Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis

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Summary

Background There is a growing armamentarium for the treatment of moderate-to-severe ulcerative colitis. We aimed to compare the relative efficacy and safety of biologics and small molecule drugs for the treatment of patients with moderate-to-severe ulcerative colitis.

Methods In this systematic review and network meta-analysis, we searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials without language restrictions for articles published between Jan 1, 1990, and July 1, 2021. Major congresses' databases from Jan 1, 2018, to July 3, 2021, were reviewed manually. Phase 3, placebo-controlled or head-to-head randomised controlled trials (RCTs) assessing the efficacy and safety of biologics or small molecule drugs as induction or maintenance therapies for patients with moderate-to-severe ulcerative colitis were included. Phase 2 RCTs were excluded because of their small sample sizes and inclusion of doses not further explored in phase 3 RCTs. Summary data from intention-to-treat analyses were extracted from included reports by JSL and PAO. The primary outcome was the induction of clinical remission. A network meta-analysis was done under the frequentist framework, obtaining pairwise odds ratios (ORs) and 95% CIs. The surface under the cumulative ranking (SUCRA) was used to rank the included agents for each outcome. Higher SUCRA scores correlate with better efficacy, whereas lower SUCRA scores correlate with better safety. Maintenance data on efficacy for treat-straight-through and randomised responder trials are also presented. This study is registered with PROSPERO, CRD42021225329.

Findings Our search yielded 5904 results, from which 29 studies (four being head-to-head RCTs) fulfilled our inclusion criteria and were included. Of these, 23 studies assessed induction therapy with either a biologic or small molecule drug, comprising 10 061 patients with ulcerative colitis. A risk of bias assessment showed a low risk of bias for most of the included studies. Upadacitinib was significantly superior to all other interventions for the induction of clinical remission (infliximab [OR 2·70, 95% CI 1·18–6·20], adalimumab [4·64, 2·47–8·71], golimumab [3·00, 1·32–6·82], vedolizumab [3·56, 1·84–6·91], ustekinumab [2·92, 1·31–6·51], etrolizumab [4·91, 2·59–9·31], tofacitinib [2·84, 1·28–6·31], filgotinib 100 mg [6·15, 2·98–12·72], filgotinib 200 mg [4·49, 2·18–9·24], and ozanimod (2·70, 1·18–6·20), and ranked highest for the induction of clinical remission (SUCRA 0·996). No differences between active interventions were observed when assessing adverse events and serious adverse events. Vedolizumab ranked lowest for both adverse events (SUCRA 0·184) and serious adverse events (0·139), whereas upadacitinib ranked highest for adverse events (0·843) and ozanimod ranked highest for serious adverse events (0·831).

Interpretation Upadacitinib was the best performing agent for the induction of clinical remission (the primary outcome) but the worst performing agent in terms of adverse events in patients with moderate-to-severe ulcerative colitis. Vedolizumab was the best performing agent for safety outcomes. With the paucity of direct comparisons in the published literature, our results might help clinicians to position drugs in treatment algorithms.

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Introduction

Ulcerative colitis is a chronic, idiopathic, potentially disabling condition that is clinically characterised by bloody diarrhoea, abdominal pain, and tenesmus.[1] Ulcerative colitis most commonly presents during the third and fifth decades of life, and is associated with an impaired health-related quality of life and considerable economic burden.[2,3]

Nearly 20 years ago, the advent of anti-tumour necrosis factor biologics (eg, infliximab, adalimumab, and golimumab) revolutionised therapeutics for ulcerative colitis, enabling better disease control in terms of increasing the rates of mucosal healing, deep remission, and corticosteroid-free remission, and improving quality of life. Biologics with other targets were later approved for the treatment of moderate-to-severe ulcerative colitis, namely vedolizumab and, more recently, ustekinumab. However, treatment with biologics has several limitations, including limited efficacy, primary non-response, secondary loss of response, immunogenicity,

Research in context

Evidence before this study

The therapeutic armamentarium for moderate-to-severe ulcerative colitis has expanded considerably in recent years. Drug development has shifted over the last decade to small molecule drugs in an effort to overcome the intrinsic limitations of treatment with biologics. In this context of ever-expanding treatment options, frequent updates of indirect comparisons are warranted. We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials without language restrictions for articles published between Jan 1, 1990, and July 1, 2021, using the search terms ["biologics" OR "anti-TNF" OR "infliximab" OR "adalimumab" OR ("golimumab" OR "CNTO-148") OR "anti-integrin" OR ("vedolizumab" OR "MLN-0002") OR ("etrolizumab" OR "rhuMAb Beta7") OR ("ustekinumab" OR "CNTO-1275") OR "JAK inhibitor" OR ("tofacitinib" OR "CP-690550") OR ("filgotinib" OR "GLPG0634") OR ("upadacitinib" OR "ABT-494") OR "sphingosine-1-phosphate receptor modulator" OR ("ozanimod" OR "RPC1063") OR "etrasimod" OR "TD-1473"] AND ["ulcerative colitis" OR "inflammatory bowel disease"] AND ["efficacy" OR "safety" OR "adverse events"]. Additionally, we manually reviewed major congresses' databases (European Crohn's and Colitis Organization, Digestive Disease Week, and United European Gastroenterology Week) from Jan 1, 2018, to July 3, 2021. With the paucity of direct head-to-head trials, indirect comparisons have become useful in the clinic to determine drug positioning. Several network meta-analyses have compared approved therapeutic options for ulcerative colitis, but did not include recent data on the small molecule drugs ozanimod, filgotinib, and upadacitinib.

