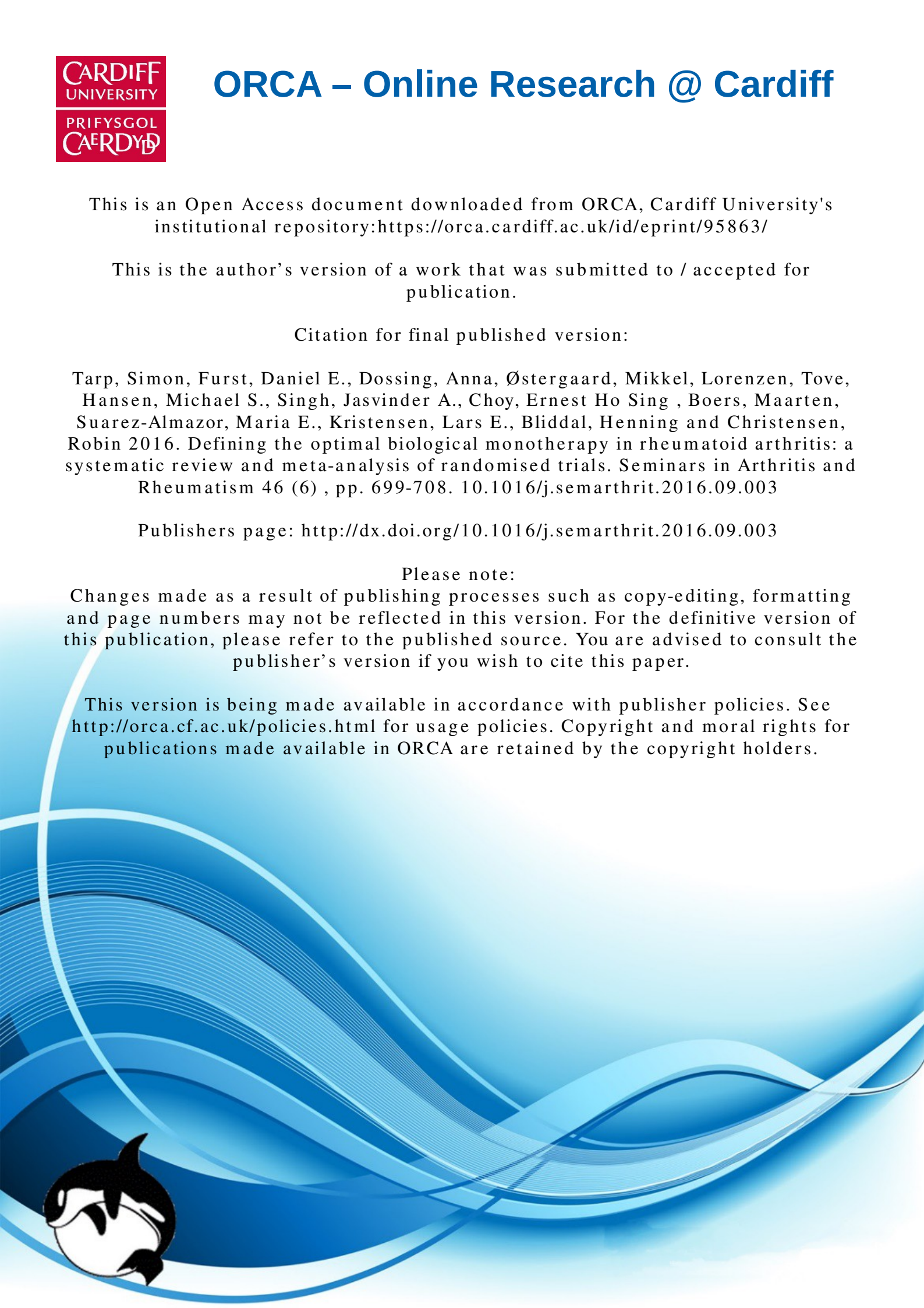

Defining the optimal biological monotherapy in rheumatoid arthritis: A systematic review and network meta-analysis of randomised trials

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ABSTRACT

Objectives: To summarise and compare the benefits and harms of biological agents used as monotherapy for rheumatoid arthritis (RA).

