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.

Funding
Oak Foundation; Osterlund and Kock Foundations; Reumatikerforbundet (Rhuematism Association), Sweden; Danish Rheumatism Association; King Gustav V 80-year fund; Lund University Medical Faculty, Sweden.

Bibliographic details

PubMedID
20950126

DOI
10.3109/03009742.2010.491834

Original Paper URL

Additional Data URL
http://informahealthcare.com/doi/abs/10.1080/03009740701607067
Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Antibodies, Monoclonal /therapeutic use; Antirheumatic Agents /therapeutic use; Arthritis, Rheumatoid /drug therapy; Biological Products /therapeutic use; Databases, Bibliographic; Double-Blind Method; Female; Humans; Male; Middle Aged; Randomized Controlled Trials as Topic; Research Design; Sample Size

AccessionNumber
12011001491

Date bibliographic record published
13/04/2011

Date abstract record published
30/11/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.