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Treatment of established rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory condition that is best managed following an integrated chronic disease model of care, tailored to the individual patient.

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Rheumatoid arthritis is a chronic inflammatory condition characterised by synovial tissue inflammation in the joint. Through time, this leads to damage in the joints, cartilage and bone. The current approach to the management of rheumatoid arthritis has been the early detection and aggressive treatment of active synovitis. Outcomes are most favourable when inflammation is controlled early in the disease.

The natural course of rheumatoid arthritis is illustrated in Figure 1. Guidelines for the diagnosis and treatment of early rheumatoid arthritis are available on the RACGP website (see: www.racgp.org.au/guidelines/rheumatoid arthritis/recommendations). These guidelines cover issues relating to early diagnosis, the need for referral of patients to a rheumatologist, and the early introduction of disease-modifying antirheumatic drug (DMARD) therapy to achieve control of disease activity as early as possible.

In patients with established rheumatoid arthritis, the goal of maintaining minimum clinical and laboratory disease activity remains the primary objective of management. However, it is also important to continue maintaining patients' quality of life and their participation in work, relationships, family and social situations, as well as addressing the consequences of disease activity, treatment complications and structural damage.

Within three years of diagnosis 20 to 30% of patients with rheumatoid arthritis become permanently work-disabled if disease activity is not controlled. However, with recent advances in the treatment of rheumatoid arthritis, this can be prevented. An increased level of understanding in drug toxicity monitoring is therefore required.

Although symptoms of joint inflammation (joint swelling, pain and stiffness) are the usual presentations, it is important to appreciate rheumatoid arthritis as a systemic disease resulting in serious complications. There are also potential morbidities from drug toxicities. Patients with

IN SUMMARY

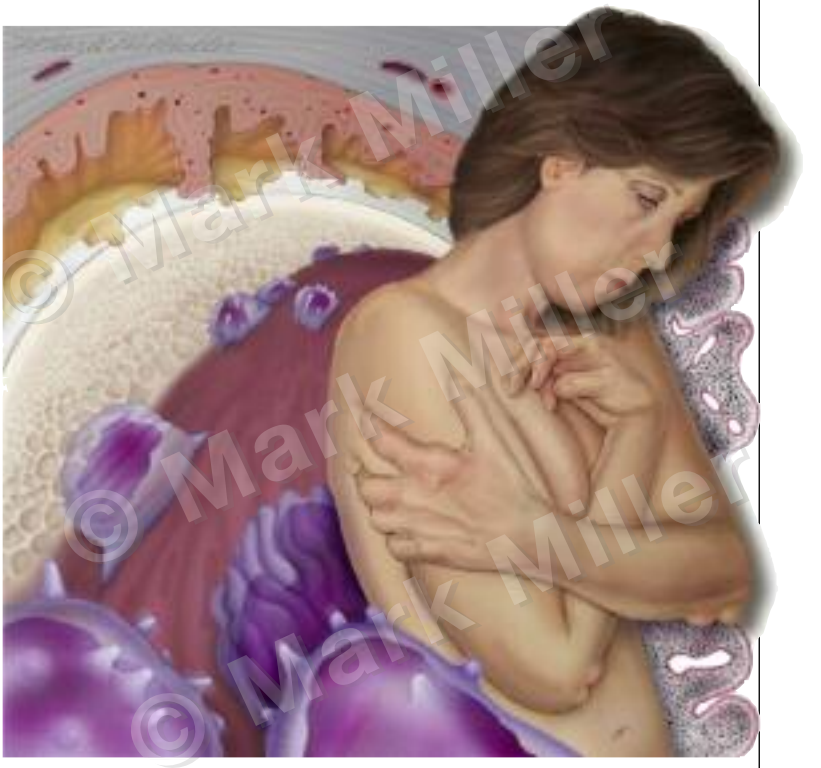
- **The primary objective of management in patients with established rheumatoid arthritis is to maintain minimum clinical and laboratory disease activity.**
- **Measurement of disease activity is used to guide adjustments in therapy with the goal to attain remission.**
- **In patients with established rheumatoid arthritis, it is important to optimise treatment while monitoring for side effects, address secondary complications of rheumatoid arthritis and maintain patients' quality of life and participation in work, relationships, family and social situations.**
- **A multidisciplinary approach is important, ideally with drug and disease monitoring by GPs and physicians, and the involvement of physiotherapists, occupational therapists and other health professionals.**
- **With the current available treatment options and better understanding of monitoring, most patients will be able to lead a normal life, free of disease activity.**

rheumatoid arthritis can have an increased length of stay in hospital and a high risk of falls because of disease activity in their joints, gait instability, anaemia, deconditioning or a combination of these. Rheumatoid arthritis is a risk for osteoporosis in itself. Wound healing is often poor and there is an increased risk of infections in patients taking immunosuppressive therapy. Particular attention should be made to septic arthritis (both native and prosthetic joints), osteomyelitis and occult sepsis. Patients with rheumatoid arthritis have an increased risk of cancers, such as lymphomas, and cardiovascular morbidity is also increased. As a result, a multidisciplinary approach is important, ideally with drug and disease monitoring by GPs and physicians, and the involvement of physiotherapists, occupational therapists and other health professionals.

The goals of management for patients with established rheumatoid arthritis are to:

- maintain patients' quality of life and participation in work and relationships
- treat-to-target to achieve remission, a normal functional status or no evidence of disease activity
- define the extent of joint damage
- optimise treatment while monitoring for side effects
- address secondary complications of rheumatoid arthritis.

Treatment of established rheumatoid arthritis



The goals of management for patients with established rheumatoid arthritis include maintaining patients' quality of life and participation in work and relationships; treating-to-target to achieve remission, a normal functional status or no evidence of disease activity; and optimising treatment while monitoring for side effects.

