SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

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

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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 a fixed-effects network meta-analysis using the frequentist approach, and calculated odds ratios (ORs) and 95% CI values. Agents were ranked using surface under the cumulative ranking (SUCRA) probabilities. Overall quality of evidence was rated using GRADE (Grading of Recommendations, Assessment, Development and Evaluation).**

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 (ustekinumab vs vedolizumab: OR, 5.99; 95% CI, 1.13–31.76 and tofacitinib vs vedolizumab: OR, 6.18; 95% CI, 1.003–8.00; moderate CE) and adalimumab (ustekinumab vs adalimumab: OR, 10.71; 95% CI, 2.01–57.20 and tofacitinib vs adalimumab: OR, 11.05; 95% CI, 1.79–68.41; moderate CE). Vedolizumab had the 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.

Ulcerative colitis affects 1 in 200 to 1 in 400 people in Western nations, and its global incidence and prevalence is increasing.[1] Although the majority of patients have a mild–moderate course, approximately 10% to 15% of patients experience a 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 now are available for the management of moderate–severe ulcerative colitis, with variable efficacy and safety profiles, and positioning different agents in the treatment course as first-line (in biologic-naïve patients) and

Abbreviations used in this paper: **GRADE, Grading of Recommendations Assessment, Development and Evaluation; OCTAVE, Oral Clinical Trials for tofAcitinib in ulceratiVE colitis; OR, odds ratio; RCT, randomized controlled trial; SUCRA, surface under the cumulative ranking; TNF, tumor necrosis factor.**

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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 a 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]

What You Need to Know

Background

A systematic review and network meta-analysis is needed to compare efficacy and safety of 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.

Findings

Infliximab was 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. More trials of direct comparisons are needed to inform clinical decision-making with greater confidence.

Implications for patient care

Patients with moderate to severely active ulcerative colitis should receive infliximab or vedolizumab as first-line therapy, or ustekinumab or tofacitinib if they have prior exposure to TNF antagonists.

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 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 2 separate pairwise and network meta-analyses of induction therapy to estimate the 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 randomized controlled trials (RCTs) that met the following inclusion criteria: (1) patients: adults (age, $>$18 y) with moderate to severe ulcerative colitis (Mayo Clinic score of 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; and (4) outcome: induction of clinical remission (Mayo Clinic score of $\leq$2 with no individual subscore of $>$1) and endoscopic improvement (Mayo endoscopy subscore of 0 or 1).

Because trials of maintenance therapy of biologic agents had different designs (treat straight-through design vs rerandomizing responders to induction therapy), we conducted separate pairwise and network meta-analyses for these different trial designs. Because safety is unlikely to be influenced significantly 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 the 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 2 investigators independently (S.S. and M.F.), and discrepancies were

resolved by consensus, referring back to the original article, in consultation with a third reviewer (W.J.S.). Two study investigators (M.F. and S.S.) 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 a Mayo Clinic score of $\leq$2, with no individual subscore $>$1), and endoscopic improvement (defined as an 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 the results 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. In addition, we qualitatively reviewed the risk of any adverse events, adverse events resulting in treatment discontinuation, and risk of serious infections. Additional details of outcome assessment are shown in the Supplementary Appendix.

Data Synthesis and Statistical Analysis

Pooled odds ratios (OR) and 95% CIs 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 greater than 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 consistency model of multivariate, random-effects meta-regression as described by White et al,[15] using STATA v.15.0 (College Station, TX). This frequentist approach provides a point estimate from the network along with 95% CIs 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 with an imaginary agent that is always the best without uncertainty (ie, SUCRA = 100%).[16] Higher SUCRA scores correspond to higher ranking for induction of clinical remission and/or endoscopic improvement, and higher ranking for safety (ie, lowest risk of serious adverse events and infections).

