RHEUMATOLOGY

Rheumatology 2011;50:552–562
doi:10.1093/rheumatology/keq343
Advance Access publication 14 November 2010

Original article

Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials

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Abstract

Objective. To assess the risk of adverse events (AEs) in patients with RA treated with tocilizumab, an IL-6 receptor antibody, in published randomized controlled trials (RCTs).

Methods. A systematic literature search was conducted using the Cochrane library, PUBMED and EMBASE for all RCTs (of the use of tocilizumab for RA) until September 2009. Fixed effect meta-analyses were conducted to compare the incidence of AEs after treatment with tocilizumab 8 and 4 mg/kg in combination with MTX, and 8 mg/kg tocilizumab monotherapy, with controls. Pooled summary odds ratios (ORs) were calculated using the Mantel–Haenszel method.

Results. Six trials were analysed (four trials included 8 mg/kg tocilizumab and MTX combination therapy, three of which also assessed the 4 mg/kg dose). Three studies assessed tocilizumab monotherapy at 8 mg/kg. Pooled ORs revealed statistical significance for an increased risk of AEs in the 8 mg/kg combination group compared with controls (OR = 1.53; 95% CI 1.26, 1.86). The risk of infection was significantly higher in the 8 mg/kg combination group compared with controls (OR = 1.30; 95% CI 1.07, 1.58). No increased incidence of malignancy, tuberculosis reactivation or hepatitis was seen.

Conclusion. Tocilizumab in combination with MTX as a treatment for RA is associated with a small but significantly increased risk of AEs, which is comparable with that of other biologics. Vigilance for untoward effects is, therefore, imperative in any patient treated with these immuno-suppressive agents.

Key words: Interleukin-6, Tocilizumab, Rheumatoid arthritis, Meta-analysis, Adverse events.

CLINICAL SCIENCE

Introduction

RA is a chronic autoimmune disease characterized by progressive joint damage, pain, fatigue and disability, affecting ~1% of the population [1–3]. Current therapies comprise traditional DMARDs including MTX and, more recently, biologic DMARDs such as TNF-α inhibitors (anti-TNF), B-cell depleting agents and T-cell co-stimulatory blockers [4–6]. Despite their efficacy, not all patients obtain benefit and improvement may not persist among responders. Many patients also experience adverse events (AEs) [6].

A novel target for the treatment of RA is IL-6, a key pro-inflammatory cytokine in RA contributing to both the articular and systemic manifestations of the disease [7, 8]. Tocilizumab, a humanized mAb, was thus developed to block the IL-6 receptor and has been extensively trialled in RA [9–11].

For a novel medication to be widely accepted, its safety is of utmost importance. Strict inclusion and exclusion criteria may render randomized controlled trials (RCTs) inadequate to detect the true incidence of AEs encountered. This limitation may be overcome by meta-analysis, which combines the results of several RCTs

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Submitted 1 April 2010; revised version accepted 13 September 2010.

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and increases statistical power to detect significant differences.

Infection risk is one of the most feared complications with biologic use [12–15]. A report from the British Society for Rheumatology Biologics Register (BSRBR) revealed that although anti-TNF-treated patients did not have a significantly higher risk of developing serious infections overall compared with patients taking traditional DMARDs, the risk of suffering a serious skin or soft tissue infection was significantly higher [16].

The objective of this study was to perform a systematic literature review and meta-analysis on published RCTs and to compare the odds ratios (ORs) of AEs [total AEs, serious AEs (SAEs), infections and serious infections] occurring in patients receiving tocilizumab with or without MTX compared with the controls receiving MTX alone.

Methods

Search strategy and study selection

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was utilized to guide the methodology of our meta-analysis [17]. A systematic literature search was conducted using the Cochrane library, PubMed and EMBASE using MeSH and free text search terms. All variants of the key search terms: tocilizumab, RA and AEs were included. The analysis was limited to late Phase II or Phase III RCTs in peer-reviewed publications to September 2009. Trial participants were adults ($\geqslant$18 years of age) with a diagnosis of RA according to the ACR 1987 criteria [18].

Data extraction and end points

All demographic, protocol, AE, laboratory and safety data were collated from each trial and extracted in duplicate with discrepancies resolved by reviewing the source material and consulting the other authors. Only four events were found to be reported in a consistent format across the trials: one or more AE, SAE, infection and serious infection. Assumptions were made that the definitions of these terms were consistent across trials, as individual study definitions were not available. Within each group of trials, the data were combined and subdivided into two tocilizumab dose regimens: low dose (4 mg/kg) and high dose (8 mg/kg). Other events, such as neutropenia, abnormal liver function tests (LFTs) and altered lipid profile, were reported; however, due to inconsistent data formatting, meta-analysis was not possible.

Statistical analysis

Within the combination therapy trial group, the following dosing groups were compared:

(i) 8 *vs* 4 mg/kg;
(ii) 8 mg/kg *vs* control; and
(iii) 4 mg/kg *vs* control.

Within the monotherapy trial group, only the 8 mg/kg dose group *vs* control group comparison was considered. For each comparison, individual meta-analyses were performed on the number of AEs, SAEs, infections and serious infections, where applicable. The effect sizes were measured using ORs.

