Risk of infections during treatment with oral Janus kinase inhibitors in randomized placebo-controlled trials: A systematic review and meta-analysis

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Janus kinase (JAK) inhibitors block pathways involved in inflammation and immune response, making JAK inhibitors useful in the treatment of various diseases. While the efficacy of these drugs has been proven in several studies, their safety profile needs to be further investigated. In this systematic review and meta-analysis, we examined the risk of infections during treatment with oral JAK inhibitors with no concomitant treatment compared to placebo in phase 2 and 3 randomized, placebo-controlled trials. The medical databases PubMed, Web of Science, and EMBASE were searched from inception through February 2024, yielding 13,567 nonduplicate articles, of which 69 were included in the final quantitative analysis. Overall, we found that treatment with oral JAK inhibitors was associated with an increased risk of infections compared to placebo across all indications (relative risk: 1.39 [95% CI: 1.096-1.76, P = .0067]) and in dermatologic indications (relative risk: 1.46 [95% CI, 1.10-1.93, P = .0097]). Remarkably, an increased risk of herpes zoster infections was found in dermatologic indications but not in nondermatologic indications. In conclusion, we identified a significantly increased risk of developing infections during treatment with oral JAK inhibitors compared to placebo across indications. In sub-analyses, we additionally found an increased risk of herpes zoster in dermatologic indications. (JAAD Int 2025;18:106-16.)

Key words: immune-mediated diseases; infections; JAK inhibitors; Janus kinase inhibitor; randomized clinical trials.

INTRODUCTION

A key inflammatory pathway in immune-mediated inflammatory diseases (IMIDs) is the Janus kinase (JAK) transducer and activator of transcription signaling pathway.[1-3] JAK inhibitors (JAKis) block enzymes involved in the signaling pathway that controls cell development and function. The JAK family comprises JAK1, JAK2, JAK3, and tyrosine kinase 2. Blocking these signaling pathways inhibits inflammation and the immune response, making JAKi useful in the treatment of various diseases. Thus, making JAKi a particular focus in the treatment of IMIDs within dermatology, rheumatology, and gastroenterology in recent years.[1-5]

Oral JAKi have shown promising efficacy,[6-8] but the safety profile, particularly the risk of infections, needs to be further investigated. This was highlighted in the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study, which reported safety concerns of JAKi related to major adverse cardiovascular events, venous thromboembolism, malignancy, all-cause mortality, and infections.[9] During a median follow-up of 4.0 years, the study found serious infections to be more frequent with tofacitinib than with a tumor necrosis factor (TNF)-α inhibitor,

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mainly due to the incidence of herpes zoster virus (HZV) infections.[9]

In this systematic review and meta-analysis, we estimated the risk of infection during treatment with oral JAKi compared to placebo in published phase 2 and 3 randomized placebo-controlled trials (RCTs).

MATERIALS AND METHODS

Protocol and registration

A study protocol was conducted before initiating the study and registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD 42024513529) and performed based on the Preferred Items for Systematic Review and Meta-Analysis guidelines.[10]

CAPSULE SUMMARY

- Oral Janus Kinase inhibitors (JAKi) are effective; however, an increased risk of infections has previously been proposed.
- We found an increased risk of infections compared to placebo across all indications and dermatologic indications. Thus, highlighting the importance of screening high-risk patients prior to treatment initiation.

Data sources and search strategy

Two authors (D.I. and M.B.J.) independently screened 3 databases (PubMed, Embase, and Web of Science) from inception through February 2024 with the search string presented in Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/s86kr78xfp/1 consisting of words relevant for infections and JAKi.

The results were uploaded to the web tool Rayyan.[11] Duplicates were removed, and records were screened according to title and abstract by 2 reviewers (D.I. and M.B.J.). Studies that met the inclusion criteria and studies with unclear eligibility based on title or abstract were selected for full-text assessment. Any disagreement between the 2 reviewers was resolved through discussion. In the absence of a consensus, the senior author (F.A.) was consulted.

Study selection and data extraction

To be eligible for inclusion, studies had to be phase 2 or phase 3 RCTs comparing JAKi to placebo and report data on the occurrence of infections during the study period. Studies had to be original and report the number of patients receiving the JAKi and placebo and the number of patients developing infection(s). Thus, non-RCTs were excluded. Studies conducted with topical JAKi were excluded. Studies allowing an active, systemic treatment other than JAKi, eg, concomitant treatment with methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine, were excluded. Studies allowing topical therapies were included. In case a study population was included in more than 1 publication, the newest or most comprehensive study was included. The reference lists of included studies were screened for additional studies.

Outcomes

The following outcomes were extracted where possible: infections overall, fungal overall, viral overall (all reported viral infections including HZV and herpes simplex virus [HSV]), HZV, HSV, tuberculosis, nasopharyngitis, urinary tract infections, folliculitis, hepatitis, pneumonia, respiratory tract infections, and candidiasis.

