RHEUMATOLOGY

Rheumatology 2017;56:417–425
doi:10.1093/rheumatology/kew442
Advance Access publication 23 December 2016

Original article

Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis

Simon Tarp[1], Daniel Eric Furst[2,3,4], Maarten Boers[5,6], George Luta[7], Henning Bliddal[1], Ulrik Tarp[8], Karsten Heller Asmussen[9], Birgitte Brock[10], Anna Dossing[1], Tanja Schjødt Jørgensen[1], Steffen Thirstrup[11] and Robin Christensen[1]

Abstract

Objectives. To determine possible differences in serious adverse effects among the 10 currently approved biological and targeted synthetic DMARDs (b/ts-DMARDs) for RA.

Methods. Systematic review in bibliographic databases, trial registries and websites of regulatory agencies identified randomized trials of approved b/ts-DMARDs for RA. Network meta-analyses using mixed-effects Poisson regression models were conducted to calculate rate ratios for serious adverse events (SAEs) and deaths between each of the 10 drugs and control (i.e. no b/ts-DMARD treatment), based on subjects experiencing an event in relation to person-years. Confidence in the estimates was assessed by applying the Grading of Recommendations Assessment, Development and Evaluation approach (GRADE).

Results. A total of 117 trials (47 615 patients) were included. SAEs were more common with certolizumab compared with abatacept (rate ratio = 1.58, 95% CI: 1.18, 2.14), adalimumab (1.36, 95% CI: 1.02, 1.81), etanercept (1.60, 95% CI: 1.18, 2.17), golimumab (1.45, 95% CI: 1.00, 2.08), rituximab (1.63, 95% CI: 1.16, 2.30), tofacitinib (1.44, 95% CI: 1.03, 2.02) and control (1.45, 95% CI: 1.13, 1.87); and tocilizumab compared with abatacept (1.30, 95% CI: 1.03, 1.65), etanercept (1.31, 95% CI: 1.04, 1.67) and rituximab (1.34, 95% CI: 1.01, 1.78). No other comparisons were statistically significant. Accounting for study duration confirmed our findings for up to 6 months' treatment but not for longer-term treatment (6–24 months). No differences in mortality between b/ts-DMARDs and control were found. Based on the GRADE approach, confidence in the estimates was low due to lack of head-to-head comparison trials and imprecision in indirect estimates.

Conclusion. Despite low confidence in the estimates, our analysis found potential differences in rates of SAEs. Our data suggest caution should be taken when deciding among available drugs.

Systematic review registration number. PROSPERO CRD42014014842.

Key words: meta-analysis, systematic review, serious adverse events, mortality, biological agents, targeted synthetic disease-modifying antirheumatic drugs, rheumatoid arthritis, indirect comparison, network meta-analysis

[1]Musculoskeletal Statistics Unit, The Parker Institute, Copenhagen University Hospital at Bispebjerg and Frederiksberg, Copenhagen, Denmark, [2]David Geffen School of Medicine, University of California Los Angeles, CA, [3]Division of Rheumatology, University of Washington, Seattle, WA, USA, [4]Division of Rheumatology, University of Florence, Florence, Italy, [5]Department of Epidemiology and Biostatistics, [6]Amsterdam Rheumatology and Immunology Center, VU University Medical Center, Amsterdam, The Netherlands, [7]Department of Biostatistics, Bioinformatics, and Biomathematics, Georgetown University Medical Center, Washington, DC, USA, [8]Department of Rheumatology, Aarhus University Hospital, Aarhus N, [9]Department of Rheumatology, Copenhagen University Hospital at Bispebjerg and Frederiksberg, Copenhagen, [10]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus N and [11]Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark

Submitted 19 April 2016; revised version accepted 31 October 2016

Correspondence to: Robin Christensen, Musculoskeletal Statistics Unit, The Parker Institute, Copenhagen University Hospital at Bispebjerg and Frederiksberg, Nordre Fasanvej 57, 2000 Copenhagen, Denmark.
E-mail: Robin.Christensen@regionh.dk

CLINICAL SCIENCE

Rheumatology key message

- Certolizumab was associated with higher rates of serious adverse events in RA compared with equally effective alternatives.

Introduction

Biological DMARDs (bDMARDs) are widely used to lower disease activity and reduce progression of joint damage in RA patients [1]. Clinical guidelines recommend use of a bDMARD in patients who have not responded adequately to conventional synthetic DMARDs (csDMARDs) (i.e. clinical remission or at least low disease activity) [1, 2]. Currently, nine different bDMARDs are approved both by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treating RA; another targeted synthetic DMARD (tsDMARD), tofacitinib, is approved only by the FDA. All currently approved bDMARDs and tofacitinib are similarly effective, with the exception of anakinra [1–3]. However, differences in important safety aspects of these drugs have not been studied exhaustively.

