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Comparative risk of herpes zoster in patients with psoriatic disease on systemic treatments: a systematic review and network meta-analysis

Hsien-Yi Chiu*, Yi-Teng Hung*, Shi-Wei Huang and Yu-Huei Huang

Abstract

Background: Numerous previous studies have examined risk of herpes zoster (HZ) in psoriatic disease; however, the results of these studies are conflicting and the relative risks associated with different treatments remain largely unknown. In this meta-analysis, we examined the relative risk of HZ associated with systemic treatments for psoriatic disease.

Methods: PubMed, EMBASE, Cochrane Library, and Web of Science databases were searched to identify relevant English-language studies published up to April 2021. Data were extracted using a standardized data extraction form. Network meta-analyses (NMA) was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. We examined the differences in HZ risk (incidence rate ratio; IRR) between treatments using a random-effects model for direct pairwise comparisons and NMA. The surface under the cumulative ranking area was calculated to rank the HZ risk for each treatment condition.

Results: This study analyzed 13 studies including 19 treatment arms involving a total of 443,104 patients with psoriatic disease. Corticosteroids (CS) [IRR, 2.56; 95% confidence interval (CI), 1.59–4.13], a Janus kinase inhibitor (JAKi; tofacitinib) (IRR, 2.34; 95% CI, 1.03–5.32), infliximab (IRR, 2.32; 95% CI, 1.27–4.21), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) + CS (IRR, 2.26; 95% CI, 1.23–4.17), anti-tumor necrosis factor-α (anti-TNF-α) + csDMARDs and/or CS (IRR, 2.13; 95% CI, 1.38–3.31), csDMARDs (IRR, 1.62; 95% CI, 1.18–2.22), and anti-TNF-α except infliximab (IRR, 1.61; 95% CI, 1.13–2.30) were all associated with a significantly higher HZ risk compared to controls. CS treatment possessed the highest HZ risk, followed by infliximab and JAKi (tofacitinib). Phosphodiesterase-4 inhibitor, anti-interleukin-17, -23 or -12/23, phototherapy, and acitretin showed a risk similar to controls without significant differences.

Conclusion: The NMA demonstrated CS, infliximab, and JAKi (tofacitinib), and several combination treatments were associated with higher HZ risk in patients with psoriasis and psoriatic arthritis. Differences in HZ risk should be taken into consideration when considering optimal psoriasis treatment.

Keywords: biologic, disease-modifying anti-rheumatic drug, herpes zoster, network meta-analysis, psoriasis, psoriatic arthritis

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Introduction

Cell-mediated immunity is essential to control varicella-zoster virus (VZV), which causes chicken pox and shingles [herpes zoster (HZ)].[1] The risk of HZ, a reactivation of latent VZV, is higher in individuals who are older, immunocompromised, and receive immunosuppressive medications that impair T cell immunity.[1] Previous studies have

shown that patients with immune-mediated inflammatory disease (IMID), including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE), are at increased risk of HZ compared to the general population,[2] and patients with psoriatic disease have been shown to have an increased propensity for HZ.[2,3] Moreover, the use of biologics and conventional disease-modifying antirheumatic drugs (DMARDs) in patients with psoriatic disease has been suggested to further enhance the risk of HZ[2,4] due to the immunosuppressive actions of these medications. Prior studies have also reported a more severe disease course and higher prevalence of complications that may require hospitalization and/or changes in the treatment regimens in the patients with IMID compared to the general population.[5,6] Medical expenditures associated with treating HZ are nearly twice as high for immunocompromised patients compared to other patients with HZ.[7]

Despite a rapid expansion in the number of highly effective treatments available and clinical trials for psoriatic disease, the majority of previous studies were either restricted to a comparison of the relative effects or overall tolerability of different treatments. There remains a paucity of data regarding head-to-head comparisons of HZ risk associated with different anti-psoriatic treatments. The risk of HZ varies for treatments whose adverse effect profiles are linked to their specific mechanisms of action (MOA). Some systemic anti-psoriatic agents have been reported to be associated with increased HZ risk in patients with psoriatic disease; however, other studies have reported conflicting results.[8–10] One recent systematic review and meta-analysis evaluated the risk of HZ in psoriasis and psoriatic arthritis patients treated with biological therapy;[11] however, whether – and indeed, which – anti-psoriatic agents confer a higher susceptibility to the development of HZ in patients with psoriatic disease is still a matter of debate. Specifically, studies quantifying the comparative risk of HZ among patients receiving interleukin (IL)-17, IL-12/23 and tumor necrosis factor-α (TNF-α) inhibitors, conventional and targeted synthetic DMARDs (tsDMARDs) and combination therapies are lacking. A better understanding of the comparative HZ risk of systemic anti-psoriatic treatments would help guide a treatment selection and consideration of HZ vaccination. Toward this, we performed a systematic review and network meta-analysis (NMA) to compare HZ risk for different anti-psoriatic systemic therapies and combinations of therapies.