Added value of this study

To our knowledge, we are the first to include the novel drugs ozanimod, filgotinib, upadacitinib, and etrolizumab in a systematic review and network meta-analysis of treatments for ulcerative colitis. Additionally, we analysed steroid-free remission as a novel outcome, which has not been evaluated in any previous network meta-analyses. The network meta-analysis allowed us to make direct and indirect comparisons between 23 randomised controlled trials that assessed induction therapy. Upadacitinib was the best performing agent for inducing clinical remission and endoscopic improvement, but ranked worst with regard to all adverse events. A similar trend towards a higher efficacy and a less favourable safety profile was seen with the other small molecule drugs.

Implications of all the available evidence

Our results of the relative efficacy and safety of all included treatment options might influence patterns of use and drug positioning. To date, published results of only four head-to-head trials in patients with ulcerative colitis are available, and, until more data become available, clinicians should rely on indirect comparisons.

and parenteral administration.[4] Drug development has shifted in the past decade to small molecule drugs in an effort to overcome these limitations. Tofacitinib, a Janus kinase (JAK) inhibitor, was the first next-generation small molecule drug to receive approval from the US Food and Drug Administration for the treatment of patients with moderate-to-severe ulcerative colitis.[5] Ozanimod became the second small molecule drug to receive approval. Other compounds, including filgotinib and upadacitinib, have been efficacious for the treatment of ulcerative colitis in phase 3 randomised clinical trials (RCTs)[6–8] and will probably become available in the clinic in the near future. With a growing therapeutic armamentarium, and a paucity of direct comparisons, drug positioning is a clinical challenge. Several network meta-analyses have compared the therapeutic options approved for ulcerative colitis, but did not include recent data related to small molecule drugs.[9–13] Additionally, subcutaneous formulations of infliximab and vedolizumab were approved by the European Medicines Agency in 2020 for the treatment of ulcerative colitis and Crohn's disease. The aim of this systematic review and network meta-analysis is to give an updated comparison of the relative efficacy and safety of biologics and small molecule drugs (approved or in a late stage of development) in the treatment of patients with moderate-to-severe ulcerative colitis.

Methods

Search strategy and selection criteria

This systematic review and network meta-analysis was done by use of an a priori established protocol, and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for systematic reviews incorporating network meta-analyses for health-care interventions.[14] Two authors (JSL and PAO) searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials without language restrictions for articles published between Jan 1, 1990, and July 1, 2021. Major congresses' databases (European Crohn's and Colitis Organization, Digestive Disease Week, and United European Gastroenterology Week) were also reviewed manually from Jan 1, 2018, to July 3, 2021. Search algorithms included the following terms: ["biologics" OR "anti-TNF" OR "infliximab" OR "adalimumab" OR ("golimumab" OR "CNTO-148") OR "anti-integrin" OR ("vedolizumab" OR "MLN-0002") OR ("etrolizumab" OR "rhuMAb Beta7") OR ("ustekinumab" OR "CNTO-1275") OR "JAK inhibitor" OR ("tofacitinib" OR "CP-690550") OR ("filgotinib" OR "GLPG0634") OR ("upadacitinib" OR "ABT-494") OR "sphingosine-1-phosphate receptor modulator" OR ("ozanimod" OR "RPC1063") OR "etrasimod" OR "TD-1473"] AND ["ulcerative colitis" OR "inflammatory bowel disease"] AND ["efficacy" OR

"safety" OR "adverse events"]. Additionally, experts in the field were contacted for any unpublished data.

We included phase 3 RCTs that met the inclusion criteria: (1) studies including adult (≥18 years) patients with moderate-to-severe ulcerative colitis (defined as a Mayo Score of 6–12, with an endoscopic sub-score of 2–3) who were either biologic-naive or had previously been exposed to at least one biologic; (2) studies either evaluating the following biologics and small molecule drugs in their approved dose regimens, infliximab (intravenous or subcutaneous), adalimumab, golimumab, vedolizumab (intravenous or subcutaneous), ustekinumab (intravenous or subcutaneous), tofacitinib, or ozanimod, or studies evaluating etrolizumab, upadacitinib, filgotinib, etrasimod, or TD-1473; (3) studies including an active comparator or placebo; and (4) studies assessing the following outcomes: clinical remission (defined as a Mayo score of ≤2, with no individual sub-score >1) and endoscopic improvement (Mayo endoscopic sub-score 0–1). We did not include phase 2 trials because treatment effects can be over-estimated or underestimated due to the intrinsically small sample sizes of these studies. Additionally, given the dose-ranging nature of phase 2 trials, many of them include doses that will not be further explored in phase 3 trials.