Approval of b/ts-DMARDs has been based on their ability to achieve clinical response relative to placebo (with or without background csDMARDs) without causing severe toxicity. However, the studies are not adequately powered to fully determine the potential harmful effects of these drugs [4]. For adverse outcomes, meta-analysis methodology may be the only way to obtain reliable estimates of harm occurring in randomized trials [5]. Multiple meta-analyses have evaluated harmful effects of bDMARDs for treating RA [3, 6–17]. Previous meta-analyses arrived at varying conclusions regarding harmful effects of each bDMARD. Inconsistencies across meta-projects make it difficult for clinicians and policy makers to prioritize among available b/ts-DMARDs. Adaptive trial designs, which mandatorily switch non-responder patients at an interim time-point to a rescue regime (i.e. withdraw them from the main study), may present a key limitation to these meta-analyses, because this trial design often leads to a high dropout rate in the control group, possibly influencing the apparent adverse event risk when compared with the intervention and control group [6, 18–20]. This important issue, at least to our knowledge, has been explored in only one meta-analysis of RA patients, in only a subgroup of the bDMARDs available today, and only in relation to placebo [15].

The choice between apparently equally effective therapies ideally should be based on harmful effects, patient preferences and, only lastly, cost [21]. In the area of b/ts-DMARD treatment of RA, an evaluation of potential harmful effects is urgently needed. Information about important safety aspects will help physicians make better recommendations to patients whose RA cannot be managed successfully with csDMARDs. Our study aimed to compare serious adverse effects and death rates between all b/ts-DMARDs approved by either the FDA or the EMA for treating RA, applying a methodology that involves adjustments for the skewed dropout between intervention and control groups.

Methods

This systematic review and meta-analysis was performed in accordance with the recommendations of the Cochrane Collaboration [22] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. The study protocol was pre-specified and registered in advance in PROSPERO (CRD42014014842).

Data sources and searches

The Cochrane Central Register of Controlled Trials, Medline, Embase and ClinicalTrials.gov were searched for published reports from the inception of each database to 16 December 2014 (supplementary Table S1, available at *Rheumatology* Online). Additional reports identified in relevant systematic reviews not retrieved through the electronic databases were then collated. Relevant reports on the FDA and EMA websites, and those of relevant pharmaceutical companies were scrutinized to identify unpublished trial data.

Study selection

As described in the protocol outlining our study methods [24], we included randomized trials that assigned RA patients (meeting the ACR criteria [25] or early RA) to one of the 10 currently EMA/FDA approved b/ts-DMARDs, administered by an approved route of administration (either as add-on treatment to csDMARDs or as monotherapy). We included both published and unpublished randomized trials evaluating abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib. In our protocol, we excluded: studies co-administrating more than one b/ts-DMARD; studies evaluating single-dose administration (except for rituximab); open-label extension trials with no relevant comparison group; studies of vaccine treatment; studies comparing only varying doses or administration forms of the same b/ts-DMARD; studies not reported in English; and studies not reporting all serious adverse event (SAEs) data (e.g. studies only reporting serious infections data).

Two reviewers independently screened titles, abstracts and relevant full citations identified by the searches according to our inclusion/exclusion criteria. Disagreements were resolved by consensus with a third reviewer.

Data extraction and quality assessment

The two major outcomes were risk of serious adverse effects, evaluated by the reported number of patients experiencing at least one SAE (as defined in the individual studies [26]), and mortality, evaluated by the number of deaths reported (without distinguishing between reported as related or unrelated to treatment [27]). These outcomes reflect what could be considered important proxies of harm for both patients and decision makers (i.e. both

included in the 2015 ACR RA guideline [2]). All outcomes were evaluated using event data from the longest available controlled period for each trial (e.g. before mandatory switch to open-label active treatment or re-randomization). For each trial, we categorized the individual treatment groups as either one of the 10 b/ts-DMARDs or as control (i.e. no b/ts-DMARD treatment). Each treatment group was subcategorized according to concomitant use of csDMARDs as no (i.e. no csDMARD treatment) or yes (i.e. allowed as background treatment or part of the allocation). Each b/ts-DMARD treatment group dose was subcategorized according to the product labelling as recommended, below recommended (low) or above recommended (high) dose. Total person years for each treatment group were extracted (if not reported, it was estimated by assuming a linear dropout rate between baseline and end of controlled period [i.e. the area under the curve] [15]). Data extractions were done independently by at least two reviewers. Disagreements were resolved by consensus with a third reviewer.

Internal validity was independently assessed by two reviewers, using the Cochrane Collaboration's risk-of-bias tool [28]. We assessed the quality of evidence between the 10 drugs' rate ratio of SAEs using criteria suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [29], including ratings of quality of evidence of direct, indirect and network meta-analysis comparison estimates [30].

