Received: 22 November 2022 | First decision: 15 December 2022 | Accepted: 17 December 2022

DOI: 10.1111/apt.17379

AP&T Alimentary Pharmacology & Therapeutics WILEY

Systematic review with network meta-analysis: Risk of Herpes zoster with biological therapies and small molecules in inflammatory bowel disease

Shahida Din[1] | Christian P. Selinger[2] | Christopher J. Black[2] | Alexander C. Ford[2,3]

[1]Edinburgh Inflammatory Bowel Diseases Unit, Western General Hospital, Edinburgh, UK

[2]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK

[3]Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK

Correspondence
Alexander C. Ford, Leeds Gastroenterology Institute, Room 125, 4th Floor, Bexley Wing, St. James's University Hospital, Beckett Street, LS9 7TF Leeds, UK.
Email: alexf12399@yahoo.com

Summary

Background: Biologics and small molecules for inflammatory bowel disease (IBD) may increase infection risk. Herpes zoster causes acute and long-term symptoms, but vaccination is not recommended in patients with IBD, unless >50 years of age.

Aims: To examine risk of Herpes zoster infection with all licensed biologics and small molecules for IBD using network meta-analysis.

Methods: We searched the literature to 4th October 2022, for randomised controlled trials of these drugs in luminal Crohn's disease or ulcerative colitis reporting data on occurrence of Herpes zoster infection during follow-up. We used a frequentist approach and a random effects model, pooling data as relative risks (RRs) with 95% confidence intervals (CIs).

Results: We identified 25 trials (9935 patients). Only tofacitinib 10 mg b.d. (RR = 6.90; 95% CI 1.56–30.63, number needed to harm (NNH) = 97; 95% CI 19–1022) and upadacitinib 45 mg o.d. (RR = 7.89; 95% CI 1.04–59.59, NNH = 83; 95% CI 10–14,305) were significantly more likely to increase risk of Herpes zoster infection. Janus kinase inhibitors were the most likely drug class to increase risk of infection, and risk increased with higher doses (RR with lowest dose = 3.16; 95% CI 1.02–9.84, NNH = 265; 95% CI 65–28,610, RR with higher dose = 5.91; 95% CI 2.21–15.82, NNH = 117; 95% CI 39–473).

Conclusions: In a network meta-analysis, the janus kinase inhibitor tofacitinib, and all janus kinase inhibitors considered as a class, were most likely to increase risk of Herpes zoster infection. Risk increased with higher doses.

As part of AP&T'S peer-review process, a technical check of this meta-analysis was performed by Dr Y. Yuan. The Handling Editor for this article was Professor Sreedhar Subramanian, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), which constitute the two main types of inflammatory bowel disease (IBD), cause chronic gastrointestinal symptoms, disability and impairments in quality of life and psychological health.[1,2] After the failure of first-line medical therapies, treatment of moderate to severe IBD requires immunosuppression with biological therapies, directed against pro-inflammatory cytokines or small molecules, targeting janus kinase or sphingosine-1-phosphate receptors. Although these treatments are highly effective,[3,4] they may carry a risk of infective complications, including opportunistic infections.[5,6]

The Varicella-zoster virus causes chickenpox/varicella and shingles/Herpes zoster.[7] Herpes zoster is caused by reactivation of latent Varicella-zoster virus infection, often during times of reduced immunity.[7] During the initial acute eruptive phase, painful vesicles develop, which may then burst and dry out. During this acute phase, lasting up to 4 weeks, patients experience severe pain, which is often refractory to standard analgesics. Patients may also experience longer-lasting symptoms of dysaesthesia, paraesthesia and neuropathic pain.[7] Herpes zoster is associated with substantial impairment in quality of life,[8] and is common, with an estimated annual incidence of 1.85–3.9 cases per 1000 in the general population.[9] There is a 20% to 30% risk of Herpes zoster during an individual's lifetime, and this increases with age, and in those with impaired immune function.[10] A meta-analysis of six cohort studies reported that patients with IBD had a 1.68-fold increased risk of developing Herpes zoster infection.[11]

Vaccination against Herpes zoster is available in the form of a live attenuated Varicella-zoster virus vaccine (Zostavax; Merck) and a recombinant non-live vaccine (Shingrix, GlaxoSmithKline),[7] but these are not currently recommended in patients with IBD, unless over the age of 50 years.[12] Zostavax is indicated for immunisation of individuals ≥50 years of age or older.[13] Shingrix has a licence for patients >50 years and patients >18 years who are at risk of Herpes zoster infection,[14] such as those who are immunocompromised due to disease or therapy. Given the potential for long-term sequelae arising from Herpes zoster infection, it is important to understand which patients with IBD are most at risk of infection, and who may therefore benefit from vaccination. As immunosuppressant drugs may increase the risk of infection, we aimed to assess the relative safety of all licensed biologics and small molecules in patients with IBD, in terms of occurrence of Herpes zoster infection, in a network meta-analysis of randomised controlled trials (RCTs).

2 | METHODS

2.1 | Search strategy and selection criteria

We conducted a search of MEDLINE (1946 to 4th October 2022), EMBASE and EMBASE Classic (1947 to 4th October 2022), and the Cochrane central register of controlled trials (issue 9, 2022). We also searched clinicaltrials.gov for recently completed trials or supplementary data for potentially eligible RCTs. In addition, we searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week and the Asian Pacific Digestive Week) between 2001 and 2022 to identify RCTs only in abstract form. Finally, we performed a recursive search of the bibliographies of all eligible articles.