Materials and methods

Search strategy

We performed this systematic review and NMA and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Supplementary Table S1). PubMed, EMBASE, the Cochrane library, and Web of Science databases were searched by two authors (H-Y.C. and Y-H.H.) for English-language studies published up to April 2021 investigating the risk of HZ in patients with psoriatic disease, including psoriasis and psoriatic arthritis. Search terms included psoriasis, psoriatic arthritis AND HZ AND systemic treatments for psoriatic disease (Supplementary Table S2). Two reviewers determined the suitability of the abstracts retrieved. After initial screening, full texts of all included studies were independently appraised by two reviewers (H-Y.C. and Y-H.H.) to verify their relevance. Bibliographies of retrieved studies were manually screened to locate additional eligible studies missed by database searches. This study was exempt from ethics approval by institutional review board of Chang Gung Memorial Hospital (No. 202200079B1) due to the study design of meta-analysis of published and non-identifiable data.

Inclusion and exclusion criteria

The types of studies included for analysis were phase II, III randomized controlled trials (RCTs), long-term extension or open-label extension studies, prospective registry studies and cohort studies. The detailed study protocol was registered in PROSPERO (the International Prospective Register of Systematic Reviews) (CRD42021250155) (Supplementary Method S1). Studies were eligible for inclusion if they met the following criteria: (1) studies in patients diagnosed with psoriatic disease; (2) studies collecting data of HZ, investigating and reporting the incidence of HZ in patients with psoriatic disease on treatments or placebo control; (3) studies including psoriatic participants receiving

at least one systemic treatment for their psoriatic disease; and (4) studies published in English. We excluded (1) studies without reports of HZ events in placebo and actively treated groups, (2) studies with incomplete data or conference abstract only, (3) studies without extractable outcomes of interest or only reporting irrelevant outcomes, (4) case reports, review, meta-analysis, editorial, or commentary studies, (5) studies with short follow-up periods, and (6) studies without a comparison group or could not be connected to other studies in the NMA.

Quality assessment

Two authors (H-Y.C. and Y-H.H.) independently assessed the quality of each study using the Cochrane Collaboration Risk-of-Bias Instrument[12] and the risk-of-bias in non-randomized studies of interventions (ROBINS-I) Instrument[13] for RCT and non-RCT studies, respectively. Agreement on quality was reached by consensus.

Data extraction

Two authors (H-Y.C. and Y-H.H.) extracted data independently using a standardized extraction form (Supplementary Tables S3 and S4). Data collected included publication details, study design, characteristics of patients and treatments, duration of follow-up, endpoint assessment, number of HZ events, number of participants with HZ events, and incidence of HZ (per 1000 patient-years) for the intervention and control groups in each study (Supplementary Method S1). Study results posted at ClinicalTrials.gov were also checked for inclusion in our NMA. A PRISMA flowchart of study selection is shown in Figure 1. Any discrepancies between the two reviewers (H-Y.C. and Y-H.H.) were resolved by discussion.

Data analysis/statistical analysis

We performed a pairwise meta-analysis of direct treatment effects comparing each treatment with the control group in the respective original study. Extracted data were combined using a random-effects model, with effect sizes expressed as incidence rate ratio (IRR) of developing HZ with corresponding 95% confidence interval (CI). Between-study heterogeneity in the meta-analysis was assessed using the I-squared metric, with values of $< 25\%$, 25–50%, or $> 50\%$ indicating low, moderate, or high heterogeneity, respectively.[14,15]