For approved agents, only approved doses were included in our analyses (intravenous infliximab: 5 mg/kg in weeks 0, 2, and 6 in induction, and 5 mg/kg every 8 weeks in maintenance; subcutaneous infliximab: 120 mg every 2 weeks in maintenance; subcutaneous adalimumab: 160 mg in week 0, 80 mg in week 2, and 40 mg in week 4 in induction, and 40 mg every other week in maintenance; subcutaneous golimumab: 200 mg in week 0 and 100 mg in week 2 in induction, and 100 mg every 4 weeks in maintenance; intravenous vedolizumab: 300 mg in weeks 0, 2, and 6 in induction, and 300 mg every 8 weeks in maintenance; subcutaneous vedolizumab: 108 mg every 2 weeks in maintenance; ustekinumab: 6 mg/kg intravenously in week 0 in induction, and 90 mg subcutaneously every 8 weeks in maintenance; oral tofacitinib: 10 mg twice daily for 8 weeks in induction, and 5 mg twice daily in maintenance; and oral ozanimod: 1 mg daily in induction and maintenance). For non-approved agents in a late stage of development (defined as the availability of results from phase 3 trials), all evaluated doses were included in the analyses (oral filgotinib: 100 mg or 200 mg daily in induction and maintenance; oral upadacitinib: 45 mg daily in induction, and 15 mg daily and 30 mg daily in maintenance; and subcutaneous etrolizumab: 105 mg every 4 weeks in induction and maintenance).

Summary data from intention-to-treat analyses were sought from the published reports. Two authors (JSL and PAO) independently reviewed the titles and abstracts of studies identified in the search and excluded those that were clearly irrelevant. The full text of the selected articles was analysed to identify whether it contained information on the topic of interest. The reference lists of selected articles (and those of relevant systematic reviews and meta-analyses) were manually searched to identify further relevant publications. Disagreements in study selection between investigators (JSL and PAO) were resolved by discussion with a third author (LP-B). JSL and PAO extracted data from the selected studies.

We followed good practices stated in the International Society for Pharmacoeconomics and Outcomes Research report on interpreting indirect treatment comparisons and network meta-analyses for health-care decision making.[15]

Data analysis

The following information from each study was extracted into a specially designed data extraction form using Microsoft Access software, version 16.0: citation data; first author's last (family) name; study design; number of patients; study duration; population characteristics; exposure definition (eg, drug, dose, and duration); and reported outcomes. Differences in data extraction were settled by consensus, referring to the original article. Two authors (JSL and PAO) independently rated the quality of the included trials using the Cochrane Risk of Bias tool, version 2.0.[16] If study results were reported in multiple publications, the most complete report of trial data was used for data extraction.

In June, 2021, an amendment to the protocol was made for the purposes of the current analysis that included the following changes: the mucosal healing outcome was changed to endoscopic improvement, histological remission was added as an exploratory outcome, and clinical response was withdrawn as an outcome of interest.

The primary outcome was the induction of clinical remission. Secondary outcomes were endoscopic improvement, steroid-free remission, adverse events, and serious adverse events. Adverse events and serious adverse events were assessed after induction therapy, regardless of the dose among active interventions. A pairwise meta-analysis comprising trials that reported rates of histological remission (Geboes score <2) was undertaken as a post-hoc exploratory analysis. Additional prespecified, exploratory pairwise and network meta-analyses were done to evaluate clinical remission and endoscopic improvement for induction therapy in biologic-naive and biologic-exposed populations, including studies with available data on previous biologic exposure.

We aimed to analyse both induction therapy and maintenance therapy for patients with ulcerative colitis. Pairwise and network meta-analyses of induction therapy were done to estimate the comparative efficacy of biologics and small molecule drugs for the treatment of patients with moderate-to-severe ulcerative colitis. Trials assessing maintenance therapy had different designs (treat-straight-through *vs* randomising responders to induction therapy). Therefore, separate pairwise and network meta-analyses for these different trial designs were done for the following outcomes: maintenance of clinical remission; endoscopic

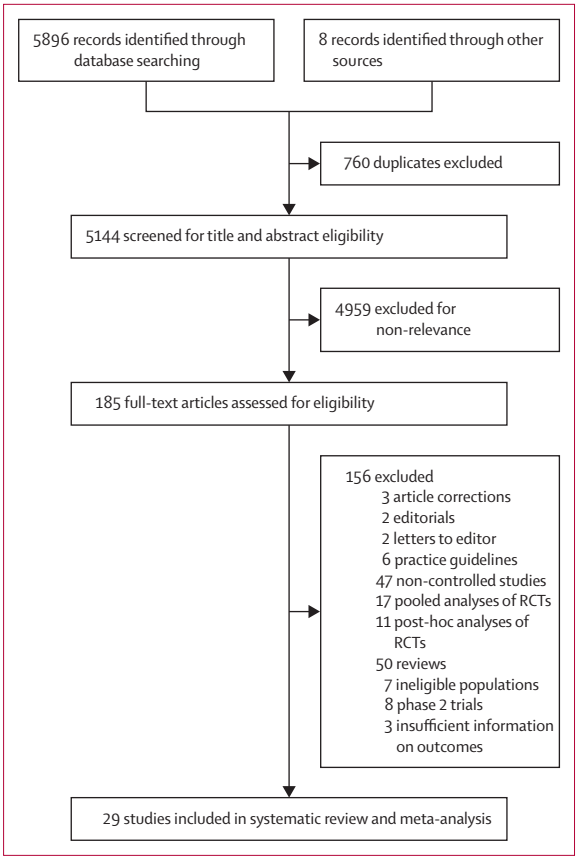

Figure 1: **Study selection**
RCTs=randomised controlled trials.

