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First- and Second-line Pharmacotherapies for Patients with Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis

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Abstract

Background & Aims: We compared the efficacy and safety of different first-line (biologic-naïve) and second-line (prior exposure to tumor necrosis factor [TNF] antagonists) agents for treatment of moderate to severely active ulcerative colitis in a systematic review and network meta-analysis.

Methods: We searched publication databases through September 30, 2019 for randomized trials of adults with moderate to severe ulcerative colitis treated with TNF antagonists, vedolizumab, tofacitinib, or ustekinumab, as first-line or second-line agents, compared with placebo or another active agent. Efficacy outcomes were induction and maintenance of remission and endoscopic improvement; safety outcomes were serious adverse events and infections. We performed fixed-effects network meta-analysis using frequentist approach, and calculated odds ratios (ORs) and 95% CI values. Agents were ranked using surface under the cumulative ranking (SUCRA) probabilities.

Results: In biologic-naïve patients, infliximab was ranked highest for induction of clinical remission (OR vs placebo, 4.07; 95% CI, 2.67–6.21; SUCRA,0.95) and endoscopic improvement (SUCRA, 0.95) (moderate confidence in estimates [CE]). In patients with prior exposure to TNF antagonists, ustekinumab (SUCRA,0.87) and tofacitinib (SUCRA,0.87) were ranked highest for induction of clinical remission and were superior to vedolizumab (OR vs ustekinumab, 5.99; 95% CI, 1.13–31.76 and OR vs tofacitinib, 6.18; 95% CI, 1.003–8.00; moderate CE) and adalimumab (OR vs ustekinumab, 10.71; 95% CI, 2.01–57.20 and OR vs tofacitinib, 11.05; 95% CI, 1.79–68.41; moderate CE). Vedolizumab had lowest risk of infections (SUCRA, 0.81), followed by ustekinumab (SUCRA, 0.63) in maintenance trials.

Conclusions: In a systematic review and network meta-analysis, we found infliximab to be ranked highest in biologic-naïve patients, and ustekinumab and tofacitinib were ranked highest in patients with prior exposure to TNF antagonists, for induction of remission and endoscopic improvement in patients with moderate to severe ulcerative colitis. More trials of direct comparisons are needed to inform clinical decision-making with greater confidence.

Keywords

GRADE; pharmacotherapy; inflammatory bowel disease; UC; comparative efficacy

INTRODUCTION

Ulcerative colitis affects one in 200-400 people in Western nations, and its global incidence and prevalence is rising.[1] While the majority of patients have a mild-moderate course, about 10-15% patients experience severe disease course with significant morbidity with frequent flares and hospitalizations, requiring immunosuppressive therapies and corticosteroids, and impose a significant direct and indirect economic burden, in population-based cohorts.[2,3] Several treatment options are now available for the management of moderate-severe ulcerative colitis, with variable efficacy and safety profile, and positioning different agents in treatment course, as first-line (in biologic-naïve patients) and second-line (in patients with prior exposure to tumor necrosis factor (TNF)-α antagonists) is a key knowledge gap. In the absence of head-to-head comparisons, prior network meta-analyses have attempted to

address this gap, but have been limited by the number of studies, especially regarding comparative efficacy of agents in patients with prior exposure to TNFα antagonists.[4,5] With the recent labeling and dosing change for tofacitinib in light of safety considerations, recent publication of the first head-to-head trial comparing vedolizumab vs. adalimumab in patients with moderate-severe ulcerative colitis and recent regulatory approval of ustekinumab for these patients, the results of these analyses warrant updating.[6,7]

Hence, we updated our prior systematic review with network meta-analyses, comparing the relative efficacy and safety of infliximab, adalimumab, golimumab, vedolizumab, tofacitinib and ustekinumab as first- and second-line agents in patients with moderate-severe ulcerative colitis. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for network meta-analysis to appraise the confidence in estimates.[8]

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 network meta-analyses for health care interventions.[9] We followed good research practices outlined in the International Society for Pharmacoeconomics and Outcomes Research report on interpreting indirect treatment comparisons and network meta-analysis for health-care decision-making.[10]

Study Selection

We conducted two separate pairwise and network meta-analyses of induction therapy to estimate comparative efficacy of different agents in biologic-naïve patients and in patients with prior exposure to TNFα antagonists for management of moderate-severe ulcerative colitis. Studies included in these meta-analyses were phase II or III RCTs that met the following inclusion criteria: (1) Patients: adults (age >18 years) with moderate to severe ulcerative colitis (Mayo Clinic Score 6-12, with an endoscopic subscore of 2 or 3) who were either treatment-naïve (first-line) or previously exposed to TNFα antagonists (second-line); (2) Intervention: biologic therapy with infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab, 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 maintenance therapy of biologic agents had different designs (treat straight-through design vs. re-randomizing responders to induction therapy), we conducted separate pairwise and network meta-analyses for these different trials designs. Since safety is unlikely to be significantly influenced by maintenance therapy trial design, to inform comparative safety, we conducted a single network meta-analysis of all trials of maintenance therapy, regardless of different trial design. Detailed inclusion criteria for trials of maintenance therapy, and exclusion criteria are listed in Supplementary Appendix.

Search Strategy, Data Abstraction and Risk of Bias Assessment

We updated our previous literature search, conducted as part the American Gastroenterological Association technical review on management of moderate-severe ulcerative colitis (date of search, March 30, 2018), on September 30, 2019, with no language restrictions. Details of the search strategy are shown in the Supplementary appendix. Data on study-, participant-, disease- and treatment-related characteristics were abstracted onto a standardized form, by two investigators (SS and MF) independently and discrepancies were resolved by consensus, referring back to the original article, in consultation with a third reviewer (WJS). Two study investigators (MF and SS) independently rated the quality of included trials using the Cochrane Risk of Bias Tool.[11]

Outcomes

For trials of induction therapy, the efficacy outcome was induction of clinical remission (defined as Mayo Clinic Score ≤2 with no individual subscore >1), and endoscopic improvement (defined as endoscopy subscore of Mayo Clinic Score of 0 or 1). Recognizing limitations of short-term trials in evaluating treatment safety, we qualitatively synthesized the overall safety of all agents, regardless of first- or second-line therapy, and presented as proportion of patients with any adverse event, adverse events leading to drug discontinuation, serious adverse events and serious infections.

For trials of maintenance therapy, efficacy outcomes were maintenance of clinical remission and endoscopic improvement, and safety outcomes were serious adverse events (study-defined) and infections, which were analyzed quantitatively. Additionally, we qualitatively reviewed risk of any adverse events, adverse events resulting in treatment discontinuation, and risk of serious infections. Additional details of outcome assessment are shown in Supplementary Appendix.

