

Abatacept for rheumatoid arthritis (Protocol)

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[Intervention Protocol]

Abatacept 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 assess the efficacy and safety of abatacept in reducing disease activity, pain, and improving function in people with rheumatoid arthritis.

BACKGROUND

Rheumatoid arthritis (RA) is a chronic auto-immune disease which affects the synovial lining of joints and tendon sheaths resulting in persistent inflammation (Schumacher 1993). It is associated with significant morbidity, disability and impaired quality of life (Badley 2003). The incidence of RA is estimated as 13–36 per 100,000 for females, less for males, with a prevalence as high as 0.8% in the UK (Woolf 2004). In terms of costs to society, the loss of 9.4 million working days to RA in the UK between 1999 and 2000 has been estimated to represent an annual loss in productivity of 833 million British pounds (ARC 2005). In the US, a recent estimate of the prevalence of RA in white adults >18 years is 0.6% Helmick 2008.

Disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (Suarez-Almazor 1998), leflunomide (Osiri 2002), hydroxychloroquine (Suarez-Almazor 2000) and sulfasalazine (Suarez-Almazor 1998b) have been shown to reduce disease activity, to slow disease progression (i.e. reduce the rate of new joint erosions) and to improve patients' quality of life.

However, the majority of RA patients are unable to tolerate these agents for long periods of time and only experience a partial benefit on these traditional DMARDs. Another class of drugs called 'biologics' have been developed over the past ten years. Biologics are designed to inhibit specific steps in the inflammatory cascade of the immune system.

Tumour necrosis factor (TNF)-alpha is a protein that the body produces during the inflammatory response. TNF-alpha promotes inflammation and subsequent pain, tenderness, swelling and fever in several inflammatory conditions including RA. There are three main biologic agents currently available that target TNF-alpha: infliximab (Remicade) is a chimeric (mouse/human) monoclonal antibody of the IgG1 isotype that binds with a high affinity to TNF-alpha, etanercept (Enbrel) is a receptor fusion protein that binds to TNF-alpha, thus competitively inhibiting the binding of TNF-alpha to the cell surface, and adalimumab (Humira) is a recombinant human IgG1 monoclonal antibody specific for human TNF-alpha. These three drugs prevent TNF-alpha from promoting inflammation and therefore reduce pain, tenderness and swelling of joints in patients with RA. Infliximab, etanercept, and adalimumab have been shown to substantially and rapidly improve RA symptoms and to slow radiographic progression (Blumenauer 2002; Blumenauer 2003; Navarro-Sarabia 2005).

Despite their effectiveness, not all patients respond to TNF-alpha blockade and therefore other therapy options are needed. Abatacept, brand name Orencia, was approved by the FDA in December 2005 for use in adult patients with moderate to severe rheumatoid arthritis who have not responded adequately either to oral DMARDs (such as methotrexate) or to the TNF-alpha antagonists. It is a selective co-stimulation modulator, inhibiting T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. It is the first biologic

to work by disrupting T-cell activation. Activated T-cells occur early in the inflammatory reaction so by preventing their activation, the chain of events that leads to joint inflammation, pain, and damage is prevented. Abatacept is administered intravenously over approximately 30 minutes and after the first dose, additional doses are given at 2 and 4 weeks and then every 4 weeks (Orencia 2007).

The use of biologics is limited by their high costs and uncertainty about the adverse events. The cost for one year of abatacept treatment is approximately \$22,000 USD (ACR 2007). At this time it is appropriate to conduct a systematic review of randomized controlled trials of abatacept to quantify the benefits and potential harms of its use.

OBJECTIVES

To assess the efficacy and safety of abatacept in reducing disease activity, pain, and improving function in people with rheumatoid arthritis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) will be included. To be eligible for inclusion, the generation of the allocation sequence must be truly random; for example, generation of the sequence by a computer or random numbers table. Trials must be a minimum of three months. Trials of less than six months duration will be used to investigate short-term efficacy and safety while studies longer than six months will address longer-term efficacy and safety. Data from published and unpublished RCTs will be considered for inclusion. Websites of regulatory agencies will be checked for reported adverse effects.

