Systematic Review and Meta-Analysis of the Efficacy and Safety of Existing TNF Blocking Agents in Treatment of Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease with a prevalence of 0.5–1.0 per cent in Northern Europe [1]. A recent epidemiological study from Sweden reported that 0.77% of the population have been diagnosed with RA while a survey from UK found the prevalence to be 0.82% [2,3]. RA is usually diagnosed before the age of 60 and is more common in women than men. Both genetic and environmental factors play a role [4]. Symptoms include joint destruction, pain and impaired movement.

Since the discovery of the role of tumour necrosis factor (TNF) in chronic inflammation in RA, five drugs based on blocking TNF have entered clinical use. Infliximab, adalimumab, golimumab and certolizumab pegol (certolizumab) are monoclonal antibodies targeted against TNF whereas etanercept is a soluble TNF-receptor [5]. However, only few clinical trials compared one TNF-blocker to other TNF-blockers. Previous systematic reviews and meta-analyses have studied the subject in various settings and comparisons [6–14]. These studies concluded that while TNF-blockers are efficacious but it may still be beneficial to use them in combination therapies. Only few differences in efficacy and safety between individual substances were discovered. However, more randomized clinical trials have been published lately with additional data available to systematic reviews and most importantly, two new substances, certolizumab and golimumab, have been introduced to clinical use.

The purpose of this systematic review and meta-analysis is to study the efficacy and safety of all five currently available TNF-blockers in the treatment of RA compared to either methotrexate or placebo.

Abstract

Background and Objectives: Five-tumour necrosis factor (TNF)-blockers (infliximab, etanercept, adalimumab, certolizumab pegol and golimumab) are available for treatment of rheumatoid arthritis. Only few clinical trials compare one TNF-blocker to another. Hence, a systematic review is required to indirectly compare the substances. The aim of our study is to estimate the efficacy and the safety of TNF-blockers in the treatment of rheumatoid arthritis (RA) and indirectly compare all five currently available blockers by combining the results from included randomized clinical trials (RCT).

Methods: A systematic literature review was conducted using databases including: MEDLINE, SCOPUS (including EMBASE), Cochrane library and electronic search alerts. Only articles reporting double-blind RCTs of TNF-blockers vs. placebo, with or without concomitant methotrexate (MTX), in treatment of RA were selected. Data collected were information of patients, interventions, controls, outcomes, study methods and eventual sources of bias.

Results: Forty-one articles reporting on 26 RCTs were included in the systematic review and meta-analysis. Five RCTs studied infliximab, seven etanercept, eight adalimumab, three golimumab and three certolizumab. TNF-blockers were more efficacious than placebo at all time points but were comparable to MTX. TNF-blocker and MTX combination was superior to either MTX or TNF-blocker alone. Increasing doses did not improve the efficacy. TNF-blockers were relatively safe compared to either MTX or placebo.

Conclusions: No single substance clearly rose above others in efficacy, but the results of the safety analyses suggest that etanercept might be the safest alternative. Interestingly, MTX performs nearly identically considering both efficacy and safety aspects with a margin of costs.
(MTX) and placebo or placebo alone and to perform an indirect comparison between individual substances in different drug combinations and doses and at different time points. We test the assumption that it is more efficacious and comparatively safer to use MTX in combination with a TNF-blocker in the treatment of RA compared to TNF-blocker monotherapy. We study if high doses of TNF-blockers differ from regular doses in efficacy and safety. Primary efficacy endpoint is the risk ratio between intervention and control group in American College of Rheumatology (ACR) 50% improvement at 6 months [15,16]. Secondary efficacy endpoints include risk ratios in ACR 20%, 50% and 70% improvements at 3, 6 and 12 months in several comparisons. Primary safety endpoint is the risk ratio between intervention and control group in the number of discontinuations due to adverse events. Secondary safety endpoints include risk ratios in the number of adverse events, serious adverse events, infections, serious infections and injection site reactions.

Methods

Study selection criteria

We performed a search for randomized clinical trials of five TNF-blockers in treatment of RA. Systematic review was conducted in accordance to methods and recommendations from the Cochrane handbook [17].

According to inclusion criteria patients had to be at least 16 years of age; be diagnosed with RA using ACR 1987 criteria; and be randomized either to intervention or control group. Studies were to have one (or more) of the TNF-blockers as intervention and either placebo or combination of placebo and methotrexate as control. The TNF-blocker had to be delivered through the same route as the commercial drug and be within the dose range recommended for the commercially available products. Efficacy was measured in terms of ACR 20%, 50% and 70% improvements and thus, at least one of these had to be reported at some time point. Information regarding safety had to be reported. Previously published systematic reviews were searched for, but excluded from the systematic review due to the inclusion criteria. The protocol of the study was not published online.