We employed the Mantel–Haenszel method to perform the meta-analysis [19]. For all fixed-effects meta-analyses, it was assumed that the true effect sizes were the same for all studies, and any difference observed was simply due to sampling variation. A χ^2-test of heterogeneity (often denoted by Q) was applied in each case to assess the fixed-effects assumption. A 10% significance level was used for the test of heterogeneity. I^2-statistics were also presented (with 95% CIs where possible) in order to estimate the proportion of variability in the effect sizes attributable to heterogeneity.

Zero total event studies were excluded from meta-analyses according to statistical recommendation [20, 21]. After excluding these, if any contingency tables contained zero values, a continuity correction was applied to the relevant tables. This consisted of adding a factor of the reciprocal of the size of the opposite treatment arm to each cell of a contingency table of treatment group against event for the relevant studies.

For each of the comparisons of interest, forest plots were produced to show the treatment effect sizes (ORs) for each of the relevant studies with corresponding 95% CIs (Fig. 1). Publication bias was investigated for each meta-analysis using funnel plots. The statistics software used was the metafor package (version 0.5-7, written by Wolfgang Viechtbauer) in R statistics software [20].

Results

Literature search results and trial characteristics

Eight trials were found following electronic searches from the Cochrane database, 93 reported in manuscripts identified by PubMed and 136 from EMBASE. After considering duplication and article relevance and design, six RCTs were selected (Fig. 2 and Table 1) [22–27]. Of these, five were Phase III [22, 23, 25–27] and one a late Phase II trial [24] comprising patients with active RA refractory to conventional DMARDs or anti-TNF treatment. The analysis included all the randomized patients who received at least one dose of tocilizumab. Table 2 shows the patient demographics and baseline characteristics.

Study selection

The trials were split into two groups according to their protocols. The first comprised tocilizumab and MTX combination therapy *vs* MTX alone [22–25] and the second comprised tocilizumab monotherapy *vs* MTX alone [26, 27]. The CHARISMA trial included both combination and monotherapy protocols; therefore, the appropriate data were distinguished and separated into each corresponding group for analysis [24]. It is noted that the end point of treatment with tocilizumab within the CHARISMA trial was 16 weeks; however, each of

FIG. 1 OR forest plots showing effect of treatment on risk of AEs and infections. Right-hand side of plots indicates a greater risk of AEs or infections for the treatment or higher dose of treatment group.

