THERAPEUTIC ADVANCES in
Chronic Disease

Meta-analysis

Comparative short-term risks of infection and serious infection in patients receiving biologic and small-molecule therapies for psoriasis and psoriatic arthritis: a systemic review and network meta-analysis of randomized controlled trials

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Abstract

Background: Infection events are a major concern for patients and physicians when making psoriasis treatment decisions.

Objective: To estimate the relative short-term risks of infection and serious infection for biologic and small molecule therapies in the treatment of moderate-to-severe plaque psoriasis (PsO) and psoriatic arthritis (PsA).

Data Sources and Methods: A systematic literature search of the PubMed, EMBASE, and Web of Science databases was conducted on 17 June 2022. We included phase II, III, or IV randomized controlled trials (RCTs) of biologic and small-molecule therapies that are licensed or likely to gain approval soon for PsO and PsA, as well as infection data reports. Two investigators independently extracted the data based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Network meta-analysis (NMA) was performed to estimate the pooled relative risks (RRs) and corresponding 95% confidence intervals of total infections and serious infections for treatments during placebo-controlled phases of RCTs. The surface under the cumulative ranking area (SUCRA) was calculated to rank the infection risk for each treatment.

Results: A total of 94 RCTs with a total of 19 treatment arms involving 54,369 participants were analyzed. For patients with PsO, bimekizumab, secukizumab, risankizumab, ustekinumab, apremilast, guselkumab, and adalimumab were associated with significantly higher risks of infection than placebo; SUCRA ranked infliximab, deucravacitinib, and bimekizumab with the highest risks of infection. For patients with PsA, bimekizumab, apremilast, and upadacitinib (30 mg daily) were associated with higher risks of infection; SUCRA ranked bimekizumab with the highest risk of infection. No treatments, except for upadacitinib (30 mg daily), were associated with a higher risk of serious infection than placebo in PsA.

Conclusion: This NMA provides a comprehensive assessment of the comparative short-term risks of infection, which could help physicians and patients to select individualized treatments for psoriasis.

Registration: CRD42022359873.

Keywords: biologic, infection, network meta-analysis, psoriasis, psoriatic arthritis, small molecule

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Introduction

A variety of biologics and small molecules have been developed for the treatment of psoriasis and psoriatic arthritis (PsA) and can remarkably improve patient outcomes.[1] However, these treatments directly target cytokines, receptors, cell-surface molecules, or intracellular signaling molecules in the host immune-surveillance system that combat invading pathogens; thus, these treatments may contribute to an increased risk of infection.[2–4] Infection is the main adverse event (AE) that leads to discontinuation of biologics for the treatment of psoriasis[5] and serious infections are particularly important as they can be life-threatening, require hospitalization, or result in significant sequelae or morbidity.[5] Nevertheless, the treatments for psoriasis and PsA may be associated with different degrees of infection risk, depending the immune molecule(s) targeted by each biologic or small molecule.

Although some prior randomized controlled trials (RCTs) have reported treatment-associated infection risks, most of these risk estimates come from individual clinical trials that were inadequately powered to detect rare serious infection events. Moreover, few head-to-head RCTs have compared the infection risks between treatments, and only two interventions were compared in each RCT.[6–20] Thus, systemic and comprehensive comparisons of the infection risks of various treatments for moderate-to-severe plaque psoriasis (PsO) and PsA are lacking. Network meta-analysis (NMA) can be used to assess the comparative risks of multiple different treatments in a single analysis through integration of direct and indirect evidence within a network of studies.[21] Nevertheless, the majority of previous NMA for PsO or PsA mainly analyzed the efficacy of treatments in terms of patient outcomes. A small number of NMA studies investigated safety outcomes, but only assessed the overall incidence of AE, severe AE, or AE leading to treatment discontinuation, rather than the rates of infection.[22,23] No NMA has yet specifically investigated the infection risks of different treatments for PsO and PsA. Moreover, in recent years, new therapies, such as interleukin (IL)-23 inhibitors, IL-17A/F inhibitors, Janus kinase inhibitors, and TYK2 inhibitors have rapidly emerged and been introduced for the treatment of PsO and PsA. However, most NMA only included a small number of the more recent treatments. Therefore, we conducted a systematic review and NMA to compare the risk of infection and serious infection for different biologic and small molecule therapies among patients with PsO and PsA.

Materials and methods

Search strategy

Based on the preferred reporting items for systematic reviews and meta-analysis extension statement (PRISMA) criteria (Supplemental Table S1),[24] a systematic literature review was conducted using PubMed, EMBASE, and Web of Science on 17 June 2022, to identify publications reporting safety data from RCTs of biologics and small molecules for PsO and PsA. This search and review followed an *a priori* established protocol that was registered on the PROSPERO International prospective register of systematic reviews (CRD42022359873; Supplemental Method S1).