Monitoring the disease

Disease activity

Measurement of disease activity in rheumatoid arthritis is used to guide adjustments in therapy with the goal to attain remission. This should be carried out in collaboration with a rheumatologist. Recent evidence suggests that 'treating-to-target' to a low disease activity state (normal C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR] and absence of swollen and tender joints) will provide the best long-term outcomes (i.e. reduced joint damage and improved survival). With current treatment regimens this can be achieved in about 30 to 50% of patients, but the aim should be to further increase these outcomes to 75 to 100% of cases.

Although there are many sensitive imaging techniques such as MRI and ultrasonography to detect for synovitis, these techniques are not currently part of routine practice. Hence, clinical joint count examination is still regarded as the gold standard for assessment of synovitis and joint inflammation. The Disease Activity Score 28 (DAS28) is a composite score including elements such as CRP or ESR with a tender and swollen joint count of 28 joints. It is a tool to evaluate disease activity and is widely used in rheumatology practice and clinical trials (see: www.das-score.nl/ www.das-score.nl/). The DAS28 score distinguishes different disease activity states; these include remission (DAS28 <2.6), low disease activity (DAS28 2.6 to 3.2) and high disease activity (DAS28 >5.1). Other tools include the clinical disease activity index or the simplified disease activity index, which includes a simple count of joints with measurement of inflammatory markers for

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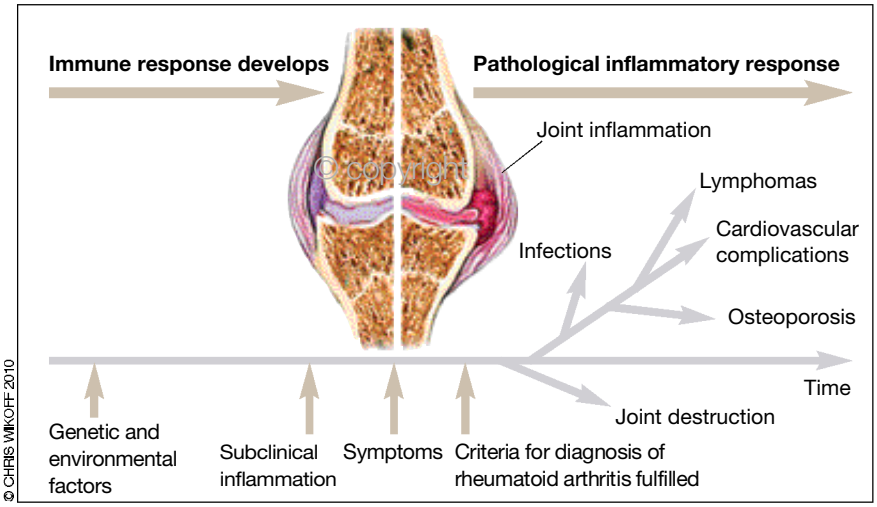

Figure 1. Longitudinal course of rheumatoid arthritis. In established rheumatoid arthritis, pathological inflammatory response continues with joint destruction if there is residual disease activity. Complications of rheumatoid arthritis and its treatment increase with time.

MODIFIED FROM: KLARESKOG L, CATRINA AI, PAGET S, ET AL. RHEUMATOID ARTHRITIS. LANCET; 2009 373: 659-672, WITH PERMISSION FROM ELSEVIER.

monitoring disease activity.

Assessment of patients' functional status and their ability to participate in work, relationship, family and social situations is also important in the management of established rheumatoid arthritis. This is usually apparent through enquiries about daily activities such as personal hygiene, cooking, eating and shopping. A more formal enquiry can be carried out with the use of a health assessment questionnaire and other health-related quality of life questionnaires.

Disease activity can be measured by blood test monitoring. This includes measurements of CRP levels and ESR every one to three months. CRP is the favoured marker because it has a shorter half-life than ESR and therefore more accurately reflects recent disease activity.

Drug toxicity

There are various traditional DMARDs available for the treatment of established rheumatoid arthritis. Common side effects of these drugs and recommended blood test monitoring, including full blood count, measurement of creatinine levels and liver function tests (every one to three months), are summarised in Table 1.

After diagnosis of rheumatoid arthritis, patients will receive serial or a combination of immunosuppressants that may include a biological DMARD. Due to the effects of these drugs, some rheumatologists screen patients for tuberculosis and hepatitis B and C, as well as performing a chest x-ray at baseline. It is also important to appreciate that rheumatoid arthritis is a smoking-associated disorder.

Complications

Patients should have x-rays taken of their hands and feet to look for progression in joint damage (carried out at baseline then yearly) and to see whether their current treatment is adequate. If there is x-ray progression, treatment should be readjusted by the treating rheumatologist.

An osteoporosis assessment should also be carried out in patients with rheumatoid arthritis, measuring calcium, parathyroid hormone and 25-hydroxy (OH) vitamin D levels (yearly), plus a bone mineral density (BMD) scan (every second year). A cardiovascular risk assessment, measuring fasting lipids (including cholesterol, low-density lipoproteins, high-density lipoproteins), blood pressure, body mass index and exercise status (every six months), is also important.

Adjusting treatment and monitoring side effects

NSAIDs

NSAIDs are useful for temporary symptomatic relief of inflammatory joint pain in rheumatoid arthritis. They do not, however, influence or improve disease outcomes. Use of proton pump inhibitors is advised, particularly in those taking conventional NSAIDs. Patients with a history of peptic ulcer disease or significant gastrointestinal oesophageal reflux disease should avoid using NSAIDs.

Alternatively, use of omega-3 fatty acids may preclude the need for NSAIDs. At least 3 to 4 g of long-chain omega-3 fatty acids a day (10 to 13 standard fish oil capsules or 10 to 15 mL of bottled fish oil) has to be taken for an anti-inflammatory effect.