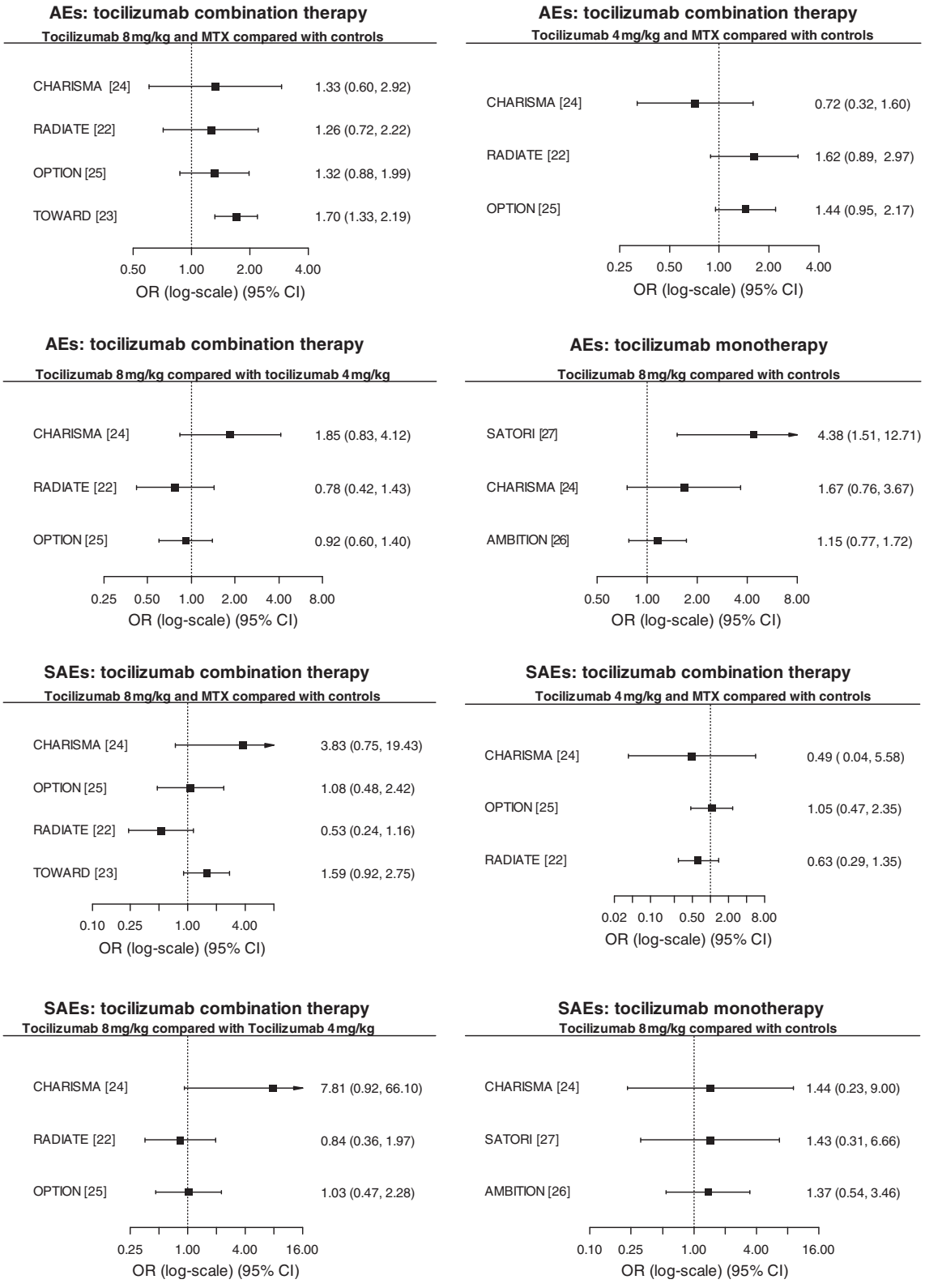
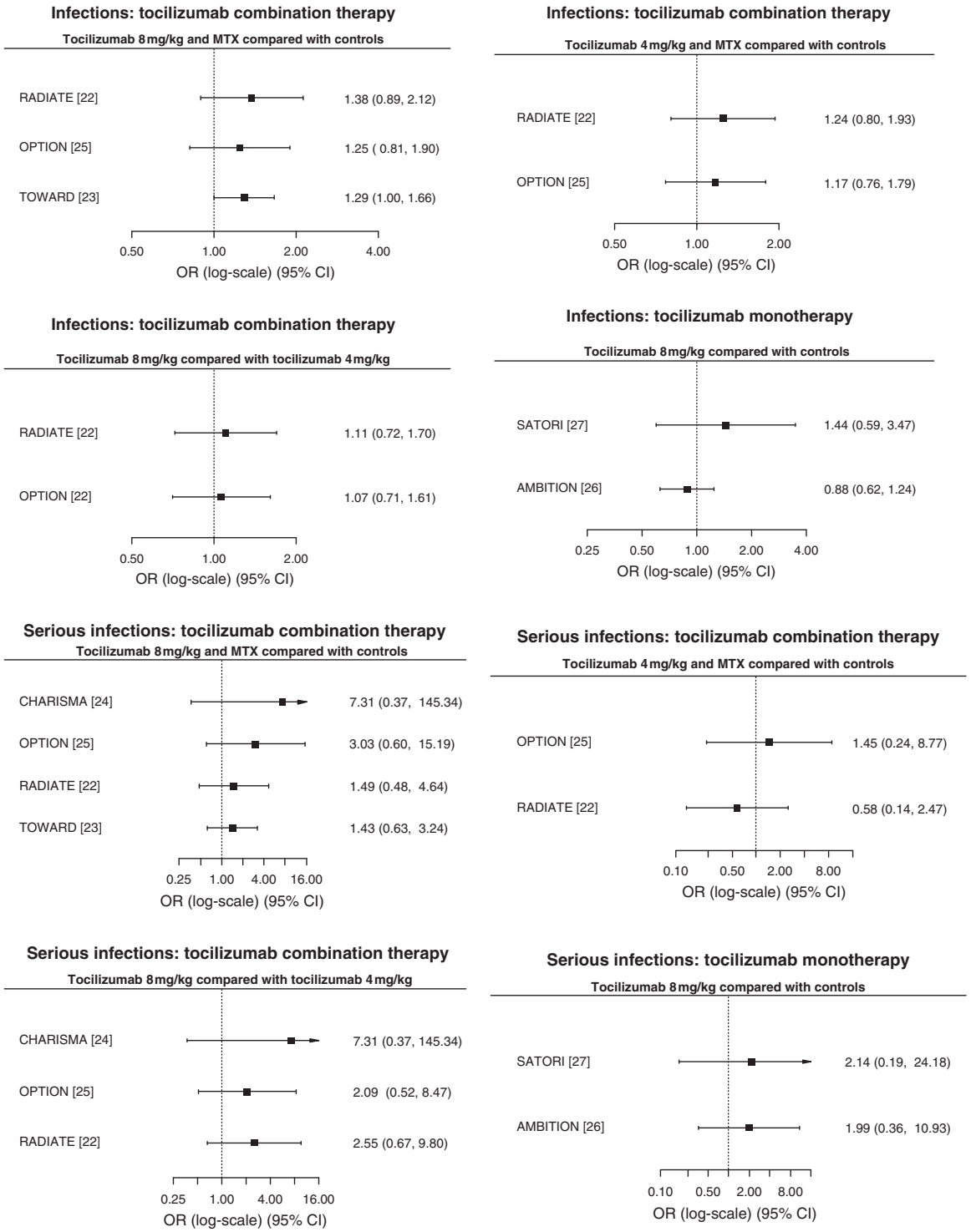