Search strategy

Search strategy was designed and performed by a librarian by our request. We used the search terms rheumatoid arthritis, anti-TNF, infliximab, etanercept, adalimumab, golimumab, certolizumab, randomized clinical trials and systematic review. Variations in spelling were taken into account. References from (Ovid®) Medline, Cochrane library (Cochrane Central register of Controlled Trials, Cochrane Database for Systematic Reviews, Health Technology Assessment, Database of Abstracts of Reviews of Effects, NHS Economic Evaluation, Cochrane Methodology Register), SCOPUS (including Embase), ISI web of knowledge and several other databases were extracted and imported to reference management software (RefWorks). Clinical trial register (clinicaltrials.gov) was hand searched for unpublished trials. Duplicate entries were removed using an automated feature. There were no restrictions on study language. For search strategy, see table S1.

Study selection

References were evaluated by two individual investigators (KA, LV) using pre-defined inclusion and exclusion criteria. Decision for inclusion was made on consensus. A third investigator (YT) made the final decision in case of disagreement. Evaluation was based on title and abstract whenever available. Full text articles from potentially relevant references were obtained in electronic or printed format and re-evaluated for inclusion by the same investigators as before. The acronym PICO (patients, interventions, comparators, outcomes and settings) was used to assess if the references fully complied with the inclusion and exclusion criteria. As full-text article was required for the systematic review and meta-analysis, references whose full-texts we could not acquire either electronically or as printed copies from the University of Helsinki medical library were excluded. Multiple reports from a single study were considered as one study.

Evaluation for bias

As instructed in the Cochrane handbook for systematic reviews of interventions, the investigators performed an evaluation of bias rather than of methodological quality. Studies included were evaluated for an eventual bias using methods described in the Cochrane handbook. The study was to be considered “possibly biased” in case a possible source of bias was found in any of the seven dimensions evaluated. The following dimensions were considered in the bias assessment tool: Allocation sequence generation, allocation concealment, blinding of participants, personnel and outcome, incomplete outcome data, selective outcome reporting and other sources of bias. Evaluation was done by two independent assessors (KA, LV) to improve the validity. The effect of possible bias on results was studied by performing all meta-analysis twice with possibly biased RCTs included and excluded.

Data extraction

Data on study design, patient status and background, efficacy and safety were extracted from the publications using an Excel data extraction form by two independent researchers (KA, LV) to improve validity.

Meta-analyses

Data were analyzed using the intention to treat results from the included studies. Meta-analyses were performed using Cochrane Collaboration Review Manager 5.0 software. Sensitivity analyses were employed to account for the possible bias. In some settings several time points were combined to increase the power. Efficacy and safety were analyzed using dichotomous data to obtain risk ratios. Dichotomous efficacy data included ACR 20%, 50% and 70% improvements whereas dichotomous safety data was composed of the proportion of patients who experienced an adverse outcome or discontinued the treatment due to adverse events. The efficacy and safety of TNF-blockers was analyzed in six different main comparisons. Random effects model was used to account for the diversity of the studies. Heterogeneity was evaluated via subgroup analysis using Chi square and I²-statistics.

Results

Search results

5308 references were identified from electronic databases by a systematic literature search performed 5-26.2.2010. 1613 were identified as duplicates by an automated feature in RefWorks. Additionally, 146 references were added via “search alerts”, which extended time coverage of the search to 30.6.2010. No additional references were identified from alternative sources including clinical trial registers.

Study selection

After removing duplicate entries, 3841 references were evaluated for inclusion based on title and/or abstract. Seventy
six potentially relevant references were included in the next stage, where the publication was to be re-evaluated based on full text (figure 1). Full text was unavailable for 12 studies most of which were conference abstracts identified from ISI Web of Knowledge [18–29]. Patients, interventions, controls, outcomes or design of the studies did not meet the inclusion criteria of the systematic review in 17 publications [30–46]. Five review articles, one letter to the editor [47] and one erratum [48] were excluded. Several of the remaining 40 publications were reporting on a single study and were thus merged into one (table S2). Publications included in the systematic review and meta-analysis are listed in the bibliography with numbers 49–88. From the 26 clinical trials included in the systematic review, 8 used adalimumab, 7 etanercept, 5 infliximab, 3 golimumab and 3 certolizumab for intervention. The included trials have 9062 patients of which 6780 and 3082 were in intervention and control groups, respectively (table S2).

**Evaluation for bias**

A potential source of bias was discovered in five trials included in the systematic review (table 1). In many clinical trials there was an early escape route for patients with insufficient treatment response to avoid rapid disease progression. In some studies this was implemented by considering all patients failing to meet a predefined treatment response criteria (e.g. ACR 20% improvement) as “non-responders” before the actual efficacy assessment. While this may be for the best interest of the study subjects, it may introduce a bias to the evaluation of the efficacy results. Another bias was caused by switching the control group to active medication.

