RHEUMATOLOGY

Rheumatology 2016;55:573–582
doi:10.1093/rheumatology/kev364
Advance Access publication 7 October 2015

Meta-analysis

Management of perioperative tumour necrosis factor α inhibitors in rheumatoid arthritis patients undergoing arthroplasty: a systematic review and meta-analysis

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Abstract

Objective. Tumour necrosis factor α inhibitors (TNFis) are widely used in RA patients who undergo surgery, and optimal perioperative management must balance the risk of infection with the risk of post-operative flare. The purpose of this study is to examine the impact of TNFi exposure on surgical site infections (SSIs) in RA patients undergoing elective orthopaedic surgery by systematic review and meta-analysis.

Methods. A systematic review of the literature and meta-analysis were performed using PUBMED, EMBASE and the Cochrane Central Register of Controlled Trials, through May 2014. Two independent reviewers screened titles and abstracts, and analysed selected papers in detail. Included studies assessed RA patients with or without TNFi exposure prior to orthopaedic surgery, and described post-operative infections. Study quality was assessed using the Oxford Centre for Evidence-based Medicine Levels of Evidence. Meta-analyses of the individual study odds ratios (ORs) were conducted, and each pooled OR was calculated using a random effects model.

Results. Eight observational studies and three case control studies met inclusion criteria; risk of bias was low in eight studies and moderate in three. Publication bias was not apparent. These studies represent 3681 patients with recent exposure to TNFis (TNFi+) and 4310 with no recent exposure to TNFis (TNFi−) at the time of surgery. The TNFi+ group had higher risk of developing SSI compared with patients in the TNFi− group (random effects model: OR 2.47 (95% CI 1.66, 3.68); $P < 0.0001$).

Conclusion. Data from the available literature suggest that there is an increased risk of SSIs in RA patients who use or have recently used TNFis at the time of elective orthopaedic surgery. Prospective studies to confirm these findings and establish the optimal withhold and restart time of TNFis, in the context of other risk factors for infection in RA patients such as higher disease activity, corticosteroid use, smoking and diabetes, are needed.

Key words: rheumatoid arthritis, tumour necrosis factor α inhibitors, surgical site infection, perioperative management, arthroplasty.

Rheumatology key messages

- Exposure to TNF-α inhibitors may contribute to the risk of surgical site infections in RA patients.
- It is not known if comorbidities in RA patients further increase surgical infection risk for patients on inhibitors of TNF-α.
- The optimal time to withhold inhibitors of TNF-α prior to orthopaedic surgery for RA patients is unknown.

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Submitted 30 September 2014; revised version accepted 2 September 2015

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Introduction

Biologic DMARDs such as the tumour necrosis factor α inhibitors (TNFis) are used widely in patients with RA. Although TNFis have improved the quality of life of RA patients and decreased radiographic progression, utilization of total knee (TKA) and total hip arthroplasty (THA) remains high [1–5]. Among patients with RA, 34–44% undergoing THA and TKA were taking biologic DMARDs at the time of arthroplasty [6, 7]. However, optimal perioperative management of TNFis is unresolved. The severe consequences of prosthetic joint infection (PJI) have led to withholding TNFis in the perioperative period to minimize infection risk. Yet evidence to support this practice has been conflicting [8–10]. In fact, recent studies have questioned the role of TNFis in the increased rate of bacterial infections in specific contexts such as the initiation of therapy in active RA [11, 12]. Nonetheless, studies have documented an increased risk of PJI in patients with RA, which is estimated to be two to four times greater than OA patients [13]. Among RA patients, having a large joint arthroplasty is a risk factor for joint infection [14], suggesting that arthroplasty creates a specific high risk context for infection for patients with RA. Importantly, the presence of a foreign body such as an orthopaedic implant creates a unique environment for bacterial growth and biofilm development, which requires cellular defence mechanisms dependent on cytokines including TNF-α [15].

Recommendations for withholding pre-operative TNFis are based on a consensus of expert opinion and vary among Rheumatology organizations, ranging from 1 to 4 weeks [16–20]. However, prolonged periods without biologic or DMARD therapy may result in a disease flare which may compromise the patient's physical rehabilitation [21]. Moreover, active RA and corticosteroid use are independent risk factors for infection [9]; stopping therapy or beginning corticosteroids to treat flares could be counter-productive [22]. The objective of this study is to systematically review the literature and perform a meta-analysis of data on surgical site infections (SSIs) in patients exposed to TNFis at the time of elective orthopaedic surgery to inform the optimal perioperative management of TNFis.

Methods

A systematic literature review and meta-analysis was performed to determine the risk of SSI in RA patients with TNFi exposure undergoing elective orthopaedic surgery.

