Advances in the medical management of rheumatoid arthritis

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New treatments, such as leflunomide and biologic therapy, are making an important impact on the management of rheumatoid arthritis. This article reviews the efficacy of these agents, the use of combination therapy, and the importance of early treatment with a disease-modifying antirheumatic drug.

Following more than a decade of relative stasis, the medical management of rheumatoid arthritis (RA) has recently entered a period of rapid change. Advances have focused primarily on therapeutic developments spanning four areas. First, the increasing use of combinations of disease-modifying antirheumatic drugs (DMARDs). Second, the introduction of a new DMARD, leflunomide, which has been shown to be effective in a series of large randomized, controlled trials that have extended over many years. Third, the introduction into clinical practice of immunotherapies based on the inhibition of tumour necrosis factor (TNF). Finally, the availability of the cyclo-oxygenase-2 (COX-2) specific non-steroidal anti-inflammatory drugs (NSAIDs) that reduce the risks of serious gastrointestinal ulcers and bleeds that have long been associated with conventional NSAIDs.

The purpose of this review is to highlight the relative benefits and limitations of those new therapies that have the potential to modify the course of RA and show where they should fit within the current treatment paradigm. This comprises new and combined DMARDs and immunotherapies but excludes COX-2 drugs, as these are entirely aimed at reducing toxicity.

It is also important to realize that, although these new treatments represent important and exciting innovations, many of the long-accepted truisms about RA have not changed. The condition still remains an unpredictable disease of unknown origin with no overall cure.

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COMBINATION THERAPY

A meta-analysis of trials evaluating a total of 749 patients published in 1994 concluded that combination treatment did not confer a substantial benefit, and that toxicity was greater (Felson et al, 1994). However, there were significant design problems in these early trials, which often studied relatively few patients for short periods of time. More recently, combination therapies have become increasingly popular in response to some encouraging results.

There are three ways of combining DMARDs:

- Parallel – all DMARDs are started together
- Step-up – one DMARD is started first and the full combination therapy is not in place for some months
- Step-down – the initial combination therapy is maximal and is gradually reduced.

Initial attempts at combining DMARDs focused on starting two or more drugs simultaneously. The disadvantage of this approach is that all patients have increased risks of side effects, but not all patients require two DMARDs. As a consequence step-up therapy has become more popular.

Triple therapy

Triple therapy with methotrexate, hydroxychloroquine and sulphasalazine came into prominence in 1996 when O'Dell et al published a landmark placebo-controlled study. This involved 102 patients with RA randomized to methotrexate alone, sulphasalazine and hydroxychloroquine in combination, or all three drugs. Substantial clinical improvements occurred in 33% taking methotrexate alone, 40% with double therapy and 77% with triple therapy. The triple therapy showed no increase in toxicity and follow-up studies showed the benefit persisted for as long as 3 years.

In 1997 the COBRA investigators (Boers et al, 1997) reported a trial involving 155 patients that compared sulphasalazine monotherapy in early RA with the combination of methotrexate, sulphasalazine and prednisolone given over 12 months. At 28 weeks there were significantly greater improvements in the combination group in almost all outcome measures (*Table 1*).

TABLE 1.
Key trials of combination therapy with disease-modifying antirheumatic drugs

Reference	Cases	Duration (months)	Drugs or combinations	Strategy	Efficacy	Increased toxicity
O'Dell et al (1996)	102	9	Methotrexate + sulphasalazine + hydroxychloroquine *vs* sulphasalazine + hydroxychloroquine *vs* methotrexate	Parallel	Moderate	No
Boers et al (1997)	155	6	Sulphasalazine + methotrexate + prednisolone *vs* sulphasalazine	Step-down	Strong	No
Möttönen et al (1999)	199	24	Methotrexate + sulphasalazine + hydroxychloroquine + prednisolone *vs* sulphasalazine	Step-down	Moderate	No
Tugwell et al (1995)	148	6	Methotrexate + cyclosporin *vs* methotrexate	Step-up	Strong	No

A final key study was reported by the FINRACo trial group (Möttönen et al, 1999). This group randomized 199 RA patients, with disease duration of less than 2 years, into two groups. The first were treated with the combination of methotrexate, sulphasalazine, hydroxychloroquine and steroids. The second received conventional monotherapy with sulphasalazine alone, which could be replaced by methotrexate together with optional steroids. After 2 years 37% of the combination group and only 18% of the monotherapy group were in remission.

