Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis

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Summary

Background **Serious infections are a major concern for patients considering treatments for rheumatoid arthritis. Evidence is inconsistent as to whether biological drugs are associated with an increased risk of serious infection compared with traditional disease-modifying antirheumatic drugs (DMARDs). We did a systematic review and meta-analysis of serious infections in patients treated with biological drugs compared with those treated with traditional DMARDs.**

Methods **We did a systematic literature search with Medline, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from their inception to Feb 11, 2014. Search terms included "biologics", "rheumatoid arthritis" and their synonyms. Trials were eligible for inclusion if they included any of the approved biological drugs and reported serious infections. We assessed the risk of bias with the Cochrane Risk of Bias Tool. We did a Bayesian network meta-analysis of published trials using a binomial likelihood model to assess the risk of serious infections in patients with rheumatoid arthritis who were treated with biological drugs, compared with those treated with traditional DMARDs. The odds ratio (OR) of serious infection was the primary measure of treatment effect and calculated 95% credible intervals using Markov Chain Monte Carlo methods.**

Findings **The systematic review identified 106 trials that reported serious infections and included patients with rheumatoid arthritis who received biological drugs. Compared with traditional DMARDs, standard-dose biological drugs (OR 1·31, 95% credible interval [CrI] 1·09–1·58) and high-dose biological drugs (1·90, 1·50–2·39) were associated with an increased risk of serious infections, although low-dose biological drugs (0·93, 0·65–1·33) were not. The risk was lower in patients who were methotrexate naive compared with traditional DMARD-experienced or anti-tumour necrosis factor biological drug-experienced patients. The absolute increase in the number of serious infections per 1000 patients treated each year ranged from six for standard-dose biological drugs to 55 for combination biological therapy, compared with traditional DMARDs.**

Interpretation **Standard-dose and high-dose biological drugs (with or without traditional DMARDs) are associated with an increase in serious infections in rheumatoid arthritis compared with traditional DMARDs, although low-dose biological drugs are not. Clinicians should discuss the balance between benefit and harm with the individual patient before starting biological treatment for rheumatoid arthritis.**

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Introduction

Biological drugs are a new class of disease-modifying treatment options for rheumatoid arthritis that have been reported to show large clinical and radiographic improvements compared with traditional drugs.[1,2] Nine biological drugs are now approved by the US Food and Drug Administration and European Medicines Agency for treatment of rheumatoid arthritis. Biological drugs are used to treat moderate-to-severe rheumatoid arthritis in patients who have not responded adequately to traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate.[3,4] Infections, especially serious infections, are one of the greatest concerns for patients considering treatment with biological drugs.

Debate continues on whether biological therapies are associated with serious infections in patients with rheumatoid arthritis, the magnitude of this risk, and whether the risk varies between subpopulations of patients with rheumatoid arthritis.[5] In our experience, the clinical perception tends towards a belief that serious infection is an issue, but this notion is not backed up by consistent research evidence. The confusion originates from the four published systematic reviews with meta-analyses[6–9] of the risk of serious infection in patients receiving biological drugs for rheumatoid arthritis. The first meta-analysis,[9] which included three of the approved biological drugs in nine trials, reported an association. However, the next three meta-analyses,[6–8] which included more biological drugs and far greater sample sizes, did not identify any association between standard-dose biological drugs and increased risk of serious infections. Furthermore, discordant results have also been reported for non-randomised studies that assessed the risk of serious infection in rheumatoid arthritis,[10–16] with some

studies[14–16] detecting an association and others[10–13] detecting no association. Accordingly, the risk of serious infection in biological treatment of patients with rheumatoid arthritis has been debated. Unlike previous analyses, many more trials are now available for a conclusive study to address this question. Additionally, all four meta-analyses[6–9] in patients with rheumatoid arthritis[6–9] had major limitations; they restricted the population of patients (eg, only methotrexate-naive patients),[8] only included a few biological drugs in their analyses,[6–9] consisted mainly of studies that were more than a decade old,[9] or did not integrate findings across low-dose, standard-dose, or high-dose biological drugs (ie, did analyses separately). Availability of more robust evidence is crucial for the development of guidelines for rheumatoid arthritis treatment, which have previously been based mainly on observational studies.[3]

See Online for appendix

We aimed to compare the risk of serious infections in rheumatoid arthritis between biological treatment and non-biological traditional treatment with DMARDs, and use network meta-analysis to compare subpopulations within rheumatoid arthritis, to synthesise data from randomised trials.