Methods: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and other sources for randomised trials that compared biological monotherapy with methotrexate, placebo, or other biological monotherapies. Primary outcomes were American College of Rheumatology 50% improvement (ACR50) and the number of patients who discontinued due to adverse events. Our network meta-analysis was based on mixed-effects logistic regression, including both direct and indirect comparisons of the treatment effects, whilst preserving the randomised comparisons within each trial.

Results: The analysis comprises 28 trials (8,602 patients), including all nine biological agents approved for RA. Of the included trials, 8 (29%) included 'DMARD-naïve', and 20 (71%) 'DMARD-Inadequate responder' (DMARD-IR) patients. All agents except anakinra and infliximab were superior to placebo with regard to ACR50. Etanercept and rituximab were superior to anakinra. Tocilizumab was superior to adalimumab, anakinra, certolizumab, and golimumab. When including only DMARD-IR trials, the same statistical pattern emerged, complemented with superiority of etanercept and tocilizumab compared with abatacept. Focusing on recommended doses, both etanercept and tocilizumab were superior to adalimumab and certolizumab. No differences in benefit among etanercept, tocilizumab, and rituximab were found. However, because rituximab was evaluated in just 40 patients, our confidence in the estimates is limited, No statistically significant differences among biological agents were found with respect to harm.

Conclusions: Evidence suggests etanercept or tocilizumab to be the most appropriate choice for RA patients treated with biological monotherapy.

INTRODUCTION

Inflammation in rheumatoid arthritis (RA) patients should be suppressed as early as possible {Emery, 2006 1954 /id}, with pharmacologic treatment directed at tight control of inflammation {Huizinga, 2010 2381 /id;Smolen, 2010 2327 /id}. Disease-modifying antirheumatic drugs (DMARDs) can interfere with the disease process {Smolen, 2014 1918 /id;Singh, 2012 2330 /id}. Conventional synthetic DMARDs (csDMARDs) include methotrexate (MTX), hydroxychloroquine, leflunomide, sulfasalazine, and glucocorticoids. csDMARDs can also be used in various combinations {Singh, 2012 2330 /id}. MTX is considered the standard csDMARD, but in high-risk patients, early combination of MTX with prednisolone or a biological agent improves outcomes {Klarenbeek, 2010 2382 /id}.

Biological agents are usually given to patients with active RA who have not achieved satisfactory response to one or more csDMARDs such as MTX {Smolen, 2014 1918 /id}. Currently, the biological agents approved for RA include the following nine drugs: five tumour necrosis factor inhibitors (TNFi) – adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; and four with other modes of action – anakinra, abatacept, rituximab, and tocilizumab {Furst, 2012 2331 /id}. Infliximab and golimumab are approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) only with concomitant use of MTX, and rituximab only with a csDMARD {Emery, 2013 2499 /id}. All other biological agents are also approved in monotherapy, albeit abatacept and anakinra only by the FDA {Emery, 2013 2499 /id}.

Recently, concerns have been raised as to whether external factors, including lack of adherence to csDMARD therapy, might reduce the anticipated benefit associated with use of biologic agents if patients discontinue use of a concomitant csDMARD. Evidence from real-life registry data shows that approximately one-third of RA patients treated with biological agents use

them as monotherapy and that when MTX is prescribed in combination with a biological agent, more than half of the patients do not take MTX as prescribed {Emery, 2013 2499 /id}.

As most biological agents have shown more favourable results in combination with csDMARD therapy {Singh, 2009 1746 /id}, and many RA patients might not adhere to their MTX prescription, it is important to evaluate the benefit and harm associated with use of biological agents as monotherapy, and not only the traditional combination therapy strategies {Bergman, 2010 1744 /id;Guyot, 2011 2376 /id;Guyot, 2012 2375 /id}. Therefore, the objective of this study was to assess the efficacy and safety of the individual biological agents applied as monotherapy in patients with RA to inform decision makers on the relative effectiveness of biological agents used in monotherapy.

METHODS

A network meta-analysis of randomised trials combined direct and indirect evidence. Methods of analysis and inclusion criteria were specified in advance and documented in a protocol (PROSPERO 2012:CRD42012002800). Both protocol and analyses were prepared according to the '*Methodological Expectations for Cochrane Intervention Reviews*' (MECIR) program. Our study conforms to the PRISMA guidelines for reporting systematic reviews {Liberati, 2009 2163 /id}.