Inclusion criteria

The population of interest was adult RA patients undergoing elective orthopaedic surgery. Pre-established criteria for included studies were as follows: adults (age $\geqslant 18$), the majority having RA ($\geqslant$70%); >80% elective large joint arthroplasty, or studies in which cases of large joint arthroplasty could be separated from those undergoing other procedures; and TNFi exposure within 3 months of surgery. RA diagnosis was validated using American College of Rheumatology (ACR) criteria or by a treating rheumatologist's diagnosis plus use of DMARDs, the latter being criteria with a high degree of specificity [23, 24]. Use of other DMARDs or corticosteroids was not systematically included or analysed. The intervention of interest was use of TNFi, with pre-operative exposure within 3 months of surgery. The comparison group was patients without recent exposure to TNFis. Studies reporting the use of other biologics were excluded where possible; where results are described as biologics the analysis could not exclude tocilizumab or abatacept [25, 26].

Outcome measure

The outcome of interest was superficial or deep SSI occurring $\leqslant 1$ year after surgery. Infections met criteria defined by the Centres for Disease Control (CDC) (purulent drainage from a surgical site, positive culture, wound dehiscence in a patient with fever or localized pain, abscess demonstrated by exam or imaging, or diagnosis of infection by the treating surgeon) or met pre-determined criteria verified by the individual authors [27]. A sub-analysis limited to THA and TKA was also performed. Authors were contacted to clarify results and provide additional information where appropriate.

Assessment of study quality

The quality of the data was assessed using the Oxford Centre Levels of Evidence permitting evidence tables to be constructed. Risk of bias was judged using a previously published methodology, in which case definition, adequacy of follow-up, outcome and rigor of analysis including multivariate regression contribute to a final score, judged low, moderate, or high risk [26, 28, 29]. No randomized controlled trials were available. High quality, peer-reviewed, retrospective and prospective cohort studies as well as retrospective case-control studies (2b and 3b using the Oxford Levels of Evidence) were included [28]. Expert opinion review articles, duplicate articles, case series and case reports or studies with inadequate information were eliminated. Selected studies were further examined by reviewing the entire papers; of these, 11 were included. Asymmetry of a funnel plot was used to assess publication bias.

Search strategy

Librarian-assisted searches were conducted in Medline via PUBMED, EMBASE via OVID Interface, and the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library. Searches were performed on 20 March 2014, with the defaulted date range for Medline from 1946 to the date of search, Embase from 1947 to the date of search, and Cochrane Central Register of Controlled Trials from 1965 to the date of search. The following key terms were used: (Surgery or arthroplasty or preoperative) and (infection or infect* [* signifies the use of a truncated term] or risk factor) and (TNF or tumour necrosis factors or etanercept or adalimumab or golimumab or infliximab or certolizumab pegol or MTX or antirheumatic agent) and RA. Keywords are exploded using a

default setting for PubMed, and manually exploded on OVID and Cochrane to include all the subheadings with no limit imposed. Automatic explosion utilizes a unique tree structure of Medical Subject Headings embedded within PubMed including all subheadings, increasing sensitivity.

Search results from each database were reviewed manually by S.M.G. and I.M. independently by title and abstract. A manual search of the references listed for the included studies was also performed. Articles were limited to the English language. Articles not fulfilling the inclusion criteria were excluded.

Data extraction

Data were extracted by two independent reviewers (S.M.G. and I.M.) and final data verified by both. Data extracted included RA diagnostic criteria, age, surgical procedure, presence of infection, infection diagnostic criteria, timing of biologic use and cessation where available, and duration of follow-up, which were entered into tables. Additional clarifying information was provided by direct communication with Inès Kramers-de Quervain, Shigeki Momohara and Alfons den Broeder.

Statistical analysis

Meta-analyses of the individual study unadjusted odds ratios (ORs) (i.e. OR for exposure to TNFi and SSI) were conducted with the use of StatsDirect statistical software (version 2.7.9 of 9 July 2012; StatsDirect, Altrincham, UK). Each pooled OR was calculated using a random effects (DerSimonian–Laird) model and forest plots were generated to display the individual study OR and the pooled OR. Random effects models were used to combine the studies because of the variability in the outcome of interest between the studies. To assess the combinability of the OR, we calculated the P-values from the Cochrane Q statistical heterogeneity test. However, regardless of the heterogeneity test P-values, the random effects analysis was used for all pooled ORs. The random effects analysis allows for more variability in the individual study OR estimates when generating the pooled OR. For the association of interest (i.e. exposure to TNFi and surgical site infection), the results of each study were expressed as an OR with an exact 95% confidence interval. For each meta-analysis, the presence of publication bias was evaluated through a funnel plot, which is a scatter plot of the log of the OR estimated from the individual studies versus a measure of study size or precision (i.e. standard error of the log of the OR for each study). In this graphical representation, larger and more precise studies are plotted at the top, near the combined (pooled) OR, whereas smaller and less precise studies will show a wider distribution below. If there is no publication bias, the studies would be symmetrically distributed on both sides of the pooled OR line. In the case of publication bias, the funnel plot may be asymmetrical, since the absence of studies would distort the distribution on the scatter plot. Egger's test and the Begg–Mazumdar rank-correlation test were used to statistically assess the presence of publication bias.

