The broadening use of leflunomide in clinical practice

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Autoimmune diseases make up a large proportion of chronic disease care. Inducing remission by immunosuppression remains the cornerstone of long-term management. This article reviews the place of leflunomide in clinical practice and outlines its potential applications beyond its licenced indication, rheumatoid arthritis.

After atherogenic diseases and cancer, autoimmune diseases comprise the largest group of conditions to afflict man in the 21st century. The goal of therapies is to suppress disease through perturbation of immune driven pathogenesis and thereby prevent or reduce target organ damage. Some autoimmune diseases only present when the target organ(s) have been largely irretrievably damaged, for example type 1 diabetes and Hashimoto's thyroiditis, where treatment is focused on replacement of function rather than immune modulation. In contrast, in many other conditions the initial presentation is at a stage when damage can still be avoided. For example in inflammatory bowel disease, psoriasis, rheumatoid and the seronegative spondyloarthritides, the connective tissue diseases, the vasculitides, the pneumonitides and the broad spectrum of allergic upper and lower respiratory airway or sinus diseases, therapy is focused on immune suppression to prevent damage or its progression.

While corticosteroids are the cornerstone of therapy for most, their long-term adverse effects require the use of alternative immunosuppressive agents. Such therapy is often more successful where there is a clear understanding of pathogenesis, as for example in targeting the mast cells in allergic conditions and the T cells in psoriasis. Sadly in many conditions a lack of understanding of pathogenesis means that more broad spectrum approaches are still required. Azathioprine and cyclophosphamide have potent effects on dividing cells but are so broad in their targets that bone marrow, gamete and gastrointestinal toxicity remain a limitation. Improved targeting to certain arms of the immune response has led to a changed and often favourable diminution in toxicity, thus cyclosporin and tacrolimus appear to preferentially target T cells and have minimal marrow effects.

Biologic therapies offer precise targeting to cells, their receptors or cytokines, and in so doing enable a dissection of the role of individual components of the immune response in the pathogenesis of different diseases. However, their cost and a lack of understanding of pathogenesis means that for the majority of patients with autoimmune disease, the future still holds a requirement for long-term immune suppression with a variety of less specific agents, depending on the individual disease and those arms of the immune response thought to contribute most to pathogenesis.

MECHANISM OF ACTION AND PHARMACOKINETICS

Leflunomide is a new immunosuppressive agent, first licenced for the treatment of rheumatoid arthritis in Europe in 1999. It is an inhibitor of de novo pyrimidine synthesis through the inhibition of the enzyme dihydroorotate dehydrogenase (Ruckemann et al, 1998). T cells preferentially utilize this enzyme in pyrimidine synthesis (Fairbanks et al, 1995) and are therefore thought to be the principal target of this drug.

Leflunomide is licensed to be given as a loading dose of 100 mg for 3 days followed by a maintenance dose of 20 mg daily. When given this way steady state plasma levels are attained promptly, within 3–5 days, leading to a rapid onset of action within 4 weeks, considerably faster than many other immunosuppressants. The drug is metabolized in the gut wall and liver to its active metabolite A77 1726, which is highly

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protein bound and has a long half life (Rozman, 2002). It undergoes enterohepatic recirculation and is partially cleared by hepatic metabolism and biliary excretion, and partially by renal excretion (Rozman, 2002). Leflunomide should therefore be used with caution in patients with either hepatic or renal insufficiency. Excretion may be accelerated with the use of a washout with cholestyramine 8 g three times daily for 10 days, after which plasma levels of A77 1726 are undetectable.

