Management of early rheumatoid arthritis

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Background

Rheumatoid arthritis (RA) is a systemic autoimmune disorder of unknown aetiology characterised by symmetrical polyarthritis of the small and large joints. The cardinal history features of active RA are:

- pain
- early morning stiffness (lasting more than 30 min)
- joint swelling
- limitation of function.

Additional features include malaise and fatigue.

Chronic synovitis, with its attendant synovial proliferation, can lead to erosions, destruction of the cartilage and instability of the joint, leading in turn to considerable disability. Furthermore, about a third of patients with RA will stop working due to disease progression within five years.[1] In the US, the estimated yearly cost of RA is $9 billion, with $4 billion in lost earnings alone. Consequently, RA has a profound impact on patients, families and society in general.

Medical management appears to have most to offer in the early stages of the disease, with the aim of preventing joint damage and loss of function. Simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) can be used for pain control but they do not control the inflammation and joint damage.

Other drugs, used for control of systemic inflammation, are known as disease-modifying antirheumatic drugs (DMARDs); they include methotrexate, sulphasalazine, leflunomide, ciclosporin, gold and antimalarials (eg hydroxychloroquine) and were previously considered as second-line agents. Recently, a new class of DMARDs ('biologics') has emerged. This group of drugs includes the anti-tumour necrosis factor agents (discussed in the accompanying article Beyond methotrexate: biologic therapy in rheumatoid arthritis).

Traditionally, the treatment of RA revolved around control of symptoms, with painkillers and NSAIDs, the more 'toxic' agents being used once these drugs had failed to control the symptoms of arthritis (hence, the concept of second-line agents). Unfortunately, studies have shown that NSAIDs and analgesics have no disease-modifying effects and that irreversible erosive changes occur early in the course of the disease. Within three months of disease onset, 10–26% of patients will have joint erosions evident on X-ray[2] – the figure may be greater with imaging modalities like magnetic resonance imaging and ultrasound. Within five years, about 95% of patients are likely to have erosive disease.[3] With increasing knowledge about long-term prognosis and the risks of delaying potentially disease-modifying therapy, there has been a marked change in the management of early RA. Rheumatologists now use DMARDs as early as possible in the natural history of the disease. Recent guidelines for the management of RA published by the American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines (2002 update)[4] state that:

> *the majority of patients with newly diagnosed RA should be started on a disease-modifying antirheumatic drug within three months of the diagnosis.*

Key Points

For patients in whom inflammatory arthritis is suspected, the presence of polyarticular symptoms, particularly with hand or foot involvement and morning stiffness more than 30 minutes warrants specialist opinion

Disease-modifying antirheumatic drugs (DMARDs) are started early in the treatment of inflammatory arthritis, sometimes even before the confirmation of diagnosis

KEY WORDS: disease-modifying antirheumatic drugs (DMARDs), early arthritis, rheumatoid arthritis, treatment

Early inflammatory arthritis

A number of factors lead to delay in diagnosis and treatment, including:

- delay on the part of the patient in seeking medical care
- delay in primary care
- waiting time to be assessed in secondary care
- time to initiation of a DMARD in secondary care.

Research shows that any delay in initiating DMARDs can lead to substantial differences in long-term outcome.[5,6] As a result, the concept of early inflammatory arthritis has emerged. The first early arthritis cohort was established in 1957 in Bath but the concept of early arthritis clinics emerged only in the late 1980s.[7] In recent years, a number of studies have focused on early inflammatory arthritis, addressing whether early treatment with DMARDs improves outcome. In several placebo-controlled studies in early arthritis (duration <2 years) using agents like methotrexate, sulphasalazine, gold and hydroxychloroquine, patients treated with DMARDs showed significant reduction in signs and symptoms and improved patient function.[8] Similar results are seen with oral prednisolone, which seems to have both symptom controlling and disease-modifying effects.[9] Analysis of delayed treatment trials (extensions of placebo-controlled treatment investigations in which the placebo group is switched to active treatment at the end point of the initial study) shows that the early treatment group had significantly better efficacy parameters, including improved patient function (reduced Health Assessment Questionnaire

scores), decreased swollen joint counts, and reduced or slowed radiographic progression.[10–12]

In addition to monotherapy with DMARDs, a number of DMARD combinations have been studied and may have superior efficacy compared with monotherapy in early disease, but those that do not include methotrexate fail to show the same levels of efficacy. The combinations include:

- methotrexate/sulphasalazine/steroids[13]
- methotrexate/hydroxychloroquine
- methotrexate/ciclosporin
- methotrexate/leflunomide.

