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

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BACKGROUND & 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 in adults with moderate-to-severe UC, comparing different advanced therapies (tumor necrosis factor antagonists, vedolizumab, sphingosine-1-phosphate receptor modulators, interleukin 12/23 or selective interleukin 23 antagonists, and 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 the United States Food and Drug Administration), low-certainty evidence supports clinically important benefit with infliximab, ozanimod, risankizumab, and guselkumab over adalimumab and mirikizumab for achieving remission with induction therapy in biologically naïve patients with moderate-to-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 Grading of Recommendations, Assessment, Development and Evaluation 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.

Ulcerative colitis (UC) affects nearly 1.5 million individuals in the United States.[1] It is characterized by a protracted course, leading to disease-related hospitalization or surgery in more than one-third of patients.[2,3] Moderate-to-severe disease activity develops in many patients with UC, requiring initiation of advanced immunosuppressive therapy.[3,4] The past 2 decades have witnessed significant progress in the development of these therapies, with the approval by the United States Food and Drug Administration (FDA) of 6 different therapeutic mechanisms, 10 distinct drugs, and the anticipated approval of guselkumab[5] and risankizumab[6] 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 VARSITY (An Efficacy and Safety Study of Vedolizumab Intravenous Compared to Adalimumab Subcutaneous in Participants With Ulcerative Colitis)[7] and VEGA (Guselkumab plus Golimumab Combination Therapy Versus Guselkumab or Golimumab

Abbreviations used in this paper: **CI, confidence interval; FDA, Food and Drug Administration; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; IBD, inflammatory bowel disease; IL, interleukin; JAK, Janus kinase; MCID, minimal clinically important difference; NMAs, network meta-analyses; RCT, randomized controlled trial; RR, relative risk; S1P, sphingosine-1-phosphate; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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Monotherapy in Patients With Ulcerative Colitis)[8] trials among approved therapies. Consequently, relative efficacy is often inferred through network meta-analyses (NMAs) that 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 mirikizumab,[14] guselkumab,[5] risankizumab,[6] and etrasimod,[15] evidence of efficacy for subcutaneous formulations of infliximab and vedolizumab,[16] and head-to-head comparison data between guselkumab and golimumab.[8] Prior NMAs have not critically appraised the available evidence that can inform clinical guidelines. Moreover, there have 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 (TNF)-α 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 2 separate NMAs of induction therapy to estimate comparative efficacy of different advanced therapies in biologically 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 biologically naïve or previously exposed to biologic therapy;
2. Intervention: advanced therapies, including TNF antagonists (infliximab, adalimumab, and golimumab), vedolizumab, sphingosine-1 phosphate (S1P) receptor modulators (ozanimod and etrasimod), JAK inhibitors (tofacitinib, upadacitinib, and filgotinib), interleukin (IL) 12/23 antagonists (ustekinumab), or IL23 antagonists (mirikizumab, risankizumab, and guselkumab), with a minimum duration of therapy of 14 days;
3. Comparator: another active intervention or placebo; and
4. Outcome: induction of clinical remission (Mayo Clinic Score ≤2 with no individual subscore of >1) and endoscopic improvement (Mayo endoscopy subscore, 0 or 1).

Because trials of advanced therapies for maintenance of remission had different designs (treat-through design vs rerandomization 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 rerandomization analysis, only patients who achieve clinical response at the end of induction are randomized to 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 carryover 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 had active disease at enrollment or had achieved clinical response to induction therapy with an index agent;
2. Intervention: advanced therapies, including TNF antagonists, vedolizumab, S1P receptor modulators, JAK inhibitors, IL12/23, or IL23 antagonists, with a minimum duration of therapy of 24 weeks;
3. Comparator: another active intervention or placebo; and
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 (eg, etrolizumab, AJM300, and ontamalimab), (3) trials of novel agents (eg, PRA023 and 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 with 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, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and 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 inflammatory bowel disease (IBD). Details of the search strategy are shown in the Supplementary Material.

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 prespecified 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 characteristics related to the study, participant, disease, and treatment were abstracted onto a standardized form by 2 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 2.0.

Outcomes

For trials of induction therapy, the efficacy outcomes were induction of clinical remission (defined as Mayo Clinic Score $\leq$2 with no individual subscore of $>$1), and endoscopic improvement (Mayo endoscopy subscore, 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 2 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. Outcomes for maintenance trials were assessed at the 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 were available for agents that received regulatory approval, only data for the approved dose and administration were 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" 9.0 (https://cran.r-project.org/web/packages/netmeta/index.html) in R 4.0.2 software (R Foundation for Statistical Computing).[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) and 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 2 separate analyses including and subsequently excluding this therapeutic class as first-line treatment.

Grading of Recommendations, Assessment, Development, and Evaluation 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), or publication bias, to levels of moderate, low, and very low confidence. The rating of indirect estimates starts at the lowest rating of the 2 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 clinical or methodologic characteristics).

Network consistency was evaluated by comparing the direct estimates to the indirect estimates for each comparison by using a node-splitting technique. If direct and indirect estimates were similar (ie, 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 and 50 per 1000 patients treated.

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 the 95% confidence interval (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 the upper limit and lower limit of the 95% CI of the relative risk was >3. The primary NMA results are presented as risk difference (%) with their respective GRADE certainty rating and CIs as Gordon plots (Graphic On Results Diagram of NMA).[20]

Results

Search Strategy

Our search strategy yielded 5350 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] and 3 golimumab[8,29,30]), 3 trials of anti-integrins (3 vedolizumab[7,31,32]), 5 trials of anti-IL12/23 (1 ustekinumab[33]) or anti-IL23 antibodies (2 mirikizumab,[14,34] 2 guselkumab,[5,8,35] and 1 risankizumab[6]), 5 trials of S1P modulators (2 ozanimod[36,37] and 3 etrasimod[15,38]), and 8 trials of JAK inhibitors (3 upadacitinib,[39,40] 3 tofacitinib[41,42], and 2 filgotinib[43]). Additionally, we included data from subcutaneous infliximab (CT-P13 [Infliximab] Subcutaneous Administration in Patients With Moderately to Severely Active Ulcerative Colitis [LIBERTY-UC])[44] and vedolizumab[16] (Efficacy and Safety of Vedolizumab Subcutaneously [SC] as Maintenance Therapy in Ulcerative Colitis [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 primarily analysis for our NMA because the treatment failed to meet its primary end point and is not approved for use in UC in North America or in Europe. However, data from the placebo and adalimumab arms of the HIBISCUS (A Study Comparing the Efficacy and Safety of Etrolizumab With Adalimumab and Placebo in Participants With Moderate to Severe Ulcerative Colitis [UC] in Participants Naive to Tumor Necrosis Factor [TNF] Inhibitors) trial[25] were incorporated into the evidence base. 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: VARSITY[7] (vedolizumab vs adalimumab) and VEGA[8] (golimumab vs guselkumab). We did not include the combination golimumab-guselkumab arm in our NMA given lack of FDA or European Medicines Agency approval.

Study Population

Table 1[5–8,14,15,21–43] and Supplementary Table 1 describe the characteristics of the included trials. The average age of included participants ranged from 34 to 45 years and 40% to 60% were men. Approximately two-thirds of patients in the included studies had extensive colitis, and the median disease duration at inclusion ranged from 5 to 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 with small molecules; however, patients in all trials had moderately to severely active disease despite being on immunomodulators at randomization. Approximately 20% to 55% had prior exposure to biologics. Prior biologic use consisted predominantly of TNF antagonist exposure in the earlier RCTs, whereas subsequent biologic and small molecule trials included a fraction of patients with prior vedolizumab but not TNF antagonist exposure. Trials of infliximab and golimumab 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 $\leq$1, a rectal bleeding score of 0, and an endoscopic subscore of $\leq$1 without friability. Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1. Because of a 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 histoendoscopic mucosal healing. For induction trials, clinical outcomes were typically measured at 6 to 12 weeks, whereas 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 1*A*) or where use of JAK inhibitors was permitted first line (other regions) (Figure 2*A*). 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 2*B*).

