

Rituximab for rheumatoid arthritis (Protocol)

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[Intervention Protocol]

Rituximab for rheumatoid arthritis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the efficacy and safety of rituximab for the treatment of RA.

BACKGROUND

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis that causes significant morbidity and deformity which can lead to considerable loss of function (Wolfe 1996; Grassi 1998). Early intervention allows the control of joint pain and swelling, and reduces risk of disability and permanent joint damage. Disease modifying anti-rheumatic drugs (DMARDs) remain the preferred initial treatment for RA; they have been shown to reduce disease activity, retard joint erosions and improve patients' quality of life (Fries 1996). Unfortunately, many patients either fail to respond adequately or need to stop treatment because of side effects. Recent advances in therapy include biological drugs, which are immune targeted therapies that have shown effectiveness in patients who do not respond to DMARDs (Lipsky 2000; Breedveld 2006).

In recent years, evidence has provided further insight into the role of B-cells in the pathophysiology of rheumatoid arthritis (Dörner 2003; Olsen 2004). Rituximab (MabThera/ Rituxan) is a selective, B-cell depleting, biological agent recently introduced for the treatment of refractory RA. The chimeric monoclonal antibody, targeted against CD 20, is being promoted as a therapy for patients who fail to respond to other biologics (Higashida 2005; Cohen 2006). There is evidence to suggest that, used in combination with methotrexate (MTX), rituximab is effective and well tolerated, when used to manage RA (Edwards 2001; Edwards 2004).

The side effects of rituximab are mild to moderate and usually occur during the first infusion (Mohrbacher 2005). Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, or anaphylactoid events. Therefore, to reduce the incidence and severity of infusion reactions, glucocorticoids (methylprednisolone 100 mg IV or its equivalent) should be administered 30 minutes prior to each infusion. In addition, it is recommended that premedication with acetaminophen and an antihistamine before each infusion of rituximab and institute medical management should be available in case of a fatal infusion reaction.

OBJECTIVES

To evaluate the efficacy and safety of rituximab for the treatment of RA.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) or controlled clinical trials (CCTs) comparing rituximab in combination with any DMARD or rituximab alone versus placebo or other DMARDs or any biologic will be reviewed with minimum trial duration of 6 months. Corticosteroids will be accepted if patients were on stable doses and were randomly assigned to treatment with rituximab or to treatment without rituximab.

Types of participants

Patients at least 16 years of age meeting the American College of Rheumatology 1987 revised criteria (Arnett 1988) for rheumatoid arthritis and active disease as described by authors in relation to the outcome measures.

Types of interventions

Treatment with rituximab in combination with any DMARD or rituximab alone versus placebo or other DMARDs or biologic will be eligible for inclusion. Doses of rituximab eligible for inclusion include 300 mg/m², 350 mg/m², 500 mg/m² and 600 mg/m².

Types of outcome measures

The primary efficacy outcomes included in this review will be the response of rheumatoid arthritis to treatment with rituximab as defined by the World Health Organization (WHO), the International League of Associations for Rheumatology (ILAR) core set of disease activity measures and the American College of Rheumatology outcome measures for RA clinical trials. The description of efficacy, safety, and secondary outcome measures are the following:

Major efficacy outcomes

1. ACR improvement criteria (Felson 1995).
2. Tender joint count (TJC)
3. Swollen joint count (SWJ)
4. Patient's assessment of pain using 10 cm visual analogue scale or Likert scale.
5. Patient global assessment of disease activity
6. Physician global assessment of disease activity using 10 cm visual analogue scale or Likert scale.
7. Acute phase reactants such as Westergren erythrocyte sedimentation rate or C-reactive protein.
8. Disease activity scores (DAS) (Prevoo 1995).
9. Radiographic progression for studies with a minimum of 12 months duration, including Sharp/van der Heijde and Larsen scores (van der Heijde 1999; Larsen 1973).

Definition of improvement: We will establish clinical improvement as (a) the American College of Rheumatology (ACR20, ACR50, ACR70) response that represents a 20%, 50% or 70% improvement in tender and swollen joints counts plus a 20%, 50% or 70% improvement in 3 of the 5 core measures (e.g., patient and physical global assessments, pain, functional status and an acute phase reactant) and (b) the European League Against Rheumatism (EULAR) response criteria that include not only change in disease activity but also current disease activity. Per EULAR, patients are

classified as responders if a significant change in DAS and low current disease activity is observed. It includes three categories: good, moderate, and non-responders.

Safety outcomes

Safety outcomes will include:

1. Adverse events (acute infusion reactions: urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, or anaphylactoid events; headaches; upper respiratory tract infections; nausea; fatigue; hypertension; tumor lysis syndrome; severe mucocutaneous reactions; progressive multifocal leukoencephalopathy; hepatitis B virus reactivation; other viral infections; etc.)