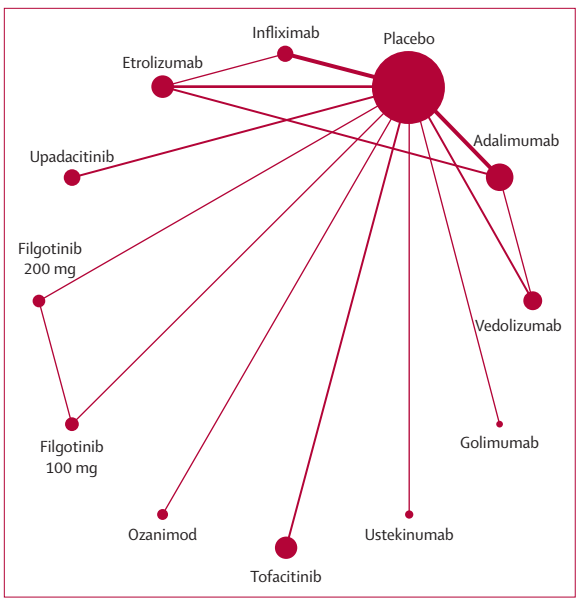

Figure 2: **Network map for induction trials assessing clinical remission in patients with moderate-to-severe ulcerative colitis (overall population)**
Node size (the size of the circle) corresponds to the number of study participants for each intervention, and connection size (line thickness) corresponds to the number of studies for each comparison.

improvement; and steroid-free remission. For comparative safety, a network meta-analysis of all trials of induction therapy was done.

Direct comparisons were done by use of RevMan software (version 5.4). Heterogeneity among studies was evaluated by I^2 tests, with values greater than 50% suggesting substantial heterogeneity. A random-effects model was used to give a more conservative estimate of the effect of individual therapies, allowing for any heterogeneity among studies. Outcome measures were described as odds ratios (ORs), with their corresponding 95% CIs. Possible publication bias was assessed with the Egger test. We then conducted a network meta-analysis using the multivariate frequentist approach described by Rücker and Schwarzer, using R software, version 4.0.3.[17] We calculated the relative ranking of agents for each outcome (ie, clinical remission, endoscopic improvement, adverse events, and serious adverse events) as their surface under the cumulative ranking (SUCRA), which represents the percentage of efficacy or safety achieved by an agent compared with an imaginary agent that is always the best without uncertainty. A higher SUCRA score means a higher ranking for efficacy outcomes. A lower SUCRA score correlates with better safety (ie, a lower ranking for adverse events and serious adverse events).

The Grading of Recommendations Assessment, Development, and Evaluation approach was followed to evaluate the confidence in estimates derived from our network meta-analysis of the outcomes. For this purpose, six domains were considered: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.[18] Our study protocol was registered with PROSPERO, CRD42021225329.

Role of the funding source
There was no funding source for this study.

Results
Our bibliographical search yielded 5904 results, of which 29 studies (four being head-to-head RCTs) that fulfilled our inclusion criteria were included (figure 1). Of these 29 studies, 23 assessed induction therapy with either a biologic or a small molecule drug, comprising a total of 10 061 patients with ulcerative colitis. There were five studies of intravenous infliximab (ACT 1 and 2,[19] Jiang and colleagues,[20] Kobayashi and colleagues,[21] and NCT01551290[22]), three studies of adalimumab (ULTRA 1 and 2[23,24] and Suzuki and colleagues[25]), one study of golimumab (PURSUIT-SC[26]), three studies of intravenous vedolizumab (GEMINI I,[27] Motoya and colleagues,[28] and VARSITY[29]), two studies of tofacitinib (OCTAVE 1 and 2[30]), one study of ustekinumab (UNIFI[31]), one study of ozanimod (True North[32]), one study of filgotinib (SELECTION[6]), four studies of etrolizumab (HIBISCUS I and II,[33] GARDENIA,[34] and HICKORY[35]), and two studies of upadacitinib (U-ACHIEVE[7] and

Figure 3: **Indirect comparison of biologics and small molecule drugs for the induction of clinical remission and endoscopic improvement in patients with moderate-to-severe ulcerative colitis (overall population) in a network meta-analysis**

Comparisons should be read from left to right; to obtain odds ratios from right to left, reciprocals should be taken. The odds ratio (95% CI) for comparisons are in the cell in common between the column-defining and row-defining treatments. The violet boxes represent statistically significant comparisons and the white boxes represent non-statistically significant comparisons.

U-ACCOMPLISH[8]). No phase 3 RCTs with etrasimod or TD-1473 were found.

Among 22 studies evaluating maintenance therapy, ten were done by use of a treat-straight-through strategy (2528 patients)[19–22,24,25,29,34,36] and 12 followed a randomised responders design (3484 patients).[6,27,28,30–32,35,37–41] Only seven studies evaluated histological remission.[6,29,31,32,35,38,41] The main characteristics of the included trials are described in the appendix (pp 2–4). All outcomes were assessed uniformly on the basis of the standard definition of the Mayo score, with follow-up durations of 6–14 weeks for induction therapy and 26–66 weeks for maintenance therapy (appendix pp 2–4). All studies were industry sponsored. A risk of bias assessment showed a low risk of bias for most of the included studies (appendix p 5). Confidence in the estimates derived from our meta-analysis is shown in the appendix (pp 6–8).