To be eligible, RCTs had to examine efficacy of biological therapies (anti-tumour necrosis factor-α (TNF-α) antibodies (infliximab, adalimumab, certolizumab or golimumab), anti-integrin antibodies (vedolizumab or etrolizumab), anti-interleukin-12/23 antibodies (ustekinumab), or anti-interleukin-23 antibodies (risankizumab or mirikizumab)) or small molecules (janus kinase inhibitors (tofacitinib, filgotinib or upadacitinib) or sphingosine-1-phosphate receptor modulators (ozanimod)) at the doses taken through into phase III clinical trials and to report occurrence of Herpes zoster infection in all patients. Studies recruited adults (≥18 years) with luminal CD or UC (Table S1), and compared biological therapies or small molecules with placebo, or each other. Trials conducted only in patients with perianal CD were ineligible. Given that length of exposure to active treatment does not appear to influence risk of Herpes zoster occurrence,[15] we included trials with a minimum follow-up duration of 4 weeks. This meant that both induction of remission and maintenance of remission trials were eligible. However, some maintenance of remission trials re-randomised patients responding to active drug to either active drug or placebo following an induction of remission phase of the same trial. In these instances, we did not include data from both the induction of remission and maintenance of remission phases of the trial. Instead, we used the phase of the RCT with the most events of interest.

We identified studies on IBD with the terms: *inflammatory bowel disease*, or *Crohn's disease*, or *colitis*, or *ulcerative colitis* (both as medical subject headings and free text terms). We used the set operator AND to combine these with studies identified with the following terms: *infliximab*, *remicade*, *adalimumab*, *humira*, *certolizumab*, *cimzia*, *golimumab*, *simponi*, *vedolizumab*, *entyvio*, *etrolizumab*, *ustekinumab*, *stelara*, *risankizumab*, *mirikizumab*, *tofacitinib*, *xeljanz*, *filgotinib*, *upadacitinib* or *ozanimod* applying a clinical trials filter. There were no language restrictions. Two investigators (CJB and ACF) evaluated all abstracts identified, independently. We obtained potentially relevant papers and evaluated them in more detail, using pre-designed forms, to assess eligibility independently according to our pre-defined criteria. We translated foreign language papers, where required. We resolved disagreements between investigators through discussion.

2.2 | Outcome assessment

Our primary outcome was occurrence of Herpes zoster infection at any point during follow-up in each trial.

2.3 | Data extraction

Two investigators (CJB and ACF) extracted data from all eligible studies independently onto a Microsoft Excel spreadsheet (XP

professional edition; Microsoft Corp) as dichotomous outcomes (Herpes zoster infection or no Herpes zoster infection). We also extracted the following data for each trial, where available: country of origin, number of centres, disease type, disease location, or disease extent, and dose and dosing schedule of active therapy and placebo. As this was a safety analysis, we used the number of patients receiving at least one dose of the study drug as the denominator in the analysis, wherever possible. We compared results of the two investigators' data extraction with all discrepancies resolved by discussion.

2.4 | Risk of bias assessment

We used the Cochrane risk of bias tool for RCTs to assess quality and risk of bias.[16] Two investigators (CJB and ACF) performed this independently, with disagreements resolved by discussion. We recorded the method used to generate the randomisation schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

2.5 | Data synthesis and statistical analysis

We performed a network meta-analysis using the frequentist model, with the statistical package "netmeta" (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 4.0.2). We explored direct and indirect treatment comparisons of safety of each drug, reporting results according to the PRISMA extension statement for network meta-analyses.[17] Network meta-analysis gives more precise estimates than standard, pairwise, analyses,[18,19] and allows ranking of drug safety.[20]

To examine the symmetry and geometry of the evidence, we produced a network plot with node size corresponding to number of study subjects, and connection size corresponding to number of studies. We used Stata version 16 (Stata Corp.) to assess for publication bias or other small study effects, via comparison-adjusted funnel plots. These are scatterplots of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line suggests no evidence of publication bias, or small study effects.[21] We used a pooled relative risk (RR) of occurrence of Herpes zoster infection with 95% confidence intervals (CIs) to judge safety of each comparison tested, utilising a random effects model as a conservative estimate. Many meta-analyses use the I^2 statistic to measure heterogeneity, which ranges between 0% and 100%.[22] This statistic is easy to interpret, and does not vary with the number of studies. However, the I^2 value can increase with the number of patients included in the meta-analysis.[23] We, therefore, used the τ^2 measure from the "netmeta" statistical package to assess global statistical heterogeneity across all comparisons. Estimates of τ^2 of approximately 0.04, 0.16 and 0.36 represent low, moderate or high levels of heterogeneity, respectively.[24] We calculated the number needed to harm (NNH) with a 95% CI, using the formula NNH = 1/(assumed control risk × (1 − RR)).

We used the P-score, which is a value between 0 and 1, to rank all biological therapies and small molecules, versus placebo or each other. P-scores are based solely on point estimates and standard errors from the network estimates, measuring mean extent of certainty that one drug is safer than another, averaged over all competing drug.[25] In this meta-analysis, lower scores indicate a lower probability of the intervention being ranked as safest,[25] but magnitude of the P-score should be considered, as well as the rank. The mean P-score value is always 0.5. Therefore, if individual drugs cluster around 0.5 they are likely to be similarly safe. However, it is also important to take the RR and corresponding 95% CI for each comparison into account when interpreting the results, rather than relying on rankings alone.[26] In our primary analysis, we pooled data for all drugs, doses and dosing schedules separately, but we also performed a priori subgroup analyses according to individual, drug class, and, for janus kinase inhibitors, according to the magnitude of dose drug used in the RCTs (higher doses included filgotinib 200 mg o.d., tofacitinib 10 mg b.d. or upadacitinib 30 mg o.d. or 45 mg o.d. and lowest doses included filgotinib 100 mg o.d., tofacitinib 5 mg b.d., or upadacitinib 15 mg o.d.).

3 | RESULTS

The search strategy generated 12,457 citations. In total, we retrieved 61 articles for further assessment. We excluded 39 that did not report occurrence of Herpes zoster infection, many of which only reported adverse events occurring in ≥5% of trial participants, leaving 22 separate articles, reporting on 25 RCTs (Figure S1).[27–47] (NCT03281304) Three articles reported on six trials within the same publications,[29,36,43] and one trial (NCT03281304) was only available on clinicaltrials.gov, with the data for Herpes zoster infection obtained from the study results provided there. Agreement between investigators for trial eligibility was excellent (kappa statistic = 0.82). These 25 RCTs included 9935 patients, randomised to active drug or placebo (Table S2). Characteristics of individual studies are provided in Table S3 and risk of bias of all trials in Table S4. Thirteen RCTs were at low risk of bias across all domains.[27,28,32,35,37–40,42,44–46] (NCT03281304).