Data synthesis and analysis

Network meta-analysis was performed to compare each of the 10 evaluated drugs. Two approaches were used. The first approach was based on number of subjects experiencing an event (numerator) and the number of randomized subjects without an event (denominator), expressed as odds ratios (ORs) with 95% CIs. Relative risk statistics might be more appropriate [31], but for computational reasons OR statistics was our primary. The second approach accounted for exposure time; it was based on total person-years (denominator) and was expressed as rate ratios with 95% CIs. Consistent with the GRADE approach specific to network meta-analysis, standard pairwise (contrast-based), indirect and network meta-analyses were conducted [30]. All tests were two-sided with a significance level of 0.05. A detailed description of the statistical analysis appears in the Supplementary Appendix Text 1, available at *Rheumatology* Online.

Results

Searches of four primary electronic databases and in existing reviews identified 4405 unique references. Of the total, 818 references proved potentially relevant for full-text review, and of these 346 (reporting 117 unique randomized trials of 10 FDA/EMA-approved b/ts-DMARDs) proved eligible (Fig. 1).

The 117 randomized trials included 47 615 patients with RA, treated for approximately 30 971 person-years. The trials covered 101 b/ts-DMARD *vs* control trials; 8 b/ts-DMARDs head-to-head trials; 5 b/ts-DMARD monotherapy *vs* csDMARDs trials; and 3 b/ts-DMARD monotherapy *vs* same b/ts-DMARD plus csDMARDs trials, comprising a total of 324 unique trial-arms (supplementary Table S2, available at *Rheumatology* Online). The network of eligible comparisons is shown in Fig. 2. Most of the included trials were of short duration, with the median length being 6 months (range, from 1 month to 2 years). Thus, all the results below should be interpreted as applying to a fairly short time frame. To compute risk in absolute terms, the median incidence rate of having an SAE across all control arms corresponded to 5%. The median control incidence rate per 100 person-years was 11 (supplementary Table S3, available at *Rheumatology* Online).

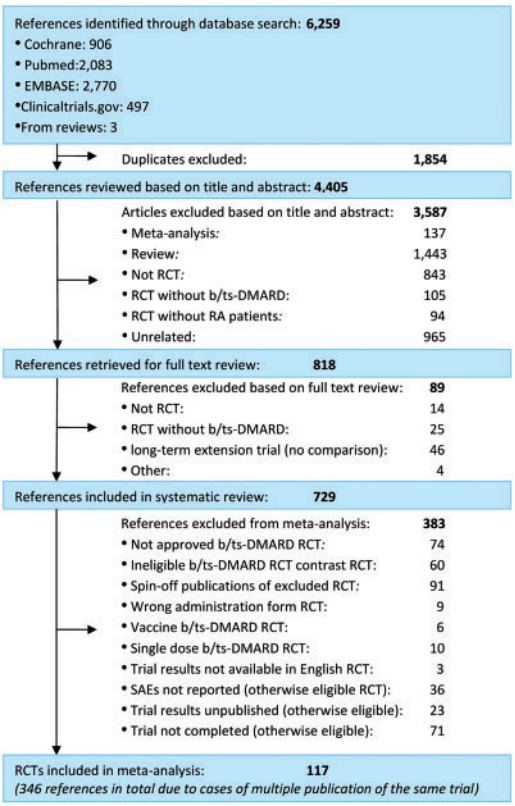
Serious adverse events

The exposure-adjusted network meta-analysis, adjusted for dose (recommended/below recommended/above recommended) and concomitant csDMARD use (yes/no), found that certolizumab pegol compared with control (i.e. no b/ts-DMARD treatment) statistically significantly increased the rate of SAEs by 45% (rate ratio 1.45, 95% CI: 1.13, 1.87) (Table 1**)**, corresponding to five more patients having an SAE per 100 person-years (from 1 to 10 more). Comparisons between treatments showed that certolizumab pegol increased the rate of SAEs compared with abatacept (1.58, 95% CI: 1.18, 2.14), adalimumab (1.36, 95% CI: 1.02, 1.81), etanercept (1.60, 95% CI: 1.18, 2.17), golimumab (1.45, 95% CI: 1.00, 2.08), rituximab (1.63, 95% CI: 1.16, 2.30) and tofacitinib (1.44, 95% CI: 1.03, 2.02), and that tocilizumab was associated with more SAEs than abatacept (1.30, 95% CI: 1.03, 1.65), etanercept (1.31, 95% CI: 1.04, 1.67) and rituximab (1.34, 95% CI: 1.01, 1.78). No other comparisons were statistically significantly different.

The pairwise meta-analysis of each drug compared with control [i.e. no b/ts-DMARD but with the same concomitant treatment (none or csDMARDs)] found, in contrast to the network analysis, that certolizumab pegol at recommended doses did not statistically significantly increase the rate of SAEs (1.31, 95% CI: 0.95, 1.80) (supplementary Fig. S1, available at *Rheumatology* Online).

