

Abatacept for Rheumatoid Arthritis: A Cochrane Systematic Review

LARA J. MAXWELL and JASVINDER A. SINGH

ABSTRACT. Objective. To perform a systematic review of efficacy and safety of abatacept in patients with rheumatoid arthritis (RA).

Methods. We searched the Cochrane Library, MEDLINE, EMBASE, ACP Journal Club, and Biosis Previews for randomized controlled trials (RCT) comparing abatacept alone or in combination with disease modifying antirheumatic drugs (DMARD)/biologics to placebo or other DMARD/biologics in patients with RA. Two reviewers independently assessed search results, risk of bias, and extracted data.

Results. Seven trials with 2908 patients were included. Compared with placebo, patients with RA treated with abatacept were 2.2 times more likely to achieve an American College of Rheumatology 50% response (ACR50) at one year (relative risk 2.21, 95% CI 1.73, 2.82) with a 21% (95% CI 16%, 27%) absolute risk difference between groups. The number needed to treat to achieve an ACR50 response was 5 (95% CI 4, 7). Significantly greater improvements in physical function, disease activity, pain, and radiographic progression were noted in abatacept-treated patients compared to placebo. Total adverse events (AE) were greater in the abatacept group (RR 1.05, 95% CI 1.01, 1.08). Other harm outcomes were not significant, with the exception of serious infections at 12 months, which were more common in the abatacept group versus control group (Peto odds ratio 1.91, 95% CI 1.07, 3.42). Serious AE were more numerous in the abatacept + etanercept group versus the placebo + etanercept group (RR 2.30, 95% CI 1.15, 4.62).

Conclusion. Abatacept seems to be efficacious and safe in the treatment of RA. Abatacept should not be used in combination with other biologics to treat RA. Further longterm studies and postmarketing surveillance are required to assess for longer-term harms and sustained efficacy. (First Release Jan 15 2010; J Rheumatol 2010;37:234–45; doi:10.3899/jrheum.091066)

Key Indexing Terms:

ABATACEPT

RHEUMATOID ARTHRITIS

COCHRANE REVIEW

From the Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada; and Rheumatology Section, Veterans Affairs Medical Center, Division of Rheumatology, Department of Medicine, University of Minnesota, Minneapolis, and Department of Health Sciences and Orthopaedic Surgery, Mayo Clinic School of Medicine, Rochester, Minnesota, USA.

Supported by NIH CTSA Award 1 KL2 RR024151-01 (Mayo Clinic Center for Clinical and Translational Research).

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the Cochrane Collaboration. None of the authors has any financial interest, direct or indirect (dual commitment), that might affect, or be perceived to affect, the conduct or reporting of the work submitted herewith.

This report is based on a Cochrane review published in The Cochrane Library 2009, Issue 4 (see www.thecochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

L.J. Maxwell, BSc, Institute of Population Health, University of Ottawa; J.A. Singh, MD, Rheumatology Section, Veterans Affairs Medical Center, Division of Rheumatology, Department of Medicine, University of Minnesota; Department of Health Sciences and Orthopaedic Surgery, Mayo Clinic School of Medicine.

Address correspondence to L. Maxwell, University of Ottawa, Institute of Population Health, 1 Stewart Street, Ottawa, Ontario K1N 6N5.

E-mail: lmaxwell@uottawa.ca

Accepted for publication September 25, 2009.

Abatacept was approved by the US Food and Drug Administration (FDA) in December 2005 for treatment of moderate to severe rheumatoid arthritis (RA) in adult patients who have not responded adequately either to oral disease-modifying antirheumatic drugs (DMARD; such as methotrexate) or to the tumor-necrosis factor- α (TNF- α) antagonists¹. It is the first biologic therapy to selectively modulate costimulation, inhibiting T cell (T lymphocyte) activation by binding to CD80 and CD86 (the costimulatory antigens), thereby blocking interaction with CD28 (the costimulatory receptor)². Use of abatacept is associated with reduction in joint inflammation, pain, and joint damage in patients with active RA.

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 roughly US \$22,000³ and Canadian \$18,480⁴. The aim of this systematic review was to examine the data from randomized controlled trials (RCT) of abatacept to quantify its benefits and potential harms.

MATERIALS AND METHODS

Types of studies, participants, and interventions. We included RCT of 3

months or longer duration comparing abatacept alone or in combination with DMARD or biologics to placebo or other DMARD or biologics in adults meeting the American College of Rheumatology (ACR) 1987 revised criteria for RA⁵. Data from published and unpublished RCT were considered for inclusion with no restrictions by duration of intervention or the dose used.

Outcome measures. The co-primary outcomes were efficacy as assessed by 50% improvement in American College of Rheumatology criteria (ACR50)⁶ and safety. An ACR20/50/70 response is defined as a 20%/50%/70% improvement in tender and swollen joint counts and the same level of improvement in 3 of the 5 following variables: patient and physician global assessments, pain, patient assessment of functional ability [using the Stanford Health Assessment Questionnaire (HAQ) or other measures], and acute-phase reactants [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)]⁶. We assessed safety by comparing the number of total and serious adverse events; specific adverse events, including allergic reactions, infections, serious infections, lymphoma; and withdrawals due to adverse events and all withdrawals. Regulatory agency websites were also reviewed for potential longer-term adverse events.

Secondary outcome measures included the following: (1) ACR20 and ACR70 response criteria and individual ACR criteria (as outlined above)⁶; (2) radiographic progression (measured by the Sharp, modified Sharp, or Larsen scores)^{7,8}; (3) Disease Activity Score (DAS; scale 0–10)⁹, a composite index including tender and swollen joint counts, patient's global assessment of disease activity, and ESR, or DAS28; (4) European League Against Rheumatism (EULAR) response criteria^{10,11}; (5) physical function as measured by changes in HAQ or modified HAQ^{12,13} scores, proportion achieving “minimal clinical important change” (MCID), defined as ≥ 0.22 ¹⁴ or ≤ 0.30 ⁶; (6) health-related quality of life (HRQOL) measured by Medical Outcomes Study Short-Form 36 (SF-36) physical and mental HRQOL^{15,16}.

Search methods for identification of studies and additional data. A trained Cochrane librarian searched the following electronic databases up to March 2007 and updated the search December 31, 2008: MEDLINE, EMBASE, ACP Journal Club, ISI Web of Science (Biosis Previews for ACR and EULAR abstracts) and The Cochrane Library, Issue 1 [including the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessments (HTA)]. The reference lists of identified clinical trials and reviews were also searched. For missing information, clarifications, and additional unpublished data, we contacted the authors of included studies and the manufacturer of abatacept. The original search strategy was not limited by language, year of publication, or type of publication.

For safety assessment, we searched the websites of the regulatory agencies (US Food and Drug Administration, European Medicines Evaluation Agency, Australian Adverse Drug Reactions Bulletin, and UK pharmacovigilance and drug safety updates) using the terms “rheumatoid arthritis,” “abatacept,” and “orencia” on April 1, 2009.