3.1 | Occurrence of herpes zoster according to individual drug

All 25 trials were included in this analysis.[27–47] (NCT03281304) In total, there were 72 (1.02%) cases of Herpes zoster infection among 7074 patients receiving active drug, compared with five (0.17%) in 2861 patients allocated to placebo. The network plot is provided in Figure 1. When data were pooled, there was low

heterogeneity ($\tau^2 = 0$), and the funnel plot appeared symmetrical (Figure S2). Upadacitinib 15 mg o.d. was most likely to increase risk of Herpes zoster infection (RR of occurrence of Herpes zoster infection = 13.09; 95% CI 0.74–230.24, P-score 0.19) (Figure 2), meaning that the probability of upadacitinib 15 mg o.d. being the safest drug was 19%. Upadacitinib 30 mg o.d. (RR = 12.58; 95% CI 0.71–221.34, P-score 0.20) tofacitinib 10 mg b.d. (RR = 6.90; 95% CI 1.56–30.63, P-score 0.24) and upadacitinib 45 mg o.d. (RR = 7.89; 95% CI 1.04–59.59, P-score 0.24) ranked similarly in second, third and fourth, respectively. However, only tofacitinib 10 mg b.d. and upadacitinib 45 mg o.d. were statistically significantly more likely to increase the risk of Herpes zoster infection than placebo. This equates to an NNH of 97 (95% CI 19–1022) with tofacitinib 10 mg b.d. and 83 (95% CI 10–14,305) with upadacitinib 45 mg o.d. All other drugs studied were no more likely to increase risk of Herpes zoster infection than placebo. After direct and indirect comparison, none of the active drugs were more likely to increase risk of Herpes zoster infection than each other.

When we pooled individual drugs together, irrespective of dose, excluding one trial comparing only two different doses of tofacitinib (NCT03281304), 24 trials contributed data.[27–47] When data were pooled, there was low heterogeneity ($\tau^2 = 0$). Upadacitinib was the most likely to increase risk of Herpes zoster infection (RR = 9.19; 95% CI 1.78–47.52, P-score 0.14, NNH = 70; 95% CI 12–734), followed by tofacitinib (RR = 4.71; 95% CI 1.06–20.82, NNH = 154; 95% CI 29–9537) (Figure 3). None of the other drugs studied were more likely to increase risk of Herpes zoster infection than placebo. After direct and indirect comparison, upadacitinib was more likely to increase risk of Herpes zoster infection than risankizumab, but there were no other significant differences (Table 1).

3.2 | Occurrence of Herpes zoster according to drug class

One trial comparing two different doses of tofacitinib was excluded from this analysis (NCT03281304). The network plot for the 24 included trials is provided in Figure S3.[27–47] There was low heterogeneity ($\tau^2 = 0$). Janus kinase inhibitors were the drug class most likely to increase risk of Herpes zoster infection (RR = 4.78; 95% 1.79–12.75, P-score 0.09, NNH = 151; 95% CI 49–724) (Figure 4). All other drug classes were no more likely to increase risk of Herpes zoster infection than placebo, with anti-IL-23 antibodies the safest class of drugs (P-score 0.72). After direct and indirect comparison, none of the drug classes were more likely to increase risk of Herpes zoster infection than each other (Table S5).

Given the results observed with janus kinase inhibitors as a class, we conducted a further analysis examining occurrence of Herpes zoster infection with the higher and lowest doses used in the 24 trials considered separately. Again, there was low heterogeneity between studies ($\tau^2 = 0$). In this analysis, higher dose janus kinase inhibitors were the most likely to increase risk of Herpes zoster