Inclusion and exclusion criteria

The detailed search strategy and search keywords are described in Supplemental Table S2. Studies were eligible for inclusion in our NMA if they met the following criteria: (1) a phase II, III, or IV RCT of biological or small-molecule therapies that are licensed or under development for treating adults with PsO or PsA; (2) that report detailed data on infection and/or serious infection outcomes in each treatment arm at the end of the placebo- or comparator-controlled period (serious infection was defined by the investigators in each study); (3) with treatment arms that included either at least two biologics/small molecules or one biologic/small molecule and placebo; and (4) published in English. Studies were excluded if they (1) did not report outcomes of interest, such as infection or serious infection; (2) only included one medication or did not include a relevant comparison group for NMA; (3) mainly included patients with other forms of psoriasis other than psoriasis vulgaris (e.g. pustular, erythrodermic, palmoplantar psoriasis, etc.); or (4) were real-world cohort or registry studies, case reports, case–control studies, reviews, meta-analyses, meeting abstracts, or case reports. When multiple publications included the same study population, we only extracted the data from the publication with the most recent and comprehensive data. The titles, abstracts, and reference lists of the

identified studies were independently screened by two reviewers (H-YC and Y-HH) to identify potentially eligible publications; any disagreements were resolved by discussion. If it was unable to come to an agreement *via* discussion, the decision was reached by incorporating the judgement of a third independent researcher (TSW).

Data extraction and quality assessment

Data were extracted by two authors (H-YC and Y-HH) independently using a pre-specified data collection table; discrepancies were resolved by discussion. The study details extracted were study design, publication characteristics, participants' characteristics, interventions and comparators studied, follow-up time, and outcomes reported (number of patients with infections and serious infections). Clinical trial registries were searched for supplemental results. The same two authors critically appraised the methodologic quality of each study using the Cochrane Collaboration Risk-of-Bias Instrument.[25]

Data analysis/statistical analysis

NMA based on the frequentist framework was performed to compare the risks of infection and serious infection associated with each biologic and small molecule therapy for the treatment of PsO and PsA. The relative risks (RRs) and Wald type 95% confidence intervals (CIs) were calculated as effect measures to quantify the risks of infection and serious infection during the placebo-controlled period of the included RCTs to perform multiaspect comparisons. As the characteristics of the study populations differ between RCTs investigating treatments for PsO and PsA,[15,26,27] our study analyzed the risks of infection in PsO and PsA trials separately. Both random-effects and fixed-effects models were run, and one of these models was chosen based on heterogeneity test results in this NMA, and the goodness-of-fit was also assessed. Studies that reported zero infection events or zero serious infection events for treatments were excluded from the analysis. For RCTs involving multiple doses of a single medication, we grouped all doses in the analysis – except for upadacitinib, as prior RCTs showed that the rates of treatment-related AE (including infections, herpes zoster, and neutropenia) were higher for the 30 mg dose than the 15 mg dose of upadacitinib.[18,28–30] Heterogeneity between studies was assessed using I2 statistics (25%, 25–50%, or more than 50% indicate low, moderate, or high heterogeneity, respectively).[31] The consistency between direct and indirect evidence within the network analysis was evaluated using a node-splitting method.[32] We also estimated the relative ranking of the risk of the different treatments for infection and serious infection by calculating the surface under the cumulative ranking curves (SUCRA)[33] and plotting the probability of each rank for these treatments using rankograms.[33] Larger SUCRA scores indicate a higher ranking, which suggests a higher probability of developing infection or serious infection. Funnel plots and Egger's tests were conducted to detect small-study effects and publication bias.[34] All analyses were conducted using the meta (version 5.2-0) and netmeta (version 2.1-1) packages of R statistical software (version 4.1.2) and $p < 0.05$ was considered a significant difference.

Results

Study selection and baseline characteristics

Using the literature searching methods described in section 'Methods', our searches yielded 850 potentially eligible articles. One hundred and sixty articles were excluded due to duplication and another 357 articles were excluded after reviewing the titles and abstracts. A total of 85 articles covering 94 RCTs met the eligibility criteria and were finally included in the NMA (Figures 1 and 2). These RCTs included a total of 54,369 patients with PsO or PsA treated with 14 biologics, five small molecules, or placebo. The detailed characteristics of the included RCTs are displayed in Supplemental Tables S3 and S4. The network maps are illustrated in 2. Overall, the risk of bias for the studies included in this NMA was low, as the majority of studies were RCTs with a double-blinded design (Supplemental Figure S1).

