Clinical review

Treatment of rheumatoid arthritis

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Rheumatoid arthritis is a systemic disease that affects the synovial joints. It is a persistent chronic disease that spreads from joint to joint and affects about 0.5% of people worldwide. Not that long ago it was believed that antirheumatic therapy made little, if any, difference to the long term outcome of the disease. It was thought to be difficult to see patients appropriately early enough in the disease’s progression, that an accurate diagnosis was not possible, and that therapies were ineffective. All this has now changed and this review examines these changes.

Sources and selection criteria

I obtained references from Medline, my personal archives, and the proceedings of the last two major international meetings—the European League against Rheumatism, Vienna and the American College of Rheumatology, San Diego. Search terms used were “inflammatory arthritis”, “rheumatoid arthritis”, “early rheumatoid arthritis”, “therapy”, “biologics”, “biologica”, “anti-TNF therapy”, “DMARDS”, and “NSAIDs”.

Conventional management of rheumatoid arthritis

The standard treatment of patients with rheumatoid arthritis has included non-steroidal anti-inflammatory drugs. Although these drugs improve symptoms and signs, they do little to alter the structural progression and long term disability associated with rheumatoid arthritis. In the past, further therapy using disease modifying antirheumatic drugs was only prescribed when there was radiographic evidence of erosions (holes in bones). Disease modifying antirheumatic drugs were thought to reduce the damage shown on radiographs (disease modification), but although objective evidence for this effect was hard to obtain, proof has now been unequivocally shown. Disease modifying antirheumatic drugs are thought to act by direct or indirect inhibition of cytokines, unlike non-steroidal anti-inflammatory drugs, which act mainly by inhibiting cyclooxygenase and thereby reducing the production of inflammatory prostaglandins (inhibiting symptoms but not influencing structural damage).

The most commonly used disease modifying antirheumatic drugs were gold, penicillamine, and sulphasalazine, all of which produced a slow response and a high level of toxicity. Consequently, few patients took the drugs long term. The addition of methotrexate to the armamentarium, especially when rheumatologists started to use higher doses, produced an improvement, but still less than 50% of patients remained on disease modifying antirheumatic drugs treatment long term.

What has changed?

For many years clinicians asserted the importance of early intervention in inflammatory arthritis in an attempt to alter the poor short term and long term outcomes. Early accurate diagnosis and prognosis with particular attention to imaging and the use of genetics and immunology was recommended. Patients who develop rheumatoid arthritis have normal radiographs in 80% of cases at presentation, whereas magnetic resonance imaging can pick up changes in over 80% of such cases, and high resolution ultrasonography can detect synovitis and classic erosions in seven times more patients than can radiography (fig 1). Imaging has allowed the identification of the pathognomonic features of rheumatoid arthritis as intra-articular synovitis with characteristic bony damage.

In addition, the association between the disease and HLA class II has been confirmed, with evidence...
that the major relation between the shared epitope (a conserved series of amino acids) and specific autoantibodies, particularly rheumatoid factor, are persistence and severity.\(^3\) More recently, anticyclic citrullinated peptides have also been associated with persistence and damage.\(^2\) As with rheumatoid factor, these antibodies may be present for years before the development of clinical disease but, importantly, unlike rheumatoid factor, are highly specific.\(^4\)

### Who will get severe disease?

During the years when only ineffective therapies were available to treat rheumatoid arthritis, much effort was put into monitoring outcome. Research focused on the factors that predicted poor prognosis. It became clear that measures of inflammation such as C reactive protein and number of swollen joints and disease specific factors, such as the presence of autoantibody rheumatoid factor (and later anticyclic citrullinated peptides), combined with the genetic association (namely, with the shared epitope) were good predictors of structural damage or erosions. Meanwhile, predictors of poor function were the patients' functional state at onset of the disease, being female, and the extent of inflammation. Composite prognostic indicators such as PISA (persistent inflammatory symmetrical arthritis) which includes all these elements, and the Leiden score,\(^5\) which in addition includes anticyclic citrullinated peptides to produce a composite predictor, have been used to select patients for more aggressive intervention.

With the availability of therapies that effectively treat many more patients, these prognostic factors for indicators of severity (indicating the need for aggressive therapy) became less important than the predictors of persistence (indicating the need for appropriate treatment). The prognostic factors remain valuable in showing that cohorts are consistent for the presence of prognostic factors over time, thereby indicating that any differences in outcome are due to therapy.