2. Withdrawals (lack of efficacy, toxicity, etc.)

Secondary outcomes

Secondary outcomes will include health-related quality of life (HRQoL) such as:

1. SF-36

2. Health Assessment Questionnaire

Search methods for identification of studies

We will follow Cochrane Musculoskeletal Group methods used in reviews. Sources of published data will include electronic databases (MEDLINE, EMBASE, CINAHL, The Cochrane Library, Web of Science), hand-searching of selected rheumatology journals, and conference proceedings. Additionally, reference lists from comprehensive reviews and identified clinical trials will be searched for possible references not otherwise found. We will contact the pharmaceutical companies that manufacture rituximab (Roche in Canada, Genetech and Biogen Idec in the USA) for details of any unpublished data. We will not apply language, year of publication or type of publication restrictions. The specific search strategy for each of the databases is shown in Appendix 1.

Data collection and analysis

Selection of studies

Two review authors will independently determine if each study meets the inclusion criteria for the review. The review authors' differences regarding inclusion will be resolved by discussion and consensus.

Assessment of risk of bias in included studies

The risk of bias of the included studies will be also assessed by two independent review authors. As recommended by the Cochrane Handbook, the following methodological domains will be assessed:

I: Sequence generation

II: Allocation sequence concealment

III: Blinding of participants, personnel and outcome assessors

IV: Incomplete outcome data

V: Selective outcome reporting

VI: Other potential threats to validity (considering external validity, e.g. relevant use of co-interventions).

Each of these criteria will be explicitly judged using: Yes=(low risk of bias); B=No (high risk of bias); C=unclear (either lack of information or uncertainty over the potential for bias)

Data extraction and management

Two review authors will independently abstract data from each study using the CMSG data abstraction forms and will be cross-checked. Discrepancies will be resolved by consensus. The extraction of data includes study design, demographics, concomitant treatment and outcome measures.

Data synthesis and analysis

When possible, we will analyse data using an intention to treat model. We will also analyse continuous data as a weighted mean difference and dichotomous data will be reported as relative risk. We will calculate the number needed to treat to provide an indication for each dichotomous outcome, reflecting the number of patients required to obtain a beneficial outcome with the intervention.

To test heterogeneity of the data, we will perform chi square test using $n-1$ degrees of freedom and a P-value of less than or equal to 0.05. Overall effects will only be estimated for groups of trials using the same intervention and several individual meta-analyses will be performed. We will estimate overall effect by meta-analysis using fixed effects models and if heterogeneity exists, we will incorporate random effects models. Data will not be pooled if significant heterogeneity exists. We will use I^2 to describe the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. A value greater than 50% may be considered substantial heterogeneity (Higgins 2008).

We will use the mean and standard deviation when available. If only median and interquartile ranges are reported, we will follow the Cochrane handbook guidelines (Higgins 2008); the median will be used as the mean and the standard deviation will be set as 1.35. If no standard deviation is given at the end of the study, the baseline standard deviation will be used at the end as well. Values will be extracted from graphs when numerical data is not reported.

Summary of findings tables

Summary of Findings tables included in RevMan 5 will be completed in order to improve the readability of the review. In addition to the absolute and relative magnitude of effect provided in the summary of findings table, the number needed to treat (NNT) will be calculated from the control group event rate (unless the population event rate is known) and the relative risk using the Visual Rx NNT calculator (Cates 2003). For continuous outcomes, the NNT will be calculated using the Wells calculator software available at the CMSG editorial office. The minimal clinically important difference (MCID) for each outcome will be determined for input into the calculator.

GRADE software will be used to provide an overall grading of the quality of the evidence.

Sensitivity and subgroup analyses

We will conduct a sensitivity and subgroup analysis to determine the effects of disease duration, previous DMARD treatment, corticosteroid use and disease activity on the response to rituximab.

Assessment of publication bias

We will evaluate potential publication bias with inverted funnel plot techniques.

ACKNOWLEDGEMENTS

The authors would like to thank Louise Falzon who kindly have contributed to developing the searches for this protocol.