Data collection and analysis. Analyses were determined a priori and published as a Cochrane Library protocol^{16a}. Two reviewers independently assessed search results (LM, JS) and disagreement was resolved by consensus. Data from the included trials was independently extracted by 2 reviewers (LM, JS) and entered into Review Manager 5.0 (RevMan 5.0)¹⁷. For missing variance measures for continuous outcomes, we obtained additional data from the authors and Bristol-Myers Squibb.

Using a structured data extraction form, we obtained study characteristics, study population characteristics, intervention characteristics, outcome measures, and results for the intention-to-treat (ITT) population (if reported).

Assessment of methodological quality. The risk of bias of the included studies was assessed by 2 independent reviewers (LM, JS), as recommended by the Cochrane Handbook¹⁸, examining the domains of randomization sequence generation, allocation sequence concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data (prima-

ry outcome data reporting, dropout rates and reasons for withdrawal, appropriate imputation of missing data, an overall completion rate $\geq 80\%$), and selective outcome reporting and other potential threats to validity (considering external validity, e.g., relevant use of cointerventions, bias due to funding source). Each criterion was explicitly judged as follows: Yes = low risk of bias; No = high risk of bias; Unclear = either lack of information or uncertainty about potential for bias.

Statistical analysis. For the main analyses, we compared abatacept (10 mg/kg and 2 mg/kg combined) + DMARD or biologics versus placebo + DMARD or biologics.

When data were sufficiently homogeneous, both clinically and statistically, we performed a metaanalysis. We calculated the mean difference (MD) or standardized mean difference (SMD) for the continuous outcomes, depending on similarity of scales measuring an outcome. For the dichotomous data, we calculated the relative risk (RR), or in the case of rare events ($< 10\%$; i.e., death), Peto odds ratio (Peto OR) was used.

Heterogeneity of data was assessed by 3 methods: (1) visually by examining the forest plots; and formally tested using (2) the chi-square, with a *p* value < 0.10 indicating significant heterogeneity, and (3) the *I*² statistic¹⁹, with values $> 50\%$ indicating substantial heterogeneity. When substantial heterogeneity was detected, we explored the data further by performing subgroup analyses, in an attempt to explain the heterogeneity.

We used a fixed-effects model (specified a priori), since abatacept is a new biologic and we expected that RCT would have been performed in similar populations with little “between-study” variation. In cases where significant heterogeneity was found and could not be explained, a random-effects model was used. We assessed the possibility of publication bias using a funnel plot.

We assessed results separately by dose, disease duration, and prior DMARD failure planned a priori. In response to concerns found in an RCT of abatacept in combination with etanercept²⁰, we undertook a post-hoc analysis to assess the effect of harms in patients on a background therapy of biologic treatment.

We performed the following sensitivity analyses (specified a priori) in order to explore effect size differences and the robustness of conclusions: (1) effect of study quality, defined as adequate allocation concealment and outcome assessor blinding; and (2) effect of imputation of missing data or statistical transformations. We calculated the number needed to treat (NNT) from the control group event rate, and the relative risk was calculated using the Visual Rx NNT calculator²¹. For continuous outcomes, the NNT was calculated using the Wells calculator software available at the Cochrane Musculoskeletal Group editorial office.

RESULTS

Figure 1 shows a diagram of the search results. Twelve articles corresponding to the following 7 clinical trials met the inclusion criteria: Genovese 2005²²; Kremer 2003²³; Kremer 2006²⁴; Moreland 2002²⁵; Weinblatt 2006²⁶; Weinblatt 2007²⁰; and Schiff 2008²⁷. The remaining 5 publications reported additional outcomes from the main trials: Kremer 2005^{27a}, Emery 2006²⁸, Russell 2007²⁹, Westhovens 2006³⁰, and Cole 2008³¹. All trials except Moreland 2002²⁵ and Schiff 2008²⁷ reported a randomization ratio of 2:1 for treatment to control. Moreland 2002²⁵ had 6 treatment arms and one placebo. Schiff 2008²⁷ had 2 treatment arms (abatacept or infliximab) and one placebo (randomized 3:3:2 to abatacept, infliximab, and placebo).

The study characteristics are presented in Table 1. A summary of findings (Table 2) shows key outcomes. The results of the search of pharmacovigilance websites is summarized in Table 3.

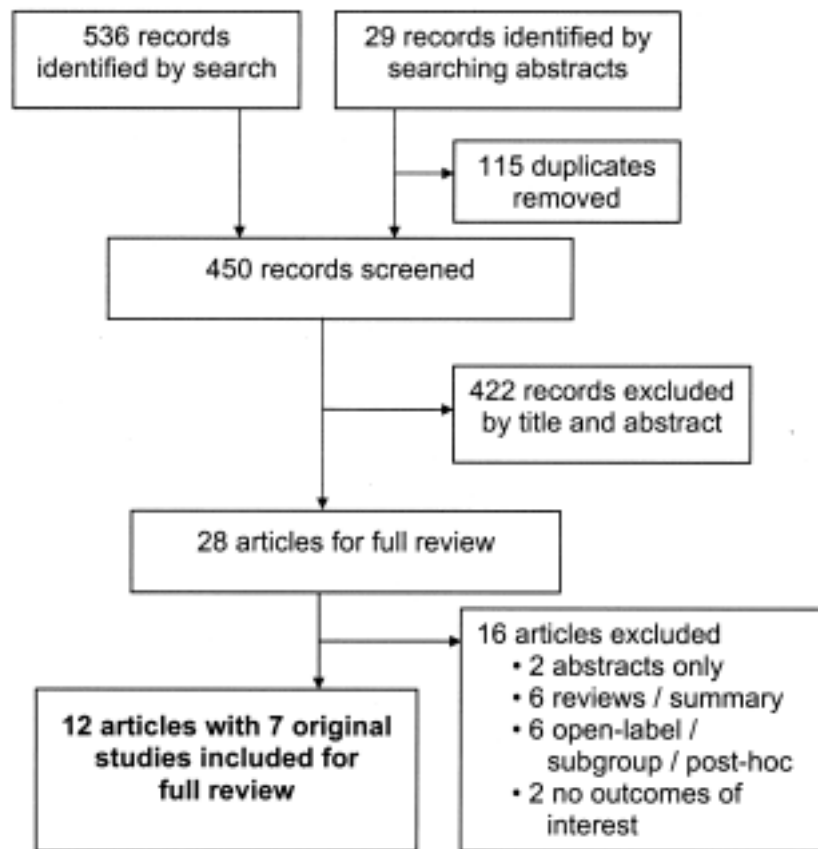


Figure 1. Selection of studies for this systematic review.