Literature search

We searched The Cochrane Central Register of Controlled Trials, Medline, Embase, and ClinicalTrials.gov for published reports from inception of each database through December 16, 2014 **(Supplement Table 1)**. We combined terms for rheumatoid arthritis with the nine biological agents of interest (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab). Search results were limited to randomised controlled trials (RCTs) by applying appropriate filters. We then collated additional reports identified in relevant systematic reviews not retrieved through the electronic databases. We also scrutinized relevant reports on FDA's and EMA's websites and searched relevant pharmaceutical companies' websites to identify unpublished trial data.

Trial selection

Double-blind randomised trials studying the administration of one of the eligible biological agents were considered eligible if they were used as monotherapy in an (FDA/EMA)-approved route of administration in RA patients. Trials were considered eligible if at least one within-study comparison was available with placebo, MTX, or another approved biological agent as

monotherapy. We did not include open label trials, trials with no full English text available, trials not reporting ACR50 responses, trials comparing the same biological agent with and without MTX, or trials comparing different doses of the same biological agent in monotherapy.

Outcome measures

The core-outcome data in each study consist of the sample size of the groups and the number of patients in each group who met the predefined outcomes of interest. *A priori* it was decided to use the outcome assessment at 6 months, if available. If 6 months data were unavailable, we used data closest to 6 months in each trial. Two major outcomes were considered co-primary {Ghogomu, 2014 2462 /id}: benefit – defined as the ACR50 response criteria {Chung, 2006 1641 /id}; and harm by proxy – determined by the number of withdrawals because of adverse events {Ioannidis, 2004 1372 /id}. ACR50 is considered a validated, clinically meaningful binary measure of benefit {Singh, 2009 1746 /id}. Withdrawals that occur because of adverse events are a measure of patients' tolerance of adverse events reported consistently {Singh, 2009 1746 /id}. The secondary outcomes were ACR20, ACR70, total number of patients who withdrew from the study, and the number of patients who experienced at least one serious adverse event (SAE).

Data collection and risk-of-bias assessment

Outcome measure extractions were based on the intention-to-treat (ITT) population whenever possible. Two independent reviewers (ST and AD) extracted all the data. Data were collected on the general characteristics of the RCT and sample size. The interventions being compared were extracted, including dosages and frequency of the administered drugs.

The internal validity of the included studies was evaluated on the basis of the

apparent risk of bias within each RCT; domains (including selection bias, performance bias, detection bias, attrition bias, and reporting bias) were assessed using the items of the risk-of-bias tool as recommended by the Cochrane Collaboration {Higgins, 2011 1853 /id}.

Data synthesis and analysis

We used random effects meta-analyses by default, assuming the true treatment effect differs from study to study {Riley, 2011 2502 /id}. Unlike a contrast-based (standard) meta-analysis approach {DerSimonian, 1986 525 /id}, an arm-based approach was used to include multiple comparisons in the network meta-analysis {Salanti, 2008 2039 /id} in order to combine both direct and indirect comparisons. We performed mixed-effects logistic regression using an (arm-based) random effects model within an *empirical Bayes* framework {Singh, 2009 1746 /id; Platt, 1999 2711 /id}. The generalised linear mixed model (GLMM) incorporates a vector of random effects and a design matrix for the random effects {Platt, 1999 2711 /id}. Allowance was made for differences in heterogeneity of effects between different drugs by specifying that the linear predictor varies at the level of study and as an interaction between study and drug. In the network meta-analyses, we measured heterogeneity (i.e., between-study variance) for the analysis using T^2 (an estimate for Tau-squared), which examines heterogeneity because of *Study* and *Study×Drug* interaction (smaller values indicate a better model *per se*).

Sensitivity analyses

Post hoc sensitivity analyses on the primary outcomes were conducted to explore impact of csDMARD history and dose: (*i*) exclusion of studies not evaluating csDMARD inadequate responder

patients; (*ii*) exclusion of trial arms not evaluating an FDA- or EMA-recommended average maintenance dose (defined in **Supplement Table 2**), including MTX comparator trial arms not evaluating an oral MTX dose of at least 10 mg weekly (or subcutaneous in equivalent dose). If only one trial arm evaluated a recommended dose, the whole study was excluded from the sensitivity analysis (placebo trial arms [i.e., no biological or csDMARD treatment] were categorised as recommended dose for technical reasons).