A network map of induction trials assessing clinical remission in patients with moderate-to-severe ulcerative colitis is shown in figure 2. When evaluating the induction of clinical remission, all interventions, except for filgotinib 100 mg (OR 1·55, 95% CI 0·98–2·46), were significantly superior to placebo in the direct, pairwise meta-analysis (appendix p 9); overall heterogeneity was substantial (I^2=81%). The results from our network meta-analysis are shown in figure 3. When comparing active treatments, adalimumab (OR 0·54, 95% CI 0·37–0·79; moderate confidence), etrolizumab (0·51, 0·36–0·72; high confidence), filgotinib 100 mg (0·41, 0·23–0·71; moderate confidence), and filgotinib 200 mg (0·56, 0·32–0·97; moderate confidence) were significantly inferior to infliximab in inducing clinical remission. Ozanimod (OR 2·27, 95% CI 1·05–4·89; moderate confidence), tofacitinib (0·46, 0·22–0·95; moderate confidence), and ustekinumab (0·47, 0·22–0·99; moderate confidence) were significantly superior to filgotinib 100 mg. Upadacitinib was significantly superior to all other interventions (figure 3; moderate-to-high confidence) and ranked highest for the induction of clinical remission (SUCRA 0·996), followed by infliximab (0·771; appendix p 10).

When evaluating the induction of endoscopic improvement, all interventions, except for filgotinib 100 mg (OR 1·38, 95% CI 0·61–3·14), were significantly superior to placebo in the direct, pairwise meta-analysis; overall heterogeneity was substantial (I^2=80%; appendix p 11). In our network meta-analysis, indirect comparison of active treatments showed that adalimumab (moderate

See Online for appendix

Ozanimod	0·89 (0·58–1·37)	1·30 (0·84–1·99)	1·14 (0·73–1·78)	0·98 (0·62–1·55)	1·41 (0·82–2·42)	1·12 (0·71–1·78)	1·16 (0·68–1·98)	1·06 (0·67–1·69)	1·16 (0·53–2·56)	1·09 (0·78–1·53)
2·02 (0·65–6·18)	Upadacitinib	1·46 (0·99–2·11)	1·27 (0·86–1·89)	1·10 (0·73–1·65)	1·58 (0·94–2·60)	1·26 (0·83–1·90)	1·31 (0·80–2·13)	1·19 (0·79–1·80)	1·30 (0·61–2·79)	1·22 (0·93–1·59)
1·22 (0·41–3·65)	0·61 (0·24–1·52)	Filgotinib	0·87 (0·59–1·29)	0·75 (0·50–1·13)	1·08 (0·66–1·78)	0·86 (0·57–1·30)	0·89 (0·55–1·46)	0·82 (0·54–1·23)	0·89 (0·41–1·91)	0·84 (0·64–1·09)
2·00 (0·66–6·03)	1·00 (0·39–2·51)	1·63 (0·66–4·01)	Tofacitinib	0·86 (0·56–1·31)	1·23 (0·74–2·06)	0·98 (0·64–1·51)	1·02 (0·62–1·69)	0·93 (0·61–1·43)	1·02 (0·47–2·20)	0·95 (0·71–1·28)
2·56 (0·80–8·19)	1·26 (0·46–3·44)	2·08 (0·79–5·51)	1·27 (0·47–3·40)	Ustekinumab	1·43 (0·85–2·42)	1·14 (0·73–1·78)	1·18 (0·71–1·98)	1·08 (0·70–1·68)	1·19 (0·54–2·58)	1·11 (0·81–1·51)
3·89 (0·94–16·04)	1·93 (0·53–6·96)	3·18 (0·90–11·21)	1·94 (0·54–6·90)	1·52 (0·40–5·70)	Vedolizumab	0·79 (0·47–1·34)	0·82 (0·46–1·48)	0·75 (0·44–1·27)	0·82 (0·36–1·88)	0·77 (0·50–1·17)
2·84 (0·85–9·46)	1·40 (0·49–4·00)	2·31 (0·83–6·40)	1·41 (0·50–3·95)	1·11 (0·37–3·30)	0·73 (0·18–2·83)	Golimumab	1·03 (0·61–1·73)	0·94 (0·61–1·47)	1·03 (0·47–2·25)	0·96 (0·71–1·32)
1·14 (0·31–4·12)	0·56 (0·18–1·76)	0·93 (0·30–2·82)	0·56 (0·18–1·74)	0·44 (0·13–1·45)	0·29 (0·07–1·22)	0·40 (0·12–1·35)	Etrolizumab	0·91 (0·54–1·53)	1·00 (0·43–2·27)	0·93 (0·62–1·41)
2·31 (0·74–7·17)	1·14 (0·43–3·00)	1·88 (0·74–4·79)	1·15 (0·45–2·96)	0·90 (0·32–2·49)	0·59 (0·16–2·16)	0·81 (0·28–2·34)	2·02 (0·64–6·41)	Adalimumab	1·09 (0·50–2·37)	1·02 (0·74–1·39)
1·85 (0·52–6·61)	0·92 (0·30–2·82)	1·51 (0·51–4·51)	0·92 (0·31–2·78)	0·72 (0·22–2·32)	0·47 (0·11–1·96)	0·65 (0·19–2·17)	1·62 (0·45–5·88)	0·80 (0·25–2·49)	Infliximab	0·93 (0·46–1·90)
1·23 (0·51–3·01)	0·61 (0·31–1·19)	1·00 (0·53–1·87)	0·61 (0·32–1·16)	0·48 (0·23–1·01)	**0·25 (0·10–0·94)**	**0·43 (0·19–0·96)**	1·07 (0·43–2·71)	0·53 (0·26–1·06)	0·66 (0·27–1·62)	Placebo

Serious adverse events

Adverse events

Figure 4: **Indirect comparison of biologics and small molecule drugs for the development of adverse events and serious adverse events in patients with moderate-to-severe ulcerative colitis (overall population) in a network meta-analysis**