Traditional pair-wise meta-analysis

In the trials for PsO, the RRs with 95% CIs for the individual trials and the pooled results are shown in Supplemental Table S5. The risks of infection were significantly higher for adalimumab, secukinumab, apremilast, and ustekinumab than placebo. Nine other drugs were also associated with higher infection risks than placebo; however, these differences were not statistically significant. No treatments for PsO were associated with a

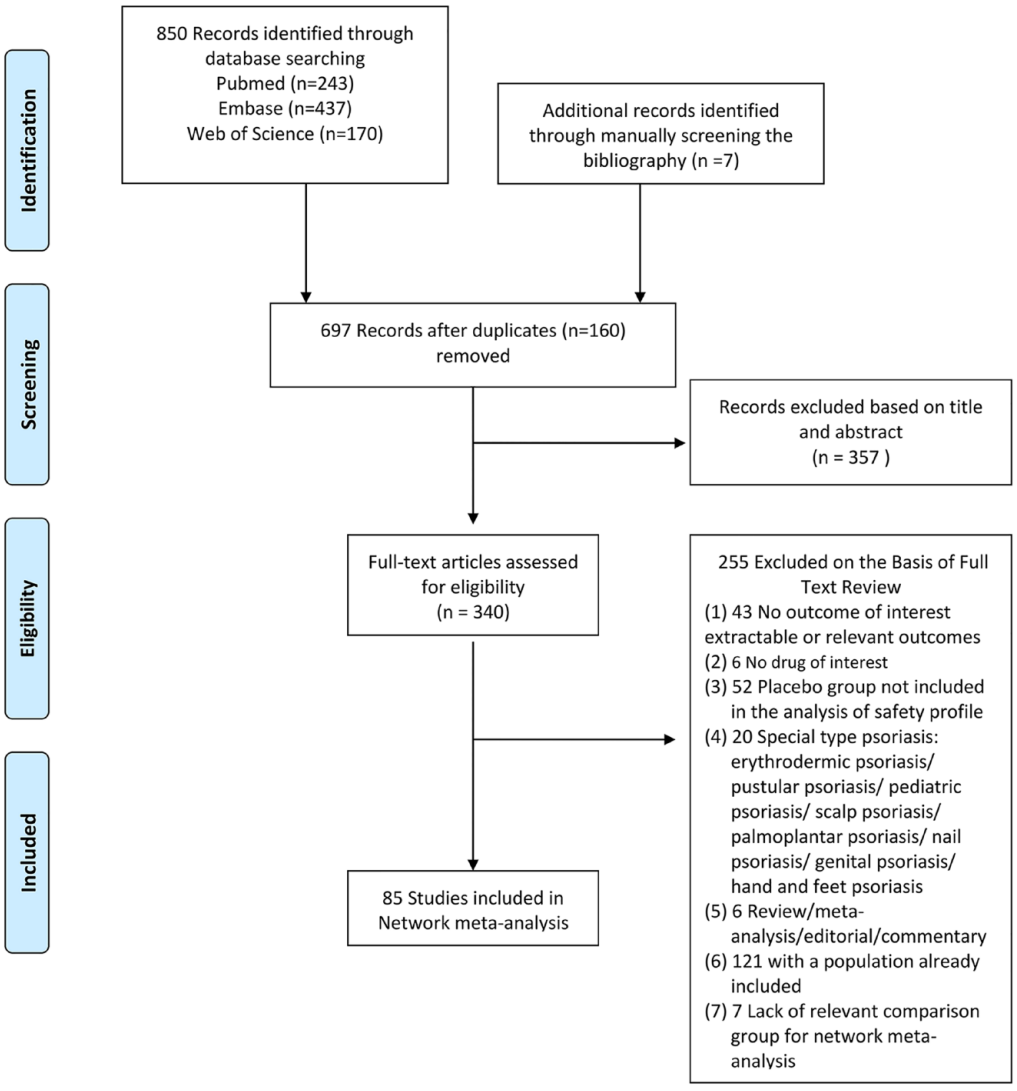

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart of study selection for the systemic review and meta-analysis.

significantly higher risk of serious infection than placebo (Supplemental Table S5).

In the trials for PsA, bimekizumab, apremilast, and upadacitinib (30 mg daily) were associated with significantly higher infection risks than placebo; the other 14 drugs were not associated with higher infection risks (Supplemental Table S5). With respect to serious infections in PsA, only upadacitinib (30 mg daily) was associated with a higher risk compared to placebo (Supplemental Table S5).

Results of NMA

For the PsO trials, the NMA revealed that bimekizumab, secukizumab, risankizumab, ustekinumab, apremilast, guselkumab, and adalimumab were associated with significantly higher infection risks than placebo, whereas the other drugs had comparable infection risks to placebo [Figure 3(a)]. Statistically significant differences between the active treatment comparators were limited to secukinumab, which had a higher infection risk than etanercept and certolizumab (Supplemental Table S6). However, no significant differences in

