



Gene-Siew Ngjan

Rheumatoid arthritis

Background

Rheumatoid arthritis is a chronic disease that can cause irreversible joint damage and significant disability. With a prevalence of 1%, it has a considerable cost to the community. Diagnosis is based on a combination of clinical and laboratory features. Patients typically present with a symmetrical polyarthritis of the small joints of the hands and feet accompanied by early morning stiffness and, occasionally, constitutional symptoms.

Objective

This review discusses the role of the general practitioner in the diagnosis and early management of rheumatoid arthritis.

Discussion

It is increasingly recognised that there is a 'window of opportunity' within which disease modifying antirheumatic drug therapy should be commenced to arrest progressive disease and joint destruction. Methotrexate is usually the first line agent in the management of rheumatoid arthritis but simple analgesia and nonsteroidal anti-inflammatory drugs are also important for symptom control.

Keywords: rheumatoid arthritis; antirheumatic agents; practice guidelines as a topic



Rheumatoid arthritis (RA) is a chronic disease with significant cost to both the individual and the community. In 2007, RA accounted for over \$400 million of Australian health expenditure.¹ With increasing recognition that uncontrolled disease leads to irreversible joint damage and progressive disability, it is imperative that RA is diagnosed in a timely fashion to allow early intervention with appropriate disease modifying antirheumatic drugs (DMARDs). With these issues in mind, The Royal Australian College of General Practitioners (RACGP) developed *Guidelines for the diagnosis and management of early rheumatoid arthritis*,² released in August 2009. This article draws on the recommendations of that guideline.

Rheumatoid arthritis has a prevalence of 1% and occurs in twice as many women as it does men.³ Its aetiology remains unknown but a model whereby repeated exposure to environmental agents is coupled with a genetic predisposition to autoimmune responses seems reasonable. The most well established genetic link is with HLA-DR4.⁴ However, this is not consistent across all populations studied and there are many other newly defined associations, including polymorphisms in PTPN22 and PADI4.³

Of the numerous environmental factors proposed to contribute to RA, tobacco smoking is perhaps the best defined. Smoking exposure has a dose response relationship with RA risk.⁵ Smoking is also known to increase citrullination of peptides (post-translational modification of the amino acid arginine to the amino acid citrulline), which could be the stimulus for generation of anticyclic citrullinated peptide (anti-CCP) antibodies (see 'Investigations') in susceptible individuals. Although several microbial pathogens have been linked to RA, no specific aetiological association has been established.

Clinical features

The onset of RA may be insidious or acute. Typically, patients present with a symmetrical arthritis affecting the wrists and the metacarpophalangeal and proximal interphalangeal joints of the hands. Involvement of the metatarsophalangeal joints of the feet is also common. Occasionally, large joints can be affected in isolation, in which case sepsis or crystal arthropathy may need to be excluded. The number of swollen or tender joints at baseline is an indicator of progressive disease and future radiographic progression.⁶ A cardinal feature of RA is early morning stiffness, which can last for over 1 hour. Systemic features include flu-like symptoms, fatigue, malaise and



weight loss. Rheumatoid nodules, commonly appearing over the extensor aspect of the elbows, are a specific feature but occur late in the disease and are only seen in 30% of patients.

An important variation from this typical presentation is the so-called 'polymyalgic' onset of RA, a pattern occasionally seen in individuals over 65 years of age. These patients present with limb girdle pain rather than peripheral arthritis and have prominent stiffness. Another atypical presentation is 'palindromic rheumatism', in which there is episodic involvement of one or several joints lasting hours to days and occurring at intervals of days to months.

There is no single clinical feature or serologic or radiologic test sufficient to make a definite diagnosis of RA.

Guideline recommendation 3

General practitioners should base a diagnosis of RA (and differential diagnosis) on clinical examination in the first instance. A strong suspicion of RA is indicated by:

- the presence of persistent joint pain and swelling affecting at least three joint areas, and/or
- symmetrical involvement of the metacarpophalangeal or metatarsophalangeal joints, and/or
- morning stiffness lasting more than 30 minutes.²

Investigations

Inflammatory markers

Erythrocyte sedimentation rate and C-reactive protein are usually elevated at diagnosis. They are of benefit in monitoring disease activity and response to treatment.

Rheumatoid factor

Rheumatoid factor (RhF) is an auto-antibody against the Fc portion of immunoglobulin G (IgG). It is positive in 60–70% of RA patients but also occurs in chronic inflammatory diseases such as systemic lupus erythematosus (SLE), Sjogren syndrome and cryoglobulinaemia. In the presence of RA it indicates more aggressive disease.

Anticyclic citrullinated peptide antibodies

Anti-CCP antibodies is a relatively new test that has a similar sensitivity but higher specificity for RA than RhF. It is a strong predictor of erosive disease. Testing for the combination of anti-CCP antibodies and RhF may be better than either antibody alone⁷ and is now recommended by the RACGP in all patients presenting with early arthritis.

Plain X-rays

Plain films of the hand and feet demonstrate erosions, although these may not be present at baseline. Serial X-rays every 1–2 years identify disease progression.