Types of participants

Patients at least 16 years of age meeting the ACR 1987 revised criteria for rheumatoid arthritis (Arnett 1988) will be included.

Types of interventions

RCTs comparing abatacept alone or in combination with DMARDs to placebo or other DMARDs. There will be no restrictions with regard to dosage or duration of intervention.

Types of outcome measures

Major outcomes

Efficacy:

The primary outcome is the ACR50 response rate to treatment with abatacept as defined by the American College of Rheumatology (ACR) (Felson 1995).

The variables included in this definition are:

- tender joint count
- swollen joint count
- patient's assessment of pain (VAS or Likert scale)
- patient and physician assessment of disease activity (VAS or Likert scale)
- patient assessment of functional ability (HAQ, AIMS, MACTAR)
- laboratory parameters (i.e., acute phase reactants, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP))

An ACR20/50/70 response is defined as a 20/50/70 per cent improvement in tender and swollen joints counts and the same level of improvement in three of the five following variables: patient and physician global assessments, pain, HAQ, and acute phase reactants.

Adverse events:

Since RCTs are usually of limited duration, mainly short-term adverse events will be assessed. However, regulatory agency websites will also be reviewed for potential longer-term adverse events.

Specific adverse event outcomes of interest:

Adverse events, including allergic reactions, infections

Serious adverse events, including serious infections, lymphoma

Withdrawals due to lack of efficacy, adverse events

Secondary outcomes

- Individual ACR criteria and ACR 20 and 70 response criteria as outlined above.
- Radiographic progression, as measured by the Sharp, modified Sharp or Larsen methods, is also considered a primary outcome for studies greater than 1 year in duration.
- European League Against Rheumatism (EULAR) criteria (Van Gestel 1996) defines response (good, moderate and none) according to certain cut-offs for both the absolute values and relative changes in the Disease Activity Score (DAS) (Van der Heijde 1993). The DAS is a composite index that includes the combination of the values of tender and swollen joints counts, patient's global assessment of disease activity, and ESR value. When a twenty-eight joint count is used the index is reported as DAS 28. A good response is defined as a decrease in the DAS or DAS 28 >1.2 from baseline with a final DAS < 2.4 (or DAS 28 < 3.2). None response is defined as a decrease in DAS or DAS 28 < 0.6 or a decrease > 0.6 and < 1.2 with a final DAS > 3.7 (or DAS 28 > 5.1). Any other scores are regarded as moderate response.
- Health-related quality of life as measured by the SF-36 or other instruments

Search methods for identification of studies

The following electronic databases will be searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ACP Journal Club, DARE, HTA, and ISI Web of Science. Current Controlled Trials will be searched for ongoing studies. An updated search will be run to capture any new publications before finalizing the review.

The search will not be limited by language, year of publication or type of publication. In addition, the proceedings of major rheumatology conferences - The American College of Rheumatology (ACR) and the European League of Rheumatology (EULAR) - will be hand searched for 2004 to 2008. The reference lists from comprehensive reviews and identified clinical trials will also be searched. Content experts and the pharmaceutical companies that manufacture abatacept will be contacted to obtain any relevant additional unpublished data.

Electronic search strategies are provided in [Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); and [Appendix 5](#)

Websites of regulatory agencies such as Current Problems in Pharmacovigilance (UK), Australian Adverse Drug Reactions Bulletin (Australia), Food and Drug Administration FDA Medwatch (US), and the European Public Assessment Reports from the European Medicines Evaluation Agency will be checked for reported adverse effects.

Data collection and analysis

Administration

Reference Manager 11 software will be used to manage the records retrieved from searches of electronic databases. The data extraction form will be created in Word and all article information except outcome results will be captured in this form. Outcome results will be tracked in an Excel spreadsheet for easier entry into RevMan.