NMA was performed using a multivariate, random-effects meta-regression model with restricted maximum likelihood for variance estimation. Models were fitted using a frequentist approach in STATA (Version 14.0, StataCorp, College Station, TX, USA) through a network module based on the *'mvmeta'* command for multiple treatment comparisons. Between-study variances were equalized, correlations were set to 0.5, and CIs were estimated based on asymptotic error variance and normal distribution. We used NMA to combine direct and indirect comparative data for the various therapeutic options across a network of studies into a single effect size and to rank the treatments. We first categorized the systemic anti-psoriatic interventions into eight groups, including corticosteroids (CS), conventional synthetic DMARDs (csDMARDs), tsDMARDs, biologics, phototherapy/acitretin, biologics + csDMARDs and/or CS, csDMRADs + CS, and control (Figure 2(a)); summary results were presented as the IRRs of HZ for each group. To understand which treatments have a higher risk of HZ, we further stratified treatments into 12 groups, including CS, csDMARDs, JAKi (tofacitinib), PDE4 inhibitor, infliximab, anti-TNF-α (except infliximab), anti-IL-17, -23 or -12/23, phototherapy, acitretin, anti-TNF-α + csDMARDs and/or CS, csDMRADs + CS, and control (Figure 2(b)). Since previous studies suggested that infliximab has a higher risk of serious infection than other anti-TNF-α drugs,[16,17] we isolated infliximab from the anti-TNF-α group in our analysis. Forest plots were used to represent quantitative results. To rank risk of HZ for all treatments, we calculated the surface under the cumulative ranking area (SUCRA) and quantified the ranks; larger SUCRA scores indicate a higher ranking, which suggests a higher probability of developing HZ.[18] Cumulative ranking probability plots were used to visually inspect ranking probabilities and uncertainty of various treatments.[18] Local inconsistency between direct and indirect estimates in the network was analyzed using a side-splitting model and global inconsistency was evaluated by comparing the fit of the consistency and inconsistency models using a design-by-treatment interaction model.[19,20]

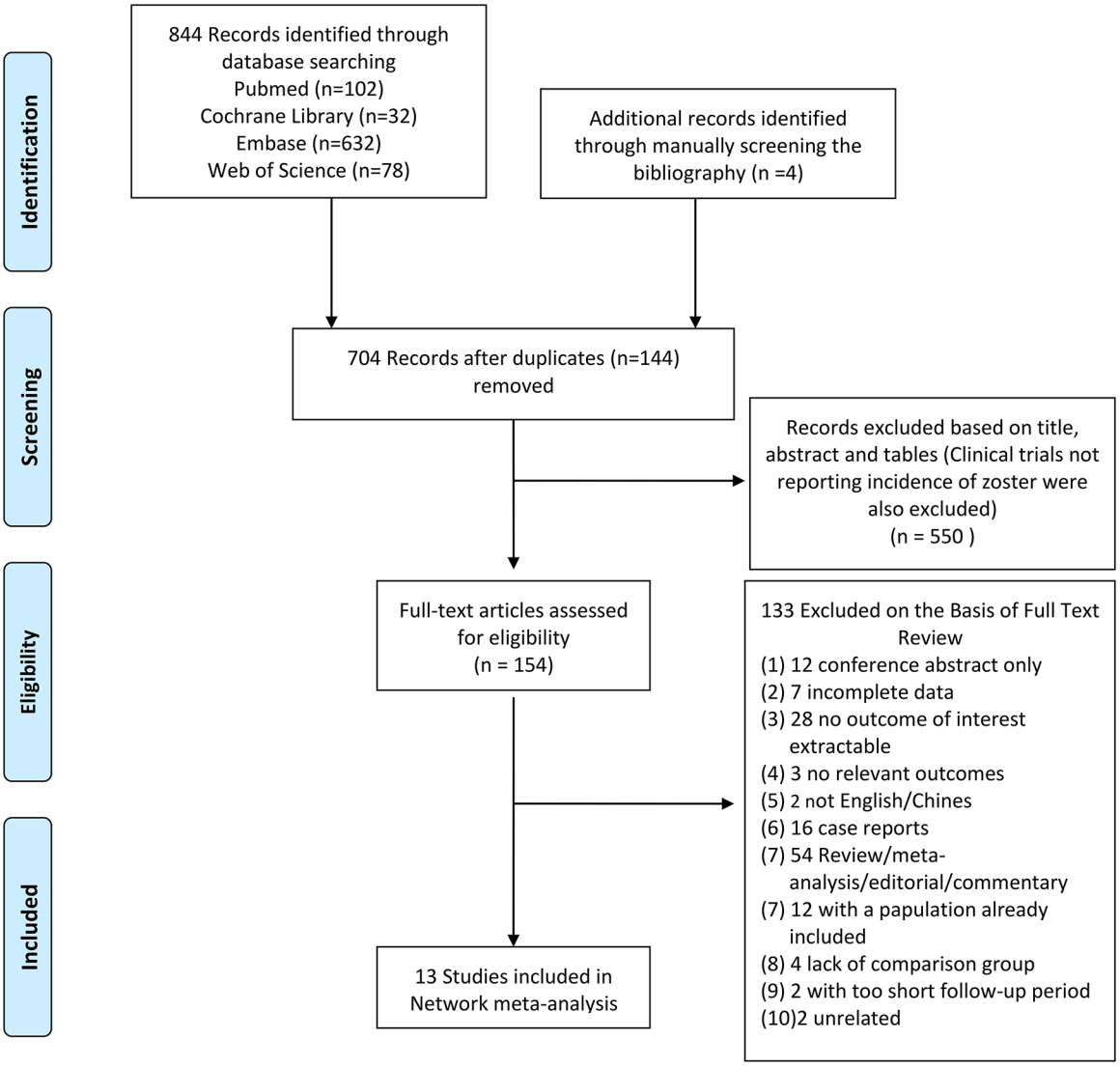

Figure 1. PRISMA flowchart. PRISMA flowchart of study selection for the systemic review and meta-analysis.

