease. Response to therapy with a single DMARD is often suboptimal and trials have found that combination therapy with methotrexate, sulfasalazine and hydroxychloroquine can be more effective.[2]

In Australia the first choices for rheumatoid arthritis treatment are methotrexate, sulfasalazine and leflunomide (see Fig. 1). They are usually begun as individual drugs or in combination with hydroxychloroquine. Their efficacy is similar so the choice of drug often relates to cost and restrictions under the Pharmaceutical Benefits Scheme (PBS), or to avoidance of adverse events secondary to alcohol consumption, sulfa allergies, or lack of contraception.

Short-term pulses of oral or depot intramuscular corticosteroids may be used to suppress flares of active rheumatoid arthritis at any stage of disease management. Similarly, intra-articular corticosteroids can be used by experienced clinicians to treat individual joints. Starting maintenance or prolonged therapy with oral corticosteroids should only be considered after treatment failures and consideration of the comorbidity they may induce.

A patient's response to therapy is optimally monitored using semi-objective criteria such as the duration of early morning stiffness, a self-reported scale for joint pain and level of functioning for household tasks, and counting of tender or swollen joints. These criteria are then combined with objective markers of inflammation (C-reactive protein and ESR) to evaluate disease activity.

Methotrexate

Although it has been in use since 1951, methotrexate is the current 'gold standard' of rheumatoid arthritis treatment. It has the highest rate of continued long-term treatment, maintaining efficacy without excessive toxicity and can be used alone or in combination. Methotrexate is proven to slow radiographic progression of disease, but it takes 6–8 weeks for the onset of benefit.

Mechanism of action

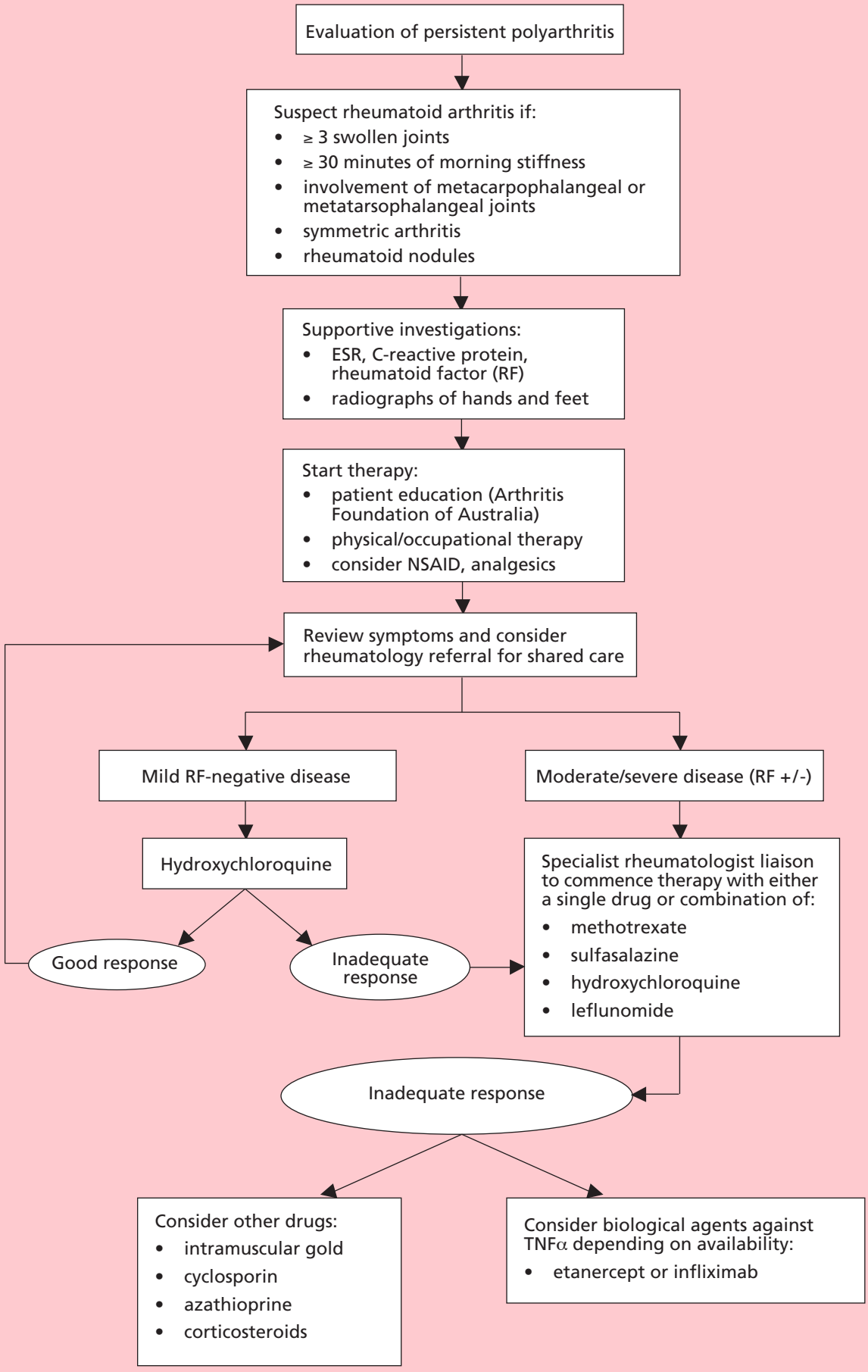
Methotrexate is a folic acid antagonist cytotoxic drug. By binding to dihydrofolate reductase, methotrexate interferes with DNA synthesis and cell replication.