Combination with cyclosporin

In 1995 Tugwell et al studied 148 patients with severe RA who were only partially responsive to methotrexate. The patients were randomized to receive additional cyclosporin or placebo. After 6 months of treatment the patients receiving cyclosporin showed significant improvements in all clinical end-points including joint counts, pain and disability scores.

LEFLUNOMIDE

Three large, phase III trials have shown that leflunomide is an effective and safe DMARD (*Table 2*). The first involved 358 RA patients randomly assigned to receive leflunomide, placebo or sulphasalazine (Smolen et al, 1999). Over 6 months leflunomide and sulphasalazine were significantly superior to placebo in reducing tender and swollen joint counts and in terms of investigators' and patients' overall assessments. In addition radiographic disease progression was significantly slower with leflunomide and sulphasalazine than with placebo.

The second trial evaluated 482 RA patients followed for 12 months (Strand et al, 1999) who were randomized to receive leflunomide, methotrexate or placebo. There were 52% responders with leflunomide and 46% with methotrexate compared to only 26% with placebo.

The final trial compared leflunomide with methotrexate in 999 RA patients over 12 months (Emery et al, 2000). There were similar improvements with both drugs.

Overall these three trials showed that leflunomide was a highly effective DMARD with comparable efficacy and toxicity to methotrexate. There is also considerable evidence that leflunomide has a sustained benefit. An extension of the 6-month study described above (Smolen et al, 1999) showed that the benefits of leflunomide were sustained at 24 months. Patients taking leflunomide showed significant improvement compared with sulphasalazine in doctor and patient global assessments, American College of Rheumatology-20 (ACR-20; 20% improvement in tender and swollen joint counts and 20% improvement in three of the five remaining ACR core set measures: patient and physician global assessments, pain, disability, and an acute phase reactant) response and functional ability (Scott et al, 2001).

An abstract presented at the American College of Rheumatology scientific meeting in San Francisco, 2001, suggested that efficacy observed after 1 year of treatment extends as long as 5 years (Kalden et al, 2001a). A group of 214 patients treated with leflunomide for 2 years

TABLE 2.
Pivotal trials involving leflunomide

Reference	Duration	Number	Drugs	ACR-20 responders	C-reactive protein (mg/dl)
Strand et al (1999)	12 months	482	Leflunomide	52%	–0.6
			Methotrexate	46%	–0.5
			Placebo	26%	+0.5
Smolen et al (1999)	6 months	358	Leflunomide	55%	–2.3
			Sulphasalazine	56%	–1.1
			Placebo	29%	–0.2
Emery et al (2000)	12 months	999	Leflunomide	51%	–2.2
			Methotrexate	65%	–2.9
Scott et al (2001)	24 months	358	Leflunomide	82%	–2.7
			Sulphasalazine	60%	–1.3
Kalden et al (2001a)	5 years	214	Leflunomide	69%	–2.5

ACR-20 = American College of Rheumatology-20

were included in an open-label 5-year extension. ACR-20, ACR-50 and ACR-70 response rates and Health Assessment Questionnaire scores at 1 year were maintained through year four or endpoint and 76.2% of patients entering the open-label extension completed the study. Leflunomide has also been shown to have major beneficial effects on X-rays (Sharp et al, 2000) and functional disability (Kalden et al, 2001b).

Leflunomide is given orally, starting with a loading dose of 100 mg daily for 3 days. The maintenance dose is 20 mg daily, although the dose can be reduced to 10 mg daily for better tolerability.

Side effects

The frequency of side effects leading to the discontinuation of leflunomide was similar to that for the control drugs in the trials. Most adverse effects of leflunomide are minor, such as gastrointestinal symptoms, skin rash, alopecia, dyspepsia, hypertension, and elevated transaminases. The drug is immunosuppressive and thus can increase the risk of infection. Leflunomide is contraindicated in pregnancy, and patients who wish to become pregnant are generally treated with cholestyramine to enhance elimination of the drug (Brent, 2001). Pancytopenia has been reported as a rare occurrence associated with leflunomide (Auer et al, 2000), and it is important to monitor the blood count in the early phase of therapy. Much recent attention has focused on the possibility that serious liver toxicity can occur in leflunomide-treated patients (Weinblatt et al, 2000). Fortunately, such toxicity appears to be uncommon. Regular monitoring of liver function during leflunomide therapy is needed, and transaminase elevations or depression of serum albumin levels should be taken seriously. Special care is needed in those patients who drink alcohol or have a history of liver disease.