Data Synthesis and Statistical Analysis

Pooled odds ratios (OR) and 95% confidence intervals (CI), were calculated using the Mantel-Haenszel fixed-effects model (in the absence of conceptual heterogeneity and if <5 studies), with sensitivity analysis using the DerSimonian-Liard random-effects model.[11-13] We assessed statistical heterogeneity using the I^2 statistic, with values over 50% suggesting substantial heterogeneity. Publication bias was assessed by evaluating small study effects by examining funnel plot asymmetry.[14] Direct comparisons were performed using RevMan v53 (Cochrane Collaboration, Copenhagen, Denmark). Next, we conducted network meta-analysis using a multivariate, consistency model, random-effects meta-regression as described by Ian White, using STATA v.15.0 (College Station, TX).[15] This frequentist approach provides a point estimate from the network along with 95% CI from the frequency distribution of the estimate.

We calculated the relative ranking of agents for induction of clinical remission as their surface under the cumulative ranking (SUCRA), which represents the percentage of efficacy or safety achieved by an agent compared to an imaginary agent that is always the best without uncertainty (i.e., SUCRA=100%).[16] Higher SUCRA scores correspond to higher

ranking for induction of clinical remission and/or endoscopic improvement, and higher ranking for safety (i.e., lowest risk of serious adverse events and infections).

Confidence in Estimates

We followed the GRADE approach to appraise the confidence in estimates derived from network meta-analysis of efficacy outcomes.[8] 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). If direct and indirect estimates were similar (i.e., coherent), then the higher of their rating can be assigned to the network meta-analysis estimates.

RESULTS

From a total 5651 unique studies identified using our search strategy, we included 15 RCTs of first-line agents (in biologic-naïve patients), (ACT 1 and 2,[17] Jiang et al,[18] NCT01551290,[19] ULTRA 1 and 2,[20,21] Suzuki et al,[22] PURSUIT Phase 2 and Phase 3 induction studies,[23] GEMINI I,[24] Motoya et al,[25] VARSITY, OCTAVE 1 and 2[26] and UNIFI) and 7 RCTs of second-line agents (in patients with prior exposure to TNFα antagonists) (ULTRA 2,[21] GEMINI I,[24] Motoya et al, VARSITY,[6] OCTAVE 1 and 2[26], UNIFI[7]), in patients with moderate-severe ulcerative colitis. Trials of infliximab (ACT 1 and 2[17], Jiang et al,[18] NCT01551290,[19]), adalimumab (ULTRA 2,[20,21] Suzuki et al[22]), vedolizumab (GEMINI I[24], Motoya et al,[25] VARSITY[6]) and ustekinumab (UNIFI)[7] also reported outcomes on maintenance therapy, within the same publication; PURSUIT-M, PURSUIT-J and OCTAVE-SUSTAIN reported outcomes for maintenance therapy with for golimumab and tofacitinib, respectively.[26-28] From our previous analysis, three additional studies were included. The schematic diagram of study selection is shown in eFigure 1 and available direct comparisons and network of trials are shown in Figures 1A and B.

Trial and patient characteristics are summarized in Table 1 Overall, the median of average age of patients was 41 (interquartile range, 40-42), and 60% (interquartile range, 56-63) were males. Median disease duration of 6.7y (interquartile range, 6.0-7.8), and 49% (interquartile range, 46-55) patients had extensive colitis. Median 40% (interquartile range, 30-50) patients were treated with concomitant immunomodulators, and 51% (interquartile range, 45-57) were on corticosteroids at baseline. Patients across all trials and treatment arms were comparable in terms of baseline prognostic variables, inclusion/exclusion criteria, and co-interventions. All outcomes were uniformly assessed based on standard definition of Mayo Clinic Score, between weeks 6 and 10 for induction therapy (infliximab, adalimumab, tofacitinib, ustekinumab, 8 weeks; golimumab, 6 weeks; vedolizumab, 6 weeks, 10 weeks and 14 weeks in VARSITY)[6] and week 30, 54 or 60 for maintenance therapy; endoscopy was read by blinded local investigators for all trials, except trials of tofacitinib, and

ustekinumab, which were read by blinded central readers.[7,26] Overall, the studies were deemed to be at low risk of bias, and all included studies were industry-sponsored.

INDUCTION THERAPY

First-line Pharmacotherapy for Moderate-Severe Ulcerative Colitis

Overall, 15 RCTs including 3747 biologic-naïve patients with moderate-severe ulcerative colitis, treated with infliximab (4 trials, 667 patients), adalimumab (4 trials, 1046 patients), golimumab (2 trials, 586 patients), vedolizumab (3 trials, 630 patients), tofacitinib (2 trials, 520 patients) and ustekinumab (1 trial, 298 patients) were included; one trial compared adalimumab vs. vedolizumab.

Induction of Clinical Remission—On direct meta-analysis, all agents were superior to placebo for induction of clinical remission, and effect size was strongest for infliximab (OR, 4.07; 95% CI, 2.68-6.16) and vedolizumab (OR, 3.10 [1.53-6.26]), with minimal to moderate heterogeneity across estimates (I^2<35%) (eFigure 2A). On network meta-analysis, compared to placebo, there was moderate confidence in estimates supporting the use of infliximab, adalimumab, golimumab, vedolizumab, tofacitinib and ustekinumab for induction of clinical remission in biologic-naïve patients (evidence rated down due to imprecision due to low event rate) (Table 2). On comparison of active interventions, there was moderate confidence in estimates supporting the use of infliximab over adalimumab (OR, 2.10; 95% CI, 1.16-3.79); none of the other comparisons between active interventions were significantly different (Table 2). Overall, infliximab (SUCRA, 0.95) was ranked highest for inducing clinical remission in biologic-naïve patients with moderate-severe UC (Figure 2A). With an estimated placebo rate of achieving remission of 10% in included trials, we anticipate that 31.1%, 17.7%, 23.7%, 22.0%, 19.1 and 18.5% of infliximab-, adalimumab-, golimumab-, vedolizumab-, tofacitinib- and ustekinumab-treated patients, respectively, would achieve induction of remission.

Induction of Endoscopic improvement—On direct meta-analysis, all agents were superior to placebo for induction of endoscopic improvement, and effect size was strongest for infliximab (OR, 3.32) and vedolizumab (OR, 2.52), with minimal heterogeneity across estimates (I^2=0%) (eFigure 2B). On network meta-analysis, compared to placebo, there was high confidence in estimates supporting the use of infliximab, adalimumab and golimumab, and moderate confidence in estimates supporting the use of vedolizumab, tofacitinib and ustekinumab for induction of endoscopic improvement in biologic-naïve patients (evidence rated down due to imprecision due to low event rate) (Table 2). On comparison of active interventions, there was high confidence in estimates supporting the use of infliximab over adalimumab (OR, 2.10; 95% CI, 1.35-3.25), golimumab (OR, 1.91; 95% CI, 1.20-3.03), and ustekinumab (OR, 1.78; 95% CI, 0.97-3.29). There was no significant difference in the efficacy of infliximab and vedolizumab as a first-line agent for induction of endoscopic improvement, with low confidence in estimates (OR, 1.32; 95% CI, 0.73-2.37) (Table 2). Overall, infliximab (SUCRA, 0.95) and vedolizumab (SUCRA, 0.76) were ranked highest for inducing endoscopic improvement in biologic-naïve patients with moderate-severe ulcerative colitis (Figure 2A). With an estimated placebo rate of achieving endoscopic

improvement of 30% in induction trials, we estimated that 58.7%, 40.4%, 42.7%, 51.9%, 46.5% and 44.4% of infliximab-, adalimumab-, golimumab-, vedolizumab-, tofacitinib-, and ustekinumab-treated patients, respectively, would achieve induction of endoscopic improvement.

