

New Disease Modifying Agents in Adult Rheumatoid Arthritis

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Abstract

In recent years, new disease modifying agents including leflunomide and tumour necrosis factor (TNF) antagonists have been used to treat patients with rheumatoid arthritis (RA). Leflunomide prevents proliferation of activated lymphocytes by inhibiting dihydroorotate dehydrogenase, a critical step in de novo pyrimidine synthesis. Leflunomide has been shown to be as effective as sulfasalazine and methotrexate (MTX) in placebo-controlled trials. It also improves physical function, quality of life measures and retards radiographic progression. TNF antagonists include infliximab and etanercept. Infliximab is a chimeric TNF monoclonal antibody. Repeated infusions of low dose infliximab (1 mg/kg) are ineffective if given alone. Addition of MTX to infliximab has been shown to prolong the duration of clinical response. Etanercept is a human TNF receptor p75 Fc fusion protein. In active RA patients with suboptimal response to MTX, additional clinical benefit was obtained by the addition of infliximab or etanercept to MTX. The main side effect of TNF antagonists is injection site reaction. However, the long-term effect of TNF antagonists in the development of infection, malignancy and autoimmune disease remains unknown.

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by symmetrical inflammatory arthritis. Most patients exhibit a chronic course. If left untreated, progressive joint erosions, joint deformity, functional disability and even premature death then ensues.^{1,2} Disease modifying anti-rheumatic drugs (DMARDs) suppress synovitis and if given early, prevent joint damage, thus modifying the disease course. In recent years, a better understanding of the pathogenesis of RA has led to the development of new disease modifying agents including leflunomide and tumour necrosis factor (TNF) antagonists.

Pathogenesis of RA

Following antigen presentation and activation of CD4 positive T lymphocytes, macrophages are stimulated to produce TNF- α . TNF is a proinflammatory cytokine which initiates a cascade of inflammatory reactions producing other inflammatory cytokines such as IL1 and IL6 which result in joint inflammation, pannus formation and joint destruction.

Leflunomide

Leflunomide prevents proliferation of activated

lymphocytes by inhibiting dihydroorotate dehydrogenase, a key enzyme that takes part in *de novo* pyrimidine synthesis.³ This leads to the arrest of activated lymphocytes at the G1 phase of the mitotic cell cycle. However, the enzyme inhibition is reversible with the addition of uridine. Leflunomide also inhibits other proinflammatory cytokines such as IL2, cyclooxygenase 2 activity and leukocyte adhesion to vascular endothelium.³

It is rapidly converted to its active metabolite A 77 1726 which is 99% protein bound, with a half-life of 15 to 18 days. Its onset of action is about 4 weeks. Due to its long half-life and relatively slow onset of action, an oral loading dose of 100 mg for the first 3 days is necessary, followed by a maintenance dose of 20 mg per day. It is non-dialysable and teratogenic. Major side effects include transaminitis and cytopenias, usually reversible on discontinuation of the drug. Cholestyramine or activated charcoal can be administered to correct leflunomide overdose³ and is recommended for subjects with elevated alanine aminotransferase greater than thrice the upper limit of normal and in those planning to conceive children. Without the drug elimination procedure, the active metabolite of leflunomide may take 2 years to reach safe plasma level. Other common adverse events include

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diarrhoea (17%), upper respiratory tract infection (15%), rash (10%), alopecia (10%), nausea (9%) and headache (7%) reported in 1339 leflunomide-treated patients from all RA trials.

Clinical Efficacy and Safety of Leflunomide

The efficacy and safety of leflunomide have been shown to be comparable to methotrexate (MTX)⁴ and significantly better than placebo in a 12-month controlled trial involving 485 patients with active RA.⁴ The 20% American College of Rheumatology (ACR) response rate, representing a 20% improvement from baseline of a core set of RA activity parameters* after 1 year treatment of leflunomide or MTX was 52% and 46%, respectively. The 50% ACR response rate, representing a 50% improvement from baseline parameters, was also similar between leflunomide and MTX (34% vs 23%) at 1 year and significantly better than placebo ($P < 0.001$). Elevated liver enzymes occurred in 11% of patients treated with leflunomide compared to 9.3% of patients on MTX and 3.4% of patients receiving placebo.

