Review: Adding newer disease-modifying drugs or biological agents to methotrexate improved rheumatoid arthritis symptoms

Hochberg MC, Tracy JK, Flores RH. **"Stepping-up" from methotrexate: a systematic review of randomised placebo controlled trials in patients with rheumatoid arthritis with an incomplete response to methotrexate.** Ann Rheum Dis. 2001 Nov;60:iii51-4.

QUESTION

In patients with rheumatoid arthritis (RA) and an incomplete response to methotrexate, does the addition of biological agents or newer, disease-modifying antirheumatic drugs (DMARDs) to methotrexate prompt a more complete response than does the addition of placebo?

DATA SOURCES

An existing systematic review was updated. Additional studies were identified by searching MEDLINE (July 1997 to December 2000) with the terms rheumatoid arthritis and combination drug therapy, bibliographies of relevant studies, and abstracts of scientific presentations of the American College of Rheumatology (ACR) from 1998 to 2000 and by contacting authors of studies that used a step-up strategy in patients with RA.

STUDY SELECTION

Studies were selected if they were randomized, double-blind, placebo-controlled trials that added therapeutic agents to methotrexate in patients with active RA.

DATA EXTRACTION

Data were extracted on patient characteristics (age, sex, race, duration of RA, proportion who were rheumatoid-factor positive), concomitant treatment, study drug and methotrexate dose and duration, eligibility criteria, baseline disease activity, and outcome measures. The primary outcome was ACR 20 response (i.e., improvement of ≥ 20% in swollen and tender joint counts in 3 of 5 ACR end points [pain, patient global assessment, physician global assessment, disability score, and erythrocyte sedimentation rate]).

MAIN RESULTS

4 trials were included (928 patients). The active treatments (in addition to methotrexate) were cyclosporin, 2.5 mg/kg of body weight per day; etanercept, 25 mg twice weekly; infliximab, 3 mg/kg every 4 or 8 weeks or 10 mg/kg every 4 or 8 weeks; and leflunomide, 100 mg/d for 2 days, then 10 mg/d. Treatment duration ranged from 24 to 30 weeks. Each of the 4 active treatments was more effective than placebo. No evidence of heterogeneity existed among the trials, and the 95% CIs for the relative risks of the individual trials overlapped (Table).

CONCLUSION

In patients with rheumatoid arthritis and an incomplete response to methotrexate, the addition of cyclosporin, etanercept, infliximab, or leflunomide led to an American College of Rheumatology 20 response in 2 to 3 times as many patients as did the addition of placebo.

Source of funding: No external funding.

For correspondence: Dr. M.C. Hochberg, University of Maryland School of Medicine, Baltimore, MD, USA. E-mail mhochber@umaryland.edu. ■

Active treatment (cyclosporin, etanercept, infliximab, or leflunomide) vs placebo for rheumatoid arthritis with incomplete response to methotrexate (4 trials)*

Outcome at 24 to 30 wk	Therapeutic agent	Active treatment	Placebo	RBI (95% CI)	NNT (CI)
ACR 20	Cyclosporin	48%	16%	192% (65 to 415)	3 (2 to 6)
	Etanercept	71%	27%	167% (44 to 394)	2 (1 to 4)
	Infliximab	53%	20%	160% (70 to 298)	3 (2 to 4)
	Leflunomide	46%	20%	136% (60 to 249)	4 (3 to 6)

*ACR 20 = American College of Rheumatology ≥ 20% improvement in tender and swollen joints. Other abbreviations defined in Glossary.

COMMENTARY

The advent of biological agents (in particular the antitumor necrosis factor agents infliximab and etanercept) has rightly been hailed as a major breakthrough in the treatment of RA, especially in patients whose RA is resistant to conventional DMARD therapy. However, it is still unclear which patients should receive these expensive new drugs that have an unknown long-term safety profile. One suggestion is that they should be used in RA patients who have not responded to methotrexate (the current "gold standard" of treatment).

The systematic review by Hochberg and colleagues identified 4 studies that compared the addition of 1 of the newer DMARDs (cyclosporin or leflunomide) or a biological agent (infliximab or etanercept) to methotrexate in patients who had partially responded to treatment with methotrexate alone. Each trial was randomized and placebo controlled. The methods used to identify the trials could be criticized because the authors updated an existing systematic review (thus assuming that all previous relevant papers had been captured), and only searched one database (MEDLINE) with a limited number of terms. Whether any major published studies were missed is unlikely, however, given the widespread interest in the introduction of these drugs, but some smaller studies using conventional DMARDs in a step-up regimen may have been overlooked.

In 4 trials, more patients responded to the addition of another active drug, whether DMARD or biological, than to the addition of placebo. Looking across the studies, no obvious evidence existed of either a greater number of responders or a greater degree of response among patients treated with biologicals than among patients treated with new DMARDs, but these are only indirect comparisons. A trial that directly compared the addition of leflunomide with etanercept, for example, would be stronger evidence than that presented in this review. The review supports the view that biological agents offer hope of a substantial improvement for patients with RA in whom methotrexate has failed, but other less expensive drugs might be equally effective. Whether there are patients with RA who will only respond to the biological agents, or who will respond better to them than they will to the newer DMARDs, remains to be tested.

Deborah P.M. Symmons, MD
University of Manchester Medical School
Manchester, England, UK