- Figure 1. (Flow diagram) Around Here -

RESULTS

Characteristics of reviewed studies

Searches of four primary electronic databases and reviews identified 4,405 unique references. Of the total, 818 proved potentially relevant for full-text review, and 45 references that reported 28 unique randomised trials of all 9 FDA/EMA approved biological agents proved eligible **(Figure 1)**.

The 28 randomised trials, comprising a total of 79 unique trial-arms, included 8,602 patients with RA: abatacept (2 trials; 350 patients), adalimumab (6 trials; 1,928 patients), anakinra (1 trial; 472 patients), certolizumab (2 trials; 421 patients), etanercept (5 trials; 2,047 patients), golimumab (4 trials; 1,279 patients), infliximab (1 trial; 58 patients), rituximab (1 trial; 80 patients), and tocilizumab (6 trials; 1,967 patients). The included trials had different study designs: 13 compared a biological agent in monotherapy with placebo; 14 compared a biological agent in monotherapy to MTX; and only one study compared two biological agents (tocilizumab in monotherapy vs. adalimumab in monotherapy) {Gabay, 2013 2418 /id} **(Table 1)**. The network of eligible comparisons for the primary efficacy outcome (ACR50) is shown in **Figure 2.** The network for withdrawals because of adverse events was essentially the same. Of the 28 included trials, 8 (29%) included 'csDMARD-naïve', 20 (71%) 'csDMARD-IR', and 0 (0%) enrolled biological agent inadequate responder patients (Table 1; references available in **Supplement Table 3**).

- Figure 2. (Network diagram) Around Here -

Benefit and harm according to primary outcomes

As illustrated in **Figure 3A,** most biological agents (as well as MTX) were statistically significantly more likely than placebo to lead to an ACR50 response; exceptions were anakinra and infliximab. Of the 28 included studies (all reporting ACR50), 24 reported withdrawals because of adverse events. Compared to placebo, withdrawals because of adverse events were not statistically significantly higher among patients for any of the drugs **(Figure 3B)**. For sensitivity, direct pairwise meta-analyses were conducted for both primary benefit and harm outcome. As presented in **Supplement Figure 1-4,** estimates from the network meta-analysis were in agreement with the direct evidence (i.e., point estimate from the network meta-analysis were included within the 95%CI of the direct estimate). The only exception was tocilizumab compared with placebo for withdrawal because of adverse events, where the point estimate from the network meta-analysis (1.84) was not included within the 95%CI of the direct estimate (0.04 to 1.29). Further, for benefit the direct pairwise meta-analysis found relevant inconsistency for certolizumab pegol compared with placebo (I^2=71%), with no obvious explanation. Relevant inconsistency was also found for etanercept and tocilizumab compared with MTX (I^2=83% and 80% respectively), probably explained by the low MTX dose (8 mg weekly) used in two Japanese trials (etanercept {Takeuchi, 2012}; tocilizumab {Nishimoto, 2009}. These two trials were excluded in the sensitivity analysis of recommended dose. For harm, relevant inconsistency was also found for etanercept compared with MTX (I^2=79%), probably explained be the low MTX dose applied in the Japanese trial.

- **Figure 3A&B. (Network meta-analysis forest plots of primary benefit/harm each biological agent compared with placebo) Around Here**

Figure 4 presents all comparisons among the nine biological agents in monotherapy, MTX, and placebo in terms of both benefit (ACR50) and harm (withdrawals because of adverse events). Etanercept was more likely to lead to clinical response than anakinra (OR=3.38; 95% CI, 1.26 to 9.01) and MTX (1.54; 1.03 to 2.32; Figure 4). Rituximab also appears more effective than anakinra (4.26; 1.01 to 17.86). Tocilizumab appears superior when compared with each of the following: adalimumab (1.97; 1.22 to 3.17), anakinra (3.97; 1.49 to 10.53), certolizumab pegol (2.35; 1.06 to 5.24), golimumab (1.77; 1.00 to 3.13), and MTX (1.82; 1.23 to 2.68). All other comparisons among biological agents in monotherapy were not statistically significantly different. When harms were monitored by proxy according to all comparisons (Figure 4), none of the drugs included in the network appeared more likely than others to lead to discontinuation due to adverse events.