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**Figure 1. Flowchart of the selection process of the RCTs for the systematic review and meta-analysis.**

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- **Identification**
  - 5308 records were identified through database searching
  - 5454 records identified through systematic literature search
  - 146 records identified using "search alert" function
  - 1613 records excluded as duplicates

- **Screening**
  - 3841 records screened on basis of title and abstract
  - 3765 records excluded

- **Eligibility**
  - 76 full-text articles assessed for eligibility
  - (36) excluded based on full text
  - Reasons for exclusion:
    - Patients, interventions, control, outcomes and/or study design not meeting inclusion criteria (17)
    - Full text not available (12)
    - Review article (5)
    - Erratum (3)
    - Letter to the editor (1)

- **Included**
  - 40 publications, which report of 26 studies included in qualitative and quantitative syntheses
    - Adalimumab: 8 RCTs, 10 publications
    - Etanercept: 7 RCTs, 13 publications
    - Infliximab: 5 RCTs, 11 publications
    - Golimumab: 3 RCTs, 3 publications
    - Certolizumab: 3 RCTs, 3 publications
Efficacy

**TNF-blocker vs. control.** The primary efficacy endpoint of our study was the risk ratio of 50% improvements in the ACR-treatment response criteria at six months between intervention and control group. Fourteen trials were included and of them 2 used infliximab, 2 etanercept, 5 adalimumab, 2 golimumab and 3 certolizumab for intervention. As a group, TNF-blockers reached a risk ratio of 4.07 (95% CI 2.70–6.13) regarding the achievement of the efficacy endpoint compared to controls. For infliximab, etanercept, adalimumab, golimumab and certolizumab the corresponding figures were 3.08 (95% CI 0.91–10.43), 8.61 (3.55–20.86), 4.34 (3.30–5.70), 1.56 (0.93–2.60) and 5.95 (3.97–8.92), respectively (figure 2). These results suggest that infliximab and golimumab do not differ significantly from the control. In this comparison golimumab appears to be inferior in efficacy compared to etanercept, adalimumab and certolizumab even after accounting for the possible bias. TNF-blockers as a group were found to be significantly more efficacious than control at all time points using ACR 20, 50 or 70 as outcome measures. The risk ratios observed at 12 months were significantly lower than those at three or six months.

We found some evidence that the duration of RA predicts the efficacy of TNF-blocker treatment. Patients on either infliximab or adalimumab with disease duration more than 2 years were more likely to reach ACR 20, 50 and 70 at 12 months compared to controls than patients with disease duration less than two years (table 2).

**TNF-blocker + MTX vs. MTX.** Patients on combination therapy had significantly higher ACR outcomes than ones treated with MTX alone at all time points (table 3). A statistically significant difference was revealed between ACR 20 risk ratios of certolizumab (CI 95% 5.08, 3.46–7.48) and golimumab (1.61, 0.94–2.76). However, all certolizumab studies in this comparison were potentially biased. In a subanalysis of trials with patients who

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**Table 1.** The results of an assessment for bias in accordance to a tool by Cochrane Collaboration.*

<table>
<thead>
<tr>
<th>Study</th>
<th>Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Incomplete Outcome Data</th>
<th>Selective Outcome Reporting</th>
<th>Other Potential Threats To Validity</th>
</tr>
</thead>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>Maini 1999</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Quinn 2005</td>
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<td>Yes</td>
<td>Unnecessary</td>
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<td>Yes</td>
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<td>Yes</td>
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<td></td>
<td>Schiff 2008</td>
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<td>Yes</td>
<td>Yes until 6 mo/No</td>
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<td>Etanercept</td>
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<td>Unnecessary</td>
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<td>Yes</td>
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<tr>
<td></td>
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<td>Yes</td>
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<td>Yes</td>
</tr>
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<td></td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes until 8 wk/No</td>
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<td>Klareskog 2004</td>
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<td>Yes</td>
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<td>Yes</td>
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<td></td>
<td>Weinblatt 1999</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Adalimumab</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
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<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>Keystone 2004</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Kim 2007</td>
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<td>Yes</td>
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<tr>
<td></td>
<td>Miyasaki 2008</td>
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<td>Yes</td>
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<td></td>
<td>Van de Putte 2003</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>Van de Putte 2004</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>Weinblatt 2003</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Golimumab</td>
<td>Emery 2009</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>Keystone 2009</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes until 16 wk/No</td>
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<td>Certolizumab</td>
<td>Fleischmann 2008</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>Keystone 2008</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>Smolen 2009</td>
<td>Unclear</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Yes = free of bias, No = possible source of bias, Unclear = not enough information to make the decision.