A 2-year multicentre, double-blind trial comparing the efficacy of MTX and leflunomide showed that MTX was significantly more superior than leflunomide in the first year of treatment but there was no difference in efficacy between the 2 drugs at the end of 2 years.⁵

Leflunomide has been shown to be as effective and safe as sulfasalazine in a 6-month double-blind, placebo-controlled trial.⁶ Ten per cent of patients treated with leflunomide developed rash and 8% had alopecia. A similar number of patients treated with leflunomide and sulfasalazine developed transient liver dysfunction. Reversible agranulocytosis was reported in 2 patients treated with sulfasalazine.

Six to 12 month-long placebo-controlled trials of leflunomide have shown similar efficacy to sulfasalazine and MTX in retarding radiographic progression.⁷ Treatment with MTX or leflunomide also significantly improve patients' physical function and health-related quality of life measures.^{8,9}

The safety and efficacy of combination MTX and leflunomide therapy were assessed in a small, open labelled, 52-week trial involving 30 RA patients, whose disease remained active despite 6 months or more of MTX monotherapy. The mean dose of MTX used was 17 mg per week. Sixteen patients (53%) achieved 20% ACR response at the end of 1 year.¹⁰ Recently 1 patient from this trial was

reported to have developed early cirrhosis (Roennigk grade IV) after receiving a total cumulative dose of 4.5 g of MTX over 7.5 years and 12.9 g of leflunomide at 10 mg/day for 3.5 years.¹¹ It was difficult to ascertain whether leflunomide, MTX or the combination of both drugs could have caused this serious liver disease.

TNF antagonists

These include infliximab (Remicade) and etanercept (Enbrel). Infliximab is a chimeric IgG monoclonal antibody, composed of human constant and murine variable regions. Etanercept is a human TNF receptor p75 fusion protein that acts by competitive inhibition of TNF binding to its receptor, rendering TNF biologically inactive. Infliximab binds specifically to TNF- α whereas etanercept binds both TNF- α and lymphotoxin (TNF- β).

Infliximab

Infliximab is given intravenously at 3 or 10 mg/kg, via a 2-hour infusion, 4 to 8 weeks apart. The dosing frequency is determined by clinical response. Peak response occurs around 3 weeks.

Clinical Efficacy and Safety of Infliximab

In 1994, a single infusion of infliximab 1 or 10 mg/kg was shown to be significantly more superior than placebo in 73 active RA patients who had failed many DMARDs.¹² However, a subsequent study¹³ noted a diminished clinical response after multiple infusions, due to development of antibody to its mouse component. This attenuation of clinical response was more pronounced in those treated with 1 mg/kg of infliximab. Co-administration of 7.5 mg/week of MTX and infliximab has been shown to prolong the duration of clinical response to infliximab in a 26-week, double-blind, placebo-controlled multicentre trial involving 101 patients with active RA.¹³

Combination therapy of infliximab (3 or 10 mg/kg every 4 or 8 weeks) and MTX (median dose 15 mg/week) was also found to be significantly more efficacious than MTX monotherapy in a 30-week phase III controlled trial (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy or ATTRACT Trial) of 428 active RA patients who had failed to respond to MTX alone.¹⁴ There was no increase in serious adverse events between those on combination infliximab and MTX therapy and those on MTX alone.¹³ Infusion reactions occurred in up to 20% of patients who received infliximab. Most reactions were mild, such as headache and nausea, and could be controlled

* The ACR response rates were based on a core set of 8 RA parameters: The ACR painful and swollen joint count, patient's and physician's global assessment of disease activity, patient's assessment of pain by visual analogue scale, physical function by a validated instrument (e.g. Health Assessment Questionnaire), acute phase reactants and joint radiographs. The 20% ACR response rate is considered statistically significant although residual RA activity can be present and ACR 50 is clinically important.