Second-line Pharmacotherapy for Moderate-Severe Ulcerative Colitis

Overall, 7 RCTs including 1580 patients with moderate-severe ulcerative colitis with prior exposure to TNFα antagonists were identified. These included subgroup analysis of trials of adalimumab,[21] vedolizumab,[24,25] tofacitinib,[26] and ustekinumab.[7] There were no trials of infliximab or golimumab, in patients with prior exposure TNFα antagonists which met inclusion criteria. In trials of adalimumab, only patients with loss of response or intolerance to a prior TNFα antagonist were included. In contrast, in trials of vedolizumab, 48-58% patients had inadequate response to TNFα antagonist, and in trials of ustekinumab, 13-18% patients had prior exposure to both vedolizumab and TNFα antagonists. This data was not available for tofacitinib.

Induction of Clinical Remission—On direct meta-analysis, tofacitinib and ustekinumab, but not adalimumab or vedolizumab, were superior to placebo for induction of clinical remission (eFigure 3A), with minimal heterogeneity across estimates (I^2<30%). On network meta-analysis, there was moderate confidence in estimates supporting the use of tofacitinib (OR, 11.88; 95% CI, 2.32-60.89) and ustekinumab (OR, 11.51; 95% CI, 2.65-49.96), and low confidence in estimates supporting the use of vedolizumab (OR, 1.92; 95% CI, 0.87-4.25) over placebo, for induction of clinical remission in patients with prior exposure to TNFα antagonists (Table 3). On comparison of active interventions, there was moderate confidence in estimates supporting the use of tofacitinib and ustekinumab over adalimumab (tofacitinib vs. adalimumab: OR, 11.05; 95% CI, 1.79-68.41; ustekinumab vs. adalimumab: OR, 10.71; 95% CI, 2.01-57.20), and over vedolizumab (tofacitinib vs. vedolizumab: OR, 6.18; 95% CI, 1.00-38.00); ustekinumab vs. vedolizumab: OR, 5.99; 95% CI, 1.13-31.76) for induction of clinical remission in patients with prior exposure to TNFα antagonists. Overall, ustekinumab (SUCRA, 0.87) and tofacitinib (SUCRA, 0.87) were ranked highest for inducing clinical remission in patients with moderate-severe ulcerative colitis with prior exposure to TNFα antagonists (Figure 2B). With an estimated placebo rate of achieving clinical remission of 3% in included trials, we estimated that 3.2%, 5.6%, 26.9% and 26.3% of adalimumab-, vedolizumab-, tofacitinib-, and ustekinumab-treated patients, respectively, would achieve induction of remission.

Induction of Endoscopic improvement—On direct meta-analysis, tofacitinib and ustekinumab, but not vedolizumab or adalimumab, were superior to placebo for induction of endoscopic improvement, with minimal heterogeneity across estimates (I^2<30%) (eFigure 3B). On network meta-analysis, compared to placebo, there was moderate confidence in estimates supporting the use of tofacitinib (OR, 4.71; 95% CI, 2.23-9.92) and ustekinumab (OR, 3.64; 95% CI, 1.78-7.46) for induction of endoscopic improvement in patients with prior exposure to TNFα antagonists. (Table 3). On comparison of active interventions, there was moderate confidence in estimates supporting the use of tofacitinib and ustekinumab over adalimumab (tofacitinib vs. adalimumab: OR, 4.29; 95% CI, 1.63-11.33; ustekinumab

vs. adalimumab: OR, 3.32; 95% CI, 1.29-8.58), and over vedolizumab (tofacitinib vs. vedolizumab: OR, 3.85; 95% CI, 1.51-9.80); ustekinumab vs. vedolizumab: OR, 2.98; 95% CI, 1.20-7.41) for induction of endoscopic improvement in patients with prior exposure to TNFα antagonists. Overall, tofacitinib (SUCRA, 0.91) and ustekinumab (SUCRA, 0.83) were ranked highest for inducing endoscopic improvement in patients with moderate-severe ulcerative colitis with prior exposure to TNFα antagonists (Figure 2B). With an estimated placebo rate of achieving endoscopic improvement of 15% in included trials, we estimated that 16.3%, 17.7%, 45.4% and 39.1% of adalimumab-, vedolizumab-, tofacitinib-, and ustekinumab-treated patients, respectively, would achieve endoscopic improvement.

Comparative Safety of Induction Therapy

eTable 1 summarizes rate of all adverse events, adverse events resulting in treatment discontinuation, serious adverse events and serious infections in trials of induction therapy. Data on safety stratified by TNFα antagonist exposure status was not reported, and overall event rate for important safety outcomes was low; hence, a formal network meta-analysis was not performed. Overall, median rate of serious adverse events with active intervention was 4.7% (interquartile range, 3.6-6.9). Median rate of serious infections in induction trials with active intervention was 0.6% (interquartile range, 0.1-1.8).

MAINTENANCE THERAPY

Efficacy

Due to differences in trial design, trials of infliximab and adalimumab (treat straight-through) and of golimumab, tofacitinib, and ustekinumab (re-randomization of responders to induction therapy) were analysed separately; vedolizumab contributed to both trial designs. On network meta-analysis of treat straight-through trials in biologic-naïve patients, infliximab, adalimumab and vedolizumab were superior to placebo, and vedolizumab was superior to adalimumab for maintenance of clinical remission and endoscopic improvement (eTable 2A; eFigures 4A and B); no significant differences were observed between infliximab and vedolizumab (clinical remission: OR, 0.72; 95% CI, 0.35-1.49; endoscopic improvement: OR, 0.73; 95% CI, 0.37-1.42). Vedolizumab was ranked highest (SUCRA, maintenance of clinical remission and endoscopic improvement: 0.93 and 0.94), followed by infliximab (0.63 and 0.67). Similarly, on network meta-analysis of trials in which responders to induction therapy were re-randomized to active intervention or placebo, golimumab, vedolizumab, tofacitinib and ustekinumab were superior to placebo for maintenance of clinical remission and endoscopic improvement (eFigures 5A and B, eTable 2B). No significant difference were observed on comparison of active interventions, with all agents being equally effective for maintenance of remission in a subset of patients who responded to induction therapy (SUCRA, maintenance of clinical remission and endoscopic improvement: golimumab, 0.69 and 0.58; vedolizumab, 0.63 and 0.76; tofacitinib, 0.69 and 0.69; and ustekinumab, 0.47 and 0.46, respectively). While the maintenance trial of golimumab was conducted in only TNFα antagonist-naïve patients, trials of vedolizumab and tofacitinib included both TNFα antagonist-naïve and TNFα antagonist-exposed patients, but results were not stratified by prior TNFα antagonist exposure status.