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had previously used MTX, the results were similar. In comparison to MTX, golimumab combination therapy was still inferior in ACR 20 efficacy at 6 months to certolizumab combination therapy, with risk ratios of 2.14 (1.59–2.89) and 5.08 (3.46–7.48), respectively. At six months patients previously naïve to MTX are statistically significantly less likely to reach either ACR 20, 50 or 70 treatment responses compared to patients who had already been previously treated with MTX. The combination of TNF-blocker and MTX was superior in efficacy to monotherapy with a TNF-blocker at almost all time points (table 4).

**TNF-blocker monotherapy vs. MTX.** There are no trials comparing monotherapy of infliximab to MTX, but combined results with the remaining four other TNF-blockers show that while the risk ratios favour the TNF-blocker, the results do not

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**Figure 2. Forest plot of the ACR 50 response at 6 months.**

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reach statistical significance at any time point using ACR 20, 50 or 70 as outcome measures. Stratifying RTCs by previous exposure to MTX does not show any statistically significant differences in the treatment response to TNF-blocker monotherapy between these two groups.

**TNF-blocker monotherapy vs. placebo.** All four TNF-blockers were more efficacious than placebo with the estimates of risk ratios ranging from 2.74 (CI 95% 1.76–4.26) – 12.31 (1.64–92.41). There were no statistically significant differences in efficacy between individual substances in this comparison or, alternatively, the meta-analysis was underpowered to reveal them.

**High doses of TNF-blockers vs. normal doses.** The final meta-analysis compared higher than regular doses of TNF-blockers to normal doses (table 5). Both patients using high and normal doses had to be on concomitant MTX or on TNF-blocker monotherapy. Increasing the dose of TNF-blocker provided no additional efficacy compared to regular doses except 12 months with possibly biased results excluded.

**Sensitivity analyses**

The sensitivity analyses based on the results of the bias assessments did not reveal any statistically significant bias on the efficacy results. Occasionally, however, the statistical significance between intervention and control groups disappeared due to reduced number of studies. In the sensitivity analyses, the estimate of the risk ratio decreased, increased or remained the same in 52%, 45% and 3% of cases, respectively. In some cases there were no clearly unbiased RTCs in a comparison, thus making it impossible to perform the sensitivity analysis. Significant heterogeneity was present in the first analysis comparing any two groups.

### Table 2. Meta-analysis of the efficacy of TNF-blockers compared to control(RR, 95% CI).

<table>
<thead>
<tr>
<th>TNF-blocker</th>
<th>ACR 20 3kk RR (95% CI)</th>
<th>ACR 50 3kk RR (95% CI)</th>
<th>ACR 70 3kk RR (95% CI)</th>
<th>ACR 20 6kk RR (95% CI)</th>
<th>ACR 50 6kk RR (95% CI)</th>
<th>ACR 70 6kk RR (95% CI)</th>
<th>ACR 20 12kk RR (95% CI)</th>
<th>ACR 50 12kk RR (95% CI)</th>
<th>ACR 70 12kk RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>4.44 (1.77–11.16) 2</td>
<td>12.92 (8.91–20.02) 2</td>
<td>1.89 (1.00–3.56) 2</td>
<td>3.08 (0.91–10.43) 2</td>
<td>5.17 (0.61–43.54) 2</td>
<td>1.70 (0.86–3.38) 3</td>
<td>2.24 (1.11–4.50) 2</td>
<td>2.71 (1.09–6.70) 2</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>3.96 (1.55–10.14) 5</td>
<td>3.14 (1.93–5.10) 5</td>
<td>3.72 (1.91–7.24) 5</td>
<td>8.61 (3.55–20.86) 2</td>
<td>11.40 (2.21–58.65) 2</td>
<td>1.15 (1.03–12.29) 3</td>
<td>1.41 (1.26–14.44) 2</td>
<td>1.74 (1.44–20.93) 2</td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>5.42 (1.75–16.80) 3</td>
<td>8.25 (2.33–29.19) 3</td>
<td>2.53 (1.87–3.43) 5</td>
<td>4.34 (3.30–5.70) 5</td>
<td>4.44 (3.03–9.76) 5</td>
<td>1.56 (0.62–3.90) 2</td>
<td>2.18 (0.54–8.83) 2</td>
<td>2.47 (0.61–10.02) 2</td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>3.03 (1.82–5.04) 2</td>
<td>2.91 (1.21–7.00) 2</td>
<td>1.42 (0.95–2.12) 2</td>
<td>1.56 (0.93–2.60) 2</td>
<td>1.72 (0.74–3.99) 2</td>
<td>n/a n/a</td>
<td>n/a n/a</td>
<td>n/a n/a</td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td>n/a n/a n/a n/a</td>
<td>3.67 (1.35–9.96) 3</td>
<td>n/a n/a n/a n/a</td>
<td>n/a n/a n/a n/a</td>
<td>n/a n/a n/a n/a</td>
<td>n/a n/a</td>
<td>n/a n/a</td>
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<tr>
<td>Combined</td>
<td>2.22 (1.60–3.07) 11</td>
<td>4.01 (2.34–6.87) 11</td>
<td>3.50 (2.35–5.21) 11</td>
<td>2.50 (1.90–3.30) 10</td>
<td>4.07 (2.70–6.13) 14</td>
<td>4.94 (2.80–8.71) 14</td>
<td>2.00 (0.83–4.81) 3</td>
<td>2.86 (1.07–7.65) 3</td>
<td>3.84 (1.39–10.61) 3</td>
</tr>
</tbody>
</table>

