Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs

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CRD summary
This review concluded that tocilizumab showed a different pattern of response compared to other biologic agents in rheumatoid arthritis patients with an inadequate response to disease-modifying antirheumatic drugs. Interpretation of the authors' conclusions should be considered alongside the overall findings; the lack of quality assessment and possibility of publication bias should be borne in mind.

Authors' objectives
To compare the American College of Rheumatology (ACR) response of tocilizumab with other biologic agents in patients with rheumatoid arthritis who had inadequate response to disease-modifying antirheumatic drugs (DMARDs).

Searching
MEDLINE and EMBASE were searched for studies in English, German, French and Dutch from 1990 to 2008. Search terms were reported. Abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) that evaluated commonly used biologic agents (tocilizumab, adalimumab, etanercept, infliximab, abatacept and rituximab) in patients with rheumatoid arthritis who had an inadequate response to DMARDs or methotrexate were eligible for inclusion. Study duration needed to be at least six months. Eligible outcomes were ACR 20, ACR 50 and ACR 70 from baseline to six-month follow-up.

The included studies assessed biologic agents (tocilizumab, abatacept and rituximab) and TNF-α inhibitors (infliximab, adalimumab and etanercept). All of the included studies used placebo as control. Approximately 80% of included patients were female. Mean age was older than 50 years. Patients were previously treated with at least two DMARDs. The mean disease duration of included patients ranged from 5.6 to 13.1 years. More than 50% of the included patients used concomitant glucocorticoids, usually with non-steroidal anti-inflammatory drugs.

Two reviewers independently assessed studies for inclusion. Any disagreement was resolved by consensus.

Assessment of study quality
The authors did not state they assessed validity.

Data extraction
Data were extracted on event rates to enable the calculation of relative risks (RRs) with 95% confidence intervals (CIs). Imputation for non-response was performed using the last observation carried forward method.

Two reviewers independently performed data extraction.

Methods of synthesis
Bayesian mixed-treatment comparison was used to estimate the relative efficacy between different biologic agents because no direct comparisons were available. TNF-α inhibitors (infliximab, adalimumab and etanercept) were treated as a single TNF-α inhibitor category because evidence suggested that they had similar efficacy. Mixed-treatment comparison results were expressed as relative risk (RRs) of response for each biologic agent compared with placebo and the relative risks of response between each pairwise combination of biologic agents, with 95% credible intervals (CrIs).

Individual study results were pooled by either a fixed-effects model or a random-effects model, which was determined
by comparing the residual deviance of models using random-effects and fixed effects assumptions. The random-effects model was considered more appropriate for ACR 20 and ACR 50 responses and the fixed-effect model was considered more appropriate for ACR 70 response. Non-overlapping ACR response rates (ACR70) for each agent were compared between treatments. Separate analyses of overlapping ACR20/50/70 responses were conducted. A Kruskal-Wallis test for trend was used to test overall differences in response distribution between treatments. Cochran-Armitage tests were used to assess pairwise differences in response distribution between tocilizumab and each of the other biologic agents. Sensitivity analyses were performed by including three additional studies that did not provide background DMARD treatment. Sensitivity analyses were also conducted by excluding a trial that showed high observed response rates in the control group and excluding a trial that used sulfasalazine as its background treatment.

Results of the review
Eighteen RCTs were included in the review (n=10,419 participants). All the RCTs were double blind. Follow-up ranged from 22 to 30 weeks.

When comparing the estimated responses for non-overlapping response criteria, there was a distinctive response curve of tocilizumab compared with other biologic agents (TNF-α inhibitors, abatacept and rituximab) with more ACR 70 responders than non-overlapping ACR 20 or ACR 50 responders.

All biologic agents (tocilizumab, TNF-α inhibitors, abatacept and rituximab) were significantly more efficacious than placebo in terms of ACR 20, ACR 50 and ACR 70 responses. Analyses of pair-wise comparisons showed that tocilizumab was significantly associated with greater ACR 70 responses when compared with TNF-α inhibitors (RR 1.8, 95% CrI 1.2 to 2.6) and abatacept (RR 2.0, 95% CrI 1.3 to 3.1). There were no significant differences in ACR 20 and ACR 50 responses between tocilizumab and the other biologic agent (TNF-α inhibitors, abatacept or rituximab).

Sensitivity analyses did not materially alter the results.

Authors' conclusions
Tocilizumab showed a pattern of response that differed from that of other biologic agents in patients with rheumatoid arthritis who had an inadequate response to DMARDs. Mixed-treatment comparison analyses suggested that tocilizumab was associated with a higher likelihood of ACR70 response at week 24.

CRD commentary
This review's inclusion criteria were clear. Only two relevant databases were searched. Efforts were made to find published studies but not unpublished studies, which increased potential for publication bias. The search was limited to several popular languages, so the risk of language bias could not be ruled out. Steps were made to minimise errors and biases in the processes of study selection and data extraction. No formal validity assessment was performed. The patients' characteristics at baseline in terms of sex, age, previous treatment and baseline ACR parameters were comparable across trials. Appropriate methods were used to estimate the relative efficacy between different biologic agents. No results on statistical heterogeneity were reported. Only a small number of the included studies assessed tocilizumab, abatacept and rituximab.

Interpretation of the authors' conclusions should be considered alongside the overall findings and bearing in mind the lack of details on study quality and the possibility of publication bias.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further analyses of later follow-up time points from trials (beyond 24/30 weeks) were required to support the findings from this review.

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