Maintenance dose

For maintenance, patients ordinarily take a SINGLE WEEKLY dose of 7.5–20 mg (orally, or by intramuscular or subcutaneous injection). Intramuscular or subcutaneous weekly administration of the same methotrexate dose may reduce any nausea experienced with the oral route. It is very important that patients know that they should only take methotrexate once a week. Naming the day they should take their tablet can

Fig. 1

Management of rheumatoid arthritis



help them remember.[3,4] For example, methotrexate can be prescribed as 'Methotrexate 10 mg, take one tablet on Tuesdays ONLY'.

Co-prescription of both 2.5 mg and 10 mg tablets is not recommended, as the tablets may be confused especially by those with impaired eyesight.

Adverse effects

About 60% of patients may have mild toxicity, but less than 30% cease the drug in the first year because of adverse effects. Common adverse effects include nausea the day after the dose is taken, mouth ulcers, reversible alopecia, rash, and increased rheumatoid nodule formation. Rarer adverse effects include bone marrow suppression, hepatic fibrosis/cirrhosis (increased with alcohol consumption) and pulmonary infiltrates/allergic pneumonitis (possibly increased in smokers). Folic acid (0.5–1 mg/day) reduces gastrointestinal and mucosal adverse effects and is recommended as a concomitant prescription.

Monitoring

Patients should have a fortnightly full blood count, creatinine, and liver function tests for the first three months, monthly for three months, then six weekly thereafter once the dose is stable. Watch for changes in blood cells and monitor for 2–3 fold elevation (above the upper limit of the normal range) in liver enzymes (AST and ALT), or reduction in albumin. If, despite dosage adjustment or cessation of methotrexate, the AST or albumin are abnormal in at least five of the routine 6-weekly blood tests performed over one year, then a liver biopsy should be considered.

Contraindications

Methotrexate should not be used in patients with pre-existing bone marrow aplasia or cytopenias, immunodeficiency, severe hepatic disorders, or active infectious disease. Concomitant alcohol intake or hepatotoxic drugs are also contraindicated. Patients frequently ask about a safe level of alcohol consumption, but this has not been studied.

Drug interactions

Trimethoprim or trimethoprim-sulfamethoxazole can increase bone marrow suppression, probably by an additive antifolate effect. Non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates can inhibit the renal excretion of methotrexate. This is important for chemotherapeutic doses, but NSAIDs have no effect on the low doses of methotrexate used for rheumatoid arthritis and they can be cautiously co-prescribed. Patients and general practitioners must be aware of the pharmacy and prescribing software alerts that do not distinguish between low and high doses. Hepatotoxicity is potentially increased with the co-administration of azathioprine, sulfasalazine or leflunomide as part of combination therapy.

Advice in pregnancy/breastfeeding

Methotrexate was originally used as an abortifacient and is associated with congenital abnormalities. Breastfeeding is contraindicated because of neonatal immunosuppression, neutropenia and growth retardation.

Sulfasalazine

This drug contains an anti-inflammatory and antibiotic (acetylsalicylic acid and sulfapyridine), and slows the radiographic progression of rheumatoid arthritis. Used alone or in combination with methotrexate and/or hydroxychloroquine, it takes 6–12 weeks for the onset of its benefits.