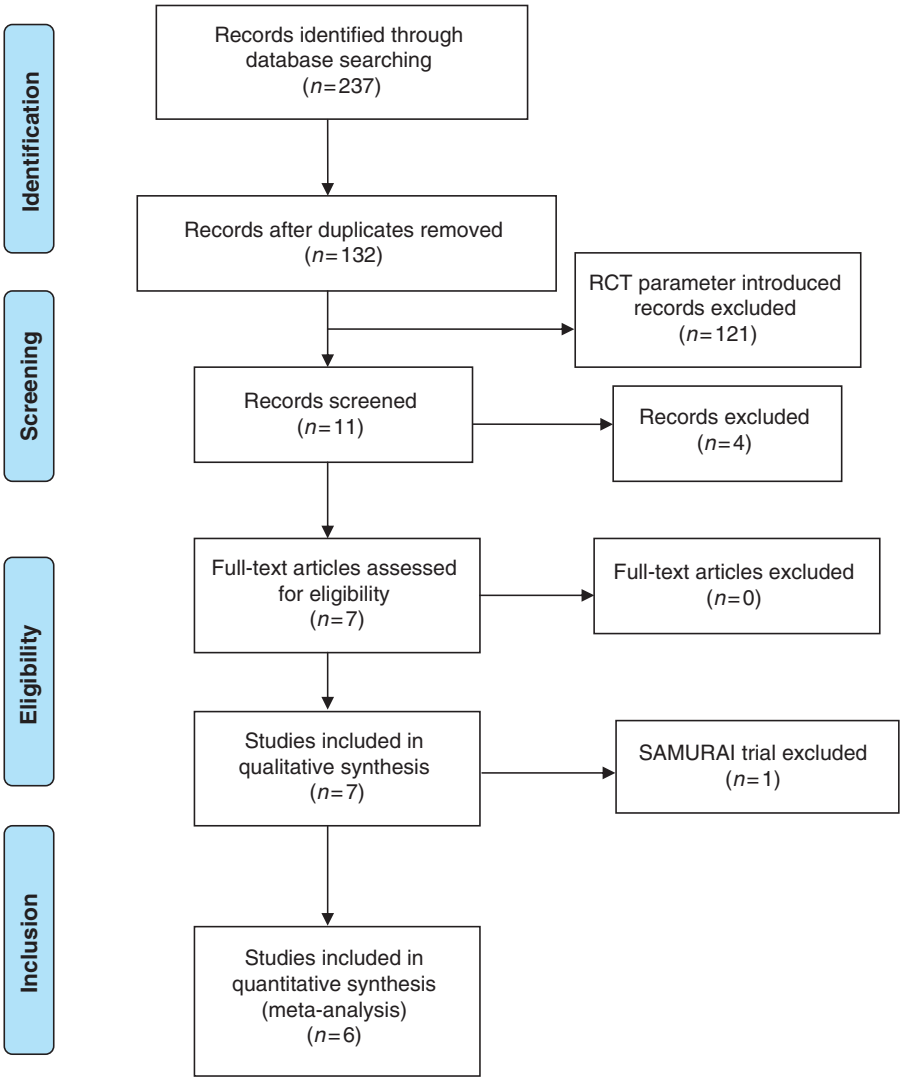
Fig. 1 Continued.



the other studies included in this meta-analysis had a duration of 24 weeks.

Although the TOWARD trial included patients on any traditional DMARD, 76% of the participants were prescribed MTX [23]. This was determined to be a high enough proportion to be comparable with the other combination therapy trials, where 100% of the participants were prescribed MTX. As TOWARD comprised the

Fig. 2 Systematic literature search selection process. CHARISMA [24] trial included in both monotherapy and combination therapy subgroups. Control group received MTX and tocilizumab placebo.



largest number of participants in any trial, it was considered that inclusion of this study would increase the precision and power of the meta-analysis.

The study of active controlled monotherapy used for RA, an IL-6 inhibitor (SAMURAI) trial was excluded, given the lack of specificity in describing the treatment arms of the patients involved; details regarding the DMARDs that patients were prescribed and the percentage of those patients taking MTX were not provided [28]. This is in contrast with the TOWARD study, which specified the percentage of patients prescribed MTX [23].

The quality of the studies was assessed by considering selection, performance, attrition and detection biases, as well as the individual analyses carried out. It was concluded that each of the six RCTs had accounted appropriately for these sources of error, and were of a sufficient quality to enable a meaningful meta-analysis to be undertaken.

Side-effect categories

Four categories of side effects were presented: patients with one or more AEs, one or more SAE, one or more infections and one or more serious infections. As the CHARISMA study did not contain results for one or more infections, it was excluded from this category [24]. The incidences of these AEs are shown in Table 3, with the corresponding summary ORs shown in Table 4.

Assessment of heterogeneity

The *Q*-tests for heterogeneity showed insufficient evidence for heterogeneity in all but two comparisons of interest. The comparison of AEs between the 8 mg/kg dose group and the control group for tocilizumab monotherapy gave a *P*-value of 0.064 for the χ^2-test of heterogeneity, which is significant at 10% but not at the 5% level. Similarly, the comparison of SAEs between the

Table 1 Characteristics of the six RCTs of tocilizumab therapy in RA included in these meta-analyses for AEs

Study	Number of patients randomized	Number of patients completing follow-up	RA features	Duration of follow-up, weeks
OPTION [25]	623	566	Phase III double-blind RCT: TCZ and MTX combination therapy in MTX-naïve, active RA patients	24
TOWARD [23]	1220	1121	Phase III double-blind RCT: TCZ in combination with one of the six DMARDs (76% of which used one DMARD, most commonly used DMARD is MTX) in MTX naïve, active RA patients	24
RADIATE [22]	499	417	Phase III double-blind RCT: TCZ and MTX combination therapy in MTX-naïve, active RA patients	24
CHARISMA [24]	359	299	Phase II double-blind RCT: both TCZ monotherapy and combination therapy with MTX in MTX-naïve, active RA patients	20
SATORI [27]	127	87	Phase III double-blind RCT: TCZ monotherapy in MTX-naïve, active RA patients	24
AMBITION [26]	673	612	Phase III double-blind, double-dummy, parallel-group RCT: TCZ monotherapy in MTX-naïve, active RA patients	24

TCZ: tocilizumab.