Comparisons should be read from left to right; to obtain odds ratios from right to left, reciprocals should be taken. The odds ratio (95% CI) for comparisons are in the cell in common between the column-defining and row-defining treatments. The violet boxes represent statistically significant comparisons and the white boxes represent non-statistically significant comparisons.

confidence), vedolizumab (moderate confidence), golimumab (moderate confidence), and etrolizumab (high confidence) were significantly inferior to infliximab for the induction of endoscopic improvement (figure 3). In addition, ozanimod (moderate confidence) and tofacitinib (moderate confidence) were significantly superior to adalimumab (figure 3). Once again, upadacitinib was significantly superior to all other interventions (figure 3; moderate-to-high confidence) and ranked highest for the induction of endoscopic improvement (SUCRA 0·999), followed by infliximab (SUCRA 0·783; appendix p 10).

In our network meta-analysis, no difference in adverse events and serious adverse events between active interventions was observed (figure 4). Upadacitinib ranked highest when considering adverse events (SUCRA 0·843; appendix p 12). When considering serious adverse events, ozanimod (SUCRA 0·831) and placebo (0·784) ranked highest, followed by etrolizumab (0·766) and filgotinib (0·755; appendix p 12). Vedolizumab ranked lowest for both adverse events (0·184) and serious adverse events (0·139; appendix p 12).

All interventions were significantly superior to placebo in maintaining clinical remission in our direct, pairwise meta-analysis of treat-straight-through studies; heterogeneity was moderate (I^2=58%; appendix p 13). In a head-to-head comparison, vedolizumab was significantly superior to adalimumab (OR 1·61, 95% CI 1·13–2·29), and subcutaneous infliximab was not different to intravenous infliximab (appendix p 13). Vedolizumab was significantly superior to adalimumab for the maintenance of clinical remission in our network meta-analysis (OR 1·60, 95% CI 1·12–2·28; moderate confidence); there was no difference in this outcome for all other active treatment comparisons (appendix p 14). Vedolizumab (SUCRA 0·906) and subcutaneous infliximab (SUCRA 0·716) ranked highest for the maintenance of clinical remission (appendix p 15).

When evaluating the maintenance of endoscopic improvement in treat-straight-through studies, all active interventions were significantly superior to placebo in our direct, pairwise meta-analysis; heterogeneity was substantial (I^2=67%; appendix p 16). In our network meta-analysis, vedolizumab was significantly superior to adalimumab in maintaining endoscopic improvement (OR 1·78, 95% CI 1·28–2·49; moderate confidence; appendix p 14). We found no other significant difference in the indirect comparison of other active interventions (appendix p 14). Vedolizumab ranked highest for the maintenance of endoscopic improvement in treat-straight-through studies (SUCRA 0·967; appendix p 15).

In our direct, pairwise meta-analysis of treat-straight-through studies, infliximab (OR 5·07, 95% CI 2·48–10·37)

and adalimumab (3·94, 1·27–12·26) were significantly superior to placebo in maintaining steroid-free remission (appendix p 17). In our network meta-analysis, no active treatment showed significant differences with each other in the maintenance of steroid-free remission (appendix p 18). Infliximab ranked highest for the maintenance of steroid-free remission in treat-straight-through studies (SUCRA 0·812; appendix p 19).

All active interventions, except for golimumab 100 mg, etrolizumab, and filgotinib 100 mg, were significantly superior to placebo in maintaining clinical remission in our direct, pairwise meta-analysis of studies with a randomised responders design (appendix p 20). Furthermore, subcutaneous vedolizumab was not different from intravenous vedolizumab (appendix p 20). In our network meta-analysis of studies with a randomised responders design, upadacitinib 15 mg and upadacitinib 30 mg were significantly superior to filgotinib 100 mg, ustekinumab, golimumab, and etrolizumab in maintaining clinical remission (moderate confidence; appendix p 21). In addition, upadacitinib 30 mg was significantly superior to ozanimod 1 mg (appendix p 21). Upadacitinib 30 mg ranked highest for the maintenance of clinical remission in this study type (SUCRA 0·954; appendix p 19).

When evaluating the maintenance of endoscopic improvement in our pairwise meta-analysis of studies of randomised responders, all interventions were significantly superior to placebo, except for filgotinib 100 mg (appendix p 22). In our network meta-analysis assessing indirect comparisons of active treatments, upadacitinib 30 mg was significantly superior to all other treatments, except for upadacitinib 15 mg (moderate confidence), in the maintenance of endoscopic improvement (appendix p 21). Upadacitinib 15 mg was significantly superior to ozanimod, filgotinib 100 mg, ustekinumab, golimumab, and etrolizumab (moderate confidence; appendix p 21). Upadacitinib 30 mg ranked highest for the maintenance of endoscopic improvement among these studies of randomised responders (SUCRA 0·987; appendix p 15).

In our evaluation of the maintenance of steroid-free remission in studies of randomised responders, all interventions but filgotinib 100 mg, golimumab, and etrolizumab were significantly superior to placebo in our direct, pairwise meta-analysis (appendix p 23). In our network meta-analysis, tofacitinib (moderate confidence) and subcutaneous vedolizumab (moderate confidence) were significantly superior to golimumab (appendix p 24). Tofacitinib was also significantly superior to etrolizumab (moderate confidence; appendix p 24). Upadacitinib 30 mg and upadacitinib 15 mg were significantly superior to ozanimod and golimumab (moderate confidence); in addition, upadacitinib 30 mg was significantly superior to intravenous vedolizumab (moderate confidence) and etrolizumab (moderate confidence; appendix p 24). Ozanimod was significantly inferior to tofacitinib and subcutaneous vedolizumab (appendix p 24). Tofacitinib ranked highest for the maintenance of steroid-free remission in randomised responders trials (SUCRA 0·868; appendix p 19).