Statistical analysis

Data analysis was performed using StatsDirect version 2.8.0 (StatsDirect). An inverse variance weighted random-effects meta-analysis was performed using the DerSimonian and Laird method.[12] A relative risk (RR) meta-analysis with 95% CIs was performed to assess the association between JAKi treatment and infections. The heterogeneity between the included studies was assessed using the Cochrane Q and I^2 statistics with a significance level of 0.05. Publication bias was assessed using funnel plots and Egger tests. A random-effects meta-analysis was used to estimate pooled proportions due to expectancy of a high level of heterogeneity. Meta-analysis was performed if an outcome was reported in ≥3 articles. The main analysis investigated the risk of infections across all indications. Subanalyses were performed according to dermatologic and nondermatologic indications and drug and drug targets where possible. A sensitivity analysis was performed on dermatologic indications excluding studies on patients with atopic dermatitis (AD). The risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool.[13] The following domains were assessed: bias due to sequence generation, allocation concealment, blinding process, incomplete results, selective reporting, and other biases. Based on these parameters, the RCTs were classified as low, moderate/unclear, or high risk of bias.

RESULTS

Search results

A total of 21,064 studies were identified through database search (PubMed = 4,641, Embase = 12,293, and Web of Science = 4130). After removing

Abbreviations used:

HSV:	herpes simplex virus
HZV:	herpes zoster virus
IMIDs:	immune-mediated inflammatory diseases
JAK:	Janus kinase
JAKi:	JAK inhibitor
ORAL:	Oral Rheumatoid Arthritis Trial
RCT:	randomized, placebo-controlled trials
TNF:	tumor necrosis factor

duplicates, 13,567 nonduplicate articles were screened for title and abstract, and 93 full-text articles were read. Of these, 69 were excluded for reasons resulting in 26 studies that were eligible for inclusion in the quantitative analysis. Forty-eight studies were excluded because they either had an active treatment in the comparator group or allowed concomitant treatment with immunosuppressants (Fig 1).

Qualitative assessment of the included studies

A total of 26 studies[7,8,14-37] published between 2012 and 2023 were included yielding a total of 9389 patients (n = 6800 JAKi and n = 2589 placebo). The average follow-up period was 24.9 weeks. The characteristics of the included studies are available in Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/s86kr78xfp/1. In total, 19 studies[7,8,14-30] were conducted in patients with dermatologic diseases including 3 in alopecia areata,[8,14,15] 6 in psoriasis,[7,16-20] 8 in AD,[21-28] and 1 each in vitiligo[29] and chronic hand eczema.[30] For nondermatologic indications, 7 studies[31-37] were included involving 2 in COVID-19[36,37] and 1 in each of Crohn's disease,[32] ulcerative colitis,[31] rheumatoid arthritis,[33] ankylosing spondylitis,[34] and psoriatic arthritis.[35] Patients were treated with baricitinib in 5 studies,[8,17,26-28] upadacitinib in 4 studies,[21,25,32,34] tofacitinib in 4 studies,[18-20,35] abrocitinib in 3 studies,[22-24] ritlecitinib in 3 studies,[14,29,31] deucravacitinib in 2 studies,[7,16] and 1 in each of brepocitinib,[31] gusacitinib,[30] ivarmacitinib,[15] nezulcitinib,[36] and peficitinib[33] (Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/s86kr78xfp/1).

All studies were assessed as having low risk of bias according to the Cochrane Collaboration Risk of Bias Tool (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/s86kr78xfp/1). Based on Cochrane Q and I^2, the heterogeneity was generally low (Supplementary Table V, available via Mendeley at https://data.mendeley.com/datasets/s86kr78xfp/1), and no publication bias was detected based on Egger test (Supplementary Table VI, available via Mendeley at https://data.mendeley.com/datasets/s86kr78xfp/1). No publication bias was detected in the funnel plots (Supplementary Figs 1 to 3, available via Mendeley at https://data.mendeley.com/datasets/s86kr78xfp/1).

Risk of infections across indications

Based on 26 studies[7,8,14-37] comprising 6800 JAKi-treated patients, and 2589 placebo-treated patients, the pooled RR of infections overall was 1.39 (95% CI 1.096-1.76, P = .0067) (Table I, and Fig 2). Any infections occurred in 1637 out of 6800 patients (24%) treated with JAKi and 382 out of 2589 patients (14.75%) treated with placebo. No other significant associations were found (Table I). No studies reported cases of tuberculosis and hepatitis, and not enough data were available to conduct meta-analysis on the risk of developing candidiasis.