Corticosteroids

In patients with established rheumatoid arthritis, the aim is to limit and preferably cease corticosteroid use due to the side effects of osteoporosis, diabetes, cardiovascular disease and weight gain. Many of the current regimens of remission-induction treatments include some corticosteroids, taken either orally, intra- articularly and/or intramuscularly. However, despite the evidence that corticosteroids can contribute to improved joint function, there remains important concerns in regards to their long-term use. Not all rheumatologists support their use.

Traditional DMARDs

Methotrexate

Methotrexate has been the cornerstone of disease-modifying therapy for rheumatoid arthritis. It is a folic acid analogue that binds to dihydrofolate reductase and antagonises folic acid. Folic acid is essential for DNA synthesis; therefore, methotrexate impairs cell division and is cytotoxic at high doses.

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Table 1. Symptomatic therapies and traditional DMARDs for rheumatoid arthritis: side effects and recommended monitoring

Drug	Main side effect and problems	Recommended monitoring
Symptomatic therapies		
NSAIDs	GORD, peptic ulcer disease, gastrointestinal bleeding; increased creatinine levels and BP, CCF, AMI (in the elderly and in those with CV comorbidities or risk factors); concomitant PPI use is useful; interaction with warfarin; interaction with antihypertensives and diuretics	• History and symptom checklist • Baseline testing and treatment for *Helicobacter pylori* • FBC on routine disease monitoring (usually 3 monthly) • BP at each visit • Iron studies if haemoglobin levels reduced
COX-2 inhibitors	As above but can be used with warfarin with care	
Corticosteroids	Osteoporosis, diabetes, weight gain, poor wound healing, infection, cataracts, proximal myopathy, fluid retention, exacerbation of CCF, increased BP, increased CV mortality	• Calcium, 25-OH vitamin D and PTH levels yearly • Monitor compliance with bisphosphonate, vitamin D and calcium therapy • BMD scan 2nd yearly • BP each visit • Fasting blood sugar level, cholesterol and triglycerides, as well as urinalysis 3 to 6 monthly
Traditional DMARDs		
Methotrexate	Mouth ulcers, nausea, abnormal LFT, decreased white cell count (especially if increased creatinine levels and in the elderly); contraindicated in pregnancy	• FBC, UEC and LFT 1 to 3 monthly • Check correct weekly dosing each visit • Monitor compliance with folic acid therapy and ensure responsible alcohol intake
Sulfasalazine	Gastrointestinal intolerance (dose-related), abnormal LFT, rash and, rarely, Stevens-Johnson syndrome	• FBC, UEC and LFT monthly for 3 months then 3 monthly
Hydroxychloroquine	Nausea, rash, maculopathy (rare)	• Eye checks (including Amsler grid, visual field exam and colour vision test) at baseline then annually by optometrist/ophthalmologist, looking for retinopathy
Leflunomide	Diarrhoea, abnormal LFT, peripheral neuropathy, hair loss; contraindicated in pregnancy	• FBC, UEC and LFT 1 to 3 monthly • Symptom checklist
Gold	Rash, photosensitivity, nephrotic syndrome	• FBC, UEC, urinalysis for protein monthly
Cyclosporin	Increased BP and creatinine levels, long-term use can cause hirsutism, gum hypertrophy, skin cancer	• BP each visit, and FBC and UEC monthly • Yearly skin checks

ABBREVIATIONS: AMI = acute myocardial infarction; BMD = bone mineral density; BP = blood pressure; CCF = congestive cardiac failure; COX-2 = cyclo-oxygenase-2; CV = cardiovascular; FBC = full blood count; GORD = gastro-oesophageal reflux disease; LFT = liver function tests; PPI = proton pump inhibitor; PTH = parathyroid hormone; UEC = urea electrolytes and creatinine.

Methotrexate is taken orally as a single dose of 7.5 to 20 mg per week (a rheumatologist will sometime recommend higher doses). It is taken with folic acid supplementation of at least 5 mg per week. Folic acid supplementation reduces gastrointestinal and liver toxicity without reducing the efficacy of methotrexate.

Patients with poor compliance to medication or underlying cognitive impairment need a reminder of the weekly administration. Deaths attributable to methotrexate when given as a low dose for arthritis have occurred when the dose has been given daily. Methotrexate toxicity is treated by folinic acid at a dose of 15 mg orally every four hours and, in this situation, the treating rheumatologist should to be notified immediately.

Side effects

Methotrexate is generally well tolerated, but dose-limiting toxicity occurs in 10 to 15% of patients with rheumatoid arthritis. Common side effects include nausea and mouth ulcers. Subcutaneous and intramuscular methotrexate is sometimes used if adverse effects limit the maximum dose, or when the maximum dose is ineffective when given orally.

Abnormal liver function tests are common in patients taking methotrexate, particularly in those with diabetes, obesity, abnormal renal function or excessive alcohol intake. The mechanism of hepatotoxicity is unknown but correlates with total cumulative dose and culminates to liver fibrosis. It is now rare to perform liver biopsies on patients with rheumatoid arthritis mainly because there are other potent DMARDs available to enable switching to occur. Patients with concurrent alcohol abuse or liver disease should receive specialist advice while taking methotrexate. Baseline testing for hepatitis B and C is also recommended for high-risk patients. Patients are advised to keep their alcohol intake within the NHMRC guidelines of no more than two standard drinks per day with at least two alcohol-free days per week during methotrexate therapy.

Haematological abnormalities such as leucopenia, thrombocytopenia and anaemia can occur but are rare. Their frequencies are higher particularly in the elderly when they are ill or if renal function is impaired. Methotrexate is contraindicated in patients with moderate-to-severe renal impairment. It should also not be used during pregnancy and breast feeding. In addition, it should not be used for at least three months before a planned pregnancy for both men and women. Contraception is important in women of child-bearing age who are taking methotrexate.