Comparative Safety of Maintenance Therapy

eTable 3 summarizes rates of all adverse events, adverse events resulting in treatment discontinuation, serious adverse events, any infections, serious infections and infusion/injection-site reactions in all trials of maintenance therapy. On network meta-analysis, no agent was significant worse than placebo in rates of serious adverse events (Table 4, eFigure 6), which may be related to effective disease control; amongst active interventions, rates of serious adverse events were lower with vedolizumab and infliximab as compared to golimumab. Rate of serious infections was low, and was not deemed amenable to network meta-analysis; hence, risk of overall infections was used a surrogate safety outcome. On network meta-analysis, golimumab and tofacitinib and were associated with increased risk of infections as compared to placebo (Table 4, eFigure 7). On comparing active interventions, rate of serious infection was lower with vedolizumab as compared to tofacitinib (OR, 0.56; 95% CI, 0.32-0.98) (Table 4). Overall, vedolizumab (SUCRA, 0.81) and ustekinumab (SUCRA, 0.63) were ranked safest in terms of risk of infections.

Publication bias—There was no evidence of small study effects on evaluation of funnel plot; however, the number of studies for each comparison was small, and we cannot reliably detect publication bias.

DISCUSSION

In this updated systematic review and network meta-analysis combining direct and indirect evidence from 17 trials, we made several key observations. First, in biologic-naïve patients, while all approved agents are effective, infliximab was ranked highest for inducing clinical remission and endoscopic improvement, with moderate confidence in estimates supporting its use over adalimumab. Second, in patients with moderate-severe ulcerative colitis with prior exposure to TNFα antagonists, tofacitinib and ustekinumab are ranked highest for inducing remission, and both these agents are more effective than vedolizumab or adalimumab, with moderate confidence in estimates. Of note, there were no trials of infliximab or golimumab as second-line agents that limits inference on their efficacy if used in the setting of prior TNFα antagonist exposure. Third, vedolizumab was ranked safest with lowest rate of infections amongst active interventions, followed by ustekinumab. As compared to the previous estimates, this updated analysis has key strengths with inclusion of the first head-to-head trial comparing vedolizumab and adalimumab which forms a more connected network, and provides more robust, statistically and clinically significant results on comparative efficacy of second-line pharmacotherapy in patients with prior exposure to TNFα antagonists. Notable new findings are: (a) relative lowering efficacy of vedolizumab as first-line agent for induction of remission than prior estimates, (b) significantly superior efficacy of ustekinumab and tofacitinib over vedolizumab as second-line agents in patients with prior exposure to TNFα antagonists. With limited head-to-head trials, this information can directly inform clinical practice and guidelines and facilitate shared decision making for management of patients with moderate-severe ulcerative colitis.

Our results confirm several prior observational comparative effectiveness studies, individual patient-level analyses of clinical trials and indirect treatment comparison network meta-

analyses suggesting higher efficacy and effectiveness of infliximab over adalimumab and golimumab.[4,5,29,30] This may be related to difference in pharmacokinetics and bioavailability with different dosing schema (weight-based vs. fixed dose) and route of administration. The recent SERENE-UC trial comparing standard- vs. high-dose adalimumab in patients with moderate-severe ulcerative colitis failed to demonstrate superiority of higher dose adalimumab, suggesting that currently approved dosing of adalimumab is unlikely to change, and hence, the comparative efficacy results will remain similar.[31] Our findings also support the observation in the recent head-to-head VARSITY trial as well as propensity score-matched analyses from VICTORY consortium that vedolizumab is more effective than adalimumab for long-term maintenance of clinical remission; over 8-12 weeks of induction therapy, however, no differences were observed between the two agents.[6,32] Moreover, we did not observe any differences in efficacy of vedolizumab and infliximab in maintenance of clinical remission or endoscopic improvement on comparison of treat straight-through maintenance trials.

Perhaps the most informative results from our analyses pertain to the comparative efficacy of different agents in patients with prior exposure to TNFα antagonists. This is increasingly relevant given high rates of primary non-response or secondary loss of response to initial biologic therapy, and is an often-faced clinical scenario for which there is limited guidance. We observed that both ustekinumab and tofacitinib were significantly more effective than vedolizumab and adalimumab for induction of remission. Findings from these indirect comparisons need to be interpreted with caution since these trials did not always mirror clinical practice. For example, current trials did not utilize therapeutic drug monitoring to understand the plausible mechanism of failure of initial biologic intervention. Given potential differences in efficacy of 2nd line interventions depending on underlying reason for discontinuation of prior TNFα antagonists (primary non-response vs. secondary loss of response vs. intolerance), such information may be useful in making clinical treatment decisions in conjunction with findings from our analyses.[33,34] In these analyses, data on how many prior TNFα antagonists to which a patient had been exposed was not consistently reported. It is conceivable that since TNFα antagonists were the first class of medications to be approved, patients treated with adalimumab or golimumab in clinical trials generally had exposure to only a single TNFα antagonists; in contrast, in subsequent trials of vedolizumab, tofacitinib and ustekinumab, a significant proportion of patients may have been exposed to 2 or more biologic agents prior to clinical trial intervention, and may inherently be difficult to treat. However, trials of ustekinumab were conducted following approval of vedolizumab, and a subset of patients in these trials had failed multiple TNFα antagonists and vedolizumab, conceivably making it a more refractory patient population. Despite this, we observed superiority of ustekinumab over vedolizumab suggesting the effect is likely real and not confounded by treatment refractoriness.

In this study, by updating analyses with inclusion of ustekinumab, accounting for dose change for tofacitinib, including the first head-to-head trial of biologics in moderate-severe ulcerative colitis, appropriately comparing trials of maintenance therapy with different designs, adding the GRADE framework and assessment of absolute effect size, and performing a thorough quantitative and qualitative assessment of safety of different therapies, we have been able to contextualize our confidence in the summary estimates for

different comparisons, and more thoroughly inform positioning of different agents used in the treatment of moderate-severe ulcerative colitis. We acknowledge that there is paucity of head-to-head trials to truly inform comparative efficacy and safety. It is, however, important to note, that across trials of induction therapy, key inclusion/exclusion criteria, outcome definitions, patient and clinical characteristics, co-interventions were comparable across trials, which facilitated this network meta-analysis.