Further support for early intervention comes from a review of primary trial data from 14 randomised controlled trials of DMARD therapy in early RA. This indicated that disease duration was a significant determinant of response to treatment, patients with shorter disease duration responding more favourably.[8,14]

Safety of early intervention

An inception cohort (wherein a selection of new patients are followed from presentation onwards) of 622 patients with newly diagnosed RA were followed for up to 10 years to evaluate patient mortality, functional ability and prognostic factors for mortality.[15] This cohort, treated early and aggressively with DMARDs, showed no excess mortality within the first 10 years, and functional ability remained constant after an initial improvement from baseline.

In a recent prospective study, the concept of early inflammatory arthritis was taken further. Patients with early arthritis were divided into two groups and outcomes assessed separately:

- very early RA (VERA): duration less than three months
- late early RA (LERA): duration less than one year.

Although the inflammatory markers and swollen joint counts were no different, patients in the VERA group had better control of symptoms and signs and better retardation of radiological progression.[16] These studies highlight the importance of an early aggressive approach in improving both the disease course and outcome.

Practical management of early inflammatory arthritis

Referral

The therapeutic studies in early arthritis studies suggest a 'window of opportunity' in RA when DMARDs are more likely to be successful. Unfortunately, it can be hard to diagnose RA early in the course of the illness (Table 1) and may take some months before the classification criteria are fulfilled. Delays in confirming the diagnosis might mean that any 'therapeutic window of opportunity' is missed. Baseline clinical assessment should include symptoms of active disease (history of joint pain and swelling, duration of morning stiffness, diurnal variation of symptoms), functional status and examination evidence of synovitis.

The clinical criteria that should prompt referral to a rheumatologist and to the early arthritis clinic are:[8]

- joint swelling of three or more joints
- metacarpophalangeal or metatarsophalangeal involvement
- morning stiffness of more than 30 minutes.

Baseline investigations (Table 2)

Baseline laboratory investigations should include:

- full blood count
- erythrocyte sedimentation rate (ESR)
- C-reactive protein
- rheumatoid factor
- renal function tests
- liver function tests (including hepatic enzymes, alkaline phosphatase and albumin)
- urinalysis.

In certain instances, a synovial fluid analysis may be deemed necessary to exclude other differential diagnoses like septic arthritis or crystal arthritis. The assessment of renal and hepatic function tests is necessary as a number of treatments (including NSAIDs) can cause renal and/or hepatic damage and may be contraindicated in the presence of impairment of these organs.

Prognosis

In addition to these baseline laboratory investigations, the patient should be assessed for comorbid conditions, and a validated tool used to assess pain, disease

Table 1. American College of Rheumatology 1987 revised criteria for classification of rheumatoid arthritis.[17]

• Morning stiffness lasting more than 1 hour • Arthritis of 3 or more joint areas • Arthritis of hand joints	Need to be present for at least 6 weeks
Symmetric arthritis	
Rheumatoid nodules	
Rheumatoid factor positivity	
Radiographic changes or erosions on joint X-rays	

At least four of the seven criteria need to be fulfilled for classification of rheumatoid arthritis.

Table 2. Baseline assessment of patients with inflammatory arthritis.

- Symptoms of active disease
- Functional status (eg HAQ)
- Clinical evidence of synovitis
- Extra-articular disease
- Radiographic damage
- Laboratory investigations including:
  - FBC, ESR, U&Es, LFTs, RF
  - Urinalysis

ESR = erythrocyte sedimentation rate; FBC = full blood count; HAQ = Health Assessment Questionnaire; LFTs = liver function tests; RF = rheumatoid factor; U&Es = urea and electrolytes.

activity and quality of life. Poor prognostic markers should be identified, including early age of disease onset, high titre of rheumatoid factor, elevated ESR and swelling of more than 20 joints.[17] A worse prognosis is indicated by extra-articular manifestations of RA including:

- rheumatoid nodules
- sicca syndrome
- interstitial lung disease
- eye involvement (episcleritis, scleritis and, in later stages, scleromalacia perforans)
- interstitial lung disease
- pericardial involvement
- systemic vasculitis.

Treatment

Treatment of early inflammatory arthritis begins with patient education (the disease, the risks of joint damage and disability, the available forms of treatment and their risks and benefits). Patients are referred to physiotherapists, occupational therapists and social workers as part of a multidisciplinary approach.