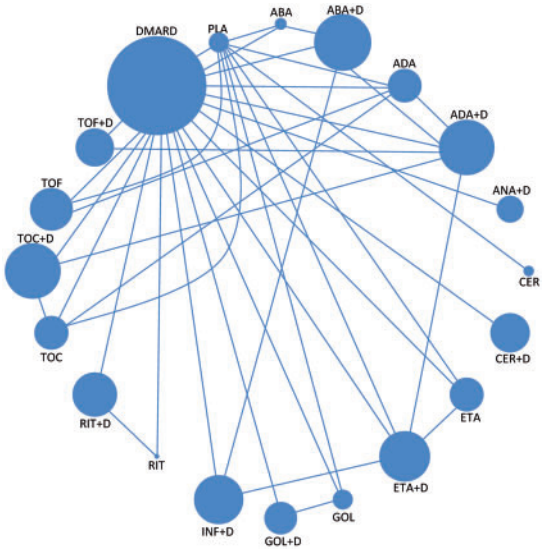
Sensitivity analysis, stratifying for concomitant csDMARD use and dose, refined the overall rate ratio network meta-analysis (supplementary Table S4, available at *Rheumatology* Online). As monotherapy and in recommended dose, this analysis only confirmed that certolizumab pegol caused significantly more SAEs than etanercept and tofacitinib. With concomitant csDMARD use and in recommended dose, this analysis only confirmed that certolizumab pegol caused significantly more SAEs than abatacept, etanercept, rituximab and control (i.e. csDMARDs alone); and tocilizumab caused more SAEs than abatacept. Furthermore, the sensitivity analysis revealed that with concomitant csDMARDs in recommended dose, abatacept caused fewer SAEs than tofacitinib. As monotherapy and in recommended dose, tofacitinib had significantly lower

Fig. 1 Flow diagram of search results



RCT: randomized controlled trials; b/ts-DMARD: biological/targeted synthetic DMARD; SAEs: serious adverse events.

Fig. 2 Network of treatment comparisons for serious adverse events



The size of the circles corresponds to the total number of person-years. Direct comparable treatments are connected with a line. ABA: abatacept; ADA: adalimumab; ANA: anakinra; CER: certolizumab pegol; +D: plus DMARD; ETA: etanercept; GOL: golimumab; INF: infliximab; PLA: placebo; RIT: rituximab; TOC: tocilizumab; TOF: tofacitinib.

rates of SAEs compared with adalimumab, tocilizumab, control (i.e. no csDMARD use) and tofacitinib + csDMARDs. Adalimumab monotherapy had a higher rate of SAEs than when used with concomitant csDMARDs. Finally, csDMARDs alone (i.e. no b/ts-DMARD treatment) caused significantly fewer SAEs than no active treatment (i.e. no csDMARD or b/ts-DMARD treatment) (0.70, 95% CI: 0.51, 0.97). There was a potential dose response for: certolizumab pegol + csDMARDs (rate ratio: low 1.08, recommended 1.38, high 1.40); adalimumab + csDMARDs (low 0.71, recommended 1.04, high 1.76); etanercept + csDMARDs (low 0.54, recommended 0.96, high not available), compared with csDMARDs alone.

Rates of SAEs in patients treated with any b/ts-DMARDs compared with control (i.e. no b/ts-DMARD treatment) varied depending on previous treatment experience; the rate of SAEs was statistically significantly decreased in bDMARD inadequate responder patients, but did not differ in patients who were csDMARD-naive or csDMARD inadequate responders (supplementary Table S5, available at *Rheumatology* Online). Excluding bDMARD inadequate responder studies from the overall rate ratio network meta-analysis did not affect the results (supplementary Table S6, available at *Rheumatology* Online).

Stratifying for study duration (<3; 3–6; 6–12; 12–24 months), rates of SAEs in patients treated with any b/ts-DMARDs compared with control (i.e. no b/ts-DMARD treatment) did not vary depending on study duration (supplementary Table S7, available at *Rheumatology* Online). When examining rates of SAEs between any b/ts-DMARDs in short-term trials (up to 3 and 3–6 months) *vs* any b/ts-DMARDs in longer-term trials (6–12 and 12–24 months), rates were statistically significantly increased in short-term trials (⩽6 months) compared with longer-term trials (>6 months) (supplementary Table S7, available at *Rheumatology* Online). Evaluating rates of SAEs among individual b/ts-DMARDs in short-term studies (77 studies) supported the results from the overall rate ratio network meta-analysis (supplementary Table S8, available at *Rheumatology* Online). However, in longer-term studies (40 studies), the differences found in the overall rate ratio network meta-analysis could not be confirmed [e.g. certolizumab pegol *vs* control (i.e. no b/ts-DMARD treatment) was not significantly increased (rate ratio = 0.77, 95% CI: 0.40, 1.46)] (supplementary Table S9, available at *Rheumatology* Online).