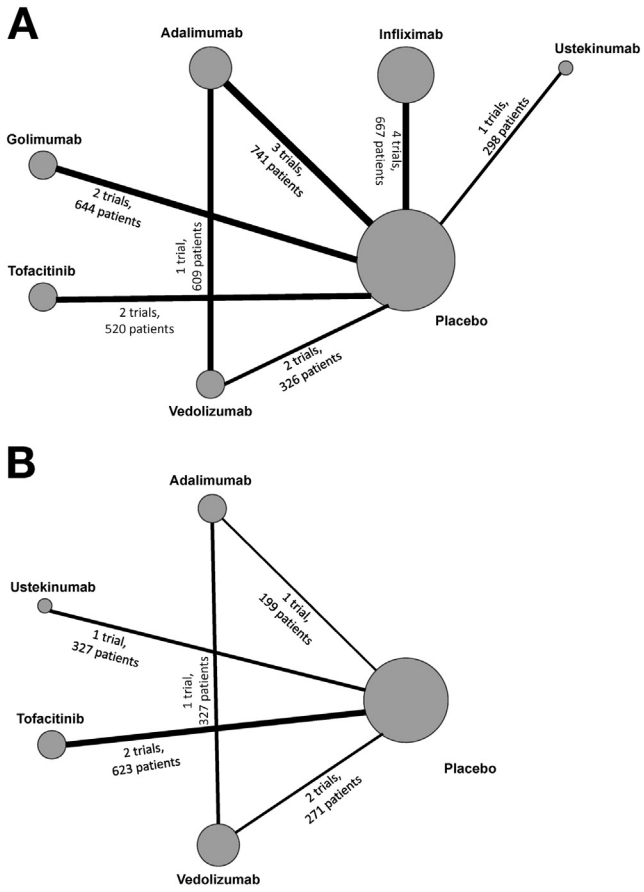

Figure 1. (*A*) Network of included studies with the available direct comparisons for induction of clinical remission in biologic-naïve patients with moderate–severe ulcerative colitis. The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively. (*B*) Network of included studies with the available direct comparisons for induction of clinical remission in patients with prior tumor necrosis factor (TNF)α 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.

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 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 terms of clinical or

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 (SD); sex (% male)	Mean disease duration (y) (SD); disease extent (% extensive colitis)	Concomitant medications		Mean CRP, *mg/L* (SD)	Prior anti-TNF therapy, %
					Immunomodulators, %	Corticosteroids, %		
Infliximab								
Active Ulcerative Colitis Trials 1[17a] (induction and maintenance therapy)	62 sites, 2002–2005; P: 121; I: IFX 5 mg/kg, wk 0, 2, 6, then q8w–121	MCS ≤2; wk 8, wk 54	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
Active Ulcerative Colitis Trials 2[17a] (induction and maintenance therapy)	55 sites, 2002–2005; P: 123; I: IFX 5 mg/kg, wk 0, 2, 6, then q8w–121	MCS ≤2; wk 8, wk 30	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[18a] (induction and maintenance therapy)	1 site (China), 2008–2013; P: 41; I: IFX 5 mg/kg, wk 0, 2, 6, then q8w–41	MCS ≤2; wk 8, wk 30	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[19a] (induction and maintenance therapy)	12 sites (China), 2012–2014; P: 49; I: IFX 5 mg/kg, wk 0, 2, 6, then q8w–50	MCS ≤2; wk 8, wk 26	Entire group: 37; NR	3.7; NR	NR	80 60	NR	0 0
Adalimumab								
ULTRA 1[20] (induction therapy)	94 sites, 2007–2010; P: 130; I: ADA 160/80/40, wk 0, 2, 4, 6–130	MCS ≤2; wk 8	P: 37 (18–72)[b]; 64 I: 37 (18–75)[b]; 64	5.4 (0.3–34.1)[b]; 56 6.1 (0.2–34.4)[b]; 46	39.9 39.2	67.6 54.6	3.2 (0.2–280)[b] 3.3 (0.1–109)[b]	0 0
ULTRA 2[21a] (induction and maintenance therapy)	103 sites, 2006–2010; P: 246; I: ADA 160/80/40, wk 0, 2, 4, 6–248	MCS ≤2; wk 8	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[c] 39[c]
Suzuki et al[22a] (induction and maintenance therapy)	65 sites, 2009–2011; P: 96; I: ADA 160/80/40, wk 0, 2, 4, 6–90	MCS ≤2; wk 8	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)[b] 2.2 (0.5–62.8)[b]	0 0
Golimumab								
PURSUIT phases 2 and 3[23] (induction therapy)	217 sites, 2007–2010; P: 331; I: GLM 200/100, wk 0, 2–331	MCS ≤2; wk 6	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
PURSUIT-M[27d] (maintenance therapy)	251 sites, 2007–2011; P: 156; I: GLM 100 mg q4w–154	MCS ≤2; wk 54	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[28d] (maintenance therapy)	49 sites (Japan), 2013–2016; P: 31 I: GLM 100 mg q4w–32	MCS ≤2; wk 54	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[24d] (induction and maintenance therapy)	211 sites, 2008–2012; P(i): 149; I(i): VDZ 300 mg, wk 0, 2–746 P(m): I(m):	MCS ≤2; wk 6(i); wk 52(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[e] 48[e] 37[f] 42[f]
Motoya et al[25] (induction and maintenance therapy)	100 sites, 2014–2018; P(i): 82; I(i): VDZ 300 mg, wk 0, 2, 6–164 P(m): 42 I(m): VDZ 300 mg q8w; 41	MCS ≤2; wk 10(i); wk 60(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	>3 mg/L: 39 >3 mg/L: 54 NR	50[g] 51[g] 33[h] 42[h]
VARSITY[a] (induction and maintenance therapy)	245 sites, 2015–2019; ADA 160/80/40, wk 0, 2, 4 then q2w; 386 VDZ 300 mg, wk 0, 2, 6, then q8w–383	MCS ≤2; wk 14	ADA: 41 (13); 56 VDZ: 41 (14); 61	6.4 (6.0); NR 7.3 (7.2); NR	25.9 26.2 Proportion of patients receiving both IM and CS not reported	36.3 36.1	NR	21[i] 21[i]
Tofacitinib								
OCTAVE 1[26] (induction therapy)	178 sites, 2012–2015; P: 122 I: tofacitinib 10 mg orally twice daily, 476	MCS ≤2, with rectal bleeding score 0; wk 8	P: 42 (15); 63 I: 41 (14); 58	6.0 (0.5–36.2)[b]; 54 6.5 (0.3–42.5)[b]; 53	NA	47.5 45.0	4.7 (0.1–82.5)[b] 4.4 (0.1–208.4)[b]	53 53
OCTAVE 2[26] (induction therapy)	182 sites, 2012–2015; P: 112 I: tofacitinib 10 mg orally twice daily, 429	MCS ≤2, with rectal bleeding score 0; wk 8	P: 40 (13); 49 I: 41 (14); 60	6.2 (0.4–27.9)[b]; 51 6.0 (0.4–39.4)[b]; 49	NA	49.1 46.2	5.0 (0.2–205.1)[b] 4.6 (0.2–156.0)[b]	58 58
OCTAVE-Sustain[26d] (maintenance therapy)	178 sites, 2012–2015; P: 198 I: tofacitinib 5 mg orally twice daily, 198	MCS ≤2, with rectal bleeding score 0; wk 8	P: 43 (14); 59 I: 42 (14); 52	7.2 (0.6–42.7)[b]; 55 6.5 (0.6–40.3)[b]; 52	0 0	50.5 51.0	1.0 (0.1–45.0)[b] 0.7 (0.1–33.7)[b]	46.5 45.5
Ustekinumab								
UNIFI (induction and maintenance therapy)	244 sites, 2015–2018; P(i): 319 I(i): UST 6 mg/kg, wk 0–322 P(m): 175 I(m): UST 90 mg q8w–176	MCS ≤2; wk 8(i); wk 44(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[j] 52[j] 50[j] 52[j]