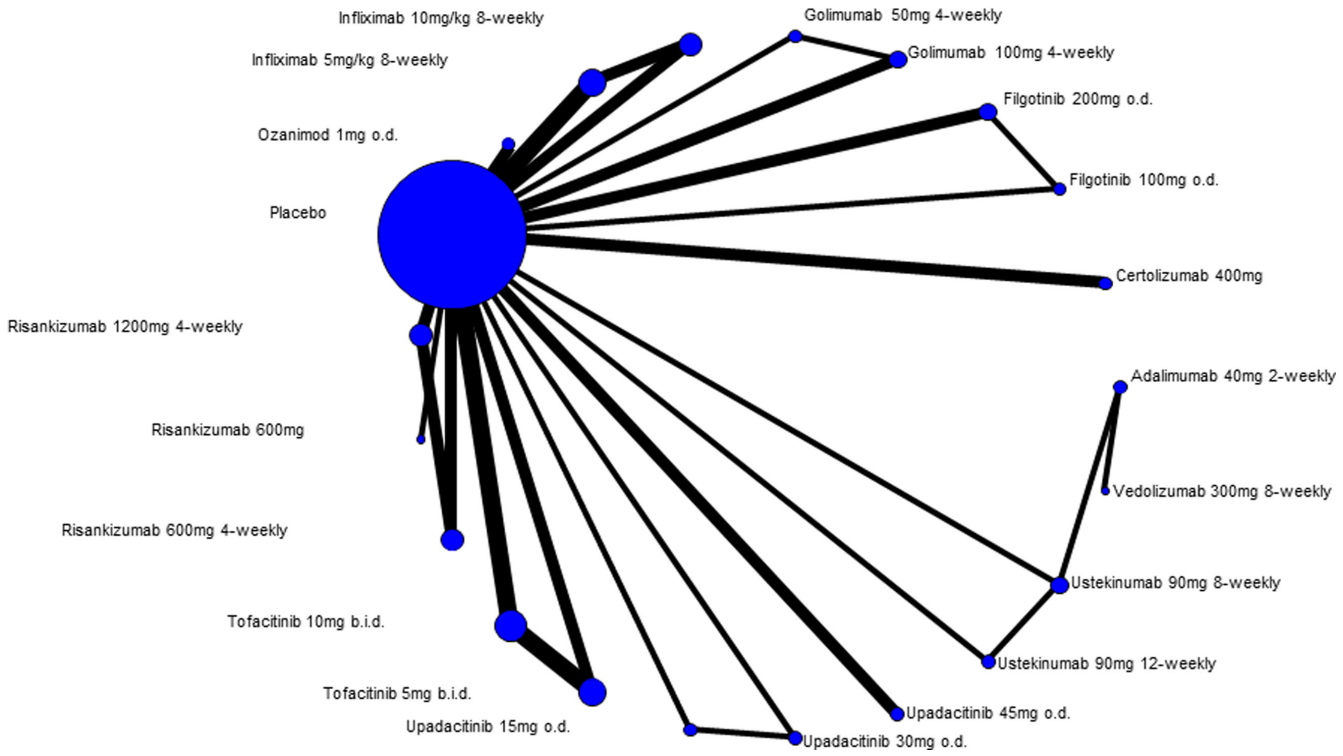

FIGURE 1 Network plot for occurrence of Herpes zoster according to individual drug, dose and dosing schedule. Circle (node) size is proportional to the number of study participants assigned to receive each drug. The line width (connection size) corresponds to the number of studies comparing the individual drugs.

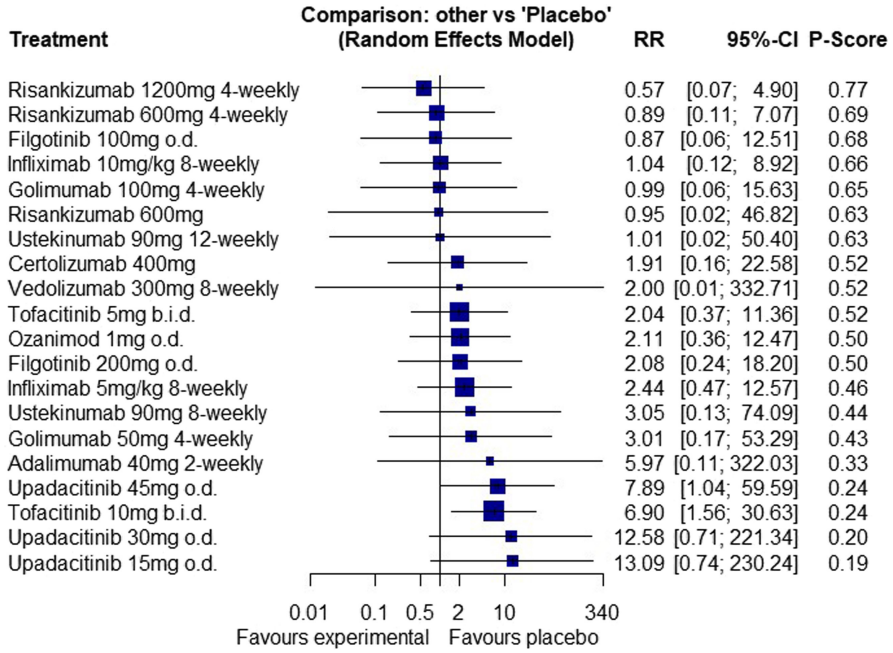

FIGURE 2 Forest plot for occurrence of Herpes zoster according to individual drug, dose and dosing schedule. The P-score is the probability of each drug being ranked as safest in the network.

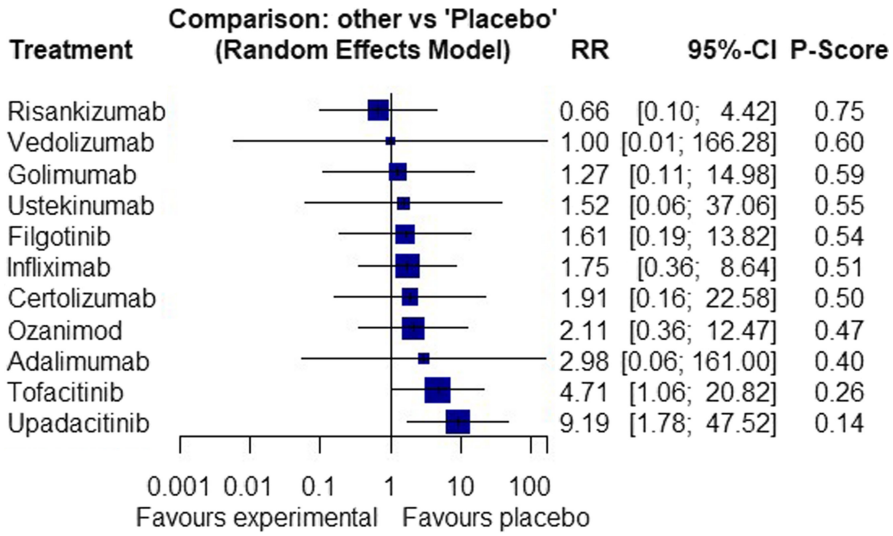

FIGURE 3 Forest plot for occurrence of Herpes zoster according to individual drug. The P-score is the probability of each drug being ranked as safest in the network.

infection (RR = 5.91; 95% CI 2.21–15.82, P-score 0.06, NNH = 117; 95% CI 39–473) (Figure 5), but the lowest doses of janus kinase inhibitors ranked second and were also more likely to increase risk of Herpes zoster infection than placebo (RR = 3.16; 95% CI 1.02–9.84, P-score 0.29, NNH = 265; 95% CI 65–28,610). After direct and indirect comparison, higher dose janus kinase inhibitors were more likely to increase risk of Herpes zoster infection than anti-IL-23 antibodies (Table S6).