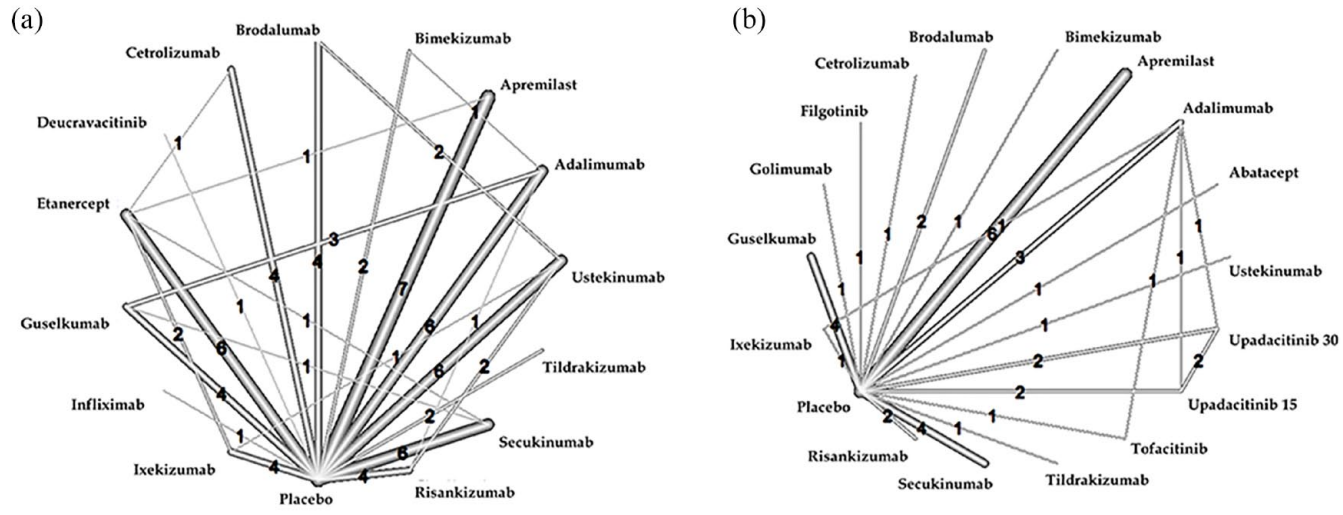

Figure 2. Evidence networks generated by NMA to compare eligible biologic and small-molecule therapies for infection events. The number of trials comparing each pair of treatments in (a) PsO and (b) PsA is indicated along each individual lines and the width of the lines is also proportional to the number of trials comparing the connected treatments.
NMA, Network meta-analysis; PsO, plaque psoriasis.

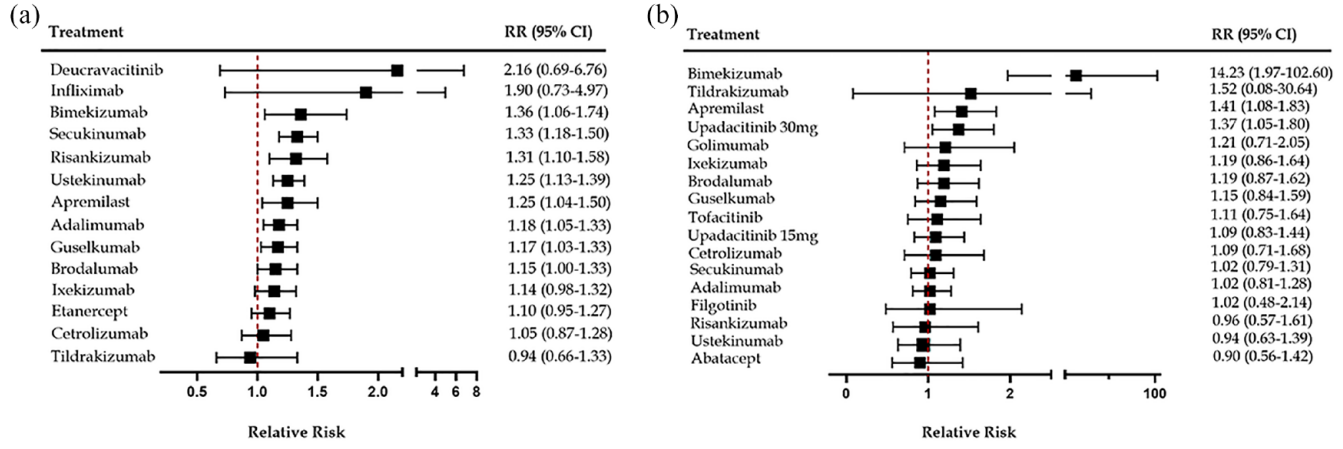

Figure 3. Forest plots of the risks of infection for various treatments compared with placebo in (a) PsO and (b) PsA. Comparisons are plotted in terms of RR and 95% CI.
PsA, psoriatic arthritis; PsO, plaque psoriasis; RR, relative risk.

the risk of serious infection were observed for any treatments for PsO compared with placebo.

In the PsA trials, bimekizumab, apremilast, and upadacitinib (30 mg daily) were associated with significantly higher infection risks compared to placebo [Figure 3(b)]. Moreover, upadacitinib (30 mg) was associated with a higher risk of serious infection than placebo (Supplemental Figure S2). Among the active treatment comparisons, bimekizumab had a significantly higher infection risk than all other treatments, except for tildrakizumab (Supplemental Table S7).

