Indirect Treatment Comparison of Abatacept with Methotrexate Versus Other Biologic Agents for Active Rheumatoid Arthritis Despite Methotrexate Therapy in the United Kingdom

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ABSTRACT. Objective. To compare the efficacy of abatacept and alternative biologic disease-modifying antirheumatic drugs (DMARD) in patients with rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX) in the United Kingdom.

Methods. A systematic literature search identified 11 individual studies investigating the efficacy of abatacept, infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab in adult patients with RA that did not respond to MTX. The clinical trials included in this analysis were similar in trial design, baseline patient characteristics, and background therapy (i.e., MTX). The key clinical endpoints of interest were the Health Assessment Questionnaire (HAQ) change from baseline (CFB) and the American College of Rheumatology (ACR) responses at 6 months (24–28 weeks). Results were analyzed using Bayesian network metaanalysis methods, and were expressed as differences in HAQ CFB and ACR20/50/70 relative risks, with 95% credible limits (CrL).

Results. Analysis of HAQ CFB at 6 months showed that abatacept is more efficacious than placebo [mean difference in HAQ CFB: –0.30 (95% CrL –0.42; –0.16)] and comparable to all other biologic agents, in patients receiving MTX as background treatment. Abatacept is also expected to result in a higher proportion of ACR responders compared to placebo, with relative risks ranging from 1.90 (95% CrL 1.24; 2.57) for ACR20 to 3.72 (95% CrL 1.50; 10.52) for ACR70, and to result in comparable proportions of ACR responders as other biologic agents, at 6 months.

Conclusion. Abatacept is expected to result in improvement in functional status comparable to other recommended biologic agents in patients with RA who are unresponsive to MTX in the UK.

Key Indexing Terms: RHEUMATOID ARTHRITIS THERAPEUTICS ANTIRHEUMATIC AGENTS REVIEW LITERATURE AS TOPIC METAANALYSIS AS TOPIC GREAT BRITAIN

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The National Institute of Health and Clinical Excellence (NICE), in the United Kingdom, has recommended early use of disease-modifying antirheumatic drugs (DMARD) to reduce disease progression and long-term disability in patients with rheumatoid arthritis (RA)\(^1\). For patients with an insufficient response to treatment with methotrexate (MTX) and/or other conventional DMARD, NICE recommends adalimumab, etanercept, infliximab, and certolizumab pegol. Most biologic agents are administered by subcutaneous injection; an exception is infliximab, which is administered by intravenous (IV) infusion. An IV infusion may have advantages for certain patient groups, such as those with significant comorbidities who would benefit from regular review at an infusion center, those who cannot self-inject, and those with compliance issues.

Abatacept is a biological DMARD and acts by selectively modulating an essential costimulatory pathway needed for T cell activation, thus inhibiting the inflammatory process at an
earlier stage than tumor necrosis factor-α (TNF-α) inhibitors. Like infliximab, abatacept is available through IV infusion. In May 2005, abatacept in combination with MTX received a UK marketing authorization in adult patients with RA who responded inadequately to previous TNF-α inhibitor therapy. In addition, a license extension was approved for patients who responded inadequately to DMARD, including MTX. The effectiveness of abatacept in this patient population has been demonstrated in a series of randomized controlled trials (RCT). Trial data on the comparative efficacy of abatacept to alternative biologic agents are lacking and can be overcome by indirect treatment comparison methods.

Our objective was to perform an indirect treatment comparison of recommended biologic agents in the United Kingdom in patients unresponsive to MTX, golimumab (in anticipation of its recommendation), and abatacept, based on a systematic review of the published clinical evidence by means of improving functional status as measured by the Health Assessment Questionnaire (HAQ) and the American College of Rheumatology (ACR) response rates. The HAQ score is often used as the key clinical driver in several cost-effectiveness analyses evolutions in RA, whereas the ACR response criteria have been recommended as key disease activity response measures by European League Against Rheumatism (EULAR)/ACR collaborative recommendations.