Besides inherent limitations of individual trials, there are limitations to our analyses. A thorough comparative analysis across all agents was limited to trials of induction therapy; due to differences in trial design of maintenance therapy, we had conduct two separate network meta-analyses limiting comparative assessments. Approaches to conducting network meta-analyses when study designs are different have been proposed, but it is difficult to assess their validity.[35,36] Most of the included trials relied on local investigators for endoscopic reading of endoscopic disease activity for trial recruitment and outcome assessment, whereas trials of tofacitinib and ustekinumab included blinded central readers, which can influence absolute event rates of clinical remission and endoscopic improvement; additional the efficacy outcome in OCTAVE induction trials of tofacitinib were more robust, with requirement of a rectal bleeding subscore of 0.[26] There were differences in timing of outcomes assessment in induction studies (week 6-14), and time-dependent variability in efficacy could not be analysed in detail. While corticosteroid-free remission may be a more relevant clinical endpoint, this was inconsistently reported in included trials; across all trials of induction therapy, no corticosteroid tapering was attempted. We are unable to inform the comparative efficacy of biologic monotherapy vs. combination therapy with immunomodulators. We specifically opted to exclude UC-SUCCESS for the following reasons: (a) inclusion of this trial with 3 active arms (including one arm of thiopurine monotherapy) would have resulted in a disconnected network, and (b) efficacy of thiopurine monotherapy as a separate intervention would have been hard to interpret and biased since other older trials of thiopurines for induction and maintenance, which were systematically different from contemporary trials, were being excluded. This trial has suggested, in patients who are naïve to biologics and immunomodulators, combination therapy of infliximab and thiopurines may be more efficacious than infliximab monotherapy for achieving endoscopic improvement, but not clinical remission. We also urge caution in interpreting our findings solely in terms of ranking or SUCRA. There are no thresholds for clinically meaningful differences between SUCRA values between different agents, and generally, values closer to 1 suggest that the intervention may be among the top-ranking interventions, and values closer to 0 suggest that the intervention may be among the bottom ranking interventions. SUCRA does not consider the magnitude of differences in effects between treatments, for which we rely on ORs of specific comparisons.

Beyond treatment efficacy, safety is an integral part in determining risk-benefit balance of each intervention and informing shared decision-making.[37] While comparative analysis of maintenance trials suggested higher safety with vedolizumab, rates of important events like serious infections was low and other serious events like malignancy could not be thoroughly evaluated. Moreover, differences in study design of maintenance therapy (treat straight-through vs. re-randomization of responders), as well as lack of information on safety stratified by prior TNFα antagonist exposure status, may potentially bias safety results. Post-

marketing surveillance studies of these different agents may better inform relative safety of these agents. Safety of tofacitinib seems to be dose-dependent, and in instances where higher 10mg twice/day dose of tofacitinib is used for long-term maintenance, safety concerns should be adequately discussed with patients.

Integrating findings from this meta-analysis and other studies, current evidence favors infliximab or vedolizumab as preferred first-line agents for moderate-severe ulcerative colitis. In patients who fail infliximab, ustekinumab and tofacitinib would likely be most efficacious, and ustekinumab's superior safety profile may be attractive in light of recent concerns around venous thromboembolism with tofacitinib. However, besides quality of evidence, several other factors including a balance of risk-benefit profile, specific patient attributes (age, comorbid conditions including rheumatic or dermatological diseases, etc.), clinical judgment and experience of the treating physicians, values and preferences of patients (dosing route, regimen, acceptability of risk-benefit trade-offs, etc.) as well as costs/resources available are important to facilitate shared decision-making, in developing a personalized treatment strategy for each patient, and shape healthcare policy on positioning different agents. Pragmatic head-to-head trials in both biologic-naïve and biologic-exposed patients are warranted to optimally inform relative positioning of newly available agents in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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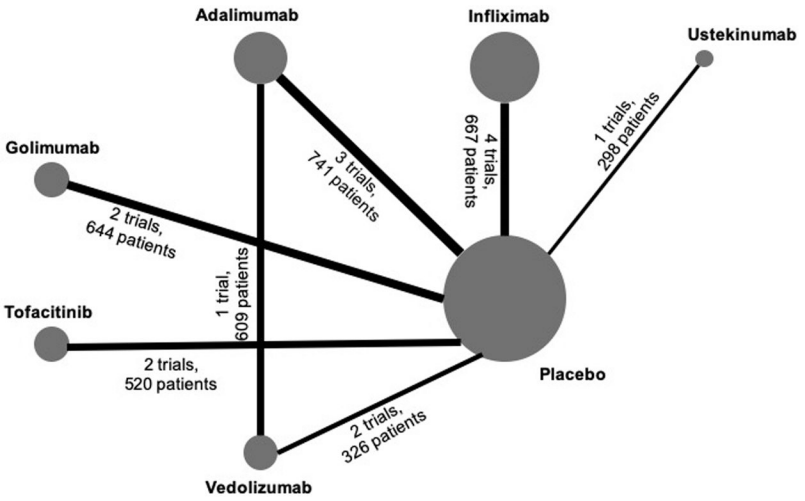

Figure 1A.

Network of included studies with the available direct comparisons for induction of clinical remission in biologic-naïve patients with moderate-severe ulcerative colitis. The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively.

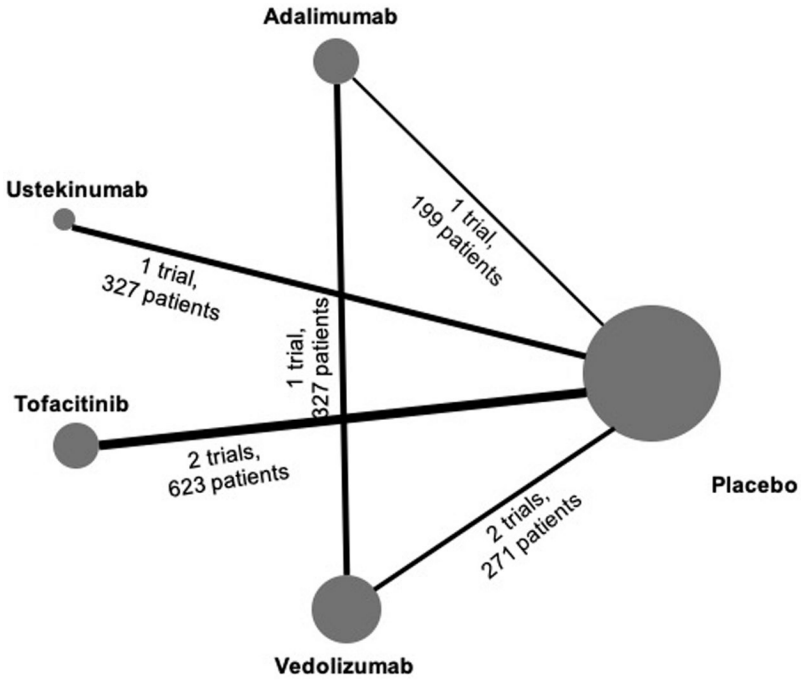

Figure 1B.