The SUCRA analysis of the PsO trials revealed that infliximab was ranked as the treatment with

the highest risk of infection, followed by deucravacitinib, bimekizumab, and secukinumab; tildrakizumab was ranked the treatment with the lowest risk of infection (Figure 4 and Supplemental Table S8). In the PsA trials, SUCRA ranked bimekizumab with the highest risk of infection, followed by apremilast, upadacitinib (30 mg daily), and ixekizumab (Supplemental Figure S3 and Table S9).

The local test of loop inconsistency based on node splitting did not identify any significant inconsistency within the network for any outcomes (Supplemental Tables S10 and S11). The funnel plots and Egger's test indicated no significant publication bias (Supplemental Figures S4 and S5).

Discussion

Due to the immunosuppressive properties of anti-psoriatic therapies, a number of studies have evaluated the risk of infection among patients with psoriasis exposed to biologic and small-molecule therapies. However, most studies that assessed the safety profiles of multiple anti-psoriatic treatments were observational studies and only evaluated serious infection as an outcome.[35,36] A small number of studies investigated the overall risk of infection or the risk of specific types of infections for these targeted therapies, but these analyses mostly used various conventional immunosuppressive or biological treatments as comparators.[4,37] For instance, the BIOBADADERM registry study reported a significant increase in the overall adjusted risk of infection in the psoriasis population treated with tumor necrosis factor-antagonist drugs (such as infliximab and etanercept) compared to the group treated with methotrexate.[37] Another large cohort study also demonstrated a significantly elevated risk of skin and soft tissue infection [adjusted hazard ratio (aHR), 1.75; 95% CI, 1.19–2.56] among patients with psoriasis receiving biologic therapy compared with non-biologics.[4] A meta-estimate generated from the placebo-controlled periods of phase III pivotal trials reported a higher risk of respiratory tract infections among patients with psoriasis receiving IL-17 inhibitors than patients receiving placebo (odds ratio, 1.56; 95% CI, 1.04–2.33).[38] A recent systemic review (SR) observed an increased risk of candidiasis infections among patients with psoriasis treated with IL-17 inhibitors *versus* placebo (1.7–4.0% *versus* 0.3%, respectively).[39] To fill this knowledge gap, the results of our SR and NMA suggest that targeted systemic therapies – including bimekizumab, secukizumab, ixekizumab, risankizumab, ustekinumab, apremilast, guselkumab, adalimumab, upadacitinib, and apremilast – are associated with significantly higher risks of infection *versus* placebo in patients with PsO and PsA. SUCRA indicated that infliximab, deucravacitinib, and bimekizumab are associated with the highest risks of infection, followed by secukinumab, among patients with moderate-to-severe psoriasis. These findings are in line with data from the Psoriasis Longitudinal Assessment and Registry (PSOLAR)[3] and BIOBADADERM registry,[37] which indicated infliximab leads to the highest rate of serious infections. The dual inhibition of IL-17A and 17F by bimekizumab may contribute to its higher risk of infection.[40,41] This notion is also supported by previous reports that bimekizumab is associated with an increased incidence of oral candidiasis compared with other IL-17 inhibitors.[40,41]

Several observational studies have analyzed the risk of serious infection related to targeted therapies in patients with psoriasis; however, these studies provided inconsistent results. One large observational study conducted in the United States found that the risk of serious infection was slightly higher for biologic therapies compared with non-biologics (aHR, 1.31; 95% CI, 1.02–1.68).[4] Analysis of data from the PSOLAR and BIOBADADERM registries found that individuals with psoriasis prescribed infliximab were more likely to develop a serious infection compared to patients treated with non-biologic therapy.[3,37] Conversely, two BADBIR registry studies did not observe higher rates of serious infection among users of adalimumab, etanercept, or ustekinumab compared to non-biologic systemic therapies.[42,43] A recent study of data from two large US claims databases showed that the rates of serious infections were not significantly higher among new users of adalimumab, infliximab, etanercept, ustekinumab, or apremilast than patients taking methotrexate for psoriasis.[44] Our NMA of a much broader range of studies and evidence showed that none of these targeted therapies are associated with a higher short-term risk of serious infection compared with placebo in RCTs. This discrepancy between the results of our NMA and some of the prior studies may stem from differences in the