Seven trials with 2908 patients were included in this analysis. Most were multicenter, international RCT. Altogether 1863 patients were randomized to abatacept and 1045 to placebo. The majority of patients were White women with mean age in mid-50s (range 48.3–55.8 yrs in the control group) with active RA despite treatment with DMARD^{23,24,27}, anti-TNF therapy^{20,22}, or DMARD or biologics^{25,26}. The average RA disease duration was between 8 and 13 years, except in one study where it was only 3.4 years²⁵.

Abatacept was administered intravenously in all trials. Most trials used a dosage of abatacept of 10 mg/kg + DMARD with 3 exceptions: in Moreland 2002²⁵, 2 mg/kg dose was also used and no concurrent DMARD use was allowed; in Weinblatt 2007²⁰, only 2 mg/kg dose was used and patients also received etanercept; and in Kremer 2003²³, 2 doses were used (2 and 10 mg/kg). Schiff 2008²⁷ had 2 treatment arms (abatacept or infliximab) and one placebo arm. Trial duration ranged from 85 days to 12 months. All trials were sponsored by Bristol-Myers Squibb, the manufacturer of abatacept.

The risk of bias for each included study is summarized in Figure 2 (additional details available from the author upon request). For the primary outcome ACR50 response, the studies included in the metaanalysis rate well in terms of

adequate allocation concealment, blinding, and reporting of appropriate outcomes. However, there is a concern of bias in terms of incomplete outcome data given the high dropout rate in 2 studies^{20,23}, and that 2 studies excluded participants from efficacy analyses, but included them in safety analyses^{24,26}. All studies were sponsored by the manufacturer of abatacept and it is known that industry-sponsored trials may overestimate the treatment effect³².

Primary outcomes. Abatacept was associated with significantly higher likelihood of achieving ACR50 compared to placebo at 6 and 12 months, but not at 3 months (only one study) with RR of 2.47 (95% CI 2.00, 3.07), 2.21 (95% CI 1.73, 2.82), and 2.50 (95% CI 0.52, 11.96), respectively (Figure 3). The moderate heterogeneity for 6-month results ($I^2 = 44\%$, $p = 0.13$) decreased when analyses were performed by excluding the Weinblatt 2007 trial²⁰, which was the only trial to use abatacept 2 mg/kg in combination with etanercept and not statistically significant; however, the pooled RR changed minimally, to 2.59 (95% CI 2.07, 3.25). For the ACR50 response, there was an absolute difference of 21% (95% CI 16%, 27%; Table 2). The NNT to achieve an ACR50 response at 1 year was 5 (95% CI 4 to 7).

We found that the total number of adverse events was significantly greater in the abatacept group compared to placebo but the relative risk was low (RR 1.05, 95% CI 1.01,

Table 1. Details of studies.

Study*	Duration	Prior Therapy Failed	Intervention and Comparator Groups	Abatacept Group Characteristics	Comparator Group Characteristics	Outcomes
Genovese ²² ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders)	6 mo	Inadequate response to anti-TNF therapy with etanercept, infliximab, or both at the approved dose after at least 3 mo of treatment	Abatacept 10 mg per kg + DMARD or placebo + DMARD in 2:1 ratio	N = 258; mean age 53.4 (SD 12.4) yrs; females 77.1%; duration of RA mean 12.2 (SD 8.5) yrs	N = 133; mean age 52.7 (SD 11.3) yrs; females 79.7%; duration of RA mean 11.4 (SD 8.9) yrs	Two primary: ACR20 response and proportion of patients with an improvement of at least 0.3 from baseline in HAQ (exceeding MCID of 0.22) at 6 mo Secondary: ACR50 and ACR70 at 6 mo; DAS28; HRQOL (SF-36); adverse events
Kremer 2003 ²³	6 mo	Inadequate response to MTX for 6 mo	Abatacept 2 mg/kg + MTX or abatacept 10 mg/kg + MTX or placebo + MTX in 2:1 ratio	N = 220 (for both doses); mean age 54.7 yrs (range 23–80); females 66%; duration of RA mean 8.9 (SD 8.3) yrs	N = 119; mean age 55.8 yrs (range 17–83); females 75.0%; duration of RA mean 9.7 (SD 9.8) yrs	Primary: ACR20 response at 6 mo Secondary: ACR50 and ACR70; HRQOL (SF-36); adverse events
Kremer 2006 ²⁴ AIM (Abatacept in Inadequate Responders to Methotrexate)	12 mo	Inadequate response to MTX for 3 mo	Abatacept 10 mg/kg + MTX or placebo + MTX in 2:1 ratio	N = 433; mean age 51.5 (SD 12.9) yrs; females 77.8%; duration of RA mean 8.5 (SD 7.3) yrs	N = 219; mean age 50.4 (SD 12.4) yrs; females 81.7%; duration of RA mean 8.9 (SD 7.1) yrs	Three primary: ACR20 response at 6 mo; proportion of patients in each group with clinically significant improvement (≥ 0.3 unit) in HAQ-DI score at 1 yr; and radiographic progression of joint erosions (assessed by comparing changes from baseline in the Genant-modified Sharp score) at 1 yr Secondary: ACR50 and ACR70 at 6 mo and all ACR responses at 1 yr; DAS28; HAQ-DI; HRQOL (SF-36); adverse events
Moreland ²⁵	85 days	Inadequate response to at least 1 DMARD or etanercept	Abatacept at 0.5 mg/kg, 2 mg/kg, or 10 mg/kg; LEA29Y at 0.5 mg/kg, 2 mg/kg, or 10 mg/kg; or placebo	N = 214; mean age 51.5 (SD 11.5) yrs; females 69%; duration of RA mean 3.4 (SD 2.1) yrs	N = 32; mean age 48.3 (SD 11.7) yrs; females 81%; duration of RA mean 3.2 (SD 2.0) yrs	Primary: ACR20 on day 85 Secondary: ACR50/70 core set measures; adverse events
Schiff ²⁷ ATTEST (Abatacept or infliximab vs placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis)	12 mo	Inadequate response to MTX	Abatacept 10 mg/kg + MTX or infliximab 3 mg/kg + MTX or placebo + MTX in a 3:3:2 ratio	N = 156; mean age 49 (SD 12.5) yrs; females 83.3%; duration of RA mean 7.9 (SD 8.6) yrs	N = 110; mean age 49.4 (SD 11.5) yrs; females 87.3%; duration of RA mean 8.4 (SD 8.6) yrs	Primary outcome: DAS28 (ESR) Secondary: EULAR criteria were used to assess good responses ACR20, 50, and 70; physical function (HAQ-DI); HRQOL (SF-36); adverse events

Table 1. Details of studies continued.

