Efficacy of biologicals in the treatment of rheumatoid arthritis: a meta-analysis
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CRD summary
The authors concluded that biological agents were effective in the treatment of rheumatoid arthritis, both in treatment-naive and in methotrexate-refractory patients. The reliability and applicability of the authors’ conclusions are difficult to determine due to poor reporting and methodological weaknesses, in particular the possible duplication of data and failure to test for statistical differences between the studies.

Authors’ objectives
To evaluate the efficacy of biological agents for treating refractory rheumatoid arthritis.

Searching
The following databases were searched up to January 2007: MEDLINE, EMBASE and the Cochrane Library. Search terms were reported. Index Medicus and references from the retrieved articles were also checked.

Study selection
Double blind randomised controlled trials (RCTs) comparing biological agents with placebo were eligible for inclusion. Participants were required to have active rheumatoid arthritis as defined by American College of Rheumatology criteria, despite treatment with a traditional disease-modifying anti-rheumatic drug. The biological agents dose was required to be fixed throughout the trial, without dose titration. The duration of treatment was required to be at least 12 weeks. Trials in which both groups received methotrexate or another disease-modifying anti-rheumatic drug were eligible for inclusion. Outcomes of interest were rates of improvement in American College of Rheumatology (ACR) criteria of 20%, 50% and/or 70% (ACR 20, 50, 70) at 24, 54 and 96 weeks of treatment.

The trials in the review compared the following biological agents with placebo: infliximab, etanercept, adalimumab, abatacept and anakinra. Doses and dosing frequencies varied across trials; some trials included more than one dose of biological agents. In over half the trials, both groups received methotrexate. The dose of methotrexate used in most trials was low to moderate (12.5 milligrams (mg) per week, titrated up to about 20 mg per week). It was administered either parenterally or orally (where stated). Some trials used other disease-modifying anti-rheumatic drugs in both groups, and a few compared biological agents with placebo only. Where stated, participants had a history of methotrexate use for three months prior to the trial. However, for most trial, prior disease-modifying anti-rheumatic drug use was not described in the review. Trial duration varied from 22 to 104 weeks. Two reviewers independently selected eligible studies.

Assessment of study quality
The following aspects of study quality were considered: allocation concealment, comparability of groups, blinding, and handling of withdrawals. Unblinded and non-randomised studies were excluded.

The authors did not state how the assessment was performed.

Data extraction
Odds ratios were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals. Where data were reported as percentages they were converted into the number of patients. Data for the 24 week time point included data from weeks 22 to 30; for 54 weeks it included weeks 46 to 54, and for 96 weeks it included weeks 96 to 104.

The authors did not state how the data were extracted for the review or how many reviewers performed the data extraction.

Methods of synthesis
Studies were grouped by outcomes and data were combined to calculate pooled odds ratios and 95% confidence intervals, using the random-effects model of DerSimonian and Laird. Publication bias was assessed with a funnel plot.
The effect of treatment duration on effect size was plotted graphically, and differing effects by type, dose and/or route of drugs used were discussed in a narrative synthesis.

**Results of the review**

It appears that 21 RCTs (randomised controlled trials) were included (n=8,807 participants). However, trial numbers were unclear; the authors stated that 25 trials were included (26 in the abstract), with 11,252 participants. The text was inconsistent with the table of trials; some of the trials appeared to be multiple publications reporting the same study cohort. All the RCTs achieved baseline comparability of groups and blinding of participants, assessors and study administrators. All RCTs explained withdrawals and used intention to treat principles in analysis. However, no RCTs reported adequate allocation concealment or blinding of assessment procedures; none included more than 80% of randomised participants in analysis.

**Biological agents versus placebo** (with or without methotrexate in both groups)

American College of Rheumatology criteria 20% improvement: Improvements were significantly better in the intervention group at 24 weeks (odds ratio 3.69, 95% confidence interval (CI): 3.48 to 3.87; 26 RCTs), 54 weeks (odds ratio 3.31, 95% CI: 2.98 to 3.64; 16 RCTs) and at 96 weeks (odds ratio 3.0, 95% CI: 2.64 to 3.35; eight RCTs). American College of Rheumatology criteria 50% improvement: Improvements were significantly better in the intervention group at 24 weeks (odds ratio 4.26, 95% CI: 4.06 to 4.45; 24 RCTs), 54 weeks (odds ratio 3.60, 95% CI: 2.93 to 4.26; 10 RCTs) and at 96 weeks (odds ratio 3.20, 95% CI: 2.65 to 3.76; eight RCTs). American College of Rheumatology criteria 70% improvement: Improvements were significantly better in the intervention group at 24 weeks (odds ratio 4.21, 95% CI: 3.92 to 4.50; 22 RCTs) and 54 weeks (odds ratio 4.06, 95% CI: 2.45 to 5.67; four RCTs). At 96 weeks there was no statistically significant difference between the groups (odds ratio 1.34, 95% CI: 0.01 to 2.69; two RCTs).

The shape of the funnel plot suggested possible publication bias.

When the odds ratio for American College of Rheumatology criteria versus placebo was plotted over time, a uniform decline in the efficacy of American College of Rheumatology criteria was evident.

Other results were reported in the review.

**Authors’ conclusions**

Biological agents are effective in the treatment of rheumatoid arthritis, both in treatment-naive and in methotrexate-refractory patients.

**CRD commentary**

The objectives and inclusion criteria of the review were not entirely clear, as the text was inconsistent as to whether comparisons of different biological agents were eligible for inclusion. It was also unclear whether participants in all RCTs had been unsuccessfully treated with a disease-modifying anti-rheumatic drug, as required by the inclusion criteria; the authors’ conclusions implied that participants in some trials were treatment naive. Relevant sources were searched for studies, but it was unclear whether the search was restricted by language, so the review may have been subject to language bias. Relevant criteria were used to assess study quality. Steps were taken to minimise reviewer bias and error by having more than one reviewer independently select studies for inclusion. However, the processes used for validity assessment and data extraction were not described.

Few details were provided about the characteristics of the included trials, such as participant demographics, disease severity or numbers of drop-outs. An appropriate statistical approach was used to combine the trials, but it was unclear which trials contributed to each analysis, and it appeared that some data may have been counted more than once. Also, statistical heterogeneity was not formally assessed. Parts of the text were potentially confusing as they suggested that the comparison of interest was biological agents versus methotrexate. The reliability and applicability of the authors’ conclusions are difficult to determine due to poor reporting and methodological weaknesses, in particular the possible duplication of data and failure to test for statistical differences between the trials.

**Implications of the review for practice and research**

**Practice:** The authors stated that close attention should be given to the dose of biological agents used in order to achieve maximum benefit.
Research: The authors did not state any implications for research.

Funding
Not stated.

Bibliographic details

PubMedID
18957873

DOI
10.1159/000165777

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Antirheumatic Agents /pharmacology /therapeutic use; Arthritis, Rheumatoid /drug therapy /epidemiology /immunology; Clinical Trials as Topic; Drug Delivery Systems; Female; Humans; Immunologic Factors /pharmacology /therapeutic use; Male; Odds Ratio; Prevalence; Sex Factors; Synovitis /drug therapy /etiology; Time Factors

AccessionNumber
12009102770

Date bibliographic record published
06/05/2009

Date abstract record published
05/08/2009

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.