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-to-severe UC (Table 2). We also observed that infliximab, ozanimod, risankizumab, and guselkumab were possibly associated with higher likelihood of achieving remission

Table 1. Trial and Patient Characteristics in Included Trials of Induction Therapy for Moderate-to-Severe Ulcerative Colitis

Trial	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 (IFX)									
ACT 1[21]	62 sites, 2002–05; P: 121; I: IFX 5 mg/kg, wk 0, 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 5 mg/kg, wk 0, 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 5 mg/kg, wk 0, 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 5 mg/kg, wk 0, 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 5 mg/kg, wk 0, 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 (ADA)									
ULTRA 1[27]	94 sites, 2007–10; P: 130; I: ADA 160/80/40, wk 0, 2, 4, 6–130	MCS ≤2 with no score >1; W8	P: 37 (18–72)[a]; 64 I: 37 (18–75)[a] ; 64	5.4 (0.3–34.1)[a]; 56 6.1 (0.2–34.4)[a]; 46	39.9 39.2	67.6 54.6	3.2 (0.2–280)[a] 3.3 (0.1–109)[a]	0/0/0 0/0/0	9
ULTRA 2[28]	103 sites, 2006–10; P: 246; I: ADA 160/80/40, wk 0, 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, wk 0, 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)[a] 2.2 (0.5–62.8)[a]	0/0/0 0/0/0	11

Table 1. Continued

Trial	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 (%)			
HIBISCUS I[25]	97 sites, 2014–20; P: 72; I: ADA 160/80/40, wk 0, 2, 4, 6–142	MCS ≤2 with no score >1 and RBS 0; W10	P: 36 (19–78)[a] ; 54 I: 41 (19–75)[a] ; 58	4.7 (0.3–48)[a]; 39 4.0 (0.3–36.4)[a]; 41	35 36	47 47	2.7 (1.2–9.4)[a] 5.5 (1.8–9.6)[a]	0/0/0 0/0/0	7
HIBISCUS [25]	110 sites, 2014–20; P: 72; I: ADA 160/80/40, W 0, 2, 4, 6–143	MCS ≤2 with no score >1 and RBS 0; W10	P: 37 (18–68)[a] ; 53 I: 38 (18–71)[a]; 57	4.0 (0.3–24)[a]; 34 4.1 (0.3–37.9)[a]; 40	32 33	46 46	2.6 (1.0–9.4)[a] 2.8 (1.1–7.9)[a]	0/0/0 0/0/0	11
Golimumab (GLM)									
PURSUIT Phase 2 and Phase 3[29, 30]	217 sites, 2007–10; P: 331; I: GLM 200/100, wk 0, 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 31.7	42.9 44.7	10.7 (16.8) 11.3 (15.3)	0/0/0 0/0/0	10
VEGA[8]	54 sites, 2018–21; I1: SC GLM 200/100, wk 0, 2, 6, 10–72 I2: IV GUS 200, wk 0, 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 0	43 39	2.5 (1.2–7.7) 3.4 (1.0–12.1)	0/0/1 0/4/1	6
Vedolizumab (VZD)									
GEMINI I[31]	211 sites, 2008–12; P: 149; I: VDZ 300 mg, wk 0, 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 35.4	56.3 53.2	NR	49/0/0 48/0/0	5
Motoya et al[32]	100 sites, 2014–18; P: 82; I: VDZ 300 mg, wk 0, 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 48.8	30.5 31.7	>3 mg/L: 39 >3 mg/L: 54	50/0/0 51/0/0	12
VARSITY[7]	245 sites, 2015–19; ADA 160/80/40, wk 0, 2, 4 then every 2 wk; 386 VDZ 300 mg, wk 0, 2, 6, then every 8 wk–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 26.2	36.3 36.1	NR	21/0/0 21/0/0	-
Tofacitinib									
OCTAVE 1[41]	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)[a]; 54 6.5 (0.3–42.5)[a]; 53	NA	47.5 45.0	4.7 (0.1–82.5)[a] 4.4 (0.1–208.4)[a]	53.3/0/0 53.4/0/0	8

Table 1. Continued

Trial	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 (%)			
OCTAVE 2[41]	169 sites, 2012–15; P: 112; I: Tofacitinib 10 mg po b.d. – 429	MCS ≤2, with RBS 0; W8	P: 40 (13); 49 I: 41 (14); 60	6.2 (0.4–27.9)[a]; 51 6.0 (0.4–39.4)[a]; 49	NA	49.1 46.2	5.0 (0.2–205.1)[a] 4.6 (0.2–156.0)[a]	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 every day – 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 every day – 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 every day – 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)[a] 6.3 (0.2–67)[a]	71.7/50/0 69.6/41.1/0	0
Filgotinib									
SELECTION A[43]	341 sites, 2016–20; P: 137; I: Filgotinib 200 mg every day – 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 every day – 262	Adapted Mayo score ≤2, SFS ≤1 and at least 1-point decrease from baseline, RBS = 0, MES ≤1 without friability; wk 10	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

Table 1. Continued

Trial	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; 2012–15; P: 65; I: Ozanimod 1 mg every day – 67	MCS ≤2 with no subscore >1; wk 8	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 every day – 429	Adapted Mayo score ≤2, SFS ≤1 and at least 1-point decrease from baseline, RBS = 0, MES ≤1 without friability; wk 10	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; 2015–18; P: 54; I: Etrasimod 2 mg every day – 50	Adapted Mayo score ≤2, SFS ≤1 and at least 1-point decrease from baseline, RBS = 0, MES ≤1 without friability; wk 12	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; 2020–21; P: 116; I: Etrasimod 2 mg every day – 238	Adapted Mayo score ≤2, SFS ≤1 and at least 1-point decrease from baseline, RBS = 0, MES ≤1 without friability; wk 12	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; 2019–21; P: 144 I: Etrasimod 2 mg every day – 289	Adapted Mayo score ≤2, SFS ≤1 and at least 1-point decrease from baseline, RBS = 0, MES ≤1 without friability; wk 12	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 (UST)									
UNIFI[33]	244 sites, 2015–18 P: 319 I: IV UST 6 mg/kg, wk 0 – 322	MCS ≤2 with no subscore >1; wk 8	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

Table 1. Continued

Trial	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 (%)			
Mirikizumab (MIR)									
AMAC phase 2[34]	75 sites, 2016–17 P: 63 I: IV MIR 200 mg wk 0, 4, 8–62	Adapted Mayo score ≤2, SFS ≤1 and at least 1–point decrease from baseline, RBS = 0, MES ≤1 without friability; wk 12	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, 2018–21 P: 294 I: IV MIR 300 mg wk 0, 4, 8 every 4 wk – 868	Adapted Mayo score ≤2, SFS ≤1 and at least 1–point decrease from baseline, RBS = 0, MES ≤1 without friability; wk 12	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)[a] 4.1 (1.5–9.6)[a]	33/20.1/2 37.4/18.3/3.9	13
Risankizumab (RIS)									
INSPIRE[6]	Site # NR; 2018–22; P: 325 I: IV RIS 1200 mg wk 0, 4, 8 – 650	Adapted Mayo score ≤2, SFS≤1 and not greater than baseline, RBS = 0, MES ≤1 without friability; wk 12	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)[a] 3.5 (0.20–199.0)[a]	Any prior advanced therapy: P: 52.3 I: 51.2	6

