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Comparative Efficacy of Advanced Therapies for Management of Moderate-to-Severe Ulcerative Colitis: 2024 AGA Evidence Synthesis

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Abstract

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Background and Aims: We performed an updated systematic review and network meta-analysis to inform the 2024 American Gastroenterological Association (AGA) Clinical Guidelines on the management of moderate-to-severe ulcerative colitis (UC).

Methods: We searched multiple electronic databases through November 21, 2023 to identify randomized controlled trials (RCTs) in adults with moderate-to-severe UC, comparing different advanced therapies [tumor necrosis factor (TNF)-antagonists, vedolizumab, sphingosine-1-phosphate (S1P) receptor modulators, interleukin (IL)-12/23 or selective IL-23 antagonists, and/or Janus kinase (JAK) inhibitors] against placebo or another active comparator. Our primary outcomes were induction and maintenance of clinical remission, and our secondary outcome was endoscopic improvement. We performed a network meta-analysis using a frequentist approach, and applied Grading of Recommendations, Assessment, Development and Evaluation (GRADE) to appraise certainty of evidence.

Results: After excluding JAK inhibitors as potential first-line treatment (in accordance with FDA), low-certainty evidence supports clinically important benefit with infliximab, ozanimod, risankizumab and guselkumab over adalimumab and mirikizumab for achieving remission with induction therapy in biologic-naïve patients with moderate-severe UC, with risankizumab and ozanimod being ranked the highest for induction of clinical remission. With the inclusion of JAK inhibitors as first-line therapy, upadacitinib was more efficacious compared with all other medications except ozanimod and risankizumab with low to moderate certainty evidence. In patients with prior biologic exposure, upadacitinib, tofacitinib and ustekinumab were ranked highest for achieving remission.

Conclusions: Using GRADE to appraise quality of evidence, this updated network meta-analysis will be used to inform comparative efficacy and positioning of advanced therapies for the treatment of biologic-naïve and biologic-exposed patients with moderate-to-severe UC.

Keywords

Positioning; biologics; guidelines; inflammatory bowel diseases; comparative effectiveness

INTRODUCTION

Ulcerative colitis (UC) affects nearly 1.5 million individuals in the United States¹. It is characterized by a protracted course, leading to disease-related hospitalization or surgery in over one-third of patients^{2, 3}. Many patients with UC develop moderate-to-severe disease activity, requiring initiation of advanced immunosuppressive therapy^{3, 4}. The past two decades have witnessed significant progress in the development of these therapies, with the approval by the United States Food and Drug Administration (FDA) of six different therapeutic mechanisms, ten distinct drugs, and the anticipated approval of guselkumab⁵ and risankizumab⁶ in 2024. The increase in the number of available treatments has brought to the forefront the importance of appropriate positioning and sequencing of treatments and therapeutic mechanisms. Head-to-head trials in moderately-to-severely active UC to help guide these clinical decisions have been sparse and are limited to the VARSITY⁷ (vedolizumab versus adalimumab) and VEGA⁸ (guselkumab versus golimumab) trials among approved therapies. Consequently, relative efficacy is often inferred through network

meta-analyses (NMAs), which combine direct evidence from head-to-head trials and indirect evidence from placebo-controlled trials. Evidence from these NMAs have informed the 2020 American Gastroenterological Association (AGA) Clinical Guidelines on the management of moderate-to-severe UC^{9, 10}. Although NMAs have been published recently for moderate-to-severe UC^{11–13}, there have recently been substantial additions to the evidence base, including the availability of phase 3 efficacy data for mirikizumab¹⁴, guselkumab⁵, risankizumab⁶, and etrasimod¹⁵, evidence of efficacy for subcutaneous formulations of infliximab and vedolizumab¹⁶, and head-to-head comparison data between guselkumab and golimumab⁸. Prior NMAs have not critically appraised the available evidence which can inform clinical guidelines. Moreover, there has been limited data on the efficacy of different therapies stratified by prior exposure to biologic therapy, a key prognostic factor. Finally, there is discordance between options available for first-line therapy between other regions and the United States, where Janus kinase (JAK) inhibitors are approved by the FDA for use only after failure of tumor necrosis factor α (TNF) antagonists, necessitating different algorithms in these regions.

To inform a comprehensive 2024 Update to the AGA living guidelines on the management of moderate-to-severe UC, we conducted systematic reviews and NMAs to inform the comparative efficacy of different advanced therapies in biologic-naïve and biologic-exposed patients with moderate-to-severe UC. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for NMA to appraise the confidence in estimates.

METHODS

This systematic review was performed using an *a priori* established protocol, and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for systematic reviews incorporating NMAs for health care interventions.¹⁷ We followed good research practices outlined in the International Society for Pharmacoeconomics and Outcomes Research report on interpreting indirect treatment comparisons and NMA for health-care decision-making.¹⁸

Study Selection

We conducted two separate NMAs of induction therapy to estimate comparative efficacy of different advanced therapies in biologic-naïve patients and in patients with prior exposure to biologic therapy (>90% with prior exposure to TNF antagonists) for management of moderate-to-severe UC. Studies included in these meta-analyses were phase 2 or 3 randomized controlled trials (RCTs) that met the following inclusion criteria: (1) Patients: adults (age ≥ 18 years) with moderately-to-severely active UC (Mayo Clinic Score 6–12, with an endoscopic subscore of 2 or 3) who were either biologic-naïve or previously exposed to biologic therapy; (2) Intervention: advanced therapies including TNF antagonists (infliximab, adalimumab, golimumab), vedolizumab, sphingosine-1 phosphate (S1P) receptor modulators (ozanimod, etrasimod), JAK inhibitors (tofacitinib, upadacitinib, filgotinib), interleukin-12/23 (IL-12/23) antagonists (ustekinumab), or IL-23 antagonists (mirikizumab, risankizumab, guselkumab), with a minimum duration of therapy of 14

days; (3) Comparator: another active intervention or placebo; (4) Outcome: induction of clinical remission (Mayo Clinic Score ≤ 2 with no individual subscore of >1) and endoscopic improvement (Mayo endoscopy sub-score, 0 or 1).

Since trials of advanced therapies for maintenance of remission had different designs (treat-through design vs. re-randomization of responders to induction therapy), we conducted separate pairwise comparisons and NMAs accounting for these differences. In treat-through trials, patients are assigned to active treatment or placebo at screening and continue this through both the induction and maintenance phases. In responder re-randomization analysis, only patients who achieve clinical response at the end of induction are randomized to either placebo or active treatment during the maintenance phase. By virtue of selecting patients who are responders, the overall rates of response at the end of maintenance in such treatment trials are higher. Additionally, patients randomized to placebo for maintenance may have received active treatment during induction, and consequently there may be a carry-over effect of different duration and magnitude for different treatment mechanisms. Studies included in these meta-analyses were phase 2 or 3 RCTs that met the following inclusion criteria: (1) Patients: adults (age >18 years) with moderate-to-severe UC (Mayo Clinic Score 6–12, with an endoscopic subscore of 2 or 3), who either had active disease at enrollment, or had achieved clinical response to induction therapy with index agent; (2) Intervention: advanced therapies including TNF antagonists, vedolizumab, S1P receptor modulators, JAK inhibitors, IL-12/23, or IL-23 antagonists, with a minimum duration of therapy of 24 weeks; (3) Comparator: another active intervention or placebo; (4) Outcome: maintenance of clinical remission and endoscopic improvement.

We excluded the following studies: (1) trials where results were not stratified by prior exposure to biologic therapy, (2) trials of advanced therapies that have not yet been, or are unlikely to be approved by the FDA, based on registration trials (e.g., etrolizumab, AJM300, ontamalimab), (3) trials of novel agents (e.g., PRA023, olamkicept) or novel approaches (combination therapy of advanced therapies) in development but yet without phase 3 RCT data, (4) pediatric studies, or (5) trials conducted in patients hospitalized with acute severe UC. We also excluded trials of methotrexate for moderate-to-severe UC (not recommended as monotherapy for induction of maintenance of remission), and thiopurines (not effective for induction of remission, and limited transitivity in maintenance trials compared to contemporary trials of biologic agents and targeted small molecules).

Search Strategy, Data Abstraction and Risk of Bias Assessment

We conducted a comprehensive search of multiple electronic databases through November 21, 2023, with no language restrictions. The databases included Ovid MEDLINE, Ovid EMBASE, and Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, as well as clinical trial registries. The search strategy was designed and implemented by an experienced medical librarian, with input from a GRADE methodologist (S.S.), using controlled vocabulary supplemented with keywords, for RCTs of biologic therapy and small molecules in patients with IBD. Details of the search strategy are shown in the online supplement. We searched the bibliographies of these selected articles, systematic reviews, and clinical trial registries (www.clinicaltrials.gov)

to identify any additional studies. We also conducted a manual search of abstracts from major gastroenterology conferences (Digestive Disease Week, American College of Gastroenterology annual meeting, European Crohn's and Colitis Organization annual meeting, and United European Gastroenterology Week) from 2021 to 2023 to identify additional abstracts on the topic. Finally, we contacted experts in the field to identify other unpublished studies. Two sets of investigators independently reviewed the title and abstract of studies identified in the search to exclude studies that did not address the research question of interest based on pre-specified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information. Conflicts in study selection at this stage were resolved by consensus.

Data on study-, participant-, disease- and treatment-related characteristics were abstracted onto a standardized form, by two sets of investigators independently, and discrepancies were resolved by consensus. Two sets of study investigators independently rated the quality of included trials using the Cochrane Risk of Bias Tool version 2.0.

Outcomes

For trials of induction therapy, the efficacy outcomes were induction of clinical remission (defined as Mayo Clinic Score ≤ 2 with no individual subscore of >1), and endoscopic improvement (Mayo endoscopy sub-score, 0 or 1). The guideline panel rated clinical remission as a critical outcome for decision-making, and endoscopic improvement as an important outcome. We defined a minimal clinically important difference (MCID) of 50 per 1000 patients treated between two agents to define important vs. trivial differences. The timing of outcome assessment with induction trials was up to 14 weeks; when outcomes at multiple time points were reported, we used outcomes at week 8 or 6. For trials of maintenance therapy, efficacy outcomes were maintenance of clinical remission and endoscopic improvement. For maintenance trials, outcomes were assessed at last point of follow-up in the placebo-controlled arm, usually week 52. Recognizing limitations of trials in evaluating treatment safety, we qualitatively synthesized the overall safety of all agents, regardless of first- or second-line therapy, and presented these estimates as proportions of patients with any adverse event, adverse events leading to drug discontinuation, serious adverse events and serious infections. When data for multiple doses of the same medication was available, for agents that have received regulatory approval, only data for the approved dose and administration was considered. The denominator used in all trials was based on intention-to-treat analysis, and all dropouts were assumed to be treatment failures for the primary outcome of clinical remission; for endoscopic improvement, only patients with follow-up endoscopy were included. For safety outcomes, last-observation-carried-forward imputation was used.

Data Synthesis and Statistical Analysis

We performed NMAs using the frequentist approach, with the statistical package "netmeta" (version 9.0, <https://cran.r-project.org/web/packages/netmeta/index.html>) in R (version 4.0.2)¹⁹. We examined local incoherence in each node by comparing the results of head-to-head estimates and indirect estimates. We provide the P-score to rank the efficacy of treatments, which is analogous to the surface under the cumulative ranking curve. The

P-score ranges from a value between 0 (worst) to 1 (best) and is determined solely on the point estimates and standard errors of the network estimates under the normality assumption. However, the difference between consecutively ranked treatments may not be statistically significant. Reflecting the recommendation of the FDA restricting use of JAK inhibitors only in patients with failure or intolerance of TNF antagonist therapy, we performed two separate analyses including and subsequently excluding this therapeutic class as first-line treatment.

GRADE Certainty of Evidence

We followed the GRADE approach to appraise the confidence in estimates derived from NMA of efficacy outcomes. In this approach, direct evidence from RCTs starts at high confidence and can be rated down based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity) and/or publication bias, to levels of moderate, low, and very low confidence. The rating of indirect estimates starts at the lowest rating of the two pairwise estimates that contribute as first-order loops to the indirect estimate but can be rated down further for imprecision or intransitivity (dissimilarity between studies in terms of clinical or methodological characteristics). Network consistency was evaluated by comparing the direct estimates to the indirect estimates for each comparison, using a node-splitting technique. If direct and indirect estimates were similar (i.e., coherent), then the higher of their rating can be assigned to the NMA estimates. For all estimates, we considered the difference between an active agent vs. comparator as 'important' if the absolute risk difference of achieving remission crossed the MCID threshold of >50 per 1000 patients treated (5%), and 'trivial' if the absolute risk difference was between 0 to 50 per 1000 patients treated. In order to ascertain imprecision for the NMA, we relied on absolute risk difference. To calculate this absolute risk for each comparison between active agents, we relied on estimated control risk derived from the corresponding relative risk of drug vs. placebo in biologic-naïve and biologic-exposed patients, assuming a placebo control rate of 10% in biologic-naïve patients and 5% in biologic-exposed patients. In assessing imprecision, we rated down evidence twice for very serious imprecision if the lower limit of 95% CI for a comparison crossed the MCID and line of unity (no difference in efficacy) and rated down once for serious imprecision if only the MCID was crossed, but not the line of unity. In instances where evidence was not rated down for imprecision, we rated down for failure to meet optimal information size if the ratio of upper limit of 95% CI and lower limit of 95% CI of the relative risk was >3. 'The primary NMA results are presented as risk difference (%) with their respective GRADE certainty rating and confidence intervals as Gordon Plots (Graphic On Results Diagram of NMA).'²⁰

RESULTS

Search Strategy

Our search strategy yielded 5,350 unique studies. From among these, we identified 35 trials of treatments for moderate-to-severe UC. This included 13 trials of TNF antagonists (5 infliximab^{21–24}, 5 adalimumab^{25–28}, 3 golimumab^{8, 29, 30}), three trials of anti-integrins (3 vedolizumab^{7, 31, 32}), five trials of anti-IL 12/23 (1 ustekinumab³³) or anti-IL23 antibodies (2 mirikizumab^{14, 34}, 2 guselkumab^{5, 8, 35}, 1 risankizumab⁶), five trials of S1P modulators (2 ozanimod^{36, 37}, 3 etrasimod^{15, 38}), and eight trials of JAK inhibitors (3 upadacitinib^{39, 40}, 3

tofacitinib^{41, 42}, 2 filgotinib⁴³). Additionally, we included data from subcutaneous infliximab (LIBERTY-UC)⁴⁴ and vedolizumab¹⁶ (VISIBLE) in the evidence base for those treatments in maintaining remission, consistent with their approved indications. We excluded the Phase 3 RCTs of etrolizumab from primary analysis for our NMA as the treatment failed to meet its primary endpoint and it is not approved for use in UC either in North America or Europe. However, data from the placebo and adalimumab arms of the HIBISCUS trial²⁵ were incorporated into the evidence base. However, in a sensitivity analysis, given the availability of phase 3 RCT data, we included etrolizumab as a treatment option in both the induction and maintenance arms. Two head-to-head active comparator trials were included in our NMA: VARSITY⁷ (vedolizumab versus adalimumab) and VEGA⁸ (golimumab versus guselkumab). We did not include the combination golimumab-guselkumab arm in our NMA given lack of FDA or European Medicines Agency approval.