Methods

Search strategy and selection criteria

We did a systematic review that included both a traditional meta-analysis and network meta-analysis to assess the risk of serious infection in rheumatoid arthritis, comparing biological drugs with each other, placebo, or a control treatment (traditional DMARDs or their combinations). Network meta-analysis includes direct and indirect evidence of benefits and harm among multiple treatments simultaneously, whereas traditional meta-analysis only considers direct evidence between two treatment strategies.[6] We did this systematic review, meta-analysis, and network meta-analysis in accordance with the guidance specified in the Cochrane Handbook for Intervention Reviews,[17] ISPOR network meta-analysis guidance,[18,19] and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[20]

A Cochrane librarian (Tamara Rader) did a literature search (appendix pp 3–7) and retrieved published trials of biological drugs or tofacitinib based on the defined criteria. Data were retrieved from the following sources: the Cochrane Central Register of Controlled Trials (CENTRAL, via the Cochrane Library), Medline (from 1946), and Embase databases (from 1947) to Feb 11, 2014; the two previously published Cochrane systematic reviews of biological drugs;[21,22] two reviews comparing traditional DMARD monotherapy with traditional DMARD combination therapies;[23,24] and a search of ClinicalTrials.gov. The search protocols for both Cochrane reviews are accessible online.[21,22] Search terms included "biologics", "rheumatoid arthritis" and their synonyms (appendix pp 1–5). Studies were eligible for inclusion if they included any of the nine approved biological drugs and reported serious infections; no restrictions were applied by the length of follow-up.

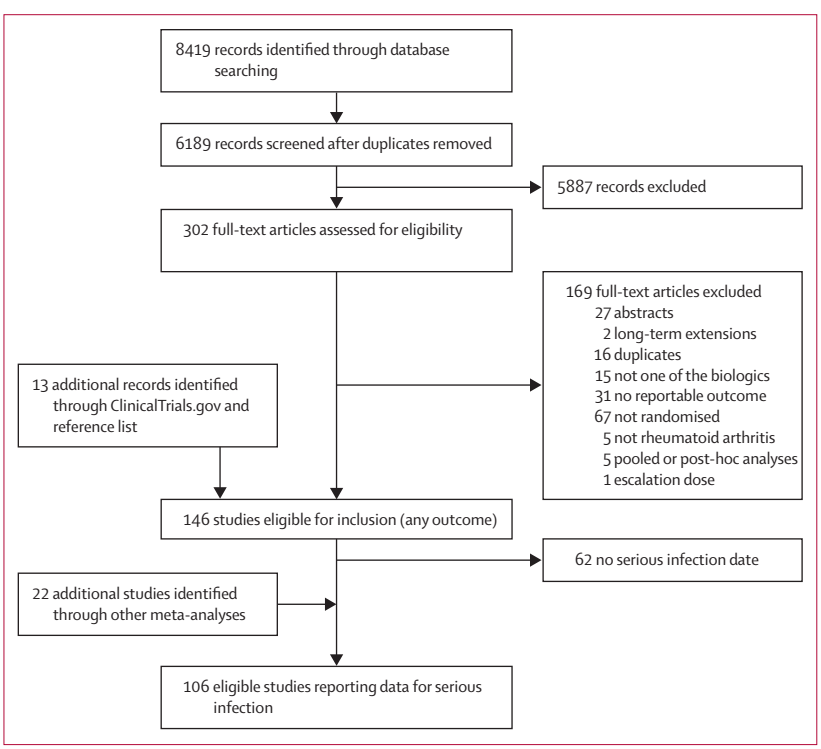

Figure 1: **Study selection**

Study selection and data extraction

We included randomised trials of rheumatoid arthritis in adults who were treated with any of the nine biological drugs approved for the treatment of rheumatoid arthritis, alone or in combination, if biological drugs were compared with each other, placebo, or traditional DMARDs (or DMARD combinations). Biological drugs included tumour necrosis factor (TNF) blockers (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), interleukin 1 antagonist (anakinra), interleukin 6 antagonist (tocilizumab), anti-CD28 (abatacept), and anti-B cell (rituximab) biological drugs in any dose. The comparators were placebo, traditional DMARDs (including methotrexate, alone or in combination), or another biological drug. We included tofacitinib doses as separate nodes in the network to improve precision of effect estimates for biological drugs (ie, by borrowing strength from indirect evidence) and help with future updates of this review, but we do not report findings for tofacitinib at this time (appendix p 6).