Methotrexate-induced pneumonitis is rare but if there is an acute change in respiratory status, the treating rheumatologist should be alerted and treatment withheld until the patient is reviewed. A baseline chest x-ray is recommended in this situation.

Drug interactions

Concomitant use of other drugs that inhibit folic acid synthesis, such as cotrimoxazole and trimethoprim, should be used with care in patients taking methotrexate due to a risk of increased haematologic toxicity. It is safe for patients to take NSAIDs and penicillin while they are taking methotrexate but because these agents block the secretion of methotrexate by the renal tubules, the concentration of methotrexate may potentially be increased.

Monitoring

A full blood count, measurement of urea, electrolytes and creatinine levels, and liver function tests should be performed monthly in patients taking methotrexate. Patients with liver function test abnormalities need more frequent monitoring. In general, if liver function tests are two to three times the upper limit of normal on three consecutive occasions, the methotrexate dose should be reduced or discontinued. If liver function test abnormalities persist despite this, referral of the patient to a gastroenterologist may be necessary. Once the dose of methotrexate is stable with no new drug additions and blood tests are normal, monitoring can be reduced to every three months.

Sulfasalazine

Sulfasalazine is a combination of 5-aminosalicylic acid (an anti-inflammatory) and sulfapyridine (an antibacterial). The two chemicals are cleaved in the large bowel by enzymes produced by resident bacteria. The sulfapyridine is absorbed, but the 5-aminosalicylic acid remains in the bowel. Sulfasalazine is not effective in patients who have had a colectomy because of the absence of colonic bacteria. It is unclear how sulfapyridine dampens inflammation but time to response in treatment usually takes one to three months. The dosage of sulfasalazine normally ranges from 500 mg twice daily to 1 g twice daily.

Nausea is the most common side effect of sulfasalazine and is often dose-related. Liver function abnormalities may also occur. Other adverse effects include reversible male infertility, rash and, less commonly, haemolytic anaemia (as a result of underlying glucose-6-phosphodehydrogenase deficiency) and Stevens-Johnson syndrome. Sulfasalazine should not be used in patients with sulfonamide allergy.

A full blood count and liver function tests should be performed monthly for three months, then every three months thereafter in patients taking sulfasalazine.

Leflunomide

Leflunomide inhibits the *de novo* synthesis of pyrimidines by competitively blocking dihydro-orotate dehydrogenase and thus inhibiting activated lymphocytes. Its onset of effect is four to 12 weeks. Dosage is usually 20 mg daily, although a lower dose may be recommended by the treating rheumatologist.

Liver function abnormalities develop in less than 5% of patients taking leflunomide, although when combined with methotrexate the risk is increased, especially in those with fatty liver disease or alcohol abuse. Diarrhoea occurs in over 10% of patients and may settle with time or with a reduced dose. Peripheral neuropathy rarely occurs.

Leflunomide is teratogenic and has a very long half-life. It may be required for patients to wait two years for the active metabolite to fall to a safe level before attempting pregnancy. A washout period with cholestyramine is recommended when the active metabolite needs to be eliminated, and pregnancy should not occur until blood testing confirms clearance of the active metabolite.

Leflunomide-induced pneumonitis is rare, but if there is an acute change in respiratory status, the treating rheumatologist should be alerted and treatment withheld until reviewed. A baseline chest x-ray is therefore recommended.

A full blood count, measurement of urea, electrolytes and creatinine levels, and liver function tests are recommended in patients taking leflunomide. These should be performed monthly for the first three months and then every three months if there is no new drug addition and normal blood monitoring results. Baseline hepatitis B and C testing is recommended in patients who are at high risk of having hepatitis infection.

Hydroxychloroquine

Hydroxychloroquine is a modestly active suppressant for a variety of inflammatory processes, but the mechanism of action is unclear. Response to therapy generally takes two to six months. It is usually given at 400 mg daily and reduced to 200 mg daily for maintenance. Dosage should not exceed 6.5 mg/kg/day (lean weight estimated in overweight patients) because this can increase the risk of retinal toxicity, especially in patients over 60 years of age or in those with renal failure.

Hydroxychloroquine is well tolerated. Side effects include nausea, rash and dizziness, which can respond to a dose reduction.

A full blood count including measurement of haemoglobin levels after one week will detect haemolysis in patients with underlying glucose-6-phosphate dehydrogenase deficiency. An eye review should be performed at baseline and repeated yearly to monitor for retinopathy.

Cyclosporin

In the treatment of rheumatoid arthritis, the initial dose of cyclosporin is 2.5 to 3 mg/kg/day. Onset of effect is two to four months. The dose of cyclosporin should be reduced if there is a 30% increase in the creatinine level, and treatment should be ceased if the creatinine level rises by 50%.

Hypertension is a common side effect and regular measurements of blood pressure and urea, electrolytes and creatinine levels are recommended. Longer-term side effects include hirsutism, gum hypertrophy and skin cancers.

Gold

Intramuscular gold can be effective for rheumatoid arthritis but is uncommonly used now. Some patients with established disease may be taking this treatment, but the mechanism of action is unclear. Between 60 to 70% of patients treated with gold respond to treatment. A test dose of 10 mg is usually started with a maintenance dose of 25 to 50 mg per week. After four to six months, the frequency and dosage can be changed if there is improvement.

The most common side effects of gold are skin rash, photosensitivity and mouth ulcers. Less commonly, it may cause leucopenia and thrombocytopenia. Proteinuria may also occur so monitoring includes monthly measurement of urea, electrolytes and creatinine levels, a full blood count and urinalysis.