Study Population

Tables 1 and Supplementary Table 1 describe the characteristics of the included trials. The average age of included participants ranged from 34–45 years and 40–60% were males. Approximately two-thirds of patients in the included studies had extensive colitis and the median disease duration at inclusion ranged from 5–9 years. Concomitant use of immunomodulators or corticosteroids was variable across studies, ranging from 30 to 80%. Patient characteristics were generally comparable across clinical trials except for a higher proportion of patients on combination immunomodulator therapy in the trials of biologic agents compared to small molecules; however, in all trials, patients had moderately to severely active disease despite being on immunomodulators at randomization. Approximately 20–55% had prior exposure to biologics. Prior biologic use comprised predominantly of TNF antagonist exposure in the earlier RCTs while subsequent biologic and small molecule trials included a fraction of patients with prior vedolizumab but not TNF antagonist exposure. Trials of infliximab and golimumab trials did not include patients with prior biologic exposure.

Clinical remission in most trials was defined using the total or adapted Mayo score, defined as a stool frequency subscore of ≤ 1 AND a rectal bleeding score of 0; and an endoscopic subscore of ≤ 1 without friability. Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1. Due to lack of generalizable data from all clinical trials, we did not perform an NMA separately for outcomes of endoscopic remission (Mayo endoscopic score of 0), histologic healing, or histo-endoscopic mucosal healing. For induction trials, clinical outcomes were typically measured at 6–12 weeks, while for maintenance trials, outcomes were usually assessed at 52 weeks. The mean placebo rate for induction of clinical remission for biologic-naïve and biologic-exposed patients was 10% (range 0–22%) and 5% (range 0–16%) respectively. Supplementary Tables 2 and 3 present the rates of adverse events in the induction and maintenance arms of the including RCTs. Most trials were deemed to be at low risk of bias.

First-Line treatment

Induction of Clinical Remission: Evidence for induction of clinical remission was available for infliximab, adalimumab, golimumab, vedolizumab, ozanimod,

etrasimod, ustekinumab, mirikizumab, risankizumab, guselkumab, tofacitinib, filgotinib and upadacitinib. Here, we performed separate analysis in scenarios where JAK inhibitors are not used as first-line agents (reflecting FDA restriction in the United States) (Figure 1a) or where use of JAK inhibitors was permitted first line (other regions) (Figure 2a). On examination of the direct evidence, all treatments were more effective than placebo in inducing clinical remission. The treatments with the greatest effect size were for upadacitinib, risankizumab, and ozanimod (Figure 2b).

After excluding JAK inhibitors as potential first-line treatment, we observed with low certainty evidence that infliximab, golimumab, ozanimod, risankizumab and guselkumab were possibly associated with higher likelihood of achieving remission compared with adalimumab with induction therapy in biologic-naïve patients with moderate-severe UC (Table 2). We also observed that infliximab, ozanimod, risankizumab and guselkumab were possibly associated with higher likelihood of achieving remission compared with mirikizumab with induction therapy (Table 2). After excluding JAK inhibitors, amongst biologic-naïve patients with moderately to severely active UC, risankizumab (P-score 0.86) and ozanimod (P-score 0.83) were ranked highest for induction of clinical remission (Figure 1b). With an estimated placebo rate of achieving remission of 10% in biologic-naïve patients with moderate-to-severe UC, we anticipate that 35%, 35%, 27%, 26%, and 26 % of risankizumab-, ozanimod-, guselkumab-, infliximab-, and golimumab-treated patients, respectively, would achieve remission with induction therapy.

With the inclusion of JAK inhibitors as potential first-line therapy, we observed with moderate certainty evidence that upadacitinib was associated with clinically important benefit in achieving remission compared with infliximab, adalimumab, etrasimod, ustekinumab, mirikizumab, tofacitinib and filgotinib, and low certainty evidence that upadacitinib was associated with higher rates of remission compared with golimumab, vedolizumab, and guselkumab (Table 3). In contrast, infliximab, golimumab, ozanimod, risankizumab and guselkumab were possibly associated with higher likelihood of achieving remission compared with tofacitinib and filgotinib (Table 3). Overall, in jurisdictions where JAK inhibitors are available for first-line adoption, amongst biologic-naïve patients with moderately to severely active UC, upadacitinib (P-score 0.96) was ranked highest for induction of clinical remission (Figure 2b). With an estimated placebo rate of achieving remission of 10% in included trials, we anticipate that 49%, 18% and 17% of upadacitinib-, tofacitinib- and filgotinib-treated patients, respectively, would achieve remission with induction therapy.

Induction of endoscopic improvement: The evidence supporting efficacy of different treatments for achieving endoscopic improvement at the end of induction was broadly consistent with induction of clinical remission data (Tables 2–4). Compared to placebo, all treatments were more effective in inducing endoscopic improvement. Overall, upadacitinib (P-score 0.97) and risankizumab (P-score 0.92) were ranked highest (eFigure 1a–b)

Treatment in biologic-exposed patients

Evidence for induction therapy in biologic-exposed patients was available for adalimumab, vedolizumab, ozanimod, etrasimod, ustekinumab, mirikizumab, risankizumab, guselkumab, tofacitinib, and upadacitinib (Figure 3a). There were no trials of infliximab or golimumab in biologic-exposed patients with moderate-to-severe UC. On NMA, compared with placebo, we observed with moderate certainty evidence that that ustekinumab, mirikizumab, risankizumab, guselkumab, tofacitinib, filgotinib and upadacitinib were probably associated with higher likelihood of achieving clinical remission; in contrast, there was low certainty evidence of trivial benefit with

adalimumab, vedolizumab, ozanimod and etrasimod in inducing clinical remission in patients with prior exposure to biologics (Figure 3b).

Against other active treatment comparators, we observed with moderate certainty evidence that upadacitinib was associated with clinically important benefit in achieving remission compared with adalimumab, vedolizumab, ozanimod, etrasimod, mirikizumab, risankizumab, guselkumab and filgotinib (Table 4). Similarly, there was moderate certainty evidence that tofacitinib was associated with clinically important benefit in achieving remission compared with adalimumab, vedolizumab and etrasimod, and low certainty evidence that tofacitinib was associated with clinically important benefit compared with ozanimod and mirikizumab (Table 4). Overall, upadacitinib (P-score 0.93), tofacitinib (P-score 0.88), and ustekinumab (P-score 0.87) ranked highest in inducing remission in biologic-exposed patients with moderate-to-severely active UC. With an estimated placebo rate of achieving remission of 5% in biologic-exposed patients with moderate-severe UC, we anticipate that 70%, 55%, 52%, 14%, and 14% upadacitinib-, ustekinumab-, tofacitinib-, guselkumab-, and risankizumab-treated patients, respectively, would achieve remission with induction therapy. As in biologic-naïve patients, endoscopic improvement data was broadly consistent with the clinical remission comparisons (Table 4).

Maintenance of Clinical Remission: We stratified the analysis of maintenance of clinical remission by trial design, separately analyzing treat-through and responder-re-randomization trials. Trials of infliximab, adalimumab, vedolizumab, and etrasimod provided information on maintenance of clinical remission at one year using a treat-through design. We observed that etrasimod was associated with higher likelihood of maintaining remission compared with infliximab (moderate certainty) and adalimumab (low certainty) (Supplementary Table 4). Vedolizumab was associated with higher likelihood of maintaining remission compared with adalimumab with moderate certainty (eFigure 2a–b).

We identified trials of adalimumab, golimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, ozanimod, tofacitinib, upadacitinib, and filgotinib for maintenance of remission using responder re-randomization analysis. All other agents provided information on maintenance of remission at 1 year using a responder re-randomization analysis. Both upadacitinib 30mg daily (RR, 2.83; 95% CI, 0.99–8.10) and 15mg daily (RR, 2.32; 95% CI, 0.81–6.68) and tofacitinib 10mg twice daily (RR, 2.41; 95% CI, 0.85–6.80) were superior to risankizumab with low certainty of evidence (Supplementary Table 5). Of note, maintenance of remission rates with placebo in trials of IL-23 antagonists were generally higher than in

trials of other agents suggesting a longer carryover period after induction therapy. Results for the outcome of maintenance of endoscopic improvement were largely similar to results observed for the maintenance of clinical remission (eFigure 3a–b).

In a sensitivity analysis including etrolizumab, in the treatment-naïve population, etrolizumab ranked near the bottom for induction of clinical remission (p-score 0.30) (eFigure 4a_ or endoscopic improvement (p-score 0.24). For induction of clinical remission in biologic-exposed patients, etrolizumab was rated similar in efficacy to IL-23 antagonists and filgotinib (eFigure 4b), while for the outcome of maintenance of clinical remission, etrolizumab had the lowest efficacy (eFigure 4c–d).

DISCUSSION

The therapeutic armamentarium for the treatment of moderate-to-severe UC has expanded significantly with the approval of three new therapeutic mechanisms – JAK inhibitors, selective IL-23 antagonists, and S1P modulators. In this updated systematic review and NMA, which is being used to inform an update to the AGA Clinical Guidelines for the management of moderate-to-severe UC, we examined direct and indirect evidence from 35 trials to inform positioning of treatments within our therapeutic algorithm. We performed a thorough critical appraisal of the body of evidence using GRADE for NMA, contextualizing the absolute magnitude of benefit after setting a minimal important difference of 5% to confirm higher efficacy of one medication over another. We make several key observations which will decisively inform positioning of newer therapies for the management of moderate-severe UC: (a) as first-line treatment, in countries outside the United States where JAK inhibitors can be used prior to failure of other advanced therapies, upadacitinib was the most efficacious in inducing clinical remission, achieving remission in ~50% patients; (b) as first-line therapy excluding JAK inhibitors as guided by the FDA approval in the United States, risankizumab and ozanimod were ranked highest in achieving clinical remission; and (c) in all regions, upadacitinib was the most effective second-line agent in biologic-exposed patients. Interestingly, in the treat-through maintenance trials, vedolizumab and etrasimod were more effective than TNF-antagonists, supporting the efficacy of anti-lymphocyte trafficking mechanisms in the treatment of bio-naïve moderate-to-severe UC.

Our findings update the results of recent NMAs^{11–13, 45} by three important methodologic additions. First, we added data on several additional therapies with available phase 3 efficacy data since the prior analyses including one S1P modulator (etrasimod) and three anti-IL-23 agents (guselkumab, risankizumab, and mirikizumab). Second, with the increasing use of biosimilars and alternate routes of administration, we also included data from trials of subcutaneous infliximab and vedolizumab. Third, we were able to further strengthen the network with addition of a second direct-head-to-head trial in UC, comparing guselkumab to golimumab. In addition, prior NMAs included 5 trials of etrolizumab, an anti-integrin, which did not meet its primary efficacy endpoint and is thus unlikely to be approved for use at this time, which may have influenced relative positioning. Also distinct from prior NMAs, we separated our analyses including and excluding JAK inhibitors as first line agents for the treatment of moderate-to-severe UC.

In regions without restrictions on the use of JAK inhibitors, our findings demonstrate that upadacitinib was more efficacious than nearly all other available therapies except ozanimod and risankizumab for induction of clinical remission. In the upadacitinib induction trials, the rate of clinical remission observed were 33% and 26%. The low placebo rates of 4% and 5% in these clinical trials further strengthened the evidence in support of superior efficacy of this drug, yielding an absolute benefit of 29% and 22% in achieving clinical remission, a margin that was greater than has been observed for other advanced therapies in UC. Data from multiple real-world cohorts has supported these high rates of remission and response with upadacitinib^{46, 47}. In the United States, a boxed warning placed by the FDA on this therapeutic class requires prior failure of, or contraindications to, TNF antagonists before the use of any JAK inhibitors. This decision by the FDA was informed by a post-marketing surveillance study of adults 50 years or age or older with rheumatoid arthritis and at least one cardiovascular risk factor treated with tofacitinib, a non-selective JAK inhibitor, in which both an increased risk of major adverse cardiovascular events (MACE) and malignancy compared to anti-TNF therapy were observed, particularly with the 10 mg BID dose of tofacitinib⁴⁸. The EMA, while not recommending against first-line use, advises caution in use in older adults and smokers. Post-hoc analyses of trials of tofacitinib in UC and observational studies did not identify a clear increase in risk of venous thromboembolism or MACE in this population compared to anti-TNF therapy^{49–51}. In a subsequent NMA, the risk of cardiovascular events was not higher with JAK inhibitors compared to TNF antagonists or anti-interleukin therapy among patients with IBD⁵². Given the superiority of upadacitinib over other therapies in most clinical scenarios, it is important to prioritize future studies of safety of this therapeutic class in those with IBD, and additionally whether the safety concerns apply equally to both selective and non-selective JAK inhibitors, as well as across specific indications for their use.