MATERIALS AND METHODS
Systematic literature review. A systematic review was performed to identify those RCT that have investigated the efficacy of biologic DMARD licensed to treat RA when MTX is insufficient. Medline and Embase databases were searched simultaneously using Datastar. Further searches were done of the Cochrane Library, the technology appraisals for the United Kingdom, and reports of the ACR and EULAR conferences. Searches included a combination of free-text and Medical Subject Headings terms for “disease terms” with “drug names,” and were limited to “human” RCT published in English between January 1980 and October 2010. The ACR and EULAR conferences were searched from 2008 to 2010. Full-text articles were assessed for inclusion by 2 reviewers according to the following selection criteria: (1) treatment combinations of MTX with abatacept, infliximab, etanercept, adalimumab, certolizumab, golimumab, or placebo in comparison with each other; (2) RA patients with an inadequate response or intolerance to previous treatment with at least 1 conventional DMARD (MTX, sulfasalazine, leflunomide, azathioprine, gold salts, or minocycline); and (3) clinical endpoints of HAQ change from baseline (CFB) at 6 months and the ACR response rates at 6 months.

The HAQ is a tool designed for patient self-assessment of physical functioning. For a clinically significant improvement, the measured difference should be at least 0.22. In the abatacept studies, the minimum clinically relevant difference was defined as a change of ≥ 0.3 units from the baseline value.

The ACR20/50/70 response criteria are defined by a 20%/50%/70% reduction in the number of swollen and tender joints, and a reduction of 20%/50%/70% in 3 of the following 5 measures: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein (CRP) or erythrocyte sedimentation rate, and degree of disability in HAQ score.

Data collection. For each selected study the details of design, selection criteria, study population characteristics, interventions, outcome measures, length of followup, and results were extracted. One researcher performed the data extraction, and another reviewed and validated the data extracted.

RESULTS
Systematic review. The systematic literature review identified 21 documents: 17 publications, 2 Clinical Study Reports, 1 NICE submission, and 1 abstract, relevant for the indirect treatment comparison (Figure 1). The 21 documents included 11 individual studies for abatacept (3 trials), infliximab (2 trials), adalimumab (2 trials), etanercept (2 trials), certolizumab pegol (2 trials), and golimumab (1 trial). Each comparison was supported by at least 1 pivotal trial, but not all trials reported findings for the HAQ CFB and ACR response rates at 6 months. All 11 studies were randomized, double-blind, and placebo-controlled trials.

Comparability of study design and included patients. The included studies generally were of comparable design, but there were some notable differences. The adalimumab studies included early escape or rescue therapy at 16 weeks for non-ACR20 responders (patients were allowed to receive rescue treatment with traditional DMARD in the DE019 trial and to roll over to an open-label continuation study with adalimumab in the ARMADA trial). The certolizumab pegol studies specifically withdrew patients who did not show an ACR20 response at Weeks 12 and 14 (63% and 87% in the placebo arm and 21% and 30% in the treatment arm for RAPID and
Figure 1. Selection of included publications.

RCT: randomized controlled trials; ACR: American College of Rheumatology; BMS: Bristol-Myers Squibb; CSR: clinical study report; EULAR: European League Against Rheumatism; NICE: National Institute for Health and Clinical Excellence (UK); STA: single technology appraisal; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug.

Search strategy:
* 1980 – Jan 2010: DataStar (Embase, Medline, Medline in progress), Cochrane RCT Library
* Jan 2010 – Oct 2010: Ovid (Embase, Medline, Medline in Progress), Cochrane RCT Library

Retrieved from: DataStar, Ovid and Cochrane RCT Library: 1744
* Other sources: BMS CSR, Conferences 2008 – 2010: ACR and EULAR and NICE/STA submission

Retrieved from: Other sources: 2 BMS CSR, 106 abstracts, 1 STA submission

Abstracts Excluded: 1620
Non-RCT (882)
Other disease (258)
Juvenile arthritis or non-adults (61)
Intervention or comparison out of scope (219)
Outcome not of interest (161)
Other (16)

Conferences excluded: (105)
Outcome not of interest or naïve patients (86)
Publication available (duplicate) (19)