We used comparison-adjusted funnel plots in which treatments were ordered according to their point estimate and Egger's tests to examine potential publication bias and the small study effect.[21]

Results

Study selection and characteristics of the included studies

A flow diagram of the literature search and study selection process is shown in Figure 1. Five studies including RCTs[22–27] and eight cohort studies[9,10,17,28–32] comprising a total of 443,104 patients and collectively evaluating 19 treatments were included. The mean (± standard deviation) duration of follow-up was 19,664.5 patient-years (PYs; ± 72,503.2; range, 74.6–503,744.0 PYs). Supplementary Tables S3 and S4 summarize the essential characteristics of the eligible studies.

Risk of bias and consistency

The risk of bias was low for most RCTs; nevertheless, a risk of bias was observed in some studies because their analysis included a period of open-label extension and thus blinding was not performed (Supplementary Figure S1). ROBINS-I assessment of non-RCT studies

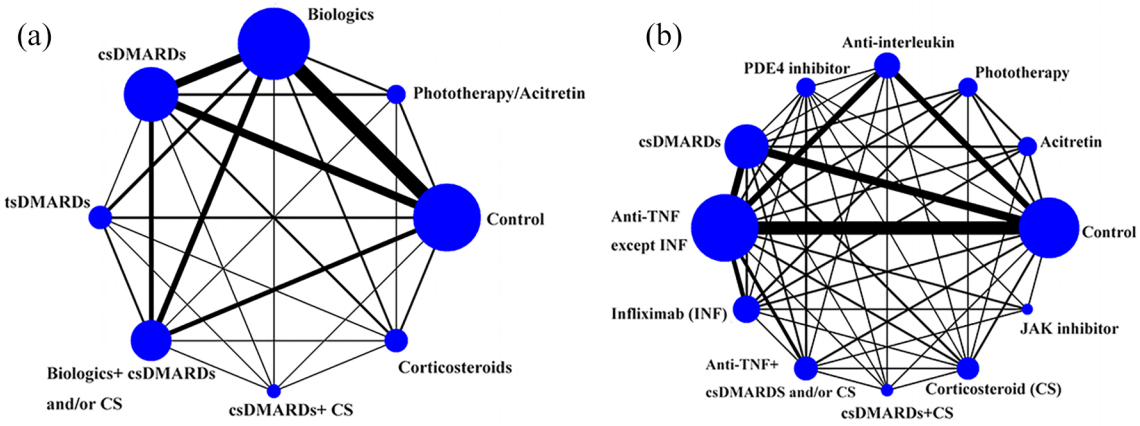

Figure 2. Network graph of eligible systemic treatments comparisons for HZ event. Line width and size of circle is proportional to the number of trials comparing each pair of treatment and the number of participants assigned to receive the treatment, respectively.
Anti-interleukin includeds anti-IL-17, -23 or -12/23 therapy; Anti-TNF-α, anti-tumor necrosis factor-α; CS, corticosteroids; csDAMRDs, conventional synthetic disease-modifying anti-rheumatic drugs; JAK inhibitor, Janus kinase inhibitor; INF, infliximab; PDE4 inhibitor, phosphodiesterase type 4 inhibitor.

showed moderate-to-serious risks due to insufficient control of confounding factors and concealment of allocation management (Supplementary Figure S2).

Conventional pairwise meta-analysis of direct comparisons

A significantly higher risk of HZ compared to control was observed for biologics, csDMARDs, biologics + csDMARDs and/or CS, and csDMRADs + CS (Supplementary Table S5). Further analyses showed that infliximab, anti-TNF-α (except infliximab), csDMARDs, anti-TNF-α + csDMARDs and/or CS, and csDMARDs + CS had higher IRR for HZ compared to control (Supplementary Table S6). There was no significant difference in risk of HZ between CS and control; however, high heterogeneity was observed for this comparison ($p < 0.01$, I2 = 95.7%).

