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Risk of malignancies in patients with spondyloarthritis treated with biologics compared with those treated with non-biologics: a systematic review and meta-analysis

Yu Heng Kwan*, Ka Keat Lim*, Warren Fong, Hendra Goh, Linkai Ng, Benjamin Haaland, Jie Kie Phang, Lian Leng Low, Joo Guan Yeo, Feng Huang, Ying Ying Leung, Julian Thumboo and Truls Østbye

Abstract

Background: The aim of our study was to synthesize evidence on the occurrence of malignancy in spondyloarthritis (SpA), from randomized controlled trials (RCTs) comparing biologics with non-biologics and biologics to each other.

Methods: We systematically searched Medline, Cochrane Library, EMBASE, Scopus and ClinicalTrials.gov from inception until 31 October 2018. RCTs with ⩾24-week follow-up were included. We extracted data using standardized forms and assessed the risk of bias using the Cochrane Risk of Bias Tool. We performed pair-wise meta-analyses and network meta-analyses to compare the risk of malignancy for each biologics class and SpA type. We reported the Peto odds ratio (OR) of any malignancy along with 95% confidence intervals (95% CI). Bayesian posterior probabilities comparing risk of malignancy of each biologic class with non-biologics were computed as supplementary measures.

Results: Fifty-four trials were included; most (44/54) had follow-up <1 year. Among 14,245 patients, 63 developed a malignancy. While most Peto ORs were >1, they had wide 95% CI and $p > 0.05$. The overall Peto OR comparing biologics with non-biologics was 1.42 (95% CI 0.80–2.53). Only interleukin-17 inhibitors in peripheral SpA had $p < 0.05$ (Peto OR 2.77, 95% CI 1.07–7.13); the posterior probability that the risk was higher than non-biologics was 98%. Stratified analyses revealed no consistent trend by prior exposure to biologics, duration of follow-up, study quality, study-arm crossover, analytical approaches and type of malignancy.

Conclusions: Our findings indicate no overall elevated risk of malignancy with biologics in SpA. As our meta-analyses are unable to conclude on the long-term risk, long-term pharmacovigilance of biologics in SpA may still be warranted.

Keywords: Biological therapy, malignancy, meta-analysis, network meta-analysis, spondyloarthritis, systematic review

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Correspondence to:
Julian Thumboo
Department of Rheumatology and Immunology, Singapore General Hospital, 20 College Road, Singapore, 169856, Republic of Singapore.
julian.thumboo@sgh.com.sg

Truls Østbye
Level 4, Programme in Health Services & Systems Research, Duke NUS Medical-School, 8 College Road, Singapore 169857, Republic of Singapore.
truls.ostbye@duke-nus.edu.sg

Yu Heng Kwan
Programme in Health Services and Systems Research, Duke-NUS Medical School, Singapore, Republic of Singapore
Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Republic of Singapore

Ka Keat Lim
Programme in Health Services and Systems Research, Duke-NUS Medical School, Singapore, Republic of Singapore
Department of Population Health Sciences, Kings College London, London, UK

Warren Fong
Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Republic of Singapore
Duke-NUS Medical School, Singapore, Republic of Singapore Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Republic of Singapore

Introduction

Spondyloarthritis (SpA) is a group of chronic auto-inflammatory diseases. As SpA affects the joints and the entheses (where ligaments and tendons attach to the bones), it impairs physical function and reduces quality of life.[1] There are two main types of SpA, axial SpA and peripheral SpA; the former predominantly affects spine or sacroiliac joints, whereas the latter predominantly affects the peripheral joints. Nosological entities of axial SpA are ankylosing spondylitis (AS) and non-radiographic axial SpA; nosological entities of peripheral SpA are psoriatic arthritis (PsA) and inflammatory-bowel-disease-related arthritis.[2] The

Hendra Goh
Linkai Ng
Jie Kie Phang
Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Republic of Singapore

Ying Ying Leung
Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Republic of Singapore

Duke-NUS Medical School, Singapore, Republic of Singapore

Benjamin Haaland
Department of Population Health Sciences and Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

Lian Leng Low
Department of Family Medicine and Continuing Care, Singapore General Hospital, Singapore, Republic of Singapore

Post Acute and Continuing Care, SingHealth Community Hospitals, Singapore

SingHealth Duke-NUS Family Medicine Academic Clinical Program, Singapore

Pulses Centre Grant, SingHealth Regional Health System, Singapore

Joo Guan Yeo
Duke-NUS Medical School, Singapore, Republic of Singapore

Translational and Immunology Institute, SingHealth Duke-NUS Academic Medical Centre, Singapore, Republic of Singapore

Division of Medicine, KK Women's and Children's Hospital, Singapore, Republic of Singapore

Feng Huang
Department of Rheumatology, Chinese People's Liberation Army General Hospital, Beijing, People's Republic of China

*co-first authorship

prevalence of SpA varies across geographical regions (0.20% in south-east Asia to 1.61% in the northern Arctic community).[3] Biologics are the next-line treatment for SpA after non-steroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).[4] The proportion of patients with axial SpA treated with biologics varies and can range from 16% to 60%.[5,6] Despite providing clinically important improvement, there has been concern over the risk of infections and malignancies with the use of biologics due to their immunosuppressive properties.[7,8]

The risk of malignancy has been investigated among patients with rheumatoid arthritis (RA) in meta-analyses of randomized controlled trials (RCTs)[9,10] and observational studies.[11] These meta-analyses found no or inconclusive risk of malignancy with biologics compared with placebo and/or csDMARDs. Nevertheless, this may not apply to SpA which has different patient demographic and pathophysiology. In terms of patient demographic, patients with SpA, especially axial SpA, are younger and have fewer effective non-biologics treatment options than patients with RA.[12] Hence, patients with SpA are more likely to be exposed to biologics and at a much younger age than patients with RA.[12] In terms of pathophysiology, while patients with SpA and RA are both affected by Th-17, the tendency for pathognomonic accumulation of Th-17 cells is higher in SpA than in RA.[13] The Th-17 cells can either promote or suppress tumor progression depending on the malignancy and course of therapeutic intervention.[14–16] The longer exposure to biologics among patients with SpA and the complex role of Th-17 cells in tumor progression imply that the safety of biologics may vary between patients with SpA and patients with RA, including the risk of malignancy.