Network of included studies with the available direct comparisons for induction of clinical remission in patients with prior TNFα antagonist exposure with moderate-severe ulcerative colitis. The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively.

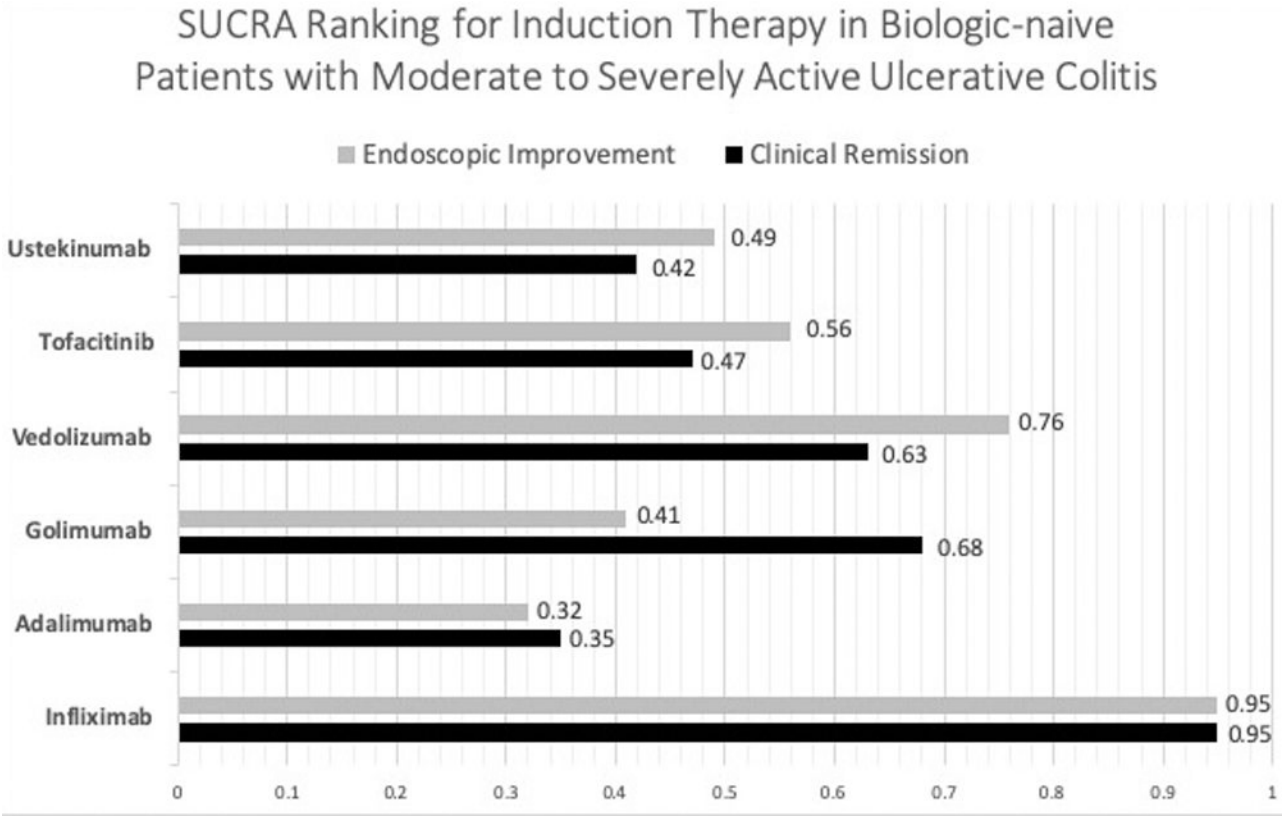

Figure 2A.

Relative efficacy of different interventions for induction of clinical remission and endoscopic improvement in biologic-naïve patients with moderate to severely active ulcerative colitis

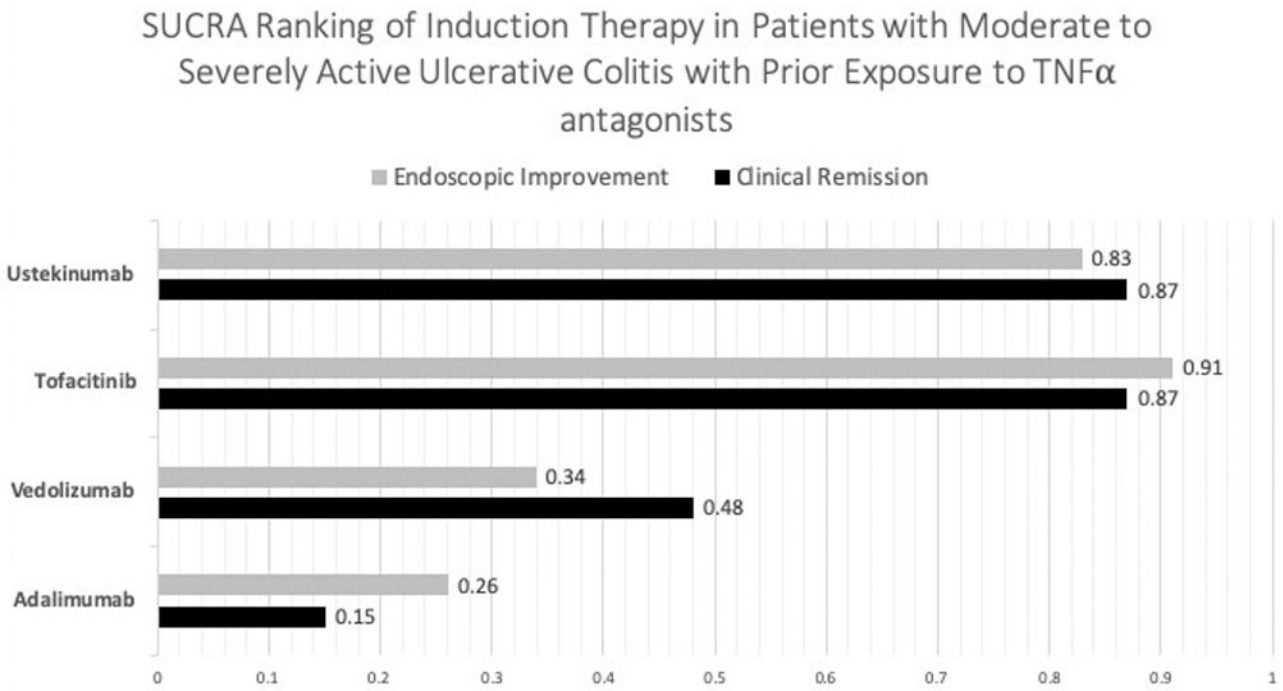

Figure 2B.

Relative efficacy of different interventions for induction of clinical remission and endoscopic improvement in patients with moderate to severely active ulcerative colitis with prior exposure to TNFα antagonists.

Table 1.