Independently, two reviewers assessed titles and abstracts (SN, MT) and full text articles (SN, TC), and extracted the data (SN, MT)—any disagreements were resolved by consensus and, when needed, a third reviewer (JAS). We extracted the data for serious infections, the total number of patients in each treatment group, and key characteristics of the patients and studies

(appendix pp 7–9) using a standardised data abstraction sheet. We assessed the risk of bias using the Cochrane Risk of Bias Tool.[25]

Outcome

Serious infection was the outcome of interest, as defined in each study. Definitions mostly included infections associated with death, admission to hospital, or use of intravenous antibiotics.

Statistical analysis

The odds ratio (OR) of serious infection was the primary measure of treatment effect. We also calculated absolute risk differences per 1000 patients per year treated using the mean annualised baseline risk of serious infection in traditional DMARD groups of included studies more than 6 months in duration. We did traditional meta-analyses, cumulative meta-analyses (meta-analyses over time), and Bayesian network meta-analysis. We did traditional and cumulative meta-analyses (comparing standard-dose [approved] biological drug *vs* traditional DMARD) with Comprehensive Meta-Analysis (version 2.2.064). We used the Mantel-Haenszel method with a fixed effects model and an adjusted continuity correction factor centred around 0·5 to handle zero cells.[26]

We used WinBUGS software (version 1.4.3) to do the Bayesian network meta-analysis.[27] We used a binomial likelihood model,[28] which allows for the use of multi-arm trials, for Bayesian network meta-analysis because many studies included multi-arms trials. We did both fixed-effects and random-effects network meta-analysis, although we used the random-effects model with an informative prior[29] for the between-study variance of the primary analysis. We derived point estimates and 95% credible intervals (CrI) for ORs using Markov Chain Monte Carlo methods. We assessed model fit and inconsistency[30] with standard approaches (appendix pp 8–10).

For traditional and cumulative meta-analyses, we used the standard-doses of the biological drugs (appendix pp 7–9). We included all doses of biological drugs (low, standard, and high) for the network meta-analysis. We assessed prespecified characteristics of studies and patients to ensure similarity and investigate the potential effect of heterogeneity on effect estimates (appendix pp 8–10). We stratified results by the following pre-defined populations: methotrexate-naive, methotrexate-experienced, and anti-TNF biological drug-experienced patients. We also did several sensitivity analyses related to methods for handling zero events.[26]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JS, CC, and GAW had full access to all the data in the study and JS had final responsibility for the decision to submit for publication.

Results

We identified 106 randomised trials published between 1992 and Feb 11, 2014, which included 42 330 patients with rheumatoid arthritis (figure 1; appendix pp 10–21). We separated these studies into those that included methotrexate-naive, traditional DMARD-experienced, and anti-TNF biological drug-experienced patients (table; figure 2). Treatment duration ranged from 2 to 36 months, and the mean rheumatoid arthritis duration ranged from 0·1 to 13·5 years (table). Randomised trials reported serious infection on an intention-to-treat (70%) or modified intention-to-treat (30%) basis. The appendix shows the detailed characteristics of included studies (pp 10–21) and the risk of bias assessment (pp 22–27).

In the tratidional meta-analysis, 59 trials assessed standard-dose biological drugs with or without traditional DMARD. Of these 59 trials, 53 (90%) reported at least

	All populations	Traditional DMARD-naive patients	Traditional DMARD-experienced patients	TNF-experienced patients
Number of trials	106 (100%)	24 (23%)	71 (67%)	11 (10%)
Number of patients in trials	42 330 (100%)	8375 (20%)	29 167 (69%)	4788 (11%)
Number of patients with serious infection	965 (100%)	227 (24%)	646 (67%)	92 (10%)
Median year of publication	2008 (1992–2013)	2006 (1992–2013)	2008 (1994–2013)	2008 (2005–2013)
Number of treatment nodes	10	5	10	6
Number of two-arm trials	63 (100%)	19 (30%)	38 (60%)	6 (10%)
Number of multi-arm trials	43 (100%)	5 (12%)	33 (77%)	5 (12%)
Mean follow-up duration (months)	9·0 (8·0, 1–60)	13·1 (6·9, 3–24)	8·0 (8·5, 1–60)	6·3 (3·2, 2–12)
Number of trials with duration ≥12 months	33 (31%)	17 (71%)	18 (25%)	2 (18%)
Mean rheumatoid arthritis duration (years)	6·9 (4·0, 0·1–13·5)	0·7 (0·7, 0·1–3·5)	8·5 (2·3, 2·2–13·5)	10·8 (2·0, 6·4–12·9)
Mean annualised baseline risk of serious infection in traditional DMARDs arms*	2% (2, 0–9%)	2% (2, 0–9%)	2% (2, 0–8%)	2% (2, 0–5%)

Data are n (%), year (range), mean (SD, range), or % (range). TNF=tumour necrosis factor. *Only included trials more than 6 months in duration for calculation. DMARD=disease-modifying antirheumatic drugs.