Study*	Duration	Prior Therapy Failed	Intervention and Comparator Groups	Abatacept Group Characteristics	Comparator Group Characteristics	Outcomes
Weinblatt 2006 ²⁰ ASSURE (Abatacept Study of Safety in Use with Other RA Therapies)	12 mo	Inadequate response to DMARD or biologics for 3 mo	Abatacept 10 mg/kg or placebo. Patients continued to receive background RA therapies (biologic DMARD, nonbiologic DMARD, or a combination)	N = 959. All participants overall: mean age 52.3 (SD 11.8) yrs; duration of RA mean 9.7 (SD 8.9) yrs	N = 482	Primary: occurrence of AE, SAE, discontinuations due to AE, death, clinically significant changes. Secondary: HAQ Disability Index; patient's global assessment of disease activity, patient's global assessment of pain, and physician's global assessment of disease activity on 100 mm VAS
Weinblatt 2007 ²⁶	6 mo	Etanercept 25 mg twice weekly for > 3 mo	Abatacept (2 mg/kg) + etanercept (25 mg twice weekly) or placebo + etanercept (25 mg twice weekly)	N = 85, mean age 49.8 (SD 23.7) yrs; females 78%; duration of RA mean 13 (SD 10) yrs	N = 36, mean age 54.3 (SD 28.7) yrs; females 72%; duration of RA mean 12.8 (SD 8.6) yrs	Primary: modified ACR20, defined as > 20% improvement in tender joints and swollen joints and > 20% improvement in 2 of the remaining 4 core measures (pain, physical function, modified HAQ, and patient and physician global assessments. CRP values were excluded from the definition) Secondary: modified ACR50/70, standard ACR20/50/70, and improvements in individual ACR criteria components

* All studies were randomized, double-blind, phase III multicenter trials; except Moreland 2002 was phase II. MTX: methotrexate; DMARD: disease modifying anti-rheumatic drug; CRP: C-reactive protein; HRQOL: health-related quality of life; AE: adverse event; SAE: serious adverse event.

1.08; Figure 4A). We noted a greater number of serious infections at 12 months in the abatacept-treated group (Peto OR 1.91, 95% CI 1.07, 3.42; Figure 4B). This analysis included the Weinblatt 2007 trial²⁰ in which abatacept was given in combination with etanercept. Removing this study resulted in a lower OR, which was just statistically significant (Peto OR 1.82, 95% CI 1.00, 3.32). Total withdrawals favored the abatacept-treated group (RR 0.60, 95% CI 0.52, 0.70). Numbers of total serious adverse events, withdrawals due to adverse events, serious infections, upper respiratory infections, cough, nausea, malignancies, and mortality were not statistically significantly different between the treatment and control groups, based on pooled results at 6 and 12 months. There was a higher number of headaches and infusion reactions reported in the abatacept group (details available from the author upon request). We undertook a post hoc analysis to assess the effect of harms in patients on a background therapy of biologic treatment (for both 2 mg and 10 mg/kg doses) compared to placebo. The RR of total serious

adverse events in the abatacept group was statistically significantly greater than that in the placebo group, 2.30 (95% CI 1.15, 4.62), as well as withdrawals due to adverse events (Peto OR 2.68, 95% CI 1.07, 6.72).

Table 3 summarizes the safety warnings from regulatory agencies.

Secondary outcomes. Significantly more abatacept-treated patients compared to control group achieved an ACR20 response at 6 and 12 months, but not at 3 months (1 study) with RR of 1.79 (95% CI 1.59, 2.02), 1.79 (95% CI 1.55, 2.07), and 1.70 (95% CI 0.93, 3.12), respectively. A significantly greater proportion achieved an ACR70 response compared to placebo at 6 and 12 months, but not at 3 months, with RR 3.53 (95% CI 2.41, 5.16), 4.02 (95% CI 2.62, 6.18), and 5.00 (95% CI 0.25, 100.2), respectively.

Only one RCT reported radiographic results using the Genant-modified Sharp score²⁴ and it found that compared to placebo, abatacept statistically significantly reduced the progression of joint damage after 12 months, although the

Table 2. Summary of findings: comparison of abatacept (2 and 10 mg/kg) + DMARD/biologic versus placebo + DMARD/biologic for RA.

Outcomes	Illustrative Assumed Risk Placebo + DMARD/Biologic	Comparative Risks* (95% CI) Corresponding Risk Abatacept (2 and 10 mg/kg) + DMARD/Biologic	Relative Effect (95% CI)	No. of Participants (No. Studies)	Quality of Evidence (grade [†])	Comments (95% CI)
ACR 50% improvement Followup 12 mo	168 per 1000	371 per 1000 (291 to 474)	RR 2.21 (1.73 to 2.82)	993 (3)	+++— moderate ^{1,2,3}	Absolute risk difference 21% (16% to 27%). Relative change = 121% (73% to 182%). NNT = 5 (4 to 7) ⁴
Pain: measured at end of study on a 100 mm VAS from 0 (better) to 100 (worse) Followup 12 mo	Mean pain in control groups = 49.24 mm	Mean pain in intervention groups = 10.71 lower (12.97 to 8.45 lower)		1425 (1 ⁵)	+++— moderate ²	Absolute risk difference –11% (–13% to –8.5%). Relative change = –18% (–22% to –14%). NNT = 5 (4 to 6) ⁴
Improvement in physical function (HAQ: > 0.3 increase from baseline, 0–3 scale) Followup 12 mo	393 per 1000	637 per 1000 (531 to 766)	RR 1.62 (1.35 to 1.95)	638 (1 ⁶)	+++— moderate ¹	Absolute risk difference 24% (16% to 32%). Relative change = 62% (35% to 95%). NNT = 5 (4 to 7) ⁴
Achievement of low disease activity state (DAS 28 < 3.2, scale 1–10) Followup 12 mo	98 per 1000	424 per 1000 (278 to 646)	RR 4.33 (2.84 to 6.59)	638 (1 ⁶)	+++— moderate ¹	
Total serious adverse events Followup 6 to 12 mo	121 per 1000	127 per 1000 (105 to 155)	RR 1.05 (0.87 to 1.28)	3151 (6)	+++— moderate ^{1,2,3,7}	Absolute risk difference 1% (–2% to 3%). Relative change = 5% (–14% to 29%). NNT = NA ⁴
Change in radiographic progression: measured by Genant-modified Sharp erosion score (increase in score means more joint damage). Scale 0 to 145 Followup 12 mo	Median change in radiographic progression in control group = 0.27 units	Median change in radiographic progression in intervention group = 0 units		586 (1 study ⁶)	+++— moderate ^{1,8}	Note there was no change in the abatacept group. MD –0.27 (–0.42, –0.12). Absolute risk difference = –0.2% (–0.3% to –0.08%). Relative change = –1.2% (–1.9% to –0.6%)
Longterm serious adverse events Followup 2 yrs	See comment	See comment	Not estimable	950 (2 ⁹)	++— low ¹⁰	No. of patients with SAE: Genovese 2005 ²² : 103/357; 23.4 SAE/100 patient-yrs; 70% completed the LTE. Kremer 2006 ²⁴ : 149/593; 16.3 SAE/100 patient-yrs; 90.5% completed the LTE

