

“Stepping-up” from methotrexate: a systematic review of randomised placebo controlled trials in patients with rheumatoid arthritis with an incomplete response to methotrexate

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Methotrexate is presently the standard disease modifying antirheumatic drug (DMARD) for patients with active rheumatoid arthritis (RA).¹ Despite its short term efficacy in clinical trials and long term effectiveness in clinical practice,^{2–5} many patients continue to have signs and symptoms of active disease while taking a maximally tolerated dose.

Over the past decade there has been increasing interest in the use of combination therapy in patients with RA. Boers and Ramsden published the first systematic review of combination therapy in 1991 and identified two trials that provided moderate or strong evidence; neither of these studies used methotrexate.⁶ Tugwell and Boers updated this review in 1994 and identified four new trials that provided moderate or strong evidence; two of these trials used methotrexate in a parallel combination strategy.⁷ Verhoeven and colleagues updated this review a second time in 1998 and identified 14 new trials published between August 1992 and July 1997.⁸ In their analysis, they combined these 14 new trials with the six previous trials and categorised the trials by the strategy of combination therapy: parallel, “step-up”, and “step-down”. Of these 20 trials, six used methotrexate in a parallel combination strategy, one of these trials used methotrexate in a step-down strategy, and two of these trials used methotrexate in a step-up strategy.⁸ Of the two trials which employed the step-up strategy in patients with an incomplete response to methotrexate, one compared the monoclonal anti-CD4 antibody cM-T412 with placebo and failed to show clinical efficacy,⁹ whereas the other compared cyclosporin with placebo and did demonstrate additional efficacy with the combination compared with placebo.¹⁰

With the advent of newer biological treatments directed at cytokines which play a part in the pathophysiology of RA, particularly tumour necrosis factor (TNF),¹¹ additional trials of combination therapy based on the step-up strategy in patients with RA who have had an incomplete response to methotrexate have been performed. We updated the systematic review of Verhoeven and colleagues to test the hypothesis that the addition of anti-TNF treatments will be associated with a more robust response than the addition of other oral DMARDs to patients with an incomplete response to methotrexate.

Methods

LITERATURE REVIEW

The Medline database was searched from July 1997 (the closing date of the systematic review by Verhoeven and colleagues⁸) to December 2000 using the MeSH headings: “arthritis, rheumatoid” and “drug therapy, combination”. A total of 196 citations limited to humans were identified. The titles and abstracts of these articles were read and 29 were selected for review. The bibliographies of all retrieved articles were also reviewed to identify additional relevant studies. Abstracts of scientific presentations from the 1998, 1999, and 2000 annual meetings of the American College of Rheumatology (ACR) were searched to identify trials of combination therapy. Authors of studies that used a step-up strategy in patients with RA who had an incomplete response to methotrexate were then contacted to obtain additional information, including full unpublished manuscripts if possible.

DATA EXTRACTION

Studies that were placebo controlled, double blind, randomised clinical trials were selected for inclusion in this review. The quality of the studies was assessed using criteria developed by Jadad *et al.*¹² This is a five point scale; trials with scores of three or above are considered to provide strong evidence of an effect.

Data extracted included baseline patient characteristics (age, sex, race, duration of RA, proportion rheumatoid factor positive), concomitant treatment (use of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids), study treatment (study drug and regimen, methotrexate dose and duration), eligibility criteria (definition of active disease), baseline values for the WHO/ILAR core set variables (number of painful/tender joints, number of swollen joints, pain scores, patient and global assessment of disease activity, acute phase reactants, and physical disability scores¹³), and outcome measures (ACR 20, 50, and 70 at the end of the trial).

The proportion of patients achieving an ACR 20 response at the completion of the trial was used as the primary outcome in this analysis.¹⁴ It was reported in all studies included in this analysis.

DATA ANALYSIS

The proportion of patients randomly allocated to receive placebo who achieved an ACR 20 response was compared across trials using a χ^2

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test. Similarly, the proportion of patients randomly allocated to receive the active study drug who achieved an ACR 20 response was compared across trials using a χ^2 test. The relative rate of developing an ACR 20 response with its 95% confidence interval (CI) was calculated for each study treatment compared with placebo. These relative rates were compared to test for homogeneity of the rate ratio. The absolute difference between the proportion of patients developing an ACR 20 response who received the study drug and placebo with its 95% CI was calculated for each study treatment compared with placebo; this was then used to estimate the number needed to treat to achieve an ACR 20 response.