### Does early treatment make a difference?

With the establishment of clinics for dealing with early arthritis it was clear that earlier intervention produced a better outcome, although it was debatable as to whether a true “window of opportunity” could be proved or even existed. The principle of this concept is that an intervention at one particular time produces a disproportionate benefit long term. Undoubtedly evidence showed a quantitative benefit (equivalent to debulking in oncology) but whether this was qualitative remained debatable.\(^1\)

Meanwhile a second principle of management, the “tight control” of disease activity, was proposed. This followed the lead of diabetologists, who showed that better control of diabetes on a day to day basis led to less organ damage. In practice, tight control for rheumatoid arthritis meant that therapy was increased if disease activity was not suppressed below a predefined level (ideally that of remission). Several studies have now shown that escalation of therapy on the basis of objective evidence of continued disease activity using a validated outcome measure rather than the global impressions of patients or doctors produces a significantly better result. In particular, the tight control for rheumatoid arthritis study from Glasgow (TICORA) showed excellent improvement in symptoms and signs with the more aggressive intervention.\(^6\)

In the aggressive intervention arm more frequent assessment and escalation of therapy on the basis of disease activity were effective, although which was the more important component of these two aspects could not be distinguished.

### What therapy is now available in secondary care?

Given that most patients who develop severe persistent inflammatory arthritis do not have serum test results or radiographic changes suggestive of disease at baseline, there is logic for referring all new patients with symptoms of inflammatory arthritis during the early more treatable phase of the disease. Although statistically only a small proportion of these will develop rheumatoid arthritis, evidence already shows that other patients with less well defined disease, such as undifferentiated arthritis, and even those with so called “inflammatory” osteoarthritis will benefit from appropriate targeted intervention long term. Although referral will depend on the availability of facilities in secondary care and the willingness of general practitioners to refer, there can be little doubt about the cost-benefit of this approach. For every patient in whom lifelong chronic inflammatory arthritis is prevented the direct and indirect savings are enormous, thus the onus must be for primary care to consider referral in all new cases. If referral is doubtful then the level of anticyclic citrullinated peptides should be measured as this is a strong predictor of persistence (fig 2). How this will work in practice is still to be established. Yorkshire already has a network of 18 early arthritis clinics, which operate as a regional centre with subregional units. Pilot studies in primary care should establish the value of even earlier screening.

Meanwhile a revolution occurred in the therapy of rheumatoid arthritis with the realisation that the proinflammatory cytokine tumour necrosis factor α (TNF-α) played a central and hierarchical part in the pathogenesis of the disease, and that its blockade would lead to major improvements in symptoms and signs.\(^7\) The availability of TNF-α antagonists (both monoclonal antibodies and a receptor fusion protein) led to landmark studies, which showed that these agents were remarkably effective in patients who had not responded to disease modifying antirheumatic drugs, including methotrexate.\(^8\)

Furthermore, the studies showed that blockade of TNF-α dramatically inhibited structural damage—for
example, in a study of patients who had not responded to methotrexate, the addition of infliximab virtually halted progression of damage. A recent study on the combination treatment of receptor fusion protein and methotrexate actually showed a significant improvement in radiographic score. A recent study of patients with relatively early disease provided data on the relative value of monotherapies and combination treatment. It compared high dose methotrexate with monotherapy anti-TNF-α and with the two drugs combined, in patients who had features predicting rapid damage. At two years, half the patients receiving combination therapy were in remission. This must now be the goal for patients with early disease.

This study also showed that although little separated the two monotherapies in terms of symptoms and signs, anti-TNF-α halved the structural progression seen with methotrexate, whereas the combined therapy reduced this damage by four fifths. (It is believed that inhibition of tumour necrosis factor prevents the activation of osteoclast by RANK (receptor activator nuclear factor-κB) ligand, thereby stopping bony damage.) This is consistent with the data from the tight control for rheumatoid arthritis study, where the excellent improvement in symptoms and signs produced by conventional disease modifying antirheumatic drugs was still accompanied by significant structural progression. The probable explanation for this progression is that disease modifying antirheumatic drugs rarely suppress synovitis and that patients have measurable inflammation even when in remission while taking these drugs.