Results

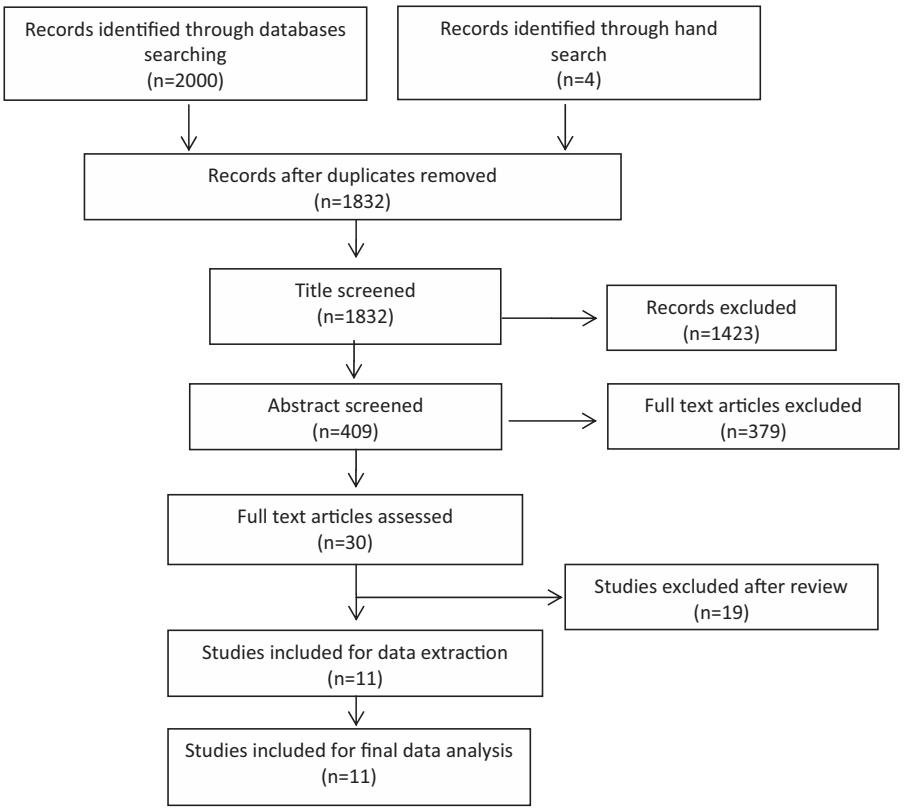
After combining searches from the three databases [PubMed (423), Cochrane (8), Embase (1569), and four manual searches of relevant bibliographies], screening retrieved 2004 titles and abstracts for review by SG and IM (Fig. 1). There were 168 eliminated as duplicates, and 1832 were screened by title; 1423 were eliminated as wrong subject or reviews, leaving 409 relevant abstracts to be reviewed. The majority (93%) were excluded by abstract. Of 100 remaining abstracts, 70 were further eliminated as wrong subject/review or opinion articles. Of 30 papers reviewed in detail, 11 fit all the inclusion criteria and were used in our analysis.

Table 1 summarizes the study results: 3681 RA patients underwent a major orthopaedic surgery, primarily THA or TKA with recent (range 12 days to 3 months) pre-operative exposure to TNFis (TNFi+) and 4310 surgery patients with no recent exposure to TNFis (TNFi−). RA cases undergoing elective orthopaedic surgery were identified in the included studies and formed the basis of this analysis, which was based on the univariate results. SSIs were reported in 116 of the TNFi+ group, and 126 SSIs of the TNFi− group. Greater than 70% of both groups were RA. ACR criteria for RA were met in five studies; in six, diagnosis was validated by a specialist plus use of a DMARD or biologic. A subset analysis was performed using only the five studies in which the diagnosis of RA was made by ACR criteria; TNFi exposure favoured infection with an OR of 3.16 (random effects model) of 3.16 (95% CI 1.55, 6.43; $P = 0.0015$). CDC criteria for SSI were met in six studies, while pre-established criteria were met in five. An additional analysis was performed using only those six studies meeting CDC criteria for infection. Exposure to TNFi favoured infection, with an OR of 3.01 (95% CI 1.88, 4.84; $P < 0.0001$). Eight of the included studies had a low risk of bias, and three had a moderate risk of bias, according to the Oxford levels of evidence [28]. All studies were retrospective; the studies by Galloway *et al.* and Momohara *et al.* utilized data from prospectively gathered cohorts, and the study by Ruyssen-Witrand *et al.* used historical controls [4–6].

Meta-analysis

Of the 11 studies comparing SSI rates in regards to TNFi exposure in a meta-analysis based on the unadjusted ORs, patients in the TNFi+ group had a higher odds of developing a SSI compared with patients in the TNFi− group (pooled random effects model OR 2.47; 95% CI 1.66, 3.68; $P < 0.0001$) (Fig. 2). For the four studies in which TKA/THA patient data could be separately identified, there was a trend for more patients in the TNFi+ exposed group to develop a SSI compared with patients in the TNF− unexposed group (Fig. 3), which was not statistically significant (pooled random-effects OR 3.08; 95% CI 0.87, 10.95; $P = 0.08$) when using a 5% significance threshold [26]. A funnel shaped bias assessment

Fig. 1 Screening process by which papers were selected for this study



plot was produced (Fig. 4), demonstrating no publication bias.