4 | DISCUSSION

Patients with IBD are at an increased risk of Herpes zoster and immunosuppressive therapies may increase this risk further.[11] We report a systematic review and network meta-analysis examining risk of Herpes zoster infection with biological therapies and small molecules in IBD, including data from almost 10,000 patients in 25 separate trials. Overall, although upadacitinib 15 mg and 30 mg ranked as the most likely, and second most likely, drug to increase risk of Herpes zoster infection, these differences were not statistically significant versus placebo. However, tofacitinib 10 mg b.d., which ranked third, and upadacitinib 45 m o.d., which was fourth, were associated with a statistically significantly higher risk of Herpes zoster infection than placebo, with an NNH of 97 and 83, respectively. This means 97 more people would need to be treated with tofacitinib 10 mg b.d. than with placebo to cause one extra Herpes zoster infection. When we examined Herpes zoster infection according to drug class, anti-IL-23 antibodies were ranked as the safest drug. In contrast, janus kinase inhibitors were significantly more likely to increase risk of Herpes zoster infection. In our subgroup analysis according to dose of janus kinase inhibitor used, the risk of Herpes zoster infection was highest in trials using a higher

dose, with an NNH of 117, but was still statistically significantly higher in trials using the lowest doses. Finally, higher dose janus kinase inhibitors were more likely to increase risk of Herpes zoster infection than anti-IL-23 antibodies.

Limitations include the fact that only 13 of 25 induction RCTs were at low risk of bias across all domains. In addition, we excluded data from 39 trials, because they did not report adverse events in sufficient detail to ascertain whether Herpes zoster infections had occurred or not. One of the included trials of tofacitinib has yet to be published in full, and two of the RCTs of upadacitinib are only available as abstracts.[46,47] Some of the trials we identified were studying the maintenance of remission of IBD, and there were inherent differences in the design of these trials. Some of these RCTs treated patients through with active drug or placebo from study entry, whereas others re-randomised patients who responded to active drug following an induction of remission phase of the trial. Patients receiving placebo in these re-randomised studies were, therefore, exposed to active drug during induction therapy. This may mean occurrence of Herpes zoster infection has been overestimated in the placebo arm of these trials. As an example, in one trial of tofacitinib and one trial of ozanimod patients in the placebo arms developed Herpes zoster infection, but in both these trials placebo patients would have been exposed to active drug in the induction phase of the trial.[33,34] Therefore, of a total of five cases of Herpes zoster infection occurring in 2861 patients receiving placebo, two occurred in patients previously exposed to the active drug under study. As Herpes zoster infection was rare in all RCTs and some of the trials included a small number of participants, there is the possibility that biases due to sparse data or sampling error have been introduced.[48,49] The former is suggested by the large RR estimates and wide 95% CIs. There may also be other individual patient factors that make Herpes zoster more likely with the drugs we studied, such as age or concomitant medications, including glucocorticosteroids, or previous exposure to biologics. However, as we did not have access to individual patient-level data we could not assess these issues. Finally, our meta-analysis only included patients in clinical trials, who are unlikely to be representative of a real-world patient population, and in whom risk of Herpes zoster infection may be even higher.

A core assumption of any network meta-analysis relates to transitivity, where indirect comparisons between drugs assume that any patient included in the network could, theoretically, have been recruited to any of the trials and assigned to any of the drugs. This assumption can be jeopardised by underlying differences between RCTs. For instance, a trial conducted in the early 2000s may have recruited patients who were less likely to be vaccinated against Herpes Zoster than a trial conducted more contemporaneously. However, given there are no current recommendations to vaccinate all patients with IBD against Herpes zoster, we feel this is unlikely. Nevertheless, there may be other differences relating to design of trials that affect transitivity, as these differences are not protected by randomisation.

Although the incidence of Herpes zoster in the general population is clearly linked to age, available studies in patients with IBD lack sufficient detail to determine the exact risk of infection in younger patients. One Canadian population-based study of almost 40,000 patients with IBD reported 2158 incident cases of Herpes zoster.[50] Compared with the background population, the standardised incidence ratio was significantly higher across all age groups, except those aged >60 years, although the effect of IBD-related therapies was unaccounted for. Given that Herpes zoster infection causes troublesome symptoms and impairment in quality of life,[51] prevention in at-risk patients with IBD should be prioritised. Providing Herpes zoster vaccination to all patients with IBD prior to them commencing janus kinase inhibitors could mitigate against some of this additional risk, and this approach has been suggested by others.[52,53] As many of these patients are likely to be prescribed glucocorticosteroids or biologics at the time of a treatment decision to commence janus kinase inhibitors, they would require Shingrix, as Zostavax is a live attenuated vaccine. A meta-analysis comparing the efficacy of the live and recombinant vaccines reported that the recombinant vaccine was more effective, with a more durable response of up to 8 years after vaccination.[54]

The Advisory Committee on Immunization Practices conducted a systematic review and GRADE evaluation of the evidence for use of the recombinant vaccine in immunocompromised adults and concluded that it was effective for preventing Herpes zoster,[55] with efficacy ranging from 68.2% to 90.5% among several immunocompromised groups >18 years of age. Specifically in IBD, the full dose of the recombinant vaccine has been shown to reduce occurrence of shingles significantly in patients with IBD >50 years, compared with unvaccinated individuals.[56] In another study in patients with IBD ≥50 years of age, the rate of Herpes zoster infection in vaccinated patients was significantly lower compared with the general population.[57] This study also demonstrated that unvaccinated patients with IBD were six times more likely to develop Herpes zoster infection than the general population. Despite, the proven efficacy of recombinant zoster vaccine against a preventable disease, several barriers exist that prevent widespread adoption into healthcare programmes, such as cost, patient education and global availability. Shingrix has proven to be more effective and safer in immunocompromised patients and has become the vaccine of choice in multiple countries including the US, Canada, China and Germany.[58]