While there have been studies examining the risk of malignancy with biologics in patients with SpA,[17,18] there are several important gaps. To date, four meta-analyses of RCTs have concluded no increased risk of malignancy with biologics in patients with SpA.[7,19–21] However, they focused solely on tumor necrosis factor alpha (TNF-A) inhibitors and did not consider interleukin-17 (IL-17) inhibitors, another common class of biologics in SpA, or other classes of biologics (non-IL-17 and non-TNF-A inhibitors). Additionally, axial and peripheral SpA have different symptom manifestations, and RCTs have usually recruited patients with either type of SpA but not both. Yet, no systemic review or meta-analysis has investigated the risk of malignancy of different classes of biologics in both types of SpA.

Therefore, our study aimed to compare the risk of malignancy of biologics among patients with SpA against that of non-biologics, and to compare the biologics against each other by pooling evidence from published RCTs using meta-analyses. To compare the classes of biologics (IL-17 inhibitors, TNF-A inhibitors, others) against placebo, we used traditional meta-analyses. To compare the classes of biologics against each other, we used network meta-analyses. We separated the analyses into axial and peripheral SpA to examine how different classes of biologics affect the risk of malignancy in both types of SpA.

Methods

We designed the search strategy, screened the articles, performed the analysis and reported the findings according to the Preferred Reporting Items for Systematic Review and Meta-Analyses for Network Meta-Analysis statement, the Cochrane Handbook for Intervention Reviews, and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) good research practices for network meta-analysis.[22–24]

Data sources and searches

The protocol for the systematic review was prospectively registered on International Prospective Register of Systematic Reviews [PROPSERO ID: CRD42018112345].

We performed systematic searches of five bibliographic databases (PubMed, Cochrane Library, EMBASE, Scopus, and ClinicalTrials.gov) from inception of the respective databases until 31 October 2018. We developed the search strategy (see Appendix 1) based on similar systematic reviews,[8,9] guided by a medical librarian and in consultation with practicing rheumatologists. Our search strategy included three concepts: RCTs, biologics and SpA. We included the generic and the brand names of existing biologics to improve the sensitivity of our search terms.

Study selection

We removed duplicate citations in Microsoft Excel® (Microsoft, Seattle, WA) and EndNote (Clarivate Analytics, Philadelphia, USA) before screening. Two co-authors (HG and LN)

independently screened the titles and abstracts for potential eligibility, before screening the full texts of potentially eligible articles. Both co-authors resolved their disagreements *via* consensus, failing which, they consulted a third co-author (YHK).

Inclusion and exclusion criteria

We included RCTs that compared the safety of any biologics against non-biologics (placebo or NSAIDs or csDMARDs) or against each other, examined only patients with SpA, with a minimum of 24 weeks of follow-up. We excluded non-English studies, studies which did not examine malignancy as an outcome measure, follow-up reports of original publications (parent studies), and open-label studies without a control arm.

Data extraction

From eligible articles, two co-authors (HG and LN) extracted study characteristics, their eligibility criteria, the number of patients recruited in treatment and control arms, duration of follow-up, the number of patients who had developed a malignancy by the end of the follow-up in each arm, and the type of malignancies using a standard data abstraction sheet. For studies with crossover for example, to an open-label phase, we assigned the malignancy cases that occur after crossover to the original arm(s). Two co-authors (YHK and JKP) checked the data for accuracy.

Quality assessment

Two reviewers (HG and LN) independently assessed the risk of bias using the Cochrane Risk of Bias Tool.[25] The tool appraises studies on six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases (namely, baseline imbalance, carryover, and funding). Each domain was rated 'yes' (low risk of bias), 'no' (high risk of bias), and 'unclear' (lack of information or uncertainty about the potential for bias). A summary rating was then derived: 'high' for studies with bias that is unlikely to alter the results; 'fair' for studies with bias that raised doubts on the results; and 'low' for studies with bias that weakened confidence in the results.

Data synthesis and analysis

We first described the characteristics of included RCTs using median and range, mean ± standard deviation or number and percentages, where appropriate.

Due to the small number of studies ($n = 4$) comparing biologics with non-biologics such as NSAIDs and csDMARDs, we did not differentiate non-biologics from placebo (hereafter 'non-biologics'). As the number of malignancy cases were small, we could not compare doses or frequencies of administration. Thus, for studies examining different doses and frequencies of the same biologics, we combined the malignancy cases across the different doses and frequencies for analyses.