EFFICACY IN RHEUMATOID ARTHRITIS

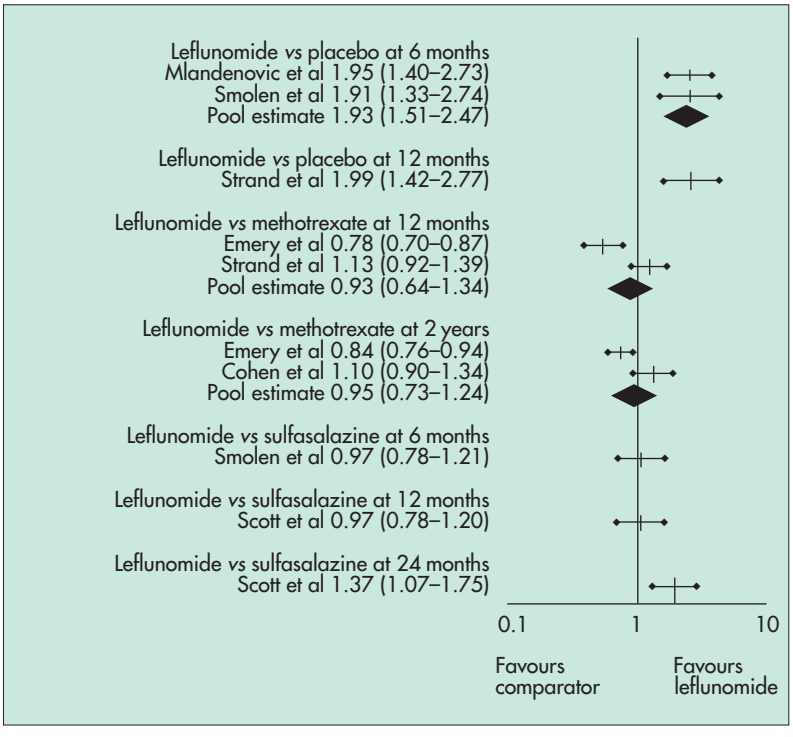
In rheumatoid arthritis, leflunomide has been shown to reduce symptoms and signs of active inflammation, to retard the progression of joint damage, demonstrated by preservation of joint space and reduction in erosions, and to improve physical function. Large randomized double blind trials comparing leflunomide to methotrexate have demonstrated an equivalent therapeutic effect at 12 (Strand et al, 1999) and 24 months (Cohen et al, 2001) and a statistically better outcome with methotrexate at 12 months, tending to equivalence at 24 months (Emery et al, 2000).

Similar rigorous comparisons with sulphasalazine have shown equivalent clinical efficacy at 6 months (Smolen et al, 1999) leading to statistically better outcome with leflunomide at 24 months (Scott et al, 2001). The same studies show leflunomide to have a statistically equivalent or better effect on physical function compared with methotrexate at 12 and 24 months (Strand et al, 1999; Emery et al, 2000; Cohen et al, 2001) and to be statistically better than sulphasalazine at 6 and 24 months (Smolen et al, 1999; Scott et al, 2001).

Radiographic analyses demonstrate statistical superiority of leflunomide in comparison with methotrexate at 12 months (Strand et al, 1999) with equivalence at 24 months (Cohen et al, 2001), and equivalence at 12 months with superiority of methotrexate at 24 months (Emery et al, 2000). Efficacy has been maintained in open label continuation studies for up to a mean of 4.6 years (Kalden et al, 2003). Meta-analyses including a total of 2044 patients treated with leflunomide, methotrexate or sulphasalazine has confirmed statistically improved clinical, functional and radiographic outcome compared to placebo for leflunomide and statistical equivalence between all three agents (*Figure 1)* (Osiri et al, 2003; Maddison et al, 2004). As such, leflunomide fulfills the criteria of the Outcomes Measures in Arthritis Clinical Trials (OMERACT) definition of a disease-modifying antirheumatic drug (DMARD) and it now has an established place as a DMARD in routine rheumatoid arthritis management, before recourse to biologic therapies.

Recent trends in the management of rheumatoid arthritis favour an early aggressive approach, with an escalation in therapy to the use of two or more DMARDs in combination for patients failing to demonstrate a satisfactory response to such agents used alone. In this context, leflunomide has been shown to result in a statistically better outcome at 24 weeks when added to methotrexate monotherapy in patients with persistently active rheumatoid arthritis in comparison to ongoing methotrexate monotherapy with additional placebo (Kremer et al, 2002). Data are also emerging of encouraging efficacy in combination with infliximab, although toxicity issues are a concern in this particular context (Kiely and Johnson, 2002).