**Bolded** risk ratios highlight statistically significant results (P<0.05), TNF = Tumour Necrosis Factor. Superscript indicates the number of RTCs included in the comparison, RA = Rheumatoid Arthritis.

doi:10.1371/journal.pone.0030275.t002
### Table 3. Meta-analysis of the efficacy of combination TNF-blocker and MTX compared to MTX (RR, 95% CI).

<table>
<thead>
<tr>
<th>TNF-blocker + MTX vs. MTX (both MTX naive patients and patients with previous experience with MTX)</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Golimumab</th>
<th>Certolizumab</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Risk ratio (95% CI)</td>
<td>1.51 (1.16–1.95)</td>
<td>1.77 (1.60–1.97)</td>
<td>1.63 (1.34–2.00)</td>
<td>1.67 (1.32–2.12)</td>
<td>n/a</td>
<td>1.78 (1.38–2.30)</td>
</tr>
</tbody>
</table>

### Table 4. Meta-analysis of the efficacy of combination TNF-blocker and MTX compared to TNF-blocker monotherapy (RR, 95% CI).

<table>
<thead>
<tr>
<th>TNF-blocker + MTX vs. TNF-blocker</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Golimumab</th>
<th>Certolizumab</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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</tr>
<tr>
<td>Risk ratio (95% CI)</td>
<td>1.25 (1.04–1.49)</td>
<td>1.25 (1.04–1.49)</td>
<td>1.67 (1.35–2.03)</td>
<td>1.54 (1.30–1.81)</td>
<td>n/a</td>
<td>1.16 (1.05–1.29)</td>
</tr>
</tbody>
</table>

**Bolded** risk ratios highlight statistically significant results (P<0.05). RA = Rheumatoid Arthritis, MTX = Methotrexate. Superscript indicates the number of RCTs included in the comparison, TNF = Tumour Necrosis Factor.
Golimumab increased the odds for an unspecified adverse event reactions but these findings did not reach statistical significance. Elevated risk ratios of multiple safety endpoints excluding injection differences between treatment groups. There was a trend of combination treatment to monotherapy there were only few 1.09. Combined results from all substances now reached statistical significance. Etanercept no longer significantly decreased the likelihood of infusion reactions (RR 5.20, CI 95% 2.62–10.31).

To investigate the possible effect of study patients’ baseline disease activity on efficacy, two additional analyses were performed. Using ACR 50 at six months as outcome and stratifying trials into two categories by the number of swollen joints or Health Assessment Questionnaire (HAQ) score revealed no statistical differences between the subgroups. Trials with low swollen joint count and low HAQ score had risk ratios of 3.43 (CI 95% 2.03–5.78) and 3.68 (2.11–6.42), respectively, whereas trials with high swollen joint count and high HAQ score had risk ratios of 5.15 (2.72–9.75) and 4.64 (2.59–8.31), respectively.

Safety

**TNF-blocker vs. control.** The primary safety endpoint of the systematic review was the discontinuation of study due to adverse events. There were 25 studies with 6292 patients in the intervention and 2994 in the control group in this analysis (table 6). As a group, the TNF-blockers did not statistically significantly differ from the control (RR 1.26, CI 95% 0.93–1.71). While the patients on infliximab (3.22, 1.76–5.91), adalimumab (1.59, 1.13–2.23), and certolizumab (2.72, 1.23–6.01), had an increased risk to discontinue, the patients on etanercept (0.71, 0.54–0.92) had a decreased risk (figure 3). Patients using certolizumab had a higher risk to experience a serious adverse event than patients on etanercept with risk ratios of 2.24 (1.38–3.63) and 0.90 (0.68–1.20), respectively. Infliximab, etanercept and golimumab increased the likelihood of an injection or infusion reaction while adalimumab and certolizumab did not statistically significantly differ from the controls in this respect although their risk ratios leaned to the same direction.

**TNF-blocker + MTX vs. MTX.** In this comparison, etanercept no longer significantly decreased the likelihood of discontinuation due to adverse event (RR 0.78, CI 95% 0.56–1.09). Combined results from all substances now reached statistical significance (1.37, 1.01–1.87). In an analysis comparing the combination treatment to monotherapy there were only few differences between treatment groups. There was a trend of elevated risk ratios of multiple safety endpoints excluding injection reactions but these findings did not reach statistical significance. Golimumab increased the odds for an unspecified adverse event (1.14, 1.03–1.26) while others did not.