Specific study results

The study of Kubota *et al*. [30] assessed SSI in RA patients; the 267 biologic treated patients in their study included 247 patients on TNFis and 300 not treated with TNFis. In a multivariate logistic regression (adjusting for age, duration of RA, biologic agents, prednisolone usage, and foot and ankle surgery), use of biologic agents was not a risk factor for post-operative or late infection (OR 3.88; 95% CI 0.80, 18.86; P = 0.09) when using a 5% significance threshold, although foot and ankle surgery was a risk factor for infection (OR 19.2; 95% CI 4.67, 79.45; P = 0.001). In contrast, the unadjusted OR was 4.35 (95% CI 0.82, 43.14).

Scherrer *et al*. [31] identified 50 359 patients who underwent orthopaedic surgery. Of these, 2472 had inflammatory rheumatic diseases, including 82.9% with RA. Information about disease-related medications was available in 54%. Multivariate regression analysis adjusted with propensity scores indicated patients with inflammatory rheumatic disease taking TNFis (OR 2.54; 95% CI 1.08, 5.97; P = 0.032) were at increased risk of infection, which increased further when the last dose was less than one dose interval prior to surgery. (Unadjusted OR used in the meta-analysis of pooled data 2.56; 95% CI 0.92, 6.17.)

Johnson *et al*. [32] identified 268 RA cases undergoing TKA, and analysed risk and use patterns of TNFi in the perioperative period. Stop dates correlated with the dosing schedule. Seven (3%) SSIs occurred overall, including one deep SSI (0.4%). There were 3 infections among 92 TNFi treated patients (3.26%) vs 3 infections in 143 without TNFi (2.10%), which was not statistically significant (P = 0.68).

Using the prospective Biologics Registry of the British Society for Rheumatology (BSR), Galloway *et al*. [14] analysed the risk of septic arthritis among 11 881 TNFi-treated RA patients and 3673 RA patients who were on non-biologic DMARDs (nbDMARDs), and reported 199 patients overall with septic arthritis. A secondary analysis was performed in 2689 RA patients with prosthetic joints, with 41 cases of septic arthritis. For the subgroup with prosthetic joints, the unadjusted OR used in the meta-analysis for all cases of infection was 1.69 (95% CI 0.71, 4.88), compared with the adjusted Hazard Ratio (HR) of 1.2 (95% CI 0.4, 3.4) (adjusted for age, gender, disease duration, DAS28, HAQ, steroid exposure, prior joint replacement and calendar year of entry into the study) or significant predictors of infection such as chronic obstructive pulmonary disease, and diabetes. Adjustment for these potential confounders was made using propensity scores). Infection within 90

Table 1 Overview of the publications reviewed in this study

Study, study type, period of study, country	Study quality	Total RA patients	TNFi+ intervention	Infection TNF+	TNFi- comparator no.	Infection TNF −	Orthopaedic procedure	Follow-up: post-surgery	Outcome measures
Kubota *et al.* [26], retrospective cohort, 2006–2011, Japan	2b[a] Moderate risk of bias[b]	567	247	7	300	2	THA, TKA and other joint surgeries	1 year	Delayed wound healing, superficial or deep SSI[c]
Scherrer *et al.* [31], retrospective cohort, 2000–2008, Switzerland	2b[a], Low risk of bias[b]	2050	122	7	1207	28	Foot, Elbow, THA, TKA	>2 year	Superficial or deep SSI[c]
Johnson *et al.* [32], retrospective cohort, 2007–2011, USA	2b[a] Low risk of bias[b]	248[d] 268[e]	92[e]	4	143[e]	3	TKA	6 months	Post-op AE Including superficial or deep SSI[c]
Galloway *et al.* [14], prospective observational study, 2001–2008, UK	2b[a] Low risk of bias[b]	15554[d]	2689	41	659	6	Large joint replacements	3 years	Septic arthritis SSI[c]
Momohara *et al.* [25], retrospective cohort, 2005–2009, Japan	2b[a] Low risk of bias[b]	420[f]	48 all biologics, 42 TNF+	10	372	17	THA, TKA	Not given	Superficial and deep SSI[c]
Kawakami *et al.* [33], case control, 2004–2009, Japan	3b[a] Low risk of bias[b]	128	64	8	64	1	TKA, THA (includes other joint surgeries)	Not given	Superficial and deep SSI[c]
Hirano *et al.* [34], retrospective cohort, 2004–2007, Japan	2b[a] Moderate risk of bias[b]	113	39	3	74	5	THA, TKA	4 weeks	Wound dehiscence pre-determined criteria for SSI[g]
Bongartz *et al.* [13], case control, 1996–2004, USA	2b[a] Low risk of bias[b]	462[f] 657[e]	50	3	412	20	THA, TKA	>1 year	Predetermined published criteria for wound infections[g]
Den Broeder *et al.* [36], retrospective (parallel) cohort, 1997; 2001–2004, The Netherlands	2b[a] Low risk of bias[b]	768[f] 1219[e]	196[e]	14	1023[e]	41	1219 elective orthopedic surgery	1 year	Post-op AE's including superficial and deep SSI[c]
Ruyssen-Witrand *et al.* [36], retrospective cohort, 1997–2004, France	3b[a] Moderate risk of bias[b]	92[d] 127[e]	107[e]	6	0	0	Orthopedic procedures 107 (joint replacement)	1 year	Predetermined published criteria for wound infections[g]
Giles *et al.* [38], case control, 1999–2004, USA	3b[a] Low risk of bias[b]	91[f]	35	7	56	3	Orthopaedic surgery	30 days post-op	Predetermined published criteria for wound infections[g]