Results

LITERATURE REVIEW

Previous work by Verhoeven and colleagues had identified two studies of combination therapy that added therapeutic agents to methotrexate in a step-up strategy.^{9, 10} The current search identified five new double blind, placebo controlled, randomised clinical trials that studied the addition of therapeutic agents to methotrexate in a step-up strategy in patients with active disease.¹⁵⁻¹⁹ The study by Moreland and colleagues was not included in the present analysis because the clinical efficacy after three months of treatment was not given.⁹ The study by St Clair and colleagues was not included in this analysis because it was a phase II dose-escalating study examining different regimens of the DR4/1 peptide, with the primary outcomes being safety and changes in immune function.¹⁸ Two articles reported results from the trial adding infliximab to methotrexate^{16, 17}; only that article reporting results after 30 weeks of treatment was included in this analysis in order to compare the efficacy of infliximab with cyclosporin, etanercept, and leflunomide after a comparable treatment duration of 24–26 weeks. Thus four placebo controlled, double blind, randomised clinical trials employing a step-up strategy that were of approximately six months in duration were included in the present analysis.

STUDY DESCRIPTIONS

Tugwell and colleagues added cyclosporin, beginning at a dose of 2.5 mg/kg/day, or placebo to 148 patients with RA who had been receiving their maximal tolerated dose of methotrexate of 15 mg/week or less at a stable dose for at least three months, and had active synovitis, defined as six or more actively inflamed tender or swollen joints.¹⁰ Twelve of 61 placebo treated and 36 of 56 cyclosporin treated patients who completed six months of treatment achieved an ACR 20 response.

Weinblatt and colleagues added etanercept at a dose of 25 mg or placebo injected subcutaneously twice weekly to 89 patients with RA who had been receiving methotrexate for at least six months and a stable dose of 15–25 mg/week for the past four weeks, and had active disease manifest by at least six joints that were swollen and six that were tender at the time of

enrolment.¹⁵ The mean weekly dose of methotrexate at entry was 18 mg in the placebo group and 19 mg in the etanercept group. Eight of 24 placebo treated and 42 of 57 etanercept treated patients who completed 24 weeks of treatment achieved an ACR 20 response.

Maini and colleagues added infliximab at four different dosage regimens or placebo by intravenous infusion to 428 patients with RA who had been receiving oral or parenteral methotrexate for at least three months and a stable dose of at least 12.5 mg/week for at least four weeks, and had active disease defined as six or more swollen and tender joints with two of the following: morning stiffness of at least 45 minutes, erythrocyte sedimentation rate greater than 28 mm/1st h, and C reactive protein greater than 20 mg/l.¹⁶ The median weekly dose of methotrexate was 15 mg and 72% of patients were receiving at least 15 mg/week; there was no significant difference in methotrexate dose or duration of treatment across treatment groups. As there were no significant differences either in baseline variables or in the proportion of patients with an ACR 20 response after 30 weeks of treatment between the four infliximab treatment groups, data from these four groups were pooled for the purposes of the present analysis. Eighteen of 53 placebo treated and 181 of 293 infliximab treated patients who completed 30 weeks of treatment achieved an ACR 20 response.

Kremer and colleagues added leflunomide at a dose of 100 mg/day for two days followed by 10 mg/day or placebo to 263 patients with RA who had been receiving methotrexate at their maximal tolerated dose of between 15 and 20 mg/week for at least six months and a stable dose for at least eight weeks, and had active disease defined by three of the following: nine or more tender joints, six or more swollen joints, morning stiffness of at least 45 minutes, and an erythrocyte sedimentation rate of 28 mm/1st h or greater.¹⁹ Twenty six placebo treated and 60 leflunomide treated patients achieved an ACR 20 response after 24 weeks of treatment.

ACR 20 RESPONSES

The proportion of patients with an incomplete response to methotrexate who were randomly allocated to receive placebo, completed 24–30 weeks of treatment, and obtained an ACR 20 response varied from 16 to 27% across the studies, but this was not significant (table 1). The proportion of patients with an incomplete response to methotrexate who were randomly allocated to receive active treatment, completed 24–30 weeks of treatment, and obtained an ACR 20 response varied from 46 to 71% across the studies, but the difference was not significant (table 1).

The rate ratio (95% CI) of completing 24–30 weeks of treatment and obtaining an ACR 20 response among patients randomly allocated to active treatment varied from 2.36 (1.60 to 3.49) to 2.92 (1.65 to 5.15) across the studies (table 1, fig 1). There was no evidence of heterogeneity of rate ratios across studies

Table 1 Number of patients (proportion of patients randomly allocated to receive placebo or active treatment who obtained an ACR 20 response), rate ratio, absolute rate difference, and number needed to treat for placebo controlled, double blind, randomised clinical trials of the addition of active treatment to methotrexate in patients with rheumatoid arthritis