* The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention. [†] Working Group grades of evidence as follows. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.¹ Kremer2006²⁴: Intention-to-treat analysis not performed. 9 patients in abatacept group and 5 in placebo group excluded from analysis. ² Weinblatt 2007²⁰: 15 people randomized were not treated and not included in analysis. ³ Kremer 2003²³: Risk of attrition bias; less than 80% completion rate in treatment group at 12 months. ⁴ Number needed to treat (NNT) = not available (NA) when result is not statistically significant. NNT for dichotomous outcomes calculated using Cates' NNT calculator²¹. NNT for continuous outcomes calculated using the Wells calculator (Cochrane Musculoskeletal Group editorial office). ⁵ Outcome based on Weinblatt 2007²⁰. ⁶ Outcome based on Kremer 2006²⁴. ⁷ Weinblatt 2006²⁶; risk of attrition bias: less than 80% completion rate in the treatment group at 12 months. ⁸ Radiographic data obtained for 90% of study participants. ⁹ Based on 2 longterm extension studies (LTE) of RCT. Participants on placebo in the RCT switched to abatacept treatment. ¹⁰ Longterm serious adverse events based on observational data. Two RCT had a LTE phase in which people in the placebo group during the RCT switched to abatacept for the LTE. RR: Risk ratio; RCT: randomized controlled trial.

progression was minimal in both groups. It reported a 50% reduction in change from baseline values in the abatacept

group compared to placebo at 12 months. With respect to median change from baseline, there was no change in the

Table 3. Safety warnings from regulatory agencies in a Web search up to April 1, 2009.

Regulatory Agency/Source	No. of Items Found	Summary of Warnings and Conclusions
US Food and Drug Administration ³⁸	70	The abatacept label information highlighted the increase in serious infections, lymphoma, and lung cancer in patients taking abatacept compared to placebo. Label also included warning about using abatacept concurrently with anti-TNF therapy. No significant benefit in terms of efficacy was found with concurrent therapy and the concerns about an increase in infections and serious infections warranted a warning that abatacept should not be administered to patients on concurrent anti-TNF therapy
European Medicines Agency ³⁹	22	The European Public Assessment Report's Scientific Discussion report ³⁹ highlighted signals of a possible increased risk for infection and autoimmune disorders that will need to be further investigated as well as malignancies, given abatacept's mechanism of action. The report concluded that ongoing pharmacovigilance is needed to address concerns about "potential rare and unexpected severe adverse effects of abatacept"
Current Problems in Pharmacovigilance and Drug Safety Update, UK	0	—
Australian Adverse Drug Reactions Bulletin	0	—

	Adequate sequence generation?	Allocation concealment?	Blinding? (Patient assessed)	Blinding? (Physician assessed)	Incomplete outcome data addressed? (Efficacy outcomes)	Incomplete outcome data addressed? (Safety outcomes)	Free of selective reporting?	Free of other bias?
Genovese 2005	+	+	+	+	+	+	+	-
Kremer 2003	+	+	+	+	-	-	+	-
Kremer 2006	+	+	+	+	-	+	+	-
Moreland 2002	+	+	+	+	+	+	+	-
Schiff 2008	?	?	+	+	+	+	+	-
Weinblatt 2006	+	+	+	+	-	+	+	-
Weinblatt 2007	+	+	+	+	-	-	+	-

Figure 2. A summary of methodological quality for each study across 6 domains. "+": criteria were met; "-": criteria were not met; "?": unclear if criteria were met.

abatacept group and a 0.27 change in the placebo group for the erosion score. Due to missing variance, using an approximation, there was a statistically significant mean difference in favor of abatacept (mean difference -0.27, 95% CI -0.42, -0.12).

The ACR core components — patient global assessment, physician global assessment, physical function, tender joint count, and swollen joint count — were all statistically significant in favor of abatacept. Patient-reported pain was significantly reduced in the abatacept group compared to placebo²²⁻²⁶ (Table 2).

The abatacept group was significantly more likely to reach a low disease activity state (DAS28 < 3.2, scale 0–10) at 6 and 12 months, with RR of 3.36 (95% CI 2.28, 4.96) and 4.33 (95% CI 2.84, 6.59), respectively (Table 2). At 12 months, there was an absolute difference of 33% (95% CI 26%, 39%) in achievement of a low disease activity state (DAS28 < 3.2) between abatacept and placebo; the corresponding NNT was 4 (95% CI 3 to 5). Those in the abatacept group were significantly more likely to achieve disease remission (defined as DAS28 < 2.6) at 12 months, with RR 12.74 (95% CI 4.76, 34.15).

Clinically meaningful improvement in physical function on the HAQ (> 0.22 or > 0.3 increase from baseline; results similar regardless of the definition used) was noted in significantly more abatacept-treated than placebo patients at 6 and 12 months, with RR of 1.73 (95% CI 1.41, 2.13) and 1.62 (95% CI 1.35, 1.95), respectively (Table 2). The absolute risk difference of clinically meaningful improvement in HAQ (> 0.3) was 24% (95% CI 16%, 32%) at 12 months in favor of abatacept. The NNT to achieve a HAQ > 0.3 response at 1 year was 5 (95% CI 4 to 7).

A significantly greater proportion of patients in the abatacept group than in the placebo group reported "better" scores on the physical (PCS) and mental component summary (MCS) scores, with pooled RR of 1.90 (95% CI 1.52,