Selection of studies

Results of the various searches will be independently reviewed by two authors (LM, JS). Titles and abstracts will be reviewed and if more information is required to determine whether the trial meets the inclusion criteria, the full text will be obtained. A record of reasons for excluding studies will be kept. Disagreement will be resolved by discussion. Inter-rater agreement will be calculated using Cohen's kappa. Articles in a language other than English will be translated.

Data extraction

Data will be independently extracted from the included trials by two reviewers (LM, JS) and entered into RevMan 5.0 using the double-entry system. Data extraction forms will be pilot tested on a selection of trials. When necessary, the authors of the primary studies will be contacted to obtain additional data.

The following data will be extracted:

o General study information such as title, authors, contact address, publication source, publication year, country, study sponsor

- o Characteristics of the study: design, study setting, inclusion/exclusion criteria, quality criteria (e.g. randomization method, allocation procedure, blinding of patients, caregivers and outcome assessors, withdrawals and dropouts, ITT analysis).
- o Characteristics of the study population and baseline characteristics of the intervention and control groups (age, sex, duration of disease, treatment history, presence of co-morbidity and peripheral disease, rheumatoid factor status, concurrent treatments) and numbers in each group
- o Characteristics of the intervention, such as treatment comparators, dose, method of administration, frequency of administration and duration of treatment
- o Outcomes measures as noted above (changes in disease outcome, adverse events, withdrawal from treatment)
- o Results for the intention to treat population (where possible), outcome measures at the end of the placebo phase, and any summary measures with standard deviations, confidence intervals and P-values where given, dropout rate and reasons for withdrawal

Assessment of risk of bias in included studies

The risk of bias of the included studies will be also assessed by two independent reviewers. As recommended by the Cochrane Handbook (Higgins 2008), 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).

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 2004). 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

Measure of treatment effect

The results of the studies will be analyzed using RevMan 5.0. Data

will be summarised in a meta-analysis if they are sufficiently homogeneous, both clinically and statistically. Continuous data will be expressed as weighted mean difference (WMD) or standardized mean difference (SMD), depending on similarity of scales measuring an outcome. Dichotomous data will be expressed as relative risk (RR) or in the case of rare events (<10%) the Peto odds ratio (Peto OR) will be used.

Heterogeneity

In addition to reviewing forest plots, heterogeneity of the data will be formally tested using the chi-square with a P-value <0.10 indicating significant heterogeneity. The I² statistic (Higgins 2003) will also be assessed. A value greater than 50% may indicate substantial heterogeneity. In the case of substantial heterogeneity, the data will be explored further, including sub-group analyses, in an attempt explain the heterogeneity.

Data synthesis

Since this is a recent drug on the market, it is expected that trials will be performed in similar populations and there will be little 'between-study' variation. In the absence of significant heterogeneity, a fixed effects model will be used, otherwise a random effects model will be used for analysis. Where available, the analyses will be based on intention-to-treat data from the individual studies.

Publication bias

A funnel plot will be performed to assess the possibility of publication bias.

Sub-group analysis

The following sub-group analyses are planned a priori in order to explore possible effect size differences:

1. Intervention - different dosages, duration of treatment
2. Characteristics of participants - severity of baseline disease; age; disease duration; and sex

Sensitivity analysis

The following sensitivity analyses are planned a priori in order to explore effect size differences and the robustness of conclusions:

1. Effect of risk of bias of included studies - defined as adequate allocation concealment and outcome assessor blinding
2. Effect of imputation of missing data or statistical transformations.

ACKNOWLEDGEMENTS

Louise Falzon, Trials Search Coordinator of the Cochrane Musculoskeletal Group, for providing comments on the search strategy. This systematic review will be conducted as part of a course on systematic review methodology, taught by Dean Fergusson and David Moher, in the Masters of Epidemiology and Community Medicine program at the University of Ottawa.