by slowing the infusion rate or with prophylactic use of antihistamines.¹⁴ Three patients on infliximab 10 mg/kg every 4 weeks developed malignancy but the incidence was not higher than the age and sex-matched general population. Fifty-four (16%) patients developed low titre anti-double-stranded DNA antibodies without clinical evidence of lupus during the study period. Only 1 patient had a lupus-like syndrome with facial rash, positive antinuclear antibody and low C4 complement but no anti-double-stranded DNA antibody. This patient recovered after discontinuation of infliximab.¹⁴

Serious infections including pneumonia, cellulitis and pyelonephritis were reported in 26 of 555 (4.7%) infliximab-treated patients and 8 of 133 (6%) placebo-treated patients. Two patients in the ATTRACT trial died, 1 had disseminated tuberculosis while the other had disseminated coccidioidomycosis. Many of these patients were on concomitant immunosuppressive therapy that might predispose them to infections.

Etanercept

The therapeutic dose is 25 mg twice a week, given subcutaneously. Onset of action varies from 1 to 2 weeks with a half-life of 3 to 4 days. It is cleared by the reticulo-endothelial system. It is teratogenic and unlike infliximab, no neutralising antibody has been reported.

Clinical Efficacy and Safety of Etanercept

Etanercept has been shown to be effective in active RA patients who failed conventional DMARD therapy. In a study of 234 patients randomised to receive either placebo or subcutaneous injections of 10 mg or 25 mg etanercept twice weekly for a 6-month duration, etanercept 25 mg was found to be significantly more effective than 10 mg etanercept or placebo with higher 50% ACR response rate.¹⁴ Etanercept 10 or 25 mg twice weekly injections also significantly improved patients' functional ability and quality of life indices.^{15,16}

The safety and efficacy of combination etanercept and MTX therapy was compared with MTX monotherapy in a 6-month placebo-controlled trial. Eighty-nine active RA patients had been on a minimum of 6 months therapy of MTX before twice weekly 25 mg etanercept or placebo was added. At 6 months, the 20% and 50% ACR response rates were significantly higher in the group receiving combination etanercept / MTX therapy without an increase in toxicity.¹⁷ The main adverse event was injection site reactions which were usually mild and transient, consisting of erythema with or without pain or swelling, which often resolved spontaneously or with topical steroids or antihistamines.

So far, 50 of 1197 subjects treated with etanercept for up to 36 months experienced serious infections including pyelonephritis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, pneumonia and sepsis. Death and serious infections have been reported with post-marketing use of etanercept. Many of these serious events occurred in RA patients who had concomitant diabetes mellitus or history of active or chronic infections.

Auto-antibodies including antinuclear antibody and anti-double-stranded DNA antibody have been reported with the use of etanercept.¹⁷ No patient treated with etanercept has developed systemic lupus erythematosus (SLE) or other autoimmune diseases in an ongoing 2-year trial to determine the long-term safety of etanercept.¹⁸ A total of 17 malignancies were reported in 1197 RA patients treated with etanercept for up to 36 months. There was no increase in incidence of malignancy compared to an age and sex-matched population.¹⁸ There is an ongoing trial to assess the efficacy of etanercept in RA patients whose disease duration is less than 3 years.

As treatment of TNF antagonists are extremely expensive (The annual average costs of infliximab and etanercept are \$19,000.00 and \$21,000.00, respectively), these drugs are currently only indicated in patients with active RA who have had an inadequate response to one or more of the conventional disease modifying agents.¹⁹ Unless contraindicated, patients with a suboptimal response to a single disease modifying agent other than MTX should have a trial of MTX before TNF antagonist is added. Their use should be limited to less than 16 weeks if no clinical benefit is apparent.