In biologic-naïve patients excluding use of JAK inhibitors as first line, our NMA demonstrated the superiority of several agents (infliximab, vedolizumab, risankizumab, ozanimod) over adalimumab. These findings are different from several recent NMAs which did not show a difference between the two treatments. This is an important observation as adalimumab is one of the most commonly prescribed biologics for UC⁵³, influenced by both physician and patient preferences and payor restrictions. While efficacy differences on indirect comparisons are only one factor in determining therapeutic positioning of available therapies, it is important that any positioning restriction reflect treatment effectiveness and the impact on patient outcomes to ensure the highest-value care.

Our study also highlights the importance of prior treatment exposure on subsequent therapy selection in moderate-to-severe UC. Absent data on infliximab or golimumab, the most efficacious treatment in biologic-exposed patients was upadacitinib, which demonstrated superior efficacy despite 30–35% of patients in its clinical trials having failed two or more prior biologics. Intriguingly, the difference in relative efficacy of a drug in biologic-exposed vs. biologic-naïve patients was significantly greater for some drugs, most notably for vedolizumab and ozanimod in our analysis. Ozanimod was highly efficacious in inducing clinical remission in biologic naïve-patients and superior to both adalimumab and mirikizumab. In contrast, it failed to achieve superiority over placebo in inducing clinical remission in biologic-exposed patients. This observation is consistent with results from the

pivotal clinical trial where both in biologic-naïve and in patients with only one prior biologic exposure, ozanimod had rates of clinical remission of 23% and 17% compared to 7% and 8% in placebo⁵⁴. However, in those who were exposed to 2 or more biologics, ozanimod was no better than placebo in achieving clinical remission after induction (4% vs. 3%). The exact mechanism(s) of this drop in efficacy in a biologic exposed population remains to be robustly determined, but our findings highlight the critical determinative nature of this as a prognostic variable in therapy selection.

Both this study and prior NMAs demonstrate that the efficacy of different drugs within the same therapeutic class may not be comparable. We found infliximab to be superior to adalimumab, upadacitinib to be superior to both tofacitinib and filgotinib, and risankizumab to be superior to mirikizumab in biologic-naïve patients. The mechanism(s) for a potential difference in efficacy within agents in the same class is unclear and may be driven by both methodological considerations related to trial design and biologic plausibility. Multiple observational studies have compared the effectiveness of infliximab and adalimumab in real-world cohorts, demonstrating a benefit favoring infliximab in many but not all studies^{55, 56}. The mechanism(s) for this difference in efficacy does not appear to be related to either the weight-based dosing of infliximab or induction or maintenance dose of adalimumab, as no incremental evidence of greater efficacy with high-dose adalimumab induction was observed in the SERENE-UC trials⁵⁷. The greater JAK selectivity of upadacitinib may allow for a better dosing profile without compromising safety leading to superior efficacy^{58, 59}. This efficacy difference was also observed in real-world cohort studies, supporting our conclusion⁴⁶.

Our NMA suggested upadacitinib, tofacitinib, and ustekinumab to be superior to vedolizumab in those with prior biologic failures. This is also consistent with recent observational data. Buisson *et al.* conducted a propensity-matched analysis of vedolizumab and tofacitinib in those with a prior anti-TNF failure. While there was no difference in clinical remission rates at week 16 between both agents, vedolizumab was inferior to tofacitinib in achieving endoscopic improvement and histologic healing⁶⁰. A large Dutch registry-based study similarly demonstrated superior efficacy of tofacitinib over vedolizumab⁶¹. In contrast, while a US insurance-based study demonstrated lower persistence of tofacitinib over vedolizumab, this lacked granular data to discern differences in treatment efficacy⁶². There are few real-world studies comparing ustekinumab to vedolizumab in biologic-exposed patients with UC. However, our observation of superiority of ustekinumab over vedolizumab is consistent with the signal observed in the phase 3 clinical trials. In the GEMINI 1 trial, the magnitude of clinical benefit of vedolizumab over placebo in TNF antagonist-naïve patients was 16.5% compared to only 6.5% in TNF antagonist-exposed patients. In contrast, in the UNIFI studies, ustekinumab achieved a similar benefit over placebo in both TNF antagonist-naïve (delta=8.5%) and TNF antagonist-exposed individuals (delta=11.5%)⁶³.

There are several limitations to our work. The direct and indirect evidence was informed by RCT data of FDA-approved doses of each agent. Modification of dosing in real-world practice may alter comparative efficacy and was not included in our models. For example, early proactive trough assessment and dose optimization for TNF antagonist

therapy, combination immunomodulator therapy for infliximab, and extended induction for tofacitinib or upadacitinib have been shown to incrementally increase rates of remission over therapy with the standard induction dose alone^{64, 65}. Second, while our analysis stratified by prior biologic exposure status, it is acknowledged that with the increasing complexity of our therapeutic armamentarium, this comparison will become more nuanced. Apart from TNF antagonists, S1P modulators, JAK inhibitors, and IL-23 inhibitors, all have multiple agents within the same therapeutic class. Prior failure of a drug within that class may have specific implications for other drugs within that class but not other mechanisms of action. In addition, trials of subsequent agents within a therapeutic class often exclude patients previously exposed to that mechanism of action. In many of the early clinical trials, most prior biologic exposure comprised of TNF antagonist failure. In more recent studies, a small fraction entering the trials may have failed vedolizumab but not other mechanisms. How these prior exposures to available biologic or small molecule therapies affect subsequent treatment efficacy remains to be established. Third, we focused on induction of clinical remission as the critical outcome of interest. Other outcomes including corticosteroid-free remission are clinically meaningful. However, there is significant heterogeneity between trials in how concomitant steroid use is handled. Almost all induction trials require stable doses of steroids during the trial, but studies differed by whether steroid taper was mandated during maintenance, and the pace of such tapers. Consequently, we elected not to use steroid-free remission as an outcome for our analysis. We did not separately stratify by both concomitant immunomodulator use and prior biologic exposure due to lack of statistical power for this comparison given wide range of immunomodulator use and that most patients entering the trials had failed immunomodulator or 5-aminosalicylate therapy prior to study entry. Similarly, both the paucity of data (particularly in older trials) and heterogeneity in definition between studies precluded comparisons of endoscopic remission (endoscopic subscore=0) or histologic healing. These may increasingly be relevant for future analyses but it will remain a challenge to integrate such data for newer agents with the absence of ascertainment of these endpoints for older trials. We also selected a threshold of an absolute difference of 5% in defining superiority of one agent over the other. Anchored against the approximately 25% and 15% clinical remission rates for biologic-naïve and exposed patients respectively, these represent a 20% and 33% increase in efficacy which was felt to be a meaningful difference. In future studies, engaging patients and providers to ascertain what a clinically meaningful difference might be would be helpful to refine this threshold. Therapy choice is influenced not just by efficacy but also safety of treatments under consideration. We did not perform an NMA of safety between different therapies for several reasons. Serious adverse events including infections and malignancy risk were low with all examined treatments within clinical trials, limiting statistical power for meaningful comparison between treatments. Larger observational cohorts with longer duration of follow-up have been more meaningful in informing comparative safety in this population. For example, such studies have demonstrated lower rates of infection with vedolizumab when compared to TNF antagonists, and similar risks with TNF antagonist and JAK inhibitor treatment^{50, 66}. More than efficacy, decisions about safety are more nuanced incorporating patient characteristics such as age, race, ethnicity, geography, comorbidity, concomitant treatments (including steroid use), and frailty. Consequently, NMAs may be less applicable for extrapolation of safety at the level of individual patients.

In conclusion, our NMA highlights upadacitinib as the most effective therapy for moderately-to-severely active UC in both bio-naïve and bio-exposed populations, demonstrating the urgent importance of studies of long-term safety of this treatment in patients with UC to inform the need for usage restriction. We also identify within-class differences in treatment efficacy across different therapeutic mechanisms and highlight the importance of prior biologic exposure as a key determinant of treatment selection in moderate-to-severe UC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Lewis JD, Parlett LE, Jonsson Funk ML, et al. Incidence, Prevalence, and Racial and Ethnic Distribution of Inflammatory Bowel Disease in the United States. *Gastroenterology* 2023;165:1197–1205 e2. [PubMed: 37481117]
2. Pillai N, Dusheiko M, Maillard MH, et al. The Evolution of Health Care Utilisation and Costs for Inflammatory Bowel Disease Over Ten Years. *J Crohns Colitis* 2019;13:744–754. [PubMed: 30916775]
3. Fumery M, Singh S, Dulai PS, et al. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. *Clin Gastroenterol Hepatol* 2018;16:343–356 e3. [PubMed: 28625817]
4. Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. *Lancet* 2023;402:571–584. [PubMed: 37573077]

5. Rubin DT, Allegretti JR, Panes J, et al. The efficacy and safety of guselkumab as maintenance therapy in patients with moderate to severely active ulcerative colitis: REsults from the Phase 3 Quasar Maintenance study. *Gastroenterol* 2024 166:S-180.
6. Louis E, Panaccione R, Parkes G, et al. Risankizumab induction therapy in patients with moderately to severely active ulcerative colitis: Efficacy and Safety in teh randomized phase 3 INSPIRE study. *United European Gatsroenterology Journal* 2023;11:26–28.
7. Sands BE, Peyrin-Biroulet L, Loftus EV, Jr., et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. *N Engl J Med* 2019;381:1215–1226. [PubMed: 31553834]
8. Feagan BG, Sands BE, Sandborn WJ, et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. *Lancet Gastroenterol Hepatol* 2023;8:307–320. [PubMed: 36738762]
9. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology* 2020;158:1450–1461. [PubMed: 31945371]
10. Singh S, Allegretti JR, Siddique SM, et al. AGA Technical Review on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology* 2020;158:1465–1496 e17. [PubMed: 31945351]
11. Singh S, Murad MH, Fumery M, et al. First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis. *Clin Gastroenterol Hepatol* 2020;18:2179–2191 e6. [PubMed: 31945470]
12. Burr NE, Gracie DJ, Black CJ, et al. Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis. *Gut* 2022;71:1976–1987.
13. Lasa JS, Olivera PA, Danese S, et al. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2022;7:161–170. [PubMed: 34856198]
14. D’Haens G, Dubinsky M, Kobayashi T, et al. Mirikizumab as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2023;388:2444–2455. [PubMed: 37379135]
15. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. *Lancet* 2023;401:1159–1171. [PubMed: 36871574]
16. Sandborn WJ, Baert F, Danese S, et al. Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis. *Gastroenterology* 2020;158:562–572e12. [PubMed: 31470005]
17. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84. [PubMed: 26030634]
18. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health* 2011;14:417–28. [PubMed: 21669366]
19. Balduzzi S, Rücker G, Nikolakopoulou A, et al. netmeta: An R Package for Network Meta-Analysis Using Frequentist Methods. *Journal of Statistical Software* 2023;106:1–40. [PubMed: 37138589]
20. Gordon M Maintaining remission in Crohn’s disease post surgery: what can we learn from Cochrane? *Frontline Gastroenterol* 2024;15:241–246. [PubMed: 38665790]
21. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis.[Erratum appears in *N Engl J Med*. 2006 May 18;354(20):2200]. *New England Journal of Medicine* 2005;353:2462–76. [PubMed: 16339095]
22. Jiang XL, Cui HF, Gao J, et al. Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis. *J Clin Gastroenterol* 2015;49:582–8. [PubMed: 25844841]

23. Ltd. X-JP. A Study to Evaluate the Effectiveness and Safety of Infliximab in Chinese Patients With Active Ulcerative Colitis. Volume 2017. clinicaltrials.gov, 2015.
24. Kobayashi T, Suzuki Y, Motoya S, et al. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. *J Gastroenterol* 2016;51:241–51. [PubMed: 26162647]
25. Rubin DT, Dotan I, DuVall A, et al. Etrolizumab versus adalimumab or placebo as induction therapy for moderately to severely active ulcerative colitis (HIBISCUS): two phase 3 randomised, controlled trials. *Lancet Gastroenterol Hepatol* 2022;7:17–27. [PubMed: 34798036]
26. Suzuki Y, Motoya S, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. *J Gastroenterol* 2014;49:283–94. [PubMed: 24363029]
27. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011;60:780–7. [PubMed: 21209123]
28. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012;142:257–65.e1–3. [PubMed: 22062358]
29. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:85–95; quiz e14–5. [PubMed: 23735746]
30. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:96–109 e1. [PubMed: 23770005]
31. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *New England Journal of Medicine* 2013;369:699–710. [PubMed: 23964932]
32. Motoya S, Watanabe K, Ogata H, et al. Vedolizumab in Japanese patients with ulcerative colitis: A Phase 3, randomized, double-blind, placebo-controlled study. *PLoS One* 2019;14:e0212989. [PubMed: 30807613]
33. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2019;381:1201–1214. [PubMed: 31553833]
34. Sandborn WJ, Ferrante M, Bhandari BR, et al. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Ulcerative Colitis. *Gastroenterology* 2020;158:537–549 e10. [PubMed: 31493397]
35. Peyrin-Biroulet L, Allegretti JR, Rubin DT, et al. Guselkumab in Patients With Moderately to Severely Active Ulcerative Colitis: QUASAR Phase 2b Induction Study. *Gastroenterology* 2023;165:1443–1457. [PubMed: 37659673]
36. Sandborn WJ, Feagan BG, D’Haens G, et al. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2021;385:1280–1291. [PubMed: 34587385]
37. Sandborn WJ, Feagan BG, Wolf DC, et al. Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis. *N Engl J Med* 2016;374:1754–62. [PubMed: 27144850]
38. Sandborn WJ, Peyrin-Biroulet L, Zhang J, et al. Efficacy and Safety of Etrasimod in a Phase 2 Randomized Trial of Patients With Ulcerative Colitis. *Gastroenterology* 2020;158:550–561. [PubMed: 31711921]
39. Danese S, Vermeire S, Zhou W, 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;399:2113–2128. [PubMed: 35644166]
40. Sandborn WJ, Ghosh S, Panes J, et al. Efficacy of Upadacitinib in a Randomized Trial of Patients With Active Ulcerative Colitis. *Gastroenterology* 2020;158:2139–2149 e14. [PubMed: 32092309]
41. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2017;376:1723–1736. [PubMed: 28467869]
42. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012;367:616–24. [PubMed: 22894574]