Risk of infections in dermatologic indications

In dermatologic indications, the RR of developing any infection was 1.46 (95% CI, 1.10-1.93, P = .0097) based on 19 studies[7,8,14-30] including 7929 patients (n = 5745 JAKi and n = 2184 placebo) (Table I and Fig 3). Any infections were reported in 1415 patients out of 5745 JAKi-treated patients (24.63%), while 320 infections were reported in 2184 placebo-treated patients (14.65%). When studies conducted on patients with AD were removed, the RR of developing infections was nonsignificant (RR: 1.25, 95% CI 0.94-1.67, P = .11) (Table I).

The risk of HZV was assessed in 12 studies[7,8,16-18,20-24,27,28] yielding a pooled RR of 2.33 (1.04-5.20, P = .037). HZV occurred 50 times in 4190 JAKi-treated patients (1.19%), and 3 times in 1708 placebo-treated patients (0.17%). In sensitivity analysis on dermatologic indications without AD, the RR of HSV was insignificant (RR: 2.27, 95% CI 0.72-7.085, P = .73). No significantly increased or decreased risk of other individual infections was found (Table I).

Risk of infections in nondermatologic indications

Based on 7 studies,[31-37] the RR of infections overall for nondermatologic patients was 1.13 (95% CI, 0.85-1.52). The RR of any viral infection was 0.64 (95% CI, 0.17-2.44) based on 4 studies,[31-34] including an estimate of 0.64 (95% CI, 0.17-2.44) for HZV based on 3 studies.[31-33] No significant associations between the risk of infections and treatment with JAKi in nondermatologic indications were found (Table I). The risk of respiratory tract infection, folliculitis, hepatitis, pneumonia, tuberculosis, HSV, fungal overall, and candidiasis could not be assessed since the criteria of studies reporting the infections were not met.