Biological DMARDs

In Australia, biological DMARDs are normally reserved for patients with moderate-to-severe rheumatoid arthritis if treatment with traditional DMARDs has failed. Currently, six biological DMARDs are available on the PBS (authority required) for severe active rheumatoid arthritis (see below for more details). Clinical trials of these agents have provided evidence of their superiority over traditional DMARDs in dampening disease activity and halting joint progression.[1-5] Efficacy needs to be balanced against their safety and high cost. Prescription of these drugs requires a rheumatologist who is experienced in their use (see: www.rheumatology.org.au). A summary of the biological DMARDs available on the PBS, their side effects and suggested monitoring is outlined in Table 2.

Tumour necrosis factor inhibitors

Mechanism of action

Tumour necrosis factor (TNF) inhibitors were the first biological DMARDs that marked the breakthrough in the development of treatments that target distinct parts of the innate immune system. These agents act by partly neutralising TNF in the circulation and synovial fluid, and they are most effective when used in combination with methotrexate.

The three preparations available on the PBS (authority required) for severe active rheumatoid arthritis are:

- adalimumab, a human monoclonal antibody with a high specificity for TNF that is given subcutaneously every two weeks at a dose of 40 mg
- etanercept, a fusion protein soluble receptor that is given subcutaneously at a dose of 50 mg a week; an effect is usually apparent within two to four weeks
- infliximab, a human mouse chimeric antibody with high specificity for TNF that is given as an infusion in hospital at 3 mg/kg intravenously with an initial

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Table 2. Some biological DMARDs available on the PBS for rheumatoid arthritis: side effects and recommended monitoring

Drug	Usual dosages	Main side effects		Recommended monitoring
		Agent-related	Class effect	
TNF inhibitors				
Adalimumab	40 mg subcutaneously (fortnightly)	Injection site	Flu-like symptom, infection, TB, exacerbation of CCF, MS, SLE-like syndrome, possibly cancer	• TB check with Mantoux or Quantiferon-TB Gold tests, chest x-ray and hepatitis B and C at baseline • FBC, LFT, UEC, ESR, CRP measurements initially monthly then 3 monthly • Screening for cancer prior to starting: history, chest x-ray, up-to-date mammogram, PAP smears, faecal occult blood screen
Etanercept	50 mg subcutaneously (weekly)	Injection site		
Infliximab	3 mg/kg intravenously every 8 weeks	Infusion reaction		
AntiCD20 monoclonal antibody				
Rituximab	1 g intravenously at day 0 and 14; can be repeated 6 months later if needed with a demonstrated initial response	Infusion reactions (more common with first dose), increased risk of infection including viral infections such as reactivation of hepatitis B		• Hepatitis B and C screen • FBC, UEC, LFT, ESR, CRP measurements initially monthly then usually every 3 monthly
T-cell co-stimulatory signal inhibitor				
Abatacept	500 to 1 g intravenously at week 0, 2 and 4 and then monthly	Dizziness, headache, increased infection, risk of TB is unclear at present, risk of cancer is unclear at present, current data show patients with COPD have more side effects		• Baseline TB check as per anti-TNF guidelines and hepatitis B and C screen each visit • FBC, LFT, UEC, ESR, CRP measurements initially monthly then usually 3 monthly

ABBREVIATIONS: CCF = congestive cardiac failure; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FBC = full blood count; LFT = liver function tests; MS = multiple sclerosis; SLE = systemic lupus erythematosus; TB = tuberculosis; UEC = urea electrolytes and creatinine.

loading dose. It is approved for use in combination with methotrexate.

Other preparations not currently listed on the PBS include:

- golimumab, a human monoclonal antibody with high specificity for TNF that is given subcutaneously once a month
- certolizumab pegol, an antigen-binding fragment of a humanised monoclonal antibody with high specificity for TNF; it is coupled with polyethylene glycol.

Adverse effects

Injection-site reactions are common in 30% of patients taking adalimumab and etanercept. These are best treated by rotating injection sites and, if severe, use of prophylactic antihistamines.

TNF inhibitors increase the risk for specific infections, in particular tuberculosis. In about 50% of cases of reactivation of tuberculosis, the site of the infection is extrapulmonary, including lymph nodes, peritoneum, bone and meninges. Reactivations usually occur within the first few months. All patients who start TNF inhibitor treatment are screened for tuberculosis and treated

accordingly if there is evidence of latent bacterial tuberculosis infection (see: www.rheumatology.org.au – go to members and trainees/biological guidelines/April 2010 LBTI guidelines).

Overall, patients taking TNF inhibitors have a two- to three-fold relative increased risk of bacterial infections, particularly of the skin, soft tissues and joints, and the risk may be highest in the first six months of treatment.

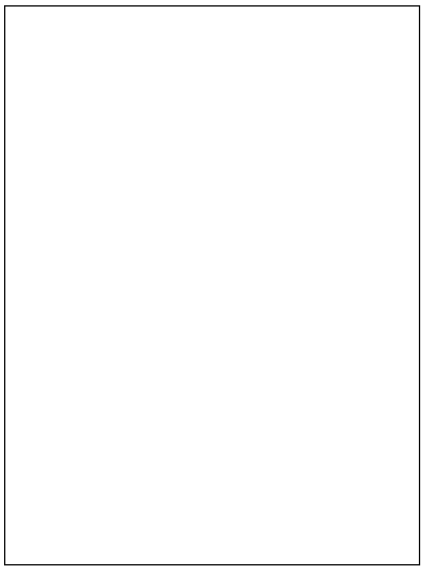
Cancers, in particular lymphomas, are another concern. Data obtained to date indicate that most of the raised risk for lymphoma in patients taking TNF inhibitors is due to rheumatoid arthritis disease activity rather than the drugs used. For solid cancers, findings from randomised controlled trials and registry-based studies are somewhat contradictory and no indications for an increased risk of such cancers and have been obtained to date.[6-8] Continued surveillance is needed before definite conclusions about long-term effects of these drugs can be made.