Excluded: 57
Study design (15)
Outcomes not of interest (13)
Population (8)
No MTX background, etc. (16)
Other (7)

Excluded for MTC: 46
Open-label extension (11)
Outcome not of interest (15)
Other cDMARDS (5)
Naïve patients (6)
Non-relevant biologic (8)
Duplicate information (1)

Included for MTC 21 documents:
Abatacept (5 pub, 2 CSR), Adalimumab (2 pub), Certolizumab (3 pub) + (1 STA report), Etanercept (3 pub), Golimumab (1 pub) + (1 abstract) and Infliximab (3 pub)
RAPID II, respectively). The golimumab trial provided rescue therapy for patients who did not achieve at least 20% improvement in both tender joint count (TJC) and swollen joint count (SJC) by Week 16 (32% of the patients in the placebo group switched to golimumab and 17% of the patients in the golimumab group switched to a higher dose of golimumab). The other studies, including the abatacept trials, did not report any escape or rescue therapy in their protocols. Another difference is that the TEMPO trial included patients who showed an inadequate response to DMARD rather than explicit inadequate response to MTX. In addition, patient eligibility criteria only required patients to have an SJC and TJC of ≥ 4 in GO-FORWARD (golimumab), ≥ 6 in Weinblatt, et al21 (etanercept) and ATTRACT (infliximab), and ≥ 6 for SJC and ≥ 9 for TJC in ARMADA and DE019 (adalimumab). These criteria are less stringent than those in other trials and may reflect a less advanced state of RA (for example, in the AIM trial, eligible patients had to have ≥ 10 swollen joints and ≥ 12 tender joints).

An overview of the baseline patient characteristics is provided in Table 1. The studies were not completely homogeneous in terms of patient and disease duration characteristics. Some studies (GO-FORWARD25, RAPID I22,26, RAPID II24, and TEMPO19,20) reported shorter disease duration, with a mean of 4.5–6.8 years, while the other studies reported longer disease durations (with means 7.3–13 years). In terms of patient characteristics, the GO-FORWARD study included patients with an SJC of 11–13 compared with 17–23 for the other studies, and lower CRP levels (8–10 mg/l compared with 13–40 mg/l for the other studies).

All studies reported similar HAQ scores at baseline, except for the abatacept study by Kremer, et al7, which presented a

Table 1. Overview of characteristics of patients by treatment arm and trial. The treatment arms not used in the network metaanalysis do not appear; only treatment arms presenting the recommended dosages are reported.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Arm</th>
<th>Sex, Mean Age, Mean Yrs Since Diagnosis, Mean No. % Pts Taking DMARD</th>
<th>% Pts Previous DMARD (not MTX)</th>
<th>% Pts Taking NSAID</th>
<th>% Pts Taking Corticosteroids</th>
<th>Mean TJC</th>
<th>Mean SJC</th>
<th>Mean HAQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIM Placebo + MTX Abatacept 10 mg/kg every 4 wks + MTX</td>
<td>81.7 50.4 8.9 1.2</td>
<td>82.6 68.5 32.3 22.1 1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kremer Placebo + MTX Abatacept 10 mg/kg every 4 wks + MTX</td>
<td>77.8 51.5 8.5 1.3 NR</td>
<td>85.5 72.1 31 21.4 1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTEST Placebo + MTX Abatacept 10 mg/kg every 4 wks + MTX Infliximab 3 mg/kg every 8 wks + MTX</td>
<td>66 54.7 8.9 NR 21</td>
<td>67.2 29.2 21.8 1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARMADA Placebo + MTX Adalimumab 40 mg every other wk + MTX</td>
<td>75 55.8 9.7 16.5</td>
<td>60 30.8 21.3 1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DE019 Placebo + MTX Adalimumab 40 mg every other wk + MTX</td>
<td>83.3 49.4 8.4 1.8 NR</td>
<td>84.5 70 30.3 20.1 1.8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RAPID I Placebo + MTX CZP 200 mg every other wk + MTX</td>
<td>83.3 49.4 8.4 1.8 NR</td>
<td>84.5 70 30.3 20.1 1.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAPID II Placebo + MTX CZP 200 mg every other wk + MTX</td>
<td>83.3 49.4 8.4 1.8 NR</td>
<td>84.5 70 30.3 20.1 1.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinblatt Placebo + MTX Etanercept 25 mg twice wky + MTX</td>
<td>73 53 13 13.7</td>
<td>75 53 13 13.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEMPO Placebo + MTX Etanercept 25 mg twice wky + MTX</td>
<td>79 53 6.8 2.3</td>
<td>88 62 34.2 22.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GO-FORWARD Placebo + MTX Golimumab 50 mg every 4 wks + MTX</td>
<td>82 52 6.5 NR 70.7 20.5 21 12 1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTRACT Placebo + MTX Infliximab 3 mg/kg every 8 wks + MTX</td>
<td>81 56 8.4 2.8 NR 79 63 32 19 1.8</td>
<td></td>
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</tr>
</tbody>
</table>