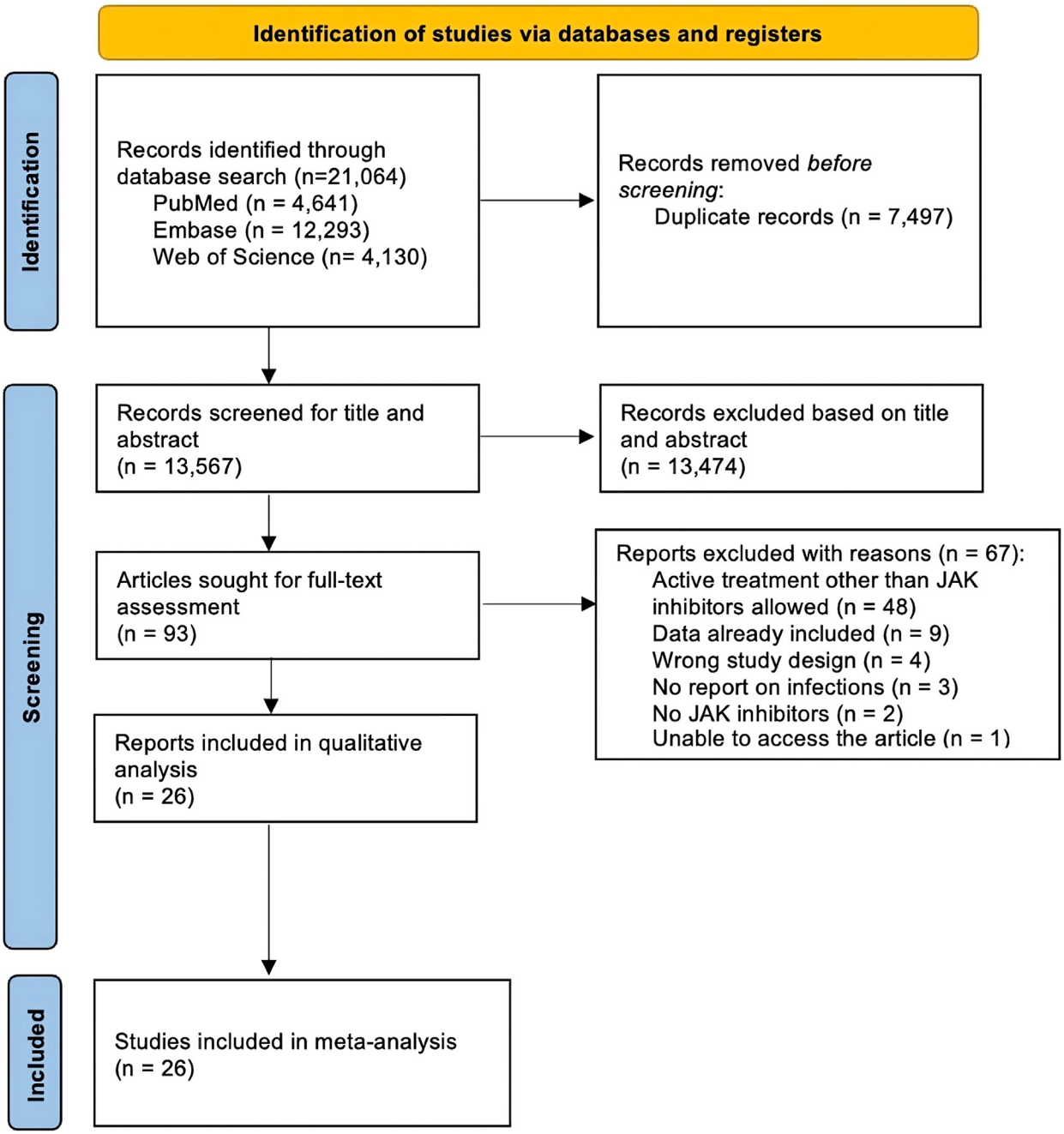

Fig 1. Preferred Items for Systematic Review and Meta-Analysis flowchart. *JAK*, Janus kinase.

Risk of infections in different JAKi and according to drug target

For abrocitinib, the RR of infections overall was 2.23 (95% CI, 0.91-5.43) based on 3 studies.[22-24] For baricitinib, the RR of developing infections overall was 1.24 (95% CI, 0.65-2.36) based on 5 studies.[8,17,26-28] The risk of infections overall during treatment with ritlecitinib was reported in 4 studies[14,29,31,38] yielding a RR of 1.00 (95% CI, 0.66-1.52). For tofacitinib, the RR of infections overall was 1.35 (95% CI, 0.78-2.33) based on 4 studies.[18-20,35] No significant associations were found for infections during treatment with different JAKi compared to placebo (Table I).

Subanalyses according to the specific drug target were conducted where possible. Comparative analyses according to the drug target revealed no significant increase or decrease in the risk of infections compared with the placebo (Table I).

Table I. Relative risk of different infections according to drug and indication

Type of infection	Number of studies	Random-effects model			Fixed-effects model		
		Relative risk	95% CI	*P* value	Relative risk	95% CI	*P* value
Overall							
Infections overall	26	1.39	1.096-1.76	**.0067**	1.58	1.42-1.74	**<.0001**
Viral infections overall	16	1.42	0.75-2.68	.27	1.77	1.25-2.52	**.0012**
Fungal overall	3	1.14	0.24-5.28	.86	1.24	0.28-5.41	.76
Herpes simplex virus	10	1.02	0.45-2.32	.95	1.53	0.93-2.51	.093
Herpes zoster virus	15	1.71	0.84-3.51	.13	2.37	1.25-4.49	**.0075**
Nasopharyngitis	19	1.15	0.87-1.52	.31	1.33	1.33-1.57	**.0005**
Respiratory tract infection	18	1.06	0.71-1.58	.76	1.11	0.92-1.34	.27
Pneumonia	7	0.95	0.29-3.11	.93	1.18	0.38-3.60	.77
Urinary tract infection	10	0.93	0.54-1.62	.81	1.10	0.65-1.85	.71
Folliculitis	9	1.12	0.30-4.18	.85	1.68	1.03-2.77	**.039**
Dermatologic indications							
Infections overall	19	1.46	1.10-1.93	**.0097**	**1.65**	**1.48-1.84**	**<.0001**
Viral infections overall	12	1.68	0.80-3.48	.16	1.92	1.33-2.77	**.0005**
Herpes simplex virus	9	1.01	0.41-2.49	.96	1.55	0.93-2.57	.085
Herpes zoster virus	12	2.33	1.04-5.20	**.037**	2.86	1.39-5.87	**.0041**