Figure 1. Relative efficacy (American College of Rheumatology 20% composite outcome score, ACR20) with 95% confidence interval from a meta-analysis of 2044 rheumatoid arthritis patients treated with leflunomide vs placebo, methotrexate or sulphasalazine. From Osiri et al (2003).



ADVERSE EVENTS AND STRATEGIES FOR MANAGEMENT

A large post-marketing cohort analysis of 40 000 patients has reported that the overall adverse event rates for leflunomide were lower than methotrexate or other DMARDs (*Table 1)* (Emery et al, 2002). In particular, leflunomide does not appear to be associated with serious adverse events any more frequently than other

immunosuppressive agents and, notably, appears to have minimal bone marrow toxicity. Adverse events which necessitate immediate reduction or cessation of therapy and washout include greater than three to five times the upper limit of normal (ULN) elevation of liver enzymes, severe hypertension and dermatological reactions including Stevens–Johnson syndrome.

A recent meta-analysis of published trials in rheumatoid arthritis suggests that a comparable proportion of patients (4–5%) treated with leflunomide and sulphasalazine develop elevations in liver enzymes greater than three times the ULN, in contrast to methotrexate where this occurs in 17% of patients (Maddison et al, 2004). This is supported by Osiri et al (2003), who found in a separate meta-analysis no difference in the frequency or number of withdrawals resulting from elevated liver enzymes between leflunomide, methotrexate and sulphasalazine. Nevertheless, serious adverse events require patients to avoid a high intake of alcohol and to undergo monitoring of liver enzymes and blood pressure at frequent intervals to ensure early detection and appropriate action.

Leflunomide is associated with a number of less serious adverse events which, while not life threatening, are a nuisance to the patient and may lead to loss of confidence in the drug and unnecessary cessation of therapy. Indeed, the total number of patients withdrawn as a result of adverse events from leflunomide in published trials is approximately 20%. While this may be lower or similar to that seen for sulphasalazine and similar or higher than that seen with methotrexate (Osiri et al, 2003; Maddison et al, 2004), the total number is high.

Such 'nuisance' adverse events include nausea, diarrhoea, pruritis, alopecia, mild hypertension and weight loss. Many of these adverse events are transient and may be controlled symptomatically, for example with anti-emetics. Persistent symptoms may be managed with a dose reduction or longer term symptomatic treatment. The patient may well have a preference with regard to this choice, particularly if faced with a potential loss of efficacy following dose reduction.

A simple dose reduction of leflunomide from 20 mg to 10 mg daily will not lead to a new steady state level for some time as the half-life of A77 1726 is approximately 2 weeks (Rozman, 2002). If the adverse event is not controlled satisfactorily with symptomatic treatment, taking advantage of the enterohepatic recirculation and administering a partial wash out with cholestyramine 8 g three times daily for 1–3 days may achieve prompt resolution. This will lead to a rapid diminution of plasma drug levels, cessation of the adverse events, and enable the lower 10 mg daily dose to be continued without loss of efficacy.

There is some evidence that use of the loading dose may be associated with a higher incidence of such 'nuisance' adverse events and discontinuation of therapy (Chokkalingam et al, 2002; Sinha et al, 2002; Erra et al, 2003). As a result, the loading dose is often omitted in UK rheumatological practice, although this will mean a prolongation of the time to achieve steady state plasma levels from 3–5 days to 2 months, with loss of the rapid onset of action that is a particular advantage of leflunomide over other immunosuppressants. The decision

TABLE 1.
Adverse events per 100 patient years from a retrospective cohort analysis of 40594 rheumatoid arthritis patients treated with leflunomide, methotrexate or other disease-modifying anti-rheumatic drug