To compare each class of biologics with non-biologics in terms of their risks of malignancy, we, similar to a previous study on RA,[9] used traditional meta-analyses and pooled the studies using Peto's method, which is recommended for meta-analyses of rare events.[26] The resulting odds ratio (OR) is known as the Peto's OR. Peto's OR (hereafter 'OR') has been shown to be the least biased in meta-analyses for event rates $<1\%$, small-effect sizes and balanced sample sizes between study arms.[26] However, some pooled-effect sizes appeared large ($OR > 3$), and some studies have imbalanced sample sizes between study arms. To examine the robustness of the OR estimates, we also pooled the studies using the Mantel–Haenszel (MH) method with treatment-arm continuity correction (TACC) in sensitivity analyses.[27] Unlike Peto's method, which pools studies with single zero without continuity correction, the MH method with TACC applies continuity correction by a factor of the reciprocal of the size of the opposite arm. The MH method with TACC has been shown to be give the least biased results when there are imbalanced sample sizes between study arms.[27]

To examine the effect of study heterogeneity on the pooled ORs, we performed six stratified meta-analyses by prior exposure to biologics (experienced, naïve, both experienced and naïve, not specified), duration of follow-up (24 weeks, >24–52 weeks, >52 weeks), study quality (high- or fair- *versus* low-quality rating), whether the study allowed crossover (yes *versus* no), analysis approach (per protocol, intention to treat, modified intention to treat), and type of malignancy (melanoma skin cancer, non-melanoma skin cancer, lymphoma, hematologic cancer, lymphoma, solid tumor, unspecified). We separated the analyses by SpA types to investigate how different

classes of biologics affect the risk of malignancy in each SpA type. We assessed heterogeneity based on the I^2 index.[22]

To compare each class of biologics with each other, we used Bayesian network meta-analyses (NMA). We used a binomial likelihood model with informative prior for between-study variance.[28] We derived the ORs and corresponding 95% confidence intervals (95% CI) using four independent chains of Markov Chain Monte Carlo, each with 5000 burn-ins followed by 50,000 additional iterations. We also used Bayesian NMA to estimate the posterior probability of each biologic class having higher malignancy risk than non-biologics in each SpA type. We explored transitivity by assessing distribution of clinical and methodological variables (follow-up duration, study quality, inclusion of participants with prior exposure to biologics, criteria used to categorize SpA, and whether the studies allow crossover) that might affect the outcome of interest.

We performed traditional meta-analyses using the 'meta' package[29] and Bayesian NMA using the 'gemtc' package[30] in R ×64 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). All models were random-effects models.

We assessed and quantified publication bias using funnel plot, modified Egger's linear regression[31] and rank correlation tests.[32]

In all statistical analyses, we considered $p<0.05$ as statistically significant.

Results

Study characteristics

Our database search retrieved 11,372 articles, of which 6985 were unique. A total of 169 articles remained after title and abstract screening. After full-text screening, 53 articles reporting 54 RCTs were eligible for data extraction and meta-analyses, including 3 from ClinicalTrials.gov (findings not reported in peer-reviewed articles) and 7 from hand-searches of reference lists. The most common reasons for exclusion were no mention of malignancy ($n=99$), <24 weeks of follow-up ($n=17$), and open-label or long-term extension studies ($n=7$; Figure 1).

The 54 RCTs were published between 2003 and 2018 and included 14,245 patients with SpA, of which 24 examined axial SpA (5268 patients) and 30 examined peripheral SpA (8977 patients). Most RCTs were two-arms trials (61.1%), with follow-up duration ranging from 24 to 156 weeks. Most RCTs reported malignancy endpoints after crossover (66.7%) and were analysed using an intention-to-treat approach (79.6%). Only 29 RCTs observed malignancies at either arm at the end of the follow-up. Out of the 63 patients who developed malignancies, 23 had solid tumors, 19 had non-melanoma skin cancers, 3 lymphomas, 3 melanoma skin cancer and the remaining 15 unspecified. These are summarized in Table 1; detailed characteristics of each included study are available in Appendix 2.

In terms of study quality, most studies (68.5%) had high or fair-quality rating (Table 1, Appendix 2). The main quality domain contributing to high- or fair-quality rating was incomplete outcome data (81.5% rated low risk of bias), followed by selective reporting (79.6%), blinding (72.2%), other bias (72.2%), sequence generation (55.6%), and allocation concealment (55.6%). While each domain only had one or two studies rated low-quality (high risk of bias), each domain had a sizeable proportion of the studies reporting insufficient information, and hence were rated unclear (14.8%, 18.5%, 24.1%, 24.1%, 40.7%, 42.6%, respectively).

Figure 2 illustrates the network of evidence in the meta-analyses. Each line represents a comparison; the thicker the line, the higher the number of RCTs making the comparison. Each node represents a treatment; the larger the node, the larger the number of comparisons including the node. Out of the 54 included RCTs, 19 compared TNF-A inhibitors in axial SpA with non-biologics, 14 TNF-A inhibitors in peripheral SpA, 9 other biologics in peripheral SpA, 8 IL-17 inhibitors in peripheral SpA, 3 IL-17 inhibitors in axial SpA and 2 other biologics in axial SpA. All included RCTs compared a single class of biologics against non-biologics, except one that compared two classes of biologics against non-biologics.[33]

Comparison between biologics and non-biologics

Meta-analyses with Peto's method and Mantel–Haenszel method. Overall, the pooled OR (Figure 3) was 1.42 (95% CI 0.80–2.53). For most comparisons of biologics with non-biologics, the ORs had wide 95% CI with $p>0.05$ (non-statistically significant), except for IL-17 inhibitors