Mechanism of action

Sulfasalazine is cleaved in the colon by bacterial enzymes to release acetylsalicylic acid and sulfapyridine. The method of action of sulfapyridine is unclear but may involve inhibition of the transcription factors which are increased in inflammation.

Maintenance dose

Patients take 1–1.5 g twice a day, starting at 500 mg/day and increasing by 500 mg a week. Some rheumatologists escalate the dose more slowly than this.

Adverse effects

Up to 30% of patients experience mild gastrointestinal disturbances (nausea, vomiting, loss of appetite, diarrhoea), skin rash and pruritus. Neurological symptoms of headache, dizziness or depression also occur. In males there is oligospermia with impaired motility. This does not act as a contraceptive and reverses three months after stopping treatment. Rarer adverse effects include leucopenia, bone marrow depression, haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency, abnormal liver function tests, hepatitis and abdominal pain. As sulfasalazine inhibits absorption of folate it can cause folate deficiency.

Monitoring recommended

Full blood count and liver function are tested every two weeks for three months, then three monthly thereafter.

Contraindications

Sulfasalazine should not be prescribed for patients who are hypersensitive to salicylates or sulfonamide derivatives. It is also contraindicated in patients with haematological, renal or hepatic dysfunction.

Advice in pregnancy/breastfeeding

Sulfasalazine can be used in pregnancy. Very small amounts of drug are found in breast milk, so it can be used cautiously by breastfeeding mothers.

Leflunomide

Leflunomide is the newest of the commonly used DMARDs. It has comparable clinical and radiographic efficacy to methotrexate and sulfasalazine. Due to its cost leflunomide is only subsidised by the PBS for patients in whom methotrexate is ineffective or inappropriate. While leflunomide is predominantly taken alone it is sometimes given with methotrexate, but this increases the risk of toxicity.

Mechanism of action

Leflunomide primarily inhibits replication of activated lymphocytes by blocking the *de novo* synthesis of pyrimidines and hence DNA. It also has a weak anti-inflammatory action.

Maintenance dose

A loading dose of 100 mg/day is given for three days. This is followed by 20 mg/day unless adverse effects necessitate 10 mg/day. A loading dose results in a faster time of onset of benefit compared to methotrexate. However, loading doses are increasingly not being used because of gastrointestinal adverse effects.

Adverse effects

The commonest adverse effects are nausea and diarrhoea which are experienced by 20–30% of patients, but they may settle with continued treatment. Skin rash and reversible alopecia occur in 5–10%. Elevations of liver enzymes (AST and ALT) occur with sole use of leflunomide, and affect up to 60% of patients if it is combined with methotrexate. Rarer adverse effects include severe bone marrow suppression, infections and persistent abnormal liver function tests despite dose reduction.

Monitoring recommended

Full blood count, creatinine, and liver function are tested monthly for the first six months, and 1–2 monthly thereafter. If combined with methotrexate, monthly testing is recommended.

Contraindications

Leflunomide should not be given to patients with severe immunodeficiency, impaired bone marrow function, or severe uncontrolled infections. As liver impairment is also a complication, excessive alcohol consumption should be avoided.

Drug interactions

Methotrexate increases the risk of hepatotoxicity in patients taking leflunomide. As leflunomide inhibits cytochrome P450 2C9, it can interfere with drugs such as phenytoin, warfarin and tolbutamide.

Advice in pregnancy/breastfeeding

Leflunomide is teratogenic and is contraindicated in both pregnancy and breastfeeding. Due to a prolonged enterohepatic recirculation, women should not conceive for one year after stopping treatment, unless they have a 'washout' procedure with cholestyramine (8 g three times a day for 11 days). Men wishing to father a child should consider discontinuing leflunomide and undergoing a cholestyramine washout.

Hydroxychloroquine

Primarily used in combination with other drugs, hydroxychloroquine may be used as the sole drug in patients with mild rheumatoid arthritis and the absence of adverse prognostic factors. It has a slow onset (2–6 months) and has been shown to improve long-term functional outcome, although no studies have been undertaken to document retardation of radiographic damage.[5]

Mechanism of action

Hydroxychloroquine interferes with antigen presentation and the activation of the immune response by increasing the pH within macrophage phagolysosomes.

Maintenance dose

Treatment begins with 200–400 mg daily for 1–3 months. Once a response is achieved, the dose can be reduced to 200 mg daily.