Table: **Characteristics of patients and studies**

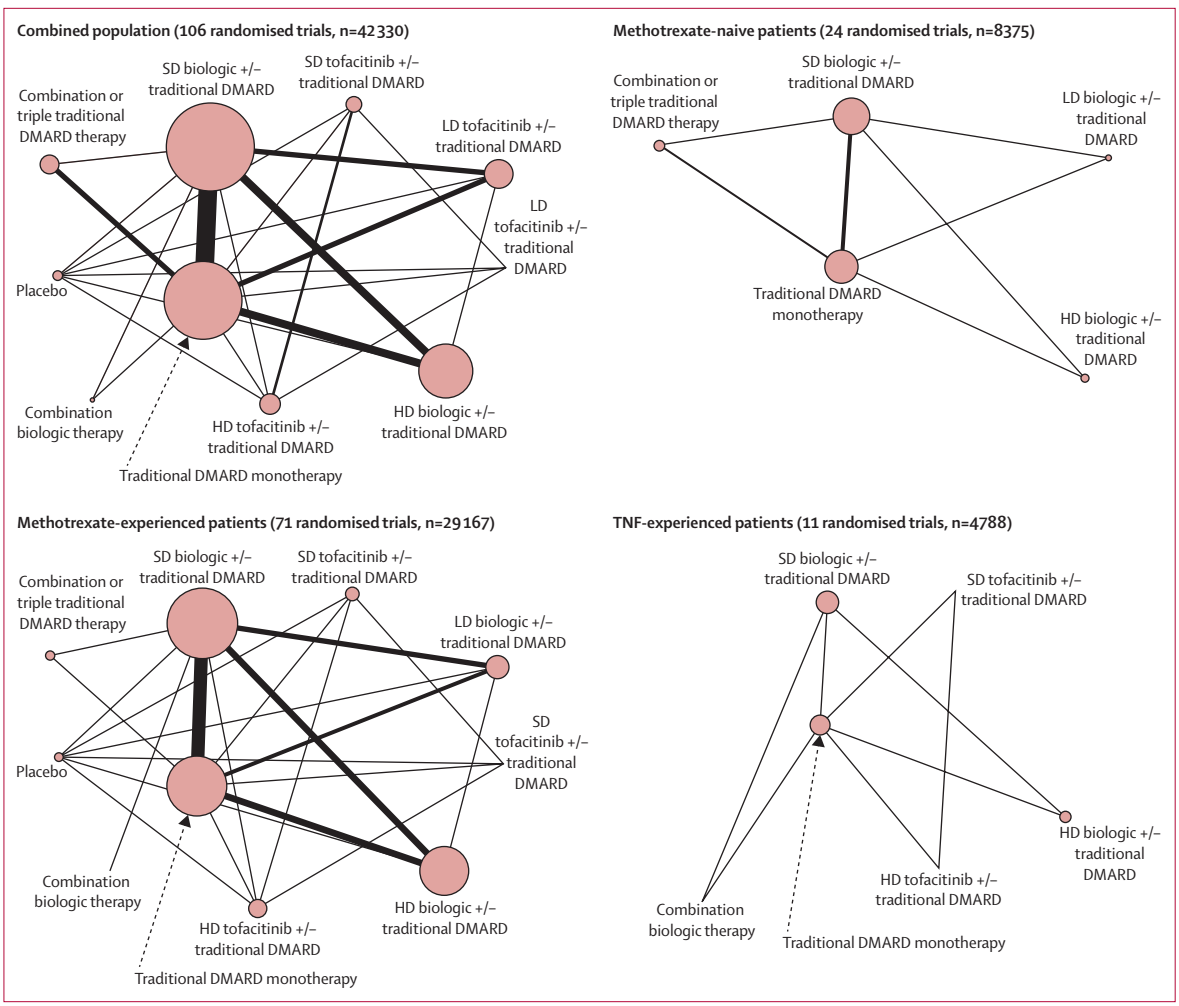

Figure 2: **Evidence networks for serious infection in populations**
The width of the lines is proportional to the number of randomised trials being compared in each pair of treatments. The size of each treatment node is proportional to the number of participants (sample size). Doses are defined in the appendix. DMARD=disease-modifying antirheumatic drugs. SD=standard dose. HD=high dose. LD=low dose.

one serious infection in the study. In total, 525 serious infections were reported in the 59 trials, including 68 comparisons between standard-dose biological drugs with or without traditional DMARD (342 events) and traditional DMARD monotherapy (183 events). We identified a significant increase in serious infections in patients receiving biological drugs (OR 1·27, 95% CI 1·05–1·52, p=0·012; figure 3). The risk of serious infections in patients treated with biological drugs varied depending on previous treatment experience; risk was significantly increased in methotrexate-experienced patients, but did not significantly differ in patients who were methotrexate-naive or anti-TNF-biological drug-experienced (figure 3).