According to current UK government guidance,[59] vaccination against Herpes zoster is available for all individuals aged 70–79 years, with Shingrix reserved for those with severe immunosuppression, for the reasons mentioned earlier. However, in the UK, there is no explicit recommendation to vaccinate patients with IBD younger than 70 years, and such a strategy is not reimbursed currently,[59] despite the fact that patients with IBD, as well as rheumatoid arthritis and other immune-mediated diseases, are recognised as having an increased risk of Herpes zoster. Currently, the American College of Rheumatology strongly recommend the recombinant Herpes zoster vaccine in patients >18 years with rheumatological or musculoskeletal diseases on immunosuppressive medications (Table S7),[60] and the British Society of Rheumatology recommends vaccination in patients over 50 years of age starting biologics.[61] The European Medicines Agency Committee for

TABLE 1 League table for occurrence of Herpes zoster infection according to individual drug

RIS	0.66 (0.10–4.42)				
0.66 (0.10–4.42)	PLA		0.79 (0.07–9.30)	0.66 (0.03–16.04)	0.62 (0.07–5.34)
0.66 (0.00–155.11)	1.00 (0.01–166.19)	VED			
0.52 (0.02–11.77)	0.79 (0.07–9.30)	0.79 (0.00–230.50)	GOL		
0.44 (0.01–17.93)	0.66 (0.03–16.04)	0.66 (0.01–35.69)	0.83 (0.01–47.28)	UST	
0.41 (0.02–7.27)	0.62 (0.07–5.34)	0.62 (0.00–159.62)	0.79 (0.03–20.86)	0.95 (0.02–44.45)	FIL
0.38 (0.03–4.51)	0.57 (0.12–2.81)	0.57 (0.00–120.88)	0.72 (0.04–13.67)	0.87 (0.02–30.78)	0.92 (0.06–13.34)
0.35 (0.02–7.83)	0.52 (0.04–6.19)	0.52 (0.00–153.30)	0.66 (0.02–21.84)	0.80 (0.01–45.14)	0.84 (0.03–22.28)
0.31 (0.02–4.22)	0.47 (0.08–2.79)	0.47 (0.00–106.15)	0.60 (0.03–12.56)	0.72 (0.02–27.79)	0.76 (0.05–12.38)
0.22 (0.00–18.50)	0.34 (0.01–18.16)	0.34 (0.01–8.22)	0.43 (0.00–46.49)	0.51 (0.05–5.58)	0.54 (0.01–50.25)
0.14 (0.01–1.57)	0.21 (0.05–0.94)	0.21 (0.00–43.64)	0.27 (0.02–4.81)	0.32 (0.01–10.94)	0.34 (0.02–4.67)
0.07 (0.01–0.89)	0.11 (0.02–0.56)	0.11 (0.00–23.42)	0.14 (0.01–2.68)	0.17 (0.00–6.01)	0.18 (0.01–2.62)

Note: Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall safety. The drug in the top left position is ranked as safest after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the drug labels, and indirect comparisons are below. Boxes shaded green denote a statistically significant difference.

Abbreviations: ADA, adalimumab; CER, certolizumab; FIL, filgotinib; GOL, golimumab; IFX, infliximab; OZA, ozanimod; PLA, placebo; RIS, risankizumab; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

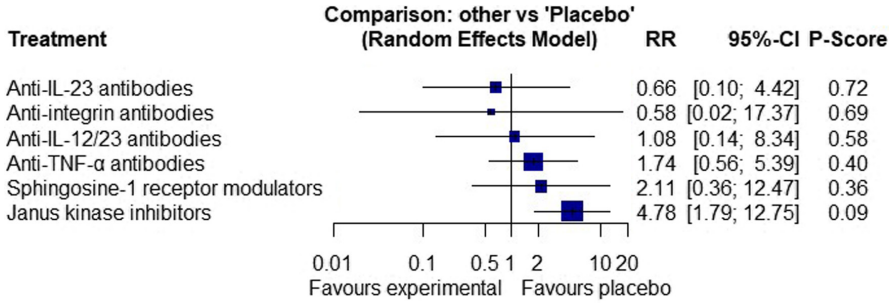

FIGURE 4 Forest plot for occurrence of Herpes zoster according to drug class. The P-score is the probability of each drug class being ranked as safest in the network.

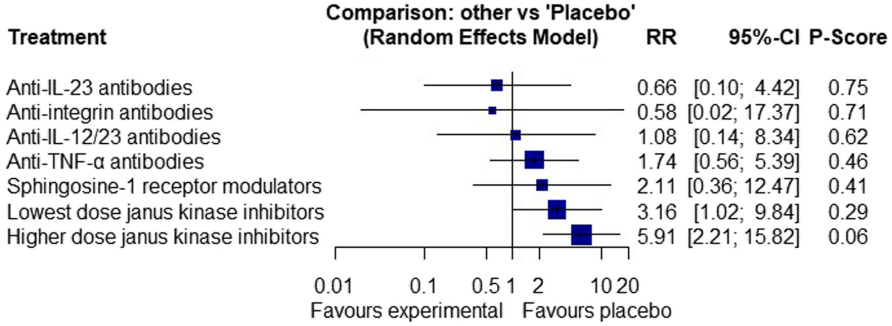

FIGURE 5 Forest plot for occurrence of Herpes zoster according to drug class and dose of janus kinase inhibitor used. The P-score is the probability of each drug class being ranked as safest in the network.