**TNF-blocker monotherapy vs. MTX.** TNF-blocker and MTX were comparable in all respects other than injection and infusion reactions (RR 5.20, CI 95% 2.62–10.31).
### Table 6. Meta-analysis of the safety of TNF-blockers in different comparisons (RR, 95% CI).

<table>
<thead>
<tr>
<th></th>
<th>Discontinuation due to adverse event</th>
<th>All adverse events</th>
<th>Serious adverse events</th>
<th>All infections</th>
<th>Serious infections</th>
<th>Injection or infusion reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNF-blocker vs. control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>3.22 (1.76–5.91)</td>
<td>1.02 (0.93–1.13)</td>
<td>1.01 (0.70–1.47)</td>
<td>1.51 (0.92–2.47)</td>
<td>1.45 (0.63–3.35)</td>
<td>1.76 (1.03–3.03)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>0.71 (0.54–0.92)</td>
<td>1.02 (0.97–1.07)</td>
<td>0.90 (0.68–1.20)</td>
<td>0.88 (0.65–1.20)</td>
<td>0.87 (0.48–1.58)</td>
<td>4.46 (3.13–6.36)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.59 (1.13–2.23)</td>
<td>1.04 (0.94–1.15)</td>
<td>1.03 (0.71–1.49)</td>
<td>1.34 (0.93–1.94)</td>
<td>2.89 (0.88–12.36)</td>
<td>3.08 (0.94–10.13)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>0.98 (0.46–2.08)</td>
<td>1.05 (0.97–1.13)</td>
<td>1.24 (0.57–2.73)</td>
<td>1.03 (0.74–1.44)</td>
<td>1.41 (0.53–3.72)</td>
<td>2.20 (1.15–4.19)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>2.72 (1.23–6.01)</td>
<td>1.15 (0.89–1.48)</td>
<td><strong>2.24 (1.38–3.63)</strong></td>
<td>0.62 (0.37–1.22)</td>
<td>6.11 (0.78–47.93)</td>
<td>1.53 (0.15–15.28)</td>
</tr>
<tr>
<td>Combined</td>
<td>1.26 (0.93–1.71)</td>
<td>1.04 (1.00–1.09)</td>
<td>1.10 (0.91–1.34)</td>
<td>1.10 (0.89–1.36)</td>
<td>1.40 (0.93–2.10)</td>
<td><strong>2.46 (1.63–3.70)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Bolded</strong> risk ratios highlight statistically significant results (P&lt;0.05). <strong>RA</strong> = Rheumatoid Arthritis, <strong>MTX</strong> = Methotrexate. Superscript indicates the number of RCTs included in the comparison, <strong>TNF</strong> = Tumour Necrosis Factor. doi:10.1371/journal.pone.0030275.t006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the second and third meta-analysis the efficacy of MTX and TNF-blocker combination was found to be superior to either MTX or TNF-blocker alone, respectively. The increase in the number of discontinuations due to adverse events (RR 1.37 95% 1.01–1.87) compared to MTX alone is likely to be acceptable. Patients with previous exposure to MTX were more likely to benefit from the combination therapy compared to MTX naive patients. Compared to monotherapy with a TNF-blocker the
### A Systematic Review of TNF-Blockers in RA

Figure 3. Forest plot of the number of discontinuations due to an adverse event.

doi:10.1371/journal.pone.0030275.g003

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TNF-blocker</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Infliximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abe 2006</td>
<td>5 100</td>
<td>1 47</td>
<td>2.35 [0.28, 19.56]</td>
</tr>
<tr>
<td>Quinn 2005</td>
<td>1 10</td>
<td>0 10</td>
<td>3.00 [0.14, 65.90]</td>
</tr>
<tr>
<td>Schiff 2008</td>
<td>8 165</td>
<td>1 110</td>
<td>5.33 [0.68, 42.05]</td>
</tr>
<tr>
<td>St. Clair 2004</td>
<td>69 722</td>
<td>9 298</td>
<td>3.16 [1.60, 6.25]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>997 465</td>
<td>11.9%</td>
<td>3.22 [1.76, 5.91]</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>83 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 3.32, df = 3 (P = 0.86); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.76 (P = 0.0002)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Etanercept        |             |         |            |
|                   |             |         |            |
| Bathon 2000       | 11 207      | 24 217  | 0.48 [0.24, 0.96] |
| Emery 2008        | 28 265      | 34 268  | 0.83 [0.52, 1.33] |
| Keystone 2004(a)  | 10 367      | 4 53    | 0.36 [0.12, 1.11] |
| Klareskog 2004    | 49 454      | 32 228  | 0.77 [0.51, 1.17] |
| Lan 2004          | 1 29        | 1 29    | 1.00 [0.07, 15.24] |
| Moreland 1999     | 2 78        | 3 80    | 0.68 [0.12, 3.98] |
| Weinblatt 1999    | 2 59        | 1 30    | 1.02 [0.10, 10.77] |
| Subtotal (95% CI) | 1459 905    | 35.7%   | 0.71 [0.54, 0.92]  |
|                   | Total events |         |             |
|                   | 103 99      |         |             |
| Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 6 (P = 0.76); I² = 0% |
| Test for overall effect: Z = 2.54 (P = 0.01) |