Table 1. Continued

Trial	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 (%)			
Guselkumab (GUS)									
QUASAR 2B[35]	141 sites; 2019–22 P: 105 I: IV GUS 200 mg wk 0, 4, 8–101	Adapted Mayo score ≤2, SFS ≤1 and not greater than baseline, RBS = 0, MES ≤1 without friability; wk 12	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)[a] 4.3 (1.6–17.8)[a]	43.8/27.6/14.3 40.5/28.7/9.9	10
QUASAR[35]	Site # NR; 2019–23 P: 280 I: IV GUS 200 mg wk 0, 4, 8–421	Adapted Mayo score ≤2, SFS ≤1 and not greater than baseline, RBS = 0, MES ≤1 without friability; wk 12	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)[a] 4.3 (1.5–11.2)[a]	42.5/26.4/7.9 43.2/26.6/9.5	8

NOTE. ACT, Active Colitis Trials; ADA, adalimumab; AMAC, A Study of Mirikizumab (LY3074828) in Participants With Moderate to Severe Ulcerative Colitis; b,d, twice daily; CRem, clinical remission; CRP, C-reactive protein; ELEVATE 12, E:trasimod Versus Placebo as Induction Therapy in Moderately to Severely Active Ulcerative Colitis; ELEVATE 52, Etrasimod Versus Placebo for the Treatment of Moderately to Severely Active Ulcerative Colitis; GEMINI, Study of Vedolizumab (MLN0002) in Patients With Moderate to Severe Ulcerative Colitis; HIBISCUS, Study Comparing the Efficacy and Safety of Etrolizumab With Adalimumab and Placebo in Participants With Moderate to Severe Ulcerative Colitis (UC) in Participants Naive to Tumor Necrosis Factor (TNF) Inhibitors; I, induction; IMM, immunomodulator; INSPIRE, A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Evaluate the Efficacy and Safety of Risankizumab in Participants With Moderately to Severely Active Ulcerative Colitis IV, intravenous; LUCENT, An Induction Study of Mirikizumab in Participants With Moderately to Severely Active Ulcerative Colitis; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Score; NCT01551290, A Study to Evaluate the Effectiveness and Safety of Infliximab in Chinese Patients With Active Ulcerative Colitis; NR, not reported; OASIS, Safety and Efficacy of Etrasimod (APD334) in Patients With Ulcerative Colitis; OCTAVE 1, A Study Evaluating The Efficacy And Safety Of CP-690,550 In Patients With Moderate To Severe Ulcerative Colitis; OCTAVE 2, A Study To Evaluate Both The Efficacy and Safety Profile of CP-690,550 In Patients With Moderately to Severely Active Ulcerative Colitis; P, placebo; po, oral; PURSUIT, A Safety and Effectiveness Study of Golimumab in Japanese Patients With Moderately to Severely Active Ulcerative Colitis; QUASAR, A Study of Guselkumab in Participants With Moderately to Severely Active Ulcerative Colitis; RBS, rectal bleeding score; SC, subcutaneous; SD, standard deviation; SELECTION A, Study to Evaluate the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Adults With Moderately to Severely Active Ulcerative Colitis; SFS, stool frequency subscore; TOUCHSTONE, An Extension Study of RPC1063 as Therapy for Moderate to Severe Ulcerative Colitis; TRUE NORTH Safety and Efficacy Trial of RPC1063 for Moderate to Severe Ulcerative Colitis; U-ACCOMPLISH, A Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Participants With Moderately to Severely Active Ulcerative Colitis; U-ACHIEVE, A Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis (UC); ULTRA 1, Ulcerative Colitis Long-Term Remission and Maintenance With Adalimumab; ULTRA 2, Efficacy and Safety of Adalimumab in Subjects With Moderately to Severely Active Ulcerative Colitis; UNIFI, Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis; VARSITY, An Efficacy and Safety Study of Vedolizumab Intravenous Compared to Adalimumab Subcutaneous in Participants With Ulcerative Colitis; VEGA, A Study of Efficacy and Safety of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis.

[a]Median (range).

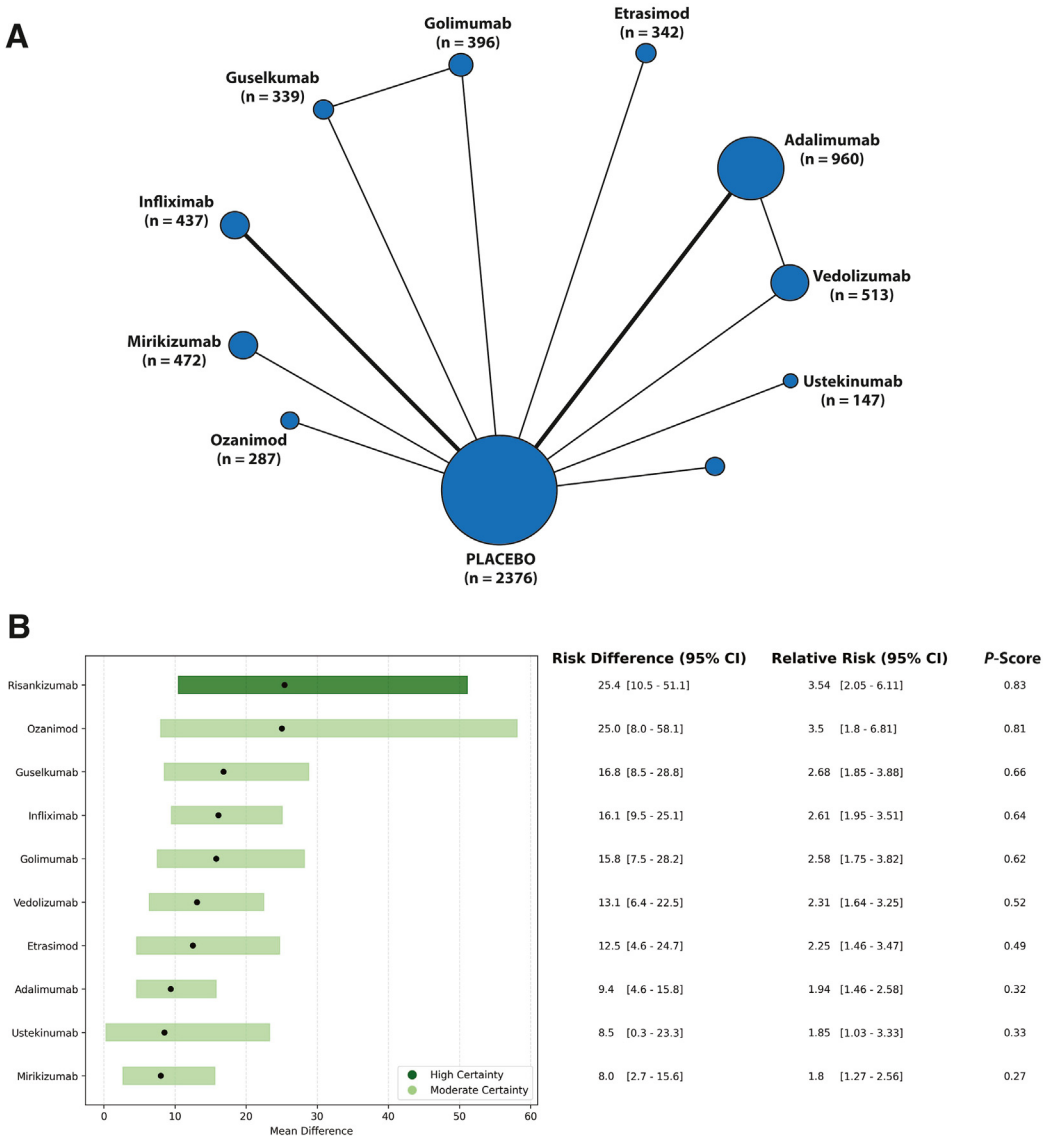

Figure 1. (*A*) Network of included studies examining treatments for induction of clinical remission in biologic-naïve patients with moderately-to-severely active UCs, excluding JAK inhibitors. (*B*) Forest plot, presented as a Gordon plot, for induction of clinical remission in biologic-naïve patients with moderately-to-severely active UC, excluding JAK inhibitors. The *P* score is the probability of being ranked best in the network.

compared with mirikizumab with induction therapy (Table 2). After excluding JAK inhibitors, among 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 1*B*). 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 a higher likelihood of achieving remission compared with tofacitinib and filgotinib (Table 3). Overall, in jurisdictions where JAK inhibitors are available for first-line adoption, among biologic-naïve patients with moderately to severely active UC, upadacitinib (*P* score, 0.96) was ranked highest for induction of clinical remission (Figure 2*B*). 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.