A *post hoc* analysis stratifying for publication year of SAEs in patients treated with any b/ts-DMARDs compared with control (i.e. no b/ts-DMARD treatment) did not indicate any subgroup differences (supplementary Fig. S2, available at *Rheumatology* Online). The overall rate ratio network meta-analysis model accounted for

Table 1 Rate ratios of serious adverse events of biological and targeted synthetic drugs (all doses)

Rate ratios with 95% confidence intervals										
ABA	0.82(0.55, 1.21)					0.52(0.28, 0.97)				0.92(0.75, 1.14)
0.86 (0.70, 1.06)	**ADA**			0.81 (0.27, 2.43)				0.58 (0.19, 1.75)	0.59 (0.30, 1.15)	1.04 (0.86, 1.26)
0.86 (0.56, 1.32)	1.00 (0.66, 1.52)	**ANA**								1.05 (0.69, 1.60)
0.63 (0.47, 0.85)	**0.73 (0.55, 0.98)**	0.74 (0.46, 1.17)	**CER**							1.31 (0.95, 1.80)
1.01 (0.79, 1.29)	1.18 (0.94, 1.47)	1.18 (0.76, 1.82)	**1.60 (1.18, 2.17)**	**ETA**		4.90 (0.23, 104)				0.95 (0.75, 1.20)
0.91 (0.66, 1.26)	1.06 (0.78, 1.44)	1.06 (0.66, 1.72)	**1.45 (1.00, 2.08)**	0.90 (0.65, 1.25)	**GOL**					0.96 (0.65, 1.43)
0.86 (0.66, 1.12)	1.00 (0.78, 1.29)	1.00 (0.64, 1.57)	1.36 (0.99, 1.88)	0.85 (0.65, 1.12)	0.94 (0.67, 1.32)	**INF**				1.00 (0.77, 1.30)
1.03 (0.77, 1.37)	1.20 (0.91, 1.58)	1.20 (0.76, 1.90)	**1.63 (1.16, 2.30)**	1.02 (0.76, 1.36)	1.13 (0.79, 1.62)	1.20 (0.87, 1.64)	**RIT**			0.84 (0.64, 1.10)
0.77 (0.61, 0.97)	0.90 (0.72, 1.11)	0.90 (0.58, 1.38)	1.22 (0.90, 1.64)	**0.76 (0.60, 0.97)**	0.84 (0.61, 1.16)	0.89 (0.68, 1.17)	**0.75 (0.56, 0.99)**	**TOC**		1.14 (0.91, 1.44)
0.91 (0.69, 1.21)	1.06 (0.82, 1.37)	1.06 (0.67, 1.68)	**1.44 (1.03, 2.02)**	0.90 (0.68, 1.20)	1.00 (0.71, 1.41)	1.06 (0.78, 1.44)	0.89 (0.64, 1.23)	1.18 (0.89, 1.57)	**TOF**	0.88 (0.44, 1.76)
0.91 (0.77, 1.09)	1.06 (0.92, 1.24)	1.07 (0.72, 1.58)	**1.45 (1.13, 1.87)**	0.91 (0.75, 1.09)	1.00 (0.76, 1.32)	1.06 (0.86, 1.32)	0.89 (0.70, 1.13)	1.19 (0.9998, 1.42)	1.00 (0.79, 1.28)	**Control**

Results above the diagonal are the rate ratios with 95% confidence intervals from the pairwise meta-analyses of direct comparisons between the column-defining treatment and the row-defining treatment (rate ratios greater than 1 favour the column-defining treatment). Results below the diagonal are the rate ratios with 95% confidence intervals from the network meta-analysis of direct and indirect comparisons between the row-defining treatment and the column-defining treatment (rate ratios greater than 1 favour the row-defining treatment. Numbers in bold highlight statistically significant results ($P < 0.05$). To obtain rate ratios for reversed comparisons, reciprocals of the estimates should be taken. ABA: abatacept; ADA: adalimumab; ANA: anakinra; CER: certolizumab pegol; ETA: etanercept; GOL: golimumab; INF: infliximab; RIT: rituximab; TOC: tocilizumab; TOF: tofacitinib; Control: no b/ts-DMARDs.

dose and concomitant csDMARD. The uncorrected results were precisely the same as the adjusted results to the second decimal point (supplementary Table S10, available at *Rheumatology* Online). For these reasons, we concentrated on the adjusted results.

Results obtained with the meta-analysis unadjusted for exposure time (i.e. OR method) are shown in Table 2 and described in detail in Appendix Text 2 (supplementary Fig. S3 and Tables S11–S12, available at *Rheumatology* Online).

Confidence in rate ratio estimates—recommended doses

The quality of the evidence obtained using the GRADE approach for direct, indirect, and network meta-analysis appears in supplementary Table S13, available at *Rheumatology* Online. For interpretational reasons and due to the potential dose response for some drugs, we focused on recommended doses. We assessed the confidence in the SAE rate ratios as moderate to very low for all 55 comparisons (moderate 24%, low 34%, very low 42%), suggesting the true effects are likely to be different from the estimated effects. Although lack of blinding was present in 12% of the trials, and in 12% of the trials it was unclear which patients were included in the SAE analysis, our confidence in the estimates remained unaffected because these potentially biased trials were distributed across drugs (supplementary Table S2, available at *Rheumatology* Online). The search identified 36 published trials not reporting SAE data, plus 23 unpublished trials (supplementary Table S14, available at *Rheumatology* Online). Although data from these otherwise eligible trials could have changed our estimates, confidence in the estimates was not further downrated.