Conclusion

A better understanding of the pathogenesis of RA has led to the development of new disease modifying agents including leflunomide and TNF antagonists. These agents used solely or in combination with MTX have offered alternative options to patients with persistently active RA and suboptimal response to MTX alone. However, the long-term safety of these agents, especially the TNF antagonists, in regard to the development of infection, malignancy and autoimmune disease warrants further research to better define the subset of RA patients who will benefit from such expensive treatment. TNF antagonists should be discontinued in the presence of active infection as the host's response to infection might be impaired. Also, caution should be exercised when considering the use of TNF antagonists in patients with history of recurrent infections or medical conditions that might predispose them to infections.

REFERENCES

1. Hochberg M C. Adult and juvenile rheumatoid arthritis: current epidemiologic concepts. *Epidemiol Rev* 1981; 3:27-44.
2. Pincus T, Wolfe F, Callahan L F. Updating a reassessment of traditional paradigms concerning rheumatoid arthritis. In: Wolfe F, Pincus T, editors. *Rheumatoid Arthritis: Pathogenesis, Assessment, Outcome and Treatment*. New York: Marcel Dekker, 1994:1-74.
3. Fox R. Mechanism of action of leflunomide in rheumatoid arthritis. *J Rheumatol* 1998; 25 (suppl 53):20- 6.
4. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999; 159:2542-50.
5. Emery P, Breedveld F C, Lemmel E M, Kaltwasser J P, Dawes P T, Gowor B, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2000; 39:655-65.
6. Smolen J S, Kalden J R, Scott D L, Rozman B, Kvien T K, Larsen A, et al. Efficacy and safety of leflunomide compared with placebo and sulfasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. *Lancet* 1999; 353:259-66.
7. Sharp J T, Strand V, Leung H, Hurley F, Loew-Friedrich I. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis. *Arthritis Rheum* 2000; 43:495-505.
8. Strand V, Tugwell P, Bombardier C, Maetzel A, Crawford B, Dorrier C, et al. Function and health-related quality of life. Results from a randomised controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. *Arthritis Rheum* 1999; 42:1870-8.
9. Tugwell P, Wells G, Strand V, Maetzel A, Bombardier C, Crawford B, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2000; 43:506-14.
10. Weinblatt M E, Kremer J M, Coblyn J S, Maier A L, Helfgott S M, Morrell M, et al. Pharmacokinetics, safety and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. *Arthritis Rheum* 1999; 42:1322-8.
11. Weinblatt M E, Dixon J A, Falchuk K R. Serious liver disease in a patient receiving methotrexate and leflunomide. *Arthritis Rheum* 2000; 43: 2609-11.
12. Elliott M J, Maini R N, Feldmann M, Kalden J R, Antoni C, Smolen J S, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor- α (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994; 344:1105-10.
13. Maini R N, Breedveld F C, Kalden J R, Smolen J S, Davis D, Macfarlane J D, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor a monoclonal antibody combined with low dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; 41:1552-63.
14. Maini R, St Clair E W, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumor necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999; 354:1932-9.
15. Moreland L W, Schiff M H, Baumgartner S W, Tindall E A, Fleischmann R M, Bulpitt K J, et al. Etanercept therapy in rheumatoid arthritis: a randomised, controlled trial. *Ann Intern Med* 1999; 130:478-86.
16. Mathias S D, Colwell H H, Miller D P, Moreland L W, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. *Clin Ther* 2000; 22:128-39.
17. Weinblatt M E, Kremer J M, Bankhurst A D, Bulpitt K J, Fleischmann R M, Fox R I, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340:253-9.
18. Moreland L W, Baumgartner S W, Tindall E A, Schiff M H, Fleischmann R M, Weaver A L, et al. Longterm safety and efficacy of TNF receptor p75 Fc fusion protein (TNFR:Fc; Enbrel) in DMARD refractory rheumatoid arthritis. *Arthritis Rheum* 1998; 41 (9 Suppl):S364.
19. Smolen J S, Breedveld F C, Burmester G R, Combe B, Emery P, Kalden J R, et al. Consensus statement on the initiation and continuation of tumour necrosis factor blocking therapies in rheumatoid arthritis. *Ann Rheum Dis* 2000; 59:504-5.