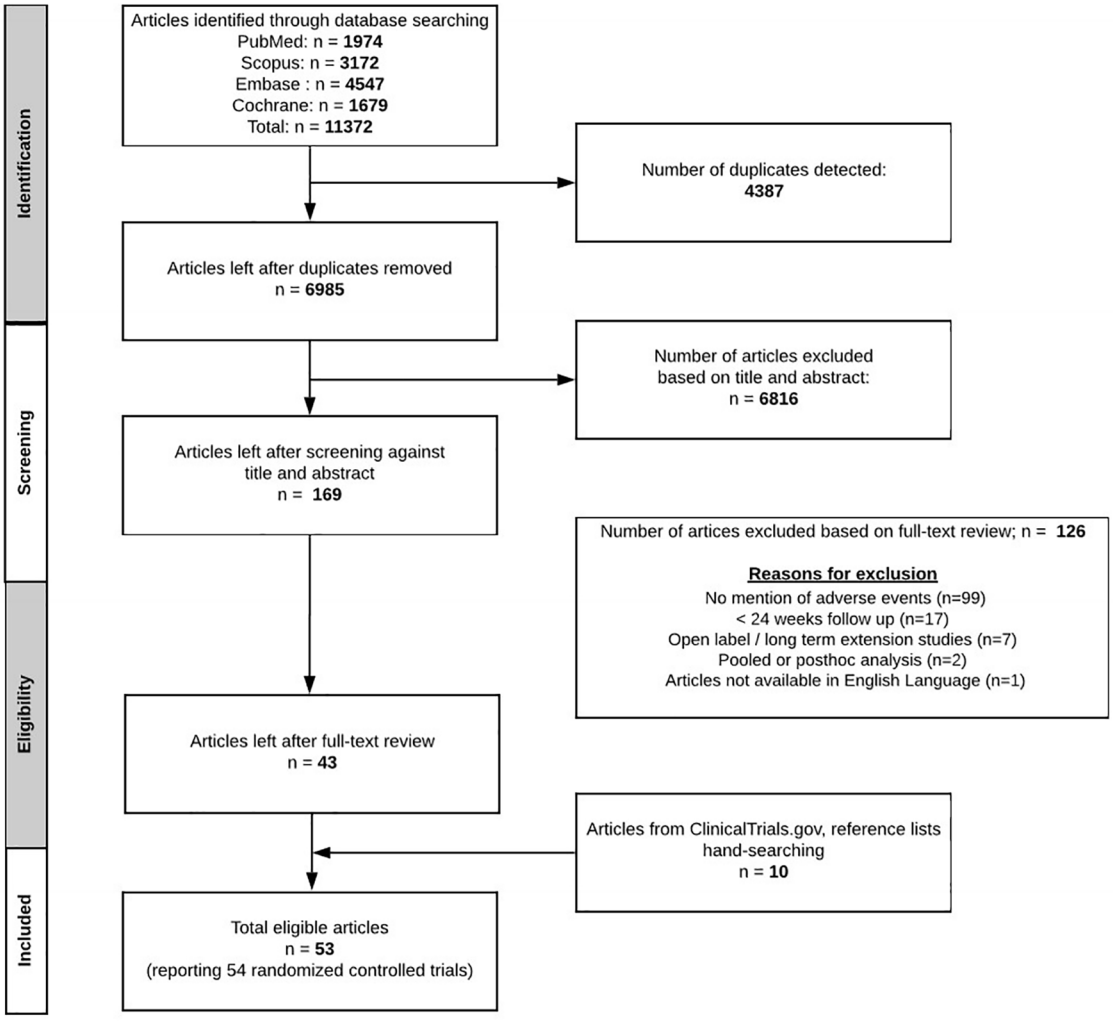

Figure 1. Study selection flow chart.
PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.

in peripheral SpA compared with non-biologics. Specifically, the pooled ORs were 2.77 (95% CI 1.07–7.13) for IL-17 inhibitors in peripheral SpA, 2.30 (95% CI 0.52–10.23) TNF-A inhibitors in axial SpA, 1.81 (95% CI 0.28–11.75) for IL-17 inhibitors in axial SpA, 0.88 (95% CI 0.27–2.84) for TNF-A inhibitors in peripheral SpA, 0.58 (95% CI 0.14–2.43) for other biologics in peripheral SpA. Sensitivity analyses using the MH method with TACC gave similar ORs, all with $p > 0.05$, including that for IL-17 inhibitors in peripheral SpA (OR 2.13, 95% CI 0.63–7.19; Appendix 3). In all pooled ORs, heterogeneity was low (I^2 0–40%) to moderate (I^2 40–60%).

Stratified analyses. Across all stratified analyses, we observed no consistent trend, whether there was prior exposure to biologics (Appendix 4), duration of follow-up (Appendix 5), and study quality (Appendix 6), study-arm crossover (Appendix 7), analytical approaches of individual RCTs (Appendix 8), and type of malignancy (Appendix 9). Almost all stratified analyses, similar to the main analyses, had wide 95% CIs that crossed 1, with $p > 0.05$ (non-statistically significant). The only stratified analyses with $p < 0.05$ were for IL-17 in peripheral SpA: among studies that included both patients with or without prior exposure to biologics (OR 3.34, 95% CI 1.19–9.35; Appendix 4); among studies with >24–52 weeks of follow-up (OR 3.28, 95% CI 1.13–9.48; Appendix 5); among studies with study-arm crossover (OR 2.77, 95% CI 1.07–7.13; Appendix 7); among studies analyzed with intention-to-treat approach (OR 2.77, 95% CI 1.07–7.13; Appendix 8).

Table 1. Characteristics of included trials ($n = 54$).