8 mg/kg dose group and the control group for the tocilizumab combination therapy gave a *P*-value of 0.065 for the χ^2-test of heterogeneity. All I^2-statistics were 0 except for the following comparisons: SAEs between the 8 mg/kg dose group and the control group for tocilizumab combination therapy ($I^2 = 0.59$; 95% CI 0, 0.86); AEs between the 4 mg/kg dose group and the control group for tocilizumab combination therapy ($I^2 = 0.30$; 95% CI 0, 0.93); AEs ($I^2 = 0.35$; 95% CI 0, 0.79) and SAEs ($I^2 = 0.46$; 95% CI 0, 0.84) between the 8 and the 4 mg/kg dose group for tocilizumab combination therapy; and AEs ($I^2 = 0.64$; 95% CI 0, 0.90) and infections ($I^2 = 0.03$) between the 8 mg/kg dose group and the control group for tocilizumab monotherapy. Note that all the 95% CIs for I^2 given above contain 0, and hence we are not able to determine significant heterogeneity in any of the meta-analysis comparisons. Hence, although overall there is insufficient evidence to suggest that the true effect size differs across trials for any of the comparisons, it is sensible to be cautious against over-interpreting the combined summary estimates corresponding to the comparison of AEs between the 8 mg/kg dose group and the control group for tocilizumab monotherapy and the comparison of SAEs between the 8 mg/kg dose group and the control group for the tocilizumab combination therapy, because these two separate meta-analysis comparisons have moderately high I^2 heterogeneity estimates and significant *Q*-test *P*-values.

AEs

In combination therapy, the estimated odds for one or more AEs was significantly greater for the 8 mg/kg dose group compared with control group (OR = 1.53; 95% CI 1.26, 1.86). The estimated odds were not significantly greater for the 4 mg/kg dose group compared with control group (OR = 1.34; 95% CI 0.98, 1.82), and the estimated odds for the 8 mg/kg dose group were not significantly different to the 4 mg/kg dose group (OR = 0.98; 95% CI 0.72, 1.34).

SAEs

In combination therapy, the estimated odds of at least one SAE in the 4 mg/kg dose group were not significantly different from control (OR = 0.78; 95% CI 0.45, 1.33) nor in the 8 *vs* 4 mg/kg dose group comparison (OR = 1.18; 95% CI 0.69, 2.02). Patients taking monotherapy (8 mg/kg) were estimated to have the odds of at least one SAE occurring ~1.39 times greater than control (95% CI 0.67, 2.89).

Infections

In combination therapy, patients taking the 8 mg/kg dose were found to have significantly greater odds of infection than control (OR = 1.30; 95% CI 1.07, 1.58). The corresponding estimated odds for infection were not significantly different for the 4 mg/kg dose group compared with controls (OR = 1.20; 95% CI 0.89, 1.63) and for the 8 mg/kg dose group compared with the 4 mg/kg dose group (OR = 1.09; 95% CI 0.81, 1.46). Patients taking monotherapy were estimated to have odds ~0.94 times those of the control (95% CI 0.68, 1.29) for developing at least one infection.

Serious infections

The odds of serious infection were not significantly different between the 4 mg/kg dose groups and control groups (OR = 0.83; 95% CI 0.28, 2.50) after excluding the CHARISMA study. The CHARISMA study was excluded