[a]Study Quality: levels of evidence based on Oxford classification criteria [28]; 2b: individual cohort study; 3b: case control study. [b]Risk of bias scores where 6 ⩽ high risk, 7–9 = moderate risk, and > 10 = low risk [29]. [c]SSI using Centre for Disease Control (CDC) criteria [27]. [d]Classified as RA by diagnosis by a specialist in addition to DMARD use. [e]Number of surgical procedures included in analysis. [f]Diagnosis of RA according to ACR 1987 Classification Criteria [23]. [g]SSI classified by previously published definitions [27] or verified by physicians. AE: adverse event; TNFi+: patients with pre-operative exposure to TNFis; TNFi−: patients with no recent exposure to TNFis.

Fig. 2 Forest plot showing ORs for SSIs

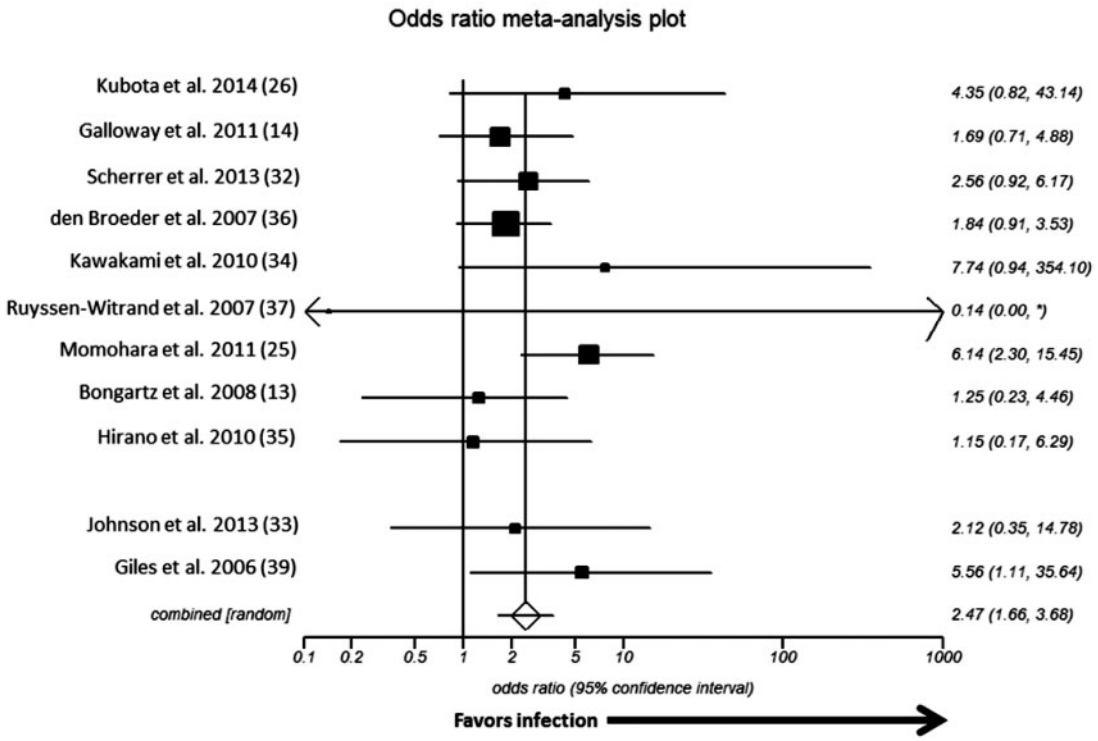
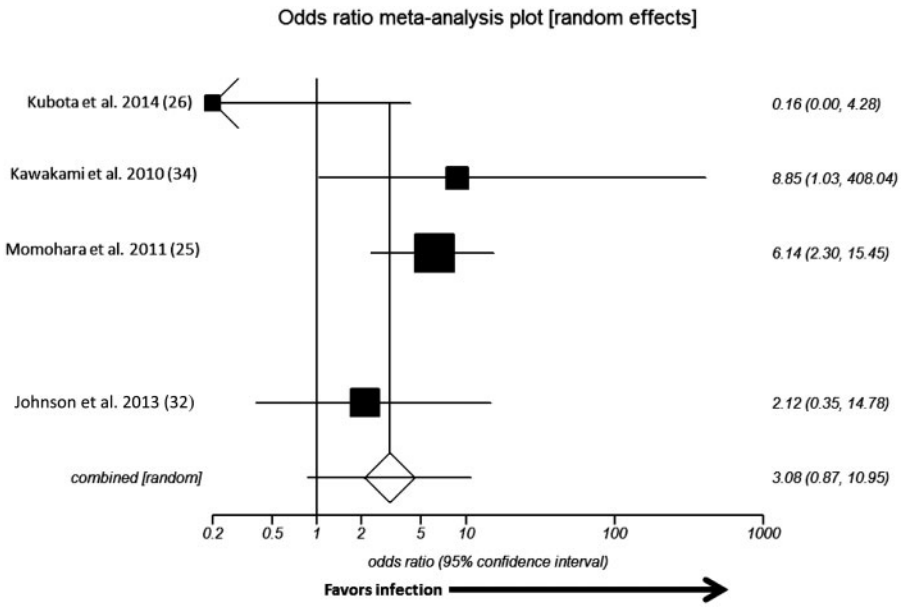
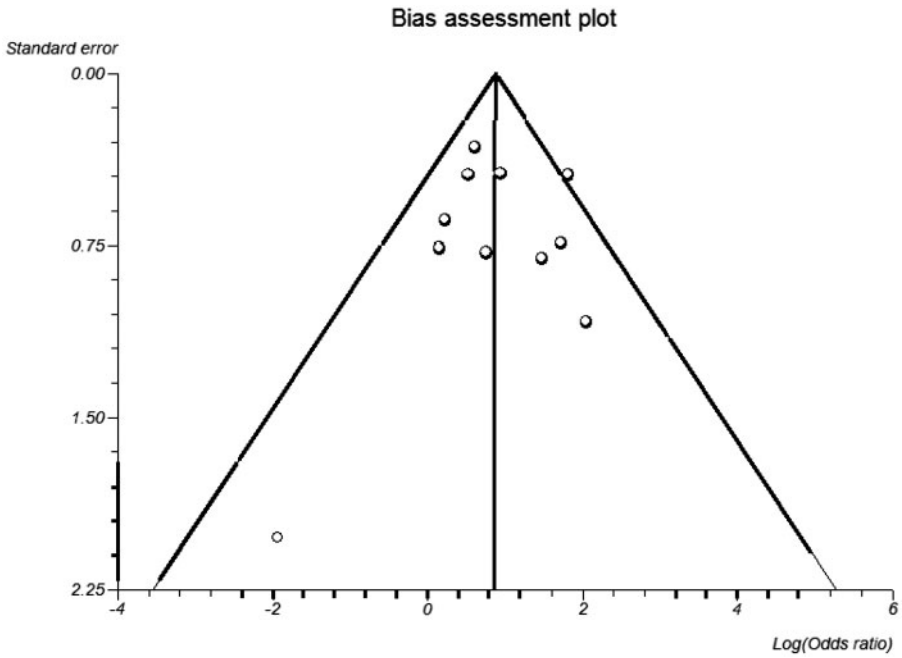