Other

Full blood count (FBC), and renal function and liver function tests (LFTs) should be performed to identify baseline abnormalities. Potential

findings in RA are anaemia of chronic disease, thrombocytosis and leucocytosis. Testing for antinuclear antibody (ANA) may be useful if a diagnosis of SLE is suspected, however some patients with RA are ANA positive. Likewise, synovial fluid analysis may be necessary to exclude gout or septic arthritis. Other tests are indicated according to potential differential diagnoses (*Table 1*).

Table 1. Differential diagnoses of RA

- Infective arthritis
 - septic (bacterial) arthritis
 - acute viral polyarthrits (parvovirus, Ross River virus, Barmah Forrest virus)
- Reactive arthritis
- Psoriatic arthritis
- Crystal arthritis
- Connective tissue diseases (SLE, Sjogren syndrome)
- Metabolic

Management

There is increasing recognition of a 'window of opportunity' within which initiation of treatment will change the course of the disease and prevent joint destruction, which can begin within weeks of symptom onset.⁶

Guideline recommendation 2

General practitioners should refer patients to a rheumatologist if there is persistent swelling beyond 6 weeks, even if RA is not confirmed. Early referral enables aggressive intervention with DMARDs, reducing long term joint damage and disability.²

Simple analgesia and nonsteroidal anti-inflammatory drugs

Patients with RA ultimately require DMARD therapy but adequate analgesia is also important. Paracetamol remains the analgesic of choice given its excellent safety profile and is prescribed in regular divided doses to a maximum of 4 g/day. Alone, however, it may provide insufficient pain relief.⁸ Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors have been shown to be more effective than simple analgesics in RA but have significant potential gastrointestinal, renal and cardiovascular toxicities that must be considered before use. If NSAIDs or COX-2 inhibitors are used, they should be used at the lowest effective dose and for the shortest possible duration. The addition of a proton pump inhibitor can reduce the incidence of gastrointestinal bleeding and is recommended for RA patients over 65 years of age and in those with a history of peptic ulcer disease.⁹ Given concerns about the increased risk of cardiac and cerebrovascular events with both conventional NSAIDs and COX-2 inhibitors, they should be used only after careful evaluation of cardiovascular status and avoided in high risk individuals.²

Omega-3 supplementation

Omega-3 fatty acid supplementation may be an effective adjunctive



treatment. This was demonstrated in a meta-analysis of 17 randomised controlled trials involving a total of 823 patients, which showed a significant beneficial effect on pain, morning stiffness, number of painful and/or tender joints and NSAID consumption.¹⁰

Corticosteroids

In patients for whom simple analgesia and NSAID therapy is inadequate, oral corticosteroids are sometimes appropriate while awaiting rheumatology review.

Guideline recommendation 19

General practitioners should consider short term, low dose, oral corticosteroid treatment when simple analgesics, omega-3 fatty acids, and NSAIDs or COX-2 inhibitors have failed to achieve symptomatic relief. This should be undertaken in consultation with a rheumatologist, and with a consideration of the patient's comorbidities and individual risk factors.²

Oral corticosteroids are effective for the short term relief of symptoms, but despite their inclusion in the RACGP clinical guidelines, are not recommended for routine use due to their adverse effects, most notably osteoporosis. Intra-articular corticosteroid injections can also be considered for local relief of symptoms and have the advantage of less systemic absorption. Any use of corticosteroids should be preceded by a discussion with the patient regarding potential side effects and adequate bone protection provided with calcium and vitamin D supplementation.

Disease modifying antirheumatic drugs

There have been significant changes in the approach to the management of RA since the mid 1990s.³ These include earlier and more aggressive intervention with DMARDs, combination DMARD therapy, and the introduction of biologic therapy for those who fail conventional DMARDs.

Disease modifying antirheumatic drugs reduce the rate of erosive change and therefore have the potential to alter disease course by preventing irreversible damage (*Table 2*). Multiple international guidelines recommend that patients be commenced on DMARD therapy as soon as possible after a diagnosis of RA is established. Methotrexate (MTX) is now the most commonly used first line DMARD because of its efficacy, favourable toxicity profile, and low cost.¹¹ It is dosed weekly, usually together with folic acid supplementation to reduce potential side effects. It is usually administered orally but can be given subcutaneously, particularly when poor oral absorption is suspected. Regular monitoring of FBC, renal function and LFTs is required, usually every 2–3 months once stable. Adverse effects of MTX include bone marrow suppression, liver damage and lung disease. Patients should be advised to avoid alcohol due to the increased risk of cirrhosis.

Because of the potential toxicities of these agents, DMARD therapy should be initiated by a rheumatologist. If this is not possible, the general practitioner should consider commencing single drug therapy with MTX or sulfasalazine in consultation with a rheumatologist.^{11,12} Before commencing DMARD therapy, hepatitis B and C status are usually checked in addition to the investigations discussed.

Table 2. Common DMARDs in current use

Traditional	Biologic
Methotrexate	Adalimumab
Sulfasalazine	Etanercept
Hydroxychloroquine	Infliximab
Leflunomide	Rituximab
	Abatacept

Summary

Given the importance of early recognition, GPs have a crucial role to play in the diagnosis and initial management of RA. Prompt DMARD therapy is central to the prevention of irreversible joint damage, however adequate analgesia is also important for patient function and quality of life.

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