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Cates 2003

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Cohen 2006

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Wolfe 1996

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* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategy

MEDLINE

1. exp arthritis, rheumatoid/
2. (felty\$ adj2 syndrome).tw.
3. (caplan\$ adj2 syndrome).tw.
4. rheumatoid nodule.tw.
5. (sjogren\$ adj2 syndrome).tw.
6. (sicca adj2 syndrome).tw.
7. still\$ disease.tw.
8. bechterew\$ disease.tw.
9. (arthritis adj2 rheumat\$).tw.
10. or/1-9
11. Antibodies, Monoclonal/
12. Immunologic Factors/
13. rituximab.tw.
14. rituxan.tw.
15. mabthera.tw.
16. or/11-15
17. 10 and 16

18. clinical trial.pt.
19. randomized.ab.
20. placebo.ab.
21. dt.fs.
22. clinical trials/
23. randomly.ab.
24. trial.ti.
25. groups.ab.
26. or/18-25
27. animals/
28. humans/
29. 27 and 28
30. 27 not 29
31. 26 not 30
32. 17 and 31

EMBASE

- 1 exp arthritis, rheumatoid/
- 2 (felty\$ adj2 syndrome).tw.
- 3 (caplan\$ adj2 syndrome).tw.
- 4 rheumatoid nodule.tw.
- 5 (sjogren\$ adj2 syndrome).tw.
- 6 (sicca adj2 syndrome).tw.
- 7 still\$ disease.tw.
- 8 bechterew\$ disease.tw.
- 9 (arthritis adj2 rheumat\$).tw.
- 10 or/1-9
- 11 rituximab/
- 12 rituximab.tw.
- 13 rituxan.tw.
- 14 mabthera.tw.
- 15 or/11-14
- 16 10 and 15
- 17 random\$.ti,ab.
- 18 factorial\$.ti,ab.
- 19 (crossover\$ or cross over\$ or cross-over\$).ti,ab.
- 20 placebo\$.ti,ab.
- 21 (doubl\$ adj blind\$).ti,ab.
- 22 (singl\$ adj blind\$).ti,ab.
- 23 assign\$.ti,ab.
- 24 allocat\$.ti,ab.
- 25 volunteer\$.ti,ab.
- 26 crossover procedure.sh.
- 27 double blind procedure.sh.
- 28 randomized controlled trial.sh.
- 29 single blind procedure.sh.
- 30 or/17-29
- 31 exp animal/ or nonhuman/ or exp animal experiment/
- 32 exp human/
- 33 31 and 32
- 34 31 not 33
- 35 30 not 34
- 36 16 and 35

CINAHL

1 exp Arthritis, Rheumatoid/
2 (felty\$ adj2 syndrome).tw.
3 (caplan\$ adj2 syndrome).tw.
4 rheumatoid nodule.tw.
5 (sjogren\$ adj2 syndrome).tw.
6 (sicca adj2 syndrome).tw.
7 bechterew\$ disease.tw.
8 (arthritis adj2 rheumat\$).tw.
9 or/1-8
10 rituximab/
11 rituximab.tw.
12 rituxan.tw.
13 mabthera.tw.
14 or/10-13
15 9 and 14
16 from 15 keep 1-30

The Cochrane Library

#1MeSH descriptor Arthritis, Rheumatoid explode all trees in MeSH products
#2felty near/2 syndrome in All Fields in all products
#3caplan near/2 syndrome in All Fields in all products
#4rheumatoid nodule in All Fields in all products
#5sjogren* near/2 syndrome in All Fields in all products
#6sicca near/2 syndrome in All Fields in all products
#7still* next disease in All Fields in all products
#8bechterew* next disease in All Fields in all products
#9arthritis near/2 rheumat* in All Fields in all products
#10(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11MeSH descriptor Antibodies, Monoclonal, this term only
#12MeSH descriptor Immunologic Factors, this term only
#13rituximab:ti,ab
#14rituxan:ti,ab
#15mabthera:ti,ab
#16(#11 OR #12 OR #13 OR #14 OR #15)
#17(#10 AND #16)

Web of Science

#1 rheumatoid arthritis or felty syndrome or sicca syndrome or caplan syndrome or still* disease or sjogren* syndrome or bechterew* disease or rheumatoid nodule*)
#2 rituximab or rituxan or mabthera
#3 trial* or random* or placebo* or control* or double or treble or triple or blind* or mask* or allocat* or prospective* or volunteer* or comparative or evaluation or follow-up or followup
#4 #1 AND #2 AND #3

WHAT'S NEW

HISTORY

Protocol first published: Issue 4, 2008

CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-authors (MSA)

Draft protocol (MLO, MAU, LM, MSA)

Run search (LF)

Identify relevant titles and abstracts from searches (MLO, MAU)

Obtain copies of trials (MLO)

Selection of trials (MLO, MAU, MSA)

Extract data from trials (MLO, MAU, LM)

Enter data into RevMan (MLO)

Carry out analysis (MLO, MSA)

Interpret data (MLO, MAU, LM, MSA)

Draft final review (MSA with contributions from all)

Update review (MLO, LM, MSA)

DECLARATIONS OF INTEREST

Dr. Suarez-Almazor is the recipient of a K24 career award from the National Institute for Musculoskeletal and Skin Disorders. She is also the Director of the Houston Centre for Education and Research on Therapeutics, funded by the Agency for Healthcare Research and Quality (AHRQ).

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External sources

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