Fig. 3 Forest Plot showing the ORs for SSI, sub-analysis



days of surgery was analysed separately in an adjusted logistic regression comparing TNFi-treated RA patients vs nbDMARD treated patients. This study determined that 47/199 septic arthritis cases (24%) were in patients with prosthetic joints, 30 within 90 days of surgery. For those cases within 90 days of surgery, there was no significant difference between TNFi users and conventional DMARD users (adjusted OR 0.8, 95% CI 0.2–3.5) (adjusted as

FIG. 4 Funnel plot assessing publication bias demonstrates low risk



described above), although the patients in the registry were likely to have discontinued the TNFi for 2–4 weeks prior to surgery.

Momohara *et al.* [25] retrospectively identified 81 THA and 339 TKA performed over a 5 year period on patients in the IORRA RA cohort. They found 10 infections (1 deep SSI) in 44 cases in the biologic DMARD group and 17/372 (2 deep) infections in the nbDMARD group, with an unadjusted OR used in the meta-analysis of 6.14 (95% CI 2.30, 15.4). A multivariate regression analysis revealed that use of biologic DMARDs (OR 5.69; 95% CI 2.07, 15.62; P = 0.0007) and duration of RA (OR 1.09; 95% CI 1.04, 1.14; P = 0.0003) were significant risk factors for SSI (adjusted for age, BMI, diabetes mellitus, smoking, past history of surgery, operative duration, disease duration, pre-operative CRP, haemoglobin, white blood cell count, revision vs primary, TKA vs THA, biologic DMARDs, non-biologic DMARDs and prednisolone use).

Kawakami *et al*. [33] studied 64 TNFi-treated RA surgeries matched to 64 nbDMARD surgeries. The orthopaedic procedures were heterogeneous. Use of TNFi was a significant risk factor for SSI (OR 21.8; 95% CI 1.23, 386.1; P = 0.036; adjusted for gender, age, BMI, disease duration, pre-operative CRP, prednisone dosage, and the use of TNFi, MTX, and SSZ). (Univariate OR used in the meta-analysis 7.74; 95% CI 0.94, 354.10.)