	LEF (2166PY)	MTX (4808PY)	Other DMARD (15717PY)	LEF + MTX (1024PY)	LEF + DMARD (2719PY)	Other DMARD + MTX (8621PY)
Any adverse event	10.06	16.23	16.93	4.58	5.85	6.96
Hepatic Severe	0.21	0.30	0.32	0.31	0.13	0.09
Other	0.42	0.66	0.73	0.14	0.25	0.36
Haematological*	0.14	0.08	0.24	0	0.04	0.10
Skin*	0	0.08	0.09	0	0.04	0.03
Hypertension	4.36	6.65	6.52	1.74	2.61	2.71
Pancreatitis*	0.29	0.25	0.41	0.14	0.18	0.16
Respiratory	2.54	5.58	5.06	1.70	1.86	2.31

*For haematological, skin, and pancreatitis adverse events, there were too few events or too little person-time to adjust for age and sex.
From Emery et al (2002). DMARD = disease-modifying anti-rheumatic drug; LEF = leflunomide; MTX = methotrexate; PY = patient year

to omit the loading dose should, therefore, be balanced, possibly reserving it for those in whom a rapid clinical effect is required and avoiding it in frail or otherwise adverse event-prone patients.

As immunosuppressive treatment options are by no means limitless, it follows that particular attention should be taken with patient selection, education, and monitoring of these therapies to maximize long-term adherence. Nurse practitioners are particularly suited in rheumatological practice to providing detailed information before starting therapy, to oversee monitoring and be readily contactable and available to manage nuisance and serious adverse events promptly. As GPs are often unfamiliar with new drugs such as leflunomide, this degree of departmental support is necessary, as are clearly defined shared care arrangements should monitoring occur in primary care.

APPLICATION TO OTHER AUTOIMMUNE DISEASES

From a mechanistic point of view, any autoimmune disease where T cells play a critical role in pathogenesis may be amenable to modulation or suppression with leflunomide. Cyclosporin and tacrolimus both inhibit T cells through a separate pathway involving calcineurin and intracellular interleukin-2 synthesis. They have similar toxicity profiles and clinical indications, including psoriasis, the spondyloarthritides, idiopathic myositis, asthma, and prevention of rejection of transplanted organs and grafts. Given the relative paucity of treatment options, leflunomide might be an attractive alternative where these existing therapies are not tolerated or have failed, given its overlapping inhibitory effects on T cells and differing adverse event profile.

Within the rheumatic diseases, evidence is accumulating for an effective role in the treatment of psoriatic arthritis. In one double-blind placebo-controlled study leflunomide treatment led to a significant reduction in clinical scores of psoriatic arthritis compared to placebo over 24 weeks and had an adverse event profile similar to that seen in rheumatoid arthritis trials. Furthermore, a highly significant improvement in the psoriasis area and severity index (PASI) was observed in the leflunomide group (Kaltwasser et al, 2004). An effect on cutaneous psoriasis has also been reported in case series (Reich et al, 2002) and further controlled trials are awaited to establish the efficacy of leflunomide in psoriasis. Other data are emerging in the closely related spondyloarthritides where, for example, an improvement has been reported in the peripheral arthritis of ankylosing spondylitis, but intriguingly not in axial disease (Haibel et al, 2003).

In Crohn's disease, an open labelled study has recently reported sustained benefit from leflunomide for an average follow up of 38 weeks in 12 patients intolerant to azathioprine or 6-mercaptopurine (Prajapati et al, 2003). The prospect of leflunomide being added to the limited choice of effective immunosuppressants in Crohn's disease is welcomed by Sachar (2003) in an accompanying editorial, given the paucity of alternatives when standard therapies fail. He argues that it is logical to try a pyrimidine antimetabolite in situations where purine antimetabolites (i.e. azathioprine and 6-mercaptopurine) or antifolate agents (i.e. methotrexate) have failed.