Network meta-analysis

Relative risk. Regarding risk of developing HZ associated with treatments, effect size estimates for the comparison of each treatment compared with all other treatments were summarized in league tables (Supplementary Tables S7 and S8). NMA showed that CS, csDMARDs, and biologics had significantly higher IRR for HZ compared to control (Supplementary Figure S3). Further analysis by stratifying the treatments into 12 groups demonstrated that CS, JAKi (tofacitinib), infliximab, csDMARDs + CS, anti-TNF-α + csDMARDs and/or CS, anti-TNF-α (except infliximab), and csDMARDs were all associated with a significantly higher risk of HZ compared to control [IRR (95% CI); 2.56 (1.59–4.13), 2.34 (1.03–5.32), 2.32 (1.27–4.21), 2.26 (1.23–4.17), 2.13 (1.38–3.31), 1.61 (1.13–2.30), 1.62 (1.18–2.22), respectively] (Figure 3). PDE4 inhibitor, anti-IL treatment, phototherapy, and acitretin showed a risk similar to control with no significant difference (Figure 3). Infliximab exhibited a significantly higher risk of HZ than anti-IL treatment [IRR (95% CI); 2.46 (1.15–5.27)] (Supplementary Table S8).

Ranking with SUCRA value. Based on SUCRA, CS was associated with the highest risk of HZ (SUCRA 87.7), whereas phototherapy/acitretin had the lowest risk (SUCRA 14.6; Supplementary Figure S4 and Table S9). Further stratification of treatments showed that CS was ranked as having the highest risk of HZ (SUCRA 86.0), followed by infliximab (SUCRA 77.1), JAKi (tofacitinib) (SUCRA 76.1), csDMARDs + CS, anti-TNF-α + csDMARDs and/or CS, anti-TNF-α (except infliximab), csDMARDs, PDE4 inhibitor, phototherapy, anti-IL, and acitretin (Figure 4 and Supplementary Table S10).

Risk of bias and inconsistency. In the first analysis consisting of eight treatment groups, publication bias was not detected by either funnel plot or