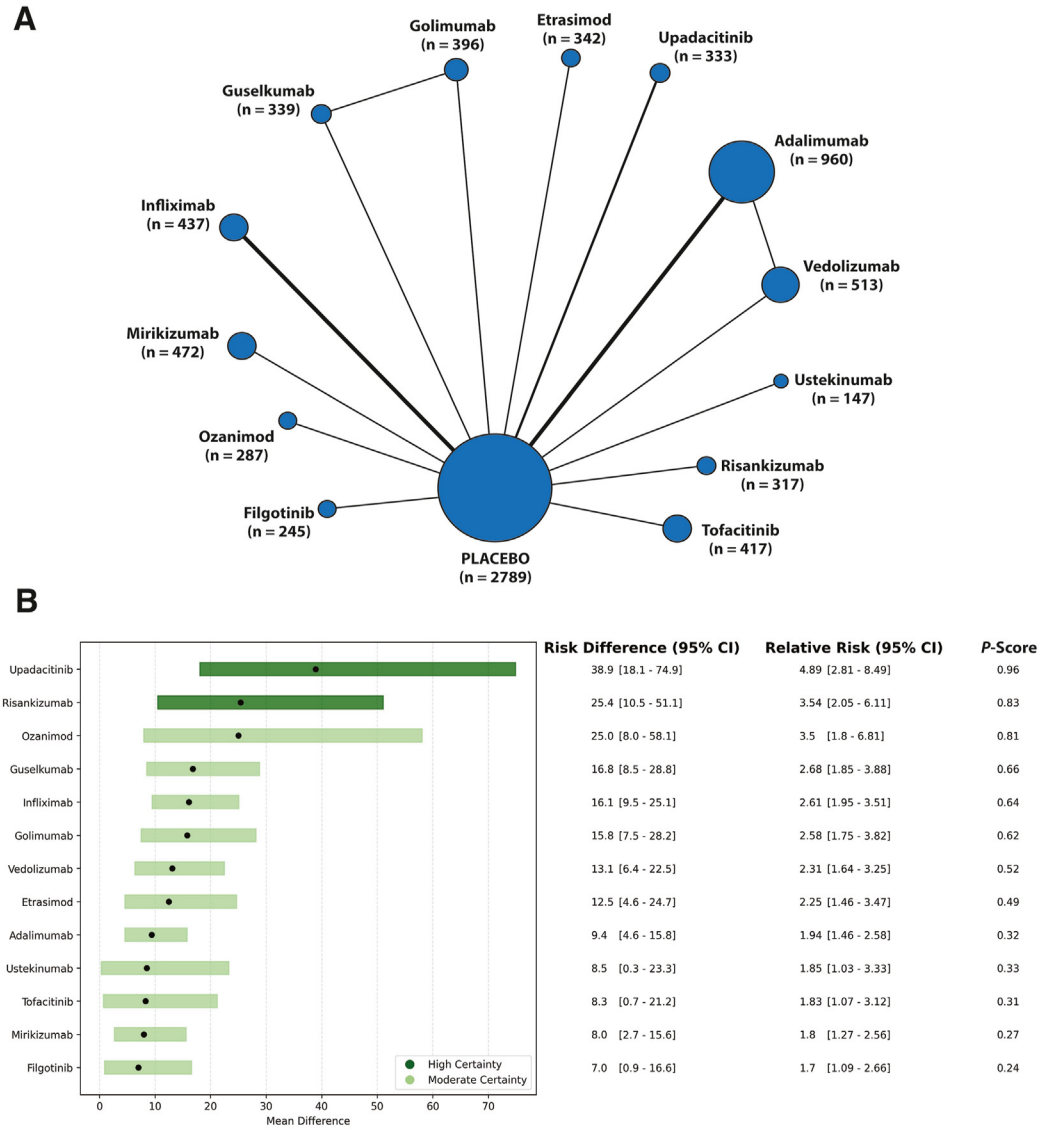

Figure 2. (*A*) Network of included studies examining treatments for induction of clinical remission in biologic naïve-patients with moderately-to-severely active UC, including JAK inhibitors. (*B*) Forest plot, presented as a Gordon plot, for induction of clinical remission in biologic-naïve patients with moderately-to-severely active UC, including JAK inhibitor. The *P* score is the probability of being ranked best in the network.

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 with 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 (Supplementary Figure 1*A* and *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 3*A*). 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 a 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 3*B*).

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

Table 2. Comparative Efficacy of Pharmacologic Therapies for Induction of Clinical Remission and Endoscopic Improvement in Biologic-Naïve Patients With Moderately-to-Severely Active Ulcerative Colitis, Excluding Janus Kinase Inhibitors