Trial and patient characteristics in included trials of induction and maintenance therapy for moderate-severe ulcerative colitis

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (standard deviation); Sex (% male)	Mean Disease duration (y) (standard deviation); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (standard deviation)	Prior anti-TNF therapy (%)
					Immunomodulators (%)	Corticosteroids (%)		
INFLIXIMAB								
ACT 1[17] ✓ (Induction and Maintenance therapy)	62 sites, 2002-05; P: 121; I: IFX 5mg/kg, w0,2,6, then q8w – 121	MCS≤2; W8, W54	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
ACT 2[17] ✓ (Induction and Maintenance therapy)	55 sites, 2002-05; P: 123; I: IFX 5mg/kg, w0,2,6, then q8w – 121	MCS≤2; W8, W30	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
Jiang et al[18] ✓ (Induction and Maintenance therapy)	1 site (China), 2008-13; P: 41; I: IFX 5mg/kg, w0,2,6, then q8w – 41	MCS≤2; W8, W30	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
NCT01551290[19] ✓ (Induction and Maintenance therapy)	12 sites (China), 2012-14; P: 49; I: IFX 5mg/kg, w0,2,6, then q8w – 50	MCS≤2; W8, W26	Entire group: 37; NR	3.7; NR	NR	80 60	NR	0 0
ADALIMUMAB								
ULTRA 1[20] (Induction therapy)	94 sites, 2007-10; P: 130; I: ADA 160/80/40, w0,2,4,6 – 130	MCS≤2; 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
ULTRA 2[21] ✓ (Induction and Maintenance therapy)	103 sites, 2006-10; P: 246; I: ADA 160/80/40, w0,2,4,6 – 248	MCS≤2; 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 § 39 §
Suzuki et al[22] ✓ (Induction and Maintenance therapy)	65 sites, 2009-11; P: 96; I: ADA 160/80/40, w0,2,4,6 – 90	MCS≤2; 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
GOLIMUMAB								
PURSUIT Phase 2 and 3[23] (Induction therapy)	217 sites, 2007-10; P: 331; I: GLM 200/100, w0,2 - 331	MCS≤2; 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

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (standard deviation); Sex (% male)	Mean Disease duration (y) (standard deviation); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (standard deviation)	Prior anti-TNF therapy (%)
					Immunomodulators (%)	Corticosteroids (%)		
PURSUIT-M[27]¶ (Maintenance therapy)	251 sites, 2007-11; P: 156; I: GLM 100mg q4w - 154	MCS≤2; W54	P: 40 (14); 48 I: 39 (13); 58	6.9 (7.0); NR 7.2 (7.0); NR	33.3 31.2	53.2 51.2	9.6 (15.5) 8.9 (14.7)	0 0
PURSUIT-J[28]¶ (Maintenance therapy)	49 sites (Japan), 2013-16; P: 31 I: GLM 100mg q4w – 32	MCS≤2; W54	P: 43 (14); 61 I: 39 (12); 69	5.7 (5.3); 39 5.4 (6.1); 38	41.9 50.0	29.0 28.1	4.1 (7.7) 5.3 (14.8)	0 0
VEDOLIZUMAB								
GEMINI I[24]¶ (Induction and Maintenance therapy)	211 sites, 2008-12; P(i): 149; I(i): VDZ 300mg, w0,2 – 746 P(m): I(m):	MCS≤2; W6(i); W52(M)	P: 41 (13); 62 I: 40 (13); 58 P(m): 40 (14); 55 I(m): 41 (13); 57	7.1 (7.2); 46 6.8 (6.2); 50 7.8 (7.0); 50 6.2 (5.0); 43	29.5 35.4 40 36	56.3 53.2 57 57	NR NR	49 * 48 * 37 ** 42 **
Motoya et al (Induction and Maintenance therapy)	100 sites, 2014-18; P(i): 82; I(i): VDZ 300mg, w0,2,6 – 164 P(m): 42 I(m): VDZ 300mg q8w; 41	MCS≤2; W10(i); W60(m)	P(i): 44 (16); 67 I(i): 42 (14); 60 P(m): 43 (14); 55 I(m): 43 (14); 51	8.6 (8.0); 62 7.2 (6.2); 62 8.7 (7.0); 55 8.6 (7.8); 68	52.5 48.8 50.0 53.8	30.5 31.7 35.7 31.8	>3mg/L: 39 >3mg/L: 54 NR	50 ∞ 51 ∞ 33 ∞∞ 42 ∞∞
VARSITY[✓] (Induction and Maintenance therapy)	245 sites, 2015-19; ADA 160/80/40, w0,2,4 then q2w; 386 VDZ 300mg, w0,2,6, then q8w - 383	MCS≤2; 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 ∂ 21 ∂
					Proportion of patients receiving both IM and CS not reported			
TOFACITINIB								
OCTAVE 1[26] (Induction therapy)	178 sites, 2012-15; P: 122 I: Tofacitinib 10mg po b.d. - 476	MCS≤2, with rectal bleeding score 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 45.0	4.7 (0.1-82.5) ❖ 4.4 (0.1-208.4) ❖	53 53
OCTAVE 2[26] (Induction therapy)	182 sites, 2012-15; P: 112 I: Tofacitinib 10mg po b.d. - 429	MCS≤2, with rectal bleeding score 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 58
OCTAVE-Sustain[26]¶ (Maintenance therapy)	178 sites, 2012-15; P: 198 I: Tofacitinib 5mg po b.d. - 198	MCS≤2, with rectal bleeding score 0; W8	P: 43 (14); 59 I: 42 (14); 52	7.2 (0.6-42.7) ❖; 55 6.5 (0.6-40.3) ❖; 52	0 0	50.5 51.0	1.0 (0.1-45.0) ❖ 0.7 (0.1-33.7) ❖	46.5 45.5

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (standard deviation); Sex (% male)	Mean Disease duration (y) (standard deviation); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (standard deviation)	Prior anti-TNF therapy (%)
					Immunomodulators (%)	Corticosteroids (%)		
USTEKINUMAB								
UNIFI (Induction and Maintenance therapy)	244 sites, 2015-18; P(i): 319 I(i): UST 6mg/kg, w0 – 322 P(m): 175 I(m): UST 90mg q8w - 176	MCS≤2; W8(i); W44(m)	P(i): 41 (14); 62 I(i): 42 (14); 61 P(m): 42(14); 61 I(m): 40 (13); 53	8.0 (7.2); 47 8.2 (7.8); 47 7.5 (6.8); 49 8.1 (6.7); 46	27.9 27.6 28.0 25.6	49.2 52.2 54.3 54.0	4.7 (1.4-10.) 4.8 (1.8-13.7) 3.4 (1.4-9.7) 4.0 (1.4-12.7)	51[Δ] 52[Δ] 50[Δ] 52[Δ]

[§] Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 0%; Secondary loss of response or intolerance, 100%;

[*] Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 48%; Secondary loss of response, 38%; Intolerance, 14%