HAQ: Health Assessment Questionnaire; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; RF: rheumatoid factor; SJC: swollen joint count; TJC: tender joint count; NR: not reported.
lower mean HAQ baseline value. This difference was likely to be due to the use of the modified HAQ instead of the traditional HAQ. Both instruments are strongly correlated, with a Pearson correlation coefficient of 0.88\(^2\), so the difference in the instruments is assumed to have no influence on the relative treatment effect.

These differences could explain potential differences in the observed relative treatment effects, and therefore lead to the use of random effects models to take heterogeneity into account across trials.

**Network metaanalysis results.** The relative difference between the HAQ CFB scores showed abatacept in combination with MTX to be more effective than placebo in combination with MTX in improving functional status (difference in HAQ CFB vs placebo: −0.30, 95% CrL −0.42; −0.16). The expected absolute HAQ CFB for abatacept (−0.57, 95% CrL −0.69; −0.43) was superior to placebo (−0.27, 95% CrL −0.30; −0.24), and comparable to the other biologics (expected mean between −0.46 and −0.65; Figure 2). Abatacept may be as efficacious as all other biological agents in patients receiving MTX as background therapy. The point estimates of the relative differences in mean HAQ CFB of abatacept versus other biological agents varied from −0.11 (vs infliximab) to 0.09 (vs certolizumab pegol; Figure 3).

**ACR response criteria at 6 months.** Abatacept was found to be more efficacious than placebo for each ACR response criterion (Figure 4). All biological agents evaluated are expected to result in comparable proportions of ACR20/50/70 responders, although the findings show that certolizumab pegol is expected to have a higher ACR20 response rate at 6 months than other biological agents. Abatacept appears to have a numerical benefit over etanercept (except for ACR70) and infliximab, but not over adalimumab, certolizumab pegol, and golimumab (Figure 5).

**Sensitivity analyses.** The TEMPO trial was included in the base case analysis as it was the pivotal trial for etanercept in this patient population. However, the TEMPO trial included a population that did not respond to DMARD and did not have recent MTX exposure or was MTX-naive, in distinction from the populations that had inadequate response to MTX and were recruited for the other trials. It also showed high observed response rates in the control group, which were substantially different from control responses in other studies. Therefore, the high response rates reported in both the test and control arms of the TEMPO study (Table 2) might be explained by the significant proportion of patients entering this trial who have not experienced MTX failure. Removing the TEMPO trial did not significantly affect the mean HAQ CFB at 6 months. Abatacept still showed comparable efficacy to the other biological treatments, including etanercept (difference in HAQ CFB vs etanercept at 6 months: −0.03, 95% CrL −0.25; 0.19).

In the base case analysis, all randomized patients were included for the AIM trial, although patients included from 1 site were excluded from the efficacy analyses because of protocol violations. A sensitivity analysis excluding this site for the AIM results was evaluated and did not change the relative efficacy of abatacept to other biological agents (data not reported).