Comparison of active therapies	Clinical remission RR (95% CI)	Absolute risk difference per 1000 patients treated (95% CI)	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**[a]	**Possibly important harm**	0.71 (0.56–0.89)
Golimumab	0.98 (0.59–1.63)	−5 (−107 to 164)	Very low[b]	Uncertain trivial harm	0.78 (0.60–1.02)
Vedolizumab	0.89 (0.55–1.43)	−29 (−117 to 112)	Very low[b]	Uncertain trivial harm	0.94 (0.65–1.35)
Ozanimod	1.34 (0.63–2.83)	88 (−96 to 476)	Very low[b]	Uncertain important benefit	1.45 (0.88–2.39)
Etrasimod	0.86 (0.50–1.48)	−36 (−130 to 125)	Very low[b]	Uncertain trivial harm	1.06 (0.72–1.56)
Ustekinumab	0.71 (0.36–1.40)	−75 (−166 to 104)	Very low[b]	Uncertain important benefit	0.84 (0.55–1.27)
Mirikizumab	**0.70 (0.43–1.14)**	−78 (−148 to 36)	**Low**[a]	**Possibly important harm**	0.84 (0.61–1.16)
Risankizumab	1.35 (0.71–2.58)	91 (−75 to 411)	Very low[b]	Uncertain important benefit	1.78 (1.15–2.76)
Guselkumab	1.02 (0.63–1.67)	5 (−96 to 174)	Very low[b]	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**[a]	**Possibly important benefit**	1.11 (0.86–1.43)
Vedolizumab	1.20 (0.89–1.60)	38 (−21 to 114)	Low[a]	Possibly trivial benefit	1.33 (0.93–1.90)
Ozanimod	**1.80 (0.86–3.80)**	**152 (−27 to 532)**	**Low**[a]	**Possibly important benefit**	2.05 (1.25–3.37)
Etrasimod	1.16 (0.68–1.99)	30 (−61 to 188)	Very low[b]	Uncertain trivial benefit	1.50 (1.03–2.19)
Ustekinumab	0.95 (0.48–1.88)	−10 (−99 to 167)	Very low[b]	Uncertain trivial harm	1.18 (0.78–1.79)
Mirikizumab	0.94 (0.58–1.52)	−11 (−80 to 99)	Very low[b]	Uncertain trivial harm	1.19 (0.87–1.63)
Risankizumab	**1.82 (0.96–3.46)**	**156 (−8 to 467)**	**Low**[a]	**Possibly important benefit**	2.52 (1.64–3.88)
Guselkumab	**1.38 (0.85–2.24)**	**72 (−29 to 236)**	**Low**[a]	**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[b]	Uncertain trivial harm	1.20 (0.82–1.76)
Ozanimod	1.36 (0.61–3.02)	94 (−101 to 525)	Very low[b]	Uncertain important benefit	1.85 (1.10–3.09)
Etrasimod	0.88 (0.48–1.61)	−31 (−135 to 159)	Very low[b]	Uncertain trivial harm	1.35 (0.91–2.02)
Ustekinumab	0.71 (0.34–1.50)	−75 (−172 to 130)	Very low[b]	Uncertain important harm	1.07 (0.69–1.65)
Mirikizumab	0.71 (0.40–1.24)	−75 (−156 to 62)	Very low[b]	Uncertain important harm	1.08 (0.76–1.51)
Risankizumab	1.37 (0.68–2.77)	96 (−83 to 460)	Very low[b]	Uncertain important benefit	2.28 (1.45–3.58)
Guselkumab	1.04 (0.66–1.64)	10 (−88 to 166)	Very low[b]	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[b]	Uncertain important benefit	1.54 (0.87–2.74)
Etrasimod	0.97 (0.54–1.73)	−7 (−106 to 168)	Very low[b]	Uncertain trivial harm	1.13 (0.70–1.82)
Ustekinumab	0.80 (0.39–1.62)	−46 (−140 to 143)	Very low[b]	Uncertain trivial harm	0.89 (0.54–1.47)
Mirikizumab	0.79 (0.46–1.33)	−48 (−124 to 76)	Very low[b]	Uncertain trivial harm	0.90 (0.59–1.38)
Risankizumab	1.52 (0.77–3.00)	120 (−53 to 460)	Very low[b]	Uncertain important benefit	1.90 (1.13–3.19)
Guselkumab	1.15 (0.68–1.97)	35 (−74 to 223)	Very low[b]	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[b]	Uncertain important harm	0.73 (0.41–1.32)
Ustekinumab	0.53 (0.21–1.32)	−165 (−277 to 112)	Very low[b]	Uncertain important harm	0.58 (0.31–1.06)
Mirikizumab	**0.52 (0.24–1.14)**	**−168 (−266 to 49)**	**Low**[a]	**Possibly important harm**	0.58 (0.34–1.01)
Risankizumab	1.01 (0.41–2.47)	4 (−207 to 515)	Very low[b]	Uncertain trivial benefit	1.23 (0.66–2.30)
Guselkumab	0.77 (0.35–1.68)	−81 (−228 to 238)	Very low[b]	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[b]	Uncertain trivial harm	0.79 (0.47–1.32)
Mirikizumab	0.81 (0.45–1.46)	−44 (−127 to 106)	Very low[b]	Uncertain trivial harm	0.80 (0.51–1.24)
Risankizumab	1.57 (0.76–3.25)	131 (−55 to 518)	Very low[b]	Uncertain important benefit	1.68 (0.99–2.87)
Guselkumab	1.19 (0.66–2.15)	44 (−78 to 265)	Very low[b]	Uncertain trivial benefit	1.08 (0.70–1.70)
vs Ustekinumab (reference, risk of achieving clinical remission = 19%)					
Mirikizumab	0.99 (0.48–2.03)	−2 (−99 to 196)	Very low[b]	Uncertain trivial harm	1.01 (0.63–1.62)
Risankizumab	**1.91 (0.83–4.42)**	**173 (−32 to 650)**	**Low**[a]	**Possibly important benefit**	2.13 (1.22–3.72)
Guselkumab	1.45 (0.70–2.99)	86 (−57 to 378)	Very low[b]	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)**	**Low**[a]	**Possibly important benefit**	2.12 (1.30–3.45)
Guselkumab	**1.47 (0.85–2.54)**	**85 (−27 to 277)**	**Low**[a]	**Possibly important benefit**	1.35 (0.90–2.03)

Table 2. Continued

Comparison of active therapies	Clinical remission RR (95% CI)	Absolute risk difference per 1000 patients treated (95% CI)	GRADE	Interpretation (for clinical remission)	Endoscopic improvement RR (95% CI)
vs Risankizumab (reference, risk of achieving clinical remission = 35%)					
Guselkumab	0.76 (0.38–1.51)	−84 (−217 to 179)	Very low[b]	Uncertain important harm	0.64 (0.39–1.06)

NOTE. 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.
[a]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).
[b]Rated down thrice for imprecision since the MCID of 50 per 1000 was crossed on both sides with the 95% CI.

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 moderately-to-severely active UC. With an estimated placebo rate of achieving remission of 5% in biologic-exposed patients with moderate-to-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 were 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-rerandomization trials. Trials of infliximab, adalimumab, vedolizumab, and etrasimod provided information on maintenance of clinical remission at 1 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 a higher likelihood of maintaining remission compared with adalimumab with moderate certainty (Supplementary Figure 2).

We identified trials of adalimumab, golimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, ozanimod, tofacitinib, upadacitinib, and filgotinib for maintenance of remission using responder-rerandomization analysis. All other agents provided information on maintenance of remission at 1 year using a responder-rerandomization analysis. Both upadacitinib, 30 mg daily (relative risk [RR], 2.83; 95% CI, 0.99–8.10) and 15 mg daily (RR, 2.32; 95% CI, 0.81–6.68), and tofacitinib, 10 mg 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 IL23 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 (Supplementary Figure 3).

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) (Supplementary Figure 4*A*) or endoscopic improvement (*P* score, 0.24). For induction of clinical remission in biologic-exposed patients, etrolizumab was rated similar in efficacy to IL23 antagonists and filgotinib (Supplementary Figure 4*B*), whereas for the outcome of maintenance of clinical remission, etrolizumab had the lowest efficacy (Supplementary Figure 4*C* and *D*).

Discussion

The therapeutic armamentarium for the treatment of moderate-to-severe UC has expanded significantly with the approval of 3 new therapeutic mechanisms—JAK inhibitors, selective IL23 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 MCID of 5% to confirm higher efficacy of one medication over another.

We make several key observations that will decisively inform positioning of newer therapies for the management of moderate-severe UC: (1) as first-line treatment, in countries outside the United States where JAK inhibitors can be used before failure of other advanced therapies, upadacitinib was the most efficacious in inducing clinical remission, achieving remission in ∼50% patients; (2) as first-line therapy

Table 3. Comparative Efficacy of Pharmacologic Therapies for Induction of Clinical Remission and Endoscopic Improvement in Biologic-Naïve Patients With Moderately-to-Severely Active Ulcerative Colitis, Including Janus Kinase Inhibitors