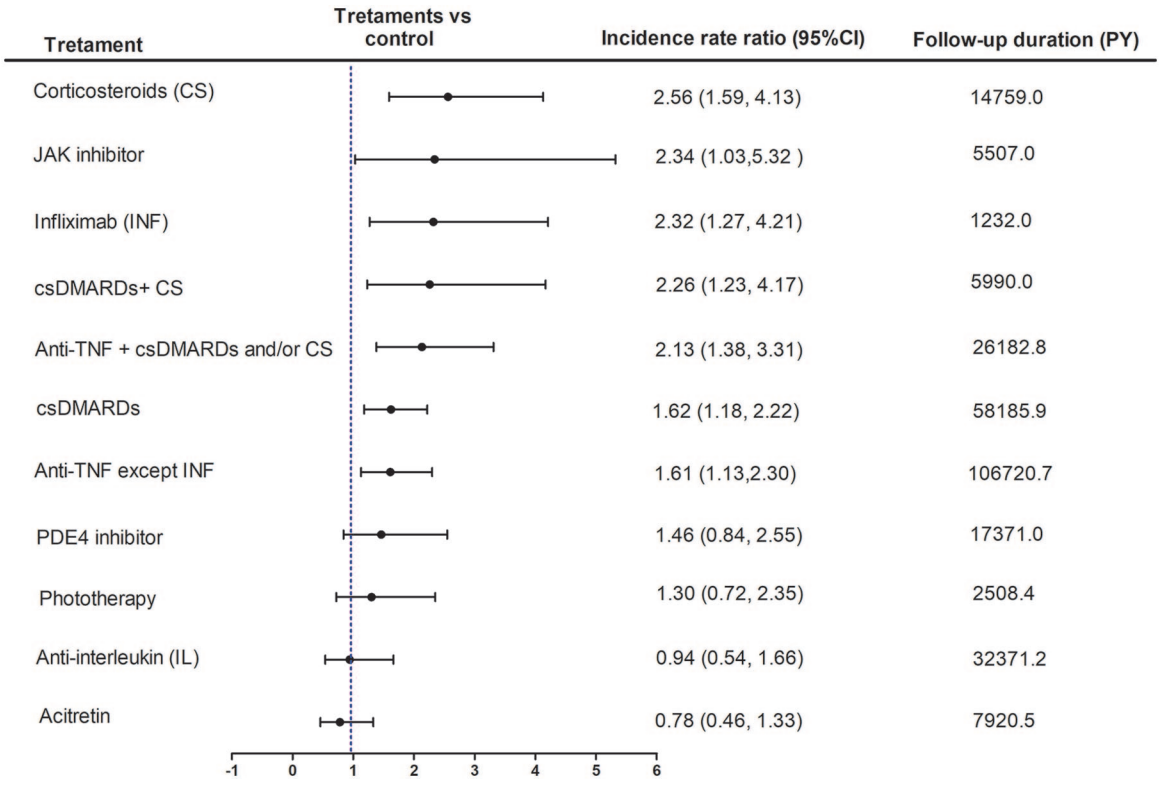

Figure 3. Forest plot. Forest plot of the risk of HZ for various treatments compared with control. Anti-IL included anti-IL-17, -23, or -12/23 therapy.
Anti-TNF-α, anti-tumor necrosis factor-α; CS, corticosteroids; csDAMRDs, conventional synthetic disease-modifying anti-rheumatic drugs; JAK inhibitor, Janus kinase inhibitor; INF, infliximab; PDE4 inhibitor, phosphodiesterase type 4 inhibitor.

Egger's test ($p = 0.135$; Supplementary Figure S5). Further stratification of the treatments into 12 groups showed no evidence of selective outcome reporting or the small study effect by funnel plot and Egger's tests ($p = 0.067$; Supplementary Figure S6). We did not observe evidence of global inconsistency in the HZ outcome using design-by treatment interaction models in either analysis ($p = 0.667$ and $p = 0.477$, respectively). Side-splitting methods showed no substantial inconsistency between direct and indirect estimates (Supplementary Tables S11 and S12).

Discussion

Our NMA indicates an increased risk for HZ in psoriatic patients treated with CS, JAKi (tofacitinib), infliximab, csDMARDs + CS, anti-TNF-α + csDMARDs and/or CS, anti-TNF-α (except infliximab), and csDMARDs compared to control. In particular, CS, infliximab, JAKi (tofacitinib), and combination treatments showed greater HZ risk than other treatments. Several studies have demonstrated that anti-TNF-α therapies are associated with elevated HZ risk in patients with RA compared with standard csDMARDs.[4,33] A recent meta-analysis of observational studies found an elevated risk of HZ [odds ratio (OR), 1.61; 95% CI, 1.16–2.23] in patients with RA who were receiving anti-TNF-α treatment ($n = 73{,}510$) compared with non-biologic DMARDs ($n = 89{,}567$).[34] However, few studies have evaluated the risk of HZ in patients with psoriasis treated with anti-TNF-α therapies. Shalom *et al.*[29] observed a significantly increased risk of HZ among new users of anti-TNF-α therapies compared with a reference cohort (combined phototherapy, systemic CS, topical CS, and immunomodulators other than methotrexate) in the Psoriasis Longitudinal Assessment and Registry (adjusted hazard ratio 3.66; 95% CI, 1.15–11.63). One systematic review and meta-analysis showed the risk of HZ in psoriasis and psoriatic arthritis patients taking TNF-α inhibitors was higher than that for non-biological systemic therapies.[11] These data appear consistent