43. Feagan BG, Danese S, Loftus EV, Jr., et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *Lancet* 2021;397:2372–2384. [PubMed: 34090625]
44. Sands BE, Hanauer S, Colombel JF, et al. Subcutaneous infliximab (CT-P13 SC) as maintenance therapy for ulcerative colitis: A Phase 3, randomized, placebo-controlled study: Results of the LIBERTY-UC study. *J Crohns Colitis* 2023;17:i623–624.
45. Panaccione R, Collins EB, Melmed GY, et al. Efficacy and Safety of Advanced Therapies for Moderately to Severely Active Ulcerative Colitis at Induction and Maintenance: An Indirect Treatment Comparison Using Bayesian Network Meta-analysis. *Crohns Colitis* 2023;5:otad009. [PubMed: 36998249]
46. Boneschansker L, Ananthakrishnan AN, Massachusetts General Hospital Cs, et al. Comparative Effectiveness of Upadacitinib and Tofacitinib in Inducing Remission in Ulcerative Colitis: Real-World Data. *Clin Gastroenterol Hepatol* 2023;21:2427–2429 e1. [PubMed: 37031712]
47. Friedberg S, Choi D, Hunold T, et al. Upadacitinib Is Effective and Safe in Both Ulcerative Colitis and Crohn's Disease: Prospective Real-World Experience. *Clin Gastroenterol Hepatol* 2023;21:1913–1923 e2. [PubMed: 36898598]
48. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N Engl J Med* 2022;386:316–326. [PubMed: 35081280]
49. Curtis JR, Regueiro M, Yun H, et al. Tofacitinib Treatment Safety in Moderate to Severe Ulcerative Colitis: Comparison of Observational Population Cohort Data From the IBM MarketScan(R) Administrative Claims Database With Tofacitinib Trial Data. *Inflamm Bowel Dis* 2021;27:1394–1408. [PubMed: 33324993]
50. Kochar BD, Cheng D, Cai T, et al. Comparative Risk of Thrombotic and Cardiovascular Events with Tofacitinib and Anti-TNF Agents in Patients with Inflammatory Bowel Diseases. *Dig Dis Sci* 2022;67:5206–5212. [PubMed: 35113275]
51. Sandborn WJ, Panes J, Sands BE, et al. Venous thromboembolic events in the tofacitinib ulcerative colitis clinical development programme. *Aliment Pharmacol Ther* 2019;50:1068–1076. [PubMed: 31599001]
52. Mattay SS, Zamani M, Saturno D, et al. Risk of Major Adverse Cardiovascular Events in Immune-Mediated Inflammatory Disorders on Biologics and Small Molecules: Network Meta-Analysis. *Clin Gastroenterol Hepatol* 2024;2:961–970.e12.
53. Armuzzi A, DiBonaventura MD, Tarallo M, et al. Treatment patterns among patients with moderate-to-severe ulcerative colitis in the United States and Europe. *PLoS One* 2020;15:e0227914. [PubMed: 31945774]
54. Sands B, Nguyen D, Pondel M, et al. Impact of Prior Biologic Exposure on Patient Response to Ozanimod for Moderate-to-Severe Ulcerative Colitis in the Phase 3 True North Study. *Am J Gastroenterol* 2021;116:S313–14.
55. Ananthakrishnan AN, Cagan A, Cai T, et al. Comparative Effectiveness of Infliximab and Adalimumab in Crohn's Disease and Ulcerative Colitis. *Inflamm Bowel Dis* 2016;22:880–5. [PubMed: 26933751]
56. Singh S, Heien HC, Sangaralingham LR, et al. Comparative effectiveness and safety of infliximab and adalimumab in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2016;43:994–1003. [PubMed: 26991059]
57. Panes J, Colombel JF, D'Haens GR, et al. Higher vs Standard Adalimumab Induction and Maintenance Dosing Regimens for Treatment of Ulcerative Colitis: SERENE UC Trial Results. *Gastroenterology* 2022;162:1891–1910. [PubMed: 35227777]
58. Choy EH. Clinical significance of Janus Kinase inhibitor selectivity. *Rheumatology (Oxford)* 2019;58:953–962. [PubMed: 30508136]
59. D'Amico F, Peyrin-Biroulet L, Danese S. Is Selectivity the JAKpot Winner for Inflammatory Bowel Disease Treatment? *Gastroenterology* 2022;163:1482–1484. [PubMed: 36155194]
60. Buisson A, Nachury M, Guillemot T, et al. Real-world comparison of effectiveness between tofacitinib and vedolizumab in patients with ulcerative colitis exposed to at least one anti-TNF agent. *Aliment Pharmacol Ther* 2023;57:676–688. [PubMed: 36401585]

61. Straatmijer T, Biemans VBC, Visschedijk M, et al. Superior Effectiveness of Tofacitinib Compared to Vedolizumab in Anti-TNF-experienced Ulcerative Colitis Patients: A Nationwide Dutch Registry Study. *Clin Gastroenterol Hepatol* 2023;21:182–191 e2. [PubMed: 35644343]
62. Adimadhyam S, Lewis JD, Simon AL, et al. Real-world Evidence Comparing Tofacitinib and Vedolizumab in Anti-TNF-experienced Patients With Ulcerative Colitis. *Inflamm Bowel Dis* 2024;30:554–562. [PubMed: 37358904]
63. Bressler B Is there an optimal sequence of biologic therapies for inflammatory bowel disease? *Therap Adv Gastroenterol* 2023;16:17562848231159452.
64. Panaccione R, Danese S, Zhou W, et al. Efficacy and safety of upadacitinib for 16-week extended induction and 52-week maintenance therapy in patients with moderately to severely active ulcerative colitis. *Aliment Pharmacol Ther* 2024;59:393–408. [PubMed: 38010661]
65. Sandborn WJ, Peyrin-Biroulet L, Quirk D, et al. Efficacy and Safety of Extended Induction With Tofacitinib for the Treatment of Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2022;20:1821–1830 e3. [PubMed: 33127596]
66. Solitano V, Facciorusso A, Jess T, et al. Comparative Risk of Serious Infections With Biologic Agents and Oral Small Molecules in Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2023;21:907–921 e2. [PubMed: 35944832]

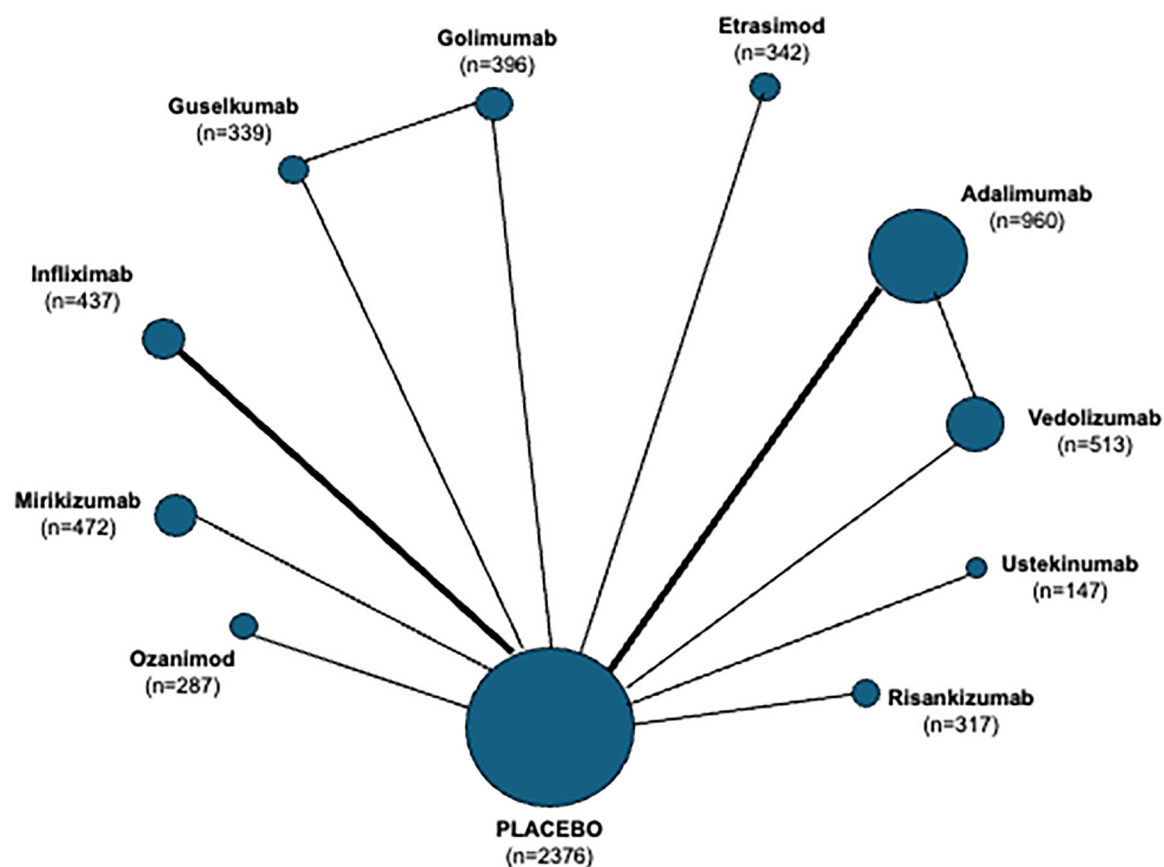


Figure 1a: Network of included studies examining treatments for induction of clinical remission in biologic-naïve patients with moderate-to-severely active ulcerative colitis, excluding Janus kinase (JAK) inhibitors

[Abbreviations: IFX – infliximab; ADA – adalimumab; GLM – golimumab; VDZ – vedolizumab; UST – ustekinumab; RISA – risankizumab; GUS – guselkumab; MIRI – mirikizumab; OZA – ozanimod; ETR – etrasimod; PBO – placebo]

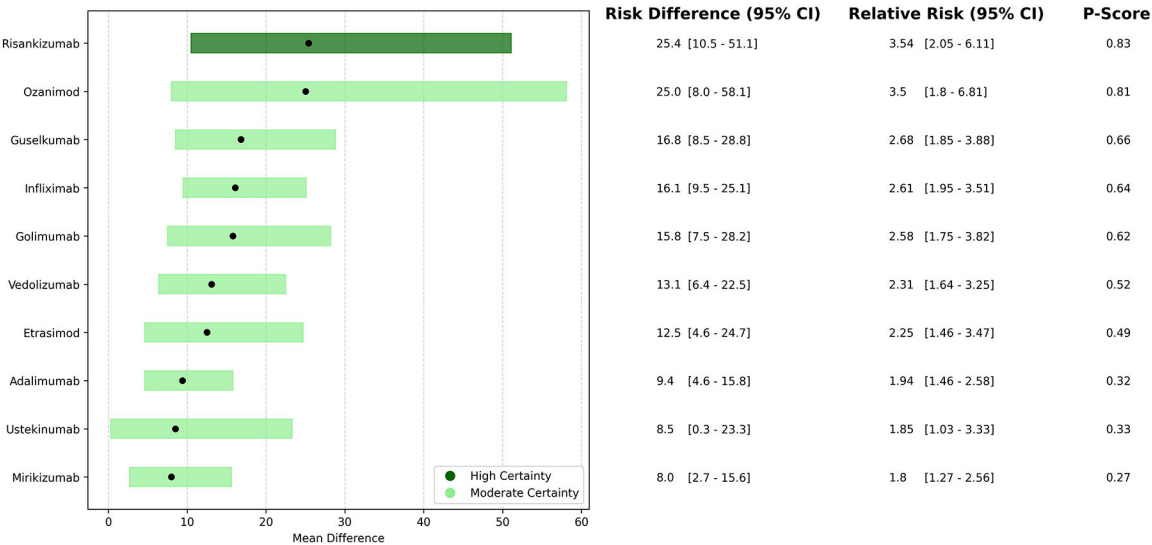


Figure 1b: Forest plot, presented as Gordon plot, for induction of clinical remission in biologic-naïve patients with moderate-to-severely active ulcerative colitis, excluding Janus kinase inhibitors. P-score is the probability of being ranking best in the network. Minimal clinically important difference threshold set at 10%.
[Abbreviations: IFX – infliximab; ADA – adalimumab; GLM – golimumab; VDZ – vedolizumab; UST – ustekinumab; RISA – risankizumab; GUS – guselkumab; MIRI – mirikizumab; OZA – ozanimod; ETR – etrasimod; PBO – placebo]