Hirano *et al.* [34] studied a cohort of 39 RA patients taking TNFis and 74 not taking TNFis, reporting SSI in 2 (5.1%) of the TNFi treated patients, and in 5 (6.8%) of the nbDMARD group (OR 0.74; 95% CI 0.138, 4.0336; P = 1.0), which was not significant at the 5% level. The moderate risk of bias was due to surgical case heterogeneity. In the univariate model contributing to the pooled data, the OR was 1.15 (95% CI 0.17, 6.29), which remained statistically insignificant.

Bongartz *et al*. [13] identified 462 patients with RA, matched to an OA cohort by age, procedure, and date of surgery. Of 50 TNFi-treated patients, there were 3 deep SSIs among the 38 whose TNFi was continued through surgery, and none among the 12 patients whose TNFi was withheld, which was not statistically significant at the 5% level. In the univariate model used in the meta-analysis, the OR was 1.25 (95% CI 0.23, 4.46), which remained non-significant. Revision surgery (HR 2.99; 95% CI 1.02, 8.75) and previous infection (HR 5.49; 95% CI 1.87, 16.14) were significant risk factors. Fifteen RA patients (4.2%) and four OA patients (1.4%) developed infection at 5 years (log rank P = 0.005), which was statistically significant after adjustment for previous infection (HR 3.74; 95% CI 1.23, 11.33).

Den Broeder *et al*. [35] studied 768 RA patients undergoing elective orthopaedic surgery to identify risk factors for SSI into three cohorts: no TNFi use; TNFi withheld for $\geqslant 4$ drug half-lives prior to surgery; and TNFi continued ($\leqslant 4$ half-lives prior to surgery). Elevated risk was seen with prior skin or wound infection (OR 13.8; 95% CI 5.2, 36.7), but not continued TNFi use by their definition (OR 1.5; 95% CI 0.43, 5.2) (adjusted for prior SSI, skin infection, elbow surgery, foot or ankle surgery, duration of surgery and sulfasalazine use). Propensity scores were used to correct for confounding by indication. In the univariate analysis contributing to the pooled data, the OR was 1.84 (95% CI 0.91, 3.53).

Ruyssen-Witrand *et al*. [36] identified all TNFi treated patients undergoing surgery by computer search to compare the rates of surgical complications between patients whose TNFi was withheld for $\geqslant 5$ half-lives vs $\geqslant 2$ half-lives prior to surgery vs not withheld. The infection rate after orthopaedic surgery was 6.5%, which did not decrease significantly when TNFi was withheld. This study was heterogeneous in regard to surgical procedures.

Giles *et al.* [37, 38] identified 91 patients attending the Johns Hopkins Arthritis Clinic who underwent orthopaedic surgery. Ten (11%) of the RA patients developed a SSI; these were more likely to be TNFi treated (P = 0.006). In a multivariate regression, prescription of a TNFi was significantly associated with a SSI (OR 4.4; 95% CI 1.10, 18.41), with adjustment for age, prednisone use, and disease duration (OR 4.6, 95% CI 1.1, 20.0). In the univariate analysis contributing to the pooled data, the OR was 5.56 (95% CI 1.11, 35.6).

Discussion

This is the first systematic literature review to examine the impact of pre-operative exposure to TNFi on SSI. Based on the studies included in this meta-analysis, results indicate there is a significant increased risk of surgical-site infection in RA patients exposed to TNFi prior to elective orthopaedic surgery. While increased infection rates were recognized early after TNFi introduction, less was known about the association with SSIs. Practice recommendations published by the ACR did not include perioperative TNFi guidelines until 2008 [19]. Despite the retrospective study designs, the pooled data indicate that pre-operative exposure to TNFi is associated with a higher risk of SSI. Although different surgical procedures were included, all were elective orthopaedic procedures. Overall, there were 116 infections among 3681 TNFi treated patients, and 126 infections among 4310 patients without TNFi exposure. The pooled data used for our meta-analysis was based on the unadjusted ORs, after excluding surgery other than orthopaedic and RA cases not treated with TNFi to produce a more homogeneous population for analysis. Our initial aim was to assess the risk of SSI in patients undergoing THA and TKA. However when we restricted the analysis to this sub-group the numerical trend did not reach statistical significance at the 5% level. In the subgroup limited to those undergoing THA and TKA, there were 22/435 SSIs (5%) among TNFi+ RA patients, and 23/1062 SSIs (2%) without TNFi exposure. This review and meta-analysis of perioperative TNFi management was warranted despite study heterogeneity, and confirms the increase in infection associated with TNFi in the context of elective orthopaedic surgery and in particular, arthroplasty.