Table 2 Patient demographics and clinical characteristics at baseline

Study	Study protocol with doses (number of patients in each group in intention-to-treat population)	Mean age, years	Sex: female, %	Mean RA duration, years	DAS-28 score	ESR, mm/h	CRP, mg/l
OPTION [25]	TCZ 8 mg/kg (every 4 weeks) with weekly MTX ($n = 205$)	50.8	85.0	7.50	6.80	51.2	26.0
	TCZ 4 mg/kg (every 4 weeks) with weekly MTX ($n = 213$)	51.4	82.0	7.40	6.80	49.2	28.0
	Control: TCZ placebo (every 4 weeks) with weekly MTX ($n = 204$)	50.6	78.0	7.80	6.80	49.7	24.0
TOWARD [23]	TCZ 8 mg/kg + DMARD(s) (76% used one DMARD, the most commonly used DMARD being MTX) ($n = 803$)	53.0	81.0	9.80	6.70	48.2	26.0
	TCZ placebo + DMARD(s) (76% used one DMARD, the most commonly used DMARD being MTX) ($n = 413$)	54.0	84.0	9.80	6.60	49.2	26.0
RADIATE [22]	TCZ 8 mg/kg (every 4 weeks) with stable MTX and folate ($n = 170$)	53.9	84.0	12.6	6.79	49.1	28.0
	TCZ 4 mg/kg (every 4 weeks) with stable MTX and folate ($n = 161$)	50.9	81.0	11.0	6.78	51.3	31.1
	Control: TCZ placebo (every 4 weeks) with stable MTX and folate ($n = 158$)	53.4	79.0	53.4	6.80	54.6	37.1
CHARISMA [24]	TCZ 8 mg/kg (every 4 weeks) + MTX placebo ($n = 52$)	50.1	73.0	0.76	6.43	39.0	22.0
	TCZ 4 mg/kg (every 4 weeks) + MTX placebo ($n = 54$)	49.3	75.9	0.82	6.55	41.0	19.0
	TCZ 8 mg/kg (every 4 weeks) + MTX at previously stabilized dose ($n = 50$)	50.1	78.0	0.89	6.47	39.0	24.0
	TCZ 4 mg/kg (every 4 weeks) + MTX at previously stabilized dose ($n = 49$)	50.2	75.5	0.65	6.34	40.0	31.0
	Control: TCZ placebo + MTX at previously stabilized dose ($n = 49$)	50.9	77.6	0.93	6.75	43.0	32.0
SATORI [27]	TCZ 8 mg/kg (every 4 weeks) plus MTX placebo ($n = 61$)	52.6	90.2	8.50	6.10	51.9	30.0
	Control: TCZ placebo plus MTX 8 mg/wk ($n = 64$)	50.8	75.0	8.70	6.20	51.9	32.0
AMBITION [26]	TCZ 8 mg/kg (every 4 weeks) ($n = 286$)	50.7	83.0	6.40	6.80	49.9	30.0
	Control: MTX 7.5 mg/week titrated to 20 mg/week within 8 weeks ($n = 284$)	50.0	79.0	6.20	6.80	49.4	31.0

TCZ: tocilizumab.

from this meta-analysis because it was identified as a zero-total event study, and no continuity correction factors were applied in this case.

When the 8 mg/kg dose was compared with the 4 mg/kg dose in the combination groups, continuity correction factors were applied. Patients taking 8 mg/kg tocilizumab were found to have significantly greater odds than in the 4 mg/kg group (OR = 2.70; 95% CI 1.09, 6.71). However, sensitivity analysis revealed that after removing the relatively small CHARISMA study, the overall conclusions changed with the summary OR no longer being significant at the 5% level (OR = 2.33; 95% CI 0.88, 6.13). Patients taking tocilizumab monotherapy did not have significantly greater odds of at least one serious infection compared with the controls (OR = 2.03; 95% CI 0.50, 8.21).

Other laboratory markers

Other AEs mentioned included changes in lipids, LFTs and neutrophil counts. Overall the LFT elevations were not associated with clinical signs or symptoms of liver disease and an increased risk of infection was not seen in individuals who developed neutropenia. In all trials other than the OPTION study [25], in most patients, the alteration in lipid profile was transient. It was not considered appropriate to undertake a statistical meta-analysis on these individual categories due to the varied presentation of the results between the trials. For example, lipid profiles, LFTs and neutropenia were all presented with varying baseline reference values across the studies. There was no apparent increase in the rate of malignancy, tuberculosis or hepatitis associated with the use of tocilizumab.

Sensitivity analysis

As CHARISMA was a small study, the sensitivity of the meta-analysis was assessed by removing this. Our conclusions changed for the comparison of serious infections in patients taking 8 mg/kg tocilizumab with those taking 4 mg/kg tocilizumab as mentioned. The comparison of AEs between the 4 mg/kg tocilizumab and control groups (combination therapy) also gave a significant summary OR when CHARISMA was removed. However, in order to be conservative in our conclusions, CHARISMA was included in the calculation of the final summary estimate. All other conclusions based on summary estimates were unaffected when CHARISMA was removed.

TABLE 3 Risk of AEs in patients with RA during tocilizumab and MTX combination therapy (CHARISMA, RADIATE, OPTION and TOWARD) and tocilizumab monotherapy (AMBITION, CHARISMA and SATORI)