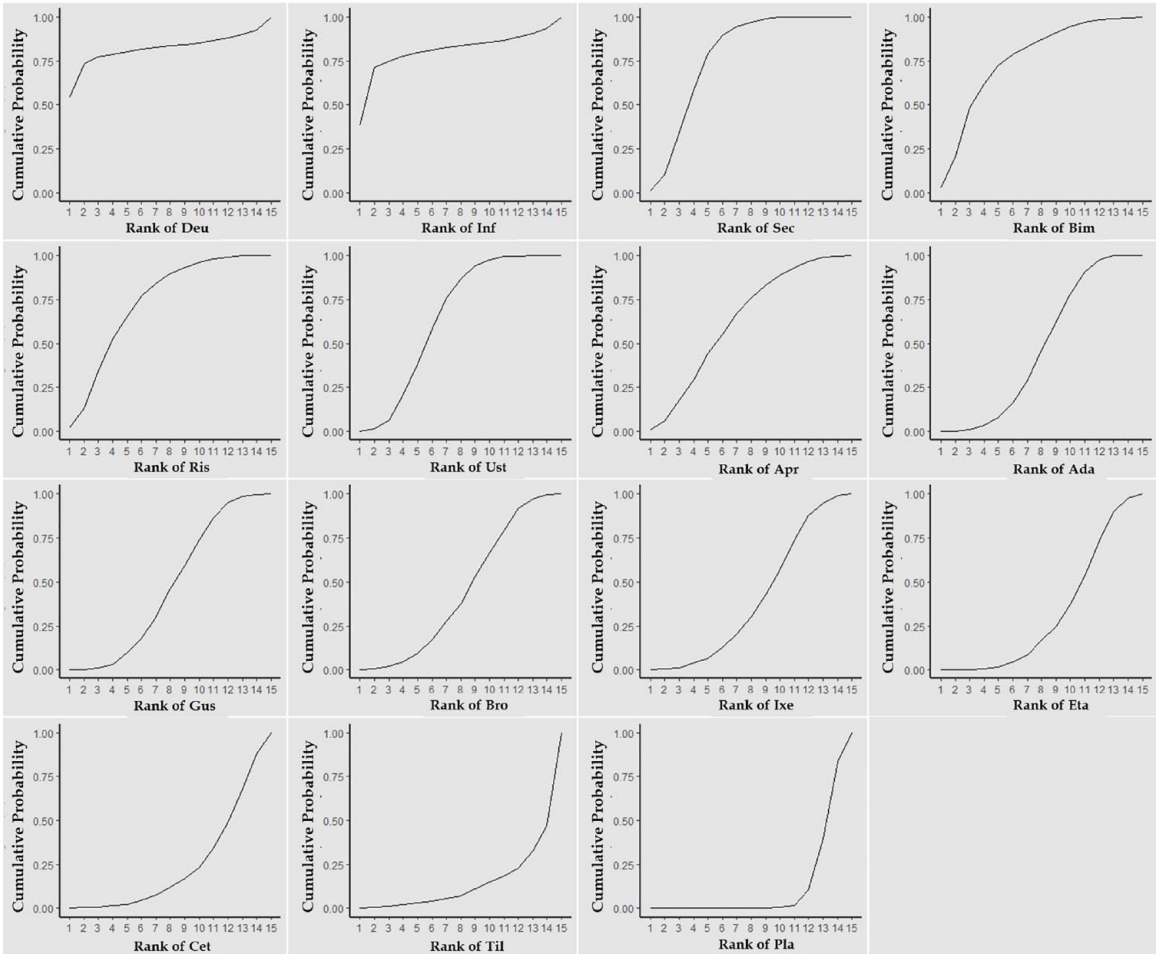

Figure 4. Rankograms of the risks of infection for various interventions in PsO trials. The horizontal axis demonstrates ranking; the vertical axis shows the cumulative ranking probability from 0 to 1.
Ada, Adalimumab; Apr, Apremilast; Bim, Bimekizumab; Bro, Brodalumab; Cet, Cetrolizumab; Deu, Deucravacitinib; Eta, Etanercept; Gus, Guselkumab; Inf, Infliximab; Ixe, Ixekizumab; Pla, placebo; PsO, plaque psoriasis; Ris, Risankizumab; Sec, secukinumab; Til, Tildrakizumab; Ust, Ustekinumab.

study designs, study populations, follow-up durations and comparators between the included studies. Most of the prior studies were observational in nature and included real-world populations. The protocols of these real-world studies could not adopt specific eligibility criteria or methods (random treatment allocation or a placebo control group) that could control for potential confounding factors. Thus, the results of these studies may be limited by confounding factors. Confounders related to comorbidities, prior therapies, and use of immunosuppressants in combination with ongoing biologic and small-molecule therapies for psoriasis in the real-world setting may have complicated the previous assessments of the risk of infection attributable to each specific drug.

Our NMA should be interpreted within the context of the following limitations. First, as the placebo is switched to an active drug after a 10–16 week induction period in most RCTs, it is difficult to assess the risks of infection related to the targeted therapies *versus* the placebo using NMA beyond this time point. Thus, in this NMA, we only quantified the short-term risks of infection and serious infection during the placebo-controlled period. The length of follow-up may affect the count and risk estimation of infection-related AEs. The short-term infection risks of these treatments may not fully represent the long-term risks. This NMA is also limited by estimating the risk of AEs by using the RR, rather than incidence ratio which captures an element of time. Second, as

this NMA was based on data from RCTs that enrolled patients those are different from heterogeneous populations in day-to-day clinical practice, the generalizability of our results is limited. Third, due to data limitations, we could not analyze the associations between different doses of individual therapies and the infection risks, as the data for all doses of each therapy (except for upadacitinib) were grouped together.

