The number needed to treat for second-generation biologics when treating established
rheumatoid arthritis: a systematic quantitative review of randomized controlled trials
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CRD summary
This review concluded that second-generation biological agents were of comparable efficacy with few adverse events in
patients with established rheumatoid arthritis taking concomitant methotrexate, but that limited data were available for
rituximab, tocilizumab, and golimumab. Absence of a quality assessment of included trials, coupled with over-
optimistic interpretation of the review results, indicates that these conclusions should be interpreted with caution.

Authors' objectives
To evaluate the number needed to treat and the number needed to harm of the second-generation biological agents
abatacept, certolizumab, golimumab, rituximab, and tocilizumab in patients with established rheumatoid arthritis taking
concomitant methotrexate.

Searching
MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) were
searched from 1990 to November 2009; search terms were reported. Reference lists of reviews and retrieved studies
were scanned.

Study selection
Double-blind randomised controlled trials (RCTs) of biologically-naive rheumatoid arthritis patients, with a mean
disease duration of at least five years and a current inadequate response to methotrexate, treated with a second
generation biological preparation or placebo were eligible for inclusion. Trials had to present data on the American
College of Rheumatology 50% response (ACR50), preferably after 12 months of follow-up (six months was used,
where no 12-month studies were found). Withdrawal due to adverse events was the main harm outcome.

Included trials studied abatacept and certolizumab (one trial each of 12 months follow-up), rituximab, tocilizumab and
golimumab (one trial each of six months follow-up). Three trials had three arms. Included trials were published from
2006 to 2008. The mean age of included patients ranged from 50 to 52 years; over three-quarters were female. Disease
duration ranged from 4.5 to 11.1 years. C-reactive protein levels ranged from 0.8 to 3.3mg/dL.

Two reviewers independently selected studies, with disagreements resolved by a third reviewer.

Assessment of study quality
The authors did not evaluate trial quality, although only double-blind randomised trials were included in the review.

Data extraction
Two reviewers independently extracted intention-to-treat data in order to calculate relative risks, risk differences and
the number needed to treat and number needed to harm, along with 95% confidence intervals (CIs). Benefit-to-risk
ratios were also calculated.

Methods of synthesis
A narrative synthesis was performed, supplemented by tables and figures.

Results of the review
Five RCTs were included in the review (n=2,643 patients).

All second-generation biological drug treatments showed statistically significant differences in American College of
Rheumatology 50% (ACR50) response rates compared with placebo in patients with rheumatoid arthritis. Risk
differences for ACR50 response and withdrawal due to adverse events ranged from 0.19 to 0.33. The number of
patients needed to treat to achieve one ACR50 response ranged from four to six patients (95% CIs ranged from 3 to 13).

There were no significant differences between treatment and placebo groups for withdrawals, except for high-dose rituximab (1,000 mg) where the number of patients needed to produce one harmful event was 32 (95% CI 17 to 150).

**Authors' conclusions**
Comparable efficacy was shown by the five biological drugs studied with few adverse events, although limited data was available for rituximab, tocilizumab and golimumab.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant studies were undertaken by searching relevant databases and checking references. However, it was unclear whether there were any language or publication type restrictions (no search appeared to have been made specifically to identify unpublished studies), so some relevant studies may have been missed. Suitable methods were employed to reduce the risks of reviewer error and bias for the processes of study selection and data extraction.

Trial quality was not appraised, so it was not possible to assess the reliability of the evidence (although only double-blind randomised trials were eligible). An appropriate narrative synthesis of the data was presented along with comprehensive trial details. The authors' conclusions for adverse events appeared a little over-optimistic and simplistic, since significant harm was associated with one treatment and trends for harm were seen for most other treatments.

In light of these limitations, the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that a low dose (500mg) of rituximab may be as effective as the recommended dose of 1,000mg. They added that the use of golimumab, rituximab, and tocilizumab was questionable since only six-month follow-up data was available.

**Research:** The authors highlighted the importance of registers and observational studies for monitoring long-term safety profiles.

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