Study	Treatment	Number of patients with at least one AE/total in treatment group (%)	Number of patients with at least one SAE/total in treatment group (%)	Number of patients with at least one infection/total in treatment group (%)	Number of patients with at least one serious infection or infestation/total in treatment group (%)
CHARISMA (TCZ combination therapy arm) [24][a]	TCZ 4 mg/kg (every 4 weeks) + MTX at previously stabilized dose	19/49 (42.0)	1/49 (2.00)	–	0
	TCZ 8 mg/kg (every 4 weeks) + MTX at previously stabilized dose	27/50 (54.0)	7/50 (14.0)	–	3/50 (6.00)
	TCZ placebo + MTX at previously stabilized dose	23/49 (47.0)	2/49 (4.10)	–	0
RADIATE [22][a]	TCZ 8 mg/kg (every 4 weeks) with stable MTX and folate	147/175 (84.0)	11/175 (6.30)	86/175 (49.1)	8/175 (4.60)
	TCZ 4 mg/kg (every 4 weeks) with stable MTX and folate	142/163 (87.0)	12/163 (7.40)	76/163 (46.6)	3/163 (1.80)
	TCZ placebo (every 4 weeks) with stable MTX and folate	129/160 (81.0)	18/160 (11.0)	66/160 (41.3)	5/160 (3.10)
OPTION [25][a]	TCZ 4 mg/kg (every 4 weeks) with weekly MTX	151/212 (71.0)	13/212 (6.10)	65/212 (31.0)	3/212 (1.40)
	TCZ 8 mg/kg (every 4 weeks) with weekly MTX	143/206 (69.0)	13/206 (6.30)	66/206 (32.0)	6/206 (2.90)
	TCZ placebo (every 4 weeks) with weekly MTX	129/204 (63.0)	12/204 (5.90)	56/204 (27.0)	2/204 (1.00)
TOWARD [23][a]	TCZ 8 mg/kg + DMARD(s) (76% used one DMARD, the most commonly used DMARD being MTX)	584/802 (72.8)	54/802 (6.70)	300/802 (37.4)	22/802 (2.70)
	TCZ placebo + DMARD(s) (76% used one DMARD, the most commonly used DMARD being MTX)	253/414 (61.1)	18/414 (4.30)	131/414 (31.6)	8/414 (1.90)
SATORI [27][b]	TCZ 8 mg/kg (every 4 weeks) plus MTX placebo ($n = 61$)	56/61 (92.0)	4/61 (6.60)	14/61 (23.0)	2/61 (3.30)
	TCZ placebo plus MTX 8 mg/week ($n = 64$)	46/64 (72.0)	3/64 (4.70)	11/64 (17.0)	1/64 (1.60)
CHARISMA (TCZ monotherapy arm) [24][b]	TCZ 8 mg/kg (every 4 weeks) + placebo	31/52 (60.0)	3/52 (5.80)	–	0
	TCZ placebo + MTX at previously stabilized dose	23/49 (47.0)	2/49 (4.10)	–	0
AMBITION [26][b]	TCZ 8 mg/kg (every 4 weeks)	230/288 (80.0)	11/288 (3.80)	99/288 (34.0)	4/288 (1.40)
	MTX 7.5 mg/week titrated to 20 mg/week within 8 weeks	220/284 (77.0)	8/284 (2.80)	106/284 (37.0)	2/284 (0.70)

AE, SAE, infections and serious infections are defined and presented in the six RCTs shown in the table. [a]Tocilizumab combination therapy trials. [b]Tocilizumab monotherapy trials. TCZ: tocilizumab.

Publication bias

It is difficult to assess publication bias in such a small number of studies. However, funnel plots were considered to help detect any evidence of large biases. All funnel plots appeared satisfactory with no clear evidence of large publication bias.

Discussion

Due to the efficacy of biologic DMARDs in RA, the goals of management have been reappraised, with disease remission being a realistic outcome [29]. Despite this, patient safety remains a chief concern. Individual RCTs are often underpowered to identify rare effects, including AEs such as severe infections; thus, pooling studies and undertaking meta-analyses provide a means to identify these.

Our meta-analyses show a small but significantly increased risk of AEs in patients taking tocilizumab 8 mg/kg with MTX, compared with controls, including an increased risk of infection. The main adverse effects reported were nasopharyngitis [27], respiratory tract disorder [23], skin and soft tissue pathology (e.g. rash) [22, 23] and gastrointestinal side effects (e.g. nausea) [22, 23]. All other comparisons appeared to have event risks that were not significantly different between groups. However, two comparisons were excluded because of concerns about heterogeneity. No summary estimate was given for the comparison of AEs between the 8 mg/kg tocilizumab monotherapy group and the control group, and neither was one given for the comparison of SAEs between the 8 mg/kg dose group and the control group for the tocilizumab combination therapy. Therefore, we were not able to investigate if a significant difference

TABLE 4 ORs (95% CIs) for tocilizumab and MTX combination and tocilizumab monotherapy studies

Outcome of interest	ORs (95% CI) for tocilizumab and MTX combination therapy			ORs (95% CI) for tocilizumab monotherapy high dose[d] *vs* control[b]
	High dose[a] *vs* control[b]	Low dose[c] *vs* control[b]	High[a] *vs* Low dose[c]	
At least one AE	1.53 (1.26, 1.86)	1.34 (0.98, 1.82)	0.98 (0.72, 1.34)	
At least one SAE		0.78 (0.45, 1.33)	1.18 (0.69, 2.02)	1.39 (0.67, 2.89)
At least one infection	1.30 (1.07, 1.58)[e]	1.20 (0.89, 1.63)[e]	1.09 (0.81, 1.46)[e]	0.94 (0.68, 1.29)[f]
At least one serious infection	1.78 (0.98, 3.23)	0.83 (0.28, 2.50)[e]	2.33 (0.88, 6.13)[e]	2.03 (0.50, 8.21)[f]

Combination trials include CHARISMA, RADIATE and OPTION studies. The TOWARD study was also included in the meta-analyses of combination therapy corresponding to the high dose *vs* control comparison. Monotherapy trials include: AMBITION, CHARISMA and SATORI studies. [a]Tocilizumab 8 mg/kg with MTX. [b]Control with MTX and tocilizumab placebo. [c]Tocilizumab 4 mg/kg with MTX. [d]Tocilizumab monotherapy 8 mg/kg. [e]CHARISMA study excluded from meta-analysis. [f]Only AMBITION and SATORI studies included in meta-analysis.

in risk existed between the groups for these specific comparisons overall. One explanation for heterogeneity within AEs, but perhaps less so for SAEs, may be that the definition of the former is extremely broad and the reporting of these events within studies would be participant and clinician dependent.