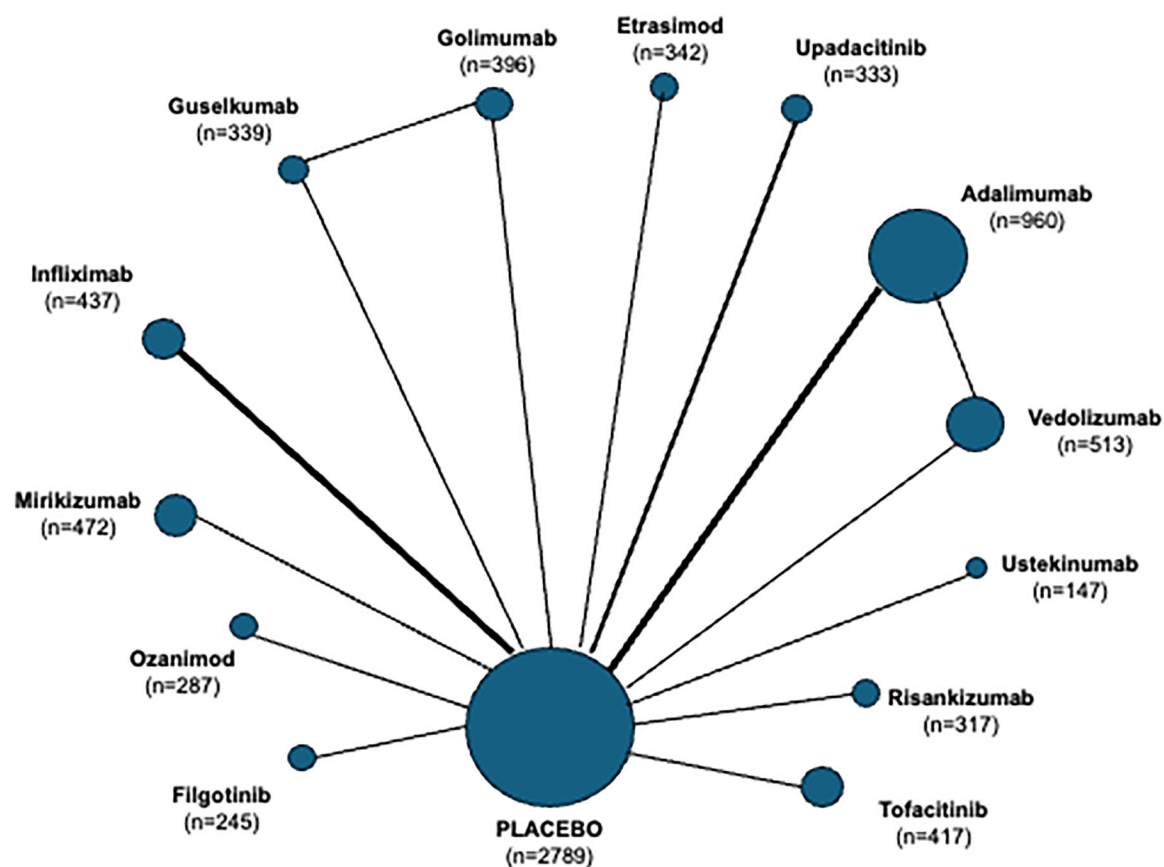


Figure 2a: Network of included studies examining treatments for induction of clinical remission in biologic naïve-patients with moderate-to-severely active ulcerative colitis, including Janus kinase (JAK) inhibitors

[Abbreviations: IFX – infliximab; ADA – adalimumab; GLM – golimumab; VDZ – vedolizumab; UST – ustekinumab; RISA – risankizumab; GUS – guselkumab; MIRI – mirikizumab; OZA – ozanimod; ETR – etrasimod; TOFA – tofacitinib; UPA- upadacitinib; FILG – filgotinib; PBO – placebo]

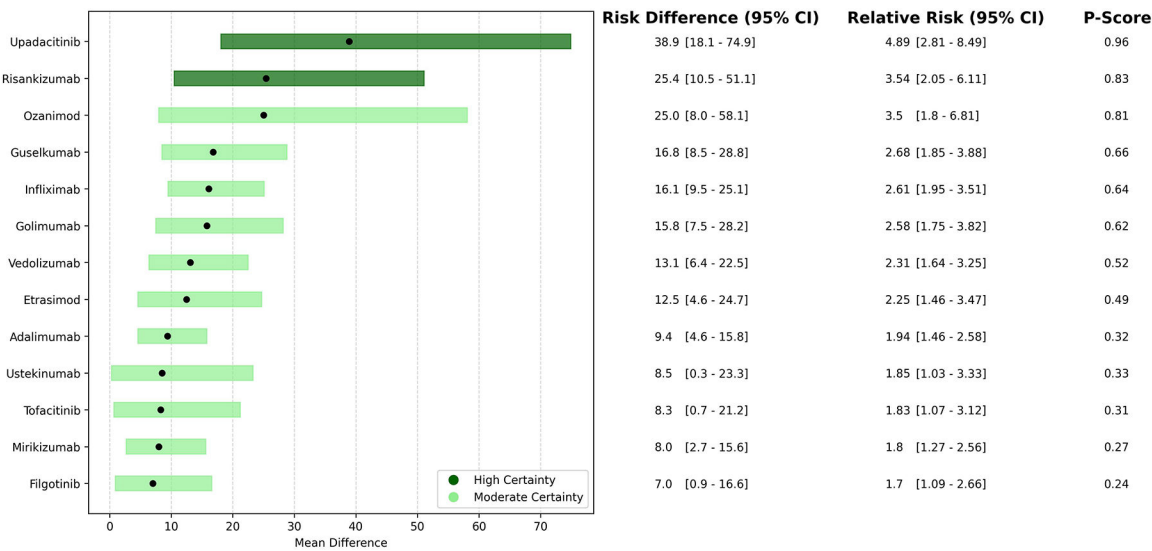


Figure 2b: Forest plot, presented as Gordon plot, for induction of clinical remission in biologic naïve patients with moderate-to-severely active ulcerative colitis, including Janus kinase inhibitor. P-score is the probability of being ranking best in the network. Minimal clinically important difference threshold set at 10%.
[Abbreviations: IFX – infliximab; ADA – adalimumab; GLM – golimumab; VDZ – vedolizumab; UST – ustekinumab; RISA – risankizumab; GUS – guselkumab; MIRI – mirikizumab; OZA – ozanimod; ETR – etrasimod; TOFA – tofacitinib; UPA- upadacitinib; FILG – filgotinib; PBO – placebo]

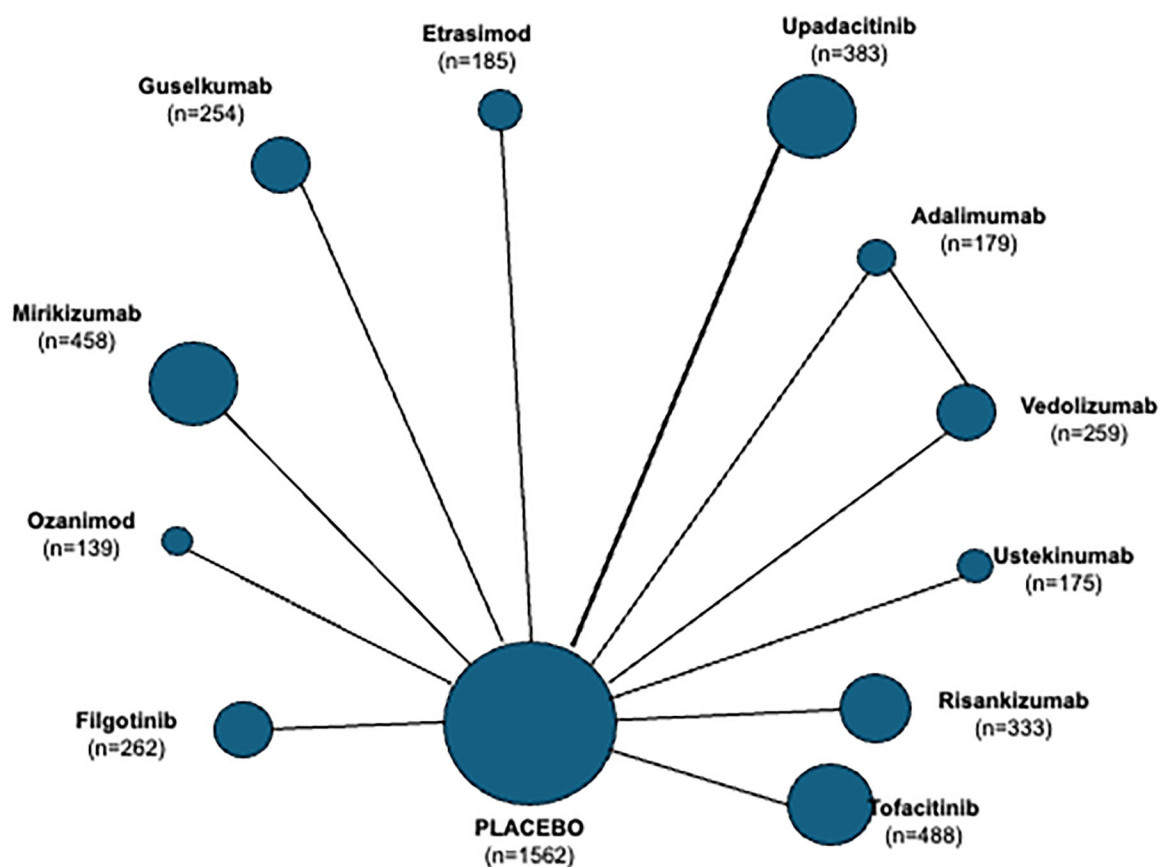


Figure 3a: Network of included studies examining treatments for induction of clinical remission in biologic exposed-patients with moderate-to-severely active ulcerative colitis

[Abbreviations: IFX – infliximab; ADA – adalimumab; GLM – golimumab; VDZ – vedolizumab; UST – ustekinumab; RISA – risankizumab; GUS – guselkumab; MIRI – mirikizumab; OZA – ozanimod; ETR – etrasimod; TOFA – tofacitinib; UPA- upadacitinib; FILG – filgotinib; PBO – placebo]

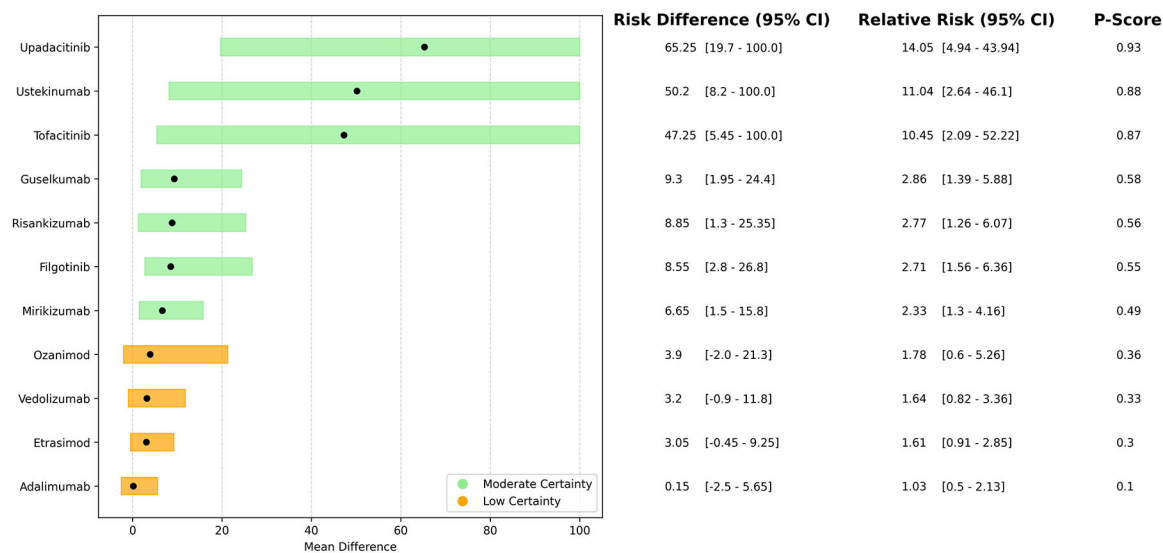


Figure 3b: Forest plot, presented as Gordon plot, for induction of clinical remission in biologic exposed patients with moderate-to-severely active ulcerative colitis. P-score is the probability of being ranking best in the network. Minimal clinically important difference threshold set at 5%. [Abbreviations: IFX – infliximab; ADA – adalimumab; GLM – golimumab; VDZ – vedolizumab; UST – ustekinumab; RISA – risankizumab; GUS – guselkumab; MIRI – mirikizumab; OZA – ozanimod; ETR – etrasimod; TOFA – tofacitinib; UPA- upadacitinib; FILG – filgotinib; PBO – placebo]

Table 1. Trial and patient characteristics in included trials of INDUCTION therapy for moderate-severe ulcerative colitis

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (SD); Sex (% male)	Mean Disease duration (y) (SD); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (SD)	Prior exposure to: TNF antagonist (%); vedolizumab (%); tofacitinib (%)	Clinical Remission rate in placebo arm (%)
					IMM (%)	Corticosteroids (%)			
INFLIXIMAB									
ACT 1 ²¹	62 sites, 2002–05; P: 121; I: IFX 5mg/kg, w0,2,6 – 121	MCS≤2 with no score >1; W8	P: 41 (14); 60 I: 42 (14); 65	6.2 (5.9); 45 5.9 (5.4); 47	43.8 54.5	65.3 57.9	17 (27) 14 (19)	0/0/0 0/0/0	15
ACT 2 ²¹	55 sites, 2002–05; P: 123; I: IFX 5mg/kg, w0,2,6 – 121	MCS≤2 with no score >1; W8	P: 39 (14); 58 I: 41 (13); 63	6.5 (6.7); 42 6.7 (5.3); 41	43.9 43.0	48.8 49.6	16 (29) 13 (23)	0/0/0 0/0/0	6
Jiang et al ²²	1 site (China), 2008–13; P: 41; I: IFX 5mg/kg, w0,2,6 – 41	MCS≤2 with no score >1; W8	P: 35 (15); 61 I: 34 (14); 63	4.4 (2.6); 61 4.4 (2.8); 59	31.7 29.3	51.2 53.7	NR	0/0/0 0/0/0	22
NCT01551290 ²³	12 sites (China), 2012–14; P: 49; I: IFX 5mg/kg, w0,2,6 – 50	MCS≤2 with no score >1; W8	Entire group: 37; NR	3.7; NR	NR	80 60	NR	0/0/0 0/0/0	10
Kobayashi 2016 ²⁴	67 sites, 2006–08; P: 104; I: IFX 5mg/kg, w0,2,6 – 104	MCS≤2 with no score >1; W8	P: 38 (13); 64 I: 40 (13); 64	7.1 (6.6); 81 8.1 (7.2); 80	47.1 48.1	66.3 65.4	7 (11) 10 (15)	0/0/0 0/0/0	11
ADALIMUMAB									
ULTRA 1 ²⁷	94 sites, 2007–10; P: 130; I: ADA 160/80/40, w0,2,4,6 – 130	MCS≤2 with no score >1; W8	P: 37 (18–72) [‡] ; 64 I: 37 (18–75) [‡] ; 64	5.4 (0.3–34.1) [‡] ; 56 6.1 (0.2–34.4) [‡] ; 46	39.9 39.2	67.6 54.6	3.2 (0.2–280) [‡] 3.3 (0.1–109) [‡]	0/0/0 0/0/0	9
ULTRA 2 ²⁸	103 sites, 2006–10; P: 246; I: ADA 160/80/40, w0,2,4,6 – 248	MCS≤2 with no score >1; W8	P: 41 (13); 62 I: 40 (12); 57	8.5 (7.4); 49 8.1 (7.1); 48	50.8 57.7	75.2 80.7	13.1 (36.7) 14.5 (32.1)	41 [§] /0/0 39 [§] /0/0	9
Suzuki et al ²⁶	65 sites, 2009–11; P: 96; I: ADA 160/80/40, w0,2,4,6 – 90	MCS≤2 with no score >1; W8	P: 41 (14); 73 I: 43 (15); 68	7.8 (7.1); 62 7.8 (6.6); 70	54.2 45.6	60.4 63.3	3.4 (0.5–87.2) [‡] 2.2 (0.5–62.8) [‡]	0/0/0 0/0/0	11