We did stratified analyses adjusting for differences in other patient-level and study-level characteristics and these are shown in appendix (pp 28–30). We detected clinically important and statistically significantly increased risk of serious infections in patients treated with biological drugs compared with those treated with traditional DMARDs in several cases: when duration of follow-up was 6–12 months; when biological drugs were used in combination with traditional DMARDs; when patients had established rheumatoid arthritis (2–10 years disease duration); when studies were published between 2000 and 2004; when studies had a low risk of bias; and when the comparator was traditional DMARD plus placebo (appendix pp 28–30). The results did not vary substantially when different statistical models were used (appendix p 31). Detailed findings from the traditional meta-analysis are reported in the appendix (pp 28–30).

In the cumulative meta-analysis, our findings (figure 4) showed that use of standard-dose biological drugs was associated with a significantly increased risk of serious infection, which became evident in 2004, when

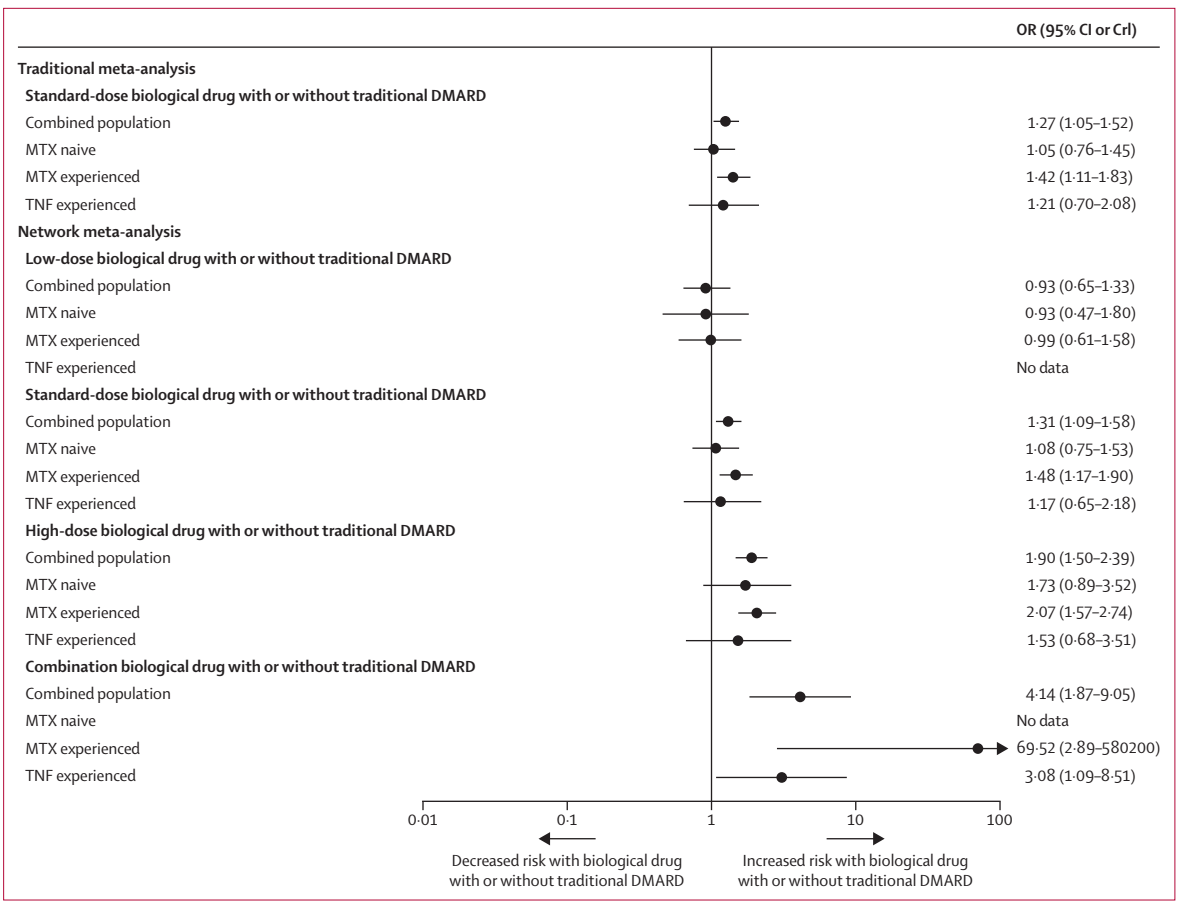

Figure 3: **Traditional meta-analysis and network meta-analysis**
Risk of serious infection among specified populations of patients compared with patients receiving traditional DMARD monotherapy. Data for the traditional meta-analysis are OR (95% CI) and data for the network meta-analysis are OR (95% CrI). OR=odds ratio. CrI=credible interval. DMARD=disease-modifying antirheumatic drugs.