**DISCUSSION**

A systematic review of the literature and an indirect treatment comparison were performed to estimate the relative efficacy of abatacept compared with other relevant biological DMARD in the treatment of patients with RA with insufficient response to MTX in the United Kingdom. Indications are that abatacept will show a comparable efficacy in HAQ score and ACR response criteria to other routinely used biological agents in combination with MTX.

![Figure 2. Expected absolute Health Assessment Questionnaire (HAQ) change from baseline (CFB), all treatments, at 6 months. Findings were based on a random effects model. Absolute CFB were calculated by adding the crude average placebo response to the treatment-specific CFB.](https://example.com/figure2.png)
Figure 3. Relative Health Assessment Questionnaire (HAQ) change from baseline (CFB) abatacept compared to all other treatments at 6 months. Findings were based on a random effects model. MTX: methotrexate.

Figure 4. American College of Rheumatology (ACR) 20/50/70 response rates at 6 months. Findings were based on a random effects model. Absolute proportions were calculated by multiplying the crude average placebo response with the treatment-specific relative risk.
An indirect treatment comparison is credible only if the trial data used in the analyses are uniform. The similarity assumption could be violated by differences across the trials (i.e., clinical heterogeneity), which would introduce bias into the findings. Our study attempted to include only studies that were comparable across patient populations and study design. However, it should be noted that the patient population in the TEMPO trial included those with an inadequate response to any conventional DMARD and not specifically MTX, and etanercept is evaluated in only 2 trials: an older and relatively small study and the pivotal trial for etanercept (TEMPO).

We decided to include the TEMPO trial in the base case analysis because of its pivotal position and to evaluate the potential effect of its exclusion in a scenario analysis. We found that its exclusion did not change the interpretation of the findings.

Other limitations in comparability of study and patient characteristics were observed with the golimumab and certolizumab pegol trials. For golimumab, the main publication reported median and interquartile range data instead of mean and SD, and this may have challenged the assumed normality of the data. Our study also included patients presenting with lower SJC, a lower CRP level, and shorter disease duration than most of the other studies. Certolizumab pegol and etanercept also had studies reporting shorter disease duration. The difference in design of the certolizumab pegol studies, i.e., that patients were withdrawn if they did not show ACR responses at 12 and 14 weeks, may partly explain the high mean HAQ CFB after adjustment estimate for certolizumab pegol. Because of the limited number of studies, the effect associated with the golimumab and certolizumab pegol studies was not explored in either metaregression or scenario analyses. Excluding 1 of these studies would have removed at least 1 treatment from the analysis, without providing any additional information on the potential presence of bias. The only effect would have been to leave the decision makers with no estimate at all for the comparison of the removed biological agents with the other comparators.

To take into account the heterogeneity across trials and try to reduce the possible confounding bias, random effect models have been used. Aside from comparability issues, the direct evidence from trials could not be supported by indirect evidence (the exception being the ATTEST trial reporting both the relative effects vs placebo for abatacept and infliximab). The introduction of bias in this indirect treatment comparison could be neither fully excluded nor fully established. However, if the analysis is indeed biased, there is no evidence that a nonbiased indirect comparison would lead to a different conclusion. The approach taken is conservative because it did indeed lead to a different conclusion, one would hypothesize a direction of bias in favor of abatacept (in the abatacept trials, the mean disease duration was higher and no rescue route was proposed). The analysis results presented here can be seen as the best estimates for the problems considered, given the data at hand, but would surely benefit from the addition of new data based on RCT with the same scope.

Other network metaanalyses have been published on bio-
logical agents for patients with RA, such as the study from the Cochrane collaboration. Our analysis was, however, different in terms of scope, justifying the need for a new analysis. We can cite other differences: the addition of certolizumab and golimumab treatments, the exclusion of anakinra and rituximab treatments, the criteria for patients who did not have an adequate response to MTX, or the combination with MTX (excluding biological agents as single therapy or in combination with other DMARD). Our study had a narrower scope; therefore, we expected less heterogeneity between the studies included and more reliable results for our specific population of interest. The numerical results were, as expected, somehow different from the Cochrane results, but the overall conclusion agreed: abatacept, adalimumab, etanercept, and infliximab showed comparable short-term efficacy in patients with RA.