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (SD); Sex (% male)	Mean Disease duration (y) (SD); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (SD)	Prior exposure to: TNF antagonist (%); vedolizumab (%); tofacitinib (%)	Clinical Remission rate in placebo arm (%)
					IMM (%)	Corticosteroids (%)			
GOLIMUMAB									
PURSUIT Phase 2 and Phase 3 ^{29,30}	217 sites, 2007–10; P: 331; I: GLM 200/100, w0,2 – 331	MCS≤2 with no score >1; W6	P: 39 (13); 53 I: 40 (14); 54	6.0 (6.7); 43 6.4 (6.2); 42	32.0	42.9	10.7 (16.8) 11.3 (15.3)	0/0/0 0/0/0	10
					31.7	44.7			
VEGA ⁸	54 sites, 2018–21; I1: SC GLM 200/100, w0,2,6,10 – 72 I2: IV GUS 200, w0,4,8 – 331	MCS≤2 with no score >1; W12	I1: 38 (10); 58 I2: 39 (14); 56	4.7 (4.5); 47 5.4 (5.7); 49	0	43	2.5 (1.2–7.7) 3.4 (1.0–12.1)	0/0/1 0/4/1	6
					0	39			
VEDOLIZUMAB									
GEMINI ³¹	211 sites, 2008–12; P: 149; I: VDZ 300mg, w0,2 – 746	MCS≤2 with no score >1; W6	P: 41 (13); 62 I: 40 (13); 58	7.1 (7.2); 46 6.8 (6.2); 50	29.5	56.3	NR	49/0/0 48/0/0	5
					35.4	53.2			
Motoya et al ³²	100 sites, 2014–18; P: 82; I: VDZ 300mg, w0,2,6 – 164	MCS≤2 with no score >1; W10	P: 44 (16); 67 I: 42 (14); 60	8.6 (8.0); 62 7.2 (6.2); 62	52.5	30.5	>3mg/L: 39 >3mg/L: 54	50/0/0 51/0/0	12
					48.8	31.7			
VARSITY ⁷	245 sites, 2015–19; ADA 160/80/40, w0,2,4 then q2w; 386 VDZ 300mg, w0,2,6, then q8w - 383	MCS≤2 with no score >1; W14	ADA: 41 (13); 56 VDZ: 41 (14); 61	6.4 (6.0); NR 7.3 (7.2); NR	25.9	36.3	NR	21/0/0 21/0/0	-
					26.2	36.1			
TOFACITINIB									
OCTAVE ¹⁴¹	144 sites, 2012–15; P: 122; I: Tofacitinib 10 mg po b.d. – 476	MCS≤2, with RBS 0; W8	P: 42 (15); 63 I: 41 (14); 58	6.0 (0.5–36.2) [‡] ; 54 6.5 (0.3–42.5) [‡] ; 53	NA	47.5	4.7 (0.1–82.5) [‡] 4.4 (0.1–208.4) [‡]	53.3/0/0 53.4/0/0	8
						45.0			

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (SD); Sex (% male)	Mean Disease duration (y) (SD); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (SD)	Prior exposure to: TNF antagonist (%); vedolizumab (%); tofacitinib (%)	Clinical Remission rate in placebo arm (%)
					IMM (%)	Corticosteroids (%)			
UPADACITINIB									
OCTAVE 2 ⁴¹	169 sites, 2012–15; P: 112; I: Tofacitinib 10mg po b.d. - 429	MCS≤2, with RBS 0; W8	P: 40 (13); 49 I: 41 (14); 60	6.2 (0.4–27.9) [‡] ; 51 6.0 (0.4–39.4) [‡] ; 49	NA	49.1 46.2	5.0 (0.2–205.1) [‡] 4.6 (0.2–156.0) [‡]	58.0/0/0 54.5/0/0	4
A3921063 Ph2 ⁴²	51 sites, 2009–10; P: 48; I: Tofacitinib 10 mg po b.d. – 33	MCS≤2, with no score >1; W8	P: 43 (15); 48 I: 43 (13); 64	8.8 (5.4); 43 10.9 (6.6); 42	0 0	27 58	9.7 (12.8) 11.3 (16.5)	31/0/0 30/0/0	10
UPADACITINIB									
U-ACHIEVE ³⁹	199 sites, 2016–18 P: 154; I: Upadacitinib 45 mg qday – 319	Adapted Mayo score ≤2, SFS≤1 and not greater than baseline, RBS=0, MES ≤1 without friability; W8	P: 45 (23); 63 I: 43 (23); 62	6.0 (10.0); 52 6.6 (9.6); 50	2 1	40 39	4.7 (12.5) 4.1 (8.1)	Any prior advanced therapy: P: 51 I: 53	5
U-ACCOMPLISH ³⁹	204 sites, 2016–18 P: 174; I: Upadacitinib 45 mg qday – 341	Adapted Mayo score ≤2, SFS≤1 and not greater than baseline, RBS=0, MES ≤1 without friability; W8	P: 42 (24); 61 I: 40 (24); 63	4.9 (7.4); 49 5.6 (7.5); 52	2 <1	41 35	4.7 (10.0) 3.8 (8.0)	Any prior advanced therapy: P: 51 I: 50	4
Sandborn Ph2 ⁴⁰	142 sites, 2016–18; P: 46 I: Upadacitinib 45 mg qday – 56	Adapted Mayo score ≤2, SFS≤1, RBS=0, MES ≤1; W8	P: 40 (21–67); 63 I: 37 (19–74); 66	5.2 (0.4–30.8); 58.7 6.5 (0.4–23.9); 53.6	P: 0 I: 0	P: 54.3 I: 50.0	5.4 (0.35–41.2) [‡] 6.3 (0.2–67) [‡]	71.7/50/0 69.6/41.1/0	0
FILGOTINIB									
SELECTION A ⁴³	341 sites, 2016–20; P: 137; I: Filgotinib 200 mg qday – 245	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W10	P: 41 (13); 64 I: 42 (13); 50	P: 6.4 (7.4); NR I: 7.2 (6.9); NR	24.1 21.6	24.8 22.0	5.8 (7.6) 8.6 (16.3)	0.0/0 0.0/0	15
SELECTION B ⁴³	341 sites, 2016–20; P: 142; I: Filgotinib 200 mg qday – 262	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W10	P: 44 (15); 61 I: 43 (14); 57	10.2 (8.2); NR 9.8 (7.6); NR	14.8 13.0	35.9 35.9	14.0 (24.3) 12.2 (14.9)	91.5/59.9/0 92.4/62.6/0	4

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (SD); Sex (% male)	Mean Disease duration (y) (SD); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (SD)	Prior exposure to: TNF antagonist (%); vedolizumab (%); tofacitinib (%)	Clinical Remission rate in placebo arm (%)
					IMM (%)	Corticosteroids (%)			
OZANIMOD									
TOUCHSTONE ³⁷	57 sites; 2012–2015; P: 65; I: Ozanimod 1 mg qday – 67	MCS ≤2 with no subscore >1; W8	P: 42 (12); 54 I: 42 (11); 72	6.1 (5.5); 37 6.7 (6.8); 39	0 0	37 40	4.9 (0.20–141.4) 4.3 (0.10–82.5)	15/0/0 19/0/0	16
TRUE NORTH ³⁶	285 sites; 2015–20; P: 216; I: ozanimod 1 mg qday – 429	Adapted Mayo score ≤2, SF5≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W10	P: 42 (14); 66 I: 41 (14); 57	6.8 (7.0); 38 I: 6.9 (6.6); 38	0 0	32.4 27.7	5.0 (2.0–12.0) 4.0 (1.0–9.0)	30.1/17.6/1.9 30.3/16.6/0.7	18
ETRASIMOD									
OASIS ³⁸	87 sites; 2015–2018; P: 54; I: Etrasimod 2 mg qday – 50	Adapted Mayo score ≤2, SF5≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W12	P: 45 (15); 59 I: 40 (12); 54	8.6 (7.2); 43 6.2 (4.7); 28	0 0	29.6 36.0	8.6 (7.2) 6.2 (4.7)	33.3/22.2/0 34/14/0	7
ELEVATE 12 ¹⁵	407 sites; 2020–2021; P: 116; I: Etrasimod 2mg qday – 238	Adapted Mayo score ≤2, SF5≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W12	P: 40 (13); 63 I: 40 (14); 57	7.7 (7.3); 35 7.3 (6.6); 32	0 0	33 33	8.1 (15.7) 7.5 (12.6)	25/9/8 24/14/6	15
ELEVATE 52 ¹⁵	315 sites; 2019–2021; P: 144 I: Etrasimod 2mg qday – 289	Adapted Mayo score ≤2, SF5≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W12	P: 39 (14); 61 I: 41 (14); 53	5.9 (5.5); 33 7.5 (8.0); 32	0 0	32 33	10.8 (18.1) 9.6 (15.5)	22/13/6 21/10/7	12
USTEKINUMAB									
UNIFI ³³	244 sites, 2015–18 P: 319 I: IV UST 6mg/kg, w0 – 322	MCS ≤2 with no subscore >1; W8	P: 41 (14); 62 I: 42 (14); 61	8.0 (7.2); 47 8.2 (7.8); 47	27.9 27.6	49.2 52.2	4.7 (1.4–10.) 4.8 (1.8–13.7)	51/0/0 52/0/0	12
MIRIKIZUMAB									

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (SD); Sex (% male)	Mean Disease duration (y) (SD); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (SD)	Prior exposure to: TNF antagonist (%); vedolizumab (%); tofacitinib (%)	Clinical Remission rate in placebo arm (%)
					IMM (%)	Corticosteroids (%)			
RISANKIZUMAB									
AMAC Ph2 ³⁴	75 sites, 2016–2017 P: 63 I: IV MIR 200mg w0/4/8 – 62	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W12	P: 43 (14); 57 I: 43 (15); 60	9.5 (9.6); NR 9.0 (9.0); NR	39.7 29.0	52.4 40.3	3.9 (1.1–11.2) 3.6 (1.4–13.7)	Any prior advanced therapy: P: 27 I: 43.5	5
LUCENT ¹⁴	383 sites, 2018–2021 P: 294 I: IV MIR 300mg w0/4/8 q4w – 868	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W12	P: 41 (14); 56 I: 43 (14); 61	6.9 (7.0); 36 7.2 (6.7); 37	23.4 24.3	38.4 41.6	4.2 (1.2–9.5) [✦] 4.1 (1.5–9.6) [✦]	33/20.1/2 37.4/18.3/3.9	13
INSPIRE ⁶									
INSPIRE ⁶	Site # NR; 2018–2022; P: 325 I: IV RIS 1200mg w0/4/8 – 650	Adapted Mayo score ≤2, SFS≤1 and not greater than baseline, RBS=0, MES ≤1 without friability; W12	P: 43 (14); 62 I: 42 (14); 59	8.1 (7.0); 53.5 7.7 (6.9); 51.4	16.3 16.6	34.5 36.3	4.0 (0.20–113.0) [✦] 3.5 (0.20–199.0) [✦]	Any prior advanced therapy: P: 52.3 I: 51.2	6
GUSELKUMAB									
QUASAR 2B ³⁵	141 sites; 2019–2022 P: 105 I: IV GUS 200mg w0/4/8 – 101	Adapted Mayo score ≤2, SFS≤1 and not greater than baseline, RBS=0, MES ≤1 without friability; W12	P: 42 (14); 63 I: 43 (14); 59	7.7 (7.2); 43.8 7.0 (6.0); 47.5	16.2 24.8	38.1 40.6	4.9 (1.4–10.8) [✦] 4.3 (1.6–17.8) [✦]	43.8/27.6/14.3 40.5/28.7/9.9	10
QUASAR 3 ⁵	Site # NR; 2019–2023 P: 280 I: IV GUS 200mg w0/4/8 – 421	Adapted Mayo score ≤2, SFS≤1 and not greater than baseline, RBS=0, MES ≤1 without friability; W12	P: 40 (13); 58 I: 41 (14); 57	7.1 (6.5); 52.5 7.8 (7.7); 44.7	19.3 21.9	42.9 43.2	3.8 (1.6–9.1) [✦] 4.3 (1.5–11.2) [✦]	42.5/26.4/7.9 43.2/26.6/9.5	8

Median (range)

[Abbreviations: ADA-Adalimumab, CRP-C-reactive protein, GLM-Golimumab, IFX-Infliximab, I-induction, LOR-Loss of response; MCS-Mayo Clinic Score; m-maintenance; NR-Not reported; P-Placebo; PNR-Primary non-response, TNF-tumor necrosis factor; VDZ-Vedolizumab, W-Week]

Table 2. Comparative efficacy of pharmacologic therapies for induction of clinical remission and endoscopic improvement in BIOLOGIC-NAïVE patients with moderate-to-severely active ulcerative colitis, EXCLUDING Janus kinase inhibitors [Rows in bold represent at least low certainty of evidence supporting clinically meaningful benefit or harm between intervention vs. reference for achieving clinical remission; benefit refers to higher likelihood of achieving remission and harm refers to lower likelihood of achieving clinical remission]