First author (ref)	Therapeutic agent	Placebo No (%)	Active Rx No (%)	Rate ratio (95% CI)	Rate diff (95% CI)	NNT (95% CI)
Tugwell (10)	Cyclosporin	73 (16)	75 (48)	2.92 (1.65 to 5.15)	32 (17 to 46)	3 (2 to 6)
Weinblatt (15)	Etanercept	30 (27)	59 (71)	2.67 (1.44 to 4.94)	44 (25 to 64)	2 (1 to 4)
Maini (16)	Infliximab	88 (20)	340 (53)	2.60 (1.70 to 3.98)	33 (23 to 43)	3 (2 to 4)
Kremer (19)	Leflunomide	133 (20)	130 (46)	2.36 (1.60 to 3.49)	27 (16 to 38)	4 (3 to 6)

ACR = American College of Rheumatology; CI = confidence interval; NNT = number needed to treat; Rx = treatment.

and there was substantial overlap of the 95% confidence intervals of the individual risk ratios.

The absolute difference (95% CI) between the proportion completing 24–30 weeks of treatment and obtaining an ACR 20 response varied from 27% (16 to 38%) to 44% (25 to 64%) across studies but did not significantly differ across studies. The number needed to treat in order to obtain an ACR 20 response was small in all trials, ranging from two to four patients.

Discussion

The results of this systematic review suggest that in patients with an incomplete response to methotrexate the addition of cyclosporin, etanercept, infliximab, or leflunomide is associated with a comparable ratio of response as defined by the ACR 20 responder criteria after 24–30 weeks of combination therapy. These findings update and extend the results of the systematic review conducted by Verhoeven and colleagues,⁸ and demonstrate that several agents are efficacious in a step-up strategy when given to patients with an incomplete response to methotrexate.

Several assumptions have to be made to allow a comparison of outcomes of different placebo controlled, double blind, randomised clinical trials. Firstly, one assumes that the samples of patients in the different trials are drawn from the same population of patients. The validity of this assumption can be assessed in part by examining the demographic and baseline clinical variables of the patients enrolled in the trials. The median age of patients was similar and ranged from 50 to 55 years. Most patients enrolled in these trials were white women. The median duration of disease was also similar and ranged from 10 to 13 years. Although there were subtle differences in the definition of active disease across

trials, the mean or median number of painful/tender joints and swollen joints was also similar across trials, ranging from 19 to 31 and 16 to 21, respectively. Other variables of disease activity included in the WHO/ILAR core set were also similar across the trials. Thus the patients enrolled in these four trials had comparable demographic and clinical features at baseline. Similarly, comparable proportions of patients were receiving concomitant treatment with NSAIDs and corticosteroids at doses of 10 mg/day or less.

Another method of assessing the validity of this assumption is to compare the proportion of patients randomly allocated to receive placebo who develop the primary study outcome. Indeed, the proportion of patients randomly allocated to placebo who completed the 24–30 weeks of the trials and developed an ACR 20 response was statistically comparable, with an overall proportion of 20%. Thus it appears that the patients enrolled in these different trials were comparable with one another.

A second assumption is that the rate ratios are derived from the intention to treat population in each trial. This assumption was validated in each trial for the primary study outcome. Thus the comparison of the rate ratios for the development of the ACR 20 response is a valid comparison of the relative efficacy of these agents in these trials.

The third assumption is that dropouts were accounted for in each trial. Although the proportion of patients completing each trial arm differed, all authors recorded the reasons for discontinuation in each trial, including death, adverse reactions, and lack of efficacy.

The conclusions of this systematic review may be limited by the use of the ACR 20 as the primary study outcome. The ACR 20 responder index was originally designed to differentiate between active DMARDs and placebo.¹⁴ This hurdle was reached by all of the agents tested in patients with an inadequate response to methotrexate in the placebo controlled trials included in the present analysis. The ACR 20 response, however, may not be sensitive enough to differentiate between two or more active agents. Indeed, three of these studies also reported ACR 50 and ACR 70 responses.^{15 16 19} There was no significant difference in the proportion of placebo treated patients who had an ACR 50 response in these three trials. Although none of the patients randomly allocated to receive placebo in the etanercept or infliximab trials achieved an ACR 70 response, three of the patients randomly allocated to placebo in the leflunomide trial

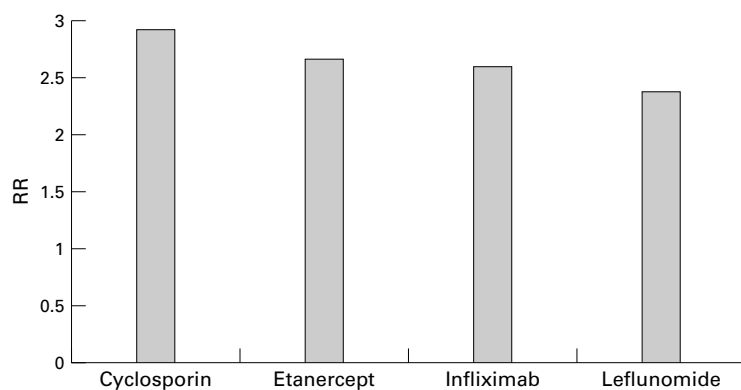


Figure 1 ACR 20 response in step-up trials in rheumatoid arthritis.

achieved this level of response. When the proportion of patients randomly allocated to active treatment who achieved an ACR 50 response, together with the rate ratios and rate differences, were compared across these three trials, no significant differences were noted (data not shown). Similar results were found when the ACR 70 response was examined, though rate ratios could not be calculated for the trials of anti-TNF agents (data not shown). Thus, even using these more stringent criteria for response, this analysis is unable to distinguish between these active agents.