Conclusion

Based on the available evidence, our NMA indicates that most biologic and small-molecule therapies do not pose an increased short-term risk of serious infection in patients with psoriasis, except for upadacitinib (30 mg daily) in patients with PsA. However, our NMA synthesized data from a large number of RCTs and observed differences in the risks of infection across the available systemic treatments for psoriasis. Bimekizumab, secukizumab, risankizumab, ustekinumab, apremilast, guselkumab, and adalimumab were associated with higher risks of infection compared to placebo in PsO. Moreover, bimekizumab, apremilast, and upadacitinib (30 mg daily) were associated with higher risks of infection in PsA. Infliximab, deucravacitinib, bimekizumab, and secukinumab were ranked as the therapies most likely to lead to an infectious AE in PsO, whereas bimekizumab, apremilast, and upadacitinib (30 mg daily) were ranked as the highest infection risks in PsA. Clinicians and patients should remain vigilant and monitor infections among patients taking these therapies for psoriasis. The data from this study will help patients and physicians to make more informed, evidence-based treatment selections for psoriasis and also provide a basis for the development and modification of treatment guidelines. Further studies in real-world settings, national and international registries, and post-marketing pharmacovigilance may provide complementary data to determine the generalizability of the findings of our NMA.

Declarations

Ethics approval and consent to participate

This study was granted an exemption from ethical approval by the institutional review board of Chang Gung Memorial Hospital as this was a meta-analysis of published and non-identifiable data.

Consent for publication

Not applicable.

Author contributions

Hsien-Yi Chiu: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Yi-Teng Hung: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Yu-Huei Huang: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

All authors have completed the ICMJE uniform disclosure form available at www.icmje.org/coi_disclosure.pdf and declare the following: HYC received speaking fees from AbbVie, Novartis Pharmaceuticals Corporation, Janssen-Cilag

Pharmaceutica, Eli-Lilly, Kyowa Hakko Kirin Taiwan, and Pfizer Limited and has conducted clinical trials for Eli-Lilly, AbbVie, and Sanofi Pharmaceuticals. YHH has conducted clinical trials while serving as a principal investigator for Galderma, Eli-Lilly, Novartis Pharmaceuticals Corporation, and Janssen-Cilag Pharmaceutica, received honoraria for serving as an advisory board member for Pfizer Limited, AbbVie, and Celgene, and received speaking fees from AbbVie, Eli-Lilly, and Novartis Pharmaceuticals Corporation. YTH has no conflicts of interest to declare.

Availability of data and materials

Raw data are available on request from the authors.

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Supplemental material

Supplemental material for this article is available online.

References

1. Griffiths CEM, Armstrong AW, Gudjonsson JE, *et al.* Psoriasis. *Lancet* 2021; 397: 1301–1315.
2. Grijalva CG, Chen L, Delzell E, *et al.* Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA* 2011; 306: 2331–2339.
3. Kalb RE, Fiorentino DF, Lebwohl MG, *et al.* Risk of serious infection with biologic and systemic treatment of psoriasis: results from the psoriasis longitudinal assessment and registry (PSOLAR). *JAMA Dermatol* 2015; 151: 961–969.
4. Dobry AS, Quesenberry CP, Ray GT, *et al.* Serious infections among a large cohort of subjects with systemically treated psoriasis. *J Am Acad Dermatol* 2017; 77: 838–844.
5. Warren RB, Smith CH, Yiu ZZN, *et al.* Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the british association of dermatologists biologic interventions register (BADBIR). *J Invest Dermatol* 2015; 135: 2632–2640.
6. Lebwohl M, Strober B, Menter A, *et al.* Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med* 2015; 373: 1318–1328.
7. Lebwohl M, Blauvelt A, Paul C, *et al.* Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks of a phase 3, multicenter, randomized, double-blind, etanercept- and placebo-controlled study (CIMPACT). *J Am Acad Dermatol* 2018; 79: 266–276 e5.
8. Langley RG, Elewski BE, Lebwohl M, *et al.* Secukinumab in plaque psoriasis–results of two phase 3 trials. *N Engl J Med* 2014; 371: 326–338.
9. Gordon KB, Blauvelt A, Papp KA, *et al.* Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med* 2016; 375: 345–356.
10. Paul C, Griffiths CEM, van de Kerkhof PCM, *et al.* Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: results from IXORA-S, a phase 3 study. *J Am Acad Dermatol* 2019; 80: 70–79 e3.
11. Warren RB, Blauvelt A, Bagel J, *et al.* Bimekizumab versus adalimumab in plaque psoriasis. *N Engl J Med* 2021; 385: 130–141.
12. Blauvelt A, Papp KA, Griffiths CE, *et al.* Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol* 2017; 76: 405–417.
13. Reich K, Armstrong AW, Foley P, *et al.* Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol* 2017; 76: 418–431.
14. Gordon KB, Duffin KC, Bissonnette R, *et al.* A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *N Engl J Med* 2015; 373: 136–144.
15. Reich K, Armstrong AW, Langley RG, *et al.* Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet* 2019; 394: 831–839.