Comparison of active therapies	Clinical remission, RR (95% CI)	Absolute risk difference (95% CI), per 1000 patients treated	GRADE	INTERPRETATION (for clinical remission)	Endoscopic improvement, RR (95% CI)
Vs. INFLIXIMAB (reference, risk of achieving clinical remission = 26%)					
Adalimumab	0.74 (0.49–1.13)	–68 (–133 to 34)	LOW ¹	Possibly important harm	0.71 (0.56–0.89)
Golimumab	0.98 (0.59–1.63)	–5 (–107 to 164)	Very low ²	Uncertain trivial harm	0.78 (0.60–1.02)
Vedolizumab	0.89 (0.55–1.43)	–29 (–117 to 112)	Very low ²	Uncertain trivial harm	0.94 (0.65–1.35)
Ozanimod	1.34 (0.63–2.83)	88 (–96 to 476)	Very low ²	Uncertain important benefit	1.45 (0.88–2.39)
Etrasimod	0.86 (0.50–1.48)	–36 (–130 to 125)	Very low ²	Uncertain trivial harm	1.06 (0.72–1.56)
Ustekinumab	0.71 (0.36–1.40)	–75 (–166 to 104)	Very low ²	Uncertain important benefit	0.84 (0.55–1.27)
Mirikizumab	0.70 (0.43–1.14)	–78 (–148 to 36)	LOW ¹	Possibly important harm	0.84 (0.61–1.16)
Risankizumab	1.35 (0.71–2.58)	91 (–75 to 411)	Very low ²	Uncertain important benefit	1.78 (1.15–2.76)
Guselkumab	1.02 (0.63–1.67)	5 (–96 to 174)	Very low ²	Uncertain trivial benefit	1.14 (0.81–1.61)
Vs. ADALIMUMAB (reference, risk of achieving clinical remission = 19%)					
Golimumab	1.33 (0.80–2.19)	63 (–38 to 226)	LOW ¹	Possibly important benefit	1.11 (0.86–1.43)
Vedolizumab	1.20 (0.89–1.60)	38 (–21 to 114)	LOW ¹	Possibly trivial benefit	1.33 (0.93–1.90)
Ozanimod	1.80 (0.86–3.80)	152 (–27 to 532)	LOW ¹	Possibly important benefit	2.05 (1.25–3.37)
Etrasimod	1.16 (0.68–1.99)	30 (–61 to 188)	Very low ²	Uncertain trivial benefit	1.50 (1.03–2.19)
Ustekinumab	0.95 (0.48–1.88)	–10 (–99 to 167)	Very low ²	Uncertain trivial harm	1.18 (0.78–1.79)
Mirikizumab	0.94 (0.58–1.52)	–11 (–80 to 99)	Very low ²	Uncertain trivial harm	1.19 (0.87–1.63)
Risankizumab	1.82 (0.96–3.46)	156 (–8 to 467)	LOW ¹	Possibly important benefit	2.52 (1.64–3.88)
Guselkumab	1.38 (0.85–2.24)	72 (–29 to 236)	LOW ¹	Possibly important benefit	1.61 (1.15–2.26)
Vs. GOLIMUMAB (reference, risk of achieving clinical remission = 26%)					
Vedolizumab	0.90 (0.52–1.56)	–26 (–125 to 146)	Very low ²	Uncertain trivial harm	1.20 (0.82–1.76)

Comparison of active therapies	Clinical remission, RR (95% CI)	Absolute risk difference (95% CI), per 1000 patients treated	GRADE	INTERPRETATION (for clinical remission)	Endoscopic improvement, RR (95% CI)
Ozanimod	1.36 (0.61–3.02)	94 (–101 to 525)	Very low ²	Uncertain important benefit	1.85 (1.10–3.09)
Etrasimod	0.88 (0.48–1.61)	–31 (–135 to 159)	Very low ²	Uncertain trivial harm	1.35 (0.91–2.02)
Ustekinumab	0.71 (0.34–1.50)	–75 (–172 to 130)	Very low ²	Uncertain important harm	1.07 (0.69–1.65)
Mirikizumab	0.71 (0.40–1.24)	–75 (–156 to 62)	Very low ²	Uncertain important harm	1.08 (0.76–1.51)
Risankizumab	1.37 (0.68–2.77)	96 (–83 to 460)	Very low ²	Uncertain important benefit	2.28 (1.45–3.58)
Guselkumab	1.04 (0.66–1.64)	10 (–88 to 166)	Very low ²	Uncertain trivial benefit	1.45 (1.05–2.02)
Vs. VEDOLIZUMAB (reference, risk of achieving clinical remission = 23%)					
Ozanimod	1.51 (0.69–3.28)	117 (–71 to 524)	Very low ²	Uncertain important benefit	1.54 (0.87–2.74)
Etrasimod	0.97 (0.54–1.73)	–7 (–106 to 168)	Very low ²	Uncertain trivial harm	1.13 (0.70–1.82)
Ustekinumab	0.80 (0.39–1.62)	–46 (–140 to 143)	Very low ²	Uncertain trivial harm	0.89 (0.54–1.47)
Mirikizumab	0.79 (0.46–1.33)	–48 (–124 to 76)	Very low ²	Uncertain trivial harm	0.90 (0.59–1.38)
Risankizumab	1.52 (0.77–3.00)	120 (–53 to 460)	Very low ²	Uncertain important benefit	1.90 (1.13–3.19)
Guselkumab	1.15 (0.68–1.97)	35 (–74 to 223)	Very low ²	Uncertain trivial benefit	1.21 (0.78–1.89)
Vs. OZANIMOD (reference, risk of achieving clinical remission = 35%)					
Etrasimod	0.64 (0.28–1.46)	–126 (–252 to 161)	Very low ²	Uncertain important harm	0.73 (0.41–1.32)
Ustekinumab	0.53 (0.21–1.32)	–165 (–277 to 112)	Very low ²	Uncertain important harm	0.58 (0.31–1.06)
Mirikizumab	0.52 (0.24–1.14)	–168 (–266 to 49)	LOW 1	Possibly important harm	0.58 (0.34–1.01)
Risankizumab	1.01 (0.41–2.47)	4 (–207 to 515)	Very low ²	Uncertain trivial benefit	1.23 (0.66–2.30)
Guselkumab	0.77 (0.35–1.68)	–81 (–228 to 238)	Very low ²	Uncertain important harm	0.79 (0.45–1.38)
Vs. ETRASIMOD (reference, risk of achieving clinical remission = 23%)					
Ustekinumab	0.82 (0.38–1.75)	–41 (–143 to 173)	Very low ²	Uncertain trivial harm	0.79 (0.47–1.32)
Mirikizumab	0.81 (0.45–1.46)	–44 (–127 to 106)	Very low ²	Uncertain trivial harm	0.80 (0.51–1.24)
Risankizumab	1.57 (0.76–3.25)	131 (–55 to 518)	Very low ²	Uncertain important benefit	1.68 (0.99–2.87)
Guselkumab	1.19 (0.66–2.15)	44 (–78 to 265)	Very low ²	Uncertain trivial benefit	1.08 (0.70–1.70)
Vs. USTEKINUMAB (reference, risk of achieving clinical remission = 19%)					

Comparison of active therapies	Clinical remission, RR (95% CI)	Absolute risk difference (95% CI), per 1000 patients treated	GRADE	INTERPRETATION (for clinical remission)	Endoscopic improvement, RR (95% CI)
Mirikizumab	0.99 (0.48–2.03)	–2 (–99 to 196)	Very low ²	Uncertain trivial harm	1.01 (0.63–1.62)
Risankizumab	1.91 (0.83–4.42)	173 (–32 to 650)	LOW¹	Possibly important benefit	2.13 (1.22–3.72)
Guselkumab	1.45 (0.70–2.99)	86 (–57 to 378)	Very low ²	Uncertain important benefit	1.36 (0.84–2.22)
Vs. MIRIKIZUMAB (reference, risk of achieving clinical remission = 18%)					
Risankizumab	1.94 (0.97–3.87)	169 (–5 to 517)	LOW¹	Possibly important benefit	2.12 (1.30–3.45)
Guselkumab	1.47 (0.85–2.54)	85 (–27 to 277)	LOW¹	Possibly important benefit	1.35 (0.90–2.03)
Vs. RISANKIZUMAB (reference, risk of achieving clinical remission = 35%)					
Guselkumab	0.76 (0.38–1.51)	–84 (–217 to 179)	Very low ²	Uncertain important harm	0.64 (0.39–1.06)

¹ Rated down twice for very serious imprecision since the lower limit of 95% CI for a comparison crossed the MCID of 50 per 1000 and the line of unity (no difference in efficacy)

² Rated down thrice for imprecision since the MCID of 50 per 1000 was crossed on both sides with the 95% CI

Table 3.

Comparative efficacy of pharmacologic therapies for induction of clinical remission and endoscopic improvement in BIOLOGIC-NAïVE patients with moderate-to-severely active ulcerative colitis, INCLUDING Janus kinase inhibitors [Rows in bold represent at least low certainty of evidence supporting clinically meaningful benefit or harm between intervention vs. reference for achieving clinical remission; benefit refers to higher likelihood of achieving remission and harm refers to lower likelihood of achieving clinical remission]

Comparison of active therapies	Clinical remission, RR (95% CI)	Absolute risk difference (95% CI), per 1000 patients treated	GRADE	INTERPRETATION (for clinical remission)	Endoscopic improvement, RR (95% CI)
Vs. UPADACITINIB (reference, risk of achieving clinical remission = 49%)					
Infliximab	0.53 (0.29–1.00)	-230 (-348 to 0)	MODERATE ¹	Likely important harm	0.46 (0.30–0.72)
Adalimumab	0.40 (0.21–0.74)	-294 (-387 to -127)	MODERATE ⁴	Likely important harm	0.33 (0.21–0.51)
Golimumab	0.53 (0.27–1.04)	-230 (-358 to 20)	LOW ³	Possibly important harm	0.36 (0.23–0.57)
Vedolizumab	0.47 (0.25–0.91)	-260 (-368 to -44)	LOW ³	Possibly important harm	0.43 (0.26–0.74)
Ozanimod	0.72 (0.30–1.70)	-137 (-343 to 343)	Very low ⁴	Uncertain important harm	0.67 (0.36–1.26)
Etrasimod	0.46 (0.23–0.93)	-265 (-377 to -34)	MODERATE ²	Likely important harm	0.49 (0.29–0.84)
Ustekinumab	0.38 (0.17–0.85)	-304 (-407 to -74)	MODERATE ²	Likely important harm	0.39 (0.22–0.68)
Mirikizumab	0.37 (0.19–0.71)	-309 (-397 to -142)	HIGH	Important harm	0.39 (0.24–0.64)
Risankizumab	0.72 (0.33–1.57)	-137 (-328 to 279)	Very low ⁴	Uncertain important harm	0.82 (0.46–1.47)
Guselkumab	0.55 (0.28–1.07)	-221 (-353 to 34)	LOW ³	Possibly important harm	0.53 (0.32–0.88)
Tofacitinib	0.37 (0.17–0.81)	-309 (-407 to -93)	MODERATE ²	Likely important harm	0.40 (0.23–0.69)
Filgotinib	0.35 (0.17–0.71)	-319 (-407 to -142)	HIGH	Important harm	0.41 (0.23–0.71)
Vs. TOFACITINIB (reference, risk of achieving clinical remission = 18%)					
Infliximab	1.43 (0.78–2.64)	77 (-40 to 295)	LOW ³	Possibly important benefit	1.16 (0.77–1.74)
Adalimumab	1.06 (0.58–1.95)	11 (-76 to 171)	Very low ⁴	Uncertain trivial benefit	0.82 (0.55–1.22)
Golimumab	1.41 (0.73–2.75)	74 (-49 to 315)	LOW ³	Possibly important benefit	0.91 (0.60–1.39)
Vedolizumab	1.27 (0.67–2.38)	49 (-59 to 248)	Very low ⁴	Uncertain trivial benefit	1.09 (0.67–1.78)
Ozanimod	1.92 (0.82–4.50)	166 (-32 to 630)	LOW ³	Possibly important benefit	1.68 (0.92–3.07)
Etrasimod	1.23 (0.62–2.45)	41 (-68 to 261)	Very low ⁴	Uncertain trivial benefit	1.23 (0.74–2.04)

Comparison of active therapies	Clinical remission, RR (95% CI)	Absolute risk difference (95% CI), per 1000 patients treated	GRADE	INTERPRETATION (for clinical remission)	Endoscopic improvement, RR (95% CI)
Ustekinumab	1.01 (0.47–2.22)	2 (–95 to 220)	Very low ⁴	Uncertain trivial benefit	0.97 (0.57–1.65)
Mirikizumab	0.99 (0.52–1.87)	–2 (–86 to 157)	Very low ⁴	Uncertain trivial harm	0.98 (0.62–1.55)
Risankizumab	1.94 (0.90–4.16)	169 (–18 to 569)	LOW³	Possibly important benefit	2.07 (1.20–3.58)
Guselkumab	1.47 (0.77–2.82)	85 (–41 to 328)	LOW³	Possibly important benefit	1.32 (0.82–2.13)
Filgotinib	0.93 (0.47–1.87)	–13 (–95 to 157)	Very low ⁴	Uncertain trivial harm	1.02 (0.60–1.73)
Vs. FILGOTINIB (reference, risk of achieving clinical remission = 17%)					
Infliximab	1.54 (0.90–2.63)	92 (–17 to 277)	LOW³	Possibly important benefit	1.14 (0.75–1.71)
Adalimumab	1.14 (0.67–1.93)	24 (–57 to 158)	Very low ⁴	Uncertain trivial benefit	0.80 (0.54–1.20)
Golimumab	1.52 (0.84–2.78)	88 (–27 to 303)	LOW³	Possibly important benefit	0.89 (0.58–1.36)
Vedolizumab	1.35 (0.78–2.38)	60 (–37 to 235)	LOW³	Possibly important benefit	1.07 (0.65–1.75)
Ozanimod	2.04 (0.92–4.55)	177 (–14 to 604)	LOW³	Possibly important benefit	1.64 (0.90–3.00)
Etrasimod	1.32 (0.71–2.46)	54 (–49 to 248)	LOW³	Possibly important benefit	1.20 (0.72–2.00)
Ustekinumab	1.09 (0.52–2.27)	15 (–82 to 216)	Very low ⁴	Uncertain trivial benefit	0.95 (0.56–1.62)
Mirikizumab	1.06 (0.60–1.85)	10 (–68 to 145)	Very low ⁴	Uncertain trivial benefit	0.96 (0.60–1.52)
Risankizumab	2.07 (1.02–4.20)	182 (3 to 544)	MODERATE²	Likely important benefit	2.02 (1.17–3.51)
Guselkumab	1.56 (0.88–2.78)	95 (–20 to 303)	LOW³	Possibly important benefit	1.29 (0.80–2.09)