Has an optimal approach been established?

It was only time before the most effective therapy was linked to intervention at the most appropriate time—namely, using biological agents at the presentation of arthritis, when damage is minimal. A pilot study showed that high dose anti-TNF-α was effective for six months, but the benefits were not long lasting after stopping therapy. However, a double blind randomised control study showed that after a year of therapy, biological agents could be withdrawn and patients left in remission with benefit beyond two years. The median response in the active arm was a normal functional state and a normal quality of life assessment. A large single blind study from the Netherlands has confirmed the importance of early aggressive intervention, with clear benefit from using biological agents and high dose steroids compared with conventional approaches. Most importantly it showed that after treatment with tumour necrosis factor blocker had produced remission for six months, it was possible to withdraw the biological agent and maintain remission in the second year. Even more strikingly, a proportion of patients were able to successfully stop taking methotrexate. These patients were actually in remission while receiving no therapy, representing “cure,” at least temporarily.

What will the future hold?

Is blockade of TNF-α the complete answer to treatment of rheumatoid arthritis? In terms of toxicity, anti-TNF-α agents fortunately have only produced side effects in line with their mode of action; infections are increased, and latent tuberculosis can be activated (partly by the known action of antitumour necrosis factor monoclonals on granulomas). It is, however, possible to screen and minimise the reactivation of tuberculosis with prophylaxis. Other problems include inducing antibodies against the drugs themselves and also switching to autoantibody production as is seen with Th2 cells. A greater problem is the need for ongoing therapy, which entails giving protein long term to patients, although it can now be a fully human monoclonal protein. Over time a finite loss of response occurs. Both a primary and a secondary non-response have been proposed for this complex mechanism.

This is a particular problem in patients currently approved for therapy by the National Institute of Health and Clinical Excellence, as these patients have long duration of disease with much damage and a greater failure rate with tumour necrosis factor blockers. Induction of remission with TNF-α blocker and maintenance with a disease modifying antirheumatic drug is a potentially attractive approach for the future, especially if it avoids long term therapy with biological agents. For the foreseeable future, a large number of patients will have tried and failed anti-TNF-α therapy owing to a mixture of inefficacy or toxicity.

Patients who have failed to respond to blockade using tumour necrosis factor require new therapies. To this end, agents that work in a completely different way are being developed, and two have been submitted for licence—one is an anti-B cell therapy (rituximab), which depletes B cells and has major effects on their actions. It is being promoted as a therapy for patients who fail to respond to tumour necrosis factor as well as producing benefits in autoantibody driven disease such as systemic lupus erythematosus. The other drug, CTLA4-Ig (abatacept), blocks the second signal thereby inhibiting T cell costimulatory pathways (T cells for full activation need stimulation through two pathways) and is being submitted for licence in patients who partially respond to methotrexate and in those who fail to respond to tumour necrosis factor.
Additional educational resources

Suzare-Almazor ME, Osiri M, Emery P. Rheumatoid arthritis: Evidence-based rheumatology. BMJ 2004;328:82-reviews the evidence for efficacy of conventional disease modifying antirheumatic drugs


Information for patients

Arthritis Research Campaign (www.arc.org.uk)—useful information about the Arthritis Research Campaign, particularly active research and grant funding activities

Arthritis Care (www.arthritis-care.org.uk)—information on patient related issues

National Rheumatoid Arthritis Society (www.arthritis.org.uk)—has particular focus on patients with rheumatoid arthritis

Will arthritis prevention be possible?

Patients with rheumatoid arthritis have been shown to have autoantibodies and evidence of minor levels of inflammation for up to 10 years before presentation. It therefore is possible to screen for a disease that is now virtually treatable. In the future, early arthritis centres (already optimistically labelled arthritis prevention centres) should be able to diagnose patients at onset of rheumatoid arthritis or even before the disease develops, and start therapy appropriate for the stage of disease before clinically important damage occurs.

In the future the outlook should be vastly different to what it was a few years ago. The result of treatment in patients newly presenting with rheumatoid arthritis has moved from inefficacy to the potential for virtual cure. General practitioners need to appreciate the unique situation of patients newly presenting with rheumatoid arthritis as a comparison with conventional radiography. Arthritis Rheum 2000;43:2762-70.