BIOLOGIC THERAPIES

The most recent additions to the rheumatologist's armamentarium are the new 'biologic' therapies etanercept and infliximab. These genetically engineered TNF inhibitors have inspired much excitement because of their unique mode of action and potential to offer efficacious care that is well tolerated by the patient.

TNF is a cytokine that is involved in the inflammatory process that leads to RA. By blocking its action, the biologics interrupt the process that leads to joint damage. Clinical trials have demonstrated the efficacy of this approach both as monotherapy and in combination with methotrexate.

Etanercept

In two placebo-controlled trials of 180 and 234 RA patients, twice weekly subcutaneous injections of etanercept 25 mg gave significant improvements (Moreland et al, 1997, 1999). The number of swollen joints decreased by approximately 50% from baseline after 3 months and 6 months of treatment respectively. Treatment with etanercept was well tolerated, and produced only minor reactions at the site of the injection. Long-term, open-label studies have shown the efficacy of continued treatment with etanercept persists for over 30 months. In other studies, etanercept was better tolerated and more effective than methotrexate in patients with early RA (Bathon et al, 2000). There was less radiographical evidence of progression of RA in patients who were receiving etanercept than in patients who were receiving methotrexate. Etanercept is also effective in combination with methotrexate (Weinblatt et al, 1999), and probably with most other DMARDs, although the evidence for this is currently incomplete.

The recommended adult dose of etanercept is 25 mg twice weekly via subcutaneous injection in the thigh, abdomen or upper arm. Patients must be instructed on the injection technique and be comfortable with this form of medication.

Infliximab

A randomized controlled trial of 73 RA patients showed a single intravenous dose of infliximab rapidly reduced the number of swollen joints as well as the serum concentration of C-reactive protein (Elliott et al, 1994). Clinically significant improvement was evident within a week of treatment beginning. In a subsequent randomized controlled trial of 101 RA patients, infliximab or placebo was given repeatedly, with or without methotrexate (Maini et al, 1998). Antibodies against infliximab developed in many patients after repeated treatment, but the incidence was reduced by concomitant treatment with methotrexate. Furthermore, moderate and high doses of infliximab gave similar significant clinical benefits. The benefit of infliximab has been confirmed in a large randomized, placebo-controlled trial of 428 RA patients (Maini et al, 1999). The infliximab-treated patients had sustained clinical improvement for over 6 months. The currently recommended dose of infliximab is 3–10 mg/kg intravenously at 4–8-week intervals.

Limitations of biologics

The major drawback to the biologics is that, in comparison to all other RA therapies, they are extremely expensive. Treating a patient for a

month with infliximab costs over £500 compared to approximately £46 with leflunomide, £13 with sulphasalazine and £8 with methotrexate (Lambert, 2000).

Another risk is infections. This has been highlighted for tuberculosis – one report has described 70 cases developing tuberculosis in relation to infliximab therapy (Keane et al, 2001).

CURRENT BEST MANAGEMENT

Patients with RA should have symptomatic treatment with analgesics and NSAIDs.

There is now persuasive evidence that early aggressive treatment of RA results not only in a more rapid reduction of disease activity but also in less radiographical progression in the long term (Albers et al, 2001). DMARD therapy should therefore be instigated at the first opportunity in all patients with active synovitis.

Although there is no clear-cut evidence about the best DMARD, in the UK methotrexate monotherapy and sulphasalazine monotherapy dominate treatment. Leflunomide is a useful 'first reserve'. Older DMARDs like injectable gold should only be used if these other drugs have failed. If DMARD monotherapy is insufficient, combination DMARDs should be used. Methotrexate, sulphasalazine and hydroxychloroquine or the combination of methotrexate and cyclosporin are both effective. When all else fails biological therapy with anti-TNF may be needed, although at present its high cost precludes its use in all cases. **HM**

Conflict of interest: Professor Scott has acted as a consultant for Aventis Pharma.

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KEY POINTS

- Disease-modifying antirheumatic drug (DMARD) therapy should be instigated at the first opportunity in all patients with synovitis.
- The step-up approach to combination DMARD therapy is increasingly used.
- Leflunomide, a new DMARD, is effective and well tolerated, and slows radiographic disease progression.
- New biologic anti-tumour necrosis factor therapies are effective, yet expensive. They should be used when DMARD therapy fails.