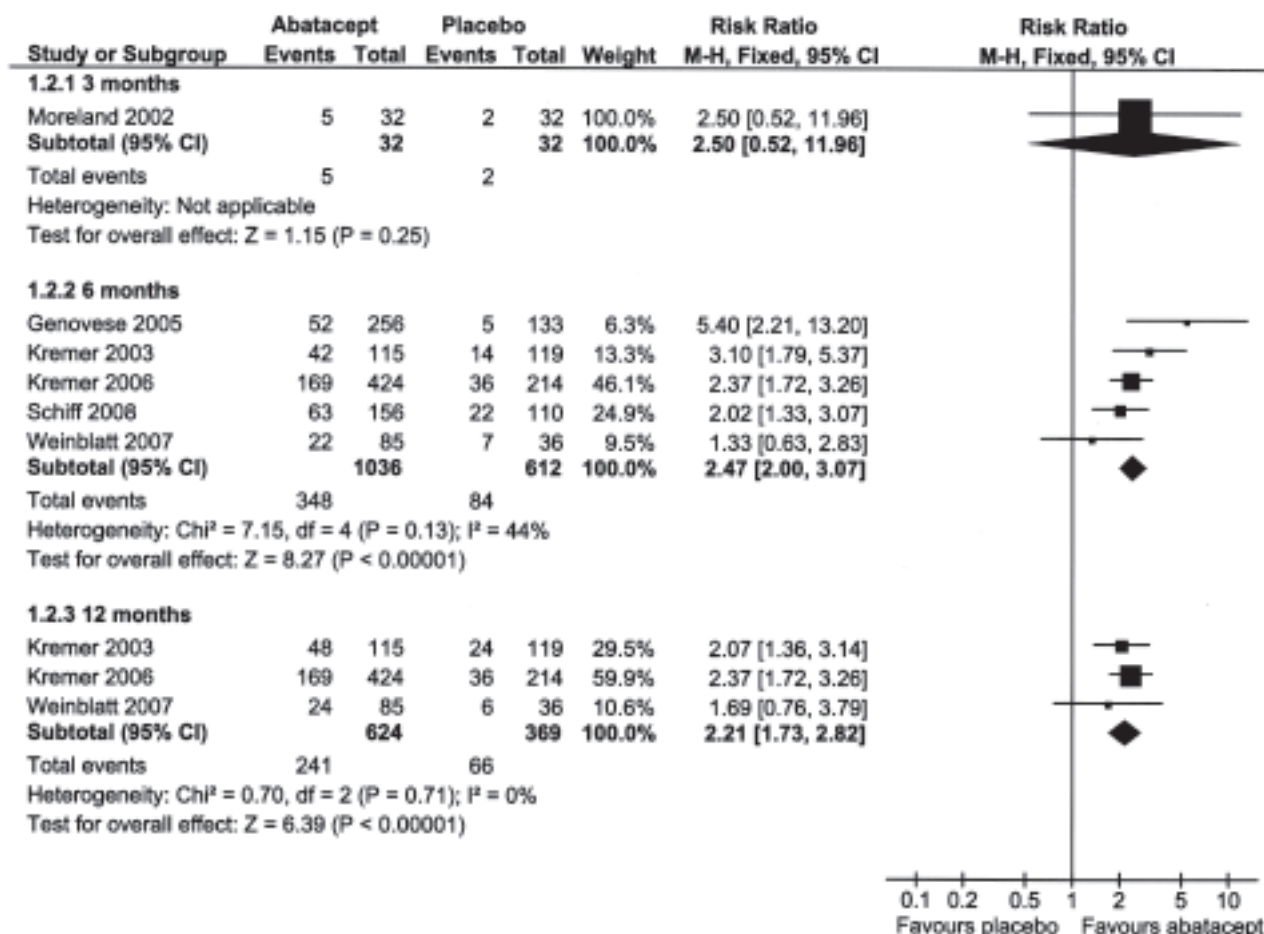


Figure 3. Metaanalysis of the risk of achieving an ACR50 response at 3, 6, and 12 months. There is low heterogeneity when the results from different studies are pooled. Abatacept has a statistically significantly better risk of achieving an ACR50 response than placebo (results favor abatacept).

2.39) and 1.42 (95% CI 1.15, 1.76), respectively. In the only study reporting this outcome, a significantly greater proportion of the abatacept-treated group compared to placebo achieved the SF-36 PCS population norms at 6 months, with RR 2.36 (95% CI 1.34, 4.14)²². On the continuous scale, the pooled mean difference in PCS and MCS scores was statistically significant in favor of abatacept at 4.29 (95% CI 3.22, 5.35) and 2.72 (95% CI 1.57, 3.87). [Other outcomes are available from the author upon request.]

Subgroup analyses. Eligibility criteria: Trials were grouped according to whether eligibility criteria for the trial required patients to be inadequate responders to methotrexate/DMARD^{23,24,27}, inadequate responders to anti-TNF- α drugs^{20,22}, or both^{25,26}. An ACR20/50/70 response was significant in the abatacept group compared to placebo in both inadequate responders to methotrexate and inadequate responders to biologic therapy. However, the pooled analysis of the ACR50 response in the biologic failure group had high heterogeneity, most likely due to the pooling of trials using different interventions (abatacept + DMARD²² compared to abatacept + etanercept²⁰).

Dose: There were no major changes to the relative risks once the 2 mg/kg dose was removed from the analysis of the combined dose. The 2 mg/kg dose was given in combination with etanercept and it was not statistically significant at any timepoint.

Disease duration: All studies except Moreland 2002²⁵ enrolled patients with a disease duration greater than 8 years. As Moreland 2002²⁵ was a pilot study that provided only 3-month data, this subgroup analysis was not undertaken.

Effect of study quality: All studies except Schiff 2008 (unclear allocation concealment)²⁷ reported adequate allocation concealment and blinding. Excluding Schiff 2008²⁷ from the ACR50 response at 6 months did not change the result significantly: with Schiff 2008, ACR50 RR 2.47 (95% CI 2.00, 3.07) and excluding Schiff 2008 ACR50, RR 2.62 (95% CI 2.05, 3.37).

Publication bias. Publication bias was assessed using a funnel plot of the ACR50 response at 6 months (details available from the author upon request). With inclusion of only 5 trials, there does not appear to be evidence of pub-