Median year of publication (range)	All	Axial SpA	Peripheral SpA
	2014 (2003–2018)	2014 (2003–2018)	2014 (2004–2018)
Number of trials	54 (100%)	24 (100%)	30 (100%)
Study arms			
Two-arm trials	33 (61.1%)	17 (70.8%)	16 (53.3%)
Multi-arm trials	21 (38.9%)	7 (29.2%)	14 (46.7%)
Follow-up			
Mean follow-up duration (weeks)	42.9 ± 25.6	50.8 ± 32.7	36.5 ± 16.1
Follow-up duration >52 weeks	10 (18.5%)	6 (25.0%)	4 (13.3%)
Malignancy cases			
Observed malignancies at the end of follow-up	29 (53.7%)	8 (33.3%)	21 (70.0%)
Classes of biological agents*			
IL-17 inhibitors	11 (20.4%)	3 (12.5%)	8 (26.7%)
TNF-A inhibitors	33 (61.1%)	15 (62.5%)	18 (60.0%)
Other classes	11 (20.4%)	6 (25.0%)	5 (16.7%)
Quality rating			
Good or fair	37 (68.5%)	16 (66.7%)	21 (70.0%)
Poor	17 (31.5%)	8 (33.3%)	9 (30.0%)
Crossover			
Yes	36 (66.7%)	16 (66.7%)	20 (66.7%)
No	18 (33.3%)	8 (33.3%)	10 (33.3%)
Analysis approach			
Per protocol	1 (1.9%)	0 (0.0%)	1 (3.3%)
Intention to treat	43 (79.6%)	18 (75.0%)	25 (83.3%)
Modified intention to treat	10 (18.5%)	6 (25.0%)	4 (13.3%)
Sponsorship			
Pharmaceutical companies	50 (92.6%)	23 (95.8%)	27 (90.0%)
Non-pharmaceutical companies	3 (5.6%)	1 (4.2%)	2 (6.7%)
Not specified	1 (1.9%)	0 (0.0%)	1 (3.3%)
Number of patients in trials	14,245 (100%)	5268 (100%)	8977 (100%)
Sample size			
Mean number of patients	263.8 ± 187.7	219.5 ± 107.2	299.2 ± 228.8
Malignancy cases			
Developed malignancy during follow-up	63 (0.44%)	15 (0.28%)	48 (0.53%)

*Sum more than the total number of trials because some trials are multi-arm.
IL, interleukin; TNF-A, tumor necrosis factor alpha.

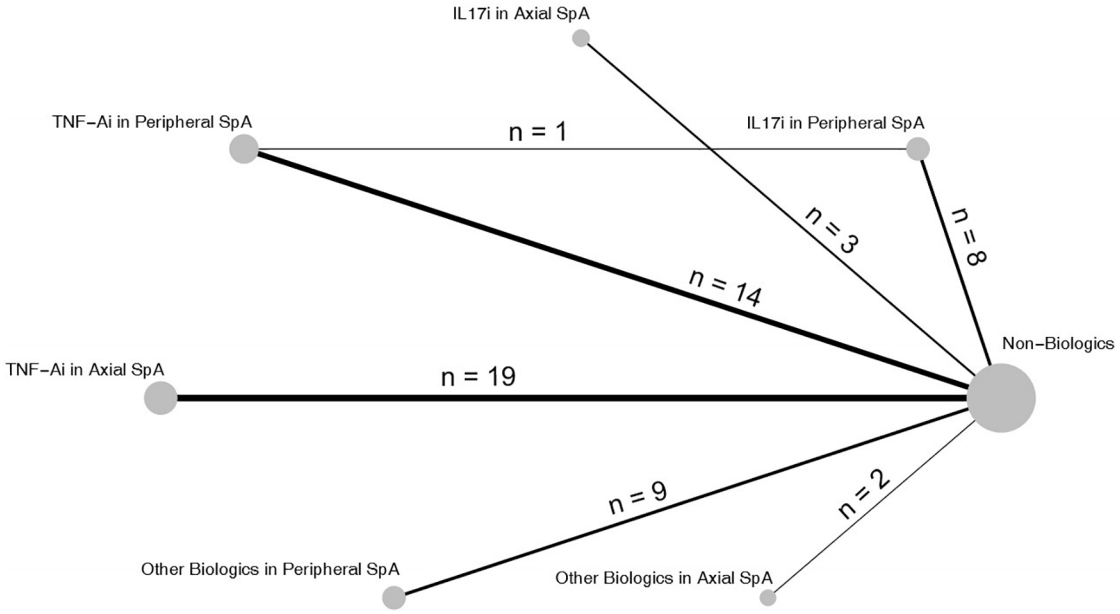

Figure 2. Evidence network.
Other biologics are biologics other than IL-17i and TNF-Ai.
Non-biologics include placebo, NSAIDS and/or DMARDS.
Each line represents a comparison; the thicker the line, the higher the number of RCTs making the comparison.
Each node represents a treatment; the larger the node, the higher the number of direct comparisons including the node.
DMARDs, disease-modifying anti-rheumatic drugs; IL-17i, interleukin-17 inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; RCT, randomized controlled trial; SpA, spondyloarthritis; TNF-Ai, tumor necrosis factor alpha inhibitor.

Although some subgroups contain only a single study (e.g. IL-17 inhibitors in peripheral SpA patients who were naïve to biologics, Appendix 4), we presented all the estimates in Appendices 4–9 for completion.

Bayesian network meta-analyses. Based on Bayesian NMA, IL-17 inhibitors had 79.0% and 98.0% posterior probabilities of having higher risk of malignancy than non-biologics in axial and peripheral SpA, respectively; TNF-A inhibitors, 90.8% and 56.8% in axial and peripheral SpA, respectively; other biologics, 23.0% in peripheral SpA.