16. Gordon KB, Strober B, Lebwohl M, *et al*. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet* 2018; 392: 650–661.

17. Mease P, Hall S, FitzGerald O, *et al*. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med* 2017; 377: 1537–1550.

18. McInnes IB, Anderson JK, Magrey M, *et al*. Trial of upadacitinib and adalimumab for psoriatic arthritis. *N Engl J Med* 2021; 384: 1227–1239.

19. Reich K, Gooderham M, Thaci D, *et al*. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet* 2019; 394: 576–586.

20. Reich K, Gooderham M, Green L, *et al*. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). *J Eur Acad Dermatol Venereol* 2017; 31: 507–517.

21. Rouse B, Chaimani A and Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med* 2017; 12: 103–111.

22. Armstrong AW, Soliman AM, Betts KA, *et al*. Long-term benefit-risk profiles of treatments for moderate-to-severe plaque psoriasis: a network meta-analysis. *Dermatol Ther (Heidelb)* 2022; 12: 167–184.

23. Xu S, Gao X, Deng J, *et al*. Comparative efficacy and safety of biologics in moderate to severe plaque psoriasis: a multiple-treatments meta-analysis. *J Dtsch Dermatol Ges* 2021; 19: 47–56.

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, Gotzsche PC, *et al*. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.

26. Truong B, Rich-Garg N, Ehst BD, *et al*. Demographics, clinical disease characteristics, and quality of life in a large cohort of psoriasis patients with and without psoriatic arthritis. *Clin Cosmet Investig Dermatol* 2015; 8: 563–569.

27. Nash P, Kirkham B, Okada M, *et al*. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet* 2017; 389: 2317–2327.

28. Simpson EL, Papp KA, Blauvelt A, *et al*. Efficacy and safety of upadacitinib in patients with moderate to severe atopic dermatitis: analysis of follow-up data from the measure up 1 and measure up 2 randomized clinical trials. *JAMA Dermatol* 2022; 158: 404–413.

29. Cohen SB, van Vollenhoven RF, Winthrop KL, *et al*. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann Rheum Dis* 2021; 80: 304–311.

30. Mease PJ, Lertratanakul A, Anderson JK, *et al*. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. *Ann Rheum Dis* 2021; 80: 312–320.

31. White IR. Multivariate random-effects meta-analysis. *Stata J* 2009; 9: 40–56.

32. Veroniki AA, Vasiliadis HS, Higgins JP, *et al*. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013; 42: 332–345.

33. Salanti G, Ades AE and Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64: 163–171.

34. Chaimani A and Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Res Synth Methods* 2012; 3: 161–176.

35. Jin Y, Lee H, Lee MP, *et al*. Risk of hospitalization for serious infection after initiation of ustekinumab or other biologics in patients with psoriasis or psoriatic arthritis. *Arthritis Care Res (Hoboken)* 2022; 74: 1792–1805.

36. Li X, Andersen KM, Chang HY, *et al*. Comparative risk of serious infections among real-world users of biologics for psoriasis or psoriatic arthritis. *Ann Rheum Dis* 2020; 79: 285–291.

37. Davila-Seijo P, Dauden E, Descalzo MA, *et al*. Infections in moderate to severe psoriasis patients treated with biological drugs compared to classic systemic drugs: findings from the BIOBADADERM Registry. *J Invest Dermatol* 2017; 137: 313–321.

38. Wan MT, Shin DB, Winthrop KL, *et al.* The risk of respiratory tract infections and symptoms in psoriasis patients treated with interleukin 17 pathway-inhibiting biologics: a meta-estimate of pivotal trials relevant to decision making during the COVID-19 pandemic. *J Am Acad Dermatol* 2020; 83: 677–679.

39. Saunte DM, Mrowietz U, Puig L, *et al.* Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. *Br J Dermatol* 2017; 177: 47–62.

40. Armstrong AW, Blauvelt A, Mrowietz U, *et al.* A practical guide to the management of oral candidiasis in patients with plaque psoriasis receiving treatments that target interleukin-17. *Dermatol Ther (Heidelb)* 2022; 12: 787–800.

41. Gordon KB, Foley P, Krueger JG, *et al.* Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial. *Lancet* 2021; 397: 475–486.

42. Yiu ZZN, Smith CH, Ashcroft DM, *et al.* Risk of serious infection in patients with psoriasis receiving biologic therapies: a prospective cohort study from the british association of dermatologists biologic interventions register (BADBIR). *J Invest Dermatol* 2018; 138: 534–541.

43. Yiu ZZN, Ashcroft DM, Evans I, *et al.* Infliximab is associated with an increased risk of serious infection in patients with psoriasis in the U.K. and Republic of Ireland: results from the british association of dermatologists biologic interventions register (BADBIR). *Br J Dermatol* 2019; 180: 329–337.

44. Dommasch ED, Kim SC, Lee MP, *et al.* Risk of serious infection in patients receiving systemic medications for the treatment of psoriasis. *JAMA Dermatol* 2019; 155: 1142–1152.