Medicinal Products for Human Use,[62] and the Advisory Committee on Immunization Practices,[63] have provided a more inclusive strategy for adult patients >18 and >19 years, respectively, at increased risk of Herpes zoster with or without additional immunosuppression. Guidance from the American College of Gastroenterology recommends that Herpes zoster vaccination should be considered in patients with IBD aged >50 years,[12] and the European Crohn's and Colitis Organisation recommends the recombinant vaccine in all patients with IBD receiving immunosuppressive therapy.[64]

In summary, this systematic review and network meta-analysis, synthesising evidence from almost 10,000 patients included in 25 trials, demonstrated that tofacitinib 10 mg b.d., upadacitinib 45 mg o.d., and janus kinase inhibitors as a class, were statistically significantly more likely to increase risk of Herpes zoster infection than placebo. The increased risk with janus kinase inhibitors was observed even in trials that used the lowest doses. In addition, three of the RCTs of janus kinase inhibitors stated specifically that patients with a past history of recurrent or disseminated Herpes zoster or ophthalmic or central nervous system zoster were ineligible to participate.[36,38,46] This will likely, therefore, have underestimated the risk of Herpes zoster infection, compared with the other drugs under study. Although the NNHs

0.57 (0.12–2.81)	0.52 (0.04–6.19)	0.47 (0.08–2.79)		0.21 (0.05–0.94)	0.11 (0.02–0.56)
			0.34 (0.01–8.22)		
			0.51 (0.05–5.58)		
IFX					
0.92 (0.05–17.38)	CER				
0.83 (0.08–9.02)	0.90 (0.04–18.93)	OZA			
0.59 (0.01–43.29)	0.64 (0.01–70.03)	0.71 (0.01–55.96)	ADA		
0.37 (0.04–3.30)	0.41 (0.02–7.25)	0.45 (0.04–4.55)	0.63 (0.01–44.70)	TOF	
0.19 (0.02–1.88)	0.21 (0.01–4.04)	0.23 (0.02–2.58)	0.32 (0.00–24.26)	0.51 (0.06–4.70)	UPA

were modest, there can be long-term sequelae from Herpes zoster infection. National and international guidelines may need to take our findings into consideration and make recommendations concerning vaccination of patients with IBD prior to commencement of these therapies.

AUTHOR CONTRIBUTIONS

Shahida Din: Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Christian Selinger:** Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Christopher Black:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Alexander Ford:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal).

ACKNOWLEDGEMENTS

Declaration of personal interests: None.

FUNDING INFORMATION

None.

DISCLOSURES

Shahida Din: grants from The Helmsley Charitable Trust, Edinburgh and Lothians Health Foundation, Pathological Society of Great Britain and Northern Ireland, Lord Leonard and Lady Estelle Wolfson Foundation, consulting fees from Abbvie, personal speaker fees from Janssen and Takeda, and meeting and travel grants from Janssen, Takeda and Dr Falk. Christian P. Selinger: unrestricted research grants from Warner Chilcott, Janssen and AbbVie, consultancy to Warner Chilcott, Dr Falk, AbbVie, Takeda, Fresenius Kabi, Galapagos, Ferring, Arena and Janssen, and speaker arrangements with Warner Chilcott, Dr Falk, AbbVie, MSD, Pfizer, Celltrion and Takeda. Christopher J. Black: none. Alexander C. Ford: none.

AUTHORSHIP

Guarantor of article: Alexander C. Ford.

ORCID

Christopher J. Black https://orcid.org/0000-0001-5449-3603
Alexander C. Ford https://orcid.org/0000-0001-6371-4359

TWITTER

Alexander C. Ford @alex_ford12399

REFERENCES

1. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1–s106.
2. Barberio B, Zamani M, Black CJ, Savarino EV, Ford AC. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6:359–70.
3. Barberio B, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut. 2022. https://doi.org/10.1136/gutjnl-2022-328052
4. Burr NE, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis. Gut. 2021;71:1976–87.
5. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-alpha therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol. 2013;108:1268–76.

6. Luthra P, Peyrin-Biroulet L, Ford AC. Systematic review and meta-analysis: opportunistic infections and malignancies during treatment with anti-integrin antibodies in inflammatory bowel disease. Aliment Pharmacol Ther. 2015;41:1227–36.
7. Patil A, Goldust M, Wollina U. Herpes zoster: a review of clinical manifestations and management. Viruses. 2022;14:192.
8. Le P, Rothberg M. Herpes zoster infection. BMJ. 2019;364:k5095.
9. Lembo AJ, Lacy BE, Zuckerman MJ, Schey R, Dove LS, Andrae DA, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med. 2016;374:242–53.
10. Johnson RW, Alvarez-Pasquin MJ, Bijl M, Franco E, Gaillat J, Clara JG, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv Vaccines. 2015;3:109–20.
11. Lai SW, Liao KF, Lin CL, Kuo YH, Liu CS, Hwang BF. The incidence rate of herpes zoster in inflammatory bowel disease: a meta-analysis of cohort studies. Medicine. 2021;100:e26863.
12. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG clinical guideline: preventive care in inflammatory bowel disease. Am J Gastroenterol. 2017;112:241–58.
13. European Medicines Agency. Annex 1: Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/zostavax-epar-product-information_en.pdf
14. European Medicines Agency. Annex 1: Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/shingrix-epar-product-information_en.pdf
15. Chen YJ, Chen YM, Huang WN, Chen HH, Liao TL, Chen JP, et al. Herpes zoster in rheumatoid arthritis patients receiving tofacitinib, a single center experience from Taiwan. Medicine. 2020;99:e22504.
16. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions: Version 5.1.0 [updated March 2011]; 2011. http://handbook-5-1cochraneorg/
17. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, 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;162:777–84.
18. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. Stat Methods Med Res. 2008;17:279–301.
19. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods. 2012;3:80–97.
20. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64:163–71.
21. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One. 2013;8:e76654.
22. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
23. Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol. 2008;8:79.
24. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. Eur Heart J. 2014;35:3336–45.
25. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015;15:58.
26. Morton SC, Murad MH, O'Connor E, Lee CS, Booth M, Vandermeer BW. AHRQ methods for effective health care. Quantitative synthesis-an update. Methods guide for effectiveness and comparative effectiveness reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018.
27. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, Danese S, Colombel JF, Törüner M, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med. 2019;381:1215–26.
28. Sands BE, Irving PM, Hoops T, Izanec JL, Gao LL, Gasink C, et al. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial. Lancet. 2022;399:2200–11.
29. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–76.
30. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:96–109.
31. Hibi T, Imai Y, Senoo A, Ohta K, Ukyo Y. Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: a phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). J Gastroenterol. 2017;52:1101–11.
32. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, et al. Tofacitinib, an oral janus kinase inhibitor, in active ulcerative colitis. N Engl J Med. 2012;367:616–24.
33. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376:1723–36.
34. Sandborn WJ, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB, et al. Ozanimod as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2021;385:1280–91.
35. Sandborn WJ, Feagan BG, Wolf DC, D'Haens G, Vermeire S, Hanauer SB, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. N Engl J Med. 2016;374:1754–62.
36. Feagan BG, Danese S, Loftus EV Jr, Vermeire S, Schreiber S, Ritter T, et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. Lancet. 2021;397:2372–84.
37. Feagan BG, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet. 2017;389:1699–709.
38. Danese S, Vermeire S, Zhou W, Pangan AL, Siffledeen J, Greenbloom S, et al. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. Lancet. 2022;399:2113–28.
39. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362:1383–95.
40. Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology. 2005;129:807–18.
41. Sandborn WJ, Schreiber S, Feagan BG, Rutgeerts P, Younes ZH, Bloomfield R, et al. Certolizumab pegol for active Crohn's disease: a placebo-controlled, randomized trial. Clin Gastroenterol Hepatol. 2011;9:670–8.
42. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016;375:1946–60.
43. D'Haens G, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. Lancet. 2022;399(ferr):2015–30.