Adverse effects

Gastrointestinal symptoms predominate (epigastric burning, nausea, bloating, diarrhoea). Skin rashes and alopecia are common and hydroxychloroquine may exacerbate psoriasis. Patients may develop hyperpigmentation in sun-exposed areas. Retinal toxicity with macular damage is rare, but patients should wear sunglasses in strong sunlight. Corneal deposits (reversible if the drug is ceased) are seen in less than 0.1% of patients but the risk increases if the dose exceeds 6 mg/kg/day.

Monitoring recommended

Ophthalmological monitoring is a controversial area because it was originally developed for chloroquine with its greater ocular toxicity. Patients taking hydroxychloroquine should have a baseline ophthalmologic review (colour vision, visual fields, fundoscopy), especially if they have pre-existing eye disease or diabetes, and then six-monthly thereafter. No specific laboratory monitoring is required.

Contraindications

Patients with pre-existing maculopathy should not take hydroxychloroquine.

Advice in pregnancy/breastfeeding

Hydroxychloroquine should be avoided in pregnancy. Low concentrations are found in breast milk, therefore caution is recommended if the patient is breastfeeding.

Gold injections

Gold has been used in the treatment of rheumatoid arthritis since 1927. It was one of the first drugs to demonstrate retardation of radiographic damage, but in the last 20 years, injectable gold has moved from being first-line treatment to at least fourth. A genuinely slow-acting drug, gold often requires therapeutic trials of up to six months.

Mechanism of action

Gold affects lysosomal membranes and inactivates lysosomal enzymes within the synoviocyte.

Maintenance dose

After test doses for allergy, patients start with 50 mg intramuscularly every week for about six months (or until 1 g total). They then continue on 25–50 mg every 2–4 weeks.

Adverse effects

There is a high attrition rate. Most of the 30% of patients who develop symptoms within the first year cease treatment. Skin rashes (pruritus, erythema, eczema), mouth ulcers and diarrhoea are common. Less common are bone marrow suppression (thrombocytopenia, aplastic anaemia, agranulocytosis) or membranous glomerulonephritis with proteinuria. The reaction of flushing, hypotension and sweating that occurs shortly after

an intramuscular injection of aurothiomalate is uncommon but frightening. Rare effects include gold deposits in the lens or cornea (reversible with cessation of therapy), peripheral neuropathy, Guillain-Barré syndrome and encephalopathy.

Monitoring recommended

The urine should be tested for protein at the time of each injection. A weekly full blood count to check for neutropenia and eosinophilic reaction is recommended for the first three months and 2–4 weekly thereafter.

Contraindications

Gold is contraindicated in patients with gross renal or liver disease, diabetes, or blood dyscrasias. Other contraindications include exfoliative dermatitis or a history of hypersensitivity to gold.

Advice in pregnancy/breastfeeding

Gold crosses the placenta and is not recommended during pregnancy, although there is no evidence of increased neonatal malformations. It is also not recommended during lactation as gold is excreted in breast milk and absorbed by the infant.

Future directions

A major advance in the treatment of rheumatoid arthritis has been the development of biological therapies, in particular drugs directed against the pro-inflammatory cytokine TNF-α.[6] Etanercept, a recombinant soluble TNF-Fc fusion protein, and infliximab, a chimeric anti-TNF monoclonal antibody, are approved for the treatment of refractory rheumatoid arthritis. Patients improve rapidly (within weeks) with these drugs and have less radiographic progression compared with methotrexate alone. However, disadvantages are the need for parenteral administration (subcutaneous or intravenous routes), the high cost and the absence of long-term safety data when used in the broader community. The annual costs of these new drugs have to be weighed against the personal and societal expense of joint replacements, hospitalisations and disability. They are likely to be restricted to patients with active ongoing joint inflammation despite oral corticosteroid therapy and treatment with the standard therapies.

Conclusion

The goals of rheumatoid arthritis treatment are to slow disease progression and achieve remission. Early liaison with a rheumatologist will enable earlier assessment and commencement of DMARD treatment to improve the long-term outcome of rheumatoid arthritis.

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FURTHER READING

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 47)

5. Patients with rheumatoid arthritis who are going to respond to hydroxychloroquine usually show evidence of benefit within one month of starting treatment.
6. Patients taking methotrexate for rheumatoid arthritis should take their dose on the same day each week.

Patient support organisation

Arthritis Foundation of Australia

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