An increased incidence of multiple sclerosis is unclear in patients treated with TNF inhibitors. The presence of antinuclear antibodies is more common after treatment with TNF inhibitors. Rarely, this is associated with autoimmune-like syndromes such as systemic lupus erythematosus.

TNF inhibitors can aggravate preexisting congestive heart failure and, therefore, are relatively contraindicated in patients with moderate-to-severe heart failure.

Monitoring

Before starting a TNF inhibitor patients should have appropriate tuberculosis screening, hepatitis B and C serology, full blood examination, renal and liver function tests, and measurement of ESR and CRP levels. The appropriate monitoring during treatment would generally be dictated by the traditional DMARD used in combination with the TNF inhibitor (usually methotrexate). Monitoring should be carried out monthly initially then every three months if previous monitoring tests have been normal.



AntiCD20 monoclonal antibody

Rituximab, a chimeric antiCD20 monoclonal antibody, acts on the surface of pre-B-cells and mature B-cells and depletes these cells from the circulation. Originally, it was used for the treatment of non-Hodgkin's lymphoma. Currently in Australia, it is PBS approved as second-line treatment for adults with severe active rheumatoid arthritis in combination with methotrexate when an initial biological DMARD, usually a TNF inhibitor, has failed. It is administered intravenously as two doses (1 g per dose) given two weeks apart with intravenous corticosteroids and oral antihistamines. Rituximab is most effective when administered with methotrexate.

Common side effects of rituximab are infusion reactions. Serum B-cells are depleted and a large number of patients have moderate decreases in immunoglobulin levels. The relative risk of serious bacterial infections compare with that of other biological DMARDs. Tuberculosis risk is not increased, but viral infections such as hepatitis B reactivation have been reported. A few cases of progressive multifocal leucoencephalopathy have been reported but most of the case reports were for patients with lupus. Cases of progressive multifocal leucoencephalopathy have been reported in patients with rheumatoid arthritis taking other biological DMARDs. Hence, this observation could be more of an effect of disease and immunosuppression by medication, leading to reactivation of the JC polyomavirus.

Patients need to have baseline hepatitis B and C tests performed and a tuberculosis assessment. Monitoring usually includes a full blood count, measurement of urea, electrolytes and creatinine levels, liver function test, and measurement of ESR and CRP levels. This is usually carried out monthly initially then every three months as dictated by the traditional DMARD used in combination (usually methotrexate).

T-cell co-stimulatory modulator

Abatacept is a recombinant fusion protein consisting of the extracellular domain of CTLA4 and a fragment of the Fc portion of immunoglobulin G that inhibits co-stimulatory signals essential for T-cell activation. It is PBS approved for the treatment of severe active rheumatoid arthritis in combination with methotrexate in patients who have had an inadequate response to traditional DMARDs or after failure of a TNF inhibitor.

Abatacept is given intravenously at monthly intervals after initial doses in the second and fourth week of commencement. Side effects include fever, chills, headaches and mild upper respiratory infections.

Abatacept, similar to other biological DMARDs, is associated with an increased risk of serious bacterial infections compared with placebo. The risk of reactivation of latent tuberculosis is less than that with TNF inhibitors, but screening patients for tuberculosis prior to commencement is recommended.

It is uncertain whether abatacept increases the risk of cancer compared with the general rheumatoid arthritis population. It has been observed that patients with chronic obstructive pulmonary disease had more adverse events when taking abatacept.[9]

Patients should have baseline hepatitis B and C testing performed and a tuberculosis assessment. Monitoring usually includes a full blood count, measurement of urea, electrolytes and creatinine levels, liver function test, measurement of ESR and CRP levels monthly initially then every three months as dictated by the DMARD used in combination (usually methotrexate).

Interleukin-6 receptor antibody

Tocilizumab is a humanised antihuman receptor antibody targeted against interleukin-6 (IL-6). Clinical trials have indicated efficacy of tocilizumab in patients with moderate-to-severe active rheumatoid arthritis when administered monthly through an intravenous infusion, especially when given in combination with methotrexate.[10-11] It is not currently PBS listed. Improvements in anaemia of chronic disease and an abrupt reduction in CRP levels have been noted. Elevations in liver function tests and lipid levels may occur, but the long-term consequences are unclear at present.

Interleukin-1 receptor antagonist

Anakinra is a recombinant human interleukin-1 (IL-1) receptor antagonist. It is significantly less potent than TNF inhibitors in most patients with rheumatoid arthritis. Infections are the most common side effects of this drug. Anakinra is to be used in conjunction with methotrexate.

Nonpharmacological management for symptom control

A multidisciplinary chronic disease model of care is recommended for patients with rheumatoid arthritis, with care plans tailored to the individual patient. GPs play a pivotal role in co-ordinating care and referring patients to relevant allied health professionals and medical and surgical specialists.

GPs also play a major role in administering nonpharmacological management strategies. Patients should be provided with information on their disease, drug treatments and self-management strategies for flares or episodes of worsening of disease that are likely to occur even in those with well-controlled rheumatoid arthritis. Access to websites and approved self-management courses are available through national consumer (e.g. Arthritis Australia: www.arthritis australia.com.au) and professional organisations (e.g. Australian Rheumatology Association: www.rheumatology.org.au).

Patients should be made aware of the benefits of the anti-inflammatory properties of high-doses of omega-3 fatty acids and the small but clinically important benefits of topical anti-inflammatory agents. Patients should be encouraged to do range of motion and strengthening exercises for joint protection, as well as maintain aerobic fitness for their overall well-being. They should also be referred to physiotherapists as required. Patients should also be counselled and assisted in achieving the best work-life balance at each stage of their disease. A combination of rest and exercise is likely to be the best approach to dealing with the fatigue that develops when control of the disease inflammation is suboptimal.