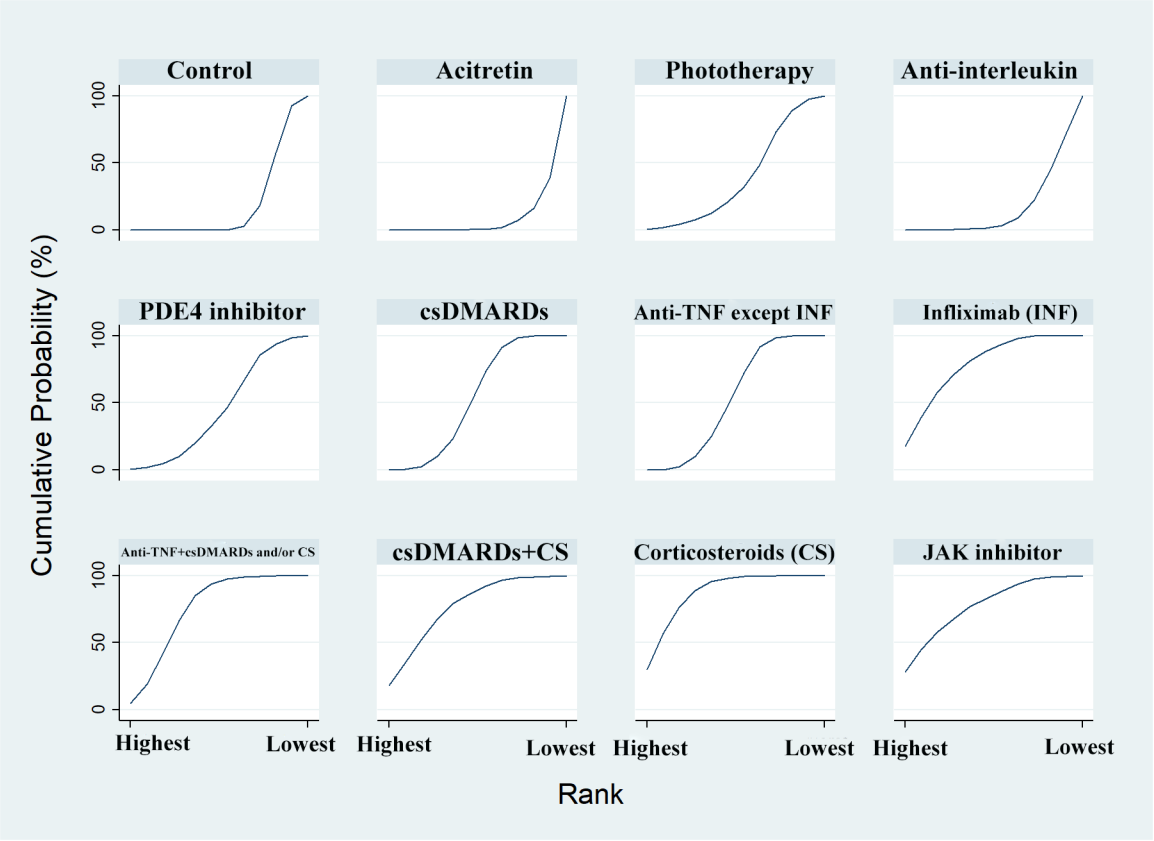

Figure 4. Rankogram of interventions stratified into 12 groups. Rankogram of HZ risk for various interventions. The horizontal axis demonstrates ranking; the vertical axis shows the cumulative ranking probability from 0 to 1. Anti-IL included anti-IL-17, -23, or -12/23 therapy.
Anti-TNF-α, anti-tumor necrosis factor-α; CS, corticosteroids; csDAMRDs, conventional synthetic disease-modifying anti-rheumatic drugs; JAK inhibitor, Janus kinase inhibitor; INF, infliximab; PDE4 inhibitor, phosphodiesterase type 4 inhibitor.

with the results of this NMA, which suggests that anti-TNF-α treatment, particularly infliximab, may be associated with an increased risk of HZ. However, another recent study reported no significant difference in risk of HZ between patients on anti-TNF-α therapy and those who did not receive systemic medications or phototherapy.[31]

Results from two phase III RCTs during the tofacitinib global clinical development program for psoriasis showed higher numbers of HZ in the tofacitinib group ($n=12$) compared with the placebo group ($n=0$).[35] A recent pooled analysis involving 3623 patients with psoriasis also reported the IR for HZ was higher for tofacitinib monotherapy [2.55 (95% CI, 2.13–3.03) cases/1000 PYs] than placebo (0 cases/100 PYs).[26] Analysis of HZ risk in patients with psoriatic arthritis (PsA) revealed similar findings to those observed in patients with psoriasis.[36,37] Two pivotal phase III studies of patients with PsA reported more HZ cases in the tofacitinib arms ($n=7$) than the placebo arms ($n=0$).[36,37] Similarly, JAKi (tofacitinib) was associated with an increased risk of HZ and was ranked as having the third highest risk of developing HZ in our NMA. The association between CS and JAKi (tofacitinib) and increased risk of HZ in NMA but not pairwise meta-analysis is likely due to a limited number of studies with high heterogeneity comparing these two drugs. NMA has the advantage of incorporating indirect comparisons of interventions that have not been studied in a head-to-head fashion from multiple studies.[15,20,21]

Recent meta-analysis and observational registry and cohort studies showed treatment with CS and csDMARDs are risk factors for HZ in patients with psoriasis[31,38] and RA.[4,38,39] In this NMA, CS were associated with the highest risk of HZ among

all therapies for psoriasis. This finding is consistent with the results of a large population-based study, which demonstrated CS use had the highest risk estimate for HZ (OR 2.51).[4] Our results also suggest that combination therapy further enhances the risk of HZ, as indicated by our finding that combined use of csDMARDs in conjunction with biologic medications elevates HZ risk beyond that of biologics alone. We also find using CS in combination with csDMARDs to be associated with higher rates of HZ than csDMARDs alone, a result supported by similar observations in previous studies.[4,31]Compared with the systemic review by Baumrin *et al.*,[40] our NMA provides more and stronger evidence to support that CS, JAKi (tofacitinib), csDMARDs and combination therapies are associated with increased HZ risk. In addition, our NMA provides additional evidence with increased statistical power using reasonable network connectivity and larger sample sizes to demonstrate that infliximab and non-infliximab anti-TNF-α are associated with a higher risk of HZ, while PDE4 inhibitor, anti-IL treatment, phototherapy, and acitretin are not. Moreover, our NMA ranked these anti-psoriatic systemic treatments in terms of HZ risk, which may assist selecting different treatments in clinical practice. In agreement with consensus by National Psoriasis Foundation[40] and based on results from our studies, we recommended that patients with psoriasis and/or psoriatic arthritis receive recombinant zoster vaccination if they are on systemic CS, tofacitinib, csDMARDs, or combination systemic treatments. We further suggest that vaccination of patients on phototherapy and PDE4 inhibitors, anti-IL, and acitretin treatment can be evaluated on a case-by-case basis.