5537 patients had been randomised and 122 events had occurred (p=0·02 at 2004). Subsequent trials increased the number of patients to 22 608, and the number of events increased to 525 for this treatment comparison. This increase resulted in a reduction in the OR, with a narrowing of CI (p=0·012 at 2013), although the point estimate remained more than one for the years after 2004, and very similar from 2007 onwards.

In our network meta-analysis, standard-dose biological drugs with or without traditional DMARD were associated with an increased risk of serious infection (figure 3; appendix p 32–34). High-dose biological drugs with or without traditional DMARD and combination biological therapy were also associated with increased risk of serious infection, although low-dose biological drugs with or without traditional DMARD were not. These findings supported those of traditional meta-analyses (appendix pp 35–36).

We saw differences among the a-priori-defined populations with rheumatoid arthritis. In patients who were methotrexate-naive, standard-dose biological drugs with or without traditional DMARD and high-dose biological drugs with or without traditional DMARD were not associated with a significant increase in risk of serious infection (figure 3). By contrast, in methotrexate-experienced patients, standard-dose biological drugs with or without traditional DMARD and high-dose biological drugs with or without traditional DMARD were associated with an increased risk of serious infections. Information on combination biological therapy was only available for methotrexate-experienced and anti-TNF biological drug-experienced patients and showed a significant increase in serious infections in both groups of patients (figure 3), with wider confidence intervals.

In patients receiving traditional DMARDs, the median absolute reported annual risk of a serious infection was roughly 2%, or 20 per 1000 patients treated per year. The absolute increase in the number of serious infections compared with traditional DMARDs was six per 1000 patients per year for standard-dose biological therapy with or without traditional DMARD, 17 per 1000 patients per year for high-dose biological therapy with or without traditional DMARD, and 55 per 1000 patients per year for combination biological treatment.

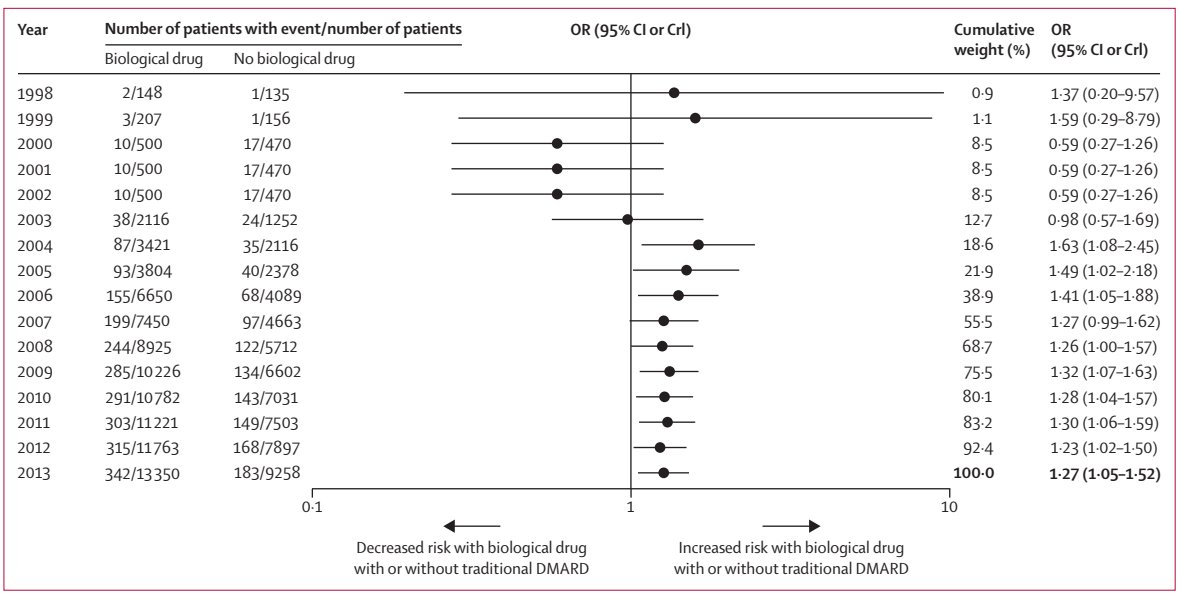

Figure 4: **Cumulative meta-analysis**
Risk of serious infection among specified populations of patients compared with patients receiving traditional DMARD monotherapy. OR=odds ratio. DMARDs=disease-modifying antirheumatic drugs.