Figure 4. (Primary Benefit and harm of all biological agents according to the network meta-analysis) Around Here

Benefit and harm according to secondary outcomes

From the primary analysis, based on the primary benefit-outcome, statistical evidence suggested etanercept to be more efficacious than anakinra and MTX. In secondary outcome analyses, this finding was supported for ACR20 but not for ACR70, where etanercept was not statistically significantly different from MTX (1.47; 0.92 to 2.36) **(Supplement Table 4)**. Rituximab was statistically significantly superior to anakinra for the primary benefit-outcome, which was supported by analyses of ACR20 and ACR70. Tocilizumab was statistically superior to adalimumab, anakinra, certolizumab pegol, golimumab, and MTX for ACR50, an effect that appeared robust

when ACR20 and ACR70 rates were evaluated (Supplement Table 4) with one exception; tocilizumab was not statistically significantly superior to golimumab (1.85; 0.97 to 3.52).

When secondary harm measures, SAEs, and the total number of withdrawals **(Supplement Table 5)** were examined, no statistically significant differences occurred for SAEs (anakinra was not included due to lack of reporting). For the total number of withdrawals, tocilizumab was statistically significantly more favourable than abatacept, adalimumab, anakinra, and MTX.

Sensitivity analyses in trials using the recommended dose

When the analysis of the primary benefit outcome (ACR50) was based on treatment with the recommended maintenance dose (**Supplement Table 6**), anakinra and infliximab were not included, as these biological agents were not evaluated at the recommended doses. The apparent superiority of etanercept over MTX could not be confirmed statistically for its recommended dose (OR= 1.25; 0.90 to 1.72). However, in its recommended dose, etanercept was now more likely to lead to clinical response than adalimumab and certolizumab pegol. The findings for tocilizumab appeared robust, with superiority over adalimumab, certolizumab pegol, and MTX. However, the apparent superiority of tocilizumab over golimumab could not statistically be confirmed for recommended dose (OR= 2.07; 0.89 to 4.85). Monitoring harms by proxy according to all comparisons (Supplement Table 6), adalimumab, etanercept, tocilizumab at their recommended doses, and MTX (≥10 mg weekly) were all more likely than placebo to lead to discontinuation due to adverse events. However, no differences among any biological agents or MTX were statistically significant.

Sensitivity analyses among DMARD-IR patients

When the analysis of the primary benefit outcome (ACR50) was based on studies of patients who had had an inadequate response to csDMARDs (DMARD-IR; see **Supplement Table 7**), the findings for etanercept were robust as it was still more likely to lead to clinical response than anakinra and MTX. The apparent superiority of rituximab over anakinra could not be statistically confirmed (3.03; 0.66 to 14.29). Also, the findings for tocilizumab appeared robust, with superiority over adalimumab, anakinra, golimumab, and MTX. However, the apparent superiority of tocilizumab over certolizumab pegol could not be confirmed in the sensitivity analysis based on DMARD-IR patients only (2.18; 0.89 to 5.32).

Further, to explore how much impact the only "biologics head-to-head" comparison study (ADACTA) {Gabay, 2013 2418 /id} had on the estimates in the network, the DMARD-IR sensitivity analyses were performed with exclusion of the ADACTA study on tocilizumab against adalimumab in DMARD-IR patients (**Supplementary Table 8)**, revealing sparse data supporting superiority of tocilizumab compared with other biological agents prior to the ADACTA study (e.g., vs. adalimumab 1.81; 0.80 to 4.15). In the ADACTA study, tocilizumab was statistically significantly superior to adalimumab (2.33; 1.47 to 3.69).

DISCUSSION

This study suggests there are differences in effectiveness but not in harm among biological agents applied as monotherapy in RA. Patient-important benefits such as ACR50 occurred more frequently with etanercept or tocilizumab monotherapy than with other biological agents. Although tocilizumab was superior to a higher number of agents than the number etanercept was superior to, no statistically significant difference between tocilizumab and etanercept was found throughout the conducted analyses. Further, in recommended dose, both etanercept and tocilizumab were superior to adalimumab and certolizumab pegol. Despite rituximab's being superior to anakinra, had response rates comparable to etanercept and tocilizumab against placebo, and no differences between rituximab and etanercept or tocilizumab were found, evidence on rituximab was based on one study only, where 40 patients were treated with rituximab monotherapy, thereby limiting our confidence in these findings.