Death

The number of deaths was reported in 99 of the included trials (85%). The overall risk in the treatment groups was 4/1000 patients (127 deaths per 30 172 patients) and in the control groups 3.6 (46/12 915). The overall incidence rate in the treatment groups was 5.6/1000 person-years (22 535 person-years) and in the control groups 5.5/1000 person-years (8435 person-years). Results from the pairwise and network meta-analyses, unadjusted for exposure time (i.e. OR method), found no increased likelihood of death compared with control and no differences between b/ts-DMARDs (supplementary Table S15, available at *Rheumatology* Online). The exposure-adjusted analyses (i.e. rate ratio method) found similar results (supplementary Table S16, available at *Rheumatology* Online).

Discussion

Although there was low confidence in the estimates, the analysis found that when used at the recommended dose, certolizumab pegol, and possibly tocilizumab, caused more SAEs than several other bDMARDs, when added to a background treatment of csDMARDs (in studies of up to 6 months).

Table 2 Odds ratios of serious adverse events of biological and targeted synthetic drugs (all doses)

Odds ratios with 95% confidence intervals															
ABA	0.81 (0.53, 1.25)							0.48 (0.25, 0.93)							0.97 (0.78, 1.21)
0.89 (0.69, 1.14)	**ADA**				0.84 (0.27, 2.67)						0.52 (0.15, 1.80)		0.58 (0.26, 1.30)		1.13 (0.93, 1.39)
0.96 (0.58, 1.60)	1.09 (0.66, 1.78)	**ANA**													1.04 (0.68, 1.61)
0.60 (0.42, 0.84)	**0.67 (0.48, 0.93)**	0.62 (0.36, 1.06)	**CER**												**1.77 (1.22, 2.56)**
0.87 (0.65, 1.16)	0.98 (0.75, 1.27)	0.90 (0.54, 1.50)	**1.46 (1.02, 2.07)**	**ETA**				5.67 (0.24, 136)							1.05 (0.79, 1.40)
0.93 (0.64, 1.36)	1.05 (0.74, 1.50)	0.97 (0.55, 1.70)	**1.57 (1.03, 2.38)**	1.08 (0.74, 1.57)	**GOL**										1.07 (0.71, 1.61)
0.84 (0.61, 1.15)	0.95 (0.70, 1.28)	0.87 (0.51, 1.48)	1.41 (0.97, 2.06)	0.97 (0.70, 1.35)	0.90 (0.60, 1.34)	**INF**									1.07 (0.80, 1.43)
1.02 (0.72, 1.43)	1.15 (0.83, 1.59)	1.06 (0.62, 1.81)	**1.71 (1.15, 2.54)**	1.18 (0.83, 1.66)	1.09 (0.72, 1.66)	1.21 (0.83, 1.77)	**RIT**								0.91 (0.68, 1.21)
0.75 (0.56, 0.99)	0.84 (0.66, 1.08)	0.78 (0.47, 1.28)	1.25 (0.89, 1.77)	0.86 (0.65, 1.14)	0.80 (0.55, 1.16)	0.89 (0.64, 1.23)	0.73 (0.52, 1.03)	**TOC**							**1.30 (1.03, 1.65)**
0.99 (0.71, 1.38)	1.11 (0.83, 1.50)	1.03 (0.60, 1.75)	**1.66 (1.13, 2.44)**	1.14 (0.81, 1.60)	1.06 (0.71, 1.58)	1.18 (0.82, 1.69)	0.97 (0.66, 1.43)	1.32 (0.95, 1.83)	**TOF**						0.95 (0.46, 1.96)
1.00 (0.82, 1.23)	1.13 (0.95, 1.35)	1.04 (0.66, 1.66)	**1.69 (1.27, 2.24)**	1.16 (0.93, 1.44)	1.08 (0.78, 1.48)	1.20 (0.92, 1.55)	0.99 (0.75, 1.31)	**1.35 (1.10, 1.64)**	1.02 (0.77, 1.34)	**Control**					

Results above the diagonal are the odds ratios with 95% confidence intervals from the pairwise meta-analyses of direct comparisons between the column-defining treatment and the row-defining treatment (odds ratios greater than 1 favour the column-defining treatment). Results below the diagonal are the rate odds with 95% confidence intervals from the network meta-analysis of direct and indirect comparisons between the row-defining treatment and the column-defining treatment (odds ratios greater than 1 favour the row-defining treatment. Numbers in bold highlight statistically significant results ($P < 0.05$). To obtain rate ratios for reversed comparisons, reciprocals of the estimates should be taken. ABA: abatacept; ADA: adalimumab; ANA: anakinra; CER: certolizumab pegol; ETA: etanercept; GOL: golimumab; INF: infliximab; RIT: rituximab; TOC: tocilizumab; TOF: tofacitinib; Control: no b/ts-DMARDs.