[**] Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 36%; Secondary loss of response, 30%; Intolerance, 18%

[∞] Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 58%; Secondary loss of response, 40%; Intolerance, 2%

[∞∞] Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 43%; Secondary loss of response, 50%; Intolerance,7%

[∂] Reasons for discontinuation of prior anti-TNF therapy: Primary non-response, 50%; Secondary loss of response, 35%; Intolerance, 7%

[Δ] Includes patients with prior exposure to TNF antagonist with or without vedolizumab (13-18% had prior exposure to vedolizumab)

[✓] Maintenance therapy with treat straight-through design

[¶] Only including patients with initial response to induction therapy who were re-randomized to placebo or active intervention

[❖] 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 pharmacological agents for induction of clinical remission and endoscopic improvement in biologic-naïve patients with moderate-severe ulcerative colitis, using network meta-analysis. Comparisons should be read from left to right. Odds ratio for comparisons are in the cell in common between the column-defining and row-defining treatment. Bold numbers with darker background are statistically significant. For induction of clinical remission, odds ratio >1 favors row-defining treatment. For induction of endoscopic improvement, odds ratio >1 favors column-defining treatment. Numbers in parentheses indicate 95% confidence interval.

	Induction of CLINICAL REMISSION						
Induction of ENDOSCOPIC IMPROVEMENT	**Ustekinumab 6mg/kg**	0.96 (0.38-2.45)	0.80 (0.35-1.83)	0.73 (0.31-1.74)	1.05 (0.48-2.32)	0.50 (0.22-1.12)	**2.04 (1.03-4.05)**
	0.92 (0.45-1.89)	**Tofacitinib 10mg b.d.**	0.84 (0.39-1.82)	0.76 (0.33-1.76)	1.10 (0.51-2.34)	0.52 (0.24-1.12)	**2.12 (1.12-4.02)**
	0.74 (0.36-1.51)	0.80 (0.4-1.62)	**Vedolizumab**	0.91 (0.44-1.86)	1.31 (0.88-1.95)	0.62 (0.34-1.15)	**2.54 (1.60-4.02)**
	1.07 (0.58-1.98)	1.17 (0.64-2.12)	1.45 (0.80-2.61)	**Golimumab**	1.44 (0.76-2.75)	0.69 (0.35-1.36)	**2.79 (1.64-4.02)**
	1.17 (0.65-2.13)	1.28 (0.72-2.29)	1.59 (0.90-2.82)	1.10 (0.71-1.71)	**Adalimumab**	**0.48 (0.26-0.86)**	**1.94 (1.30-2.88)**
	0.56 (0.30-1.04)	0.61 (0.34-1.11)	0.76 (0.42-1.37)	**0.52 (0.33-0.83)**	**0.48 (0.31-0.74)**	**Infliximab**	**4.07 (2.67-6.21)**
	1.86 (1.11-3.13)	**2.03 (1.23-3.34)**	**2.52 (1.54-4.11)**	**1.74 (1.25-2.41)**	**1.58 (1.18-2.13)**	**3.32 (2.39-4.60)**	**Placebo**

Table 3.

Comparative efficacy of pharmacological agents for induction of clinical remission and endoscopic improvement in patients with moderate-severe ulcerative colitis with prior exposure to tumor necrosis factor-α antagonists, using network meta-analysis. Comparisons should be read from left to right. Odds ratio for comparisons are in the cell in common between the column-defining and row-defining treatment. Bold numbers with darker background are statistically significant. For induction of clinical remission, odds ratio >1 favors row-defining treatment. For induction of endoscopic improvement, odds ratio >1 favors column-defining treatment. Numbers in parentheses indicate 95% confidence interval.

	Induction of CLINICAL REMISSION				
Induction of ENDOSCOPIC IMPROVEMENT	**Ustekinumab 6mg/kg**	0.97 (0.11-8.72)	**5.99 (1.13-31.76)**	**10.71 (2.01-57.20)**	**11.51 (2.65-49.96)**
	0.77 (0.28-2.18)	**Tofacitinib 10mg b.d.**	**6.18 (1.00-38.00)**	**11.05 (1.79-68.41)**	**11.88 (2.32-60.89)**
	2.98 (1.20-7.41)	**3.85 (1.51-9.80)**	**Vedolizumab**	1.79 (0.86-3.70)	1.92 (0.87-4.25)
	3.32 (1.29-8.58)	**4.29 (1.63-11.33)**	1.12 (0.48-2.59)	**Adalimumab**	1.07 (0.48-2.41)
	3.64 (1.78-7.46)	**4.71 (2.23-9.92)**	1.22 (0.70-2.15)	1.10 (0.59-2.04)	**Placebo**

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Table 4.

Comparative safety of pharmacological agents during maintenance therapy in patients with moderate-severe ulcerative colitis, using network meta-analysis. Comparisons should be read from left to right. Odds ratio for comparisons are in the cell in common between the column-defining and row-defining treatment. Bold numbers with darker background are statistically significant. For serious adverse events, odds ratio <1 favors row-defining treatment. For risk of infections, odds ratio <1 favors column-defining treatment. Numbers in parentheses indicate 95% confidence interval.

	RISK OF SERIOUS ADVERSE EVENTS						
RISK OF INFECTIONS	**Ustekinumab 90mg q8w**	1.14 (0.37,3.50)	1.18 (0.50,2.79)	0.43 (0.15,1.22)	0.85 (0.37,1.92)	1.32 (0.56,3.12)	0.87 (0.42,1.79)
	0.63 (0.35,1.16)	**Tofacitinib 5mg b.d.**	1.03 (0.39,2.71)	0.38 (0.12,1.17)	0.74 (0.29,1.87)	1.15 (0.44,3.02)	0.76 (0.32,1.77)
	1.13 (0.66,1.93)	**1.78 (1.02,3.09)**	**Vedolizumab**	**0.37 (0.15,0.88)**	0.72 (0.49,1.05)	1.12 (0.58,2.14)	0.73 (0.46,1.16)
	0.68 (0.36,1.29)	1.08 (0.56,2.05)	0.61 (0.34,1.09)	**Golimumab**	1.95 (0.85,4.48)	**3.04 (1.27,7.28)**	2.00 (0.95,4.20)
	0.89 (0.54,1.47)	1.40 (0.84,2.34)	0.79 (0.60,1.04)	1.31 (0.76,2.25)	**Adalimumab**	1.56 (0.86,2.82)	1.02 (0.71,1.49)
	0.91 (0.51,1.60)	1.43 (0.80,2.55)	0.80 (0.48,1.34)	1.33 (0.72,2.45)	1.02 (0.64,1.63)	**Infliximab**	0.66 (0.41,1.04)
	1.11 (0.73,1.69)	**1.75 (1.13,2.70)**	0.98 (0.70,1.38)	**1.62 (1.01,2.62)**	1.24 (0.95,1.63)	**1.22 (0.83,1.79)**	**Placebo**