The induction of clinical remission and endoscopic improvement was evaluated in biologic-naive and biologic-exposed populations in prespecified analyses. Data for upadacitinib according to previous biologic exposure were not available and so not included in this analysis. For the induction of clinical remission in biologic-naive patients, all interventions, except for filgotinib 100 mg, were superior to placebo in our pairwise, direct meta-analysis (data not shown); heterogeneity was substantial (I^2=57%). When comparing active treatments in our network meta-analysis in the biologic-naive population, adalimumab (moderate confidence), etrolizumab (moderate confidence), filgotinib 100 mg (moderate confidence), and filgotinib 200 mg (moderate confidence) were significantly inferior to infliximab; additionally, ustekinumab, vedolizumab, golimumab, and ozanimod were significantly superior to filgotinib 100 mg (moderate confidence; appendix p 25). Infliximab (SUCRA 0·853) and ozanimod (0·847) ranked the highest for the induction of clinical remission among biologic-naive patients (appendix p 26).

For the induction of endoscopic improvement in biologic-naive patients, all interventions, except for filgotinib 100 mg, were significantly superior to placebo in our direct, pairwise meta-analysis, with a low estimate of heterogeneity (I^2=23%; data not shown). In our network meta-analysis, indirect comparison of active treatments showed that adalimumab (moderate confidence), golimumab (moderate confidence), and etrolizumab (moderate confidence) were significantly inferior to infliximab; in addition, ustekinumab (moderate confidence) and ozanimod (moderate confidence) were significantly superior to adalimumab (appendix p 25). Overall, ustekinumab ranked highest for the induction of endoscopic improvement in biologic-naive patients (SUCRA 0·825; appendix p 26).

In our direct, pairwise meta-analysis in biologic-exposed patients, only ustekinumab, tofacitinib, and filgotinib 200 mg were significantly superior to placebo in the induction of clinical remission (I^2=36%; data not shown). Indirect comparison of active treatments in a network meta-analysis showed that tofacitinib (moderate confidence), ustekinumab (moderate confidence), and etrolizumab (moderate confidence) were significantly superior to adalimumab (appendix p 27). Additionally, tofacitinib (moderate confidence) and ustekinumab (moderate confidence) were significantly superior to vedolizumab (appendix p 27). No other indirect comparison between active treatments was statistically significant (appendix p 27). Tofacitinib (SUCRA 0·927) and ustekinumab (0·887) ranked highest for the induction of clinical remission in biologic-exposed patients (appendix p 26).

For the induction of endoscopic improvement in biologic-exposed patients, only tofacitinib and ustekinumab were

significantly superior to placebo in our direct, pairwise meta-analysis, with substantial heterogeneity (I^2=57%; data not shown). As observed for clinical remission, our network meta-analysis found that both tofacitinib and ustekinumab were significantly superior to both vedolizumab and adalimumab for the induction of endoscopic improvement (moderate confidence; appendix p 27). Tofacitinib (SUCRA 0·936) and ustekinumab (0·851) ranked highest for the induction of endoscopic improvement in biologic-exposed patients (appendix p 26).

Overall, seven studies reported rates of histological remission (ie, VARSITY, UNIFI, True North, SELECTION, VISIBLE 1, LAUREL, and HICKORY) that could be compared. Results of our post-hoc, direct, pairwise meta-analysis for histological remission are shown in the appendix (p 28).

Discussion

We reviewed available efficacy and safety data from RCTs of biologics and small molecule drugs (approved or in a late stage of development) for induction and maintenance treatment of patients with moderate-to-severe ulcerative colitis. All small molecule drugs and approved biologics, except filgotinib 100 mg, were significantly better than placebo in terms of inducing clinical remission and endoscopic improvement. A novel finding of this study was that upadacitinib ranked highest for the induction of clinical remission and endoscopic improvement, and was notably superior for these outcomes to all other interventions in our network meta-analysis. Infliximab ranked second for both outcomes. Regarding safety, vedolizumab was still ranked as the safest drug in terms of adverse events and serious adverse events, as previously observed by Singh and colleagues.[13] Upadacitinib had the highest SUCRA for all adverse events, showing that its remarkable efficacy might come at a cost of more adverse events. Results regarding filgotinib's safety were puzzling: it had the second lowest SUCRA for all adverse events, but ranked third highest for serious adverse events among active interventions. Representing another novel finding of this study, tofacitinib and infliximab were ranked highest for the maintenance of steroid-free remission in randomised responders and treat-straight-through studies, respectively.

Our study included RCTs evaluating infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, etrolizumab, tofacitinib, filgotinib, ozanimod, and upadacitinib. Evidence regarding the induction of clinical remission, endoscopic improvement, and safety outcomes from 29 studies was synthesised, and indirect comparisons between therapies were made. Since the most recent systematic review was published,[13] a large amount of new data involving novel compounds has become available. This sheer increase in the number of therapeutic options for ulcerative colitis makes frequent updates of indirect comparisons useful in the clinical setting.