Berthold *et al*. [9] compared SSIs in elective orthopaedic surgery between two time periods when policy was to discontinue vs continue TNFi perioperatively, but were unable to demonstrate that TNFi use was an independent risk factor for SSI. The difference between this study and our analysis may be due to the low overall number of infections, as well as secular changes in perioperative management. A series of foot and ankle surgeries reported no increase in infection or wound complications when TNFis were continued [8]. In both of these studies, total numbers may have been insufficient to satisfactorily support the conclusions. In our analysis, both SSIs and deep joint infection were analysed as superficial SSI is highly associated with deep tissue infection [10], and higher overall rates were seen for the TNFi treated group. The wide range in infection rates may reflect differences in case definition, with a 1% rate of septic arthritis reported by Galloway *et al.* vs a 12% rate including both superficial and deep infections in the study by Ruyssen-Witrand *et al.* [14, 36].

Many factors could not be assessed in the available literature. These include the effect of disease activity and RA flares, steroid use, age, smoking, and co-morbid conditions such as diabetes, although several of the studies included these potential co-variates in their analysis. TNFis were analysed as a class of therapies, and thus relative odds of SSI between TNFis are unavailable. Importantly, there were no randomized controlled trials and no study was blinded as to treatment, possibly producing a strong selection bias in all studies. Given one institution's standardized infection ratio for THA (0.46) a sample size of over 50 000 patients would be necessary to definitively answer this in a prospective randomized trial [39]. Therefore, retrospective studies, cohort studies and case control studies were used for this analysis.

Although these data support withholding TNFi prior to orthopaedic surgery, our conclusion must be considered in the presence of possible limitations. While misclassification of RA cases in large hospital databases is a recognized problem [24] the studies by Giles *et al.* [38], Kawakami [33], den Broader *et al.* [35], Bongartz *et al.* [13] and Momohara *et al.* [25] specify that patients met ACR 1987 criteria for RA diagnosis, while in the studies by Galloway *et al.* [14], Ruyssen-Witrand *et al.* [36] and Johnson *et al.* [32], RA diagnosis used an algorithm that included use of DMARDs. For the studies by Hirano *et al.* [34], Scherrer *et al*. [31] and Kubota *et al.* [30], the specific RA diagnostic criteria are not described. The diagnosis of SSI was made according to the CDC in six studies. Although the lack of homogeneity in the definition of infection may have led to under-ascertainment of cases, the definitions were rigorous. Moreover, when we performed two subgroup analyses of those studies meeting the ACR diagnostic criteria for RA and those studies meeting CDC criteria for SSI, pre-operative exposure to TNFi remained a significant risk factor for infection.

Another limitation is the lack of rigorously documented medication use and stop dates. Although 2/11 studies accrued and followed their patients prospectively, the identification of cases was retrospective, which may have caused heterogeneity and under-ascertainment. Patients with SSI may have received care elsewhere and thus cases may have been missed. The effect size of the risk attributed to TNF exposure may also be overestimated if disease severity or steroid use contributes to this risk. There may have been contamination between

groups as patients described as TNFi-treated may not have taken their therapy. Several studies performed multivariate analysis to account for the effect of confounders, and propensity scores utilized in the studies by den Broeder *et al.* [35] and Scherrer *et al.* [31] further attempted to correct for these potential sources of bias as described by Joffe *et al.* [40]. It would be ideal to address the risk factors for SSI in a prospective observational study where drug discontinuation times, steroid use, diabetes, smoking and other factors are more rigorously documented. In addition, the period of follow-up varied among the included studies, which could introduce bias as infections after surgery could be missed in the studies with shorter follow up periods, or we might include infections that were actually independent of the surgery, and the pooled OR could over- or underestimate the true OR.

There are several strengths of this study. We were able to include data on a large number (7995) of similar patients undergoing elective, orthopaedic surgery, with or without exposure to TNFis. The risk for publication bias was low based on the funnel plot. Assessment of bias using standardized criteria [28, 29] supports our study selections. While more information would be useful to limit confounding, this analysis approximates settings typical of care, where patients may have multiple risk factors for infection, some of which may not be apparent. We were able to show an increased risk of SSI in RA patients undergoing elective orthopaedic procedures with most studies having adjusted for confounders. While there was limited power to demonstrate this specifically for THA and TKA, the effect was consistent. Moreover, when we performed analyses on the subgroups of studies meeting ACR criteria for RA and the subgroup of studies using CDC criteria for SSI, the results remained consistent in favouring infection associated with TNFi use.

In conclusion, these data suggest an increased risk of SSI for RA patients undergoing elective orthopaedic surgery when exposed to pre-operative TNF inhibitors and support the recommendations to withhold TNFi prior to surgery. Although SSI in orthopaedics is relatively uncommon, and multiple confounders could potentiate this risk, rigorous prospective studies recording the length of time TNF therapy is withheld are needed to confirm the degree of risk these therapies confer.

Acknowledgements

P.J.C. was partially supported by the following grant: Clinical and Translational Science Centre at Weill Cornell Medical College (UL1-TR000457-06). S.M.G. was partially supported by The Block Family Foundation.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: V.P.B. has received research funding from AbbVie, Amgen, Janssen Biotech, Pfizer and UCB and is on the advisory board of Amgen Canada and UCB. All other authors have declared no conflicts of interest.

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