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* Indicates the major publication for the study

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp arthritis, rheumatoid/
2 (arthritis adj2 rheumat\$).tw.
3 (felty\$ adj2 syndrome).tw.
4 (caplan\$ adj2 syndrome).tw.
5 rheumatoid nodule.tw.
6 (sjogren\$ adj2 syndrome).tw.
7 still\$ disease.tw.
8 (spondylitis adj2 ankylosing).tw.
9 or/1-8
10 exp Immunoconjugates/tu
11 exp Antigens, Differentiation/tu
12 abatacept.tw.
13 abatacept.rn.
14 orencia.tw.
15 ctla4Ig.tw.
16 CTLA-4Ig.tw.
17 CTLA4-Ig.tw.
18 or/10-17
19 clinical trial.pt.
20 randomized.ab.
21 placebo.ab.
22 dt.fs.
23 clinical trials/
24 randomly.ab.
25 trial.ti.
26 groups.ab.
27 or/19-26
28 animals/
29 humans/
30 28 and 29
31 28 not 30
32 27 not 30
33 9 and 18 and 32

Appendix 2. EMBASE search strategy

1 exp arthritis, rheumatoid/
2 (arthritis adj2 rheumat\$).tw.
3 (felty\$ adj2 syndrome).tw.
4 (caplan\$ adj2 syndrome).tw.
5 rheumatoid nodule.tw.
6 (sjogren\$ adj2 syndrome).tw.
7 still\$ disease.tw.
8 (spondylitis adj2 ankylosing).tw.
9 or/1-8
10 abatacept.tw.
11 exp abatacept/
12 orencia.tw.

13 ctla4Ig.tw.
14 CTLA-4IG.tw.
15 CTLA4-Ig.tw.
16 CTLA-4-Ig.tw.
17 or/10-16
18 random\$.ti,ab.
19 factorial\$.ti,ab.
20 (crossover\$ or cross over\$ or cross-over\$).ti,ab.
21 placebo\$.ti,ab.
22 (doubl\$ adj blind\$).ti,ab.
23 (singl\$ adj blind\$).ti,ab.
24 assign\$.ti,ab.
25 allocat\$.ti,ab.
26 volunteer\$.ti,ab.
27 crossover procedure.sh.
28 double blind procedure.sh.
29 randomized controlled trial.sh.
30 single blind procedure.sh.
31 or/18-30
32 exp animal/ or nonhuman/ or exp animal experiment/
33 exp human/
34 32 and 33
35 32 not 34
36 31 or 35
37 9 and 17 and 36

Appendix 3. Cochrane Library search strategy

Cochrane Library: CENTRAL, DARE, HTA
#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
#6still* next disease in All Fields in all products
#7arthritis near/2 rheumat* in All Fields in all products
#8spondylitis near/2 ankylosing
#9(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10abatacept
#11orencia
#12ctla4Ig
#13CTLA-4IG
#14CTLA4-Ig
#15(#10 OR #11 OR #12 OR #13 OR #14)
#16(#9 AND #15)

Appendix 4. ACP Journal Club search strategy

Keyword search: CTLA4-Ig OR abatacept OR orenicia OR ctla4Ig OR CTLA-4IG

Appendix 5. Biosys Previews search strategy

#7 AND #1

#6 OR #5 OR #4 OR #2

#6TI=CTLA-4Ig

#5TI=CTLA4-Ig

#4TI=CTLA4Ig

#3TI=Orenicia

#2TI=abatacept

#1DS=rheumatoid arthritis

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes; Database=BIOSIS Previews; Timespan=1990-2007

WHAT'S NEW

Last assessed as up-to-date: 13 May 2008.

14 May 2008	Amended	CMMSG ID C103-P
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HISTORY

Protocol first published: Issue 3, 2008

CONTRIBUTIONS OF AUTHORS

LM wrote the first draft of the protocol; JS provided comments and suggestions on other drafts.

DECLARATIONS OF INTEREST

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Internal sources

- University of Ottawa, Canada.

External sources

- No sources of support supplied