The inflammatory bowel disease pipeline has shifted in the past 5 years towards small molecule drugs, in an effort to overcome the intrinsic limitations of biological treatment: moderate efficacy, loss of response, immunogenicity, and parenteral administration. However, available data from RCTs of small molecule drugs show that they induce similar rates of clinical remission and endoscopic improvement to biologics.[42] Moreover, safety concerns have arisen surrounding the use of tofacitinib, especially regarding the potential risk of venous thromboembolism and herpes zoster infection. One meta-analysis found an increased risk of herpes zoster infection with the use of JAK inhibitors in patients with immune-mediated inflammatory diseases, including inflammatory bowel disease.[43] This adverse event could be easily prevented by appropriate vaccination. The same meta-analysis did not find an increased risk of venous thromboembolism with the use of JAK inhibitors, although, until further evidence becomes available, caution is advised when considering JAK inhibitors as treatment options, especially in patients with known risk factors for thrombosis. Selective JAK-1 inhibitors, such as upadacitinib and filgotinib, were developed to improve the risk–benefit profile of this therapeutic class.[44] However, in our study, upadacitinib was ranked highest for all adverse events and filgotinib was ranked third highest among active interventions (ie, not including placebo) for serious adverse events, opposing this notion.

Representing a surprising finding of this study, ozanimod ranked highest for the occurrence of serious adverse events. Ozanimod is a selective sphingosine 1-phosphate modulator approved for the treatment of multiple sclerosis and ulcerative colitis in the USA. Another meta-analysis showed that sphingosine 1-phosphate modulators are associated with an increased risk of herpes zoster infection and transient cardiovascular events.[45]

Our study has several limitations besides the usual limitations of network meta-analyses. First, data from some clinical trials with newer small molecule drugs were extracted from conference abstracts, and the full data could not be completely analysed. Notably, we could only analyse outcomes for the overall population as the main analysis, and not according to previous exposure to biologics. We did do an exploratory analysis according to previous biologic exposure, but data for upadacitinib could not be included. Second, no phase 3 RCTs with etrasimod or TD-1473 were found; results from phase 3 clinical trials testing novel small molecule drugs (eg, etrasimod) in patients with moderate-to-severe ulcerative colitis are expected soon, which will warrant further updates of this analysis. Additionally, several newer biologics, especially anti-IL-23 drugs (ie, risankizumab, mirikizumab, guselkumab, and brazikumab), are also expected to yield positive results in phase 3 clinical trials, so these data should also be considered in the future to determine their position in treatment algorithms. Third, thorough

comparisons between all the included studies could only be done for induction outcomes, as different trial designs (treat-straight-through *vs* randomised responders) for maintenance studies could only be analysed in two different meta-analyses, in an approach similar to that used by Singh and colleagues.[13] Fourth, the included studies had important differences. Endoscopic outcomes were centrally read in more recent trials only; for most trials of biologics (except for the trials UNIFI[31] and VARSITY[29]), these outcomes were defined locally. Additionally, a more stringent definition of clinical remission, with a rectal bleeding sub-score of 0, was used in more recent clinical trials of small molecule drugs (ie, tofacitinib, ozanimod, filgotinib, and upadacitinib). Fifth, we analysed steroid-free remission—a more robust and clinically meaningful outcome than clinical remission—in maintenance trials only, as corticosteroid tapering was not allowed in induction trials. In addition, not all clinical trials reported on steroid-free remission, particularly the older trials. Finally, some preliminary reports, such as the trial of maintenance with subcutaneous vedolizumab, did not report relevant data for endoscopic improvement.

As with any indirect comparison, the results presented in this study should be interpreted with caution but could help clinicians to navigate the current scenario in which the number of therapeutic options for moderate-to-severe ulcerative colitis is steadily increasing. These findings should be interpreted as hypothesis-generating, until direct comparisons by means of head-to-head trials become available to fully elucidate the positioning of these therapies. Until then, these results might help clinicians to position drugs in treatment algorithms.

Contributors

LP-B contributed to the study concept and design. JSL and PAO contributed to data acquisition. JSL, PAO, and LP-B contributed to data analysis and data interpretation. PAO and JSL wrote the first draft of the manuscript. All authors critically revised the manuscript for intellectual content. SD and LP-B were guarantors of the Article. JSL and PAO accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JSL declares consulting fees from AbbVie and honoraria from Janssen. PAO declares consulting fees from AbbVie, Takeda, and Janssen; honoraria from Takeda and Janssen; and financial support for attending meetings, travel, or both from AbbVie, Takeda, Janssen, and Ferring. SD declares honoraria from AbbVie, Ferring, Hospira, Johnson and Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, and Boehringer Ingelheim. LP-B declares grants from AbbVie, MSD, Takeda, and Fresenius Kabi; consulting fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Inotrem, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera, Theravance, and Pandion Therapeutics; honoraria from AbbVie, Galapagos, Janssen, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Pfizer, Sandoz, Biogen, MSD, Arena, Gilead, Hikma, Amgen, and Vifor; financial support for attending meetings, travel, or both from AbbVie, Galapagos, Janssen, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Pfizer, Sandoz, Biogen, MSD, Arena, Gilead, Hikma, Amgen, and Vifor; participation on a data safety monitoring board or advisory board for Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Inotrem, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera, Theravance, and Pandion Therapeutics; and stock options from CT-SCOUT.

Data sharing

All data are provided in the Article and its appendix.

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