Nasopharyngitis	15	1.15	0.85-1.57	.34	1.36	1.15-1.61	**.0003**
Respiratory tract infection	16	1.058	0.69-1.62	.79	1.09	0.90-1.33	.36
Pneumonia	6	1.17	0.32-4.18	.80	1.36	0.40-4.60	.61
Urinary tract infection	7	1.049	0.57-1.90	.87	1.28	0.72-2.28	.38
Folliculitis	9	1.12	0.30-4.18	.85	1.68	1.03-2.77	**.039**
Dermatologic indications without atopic dermatitis							
Infections overall	11	1.25	0.94-1.67	.11	1.41	1.23-1.62	**<.0001**
Viral infections overall	5	2.14	0.70-6.50	.17	2.71	1.08-6.82	**.033**
Herpes simplex virus	3	0.68	0.073-6.29	.73	1.17	0.28-4.77	.82
Herpes zoster virus	6	2.27	0.72-7.085	.15	2.70	0.90-8.06	.074
Nasopharyngitis	9	1.11	0.75-1.64	.58	1.33	1.08-1.64	.0066
Respiratory tract infection	11	1.32	1.027-1.71	**.030**	**1.38**	**1.07-1.78**	**.011**
Pneumonia	3	1.20	0.207-7.028	.83	1.56	0.30-8.00	.59
Urinary tract infection	5	0.93	0.47-1.84	.84	1.01	0.52-1.97	.96
Folliculitis	8	0.95	0.25-3.62	.94	1.54	0.92-2.58	.09
Nondermatologic indications							
Infections overall	7	1.13	0.85-1.52	.37	1.15	0.88-1.50	.29
Viral infections overall	4	0.64	0.17-2.44	.51	0.65	0.18-2.30	.51
Herpes zoster virus	3	0.51	0.10-2.63	.42	0.76	0.17-3.32	.71
Nasopharyngitis	3	1.03	0.43-2.45	.92	1.08	0.45-2.54	.85
Urinary tract infection	3	0.48	0.11-2.01	.31	0.44	0.11-1.81	.26
Specific drugs across indications							
Abrocitinib (only atopic dermatitis)							
Infections overall	3	2.23	0.91-5.43	.076	2.86	2.04-4.00	**<.0001**
Viral overall	3	0.62	0.036-10.71	.74	1.09	0.56-2.14	.78
Herpes simplex virus	3	0.62	0.031-12.48	.75	1.50	0.46-4.82	.49
Herpes zoster virus	3	1.04	0.098-11.14	.97	1.75	0.54-5.70	.34
Respiratory tract infection	3	2.23	0.91-5.43	.076	2.86	2.04-4.00	**<.0001**
Baricitinib (1 psoriasis, 4 atopic dermatitis)							
Infections overall	5	1.24	0.65-2.36	.49	1.57	1.30-1.90	**<.0001**
Viral overall	5	1.92	0.98-3.73	.053	2.12	1.30-3.46	**.0024**
Herpes simplex virus	5	1.25	0.48-3.26	.63	1.61	0.91-2.85	.099
Herpes zoster virus	4	2.32	0.51-10.62	.27	3.71	0.89-15.45	.071
Nasopharyngitis	4	0.87	0.34-2.22	.78	1.33	0.93-1.90	.11
Respiratory tract infection	4	1.12	0.64-1.97	.67	1.22	0.70-2.14	.46
Pneumonia	3	1.08	0.17-6.59	.93	1.11	0.18-6.68	.90
Urinary tract infection	3	1.45	0.43-4.87	.54	1.91	0.69-5.23	.20