The 8 mg/kg tocilizumab combination therapy group showed a significantly greater risk of serious infection than the 4 mg/kg tocilizumab combination group when CHARISMA was included, although this is not apparent when compared with controls. This finding is possibly due to the CHARISMA study being an outlier in this particular effect group due to its small sample size ($n = 101$) [24].

The main infections reported were skin and subcutaneous infections as well as respiratory tract infections [22, 23, 26]. A meta-analysis of harmful effects in RCTs involving anti-TNF-α therapy concluded that the pooled OR for serious infection was 2.0 (95% CI 1.3, 3.1) in comparison with controls [30]. This may suggest that anti-TNF agents carry a higher risk of significant infection than tocilizumab as patients taking high-dose tocilizumab (8 mg/kg) in combination with MTX in our study showed only a trend towards a greater risk of serious infection when compared with controls (OR = 1.78; 95% CI 0.98, 3.23). Other authors have concluded that treatment with tocilizumab produces a similar risk of serious infections to that of anti-TNF drugs [15, 31].

As IL-6 is a pleotropic cytokine, a number of other effects were found. All studies reported elevations in LFTs; however, the format of reporting for these events was not consistent and hence it was not possible to perform statistical analyses. LFT elevations were found to be dose dependent in CHARISMA and more frequent in patients taking MTX concurrently [24]. Although some patients were withdrawn due to LFT derangement, no patient experienced clinical signs or symptoms as a result of these changes.

Tocilizumab has been linked to an alteration in lipid profiles, with high-density lipoprotein, low-density lipoprotein, cholesterol and triglycerides shown to rise variously across studies. It has been hypothesized that the hyper-inflammatory state in RA decreases plasma lipids to an abnormally low level [11, 33]; hence, upon resolution of inflammation, lipids rise to normal levels. However, we cannot exclude that tocilizumab may raise lipid levels beyond what would be expected simply by reducing inflammation. This is especially important given the increased cardiovascular risk associated with RA, and therefore further investigation into this risk factor is suggested. The anti-TNF-α biologic agent, infliximab, has also been found to elevate the lipid profile [34]. However, no increase in cardiovascular events was noted in any of the short-term tocilizumab studies [22, 23, 26]. Importantly, the recently released 5-year extension to the STREAM study [35] found no evidence of an increased risk of cardiovascular disease in patients on tocilizumab therapy.

Five of the trials analysed reported significantly reduced neutrophil counts in patients within tocilizumab protocols, compared with controls [22–26]. Unfortunately, these data were also presented in differing formats, and hence meta-analysis was not possible. Importantly, no association was identified between neutrophil levels and infection rates or infection severity and the neutropenia detected was usually transient [22–26].

Following immune system suppression, concern exists regarding possible reactivation of latent infections, most notably *Mycobacterium tuberculosis* (TB). In post-marketing surveillance, anti-TNF agents were found to increase this risk [36]. None of the tocilizumab studies analysed encountered patients with TB reactivation including those that did not screen for TB [27, 35]. However, two cases of TB in patients taking tocilizumab (not in the studies within this meta-analysis) have been reported in Japan [37]. It would, therefore, be advisable to continue to screen patients for TB before commencing any biologic agent [38]. Three trials reported an absence of opportunistic infections [22, 24, 26]; however, one patient in the TOWARD trial was diagnosed with

Mycobacterium avium intracellulare following an incidental abnormality on chest X-ray [23].

Malignancy is also of serious concern when using immunosuppressant agents. None of the studies found a significant increase in the rate of malignancy in those taking tocilizumab compared with controls. Furthermore, Yamanaka *et al.* [39] compared the incidence of malignancies in tocilizumab cohorts with a group of RA patients in the Tokyo Women's Medical University, and to the Japanese population database with no significant difference in the incidence of malignancy being found between these groups.

The possibility of publication bias is an ever-present limitation of the statistical method of meta-analysis. Funnel plots did not reveal any major indications of publication bias in our results; however, it was difficult to evaluate publication bias due to the small number of studies used in the meta-analyses.

Conclusion

This meta-analysis has revealed a small but significant increase in AEs and infections in patients treated with 8 mg/kg of tocilizumab compared with controls. This risk is comparable with other biologic agents, although the risk of serious infection may be less than that for TNF antagonists. Despite this, tocilizumab has a critical role in the treatment of RA and overall the low incidence of AEs is reassuring. Vigilance for untoward events, however, must be maintained in any patient treated with immune-modulating therapies.

Rheumatology key messages

- There is a small but significant increase in the risk of AEs and infections with tocilizumab 8 mg/kg.
- AEs and infections with tocilizumab are comparable with other biologics.
- Tocilizumab has an important role in treating RA, but vigilance for AEs remains a priority.

Disclosure statement: A.J.K.Ö. has received support from (including attendance at conferences), undertakes clinical trials and acts as a consultant to Roche, Chugai, Schering-Plough/MSD, Abbott, Wyeth, BMS, GSK, MerckSorono and UCB. All other authors have declared no conflicts of interest.

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