This would potentially widen the indications for leflunomide to any immune driven disease where there is intolerance or lack of efficacy following treatment with azathioprine or methotrexate. It is, therefore, possibly unsurprising to see reports and commentaries of its efficacy in 18 patients with systemic lupus erythematosus (Remer et al, 2001), in maintaining remission in 12 patients with Wegener's granulomatosis (Metzler et al, 1998) and in reversal of progressive renal allograft dysfunction in 22 transplant recipients (Hardinger, 2002). Intriguingly, successful application to asthma (Malaviya and Uckun, 2001) and autoimmune hepatitis (Yao et al, 2003) has also been reported in animal models. Each of these indications awaits further confirmation of efficacy and tolerance in large well-conducted trials.

CONCLUSIONS

Leflunomide is a welcome addition to the armamentarium of the physician faced with the need to suppress a chronic incurable autoimmune disease. Its action on pyrimidine biosynthesis, principally targeting T cells, is unique. Well-conducted randomized controlled trials have established its efficacy in the treatment of rheumatoid arthritis and leflunomide is now used widely in rheumatological practice as an alternative to methotrexate and sulphasalazine, either alone or in combination.

The serious toxicity profile is favourable compared to other non-specific immunosuppressants, particularly with regard to bone marrow suppression, which is no higher than placebo. Minor so-called nuisance adverse events are prevalent but may be controlled with various

strategies. This places a requirement on the prescribing unit to maintain clear lines of contact with the patient and primary care. Clearly defined shared care responsibilities for toxicity monitoring and subsequent action are needed to maintain adherence to leflunomide in the long term.

Despite this, encouraging data are emerging from a variety of autoimmune diseases to suggest that the indications for leflunomide may be as wide as for azathioprine, yet well-conducted randomized controlled trials are awaited to put flesh on the bones of the open label series which abound. **HM**

Figure 1 *is reproduced by kind permission from Osiri et al (2003) and* Table 1 *is reproduced by kind permission from Emery et al (2002).*
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Chokkalingam S, Shepherd R, Cunningham F, Eisen S (2002) Leflunomide use in the first 33 months after FDA approval: experience in a national cohort of 3325 patients. *Arthritis Rheum* **46**(Suppl): S538

Cohen S, Cannon GW, Schiff M et al (2001) Two-year blinded randomized controlled treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. *Arth Rheum* **44:** 1984–92

Emery P, Breedfeld C, Lemmel EM et al (2000) A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* **39:** 655–65

Emery P, Cannon G, Holden W, Strand V, Schiff M (2002) Results from a cohort of over 40000 rheumatoid arthritis (RA) patients: adverse event profiles of leflunomide, methotrexate and other disease-modifying antirheumatic drugs (DMARDS). *Ann Rheum Dis* **61**(Suppl): 42

Erra A, Tomas C, Barcelo P, Vilardell M, Marsal S (2003) Is the recommended dose of leflunomide the best regimen to treat rheumatoid arthritis patients? *Rheumatology* **42:** 1123–4

Fairbanks LD, Bofil M, Ruckemann K, Simmonds HA (1995) Importance of ribonucleotide availability to proliferating T-lymphocytes from healthy humans. *J Biol Chem* **270:** 29682–91

Haibel H, Rudwaleit M, Braun J, Sieper J (2003) Six months open label leflunomide (LEF) in ankylosing spondylitis. *Ann Rheum Dis* **62**(Suppl): 248

Hardinger KL, Wang CD, Schnitzler MA et al (2002) Prospective, pilot, open label, short term study of conversion to leflunomide reverses chronic renal allograft dysfunction. *Am J Transplant* **2:** 867–71

Kalden JR, Schattenkirchner M, Sorensen H et al (2003) The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year follow up study. *Arthritis Rheum* **48:** 1513–20

Kaltwasser JP, Nash P, Gladman D et al (2004) Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis. *Arthritis Rheum* **50:** 1939–50