Comparison of active therapies	Clinical remission	Absolute risk difference per 1000 patients treated		Interpretation	Endoscopic improvement
	RR (95% CI)	(95% CI)	GRADE	(for clinical remission)	RR (95% CI)
vs Upadacitinib (reference, risk of achieving clinical remission = 49%)					
Infliximab	**0.53 (0.29–1.00)**	**−230 (−348 to 0)**	**Moderate[a]**	**Likely important harm**	0.46 (0.30–0.72)
Adalimumab	**0.40 (0.21–0.74)**	**−294 (−387 to −127)**	**Moderate[b]**	**Likely important harm**	0.33 (0.21–0.51)
Golimumab	**0.53 (0.27–1.04)**	**−230 (−358 to 20)**	**Low[c]**	**Possibly important harm**	0.36 (0.23–0.57)
Vedolizumab	**0.47 (0.25–0.91)**	**−260 (−368 to −44)**	**Low[c]**	**Possibly important harm**	0.43 (0.26–0.74)
Ozanimod	0.72 (0.30–1.70)	−137 (−343 to 343)	Very low[d]	Uncertain important harm	0.67 (0.36–1.26)
Etrasimod	**0.46 (0.23–0.93)**	**−265 (−377 to −34)**	**Moderate[b]**	**Likely important harm**	0.49 (0.29–0.84)
Ustekinumab	**0.38 (0.17–0.85)**	**−304 (−407 to −74)**	**Moderate[b]**	**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[d]	Uncertain important harm	0.82 (0.46–1.47)
Guselkumab	**0.55 (0.28–1.07)**	**−221 (−353 to 34)**	**Low[c]**	**Possibly important harm**	0.53 (0.32–0.88)
Tofacitinib	**0.37 (0.17–0.81)**	**−309 (−407 to −93)**	**Moderate[b]**	**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[c]**	**Possibly important benefit**	1.16 (0.77–1.74)
Adalimumab	1.06 (0.58–1.95)	11 (−76 to 171)	Very low[d]	Uncertain trivial benefit	0.82 (0.55–1.22)
Golimumab	**1.41 (0.73–2.75)**	**74 (−49 to 315)**	**Low[c]**	**Possibly important benefit**	0.91 (0.60–1.39)
Vedolizumab	1.27 (0.67–2.38)	49 (−59 to 248)	Very low[d]	Uncertain trivial benefit	1.09 (0.67–1.78)
Ozanimod	**1.92 (0.82–4.50)**	**166 (−32 to 630)**	**Low[c]**	**Possibly important benefit**	1.68 (0.92–3.07)
Etrasimod	1.23 (0.62–2.45)	41 (−68 to 261)	Very low[d]	Uncertain trivial benefit	1.23 (0.74–2.04)
Ustekinumab	1.01 (0.47–2.22)	2 (−95 to 220)	Very low[d]	Uncertain trivial benefit	0.97 (0.57–1.65)
Mirikizumab	0.99 (0.52–1.87)	−2 (−86 to 157)	Very low[d]	Uncertain trivial harm	0.98 (0.62–1.55)
Risankizumab	**1.94 (0.90–4.16)**	**169 (−18 to 569)**	**Low[c]**	**Possibly important benefit**	2.07 (1.20–3.58)
Guselkumab	**1.47 (0.77–2.82)**	**85 (−41 to 328)**	**Low[c]**	**Possibly important benefit**	1.32 (0.82–2.13)
Filgotinib	0.93 (0.47–1.87)	−13 (−95 to 157)	Very low[d]	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)**	**Low[c]**	**Possibly important benefit**	1.14 (0.75–1.71)
Adalimumab	1.14 (0.67–1.93)	24 (−57 to 158)	Very Low[d]	Uncertain trivial benefit	0.80 (0.54–1.20)
Golimumab	**1.52 (0.84–2.78)**	**88 (−27 to 303)**	**Low[c]**	**Possibly important benefit**	0.89 (0.58–1.36)
Vedolizumab	**1.35 (0.78–2.38)**	**60 (−37 to 235)**	**Low[c]**	**Possibly important benefit**	1.07 (0.65–1.75)
Ozanimod	**2.04 (0.92–4.55)**	**177 (−14 to 604)**	**Low[c]**	**Possibly important benefit**	1.64 (0.90–3.00)
Etrasimod	**1.32 (0.71–2.46)**	**54 (−49 to 248)**	**Low[c]**	**Possibly important benefit**	1.20 (0.72–2.00)
Ustekinumab	1.09 (0.52–2.27)	15 (−82 to 216)	Very low[d]	Uncertain trivial benefit	0.95 (0.56–1.62)
Mirikizumab	1.06 (0.60–1.85)	10 (−68 to 145)	Very low[d]	Uncertain trivial benefit	0.96 (0.60–1.52)
Risankizumab	**2.07 (1.02–4.20)**	**182 (3 to 544)**	**Moderate[b]**	**Likely important benefit**	2.02 (1.17–3.51)
Guselkumab	**1.56 (0.88–2.78)**	**95 (−20 to 303)**	**Low[c]**	**Possibly important benefit**	1.29 (0.80–2.09)

NOTE. 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.

[a]Rated down once for serious imprecision because only the MCID was crossed, but not the line of unity (no difference in efficacy).

[b]Rated down once for imprecision due to failure to meet optimal information size because the ratio of upper and lower limits of the 95% CI the RR was >3.

[c]Rated down twice for very serious imprecision because 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).

[d]Rated down thrice for imprecision because the MCID of 50 per 1000 was crossed on both sides with the 95% CI.

excluding JAK inhibitors, as guided by the FDA approval in the United States, risankizumab and ozanimod were ranked highest in achieving clinical remission; and (3) 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 antilymphocyte trafficking mechanisms in the treatment of biologic-naïve moderate-to-severe UC.

Our findings update the results of recent NMAs[11–13,45] by 3 important methodologic additions. First, we added data on several additional therapies with available phase 3 efficacy data because the prior analyses included 1 S1P modulator (etrasimod) and 3 anti-IL23 agents (guselkumab,

Table 4. Comparative Efficacy of Pharmacologic Therapies for Induction of Clinical Remission and Endoscopic Improvement in Biologic-Exposed Patients With Moderately-to-Severely Active Ulcerative Colitis