Continued

Table I. Cont'd

Type of infection	Number of studies	Random-effects model			Fixed-effects model		
		Relative risk	95% CI	*P* value	Relative risk	95% CI	*P* value
Ritlecitinib (2 alopecia areata, 1 vitiligo, 1 ulcerative colitis)							
Infections overall	4	1.00	0.66-1.52	.96	0.98	0.75-1.29	.90
Nasopharyngitis	4	1.00	0.44-2.23	.99	1.07	0.70-1.62	.73
Tofacitinib (3 psoriasis, 1 psoriatic arthritis)							
Infections overall	4	1.35	0.78-2.33	.28	1.36	1.02-1.82	**.035**
Nasopharyngitis	3	0.94	0.37-2.42	.91	0.99	0.60-1.62	.98
Respiratory tract infection	4	1.59	0.78-3.22	.19	1.71	1.01-2.92	**.045**
Upadacitinib (1 Crohn's disease, 1 ankylosing spondylitis, 1 atopic dermatitis)							
Infections overall	3	1.14	0.56-2.31	.70	1.13	0.79-1.60	.48
Viral overall	3	0.86	0.13-5.39	.87	1.00	0.24-4.19	.99
Drug target							
JAK1							
Infections overall	8	1.66	0.95-2.88	.072	1.94	1.54-2.44	**<.0001**
Viral infections overall	6	0.75	0.15-3.75	.73	1.11	0.60-2.05	.73
Herpes simplex virus	3	0.74	0.047-11.67	.83	1.70	0.50-5.77	.39
Herpes zoster virus	5	1.51	0.40-5.66	.53	2.08	0.72-5.98	.17
Nasopharyngitis	4	1.31	0.82-2.10	.25	1.35	0.92-2.00	.12
Respiratory tract infection	5	0.51	0.12-2.067	.35	0.57	0.41-0.81	**.0018**
Urinary tract infection	3	0.89	0.20-4.00	.88	0.81	0.20-3.14	.76
JAK1 and JAK2							
Infections overall	6	1.16	0.62-2.19	.62	1.55	1.29-1.87	**<.0001**
Viral infections overall	5	1.92	0.98-3.73	.053	2.12	1.30-3.46	**.0024**
Herpes simplex virus	5	1.25	0.48-3.26	.63	1.61	0.91-2.85	.099
Herpes zoster virus	4	2.32	0.51-10.62	.27	3.71	0.89-15.45	.071
Nasopharyngitis	4	0.87	0.34-2.22	.78	1.33	0.93-1.90	.11
Respiratory tract infection	4	1.12	0.64-1.97	.67	1.22	0.70-2.14	.46
Pneumonia	4	1.00	0.20-4.85	.99	1.03	0.21-4.91	.96
Urinary tract infection	3	1.45	0.43-4.87	.54	1.91	0.69-5.23	.20
JAK1 and JAK3							
Infections overall	4	1.35	0.78-2.33	.28	1.36	1.02-1.82	**.035**
Nasopharyngitis	3	0.94	0.37-2.42	.91	0.99	0.60-1.62	.98
Respiratory tract infection	4	1.59	0.78-3.22	.19	1.71	1.01-2.92	**.045**