Discussion

The risk of serious infection for patients receiving biological treatment for rheumatoid arthritis and the magnitude of this effect are uncertain. Although the first meta-analysis of the association between biological drugs and serious infections detected an association, three subsequent meta-analyses reported that standard-dose biological drugs were not associated with an increased risk of serious infection compared with traditional DMARDs. Evidence can now be drawn from data for 42 330 patients with rheumatoid arthritis from 106 randomised trials, and this increased sample size can provide a more precise estimate of the risk of serious infection. To the best of our knowledge, this study is the most comprehensive meta-analysis of randomised trials of the risk of serious infections in rheumatoid arthritis that adheres to the recommended PRISMA reporting standards.[20] Our analysis exceeds the sample size of the largest previous meta-analysis of risk of infection with biological treatment of rheumatoid arthritis (18 randomised trials and 8808 patients)[7] more than five times, and includes 88 more randomised trials (appendix p 37). We included data from nine biological drugs, reported detailed stratified analyses, integrated findings for all doses of biological drugs, presented findings on both the relative and absolute scale, and tested the robustness of findings with sensitivity analyses (appendix).

We detected that standard-dose, high-dose, and combination biological drugs (with or without DMARDs) are associated with more serious infections than traditional DMARDs in patients with rheumatoid arthritis. Our comprehensive study investigated biological drug dose in rheumatoid arthritis in more detail than did previous studies (appendix p 37). Bongartz and colleagues[9] reported that two of the three biological drugs they studied (infliximab and adalimumab) were associated with significantly increased risk of serious infections (OR 2·0, 95% CI 1·3–3·1) compared with placebo in nine trials up to 2005, which included 5005 patients. By contrast, several later meta-analyses, which included more biological drugs and more randomised trials, reported different findings.[6–8] Salliot and colleagues[7] examined 12 randomised trials up to 2007 (6879 patients) and reported that the risk of serious infections with rituximab and abatacept did not differ from placebo, but was significantly increased with high doses of anakinra versus low-dose anakinra (9·63, 1·31–70·91) and versus placebo (3·40, 1·11–10·46). Leombruno and colleagues[6] analysed 18 randomised trials of three anti-TNF biological drugs up to 2007 (8808 patients) and detected no significant increase in serious infections (1·21, 0·89–1·63). They did identify an increased risk in patients receiving two-to-three times the recommended doses of anti-TNF biological drugs in unadjusted and pooled meta-analysis, but not in exposure-adjusted analyses. Thompson and colleagues[8] included six randomised trials of five anti-TNF biological drugs in early rheumatoid arthritis up to 2009 (3419 patients) and reported no significant increase in risk of serious infections with biological drugs compared with methotrexate (1·28, 0·82–2·00).

Our findings focus solely on results reported in randomised trials. These studies are often limited by underrepresentation of elderly and high-risk patients and the frequent comparison of treatments with placebo instead of active treatments. Indeed, most of the randomised trials included in our analysis compared the intervention in question with placebo. Accordingly, our risk estimates mainly represent comparisons of biological

drugs combined with DMARD versus DMARD. However, a no-treatment comparator might not be realistic in clinical practice. To compensate, we did several analyses in which we compared biological drugs with combination or triple DMARD therapy. For these analyses, the ORs were slightly higher (appendix pp 29–31, 33–36) but more uncertain because this comparison was only based on data from four randomised trials that compared biological drugs plus DMARD with combination or triple DMARD therapy. However, most trials for this comparison did report a higher number of serious infections in the biological drug group than in comparison groups. Non-randomised studies provide complementary evidence to meta-analyses of randomised trials. A 2010 review[31] summarised the range of effect estimates reported in non-randomised studies, in which effect estimates for biological drugs versus DMARDs ranged from 1·0 to 2·2. While non-randomised studies differ, these studies have reported an association with infection that is strong early in the course of treatment, but decreases with time.[31,32] However, the latter finding should be interpreted with caution—studies investigating the long-term use of DMARD treatment are limited to highly selected populations who are adherent to treatment and responding well to DMARDs.