¹ Rated down once for serious imprecision since only the MCID was crossed, but not the line of unity (no difference in efficacy)

² Rated down once for imprecision due to failure to meet optimal information size since the ratio of upper limit of 95% CI and lower limit of 95% CI of the relative risk was >3

³ Rated down twice for very serious imprecision since the lower limit of 95% CI for a comparison crossed the MCID of 50 per 1000 and the line of unity (no difference in efficacy)

⁴ Rated down thrice for imprecision since the MCID of 50 per 1000 was crossed on both sides with the 95% CI

Table 4. Comparative efficacy of pharmacologic therapies for induction of clinical remission and endoscopic improvement in BIOLOGIC-EXPOSED patients with moderate-to-severely active ulcerative colitis [Rows in bold represent at least low certainty of evidence supporting clinically meaningful benefit or harm between intervention vs. reference for achieving clinical remission; benefit refers to higher likelihood of achieving remission and harm refers to lower likelihood of achieving clinical remission]

Comparison of therapies	Clinical remission, RR (95% CI)	Absolute risk difference (95% CI), per 1000 patients treated	GRADE	INTERPRETATION (for clinical remission)	Endoscopic improvement, RR (95% CI)
vs. PLACEBO (reference, risk of achieving clinical remission = 5%)					
Adalimumab	1.03 (0.50–2.13)	2 (–25 to 57)	LOW ¹	Possibly trivial benefit	1.07 (0.68–1.68)
Vedolizumab	1.64 (0.82–3.36)	32 (–9 to 118)	LOW ¹	Possibly trivial benefit	1.05 (0.72–1.55)
Ozanimod	1.78 (0.60–5.26)	39 (–20 to 213)	LOW ¹	Possibly trivial benefit	1.15 (0.55–2.42)
Etrasimod	1.61 (0.91–2.85)	31 (–5 to 93)	LOW ¹	Possibly trivial benefit	1.94 (1.17–3.23)
Ustekinumab	11.04 (2.64–46.10)	502 (85 to 1000)	MODERATE ²	Likely important benefit	3.04 (1.65–5.61)
Mirikizumab	2.33 (1.30–4.16)	67 (15 to 158)	MODERATE ²	Likely important benefit	2.05 (1.31–3.20)
Risankizumab	2.77 (1.26–6.07)	89 (13 to 254)	MODERATE ²	Likely important benefit	2.58 (1.59–4.20)
Guselkumab	2.86 (1.39–5.88)	93 (20 to 244)	MODERATE ²	Likely important benefit	2.71 (1.46–5.01)
Tofacitinib	10.45 (2.09–52.22)	473 (55 to 1000)	MODERATE ²	Likely important benefit	3.75 (1.88–7.48)
Filgotinib	2.71 (1.56–6.36)	86 (28 to 268)	MODERATE ²	Likely important benefit	2.22 (1.18–4.15)
Upadacitinib	14.05 (4.94–43.94)	653 (197 to 1000)	MODERATE ²	Likely important benefit	10.48 (1.65–24.15)
Vs. ADALIMUMAB (reference, risk of achieving clinical remission = 5%)					
Vedolizumab	1.60 (0.86–2.98)	30 (–7 to 99)	LOW ¹	Possibly trivial benefit	0.99 (0.54–1.78)
Ozanimod	1.73 (0.47–6.35)	37 (–27 to 268)	LOW ¹	Possibly trivial benefit	1.08 (0.45–2.57)
Etrasimod	1.56 (0.62–3.93)	28 (–19 to 147)	LOW ¹	Possibly trivial benefit	1.81 (0.92–3.58)
Ustekinumab	10.73 (2.16–53.19)	487 (58 to 1000)	MODERATE ²	Likely important benefit	2.84 (1.33–6.09)
Mirikizumab	2.26 (0.90–5.71)	63 (–5 to 236)	LOW ¹	Possibly important benefit	1.92 (1.02–3.61)
Risankizumab	2.69 (0.93–1.59)	85 (–4 to 341)	LOW ¹	Possibly important benefit	2.42 (1.25–4.69)
Guselkumab	2.78 (1.00–7.70)	89 (0 to 335)	MODERATE ²	Likely important benefit	2.53 (1.18–5.43)

Comparison of therapies	Clinical remission, RR (95% CI)	Absolute risk difference (95% CI), per 1000 patients treated	GRADE	INTERPRETATION (for clinical remission)	Endoscopic improvement, RR (95% CI)
Tofacitinib	10.16 (1.74–59.21)	458 (37 to 1000)	MODERATE ²	Likely important benefit	3.51 (1.54–8.00)
Filgotinib	2.63 (0.86–8.04)	82 (–7 to 352)	LOW ¹	Possibly important benefit	2.07 (0.96–4.49)
Upadacitinib	13.66 (3.54–52.62)	633 (127 to 1000)	MODERATE ²	Likely important benefit	2.84 (3.80–25.31)
Vs. VEDOLIZUMAB (reference, risk of achieving clinical remission = 8%)					
Ozanimod	1.08 (0.30–3.91)	6 (–56 to 233)	Very low ³	Uncertain trivial benefit	1.10 (0.47–2.53)
Etrasimod	0.98 (0.40–2.40)	–2 (–48 to 112)	LOW ¹	Possibly trivial harm	1.84 (0.97–3.49)
Ustekinumab	6.70 (1.37–32.78)	456 (30 to 1000)	MODERATE ²	Likely important benefit	2.89 (1.40–5.96)
Mirikizumab	1.41 (0.57–3.49)	33 (–34 to 199)	LOW ¹	Possibly trivial benefit	1.94 (1.08–3.51)
Risankizumab	1.68 (0.59–4.79)	54 (–34 to 303)	LOW ¹	Possibly important benefit	2.45 (1.32–4.56)
Guselkumab	1.73 (0.64–4.71)	58 (–29 to 297)	LOW ¹	Possibly important benefit	2.57 (1.24–5.31)
Tofacitinib	6.34 (1.10–36.54)	427 (8 to 1000)	MODERATE ²	Likely important benefit	3.56 (1.61–7.85)
Filgotinib	1.64 (0.55–4.93)	51 (–36 to 314)	LOW ¹	Possibly important benefit	2.11 (1.01–4.40)
Upadacitinib	8.52 (2.24–32.35)	602 (99 to 1000)	MODERATE ²	Likely important benefit	9.95 (3.96–24.97)
Vs. OZANIMOD (reference, risk of achieving clinical remission = 9%)					
Etrasimod	0.91 (0.27–3.09)	–8 (–66 to 188)	Very low ³	Uncertain trivial harm	1.68 (0.68–4.13)
Ustekinumab	6.21 (1.03–37.38)	469 (3 to 1000)	MODERATE ²	Likely important benefit	2.63 (1.01–6.90)
Mirikizumab	1.31 (0.38–4.49)	28 (–56 to 314)	Very low ³	Uncertain trivial benefit	1.77 (0.75–4.22)
Risankizumab	1.56 (0.41–5.95)	50 (–53 to 446)	Very low ³	Uncertain important benefit	2.24 (0.92–5.43)
Guselkumab	1.61 (0.44–5.92)	55 (–50 to 443)	Very low ³	Uncertain important benefit	2.34 (0.89–6.15)
Tofacitinib	5.88 (0.84–40.95)	439 (–14 to 1000)	LOW ¹	Possibly important benefit	3.25 (1.18–8.95)
Filgotinib	1.53 (0.38–6.06)	48 (–56 to 455)	Very low ³	Uncertain trivial benefit	1.92 (0.73–5.07)
Upadacitinib	7.91 (1.64–38.16)	622 (58 to 1000)	MODERATE ²	Likely important benefit	9.08 (2.97–27.75)
Vs. ETASIMOD (reference, risk of achieving clinical remission = 8%)					
Ustekinumab	6.86 (1.47–32.00)	469 (38 to 1000)	MODERATE ²	Likely important benefit	1.57 (0.71–3.48)
Mirikizumab	1.45 (0.64–3.27)	36 (–29 to 182)	LOW ¹	Possibly trivial benefit	1.06 (0.54–2.08)

Comparison of therapies	Clinical remission, RR (95% CI)	Absolute risk difference (95% CI), per 1000 patients treated	GRADE	INTERPRETATION (for clinical remission)	Endoscopic improvement, RR (95% CI)
Risankizumab	1.72 (0.65–4.55)	58 (–28 to 284)	LOW ¹	Possibly important benefit	1.33 (0.66–2.69)
Guselkumab	1.78 (0.71–4.46)	62 (–23 to 277)	LOW ¹	Possibly important benefit	1.40 (0.63–3.10)
Tofacitinib	6.50 (1.18–35.84)	440 (14 to 1000)	MODERATE ²	Likely important benefit	1.93 (0.82–4.56)
Filgotinib	1.68 (0.60–4.70)	54 (–32 to 296)	LOW ¹	Possibly important benefit	1.14 (0.51–2.56)
Upadacitinib	8.74 (2.44–31.28)	619 (115 to 1000)	MODERATE ²	Likely important benefit	5.40 (2.03–14.37)
Vs. USTEKINUMAB (reference, risk of achieving clinical remission = 55%)					
Mirikizumab	0.21 (0.05–0.99)	–435 (–523 to –6)	MODERATE ²	Likely important harm	0.67 (0.32–1.44)
Risankizumab	0.25 (0.05–1.28)	–413 (–525 to 154)	Very low ³	Uncertain important benefit	0.85 (0.39–1.86)
Guselkumab	0.26 (0.05–1.28)	–407 (–523 to 154)	Very low ³	Uncertain important benefit	0.89 (0.37–2.12)
Tofacitinib	0.95 (0.11–8.14)	–28 (–490 to 1000)	Very low ³	Uncertain trivial harm	1.23 (0.49–3.11)
Filgotinib	0.25 (0.05–1.30)	–413 (–523 to 165)	Very low ³	Uncertain important benefit	0.73 (0.30–1.75)
Upadacitinib	1.27 (0.20–7.92)	149 (–440 to 1000)	Very low ³	Uncertain important benefit	3.45 (1.22–9.72)
Vs. MIRIKIZUMAB (reference, risk of achieving clinical remission = 12%)					
Risankizumab	1.19 (0.45–3.16)	23 (–66 to 259)	Very low ³	Uncertain trivial benefit	1.26 (0.65–2.44)
Guselkumab	1.23 (0.49–3.10)	28 (–61 to 252)	Very low ³	Uncertain trivial benefit	1.32 (0.62–2.82)
Tofacitinib	4.49 (0.81–24.84)	419 (–23 to 1000)	LOW ¹	Possibly important benefit	1.83 (0.80–4.16)
Filgotinib	1.16 (0.42–3.27)	19 (–70 to 272)	Very low ³	Uncertain trivial benefit	1.08 (0.50–2.34)
Upadacitinib	6.04 (1.68–21.71)	605 (82 to 1000)	MODERATE ²	Likely important benefit	5.12 (1.99–13.18)
Vs. RISANKIZUMAB (reference, risk of achieving clinical remission = 14%)					
Guselkumab	1.03 (0.36–2.99)	23 (–90 to 279)	Very low ³	Uncertain trivial benefit	1.05 (0.48–2.30)
Tofacitinib	3.77 (0.63–22.59)	388 (–52 to 1000)	Very low ³	Uncertain important benefit	1.45 (0.62–3.38)
Filgotinib	0.98 (0.31–3.11)	–3 (–97 to 295)	Very low ³	Uncertain trivial harm	0.86 (0.39–1.90)
Upadacitinib	5.07 (1.27–20.23)	570 (38 to 1000)	MODERATE ²	Likely important benefit	4.06 (1.54–10.66)
Vs. GUSELKUMAB (reference, risk of achieving clinical remission = 14%)					
Tofacitinib	3.65 (0.63–21.29)	371 (–52 to 1000)	Very low ³	Uncertain important benefit	1.83 (0.55–3.49)

Comparison of therapies	Clinical remission, RR (95% CI)	Absolute risk difference (95% CI), per 1000 patients treated	GRADE	INTERPRETATION (for clinical remission)	Endoscopic improvement, RR (95% CI)
Filgotinib	0.95 (0.31–2.89)	–7 (–97 to 265)	Very low ³	Uncertain trivial harm	0.82 (0.34–1.97)
Upadacitinib	4.91 (1.28–18.91)	547 (39 to 1000)	MODERATE ²	Likely important benefit	3.87 (1.37–10.93)
Vs. TOFACITINIB (reference, risk of achieving clinical remission = 52%)					
Filgotinib	0.26 (0.04–1.60)	–385 (–499 to 312)	Very low ³	Uncertain important harm	0.59 (0.23–1.90)
Upadacitinib	1.34 (0.19–9.66)	177 (–421 to 1000)	Very low ³	Uncertain important benefit	2.80 (0.95–10.66)
Vs. FILGOTINIB (reference, risk of achieving clinical remission = 14%)					
Upadacitinib	5.19 (1.25–21.53)	587 (35 to 1000)	MODERATE ²	Likely important benefit	3.87 (1.66–13.43)

¹ Rated down twice for very serious imprecision since the lower limit of 95% CI for a comparison crossed the MCID of 50 per 1000 and the line of unity (no difference in efficacy)

² Rated down once for imprecision due to failure to meet optimal information size since the ratio of upper limit of 95% CI and lower limit of 95% CI of the relative risk was >3

³ Rated down thrice for imprecision since the MCID of 50 per 1000 was crossed on both sides with the 95% CI