Values marked in bold indicates statistical significance (*P* values <.05).
JAK, Janus kinase.

DISCUSSION

This systematic review and meta-analysis found an increased risk of overall infections during treatment with JAKi compared to placebo in phase 2 and phase 3 RCTs across all indications. Sub-analyses indicated potentially increased risks for both dermatologic and nondermatologic conditions, but only the results for dermatologic indications were statistically significant. An increased risk of HZV in dermatologic patients was identified. No significantly increased or decreased risk of infections were observed according to the mode of action.

A systematic review and meta-analysis by Yang et al from 2023 in patients with psoriasis and psoriatic arthritis found a significantly increased risk of infections (RR 1.20, 95% CI 1.07-1.35, $P = .002$) with JAKi compared to placebo.[39] This is consistent with the findings in our study, thus further highlighting the risk of infections during treatment with JAKi. In addition, our study included more diseases than Yang et al, and subanalyses were conducted on dermatologic and nondermatologic indications to further exploit the potential risk of infections. However, a greater number of studies with dermatologic indications were included compared to nondermatologic indications. This may be because JAKi are often administered in combination therapy in other indications, and these studies were therefore excluded. However, when including studies that did not allow concomitant treatment, we obtained a risk

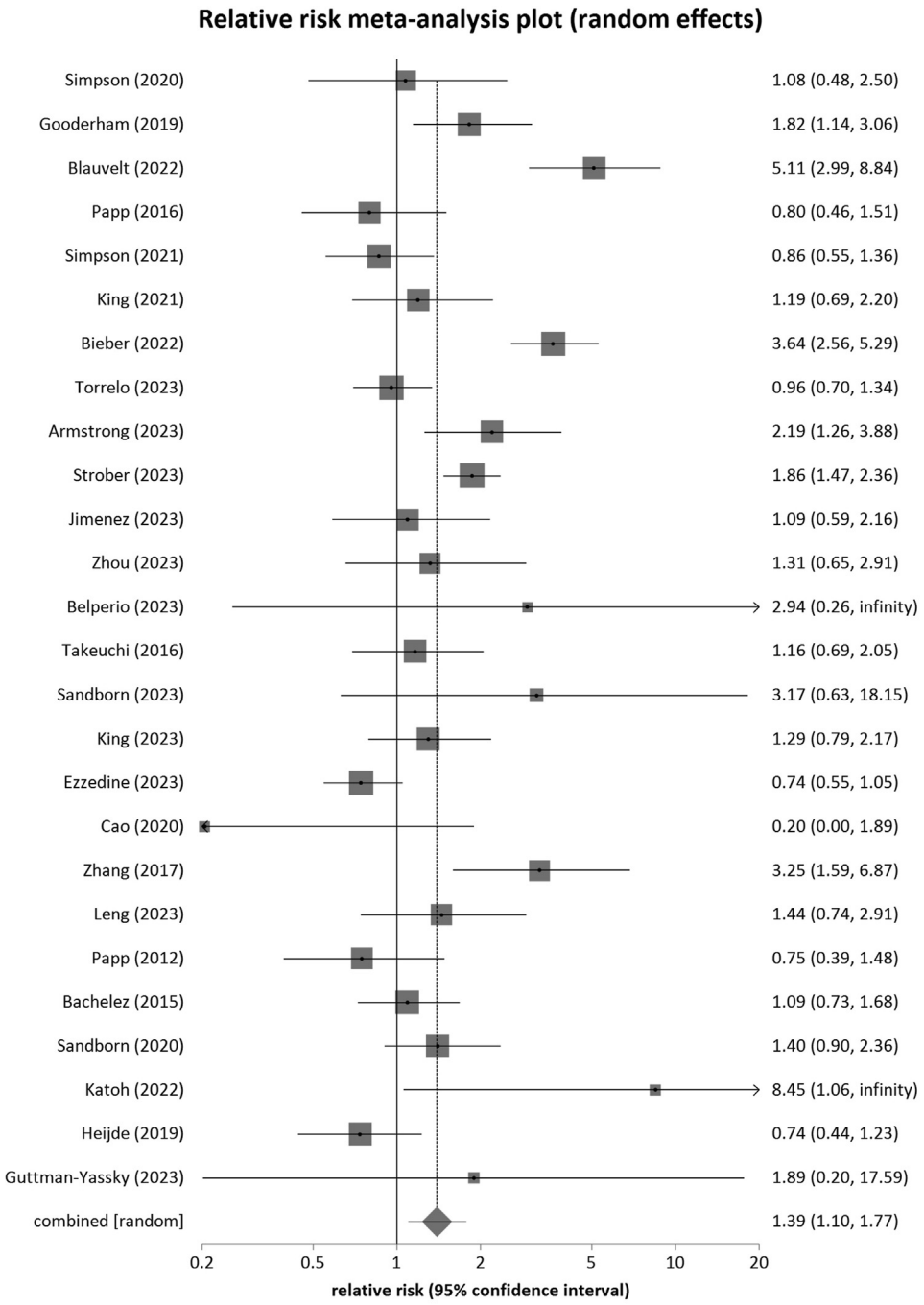

Fig 2. Forest plot for infections overall across all indications.

estimate that largely reflects the risk of infections associated with JAKi. Furthermore, previous studies have reported an increased baseline risk of infections for IMIDs[40,41]; however, these studies suggest a low risk of infections. Thus, extrapolating the RRs of this study to clinically relevant risk of infections may be challenging.

Nevertheless, the increased risk of infections observed aligns with the known immunomodulatory effect of JAKi, as they disrupt cytokine signaling pathways involved in immune regulation, leading to immunosuppression.[42] A cohort study from 2019 observed a gradual decline in lymphocytes in patients with rheumatoid arthritis undergoing treatment with tofacitinib. The study also identified a potential association between decreased lymphocyte counts and increased infection rates, offering a plausible explanation for the increased risk of