44. Panés J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D'Haens G, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut. 2017;66:1049–59.
45. Vermeire S, Schreiber S, Petryka R, Kuehbacher T, Hebuterne X, Roblin X, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. Lancet. 2017;389:266–75.
46. Colombel JF, Panes J, Lacerda AP, Peyrin-Biroulet L, D'Haens GR, Panaccione R, et al. Efficacy and safety of upadacitinib induction therapy in patients with moderately to severely active Crohn's disease who failed prior biologics: results from a randomized phase-3 U-EXCEED study. Gastroenterology. 2022;162:867f.
47. Loftus E, Colombel JF, Lacerda AP, Peyrin-Biroulet L, D'Haens GR, Panaccione R, et al. Efficacy and safety of upadactinib induction therapy in patients with moderately to severely active Crohn's disease: results from a randomized phase 3 U-EXCEL study. United European Gastroenterol J. 2022;10(supplement 8):103–4.
48. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. BMJ. 2016;352:i1981.
49. Lin L. Bias caused by sampling error in meta-analysis with small sample sizes. PLoS One. 2018;13:e0204056.
50. Côté-Daigneault J, Bessissow T, Nicolae MV, Nie R, Bitton A, Lakatos PL, et al. Herpes zoster incidence in inflammatory bowel disease patients: a population-based study. Inflamm Bowel Dis. 2019;25:914–8.
51. Sollie M, Jepsen P, Sørensen JA. Patient-reported quality of life in patients suffering from acute herpes zoster-a systematic review with meta-analysis. Br J Pain. 2022;16:404–19.
52. Colombel J-F. Herpes zoster in patients receiving JAK inhibitors for ulcerative colitis: mechanism, epidemiology, management, and prevention. Inflamm Bowel Dis. 2018;24:2173–82.
53. Winthrop KL, Melmed GY, Vermeire S, Long MD, Chan G, Pedersen RD, et al. Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. Inflamm Bowel Dis. 2018;24:2258–65.
54. Mbinta JF, Nguyen BP, Awuni PMA, Paynter J, Simpson CR. Post-licensure zoster vaccine effectiveness against herpes zoster and postherpetic neuralgia in older adults: a systematic review and meta-analysis. Lancet Healthy Longevity. 2022;3:e263–75.
55. Centers for Disease Control and Prevention. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Use of recombinant zoster vaccine in immunocompromised adults aged ≥19 years. https://www.cdc.gov/vaccines/acip/recs/grade/recombinant-zoster-immunocompromised.html#table-03b
56. Khan N, Wang L, Trivedi C, Pernes T, Patel M, Xie D, et al. Efficacy of recombinant zoster vaccine in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2022;20:1570–1578.e1571.
57. Kochhar GS, Desai A, Caldera DF, El Hachem S, Aoun E, Sandhu D, et al. Effectiveness of recombinant zoster vaccine (RZV) in patients with inflammatory bowel disease. Vaccine. 2021;39:4199–202.
58. Pan CX, Lee MS, Nambudiri VE. Global herpes zoster incidence, burden of disease, and vaccine availability: a narrative review. Ther Adv Vaccines Immunother. 2022;10:25151355221084535.
59. UK Health Security Agency. Shingles: The green book chapter 28a; 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1012943/Green_book_of_immunisation_28a_Shingles.pdf
60. American College of Rheumatology. 2022 American College of Rheumatology (ACR) guideline for vaccinations in patients with rheumatic and musculoskeletal diseases; 2022. https://www.rheumatology.org/Portals/0/Files/Vaccinations-Guidance-Summary.pdf
61. Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis—executive summary. Rheumatology. 2019;58:220–6.
62. European Medicines Agency. Shingrix. https://www.ema.europa.eu/en/medicines/human/EPAR/shingrix
63. Anderson TC, Masters NB, Guo A, Shepersky L, Leidner AJ, Lee GM, et al. Use of recombinant zoster vaccine in immunocompromised adults aged ≥19 years: recommendations of the advisory committee on immunization practices - United States. MMWR Morb Mortal Wkly Rep. 2022;71:80–4.
64. Kucharzik T, Ellul P, Greuter T, Rahier JF, Verstockt B, Abreu C, et al. ECCO guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. J Crohns Colitis. 2021;15:879–913.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Din S, Selinger CP, Black CJ, Ford AC. Systematic review with network meta-analysis: Risk of Herpes zoster with biological therapies and small molecules in inflammatory bowel disease. Aliment Pharmacol Ther. 2023;57:666–675. https://doi.org/10.1111/apt.17379