The second principle of evidence based medicine suggests that the therapeutic decision depends not only on the weight of the evidence, but also on the patient's and doctor's values.²⁰ To determine the patient's values, the doctor will need to discuss issues related to the route of drug administration (oral for cyclosporin and leflunomide, subcutaneous injection for etanercept, and intravenous infusion for infliximab), pattern and frequency of adverse events, costs, and availability of insurance coverage for reimbursement of treatment expenses.

Finally, the results of this systematic review provide strong evidence for several alternatives for the patient with RA who has had an inadequate response to methotrexate treatment. Long term observational studies are needed to examine the long term effectiveness and safety of these combinations. In addition, further placebo controlled trials are needed to examine newer treatment combinations for those patients in whom the combinations reviewed in the present analysis fail to produce an adequate response.

- 1 Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Ann Intern Med* 2001;134:695-706.
- 2 Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN, *et al.* Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med* 1985;312:818-22.
- 3 Williams HJ, Wilkens RF, Samuelson CO Jr, Alarcon GS, Guttadauria M, Yarboro C, *et al.* Efficacy of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. *Arthritis Rheum* 1985;28:721-30.
- 4 Kremer JM. Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: followup after a mean of 13.3 years. *Arthritis Rheum* 1997;40:984-5.
- 5 Weinblatt ME, Maier AL, Fraser PA, Coblyn JS. Longterm prospective study of methotrexate in rheumatoid arthritis: conclusion after 132 months of therapy. *J Rheumatol* 1998;25:238-42.
- 6 Boers M, Ramsden M. Long-acting drug combinations in rheumatoid arthritis: a formal overview. *J Rheumatol* 1991;18:316-24.
- 7 Tugwell P, Boers M. Long-acting drug combinations in rheumatoid arthritis: updated overview. In: Wolfe F, Pincus T, eds. *Rheumatoid arthritis: pathogenesis, assessment, outcome and treatment*. New York: Marcel Dekker, 1994:357-71.
- 8 Verhoeven AC, Boers M, Tugwell P. Combination therapy in rheumatoid arthritis: updated systematic review. *Br J Rheumatol* 1998;37:612-19.
- 9 Moreland LW, Pratt PW, Mayes MD, Postelthwaite A, Weisman MH, Schnitzer T, *et al.* Double-blind placebo-controlled multicenter trial using chimeric monoclonal, anti-CD4 antibody, cM-T412, in rheumatoid arthritis patients receiving concomitant methotrexate. *Arthritis Rheum* 1995;38:1581-8.
- 10 Tugwell P, Pincus T, Yocum D, Stein M, Gluck O, Kraag G, *et al.* Combination with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995;333:137-41.
- 11 Brennan FM, Feldmann M. Cytokines in autoimmunity. *Curr Opin Immunol* 1992;4:754-9.
- 12 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
- 13 Boers M, Tugwell P, Felson DT, van Riel P, Kirwan J, Edmonds J, *et al.* World Health Organization and International League for Associations of Rheumatology core endpoints for symptom modifying antirheumatoid drugs in rheumatoid arthritis clinical trials. *J Rheumatol* 1994;21(suppl 41):86-9.
- 14 Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, *et al.* The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;36:729-40.
- 15 Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, *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.
- 16 Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, *et al.* Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999;354:1932-9.
- 17 Lipsky PE, van der Heijde DMFM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;343:1594-602.
- 18 St Clair EW, Cohen SB, Lee ML, Fleischmann RM, Lee SH, Moreland LW, *et al.* Treatment of rheumatoid arthritis with a DR4/1 peptide. *J Rheumatol* 2000;27:1855-63.
- 19 Kremer JM, Caldwell JR, Cannon GW, Genovese M, Cush JJ, Bathon J, *et al.* The combination of leflunomide and methotrexate in patients with active rheumatoid arthritis who are failing on methotrexate treatment alone: a double-blind placebo controlled study [abstract]. *Arthritis Rheum* 2000;43(suppl):S224, abstr 948.
- 20 Guyatt G. Evidence-based management of patients with osteoporosis. *J Clin Densitometry* 1998;1:395-402.



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