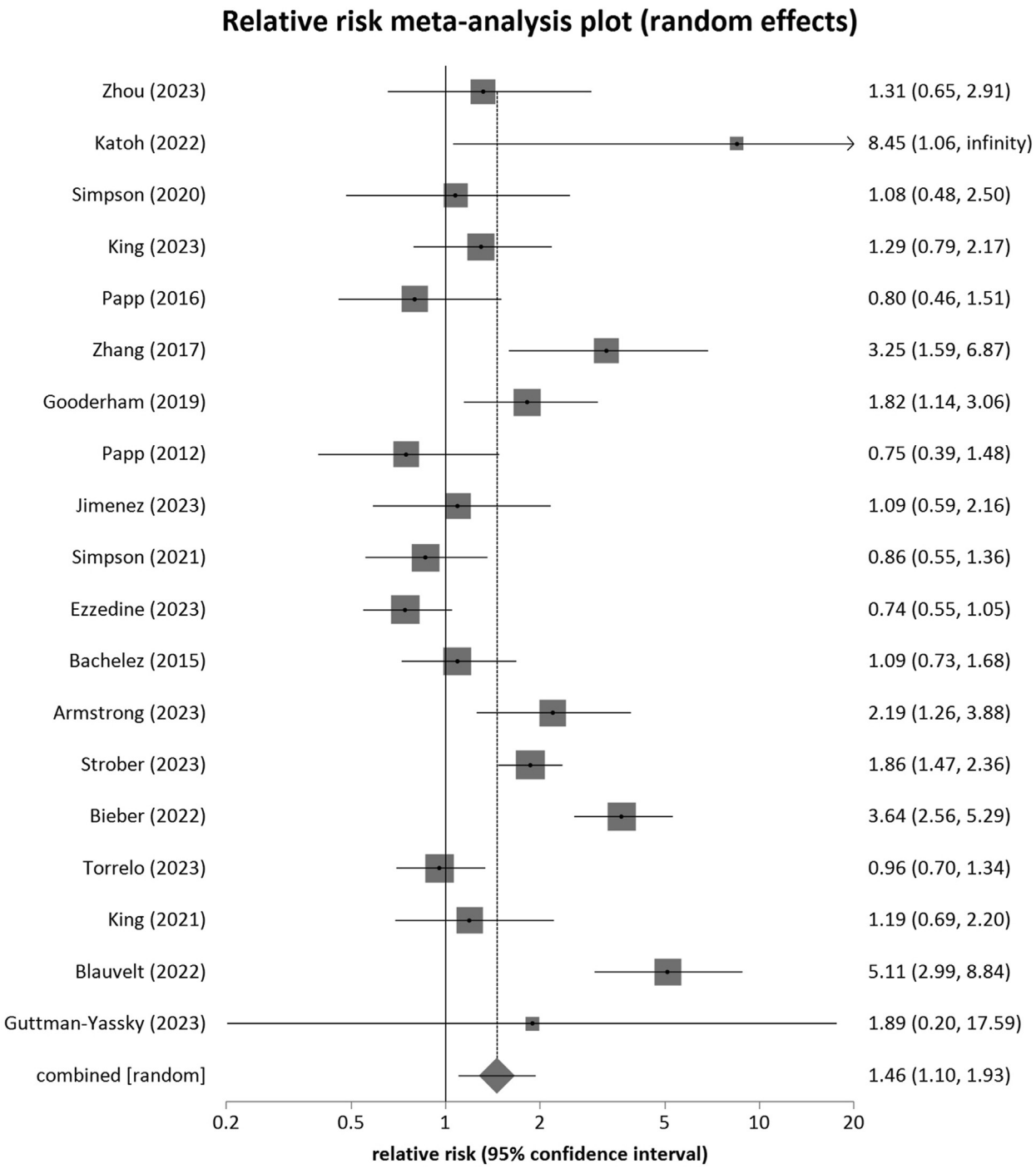

Fig 3. Forest plot for infections overall in dermatologic indications.

infections during treatment with JAKi.[43] However, it is important to recognize that the infectious risk associated with different JAKi and different indications may vary. In the current study, no significant association between individual JAKi and risk of infection was found. However, previous studies have reported tendencies for abrocitinib and RTIs, most recently by Samuel et al in 2023.[44] For dermatologic indications, we found an increased risk of HZV infection during treatment with JAKi compared to placebo. However, in sensitivity analysis excluding studies conducted on patients with AD, this finding was no longer significant. This suggests that patients with AD may be a primary driver of the increased risk of HZV infection. Moreover, most of the infections can be prevented

with an increased focus on vaccination and intensified screening of high-risk patients prior to treatment initiation.

The ORAL surveillance study reported safety concerns of tofacitinib to an increased risk of, among other things, infections.[9] Especially the incidence of opportunistic infections including, HZV and tuberculosis were higher with tofacitinib than with TNF-α inhibitors. However, important differences should be emphasized when interpreting the results. Firstly, the median follow-up of ORAL was 4.0 years, thus providing longer follow-up than the RCTs presented in this study. We only included RCTs allowing no concomitant treatment. In contrast, the ORAL study compared tofacitinib to an active comparator and allowed background therapy with methotrexate, thus providing favorable conditions for TNF-α inhibitors. While the results of our study should not be extrapolated to long-term risk of infections following treatment with JAKi, the results highlight the potentially increased risk of infections associated with JAKi across multiple indications.

Several factors could contribute to the increased risk of infections with JAKi compared to placebo, such as the specific drug, treatment duration, dosage, disease duration, and patient characteristics like age and comorbidities.[45] Although JAKi are effective, safety concerns and a lack of comprehensive knowledge about their adverse effects often make them a secondary choice, prescribed typically when biologics are unsuitable. This underscores the need for improved infection screening and monitoring protocols during JAKi treatment. Physicians should assess each patient's individual risk factors to personalize the treatment plan effectively. While most infections reported are mild, further real-world evidence is required to better understand the long-term infection risks associated with JAKi.

Strengths and limitations

This study's strengths include a large patient cohort and a pre-established protocol describing inclusion criteria and standardized data extraction methods. By pooling data from multiple RCTs, we enhanced statistical power, enabling more robust analyses and precise risk estimates of infections associated with JAKi treatment alone, as only studies comparing oral JAKi to placebo were considered.

However, there are limitations. The results derived from phase 2 and phase 3 RCTs with strict criteria should be cautiously applied to clinical practice. The sample of studies was too small to report infection risks for each drug, with only 7 studies focusing on nondermatologic conditions. Furthermore, an increased awareness of HZV in dermatologic RCTs compared to nondermatologic ones may explain the higher observed risk of HZV in dermatologic indications. Lastly, the short follow-up periods in the included RCTs limit our understanding of the long-term infection risks associated with JAKi.

CONCLUSION

In this systematic review and meta-analysis, we report a significantly increased risk of developing infections overall during treatment with JAKi compared to placebo across indications. In subanalyses, we identified an increased risk of any infections and HZV in dermatologic indications. No significantly increased or decreased risk of infections was found in nondermatologic indications, as well as in individual JAKi or according to drug targets. Prospective studies providing real-world evidence are needed to clarify the long-term safety of this novel treatment group.

Conflicts of interest

Dr Loft has been an honorary speaker for Eli Lilly, Janssen Cilag, and Sandoz. Dr Skov has been an investigator, speaker, and/or advisor for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Novo Nordisk, Pfizer, Sanofi Genzyme, Takeda, and UCB. Dr Elberling has been a speaker and/or advisor for Sanofi, Pfizer, Leo Pharma, Novartis, GSK, AstraZeneca, Almirall, AbbVie, Eli Lilly, Galderma, ALK, Takeda, and CSL Vifor. Drs Isufi, Jensen, and Alinaghi have no conflicts of interest to declare.

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