Comparison of therapies	Clinical remission RR (95% CI)	Absolute risk difference per 1000 patients treated (95% CI)	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[a]	Possibly trivial benefit	1.07 (0.68–1.68)
Vedolizumab	1.64 (0.82–3.36)	32 (−9 to 118)	Low[a]	Possibly trivial benefit	1.05 (0.72–1.55)
Ozanimod	1.78 (0.60–5.26)	39 (−20 to 213)	Low[a]	Possibly trivial benefit	1.15 (0.55–2.42)
Etrasimod	1.61 (0.91–2.85)	31 (−5 to 93)	Low[a]	Possibly trivial benefit	1.94 (1.17–3.23)
Ustekinumab	**11.04 (2.64–46.10)**	**502 (85 to 1000)**	**Moderate[b]**	**Likely important benefit**	3.04 (1.65–5.61)
Mirikizumab	**2.33 (1.30–4.16)**	**67 (15 to 158)**	**Moderate[b]**	**Likely important benefit**	2.05 (1.31–3.20)
Risankizumab	**2.77 (1.26–6.07)**	**89 (13 to 254)**	**Moderate[b]**	**Likely important benefit**	2.58 (1.59–4.20)
Guselkumab	**2.86 (1.39–5.88)**	**93 (20 to 244)**	**Moderate[b]**	**Likely important benefit**	2.71 (1.46–5.01)
Tofacitinib	**10.45 (2.09–52.22)**	**473 (55 to 1000)**	**Moderate[b]**	**Likely important benefit**	3.75 (1.88–7.48)
Filgotinib	**2.71 (1.56–6.36)**	**86 (28 to 268)**	**Moderate[b]**	**Likely important benefit**	2.22 (1.18–4.15)
Upadacitinib	**14.05 (4.94–43.94)**	**653 (197 to 1000)**	**Moderate[b]**	**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[a]**	Possibly trivial benefit	0.99 (0.54–1.78)
Ozanimod	1.73 (0.47–6.35)	37 (−27 to 268)	**Low[a]**	Possibly trivial benefit	1.08 (0.45–2.57)
Etrasimod	1.56 (0.62–3.93)	28 (−19 to 147)	**Low[a]**	Possibly trivial benefit	1.81 (0.92–3.58)
Ustekinumab	**10.73 (2.16–53.19)**	**487 (58 to 1000)**	**Moderate[b]**	**Likely important benefit**	2.84 (1.33–6.09)
Mirikizumab	**2.26 (0.90–5.71)**	**63 (−5 to 236)**	**Low[a]**	**Possibly important benefit**	1.92 (1.02–3.61)
Risankizumab	**2.69 (0.93–1.59)**	**85 (−4 to 341)**	**Low[a]**	**Possibly important benefit**	2.42 (1.25–4.69)
Guselkumab	**2.78 (1.00–7.70)**	**89 (0 to 335)**	**Moderate[b]**	**Likely important benefit**	2.53 (1.18–5.43)
Tofacitinib	**10.16 (1.74–59.21)**	**458 (37 to 1000)**	**Moderate[b]**	**Likely important benefit**	3.51 (1.54–8.00)
Filgotinib	**2.63 (0.86–8.04)**	**82 (−7 to 352)**	**Low[a]**	**Possibly important benefit**	2.07 (0.96–4.49)
Upadacitinib	**13.66 (3.54–52.62)**	**633 (127 to 1000)**	**Moderate[b]**	**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[c]	Uncertain trivial benefit	1.10 (0.47–2.53)
Etrasimod	0.98 (0.40–2.40)	−2 (−48 to 112)	Low[a]	Possibly trivial harm	1.84 (0.97–3.49)
Ustekinumab	**6.70 (1.37–32.78)**	**456 (30 to 1000)**	**Moderate[b]**	**Likely important benefit**	2.89 (1.40–5.96)
Mirikizumab	1.41 (0.57–3.49)	**33 (−34 to 199)**	Low[a]	Possibly trivial benefit	1.94 (1.08–3.51)
Risankizumab	**1.68 (0.59–4.79)**	**54 (−34 to 303)**	**Low[a]**	**Possibly important benefit**	2.45 (1.32–4.56)
Guselkumab	**1.73 (0.64–4.71)**	**58 (−29 to 297)**	**Low[a]**	**Possibly important benefit**	2.57 (1.24–5.31)
Tofacitinib	**6.34 (1.10–36.54)**	**427 (8 to 1000)**	**Moderate[b]**	**Likely important benefit**	3.56 (1.61–7.85)
Filgotinib	**1.64 (0.55–4.93)**	**51 (−36 to 314)**	**Low[a]**	**Possibly important benefit**	2.11 (1.01–4.40)
Upadacitinib	**8.52 (2.24–32.35)**	**602 (99 to 1000)**	**Moderate[b]**	**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[c]	Uncertain trivial harm	1.68 (0.68–4.13)
Ustekinumab	**6.21 (1.03–37.38)**	**469 (3 to 1000)**	**Moderate[b]**	**Likely important benefit**	2.63 (1.01–6.90)
Mirikizumab	1.31 (0.38–4.49)	28 (−56 to 314)	Very low[c]	Uncertain trivial benefit	1.77 (0.75–4.22)
Risankizumab	1.56 (0.41–5.95)	50 (−53 to 446)	Very low[c]	Uncertain important benefit	2.24 (0.92–5.43)
Guselkumab	1.61 (0.44–5.92)	55 (−50 to 443)	Very low[c]	Uncertain important benefit	2.34 (0.89–6.15)
Tofacitinib	**5.88 (0.84–40.95)**	**439 (−14 to 1000)**	**Low[a]**	**Possibly important benefit**	3.25 (1.18–8.95)
Filgotinib	1.53 (0.38–6.06)	48 (−56 to 455)	Very low[c]	Uncertain trivial benefit	1.92 (0.73–5.07)
Upadacitinib	**7.91 (1.64–38.16)**	**622 (58 to 1000)**	**Moderate[b]**	**Likely important benefit**	9.08 (2.97–27.75)
vs Etrasimod (reference, risk of achieving clinical remission = 8%)					
Ustekinumab	**6.86 (1.47–32.00)**	**469 (38 to 1000)**	**Moderate[b]**	**Likely important benefit**	1.57 (0.71–3.48)
Mirikizumab	1.45 (0.64–3.27)	36 (−29 to 182)	Low[a]	Possibly trivial benefit	1.06 (0.54–2.08)
Risankizumab	**1.72 (0.65–4.55)**	**58 (−28 to 284)**	**Low[a]**	**Possibly important benefit**	1.33 (0.66–2.69)
Guselkumab	**1.78 (0.71–4.46)**	**62 (−23 to 277)**	**Low[a]**	**Possibly important benefit**	1.40 (0.63–3.10)
Tofacitinib	**6.50 (1.18–35.84)**	**440 (14 to 1000)**	**Moderate[b]**	**Likely important benefit**	1.93 (0.82–4.56)
Filgotinib	**1.68 (0.60–4.70)**	**54 (−32 to 296)**	**Low[a]**	**Possibly important benefit**	1.14 (0.51–2.56)
Upadacitinib	**8.74 (2.44–31.28)**	**619 (115 to 1000)**	**Moderate[b]**	**Likely important benefit**	5.40 (2.03–14.37)

Table 4. Continued

Comparison of therapies	Clinical remission RR (95% CI)	Absolute risk difference per 1000 patients treated (95% CI)	GRADE	Interpretation (for clinical remission)	Endoscopic improvement RR (95% CI)
vs Ustekinumab (reference, risk of achieving clinical remission = 55%)					
Mirikizumab	**0.21 (0.05–0.99)**	**−435 (−523 to −6)**	**Moderate**[b]	**Likely important harm**	0.67 (0.32–1.44)
Risankizumab	0.25 (0.05–1.28)	−413 (−525 to 154)	Very low[c]	Uncertain important benefit	0.85 (0.39–1.86)
Guselkumab	0.26 (0.05–1.28)	−407 (−523 to 154)	Very low[c]	Uncertain important benefit	0.89 (0.37–2.12)
Tofacitinib	0.95 (0.11–8.14)	−28 (−490 to 1000)	Very low[c]	Uncertain trivial harm	1.23 (0.49–3.11)
Filgotinib	0.25 (0.05–1.30)	−413 (−523 to 165)	Very low[c]	Uncertain important benefit	0.73 (0.30–1.75)
Upadacitinib	1.27 (0.20–7.92)	149 (−440 to 1000)	Very low[c]	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[c]	Uncertain trivial benefit	1.26 (0.65–2.44)
Guselkumab	1.23 (0.49–3.10)	28 (−61 to 252)	Very low[c]	Uncertain trivial benefit	1.32 (0.62–2.82)
Tofacitinib	**4.49 (0.81–24.84)**	**419 (−23 to 1000)**	**Low**[a]	**Possibly important benefit**	1.83 (0.80–4.16)
Filgotinib	1.16 (0.42–3.27)	19 (−70 to 272)	Very low[c]	Uncertain trivial benefit	1.08 (0.50–2.34)
Upadacitinib	**6.04 (1.68–21.71)**	**605 (82 to 1000)**	**Moderate**[b]	**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[c]	Uncertain trivial benefit	1.05 (0.48–2.30)
Tofacitinib	3.77 (0.63–22.59)	388 (−52 to 1000)	Very low[c]	Uncertain important benefit	1.45 (0.62–3.38)
Filgotinib	0.98 (0.31–3.11)	−3 (−97 to 295)	Very low[c]	Uncertain trivial harm	0.86 (0.39–1.90)
Upadacitinib	**5.07 (1.27–20.23)**	**570 (38 to 1000)**	**Moderate**[b]	**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[c]	Uncertain important benefit	1.83 (0.55–3.49)
Filgotinib	0.95 (0.31–2.89)	−7 (−97 to 265)	Very low[c]	Uncertain trivial harm	0.82 (0.34–1.97)
Upadacitinib	**4.91 (1.28–18.91)**	**547 (39 to 1000)**	**Moderate**[b]	**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[c]	Uncertain important harm	0.59 (0.23–1.90)
Upadacitinib	1.34 (0.19–9.66)	177 (−421 to 1000)	Very low[c]	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**[b]	**Likely important benefit**	3.87 (1.66–13.43)

NOTE. 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.

[a]Rated down twice for very serious imprecision because 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).

[b]Rated down once for imprecision due to failure to meet optimal information size because the ratio of upper limit and lower limit of the 95% CI of the relative risk was >3.