Kiely PD, Johnson DM (2002) Infliximab and leflunomide combination therapy in rheumatoid arthritis: an open-label study. *Rheumatology* **41:** 631–7

Kremer JM, Genovese MC, Cannon GW et al (2002) Concomitant leflunomide in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. *Ann Int Med* **137:** 726–36

Maddison P, Kiely P, Kirkham B et al (2004) Leflunomide in rheumatoid arthritis: recommendations through a process of consensus. *Rheumatology* (in press)

Malaviya R, Uckun FM (2001) Leflunomide metabolite analogue alpha-cyano-beta-hydroxy-beta-methyl-N-[3-(trifluoromethyl)]propenamide inhibits IgE/Fc epsilonRI receptor-mediated mast cell leukotriene release and allergic asthma in mice. *Am J Therapeutics* **8:** 309–16

Metzler C, Low-Friedrich I, Reinhold-Keller E et al (1998) Leflunomide, a new promising agent in maintenance of remission in Wegener's granulomatosis. *Clin Exp Immunol* **112**(suppl): 56

Osiri M, Shea B, Robinson V et al (2003) Leflunomide for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. *J Rheumatol* **30:** 1182–90

Prajapati DN, Knox JF, Emmons J, Saeian K, Csuka ME, Binion DG (2003) Leflunomide treatment of Crohn's disease patients intolerant to standard immunomodulator therapy. *J Clin Gastroenterol* **37:** 125–8

Reich K, Hummel KM, Beckmann I, Moessner R, Neumann C (2002) Treatment of severe psoriasis and psoriatic arthritis with leflunomide. *Br J Dermatol* **146:** 335–6

Remer CF, Weisman MH, Wallace DJ (2001) Benefits of leflunomide in systemic lupus erythematosus: a pilot observational study. *Lupus* **10:** 480–3

Rozman B (2002) Clinical pharmacokinetics of leflunomide. *Clin Pharmacokinet* **41:** 421–30

Ruckemann K, Fairbanks L, Carrey E et al (1998) Leflunomide inhibits pyrimidine de novo synthesis in mitogen-stimulated T-lymphocytes from healthy humans. *J Biol Chem* **273:** 21682–91

Sachar DB (2003) Leflunomide in Crohn's disease – the open label case series and the Texas sharpshooter. *J Clin Gastroenterol* **37:** 99–100

Scott DL, Smolen JS, Kalden JR et al (2001) Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. *Ann Rheum Dis* **60:** 913–23

Sinha A, Amos N, Lawson TM (2002) Leflunomide – the Welsh experience. *Rheumatology* **42:** 97

Smolen JS, Kalden JR, Scott DL et al (1999) Efficacy and safety of leflunomide compared with placebo and sulfasalazine in active rheumatoid arthritis: a double blind, randomised, multicentre trial. European Leflunomide Study Group. *Lancet* **353:** 259–66

Strand V, Cohen S, Schiff M et al (1999) Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. *Arch Int Med* **159:** 2542–50

Yao HW, Li J, Jin Y et al (2003) Effect of leflunomide on immunological liver injury in mice. *World J Gastroenterol* **9:** 320–3

KEY POINTS

- Leflunomide is an inhibitor of pyrimidine biosynthesis and is thought to principally target T cells.
- Leflunomide is a new disease-modifying anti-rheumatic drug with proven efficacy in rheumatoid arthritis equivalent to methotrexate and sulphasalazine.
- The serious adverse event profile is no worse than other non-specific immunosuppressants and, with respect to bone marrow toxicity, appears better.
- Leflunomide is associated with several 'nuisance' side effects, which usually respond to symptomatic treatment, dose reduction or partial wash out with cholestyramine.
- The loading dose enables a relatively faster onset of action than comparator drugs in rheumatoid arthritis, although may be associated with greater toxicity.
- The indications for leflunomide appear to be expanding to situations where azathioprine has failed, with beneficial effects reported in psoriasis and psoriatic arthritis, Crohn's disease, prevention of allograft rejection, and other autoimmune diseases.