We were able to combine trial data from 117 randomized trials, which to our knowledge represents the largest review of SAEs associated with b/ts-DMARD therapy for RA. In view of the limited number of head-to-head trials of b/ts-DMARDs, we performed a network meta-analysis to compare evaluated therapies, cognizant of the limitations of this approach [32]. This methodology relies upon assumptions about the similarities of the included trials in terms of comparability of patient and study characteristics. However, the comparative effectiveness paradigm dictates that guideline panels (as well as clinicians and patients) are challenged by the dilemma of choosing between these therapies in the absence of robust comparative data about their relative safety differences. Estimates from the pairwise analyses, were in agreement with corresponding estimates from the network meta-analysis (i.e. point estimates from the network meta-analysis were included within the 95% CI corresponding to the direct estimates). However, in the pairwise meta-analysis of adalimumab *vs* tofacitinib and etanercept *vs* infliximab, the estimates were less robust (supplementary Table S13, available at *Rheumatology* Online).

Other meta-analyses have shown results similar to those from our (unadjusted for exposure time) analyses regarding certolizumab pegol's unfavourable profile in terms of SAEs [6, 9, 16, 17, 19, 20] (supplementary Table S17, available at *Rheumatology* Online). Evaluation of safety outcomes using traditional measures such as OR, risk ratio and risk difference statistics, based on the intention-to-treat population, do not account for differences in exposure time as a consequence of the high withdrawal rate in the control groups. This failure to account for exposure time tends to overestimate the harmful effects of the active treatment. Our exposure-adjusted analysis of SAEs frequently decreased the risk estimates compared with the OR estimates. This illustrates that odds (or risk) statistics might overestimate the true effect when analysing harm data from trials with skewed dropout rates between active treatment and control. For instance, conversion of the certolizumab pegol *vs* control (i.e. no b/ts-DMARD treatment) OR estimate to an absolute difference indicates 32 more patients out of 1000 will have an SAE on certolizumab pegol (median study duration 6 months overall) in contrast to 25 more per 1000 patients treated for 6 months based on the corresponding exposure-adjusted rate ratio estimate. By adjusting for exposure time, we believe we have overcome the limitations caused by the high withdrawal in the control group and therefore provide a more precise safety evaluation of these therapies. Although the rate ratio approach would allow analysis of the total number of SAEs accruing over time, these data were very rarely reported.

A recent paper that integrated the safety data from 10 randomized trials of certolizumab pegol reported the SAE rate per 100 person-years as 20 (260 patients with SAE per 1302 person-years) for active treatment and 16 (61/373) on placebo, across trials [33]. The rate ratio estimated by simple pooling (i.e. ignoring between-study

variability, and therefore being susceptible to Simpson's paradox [34]) was 1.22 (95% CI: 0.92, 1.61). This estimate included our point estimate from the rate ratio network meta-analysis [rate ratio = 1.45 (95% CI: 1.13, 1.87)] (Table 1). We did not collect detailed information on the type of SAEs, and this is a limitation of our study. A recent paper found increased odds of serious infections with certolizumab pegol [OR = 3.61 (95% CI: 1.31, 9.99)] and adalimumab [1.86 (95% CI: 1.15, 3.01)], but no increase for other bDMARDs that reached statistical significance [35].

Our study findings must be interpreted bearing in mind several limitations. First, we included studies that spanned a 16-year period (from 1999 to 2014)—patients enrolled in early studies may have differed from those included in more recent studies, although we found no effect of publication date bias in our analysis.

Second, historically, pharmaceutical companies have used several different systems for categorizing adverse events [36]; these varied approaches could potentially have affected our results, although within each study the SAE definition was the same for both active and placebo groups. A Cochrane overview of adverse effects of bDMARDs revealed that 66% of the included studies did not provide a clear definition of SAE [6]. The International Conference on Harmonization in 1994 defined an SAE as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongs hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect [37]. This definition is still valid today [38]. The impact of the various systems of categorizing adverse events was not investigated as this was rarely reported, but it was suspected that if there was an impact it was only to a limited extent, because the general definitions seemed similar across the trials.

Third, in this review we included only randomized trials, with their limitations of shorter duration and fewer real-life circumstances. However, although long-term observational studies, including population-based registries, can provide longer-term safety estimates of b/ts-DMARDs, they have significant limitations relating to bias and confounding. Evidence from randomized trials should preferably be complemented by observational data, especially regarding long-term safety [39, 40]. However, observational studies with a comparator group are not yet available for all approved drugs (e.g. certolizumab pegol [41, 42]). Fourth, the relative lack of head-to-head trials is a limitation for our confidence in the estimates. Safety data from ongoing head-to-head trials [e.g. comparing certolizumab pegol with tocilizumab and abatacept (NORD-STAR, NCT01491815), and certolizumab with adalimumab (RA0077, NCT01500278)] are likely to have an important impact on our estimates of SAEs.