| Adalimumab        |             |         |            |
|                   |             |         |            |
| Breedveld 2006    | 58 542      | 19 257  | 1.45 [0.88, 2.38] |
| Chen 2009         | 3 35        | 0 12    | 2.53 [0.14, 45.69] |
| Keystone 2004(b)  | 26 207      | 13 200  | 1.93 [1.02, 3.65] |
| Kim 2007          | 4 65        | 4 63    | 0.97 [0.25, 3.71] |
| Miyasaka 2008     | 15 178      | 4 87    | 1.83 [0.83, 5.36] |
| Van de Putte 2003 | 5 142       | 1 70    | 2.46 [0.29, 20.70] |
| Van de Putte 2004 | 9 216       | 1 110   | 4.58 [0.59, 35.72] |
| Weinblatt 2003    | 1 140       | 2 62    | 0.22 [0.02, 2.40] |
| Subtotal (95% CI) | 1525 861    | 31.1%   | 1.59 [1.13, 2.23] |
|                   | Total events |         |             |
|                   | 121 44      |         |             |
| Heterogeneity: Tau² = 0.00; Chi² = 5.01, df = 7 (P = 0.66); I² = 0% |
| Test for overall effect: Z = 2.66 (P = 0.007) |

| Golimumab         |             |         |            |
|                   |             |         |            |
| Emery 2009        | 14 477      | 2 160   | 2.35 [0.54, 10.22] |
| Kay 2008          | 8 137       | 3 35    | 0.68 [0.19, 2.44] |
| Keystone 2008(a)  | 7 311       | 4 133   | 0.75 [0.22, 2.51] |
| Subtotal (95% CI) | 925 328     | 11.1%   | 0.98 [0.46, 2.08] |
|                   | Total events |         |             |
|                   | 29 9        |         |             |
| Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 2 (P = 0.38); I² = 0% |
| Test for overall effect: Z = 0.06 (P = 0.95) |

| Certolizumab      |             |         |            |
|                   |             |         |            |
| Fleischmann 2009  | 5 111       | 2 109   | 2.45 [0.49, 12.39] |
| Keystone 2008(b)  | 39 783      | 3 199   | 3.30 [1.03, 10.58] |
| Smolen 2009       | 17 492      | 2 127   | 2.19 [0.51, 9.37] |
| Subtotal (95% CI) | 1386 435    | 10.2%   | 2.72 [1.23, 6.01] |
|                   | Total events |         |             |
|                   | 61 7        |         |             |
| Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0% |
| Test for overall effect: Z = 2.48 (P = 0.01) |

Total (95% CI) 6292 2994 100.0% 1.26 [0.93, 1.71]

Total events 397 170

Heterogeneity: Tau² = 0.20; Chi² = 43.84, df = 24 (P = 0.008); I² = 45%

Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable
safety of the combination treatment was equal or even improved regarding some aspects.

The fourth meta-analysis found no statistical difference between MTX and TNF-blocker monotherapy and the fifth one confirmed that TNF-blocker monotherapy was more efficacious than placebo. The last secondary efficacy meta-analysis found little benefit from increasing the dose of TNF-blockers.

In the first safety comparison between TNF-blockers and control the risk ratios reached statistical significance only in the number of patients experiencing injection or infusion reactions. Interestingly, infliximab, adalimumab and certolizumab increased the risk of discontinuation of treatment due to adverse events, but etanercept made it less likely. Certolizumab was the only TNF-blocker which increased the likelihood of experiencing a serious adverse event. While TNF-blockers as a group increased the odds to experience an injection or infusion reaction this may not be the case with adalimumab and certolizumab.

**Strengths and limitations**

It could be asked, whether TNF-blocker naive and switchers should be included in the same review, because these patients could be very different. However, fifteen trials included in this systematic review stated previous TNF-blocker use as an exclusion criterion. In eight more trials it was unclear if switchers were included and only two certolizumab trials included switchers but excluded those who had had insufficient response to previous TNF-blocker treatment. However, the percentage of previous TNF-blocker users in these two trials was small (2–4%) and a sensitivity analysis was performed.