If pain management is an ongoing issue, interventions such as acupuncture, massage and meditation techniques may provide some relief. If needed, patients should be referred for occupational therapy assessment and provision of splints, orthotics and aids for daily living.

Managing complications of rheumatoid arthritis

There are a number of complications of rheumatoid arthritis as outlined below.

Anaemia

Anaemia of chronic disease correlates with CRP levels and ESR, as well as disease activity. It is common in patients with untreated rheumatoid arthritis (75%) and reverses with treatment of the disease. Anaemia of chronic disease can sometimes be distinguished from iron deficiency through measurement of serum levels of soluble transferrin receptor (increased in patients with iron deficiency). It is also important to appreciate that one-quarter of patients with rheumatoid arthritis have iron deficiency anaemia. Initial treatment involves iron supplements but, if unresolved, further investigation is warranted.

Cancer

Risk of lymphoma has been associated with rheumatoid arthritis (two- to three-fold). This is thought to be associated more with long-term disease activity than with immunosuppressive treatments. There is currently insufficient data in biologics registries to suggest that biological DMARDs increase malignancy risk, but ongoing surveillance is warranted. As rheumatoid arthritis is associated with smoking, a chest x-ray should be considered at baseline. Surveillance for non-melanotic skin cancer is also important, considering patients are taking various immunosuppressants.

Falls

Abnormal walking mechanics of the lower limbs leads to imbalance and instability in patients with rheumatoid arthritis. This can be due to:

- disease activity leading to joint pain
- muscle deconditioning and wasting caused by reduced exercise and inflammation
- fatigue caused by disease activity or lack of sleep
- anaemia of chronic disease
- irreversible joint damage
- loss of proprioception
- peripheral neuropathy (from

underlying medications or vasculitis from rheumatoid arthritis).

The combination of treating the disease, addressing the cause of the fall and optimising falls prevention is the key. Falls prevention strategies can include exercise, tai-chi, ensuring adequate vitamin D replacement, occupational therapy, podiatry and orthotics. Treatment of skin ulcers and infections are equally important.

Occupational therapy involvement to provide advice on safety of home environment and the need for adjustments are important.

Cervical spine disease

Chronic inflammation leads to damage of the transverse ligament and subsequent instability of the atlas on axis.

Hand and joint deformities

Patients with hand deformities from rheumatoid arthritis (Figure 2) will benefit from joint protection education and splinting by their hand therapist/occupational therapist. Chronic synovitis in patients with under-treated rheumatoid arthritis may lead to joint and ligamentous destruction, requiring surgical intervention if medical therapy fails. The goals are relief of pain and restoration of function. Compression neuropathies may also occur due to synovitis in the wrists and feet.

Other connective tissue diseases

Rheumatoid arthritis can overlap with features of other connective tissue diseases, including Sjögren's syndrome. This most commonly presents as dry eyes and mouth with positive rheumatoid factor and raised inflammatory markers. In addition to treating the synovitis, attention to keeping the eyes well-lubricated with artificial tears and good oral hygiene with regular dental review are necessary.

Vasculitis in the form of leukocytoclastic vasculitis is rare because of the early potent treatments now available in containing rheumatoid arthritis disease activity, but it can present in a variety of ways including with a rash and/or mononeuritis.

Managing secondary complications

Secondary complications associated with rheumatoid arthritis can be grouped into the following: infection and wound healing, osteoporosis and cardiovascular disease.

Infections and wound healing

Infections are usually iatrogenic. Corticosteroids are commonly the precipitating factor and have a dose-related effect.[12] Prednisone increases the risk of pneumonia hospitalisation. In addition, soft tissue infections (including cellulitis) and joint, urine and nail infections are common. Good podiatry care is important particularly in patients with lower limb involvement.

Vaccinations

Vaccinations are underused in patients with rheumatoid arthritis. It is recommended that all patients with rheumatoid arthritis, including those taking biological DMARDs, receive pneumococcal and influenza vaccines. It is also recommended to check that patients' vaccinations are up-to-date three months before they start biological DMARDs. Live vaccines, if needed, should be given prior to commencement of biological DMARDs. Examples of live vaccines include BCG, oral polio and yellow fever. If a live vaccine is required while the patient is taking a biological DMARD, it is recommended to liaise with the treating rheumatologist to plan to discontinue the medication for five or more half-lives.

Although some studies of patients with rheumatoid arthritis treated with biological DMARDs have shown reduced antibody response titres to vaccination, the vaccinations did not fully inhibit their ability to develop an immune response.[13]

PHOTOLIBRARY

Figure 2. Hand deformities from rheumatoid arthritis.

Preventing infection during the perioperative period

There are no consensus guidelines relative to surgery for ceasing medication in patients with rheumatoid arthritis. Ultimately, this decision is made between the surgeon and the treating rheumatologist. In general, to minimise bleeding, NSAIDs are stopped at least seven days prior to surgery. Traditional DMARDs, such as methotrexate, leflunomide, sulfasalazine and azathioprine, are also often stopped one week prior to surgery. However, the evidence from prospective and retrospective data suggest that methotrexate does not increase perioperative infections nor does it impair wound healing.[14-15] Ceasing DMARDs may lead to an unnecessary increased risk of disease flare that may impede postoperative recovery. It is recommended that these agents only be stopped from the time that patients are nil-by-mouth until normal bowel and renal function are restored postoperatively.

Given the powerful immunosuppressive effect of biological DMARDs, it is recommended that the timing of surgery be modified where possible to take place just before the usual biological DMARD dosing time and then to withhold the medication until drains are removed, wounds are healed and the major infection risk period is past.

Preoperative considerations should include a review by the anaesthetist, in particular in regards to jaw function, for

intubation requirements and also the potential for complications in patients with atlanto-axial subluxation.