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

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 the addition of a second direct head-to-head trial in UC, comparing guselkumab with golimumab. In addition, prior NMAs included 5 trials of etrolizumab, an anti-integrin that did not meet its primary efficacy end point 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 rates 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 postmarketing surveillance study of adults aged ≥50 years with rheumatoid arthritis and at least 1 cardiovascular risk

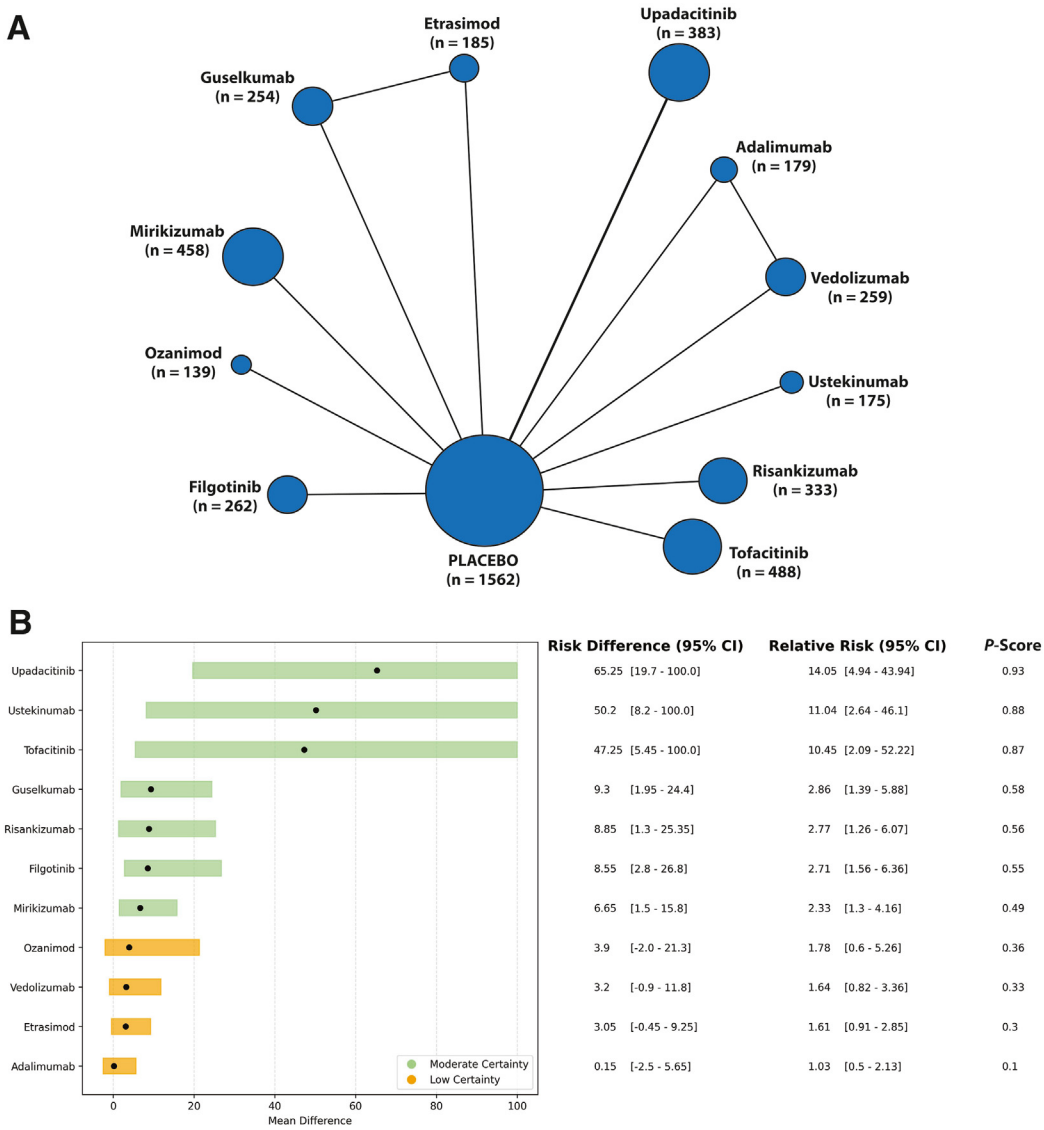

Figure 3. (*A*) Network of included studies examining treatments for induction of clinical remission in biologic exposed-patients with moderately-to-severely active UC. (*B*) Forest plot, presented as a Gordon plot, for induction of clinical remission in biologic-exposed patients with moderately-to-severely active UC. The *P* score is the probability of being ranking best in the network. MCID threshold set at 5%.

factor treated with tofacitinib, a nonselective JAK inhibitor, in which both an increased risk of major adverse cardiovascular events and malignancy compared with anti-TNF therapy were observed, particularly with the 10-mg twice-daily dose of tofacitinib.[48] The European Medicines Agency, although 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 major adverse cardiovascular events in this population compared with anti-TNF therapy.[49–51]

In a subsequent NMA, the risk of cardiovascular events was not higher with JAK inhibitors compared with TNF antagonists or anti-IL therapy among patients with IBD.[52] 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 nonselective 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, and ozanimod) over adalimumab. These findings are different from several recent NMAs that did not show a difference between the 2 treatments. This is an important observation because adalimumab is one of the most commonly prescribed biologics for UC,[53] influenced by both physician and patient preferences and payor restrictions. Although 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 prior treatment with ≥2 biologics having failed in 30% to 35% of patients in its clinical trials. 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 1 prior biologic exposure, ozanimod had rates of clinical remission of 23% and 17% compared with 7% and 8% in placebo.[54] However, in those who were exposed to ≥2 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.

This study and prior NMAs both demonstrate that the efficacy of different drugs within the same therapeutic class may not be comparable. We found infliximab was superior to adalimumab, upadacitinib was superior to both tofacitinib and filgotinib, and risankizumab was 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 methodologic 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 the weight-based dosing of infliximab or induction or maintenance dose of adalimumab, because no incremental evidence of greater efficacy with high-dose adalimumab induction was observed in the SERENE-UC (Study of a Novel Approach to Induction and Maintenance Dosing With Adalimumab in Patients With Moderate to Severe Ulcerative Colitis) trials.[57] 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 conclusion.[46]

Our NMA suggested upadacitinib, tofacitinib, and ustekinumab are superior to vedolizumab in those in whom prior biologic treatment failed. This is also consistent with recent observational data. Buisson et al[60] conducted a propensity-matched analysis of vedolizumab and tofacitinib in those with a prior anti-TNF failure. Although no difference was found in clinical remission rates at week 16 between both agents, vedolizumab was inferior to tofacitinib in achieving endoscopic improvement and histologic healing.[60] A large Dutch registry-based study similarly demonstrated superior efficacy of tofacitinib over vedolizumab.[61] In contrast, although a United States insurance-based study demonstrated lower persistence of tofacitinib over vedolizumab, this lacked granular data to discern differences in treatment efficacy.[62]

Few real-world studies have compared ustekinumab with 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 (Study of Vedolizumab [MLN0002] in Patients With Moderate to Severe Ulcerative Colitis), the magnitude of clinical benefit of vedolizumab over placebo in TNF antagonist-naïve patients was 16.5% compared with only 6.5% in TNF antagonist-exposed patients. In contrast, in the UNIFI (Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis) 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]

Our work has several limitations. 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, although our analysis was stratified by prior biologic exposure status, we acknowledge that with the increasing complexity of our therapeutic armamentarium, this comparison will become more nuanced. Apart from TNF antagonists, S1P modulators, JAK inhibitors, and IL23 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 TNF antagonist failure. In more recent studies, vedolizumab—but not other mechanisms—may have failed in a small fraction entering the trials. 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 the wide range of immunomodulator use and that immunomodulator or 5-aminosalicylate therapy had failed before study entry in most patients entering the trials. 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 integrating such data for newer agents with the absence of ascertainment of these end points for older trials will remain a challenge.

We also selected a threshold of an absolute difference of 5% in defining superiority of one agent over the other. Anchored against the ~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 MCID 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 compared with 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.

Conclusion

Our NMA highlights upadacitinib as the most effective therapy for moderately-to-severely active UC in both biologic-naïve and biologic-exposed populations, demonstrating the urgent importance of studies of long-term safety of this treatment in patients with UC to inform the need for use 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

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2024.07.046.

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