Strengths and limitations

Using NMA in this study enabled us to simultaneously analyze direct and indirect comparisons of multiple treatments across a network of numerous RCTs, cohort studies, and registries to maximize the number of studies and individuals analyzed. Compared to a previous meta-analysis by Zou *et al.*,[11] our study explicitly ranked the relative HZ risk associated with various treatments for psoriatic disease instead of scanning each individual pair-wise comparison, which may be beneficial for clinical physicians in selecting optimal treatment regimens. In 2021, Tang *et al.*[41] used NMA to investigate the risk of HZ among psoriasis patients taking biologics. However, their NMA only included five cohort studies and lacked a control group and conventional treatment groups.[41] Compared with these previous studies, our NMA included more treatments and more studies with larger cohorts and longer follow-up periods. Moreover, our study included combination therapy in the analysis of HZ risk, a topic not addressed by previous meta-analyses.[11,41]

Several limitations merit note when interpreting our findings. First, some RCTs were excluded from this NMA due to missing outcome values. In those RCTs, HZ was not reported as a separate individual entity; rather, it was reported under the category of an adverse event (AE) or serious AE. This may have resulted in a smaller number of RCTs being included in the NMA and data for some therapies only being retrieved from observational studies. However, we saw no evidence of publication bias. Second, placebo−controlled arms usually have a shorter follow-up period due to cross−over study design and higher dropout rates than other treatment comparators in the majority of psoriasis trials, which could have led to lower numbers of HZ events in the placebo arm. Nevertheless, our NMA not only collected data from RCTs but also incorporated observational data gathered from registries and cohort studies, in which the control groups had adequate long-term follow-up. Third, there was some heterogeneity among the included studies, which could be due to a combination of differences in the study design (e.g. RCT *versus* observation studies). Fourth, since different therapy groups might have different quality of evidence, this study was unable to comment on dose or duration of medications as risk factors for HZ. Fifth, there were no studies distinguishing the components of psoriatic disease (psoriasis only, psoriatic only, or both psoriasis and psoriatic arthritis) in participants. Similarly, not all potential determinants for HZ risk (e.g. age, sex, ethnicity, and disease activity)[10,26] were recorded in detail and with a consistent definition across studies. Consequently, further subgroup analysis was not performed. Finally, we performed this analysis mainly based on the drug families or classes and not on individual drugs; we note that potential differences of HZ risk may exist among members of the same drug class. Treatment rankings may change when the classification differs, a new drug class is developed or new drugs are added to a drug class. Finally, the contribution of

each drug in combination therapies to risk of HZ cannot be differentiated.

Conclusion

In conclusion, our NMA of the available evidence demonstrates that CS, JAKi (tofacitinib), infliximab, csDMARDs + CS, anti-TNF-α + csDMARDs and/or CS, anti-TNF-α (except infliximab), and csDMARDs are associated with an increased risk for HZ compared with control. Relative treatment rankings indicate that CS treatment has the highest risk for HZ, followed by infliximab and JAKi (tofacitinib). The addition of csDMARDs and/or CS to anti-TNF-α and the combination of csDMARDs with CS further enhance the HZ risk compared with anti-TNF-α and csDMARDs monotherapy, respectively. When selecting a treatment for patients with psoriasis, clinicians should take these differences in risk of HZ into consideration and, further, recombinant varicella-zoster vaccine should be considered for patients receiving medications with higher HZ risk and combination of systemic treatments.

Author contributions

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

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

Shi-Wei Huang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; 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.

Availability of data and material

Raw data are available from the authors on request.

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Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors have completed the ICMJE uniform disclosure form available at www.icmje.org/coi_disclosure.pdf, and they declare the following: H-Y.C. 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 and Sanofi Pharmaceuticals. Y-H.H. 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. Y-T.H. and S-W.H. have no conflicts of interest to declare.

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Supplemental material

Supplemental material for this article is available online.

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