Our findings are relevant because substantial numbers of patients either do not tolerate MTX (or other csDMARDs), or discontinue these agents for unknown reasons {Emery, 2013 2499 /id}. Registry data confirm that biological monotherapy is a common treatment in RA {Yazici, 2008 4353 /id;Jorgensen, 2015 4352 /id;Emery, 2013 2499 /id}. In the sensitivity analysis of csDMARD-inadequate responder patients, most agents had response rates comparable to continued use of MTX monotherapy, where only etanercept and tocilizumab monotherapy were superior to MTX.

Only one head-to-head trial comparing monotherapy with two biological agents, tocilizumab and adalimumab, has been published {Gabay, 2013 2418 /id}. We therefore performed a network meta-analysis to indirectly compare other evaluated therapies, cognisant of the limitations of this approach {Mills, 2012}. This methodology relies upon assumptions about the

similarities of the included trials in terms of comparability of patient and study characteristics {saliati 2014}. However, the comparative effectiveness paradigm dictates that guideline panels as well as clinicians and patients are challenged with the dilemma of choosing among these therapies in the absence of robust comparative data about their relative benefit and harm differences. Other (recent) network meta-analyses, to a large extent, support our findings regarding etanercept's and tocilizumab's favourable profiles in terms of ACR50 {Buckley, 2015 4355 /id;Migliore, 2015 4356 /id;Orme, 2012 4357 /id}. However, due to different study inclusion/exclusion criteria and different methodological approaches, these studies differ with respect to the comparative effectiveness between etanercept and tocilizumab. In the study by Buckley *et al.* {Buckley, 2015 4355 /id}, tocilizumab monotherapy was not statistically significantly different from TNFi monotherapy (i.e., all TNFi's were combined). Migliore *et al.* {Migliore, 2015 4356 /id}, who restricted their eligibility criteria to studies of biological agents approved in EU for RA as monotherapy; found that tocilizumab was superior to etanercept. Other discrepancies when compared to our study included the minimum treatment duration of 16 weeks, the date of search, and omission of unpublished trials (e.g., the now published FUNCTION study [tocilizumab monotherapy vs. MTX]{Burmester 2015} had results available online April 2013 in the company trial database). Although Migliore *et al.* was limited to double-blind RCTs, as was our study, it included the open-label SAMURAI study (tocilizumab monotherapy vs. csDMARDs; only x-ray reader-blinded). Further, the adalimumab monotherapy study CHANGE {Miyasaka, 2008} and the etanercept monotherapy study by Takeuchi *et al.* {Takeuchi 2012} were not included, although both fulfilled inclusion criteria and were published before date of search (September 2013). The third network meta-analysis by Orme *et al.* {Orme, 2012 4357/id} showed tocilizumab monotherapy was not statistically significantly different from etanercept monotherapy.

Our evidence synthesis also has limitations. The included studies span a 17-year period, from 1998 through 2015; so patients enrolled in early studies may differ from those included in more recent studies. Moreover, the RA patients enrolled in the different monotherapy studies are to some extent heterogeneous (encompassing different duration of diseases and differences in the extent of prior MTX failure). Further, only one head-to-head trial was identified, reducing our confidence in the comparative estimates. In other words, future biological agent monotherapy head-to-head trials will likely have an important impact on our estimates. *A priori*, we defined a hierarchical list of outcomes, giving priority to 6 months data when available. When they were not available, other time points were used (e.g., nine studies lasted only 16 weeks or less, and in six studies safety data were available only after one year or more. Comparisons among studies across different time points could potentially limit the interpretation of our results. Further, whether our results can be extrapolated to long-term efficacy and safety is not clear.

In conclusion, trial evidence suggests etanercept or tocilizumab to be the most appropriate choice to RA patients treated with biological monotherapy.

Contributors *Conception and design:* RC, ST, DEF, MØ, TL, MSH, JAS, BJE, HB. *Analysis and interpretation of the data:* All. *Drafting of the article:* ST, RC, and HB. *Critical revision of the article for important intellectual content:* All. *Final approval of the article:* All. *Statistical expertise:* RC, ST, DEF, MØ, TL, MSH, JAS. *Collection and assembly of data:* RC, ST, DEF, AD. *Obtaining of funding:* RC, MØ, TL, MSH, and HB.

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