Comparison between different classes of biologics

Bayesian network meta-analyses. The distributions of clinical and methodological variables that might affect the outcome of interest suggest transitivity (Appendix 10). Compared with other biologics (non-IL-17 and non-TNF-A inhibitors) in peripheral SpA, IL-17 inhibitors in both SpA types, TNF-A inhibitors in both SpA types and other biologics in axial SpA had OR >1. Compared with IL-17 inhibitors in peripheral SpA, TNF-A inhibitors, and other biologics in both SpA types, as well as IL-17 inhibitors in axial SpA had OR <1. Nevertheless, 95% CI for all ORs were wide and crossed 1; all p values were also >0.05 (non-statistically significant; Appendix 11).

Publication bias

There was little evidence of publication bias in the estimates, with modified Egger's test $p=0.521$ and rank correlation test $p=0.216$ (funnel plots available in Appendix 12).

Discussion

We examined the risk of malignancy with biologics in SpA, overall, as well as by classes of biologics in each SpA type. All pooled ORs had wide 95% CI and $p>0.05$ except IL-17 inhibitors in peripheral SpA compared with non-biologics, which had $p<0.05$ when pooled using Peto's method, but not when pooled using the MH method with TACC. To our knowledge, this is the largest systematic

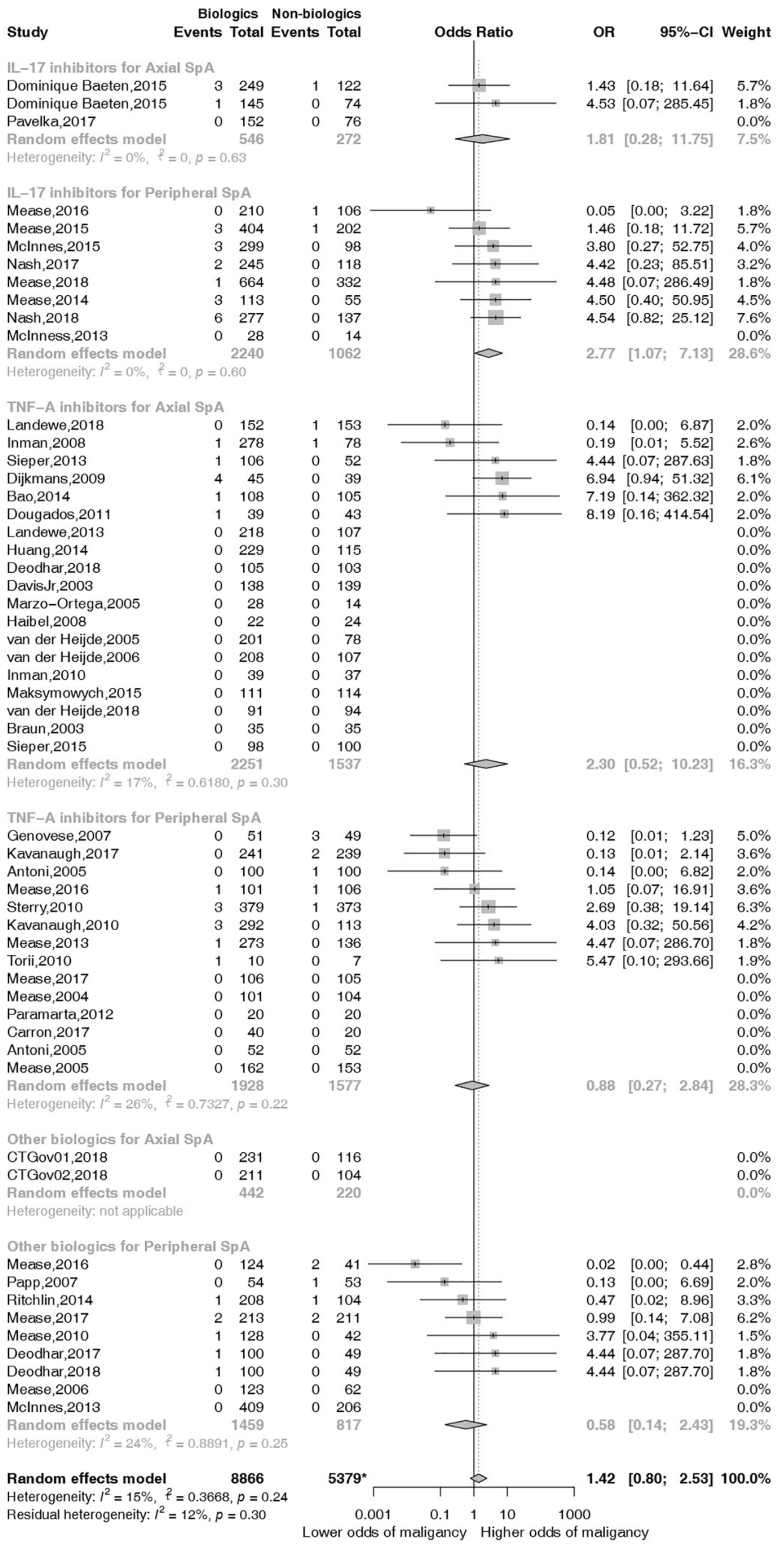

Figure 3. Meta-analyses comparing biologics *versus* non-biologics.
Other biologics are biologics other than IL-17i and TNF-Ai.
Non-biologics include placebo, NSAIDS and/or DMARDS.
*This is less than the sum of the above, because it does not double count the number of patients in the non-biologics arms in multi-arm RCTs.
CI, confidence interval; DMARDs, disease-modifying anti-rheumatic drugs; IL-17, interleukin-17; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; RCT, randomized controlled trial; SpA, spondyloarthritis; TNF-A, tumor necrosis factor alpha.

review and meta-analysis to examine the risk of malignancy with biologics in SpA.