These findings have practical implications. The benefits of biological therapy for patients with rheumatoid arthritis are well known,[1,2] and now these patients can think about these benefits alongside the absolute risk increase of serious infections (six per 1000 per year for standard-dose biological drugs and 17 per 1000 per year for high-dose biological therapy) at the time when decisions about treatment with biological drugs are made. Clinical guidelines should also incorporate the fact that this risk varies with several characteristics of patients, such as previous DMARD exposure, concurrent use of traditional DMARD or not, and established versus early rheumatoid arthritis.

Our study findings must be interpreted considering several limitations. First, our analysis includes studies that span a 15 year period. Patients enrolled in early studies might have differed from those included in more recent studies. We did a sensitivity analysis to investigate this issue and noted that the point estimate for the OR remained greater than one during the 15 year period (appendix pp 29–31), but decreased from 1995–1999 (OR 1·59, 95% CrI 0·29–8·79) to 2010–2014 (1·11, 0·76–1·62). Whether the decrease in relative effect is evidence that the risk of biological drugs causing serious infections is decreasing over time, or attributable to changes in regions where recent trials were done or to duration of placebo among included studies (ie, increased use of rescue medications for placebo group) is unclear; slight changes in the inclusion and exclusion criteria of the randomised trials we included might have occurred over time, such as the fact that an increased proportion of randomised trials have excluded patients with positive tuberculosis tests in recent years. Future research is needed to study this effect.

Several other limitations need to be addressed. We detected variability between studies in terms of duration of rheumatoid arthritis, duration of follow-up, and other covariates (appendix p 38). Therefore, we reported findings for subgroups of patients to allow comparisons between groups of patients (figure 3; appendix pp 28–29, 32). Second, meta-analyses and network meta-analysis of infrequent outcomes are challenging because of the inherent difficulties in the handling of zero cells. To manage this issue, we did several analyses that used different statistical models and assumptions.[26] Results were consistent when we used alternative approaches (appendix p 31–32). Most studies presented the data by use of intention to treat or modified intention to treat, rather than as-treated analyses, which might underestimate the serious infection risk. Additionally, withdrawals were labelled if caused by adverse events, but not serious infections, and some patients might have discontinued biological drugs before these adverse events qualified as serious infections. However, we think the magnitude is probably small, in view of the low number of withdrawals and crossovers reported. Data for compliance with drugs were not reported in most randomised trials; however, these expensive drugs are usually dispensed and adherence recorded as part of the randomised trial conduct. Finally, our analyses only incorporate published data. Future work should focus on integration of more unpublished data[5] if it becomes available. The scarcity of detailed patient-level data, especially on steroid use, also limits interpretation of these analyses.

Standard-dose and high-dose biological drugs (with or without DMARDs) are associated with an increase in serious infections compared with traditional DMARDs in rheumatoid arthritis, although low-dose biological drugs are not. This new knowledge, when balanced against the clinically important benefits of biological drugs, will help patients and their physicians to make evidence-based decisions that align with their values, preferences, and tolerance of risks of harm and benefits.

Contributors

JAS conceived the study design, did some of the data extraction, and drafted the report. CC conceived the study design, did some of the data extraction, did all of the analyses, and drafted the report. GAW conceived the study design and made major revisions to the report. PT and RC helped with the data analysis and reviewed the report for important intellectual content. SN, MT, and ETG did the systematic review and data extraction, and reviewed the report for important intellectual content. TC and DC conceived the study and reviewed the report for important intellectual content. All authors have read and approved the final version of the report.

Declaration of interests

JAS has received research grants from Takeda and Savient, and consultant fees from Savient, Takeda, Regeneron, and Allergan. JAS is a member of the executive of OMERACT, an organisation that develops outcome measures in rheumatology and receives arms-length funding from 36 companies; a member of the American College of Rheumatology's Guidelines Subcommittee of the Quality of Care Committee; and a member of the Veterans Affairs Rheumatology Field Advisory Committee. CC is a recipient of a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research and has received funding from Canadian Network and Centre for Trials Internationally and is a trainee on

the CIHR Drug Safety and Effectiveness Network team grant. PT has received grants or honoraria from Bristol Myers, Chiltern International, and UCB. GAW has received a research grant and consultant fee from Bristol-Myers Squibb; consultant fees from Abbott, Amgen, and UCB; and done data safety monitoring for Novartis. RC has received consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses from the following companies: Abbott, Astellas Pharma, Axellus, Bristol-Myers Squibb, Cambridge Nutritional Foods, Centocor, DSM Nutritional Products, HypoSafe, MSD, MundiPharma, NorPharma, Pharmavie, Pfizer, Roche, Sanofi-Aventis, and Scandinavian Clinical Nutrition. All other authors declare no competing interests.

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