Rituximab treatment of refractory rheumatoid arthritis.

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CRD summary
This review assessed the effectiveness and safety of rituximab in the treatment of refractory rheumatoid arthritis. The authors concluded that rituximab, when administered with cyclophosphamide or methotrexate, appears to be an acceptable treatment. Based on the evidence presented and the review methodology, the authors' conclusions should be interpreted with care. However, recommendations for further research are appropriate.

Authors' objectives
To ascertain whether rituximab is an effective and safe treatment for refractory rheumatoid arthritis (RA).

Searching
MEDLINE (1966 to May 2005) and EMBASE (1980 to May 2005) were searched and restricted to English language. Search terms were not reported. It was unclear whether unpublished studies were included. The reference lists of retrieved articles were examined for additional studies.

Study selection
Studies of rituximab for refractory rheumatoid arthritis were eligible for inclusion. The authors did not state specific inclusion/exclusion criteria regarding participants, interventions, outcomes or study design.

Included patients had undergone previous failed treatments including disease modifying anti-rheumatic drugs (DMARDs) and haematopoietic stem cell transplant (HSCT) in combination with cyclophosphamide. Treatment regimens varied greatly across studies where rituximab was either administered alone or in association with other agents (cyclophosphamide, prednisolone/methylprednisolone, methotrexate, leucovorin). All included trials reported end point measures using the American College of Rheumatology's (ACR) definition of criteria for improvement. Duration of follow up ranged from 24 to 52 weeks across trials and the percentage patients achieving ACR responses of 20, 50 and 70 were reported.

The authors did not state how papers were selected for the review or how many reviewers performed the selection.

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

Data extraction
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 described individually and grouped according to design. There was very brief narrative synthesis. The authors did not attempt to ascertain whether there was any publication bias.

Results of the review
Five studies (n=204) were included in the review: one RCT (n=161), four non-randomised, open labelled studies (n=42) and one case report (n=1).

In summary (across all studies), the treatment groups given rituximab total doses of at least 600mg/m2 as part of their regimen showed improvements in achievement of target ACR responses at 24 to 26 weeks, which were significantly better where rituximab was administered in combination with cyclophosphamide or methotrexate. Adverse events were infrequent across studies.

The included RCT showed that rituximab administered in combination with cyclophosphamide or methotrexate resulted
in significantly higher achievement of ACR responses of 20 and 50 at 24 weeks when compared to methotrexate monotherapy (p<0.05 and p<0.01 respectively). The rituximab monotherapy group showed no significant difference. The group receiving rituximab and methotrexate also had a significantly higher achievement of an ACR response of 70 at 24 and 48 weeks (p=0.048 and p=0.03 respectively). All three rituximab groups showed significant decreases in disease activity scores, sustained depletion of B lymphocytes and rheumatoid factor (RF) levels stayed below baseline up to week 24. There was no increased risk for the development of life threatening infections.

In the four non-randomised, open-labelled studies, similar findings were reported for rituximab administered in combination with cyclophosphamide. B lymphocytes were significantly depressed or depleted and numbers of adverse events were also small.

The one case report, using chimeric monoclonal antibody anti-CD20 therapy for four weeks, showed an improvement in symptoms at three weeks and the patient became symptom free during the following weeks.

**Authors' conclusions**
Rituximab when administered in regimens with cyclophosphamide or methotrexate seems to be an acceptable, well tolerated treatment for refractory rheumatoid arthritis.

**CRD commentary**
This review question was broad and there were no clear inclusion or exclusion criteria for participants, interventions, outcomes or study design. Two relevant databases and reference lists were searched with language restricted to English and search terms were not reported. In addition, unpublished studies were not included. Therefore, relevant studies may have been missed and the introduction of publication and language bias can not be ruled out. The potential influence of publication bias was not considered in the review. The authors did not assess validity, so the quality of the studies included was not reported; nor did they state how the data were extracted or by how many reviewers, so additional error and bias might have been introduced during the review process.

Given the wide variation between included studies in terms of treatment regimens and participants, small study numbers and sample sizes, study design (only one RCT), combined with the lack of information and weaknesses regarding the review methodology, the authors' conclusions should be interpreted with care. The authors' recommendation for further rigorous research to address the many relevant questions reflects the level of evidence presented.

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

Research: The authors stated that further research is needed to ascertain optimal dosing, response rates, comparative long term efficacy, radiographic effects and the position of rituximab in the treatment algorithm for rheumatoid arthritis.

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