Currently it is not possible to predict, on an individual basis, which patient will respond to a particular therapy — a significant unmet need that is the goal of much research. While there is still an absence of reliable biomarkers on which to base individual treatment decisions, it is important that patients have access to the full range of biological therapeutics with proven efficacy. This indirect treatment comparison strongly suggests that abatacept in combination with MTX is superior to placebo plus MTX, and also comparable to other biologic DMARD for the short-term reduction in disability and ACR response rates of RA for patients with active disease despite previous treatment with MTX. As shown in our network meta-analyses and the ATTEST trial, abatacept is expected to be as efficacious as infliximab, the only other biologic delivered by IV administration while offering another working mechanism. This could especially be of interest for patients who are potentially noncompliant and patients who require close monitoring at an infusion center. In addition, a network meta-analysis from the Cochrane collaboration on the safety of the biologic agents stated that abatacept was associated with a significantly lower risk of serious adverse events than certolizumab pegol, etanercept, and infliximab, and was associated with a significantly lower risk of serious infections than certolizumab pegol and infliximab. Therefore, based on its unique mechanism of action, efficacy, and clinical trial safety profile, abatacept appears to be a suitable alternative to currently licensed biologic DMARD, in particular infliximab.

### Table 2. Reported data for Health Assessment Questionnaire (HAQ) change from baseline (CFB) and American College of Rheumatology (ACR) 20/50/70 responses at 6 months.

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Mean HAQ CFB (SD)</th>
<th>ACR20 Responses</th>
<th>ACR50 Responses</th>
<th>ACR70 Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo + MTX</strong></td>
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<tr>
<td>AIM</td>
<td>219</td>
<td>−0.40 (0.59)</td>
<td>87</td>
<td>37</td>
<td>14</td>
</tr>
<tr>
<td>Kremer 2005, Kremer 2003</td>
<td>119</td>
<td>−0.14 (0.49*)</td>
<td>42</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>ATTEST</td>
<td>110</td>
<td>−0.29 (0.22)</td>
<td>46</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>ARMADA</td>
<td>62</td>
<td>−0.27 (0.57)</td>
<td>9</td>
<td>5</td>
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<tr>
<td>DE019</td>
<td>200</td>
<td>−0.24 (0.52)</td>
<td>59</td>
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<td>RAPID I</td>
<td>199</td>
<td>−0.17 (0.56)</td>
<td>27</td>
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<tr>
<td>RAPID II</td>
<td>127</td>
<td>−0.14 (0.45)</td>
<td>11</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Weinblatt</td>
<td>30</td>
<td>−0.40 (0.49*)</td>
<td>8</td>
<td>1</td>
<td>0</td>
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<tr>
<td>TEMPO</td>
<td>228</td>
<td>−0.63 (1.08*)</td>
<td>167</td>
<td>92</td>
<td>34</td>
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<tr>
<td>GO-FORWARD</td>
<td>133</td>
<td>−0.13 (0.58)</td>
<td>37</td>
<td>18</td>
<td>7</td>
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<tr>
<td>ATTRACT</td>
<td>88</td>
<td>−0.19 (0.49*)</td>
<td>18</td>
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<tr>
<td><strong>Abatacept + MTX</strong></td>
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<td>AIM</td>
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<td>−0.59 (0.62)</td>
<td>294</td>
<td>173</td>
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<td>Kremer 2005, Kremer 2003</td>
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<td>−0.42 (0.49*)</td>
<td>69</td>
<td>42</td>
<td>19</td>
</tr>
<tr>
<td>ATTEST</td>
<td>156</td>
<td>−0.68 (0.22)</td>
<td>104</td>
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<tr>
<td><strong>Adalimumab + MTX</strong></td>
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<td><strong>Certolizumab + MTX</strong></td>
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<tr>
<td>RAPID I</td>
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<td>−0.58 (0.59)</td>
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<td><strong>Infliximab + MTX</strong></td>
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* SD was estimated. MTX: methotrexate.
REFERENCES


