Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis

Lopez-Olivo MA, Tayar JH, Pollono EN, Cueto JP, Gonzalez-Crespo MR, Fulton S, Suarez-Almazor ME

CRD summary
This generally well-conducted review concluded that biologic response modifiers were not associated with an increased risk of malignancy (compared to placebo or traditional disease-modifying treatment) in patients with rheumatoid arthritis in trials with at least six months duration. This conclusion seems reasonable, but uncertainties surrounding the rigour of the studies to detect malignancy rates should be considered.

Authors' objectives
To assess the risk of malignancy in patients with rheumatoid arthritis enrolled in randomised controlled trials (RCTs) of biologic response modifiers.

Searching
MEDLINE, EMBASE, The Cochrane Library and Web of Science were searched up to June 2011. Abstracts of two rheumatology associations were also searched. Full search strategies were reported. Updates of new literature were monitored up to July 2012. Websites and references of identified reviews and RCTs were also checked for additional studies. Only studies reported in English, French or Spanish were eligible for inclusion.

Study selection
RCTs that compared the safety of any biologic agent with placebo or any disease modifying anti-rheumatic drug were eligible for inclusion. Trials were required to include only patients with rheumatoid arthritis and to have at least 24 weeks follow-up. Trials which did not describe any adverse events were excluded.

Most of the included studies were placebo-controlled and most patients on active treatment received a biologic agent in combination with at least one disease modifying anti-rheumatic drug. Most of the trials required that patients had active disease and had failed treatment with traditional disease modifying anti-rheumatic drugs; a minority included patients who had not previously had treatment with these agents. Some trials excluded patients who had previously had cancer. Biologic response modifiers assessed were both tumour necrosis factor (TNF) inhibitors (adalimumab, certolizumab, etanercept, golimumab and infliximab) and non-TNF inhibitors (abatacept, anakinra, rituximab and tocilizumab). Most patients were female and white, with mean ages between 44.8 and 56.5 years. The mean disease duration varied from 0.35 to 13 years.

Two reviewers independently assessed each study for inclusion. Disagreements were resolved through consensus and referred to a third reviewer where necessary.

Assessment of study quality
Studies were assessed for risk of bias using the following criteria: randomisation, allocation concealment, blinding, incomplete and selective outcome reporting, baseline comparability, carryover and funding source. Each criterion was judged as low, high or unclear risk of bias and a summary risk of bias calculated.

Two reviewers independently assessed the studies.

Data extraction
Two reviewers independently extracted data on number and type of malignancies to permit calculation of odds ratios (OR) and relative risks (RR) with 95% confidence intervals (CI). In most cases the safety population rather than the intention-to-treat population was used. Authors and pharmaceutical companies were contacted for missing data.

Data extraction was checked by two additional reviewers and discrepancies were resolved through consensus and adjudication.
Methods of synthesis
Random-effects meta-analyses were used to calculate pooled relative risks and Peto odds ratios with 95% confidence intervals. A 0.5 correction for zero events was used. The authors reported that statistical heterogeneity was formally assessed; it appeared that I^2 was used to quantify heterogeneity. Separate analyses were undertaken for each type of malignancy (solid tumours, skin cancers, types of haematological malignancy and unspecified) and for each treatment.

Subgroup analyses were used to compare monotherapy with combination treatment using traditional disease-modifying treatments, and to assess the impact of follow-up duration on treatment effect. Several sensitivity analyses were also undertaken. Bonferroni corrections for multiple comparisons were applied but were not reported. Several methods including the Egger test and funnel plot assessment were used to examine potential publication bias.

Results of the review
Sixty-three RCTs with 29,423 patients were included in the review; sample sizes ranged from 20 to 1,399. Nineteen trials had adequate allocation concealment, but only five were unblinded. The risk of bias from selective reporting was generally low. Follow-up ranged from 24 weeks up to 156 weeks. Completion rates varied, ranging from 49% to 99% in those on active treatment and 5% to 100% in control groups.

A total of 211 patients (0.72%) developed a malignancy during the trial periods; 118 of these were solid tumours and 48 were skin cancer. The remainder were haematological or unspecified. Rates were very low in all groups: biologic agent plus methotrexate (OR 0.77%, 95% CI 0.65% to 0.92%); biologic agent monotherapy (OR 0.64%, 95% CI 0.42% to 0.95%) and controls (OR 0.66%, 95% CI 0.52 to 0.84%).

There was no statistically significant difference in the total occurrence of malignancy between TNF biologic response modifiers alone versus placebo or traditional disease modifying therapy (OR 0.98, 95% CI 0.51 to 1.19; 13 RCTs) or TNF plus methotrexate versus either placebo or active comparators (OR 1.5, 95% CI 0.95 to 2.3; 29 RCTs). There were no significant differences for individual agents. There was a doubling of risk of lymphoma and a five-fold increase in other haematologic malignancies with TNF inhibitors compared to controls, but this was not statistically significant. Sensitivity analysis excluding trials that reported zero malignancy meant that a statistically significantly higher risk of malignancy was identified for TNF inhibitors plus methotrexate versus controls at 52 weeks (OR 2.0, 95% CI 1.1 to 3.8).

The only statistically significant finding from comparisons of total malignancy between non-TNF inhibitors with comparators was a reduced incidence at 24 weeks for anakinra plus methotrexate compared to methotrexate alone (OR 0.11, 95% CI 0.03 to 0.45, three RCTs). Pooled estimates for all non-TNF inhibitors were not presented.

There was no evidence of publication bias.

Authors' conclusions
The use of biologic response modifiers in patients with rheumatoid arthritis in RCTs with at least six months duration was not significantly associated with increased risk of malignancy compared to other disease modifying anti-rheumatic drugs or placebo.

CRD commentary
The review question was clear and the inclusion criteria were transparent and reproducible. Several databases and other relevant sources were searched. The authors acknowledged that language restrictions may have introduced selection bias into the review, potentially leading to omission of relevant studies. Study quality was assessed using appropriate criteria. Methods designed to reduce reviewer bias and error were used throughout.

The synthesis was generally appropriate and focused on Peto odds ratios which was reasonable for rare events. Safety was not the primary outcome of many of the included studies. It would have been preferable to see results reported with Bonferroni corrections applied when so many comparisons were undertaken. There was some uncertainty in the findings, illustrated by wide confidence intervals in the analyses, particularly for non-TNF inhibitors. The authors' conclusions seem reasonable but may not be generalisable to longer time-frames. The uncertainties surrounding the rigour of the studies to detect malignancy rates should also be considered.
Implications of the review for practice and research

**Practice:** The authors did not state any implications for practice but did note that the risk of recurrence of previous cancer in patients with rheumatoid arthritis on biologic response modifier treatment was unclear, as was the risk for patients who had known risk factors for developing cancer.

**Research:** The authors stated that systematic reviews of observational studies were required to determine the long-term risk of malignancy with biologic response modifiers in the treatment of rheumatoid arthritis.

**Funding**
No external funding for review; one reviewer supported by National Institute of Arthritis and Musculoskeletal and Skin Diseases.

**Bibliographic details**

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Arthritis, Rheumatoid; Biological Therapy; Neoplasms; Humans

**AccessionNumber**
12012040102

**Date bibliographic record published**
06/09/2012

**Date abstract record published**
08/09/2012

**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.