Advice in regards to corticosteroids and Addisonian risk should be given. The frequency of infection and early postoperative complications in patients with rheumatoid arthritis who are undergoing surgery is 10%. Corticosteroids may delay wound healing and the dose given should be as low as possible. However, when patients are dependent on long-term corticosteroids, immediate cessation can cause an Addisonian crisis. It is therefore recommended that most patients taking corticosteroids for rheumatoid arthritis should be covered with systemic administration of at least 100 mg hydrocortisone, usually given at the time of induction of anaesthesia and continued for the time that they are nil-by-mouth. Ultimately, this decision is made between the surgeon, anaesthetist and the treating rheumatologist.

Osteoporosis

Rheumatoid arthritis is a risk factor for fractures, therefore treatment of osteopenia and osteoporosis is of primary importance. Bone loss occurs within three months of regular corticosteroid use. Baseline calcium, 25-OH vitamin D and parathyroid hormone levels should be checked with a BMD scan. If patients are taking corticosteroids, they should be advised to take calcium and vitamin D supplementation. The 25-OH vitamin D level should be above 70 ng/mL.

It is desirable to treat all patients with prophylactic bisphosphonates when commencing corticosteroids. Currently, patients who have a BMD T-score of less than -1.5 and are taking at least 7.5 mg/day prednisone (or equivalent) for three months or more are eligible for PBS subsidisation for treatment with risedronate or intravenous zoledronic acid.

Cardiovascular disease

Excess mortality associated with rheumatoid arthritis is largely due to cardiovascular disease, such as ischaemic heart disease, which includes silent unrecognised heart attacks and sudden cardiac deaths.

Emerging evidence from observational cohort and case-control studies suggest that the increased risk is related to increased inflammation associated with rheumatoid arthritis, rather than traditional atherosclerotic risk factors or use of corticosteroids.[16] Hence, although the primary importance is to address disease activity, the traditional risk factors for atherosclerosis should also be strongly addressed. These include smoking cessation, lowering of lipids levels as per the cardiovascular guidelines and supporting regular aerobic exercise.

Lifestyle and physical therapy considerations

Exercise and physical therapy

A common fear is that exercise may increase pain and worsen disease activity in patients with rheumatoid arthritis. Education and reassurance are required to help patients develop the best balance between adequate rest and exercise. Patients should be encouraged to perform aerobic exercise and moderate resistance training three times a week. A program developed by the treating physiotherapist is appropriate. Hydrotherapy is a useful way of encouraging regular exercise for these patients.

Diet

Diet is a controversial area in patients with rheumatoid arthritis. There is no evidence that patients need to avoid certain foods in fear of making their arthritis worse. General advice about a balanced diet that is high in fruits, vegetables and fish is appropriate. The effects of dietary manipulation, including vegetarian, Mediterranean, elemental and elimination diets, on rheumatoid arthritis are uncertain with such studies being small, single trials with moderate to high risk of bias. Overall, maintaining a healthy bodyweight and a good healthy diet that is high in omega-3 fatty acids and antioxidants should offer the best balance.

Summary

Rheumatoid arthritis is a chronic inflammatory condition that is best managed following an integrated chronic disease model of care, tailored to the individual patient. Patients should be informed about their disease and the available treatments, and invited to take part in the decision making.

A shared-care arrangement between the GP and the rheumatologist with routine follow ups, preplanned at least three to four times a year, is recommended. With the current available treatment options and better understanding of monitoring, most patients will be able to lead a normal life, free of disease activity. MT

References

A list of references is available on request to the editorial office.

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Treatment of established rheumatoid arthritis

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References

1. Lipsky PE, van der Heidje DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumour Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000; 343: 1594-1602.
2. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. Ann Intern Med 1999; 130: 478-486.
3. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human antitumour necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003; 48: 35-45.
4. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006; 144: 865-876.
5. Emery P, Fleishmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a Phase IIB, randomized, double-blind placebo controlled, dose-ranging trial. Arthritis Rheum 2006; 54: 1390-1400.
6. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. Arthritis Rheum 2007; 56: 2886-2895.
7. Dixon WG, Watson KD, Lunt M, Mercer LK, Hyrich KL, Symmons DP; British Society For Rheumatology Biologics Register Control Centre Consortium; British Society for Rheumatology Biologics Register. Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: results from the British Society for Rheumatology Biologics Register. Arthritis Care Res (Hoboken) 2010; 62: 755-763.
8. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum 2009; 60: 3180-3189.
9. Rozelle AL, Genovese MC. Efficacy results from pivotal clinical trials with abatacept. Clin Exp Rheumatol 2007; 25(Suppl 46): S30-S34.
10. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease modifying antirheumatic drugs: the tocilizumab in combination with traditional disease modifying antirheumatic drug therapy therapy study. Arthritis Rheum 2008; 58: 2968-2980.
11. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010; 69: 88-96.
12. Wolfe F, Caplan L, Michaud K.Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum 2006; 54: 628-634.
13. Brezinschek HP, Hofstaetter T, Leeb BF, Haindl P, Graninger WB. Immunization of patients with rheumatoid arthritis with antitumor necrosis factor alpha therapy and methotrexate. Curr Opin Rheumatol 2008; 20: 295-299.
14. Scanzello CR, Figgie MP, Nestor BJ, Goodman SM. Perioperative management of medications used in the treatment of rheumatoid arthritis. HSS J 2006; 2: 141-147.
15. Grennan DM, Gray J, Loudon J, Fear S. Methotrexate and early post-operative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Ann Rheum Dis 2001; 60: 214-216.
16. Kaplan MJ. Cardiovascular complications of rheumatoid arthritis: assessment, prevention and treatment. Rheum Dis Clin North Am 2010; 36: 405-425.