While broader comparisons with larger number of trials may be more likely to reach statistically significant results (1.00 not included in the confidence interval), their validity may be questioned. Heterogeneity introduced by combining the results of trials with different settings causes random effects model to calculate wider confidence intervals than fixed effects model would do. While reducing the possibility of type I error, it may introduce a type II error. Hence, the efficacies of TNF-blockers were compared with different controls, combinations and dosages in smaller, but more homogenous comparisons.

Results of the sensitivity analyses revealed that the source of bias in the RCTs is as likely to lead to underestimation as overestimation of the risk difference between intervention and control groups. However, the homogeneity of study population, intervention, control, outcomes and study settings are likely to be more crucial to the validity of the meta-analysis. Length of exposure was not taken into account in the safety analyses, only the difference in risk ratios between intervention and control group.

The methods used in the study were derived from the Handbook for systematic reviews of interventions by Cochrane Collaboration. The team involved in study design and execution included clinicians, methodology experts and pharmacists. Two researchers independently worked at each step and afterwards combined their results to improve the validity of the study. The meta-analyses were done using Review Manager 5.0 – software. The report was written in accordance to the PRISMA-statement (table S3).

Our systematic review and meta-analysis has some limitations. The authors of the included trials were not contacted to retrieve unpublished data. Many studies that lasted for one year or more only reported results at 12 months. The meta-analyses would have been more powered if the efficacy results had been reported at all time points. Selective reporting was included in the evaluation for bias, but we were unable to identify any bias here.

**Findings in comparison to other systematic reviews**

Another systematic review and meta-analysis pooled efficacy results from different time points and found slightly different estimates for the efficacy of TNF-blockers, which is likely due to differences in study designs [12]. Several large clinical trials have been published since the aforementioned review along with the introduction of two novel TNF-blockers, certolizumab and golimumab. Our study distinguishes itself from previous systematic reviews by including larger number of clinical trials and by presenting efficacy results separately at three, six and twelve months. Our results reveal that the new substances do not offer improved efficacy or safety profile over the already existing ones. A recent systematic review concluded that certolizumab is at least as efficacious compared to older TNF-blockers [14]. However, the study did not include studies with MTX comparison nor evaluate the safety of biologic treatments. Certolizumab may be more efficacious than golimumab but may also be associated with a greater risk of serious adverse events.

A previous systematic review reached the same conclusion as we did, regarding the increased dose of TNF-blockers. Contradicting our results, they found high doses leading to two-fold risk of serious infections. In contrast to our direct approach, they however separately compared recommended and high doses of TNF-blockers to placebo [10]. Another systematic review concluded that infliximab might require an increased dosage level to reach similar efficacy as etanercept and adalimumab have [13].

**Implications for practise and research**

The novel TNF-blockers may offer an alternative to older substances but do not make them obsolete. On the contrary, etanercept may be the best choice when taking into account safety profiles of the TNF-blockers. Infliximab, etanercept and adalimumab have been in clinical use for years with extensive amount of post-marketing data available. More post-marketing information is needed on certolizumab and golimumab for comprehensive pharmacovigilance.

The annual medication costs of TNF-blockers are more than 10 000€ while the MTX treatment costs less than 100€ per year. Subgroup analysis in table 3 suggests that considering the high expenses of biologics, the treatment of RA could be initiated with MTX while combining TNF-blockers to ongoing treatment in patients with insufficient response to MTX. Even though safety was not compromised, it might not be cost-effective to use high doses of TNF-blockers. Given the limited resources in healthcare systems our results may help clinicians and decision makers to get most out of the expensive, but efficacious treatment.

The next step could be to analyze the efficacy and safety of not just TNF-blockers, but all biologics in a large systematic review and meta-analysis. One randomized clinical trial included in our systematic review actually compared abatacept to infliximab [53]. However, a systematic review is indicated to summarise the evidence.

**Supporting Information**

**Table S1** Search strategy to (Ovid®) Medline. (DOCX)

**Table S2** Description of studies included in the systematic review and meta-analysis. 1 = Evaluation based on 28 joints. 2 = Baseline data. 3 = Evaluation based on 71 joints. 4 = Values in median. 5 = placebo switched to active medication at 6 months. Ada = Adalimumab. Cer = Certolizumab pegol. Eta = Etanercept. Gol = Golimumab. Inf = Infliximab. MTX = methotrexate. (DOCX)
References


Author Contributions

Conceived and designed the experiments: KA LV AM YTK DN MB. Performed the experiments: KA LV. Analyzed the data: KA LV. Wrote the paper: KA LV AM YTK DN MB.

Table S3 PRISMA Checklist of items to include when reporting a systematic review or meta-analysis.

Acknowledgments

We would like to thank librarian Terhi Sandgren for the design and execution of the systematic search of the literature.