NSAIDs and glucocorticoids (intra-articular or low-dose oral) can be used for symptom control. Most patients with newly diagnosed inflammatory arthritis are started on DMARD therapy as soon as is practical in a bid to improve overall long-term prognosis. As discussed above, treatment may include low-dose oral prednisolone, single or combination DMARDs (Table 3). Treatment of inflammatory arthritis is an iterative process and continuous reassessment of patients is extremely important.

Conclusions and the future

Early inflammatory arthritis offers a window of opportunity for treatment intervention. Early aggressive treatment, frequently with combined therapy, may enable much improved outcomes for patients with RA. Early referral for specialist advice is therefore critical. The advent of the biologic treatments raises the question of how these new agents should be incorporated into early inflammatory arthritis management strategies.

Table 3. Dosages and approximate time to benefit of disease-modifying antirheumatic drugs used in the treatment of rheumatoid arthritis.

Drug	Approximate time to benefit	Usual maintenance dose
Adalimumab	Few days to 12 weeks	40 mg s/c every fortnight
Anakinra	2–12 weeks	30–150 mg/day s/c
Azathioprine	8–16 weeks	2.5 mg/kg/day oral
Ciclosporin	8–16 weeks	2.5–4 mg/kg/day oral
D-penicillamine	12–24 weeks	250–750 mg/day oral
Etanercept	Few days to 12 weeks	25 mg s/c twice a week
Hydroxychloroquine	8–24 weeks	200 mg twice a day oral
Gold:		
oral	16–24 weeks	3 mg twice a day
intramuscular	12–24 weeks	50 mg every 4 weeks
Infliximab + methotrexate	Few days to 16 weeks	3 mg/kg iv every 8 weeks
Leflunomide	4–12 weeks	10–20 mg/day oral
Methotrexate:		
oral	6–12 weeks	7.5–30 mg once a week
injectable	6–12 weeks	7.5–30 mg once a week
Sulphasalazine	6–12 weeks	1 g 2–3 times a day oral

iv = intravenous; s/c = subcutaneous.

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Management of systemic sclerosis

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Pathogenesis

The pathogenesis of systemic sclerosis (SSc) remains incompletely understood. The earliest events occur in the microcirculation with endothelial cell activation, followed by perivascular inflammation with monocytes and later lymphocytes. Subsequently, fibroblasts become activated and deposit increased extracellular matrix in lesional tissues including the skin and internal organs.[1] The resulting architectural disruption leads to the morbidity, and ultimately mortality, associated with SSc. There is evidence to support genetic factors in the development of SSc but few candidate susceptibility or severity genes have yet been identified.

Classification

This article focuses mainly on SSc (scleroderma with systemic involvement), but the spectrum of scleroderma encompasses Raynaud's phenomenon and localised subtypes of skin fibrosis such as morphoea (Table 1). The extent of skin involvement defines the disease subset in cutaneous SSc (Fig 1):[2]

- diffuse cutaneous SSc (dcSSc): skin involvement proximal to the elbows and knees, and
- limited cutaneous SSc (lcSSc): skin involvement distal to these joints.

A subset of patients has the clinical features of isolated Raynaud's phenomenon, with evidence of microvasculopathy based upon nailfold capillaroscopy and/or serum autoantibodies against nuclear antigens (autoimmune Raynaud's phenomenon). They have a 10–15% likelihood of developing a defined connective tissue disease (including SSc) during long-term follow-up.

The term limited SSc has recently been applied to another group of patients who lack definite skin involvement but who harbour specific antibodies against hallmark antigens or have scleroderma-associated capillaroscopic changes.[3]

In addition, a small number of patients with vascular symptoms and SSc-specific antibodies develop major organ-based complications in the

Key Points

Appropriate management of systemic sclerosis (SSc) requires accurate disease subsetting, staging of the disease within each subset and risk stratification for major organ-based complications, based upon clinical features and serology

All patients with SSc should be screened for major complications to facilitate early intervention

Hypertensive renal crisis can occur in any patients with SSc; angiotensin-converting enzyme inhibitors should be instituted as early as possible in these cases

Significant reduction in transfer factor on lung function tests may reflect either interstitial lung disease or pulmonary hypertension (PAH). Doppler echocardiography and high-resolution computed tomography of the chest are indicated

PAH should be confirmed by right heart catheterisation before considering advanced therapy for symptomatic cases

KEY WORDS: pulmonary fibrosis, pulmonary hypertension, Raynaud's phenomenon, renal crisis, scleroderma, systemic sclerosis