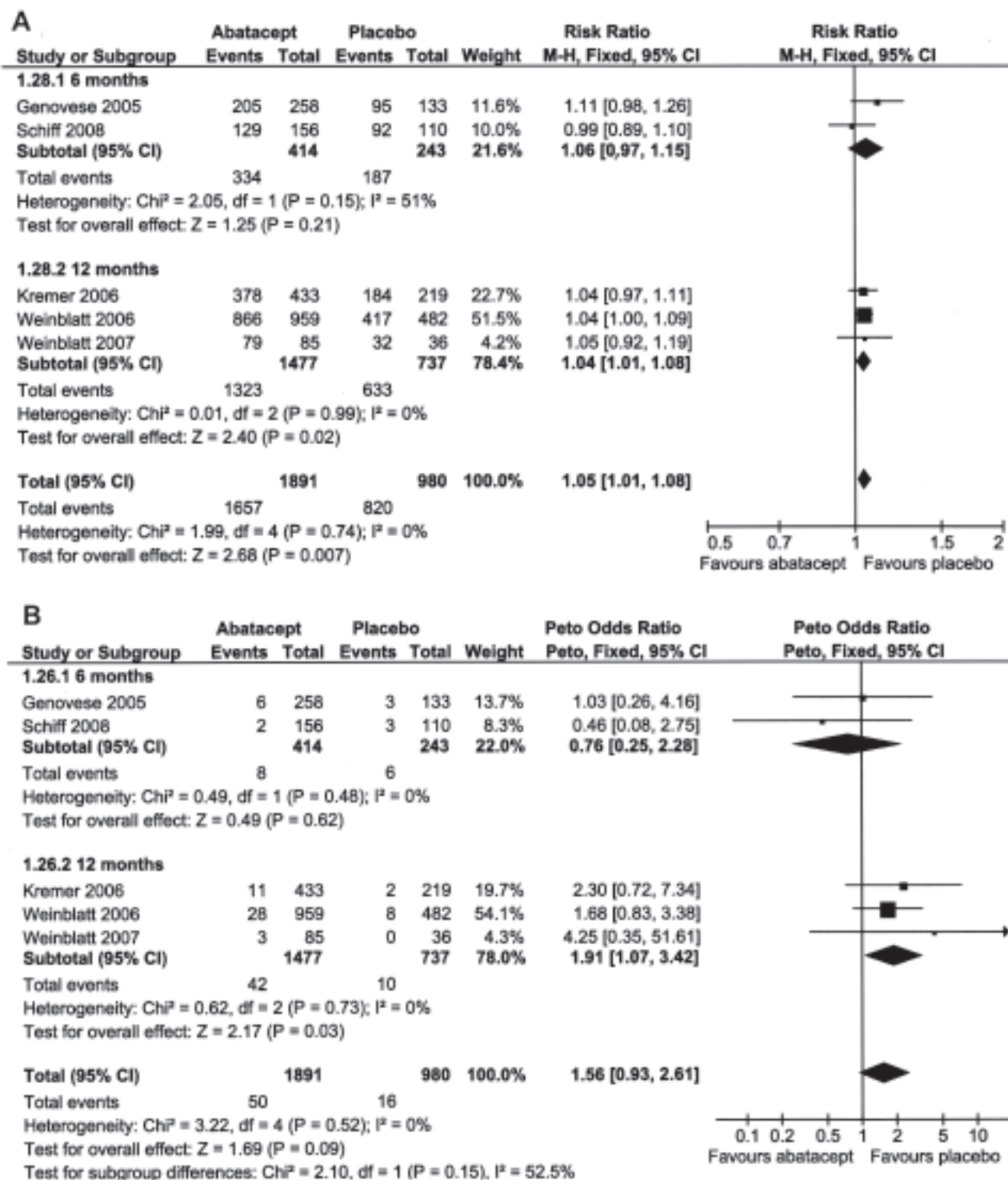


Figure 4. A. Metaanalysis of the risk of adverse events at 3 and 6 months and pooled for the 2 timepoints. There is low heterogeneity when the results from different studies are pooled. Abatacept has a statistically significantly higher risk of an adverse event than placebo (results favor placebo). B. Metaanalysis of the risk of serious infection at 3 and 6 months and pooled for the 2 timepoints. There is low heterogeneity when the results from different studies are pooled. Abatacept has a statistically significantly higher risk of serious infection than placebo (results favor placebo) at 12 months, but the pooled result is not significant.

lication bias in this review (Moreland 2002 did not provide 6-month data²⁵ and Weinblatt 2006²⁶ did not measure ACR50).

DISCUSSION

In this Cochrane systematic review of 7 RCT of abatacept including 2908 patients with RA (1863 treated with abata-

cept; 1045 treated with placebo), we examined the efficacy and short-term safety of abatacept alone or in combination with DMARD/biologics compared to placebo alone or in combination with DMARD/biologics. Abatacept was 1.7 to 4 times more efficacious than placebo in achieving an ACR20, ACR50, and ACR70 response at 12 months. In terms of the absolute risk difference between treated and control groups, the ACR50 at 12 months had a 21% absolute difference (95% CI 16% to 27%). The number needed to treat (NNT) in order to achieve an ACR50 response at one year was 5 (95% CI 4 to 7). This NNT is similar to NNT of 3.0 (95% CI 2.0 to 6.0) found in a systematic review of another biologic agent, adalimumab, an anti-TNF- α inhibitor, in patients with moderate to severe disease and failure to previous DMARD³³. Abatacept-treated patients were 3.4 to 4.3 times more likely to achieve a low disease activity state. One RCT²⁴ demonstrated that at 12 months abatacept statistically significantly slowed the progression of structural joint damage compared with placebo, although the clinical significance of this result is not known. The ACR20, ACR50, and ACR70 responses in the original abatacept group at one year were similar to those at 2 years: 81.9% and 80.3%; 54.0% and 55.6%; 32.4% and 34.3%, respectively³⁴. Radiographic progression, disease activity (measured by DAS28), physical function (measured by HAQ-Damage Index), and HRQOL (measured by SF-36) outcome responses were also maintained at 2 years³⁵. Thus, it appears that response to abatacept therapy is well maintained.

The efficacy must be balanced by assessment of safety. Numbers of adverse events and serious infections were significantly greater in the abatacept group compared to placebo group but the totals of serious adverse events, withdrawals due to adverse events, upper respiratory infections, malignancies, and mortality were not statistically significantly different. This may be due to small sample size^{36,37} and short followup duration. The FDA website highlighted the increase in serious infections, lymphoma, and lung cancer in patients taking abatacept compared to placebo³⁸, similar to the European Public Assessment Report's Scientific Discussion document on abatacept describing possible increased risk for infection and autoimmune disorders³⁹. The FDA label included a warning against using abatacept concurrently with anti-TNF therapy and the European Medicines Agency suggested that risk of malignancies needs further investigation (Table 3).

With the current evidence of its superiority to placebo, head-to-head comparator trials of abatacept with other DMARD/biologics, such as TNF inhibitors and others, may help us better understand its role in RA treatment⁴⁰. This information will also assist patients and physicians in making more informed choices.

Two recent reviews of abatacept described the outcomes from Phase II and III trials, but did not perform metaanalyses^{41,42}. In a recent metaanalysis of RCT to investigate the

risk of serious infections in use of rituximab, anakinra, and abatacept for RA, Salliot, *et al* reported no significant increase in risk of serious infection with the use of abatacept in 5 trials with a pooled Mantel-Haenszel OR of 1.35 (95% CI 0.78 to 2.32)⁴³. Similarly, we found no significant increase in serious infections with Peto OR of 1.56 (95% CI 0.93 to 2.61), when 6 and 12-month results were pooled. However, the pooled 12-month results of 3 trials did show statistically significantly higher odds of serious infections in the abatacept versus placebo-treated patients (Peto OR 1.91, 95% CI 1.07 to 3.42).

A subgroup analysis based on eligibility criteria of an inadequate response to DMARD therapy versus an inadequate response to anti-TNF therapy found that in both groups abatacept produced a statistically significant ACR50 response compared to placebo at 6 months. The group with an inadequate response to anti-TNF therapy had a slightly higher relative risk for an ACR50 response at 6 months than those with an inadequate response to DMARD therapy, but the difference between the 2 groups was not significant. Therefore, based on placebo-controlled trials of up to one year duration, it appears that abatacept is efficacious in improving signs and symptoms of patients with active, moderate to severe RA who have failed either DMARD or anti-TNF therapy.

Study strengths. For this review a systematic literature search was performed; 2 reviewers reviewed abstracts independently, extracted data independently, and resolved disagreements with consensus. We obtained additional information from the authors and Bristol-Myers Squibb, and specified analyses a priori in a published protocol^{16a}.