The comparison of IL-17 inhibitors with non-biologics in peripheral SpA was the only one that achieved statistical significance. The statistical significance was only observed with Peto's method, but not the MH method with TACC. This difference may be due to the tendency of MH with TACC to 'pull' the ORs toward no effect (OR = 1), resulting in more conservative OR estimates and a 95% CI that crosses OR = 1. Nevertheless, all eight RCTs for IL-17 inhibitors in peripheral SpA examined exclusively patients with PsA (a specific subtype of peripheral SpA). Thus, the findings may not be generalizable to other types of peripheral SpA, such as reactive arthritis and enteropathic arthritis. Interestingly, psoriasis, with and without arthritis, is shown to be associated with an overall increased risk of non-melanoma skin cancer, lymphoma, and lung cancer.[34] It is plausible that any elevated risk for malignancy may be contributed in part by the chronic inflammatory nature of the disease with the involvement of IL-17. However, the exact roles of IL-17 and the effects of its inhibition on carcinogenesis in PsA are still unclear due to its double-edged nature: it enhances angiogenesis (which increases the risk of malignancy), as well as mediates anti-tumor immunity (which decreases the risk of malignancy).[14] We recommend more high-quality RCTs, as well as laboratory-based studies to further elucidate the role of IL-17 in carcinogenesis in PsA.

Our findings underscore the need for long-term studies. An OR point estimate of >1 with TNF-A inhibitors has also been observed in two previous meta-analyses of RCTs (OR 1.31, 95% CI 0.89–1.95 in 9.2-months follow-up;[19] OR 1.48, 95% CI 0.71–3.09 in 4.5-months follow-up[20]), although their estimates also did not achieve statistical significance, similar to our findings. Another previous meta-analysis found an OR point estimate <1 (OR 0.98; 95% CI 0.25–3.85)[7] with TNF-A in AS (a specific subtype of axial SpA), but it included only three RCTs (*versus* six RCTs in our study), one of which only had 12-week follow-up. A 10-year registry-based study,[17] meanwhile, found no elevated risk of overall malignancy (relative risk, RR 0.90, 95% CI 0.70–1.10) for TNF-A inhibitors in PsA, compared with TNF-A-naïve patients. Nevertheless, the risk for breast cancer (RR 1.80, 95% CI 1.10–2.90) may be elevated.

Our findings should be interpreted with several limitations in mind. First, we included only RCTs, most of which (44/54) had follow-up < 1 year. Thus, our findings at best represent short- to medium-term risk of malignancy with biologics in controlled settings. As the events were rare, all pooled estimates had a wide 95% CI; with the exception of IL-17 inhibitors in peripheral SpA, none of the other pooled estimates achieved statistical significance. Importantly, the studies included in our meta-analysis may have had too short a follow-up to fully detect elevated risk of malignancy, and patients in some control arms received biologics after a delay of several months. It should also be noted that malignancies that occur within the short period of RCTs may not be new onset. Nevertheless, those with existing malignancies and those thought to be at high risk of malignancies were likely excluded from the RCTs as malignancy is a contraindication to biologic treatment; none of the 54 RCTs included in our meta-analyses recruited patients with existing malignancy (Appendix 2). Thus, the findings may not be generalizable to these patients. Rare occurrence of malignancies and short follow-up also makes it less meaningful to present summary measures such as rate of malignancies per person-time. Long-term studies may be required to verify the findings in real-world settings, especially on long-term risk. While we sought to include studies that compared biologics against each other, we identified no such studies. Hence, the findings from indirect comparisons between biologic classes in different SpA types should also be verified in future studies. Meta-analyses of rare events are challenging due to difficulties in handling studies with zero-outcome events. We pooled the estimates using Peto's method in main analyses (shown to be the least biased for event rates <1%, small-effect sizes and balanced sample sizes between study arms[26]) and MH method with TACC in sensitivity analyses (shown to be less susceptible to bias with larger effect sizes and imbalanced sample sizes between-study arms[27]); both methods yielded similar pooled ORs. We adopted a strict definition of biologics: they should be produced by living systems and are large molecules. Hence, small molecules such as tofacitinib were not considered as biologics in this study. Due to the small number of malignancy cases, we did not examine the effect of different doses and frequencies of biologics on malignancy. We were also unable to examine whether the effect sizes differed between types of study sponsorship, as almost all studies were sponsored by pharmaceutical companies. These could be topics for

future study. In addition, we included only RCTs in English. However, there was only one excluded study that was not in English.

Despite the limitations, our study has important clinical implications. Our findings suggest no overall elevated risk of malignancy with biologics in SpA, compared with non-biologics. Even if one were to interpret an elevated risk based on the point estimates, it is worth highlighting that the absolute risks of malignancy remain low across the study participants (<0.5% overall). Our study calls for observational studies and ongoing pharmacovigilance with long-term follow-up to verify the findings in real-world settings, and to identify the specific types of malignancies associated with biologics in SpA, if any.

Conclusion

Our study found no elevated risk of malignancy among biologics in SpA, compared with non-biologics and compared with each other. While IL-17 inhibitors compared with non-biologics in patients with peripheral SpA achieved statistical significance, there was evidence of confounding by prior exposure to biologics, duration of follow-up and study quality. The absolute risks of malignancy also remain low. Our analyses point to the need for more high-quality RCTs and observational studies with long follow-up to draw a firm conclusion.

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Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Yu Heng Kwan https://orcid.org/0000-0001-7802-9696

Supplemental material

Supplemental material for this article is available online.