Fifth, our analyses integrated only data available in the public domain. Future studies might focus on the integration of unpublished data (e.g. from the identified 23 unpublished trials as well as from the 36 published trials that did not report SAEs data).

Sixth, our study assumed that the dropout rate was linear when estimating person-years. We subsequently checked this assumption, examining the 21 trials (53 trial arms) where both dropout and person-years were reported (supplementary Table S2, available at *Rheumatology* Online). These trial arms differed by only 11% in the reported and estimated person-years (except for the placebo arm in one study [43], where the estimated person-years was 32% higher). It appears, then, that the assumption of linearity of dropouts in our data is acceptable. It remains possible that trials not reporting person-years could have influenced our results; however, we believe that if they did, it was only to a limited extent.

Finally, there is a possibility that the quality of the data, the relatively low number of trials for each drug, and the low incidence of SAEs—in particular, deaths—do not allow the strongest network meta-analysis; however, we believe this study is relevant for therapeutic decisions as the effect of any anti-rheumatic therapy on serious adverse effects is particularly important.

Despite low confidence in the estimates, our data indicate that patients using certolizumab pegol compared with some alternatives had an increased rate of SAEs in RA in the short term. In contrast to current treatment guidelines for RA, whereas most bDMARDs are equally placed in the treatment algorithm after failure of csDMARDs, our study suggests that additional therapy with certolizumab pegol should be considered more carefully than the use of other bDMARDs because it may be associated with a higher rate of SAEs compared with equally effective alternatives. On the other hand, for patients treated with certolizumab pegol, our study suggests that the long-term (up to 1 year) risk of SAEs is not different compared with other alternatives (i.e. the SAEs will likely occur early, if ever).

Funding: This work was supported by unrestricted grants from The Oak Foundation and indirectly by The Danish Health and Medicines Authority. The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or in the decision to submit the results for publication. This study is independent of its funders/sponsors.

Disclosure statement: S.Ta. has received research grants paid to his institute from AbbVie and Roche and speaker fees from Pfizer and Merck Sharp & Dohme Corp (MSD). M.B. has received consultancy fees from Mundipharma, Roche, Pfizer, GlaxoSmithKline (GSK), Novartis and Bristol-Myers Squibb (BMS). T.S.J. has received research grants paid to her institute from Roche and AbbVie. K.H.A. has received fees from MSD, Pfizer, AbbVie, Novartis and Union Chimique Belge (UCB) for advisory board memberships. S.Th. works as a regulatory consultant at NDA Regulatory Services Ltd, but does not receive fees directly from pharmaceutical companies. U.T. has held speakers bureaus for UCB, Roche and MSD. H.B. has received grant support from Abbott/AbbVie, BMS, AstraZeneca, Daiichi Sankyo, GSK, Grünenthal, Lilly, MSD, Mundipharma, Norpharma, Nycomed, Novo Nordisk,

Piere Fabre, Pfizer, Roche, Sanofi Aventis, Schering-Plough, Takeda and Wyeth and consulting fees from Abbott/AbbVie, AstraZeneca, Celgene, Grünenthal, Hospira, Eli Lilly, Mundipharma, Norpharma, Nycomed, Pfizer, Roche and Wyeth. R.C. has received consulting fees paid to his institute from Abbott/AbbVie, Bristol Myers-Squibb, Eli Lilly, Hospira, MSD, Novartis, Pfizer and Roche, and research grants paid to his institute from Abbott/AbbVie, MSD, Mundipharma/Norpharma, Novartis and Roche. B.B. has received fees advisory boards membership from Novo Nordisk and Allergen, speaker fees from Pfizer, and research grants paid to her institution from Novo Nordisk. The authors have declared no conflicts of interest. D.E.F. has acted as consultant for and received honoraria and grants from AbbVie, Actelion, Amgen, BMS, National Institutes of Health, Novartis, Pfizer, Cytori and Roche/Genetech. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

Acknowledgements

The authors of this report are responsible for its contents. The findings and conclusions do not necessarily represent the view of The Danish Health and Medicines Authority. Therefore, no statement in this report should be construed as an official position of The Danish Health and Medicines Authority. All authors fulfil the ICMJE guidelines for authorship. S.Ta. and R.C. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: S.Ta., D.E.F., M.B., G.L., H.B., R.C. Acquisition, analysis or interpretation of data: S.Ta., D.E.F., M.B., G.L., H.B., U.T., K.H.A, B.B., A.D., T.S.J., S.Th., R.C. Manuscript drafting: S.Ta., D.E.F., M.B., R.C. Critical revision of the manuscript for important intellectual content: S.Ta., D.E.F., M.B., G.L., H.B., U.T., K.H.A., B.B., A.D., T.S.J., S.Th., R.C. Statistical analysis: R.C., S.Ta. Funding procurement: S.Ta., H.B., S.Th., R.C. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analyses.

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