Study limitations. We were limited in our ability to perform metaanalysis due to lack of reporting of variance measures, to assess risk of bias due to missing details, and to uniformly analyze adverse events due to use of different systems (MedDRA version 7 versus version 8 versus a specified list) — all limitations of the included studies. Due to lack of RCT of abatacept in patients with early RA, its efficacy in early RA is unknown. Pooling the trials with 2 mg/kg and 10 mg/kg dosages of abatacept, which was done to increase the sample size, may have led to slight underestimation of adverse events than if we had included only data for the 10 mg/kg dosage. At best, RCT provide estimates of short-term safety; long-duration observational and postmarketing surveillance studies are needed for the assessment of intermediate to longterm safety to detect uncommon, rare adverse events. Methodological quality was good in general, with a few exceptions: < 80% completion rates in the treatment group in 2 studies^{20,23}, and only 3 out of 7 trials reported a proper intention-to-treat analysis.

We conclude that there is “moderate” level evidence for short-term efficacy of abatacept compared to placebo in improving disease activity and state, physical function, and HRQOL. Abatacept appears safe for short-term use. There is

no efficacy benefit of combining abatacept with an anti-TNF biologic, which leads to higher risks. Further trials/studies are needed to determine its longterm safety profile and to assess whether the level of efficacy found in the RCT included in our review is sustained over time.

REFERENCES

- Food and Drug Administration. Orenzia® (abatacept). Rockville, MD: U.S. Food and Drug Administration; 2005. [Internet. Accessed November 19, 2009.] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/1251181b1.pdf
- Teng GG, Turkiewicz AM, Moreland LW. Abatacept: a costimulatory inhibitor for treatment of rheumatoid arthritis. *Expert Opin Biol Ther* 2005;5:1245-54.
- American College of Rheumatology. ACR Hotline. Abatacept and rituximab. Atlanta: American College of Rheumatology; 2007. [Internet. Accessed November 19, 2009.] Available from: <http://www.rheumatology.org/publications/hotline/0506newdrugs.asp>
- Russell A, Beresniak A, Bessette L, Haraoui B, Rahman P, Thorne C, et al. Cost-effectiveness modeling of abatacept versus other biologic agents in DMARDS and anti-TNF inadequate responders for the management of moderate to severe rheumatoid arthritis. *Clin Rheumatol* 2009;28:403-12.
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
- Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727-35.
- Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol Diagn (Stockh)* 1977;18:481-91.
- Sharp JT, Lidsky MD, Collins LC, Moreland J. Methods of scoring the progression of radiologic changes in rheumatoid arthritis. Correlation of radiologic, clinical and laboratory abnormalities. *Arthritis Rheum* 1971;14:706-20.
- van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol* 1993;20:579-81.
- van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. *Arthritis Rheum* 1996;39:34-40.
- Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* 2005;23 Suppl 39:S93-9.
- Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.
- Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983;26:1346-53.
- Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. *J Rheumatol* 1993;20:557-60.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
- Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. *Qual Life Res* 2001;10:405-13; discussion 15-20.
- Maxwell L, Singh JA. Abatacept for rheumatoid arthritis (protocol). *Cochrane Database Syst Rev* 2008; issue 3.
- RevMan. Cochrane Information Management System (IMS); 2009. [Internet. Accessed November 19, 2009.] Available from: <http://www.cc-ims.net/revman>
- Higgins JP, Altman DG. Assessing risk of bias in included studies. In: Higgins JP, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 500 [updated February 2008]: The Cochrane Collaboration. [Internet. Accessed November 19, 2009.] Available from: <http://www.cochrane-handbook.org>
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- Weinblatt M, Schiff M, Goldman A, Kremer J, Luggen M, Li T, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. *Ann Rheum Dis* 2007;66:228-34.
- Cates C. Dr. Chris Cates' EBM Web Site. Visual Rx Version 3. [Internet. Accessed November 19, 2009.] Available from: <http://www.nntonline.net/visualrx>
- Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005;353:1114-23.
- Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003;349:1907-15.
- Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006;144:865-76.
- Moreland LW, Alten R, Van den Bosch F, Appelboom T, Leon M, Emery P, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. *Arthritis Rheum* 2002;46:1470-9.
- Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006;54:2807-16.
- Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008;67:1096-103.
- Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Shergy W, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve month results of a phase IIb, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:2263-71.
- Emery P, Kosinski M, Li T, Martin M, Williams GR, Becker JC, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. *J Rheumatol* 2006;33:681-9.
- Russell AS, Wallenstein GV, Li T, Martin MC, Maclean R, Blaisdell B, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis* 2007;66:189-94.
- Westhovens R, Cole JC, Li T, Martin M, Maclean R, Lin P, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to

- anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. *Rheumatology* 2006;45:1238-46.
31. Cole JC, Li T, Lin P, MacLean R, Wallenstein GV. Treatment impact on estimated medical expenditure and job loss likelihood in rheumatoid arthritis: re-examining quality of life outcomes from a randomized placebo-controlled clinical trial with abatacept. *Rheumatology* 2008;47:1044-50.
 32. Bhandari M, Busse JW, Jackowski D, Montori VM, Schunemann H, Sprague S, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *CMAJ* 2004;170:477-80.
 33. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. *Cochrane Database Syst Rev* 2005; CD005113.
 34. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum* 2008;58:953-63.
 35. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. *Ann Rheum Dis* 2008;67:547-54.
 36. Yazici Y. Some concerns about adverse event reporting in randomized clinical trials. *Bull NYU Hosp Jt Dis* 2008;66:143-5.
 37. Yazici Y, Adler NM, Yazici H. Most tumour necrosis factor inhibitor trials in rheumatology are undeservedly called 'efficacy and safety' trials: a survey of power considerations. *Rheumatology* 2008;47:1054-7.
 38. Food and Drug Administration. Orenzia label. FDA Center for Drug Evaluation and Research. [Internet. Accessed November 19, 2009.] Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#aphist
 39. European Medicines Agency. European Public Assessment Report. Orenzia Scientific Discussion document. [Internet. Accessed November 19, 2009.] Available from: <http://www.emea.europa.eu/humandocs/PDFs/EPAR/orenzia/H-701-en6.pdf>
 40. Boers M. Abatacept in rheumatoid arthritis: a new branch on the "biologics" tree. *Ann Intern Med* 2006;144:933-5.
 41. Massarotti EM. Clinical and patient-reported outcomes in clinical trials of abatacept in the treatment of rheumatoid arthritis. *Clin Ther* 2008;30:429-42.
 42. Buch MH, Vital EM, Emery P. Abatacept in the treatment of rheumatoid arthritis. *Arthritis Res Ther* 2008;10 Suppl 1:S5.
 43. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis* 2009;68:25-32.