References

1. Kwan YH, Fong W, How P, *et al.* The impact of axial spondyloarthritis on quality of life (QoL): a comparison with the impact of moderate to end-stage chronic kidney disease on QoL. *Qual Life Res* 2018; 27: 2321–2327.
2. Garg N, Van den Bosch F and Deodhar A. The concept of spondyloarthritis: where are we now? *Best Pract Res Clin Rheumatol* 2014; 28: 663–672.
3. Stolwijk C, van Onna M, Boonen A, *et al.* Global prevalence of spondyloarthritis: a systematic review and meta-regression analysis. *Arthritis Care Res (Hoboken)* 2016; 68: 1320–1331.
4. Sieper J. Developments in therapies for spondyloarthritis. *Nat Rev Rheumatol* 2012; 8: 280–287.
5. Wallis D, Thavaneswaran A, Haroon N, *et al.* Tumour necrosis factor inhibitor therapy and infection risk in axial spondyloarthritis: results from a longitudinal observational cohort. *Rheumatology (Oxford)* 2014; 54: 152–156.
6. Png WY, Kwan YH, Lee YX, *et al.* Factors associated with initiation of biologics in patients with axial spondyloarthritis in an urban asian city: a PRESPOND study. *J Clin Rheumatol* 2019; 25: 59–64.
7. Hou LQ, Jiang GX, Chen YF, *et al.* The comparative safety of TNF inhibitors in ankylosing spondylitis-a meta-analysis update of 14 randomized controlled trials. *Clin Rev Allergy Immunol* 2018; 54: 234–243.
8. Singh JA, Cameron C, Noorbaloochi S, *et al.* Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* 2015; 386: 258–265.
9. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, *et al.* Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. *JAMA* 2012; 308: 898–908.
10. Singh JA, Hossain A, Mudano AS, *et al.* Biologics or tofacitinib for people with rheumatoid arthritis

naive to methotrexate: a systematic review and network meta-analysis. *Cochrane Database Syst Rev* 2017; 5: CD012657.

11. Ramiro S, Sepriano A, Chatzidionysiou K, *et al.* Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2017; 76: 1101–1136.
12. Van der Horst-Bruinsma IE, Lems WF and Dijkmans BA. A systematic comparison of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009; 27(Suppl. 55): S43–S49.
13. Jandus C, Bioley G, Rivals JP, *et al.* Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. *Arthritis Rheum* 2008; 58: 2307–2317.
14. Asadzadeh Z, Mohammadi H, Safarzadeh E, *et al.* The paradox of Th17 cell functions in tumor immunity. *Cell Immunol* 2017; 322: 15–25.
15. Knochelmann HM, Dwyer CJ, Bailey SR, *et al.* When worlds collide: Th17 and Treg cells in cancer and autoimmunity. *Cell Mol Immunol* 2018; 15: 458–469.
16. Bailey SR, Nelson MH, Himes RA, *et al.* Th17 cells in cancer: the ultimate identity crisis. *Front Immunol* 2014; 5: 276.
17. Hellgren K, Dreyer L, Arkema EV, *et al.* Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. *Ann Rheum Dis* 2017; 76: 105–111.
18. Atzeni F, Carletto A, Foti R, *et al.* Incidence of cancer in patients with spondyloarthritis treated with anti-TNF drugs. *Joint Bone Spine* 2018; 85: 455–459.
19. Bonovas S, Minozzi S, Lytras T, *et al.* Risk of malignancies using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2016; 15(Suppl. 1): 35–54.
20. Dommasch ED, Abuabara K, Shin DB, *et al.* The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. *J Am Acad Dermatol* 2011; 64: 1035–1050.
21. Luo X, Deng C, Fei Y, *et al.* Malignancy development risk in psoriatic arthritis patients undergoing treatment: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2019; 48: 626–631.
22. Higgins JP and Green S. *Cochrane handbook for systematic reviews of interventions*. Chichester: John Wiley & Sons, 2011.
23. Hoaglin DC, Hawkins N, Jansen JP, *et al.* Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR task force on indirect treatment comparisons good research practices: part 2. *Value Health* 2011; 14: 429–437.
24. Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; 162: 777–784.
25. Higgins JP, Altman DG, Gøtzsche PC, *et al.* The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
26. Bradburn MJ, Deeks JJ, Berlin JA, *et al.* Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007; 26: 53–77.
27. Sweeting MJ, Sutton AJ and Lambert PC, What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004; 23: 1351–1375.
28. Turner RM, Davey J, Clarke MJ, *et al.* Predicting the extent of heterogeneity in meta-analysis, using empirical data from the cochrane database of systematic reviews. *Int J Epidemiol* 2012; 41: 818–827.
29. Schwarzer G. Meta: an R package for met-analysis. *R News* 2007; 7: 40–45.
30. Gert VV and Joel K. *gemtc: network meta-analysis using bayesian methods*, https://CRAN.R-project.org/package=gemtc (2016, accessed 25 November 2019).
31. Harbord RM, Egger M and Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*, 2006; 25: 3443–3457.
32. Schwarzer G, Antes G and Schumacher M. A test for publication bias in meta-analysis with sparse binary data. *Stat Med* 2007; 26: 721–733.
33. Mease PJ, Van der Heijde D, Ritchlin CT, *et al.* Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis* 2017; 76: 79–87.
34. Chiesa Fuxench ZC, Shin DB, Ogdie Beatty A, *et al.* The risk of cancer in patients with psoriasis: a population-based cohort study in the health improvement network. *JAMA Dermatol* 2016; 152: 282–290.