ADA, adalimumab; CRem, clinical remission; CRP, C-reactive protein; CS, corticosteroids; GLM, golimumab; I, induction; IFX, infliximab; IM, immunomodulator; MCS, Mayo Clinic Score; NR, not reported; P, placebo; PURSUIT, Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; TNF, tumor necrosis factor; VDZ, vedolizumab.

[a]Maintenance therapy with treat straight-through design.

[b]Median (range).

[c]Reasons for discontinuation of prior anti-TNF therapy: primary nonresponse, 0%; secondary loss of response or intolerance, 100%.

[d]Only including patients with initial response to induction therapy who were rerandomized to placebo or active intervention.

[e]Reasons for discontinuation of prior anti-TNF therapy: primary nonresponse, 48%; secondary loss of response, 38%; intolerance, 14%.

[f]Reasons for discontinuation of prior anti-TNF therapy: primary nonresponse, 36%; secondary loss of response, 30%; intolerance, 18%.

[g]Reasons for discontinuation of prior anti-TNF therapy: primary nonresponse, 58%; secondary loss of response, 40%; intolerance, 2%.

[h]Reasons for discontinuation of prior anti-TNF therapy: primary nonresponse, 43%; secondary loss of response, 50%; intolerance, 7%.

[i]Reasons for discontinuation of prior anti-TNF therapy: primary nonresponse, 50%; secondary loss of response, 35%; intolerance, 7%.

[j]Includes patients with prior exposure to TNF antagonist with or without vedolizumab (13%–18% had prior exposure to vedolizumab).

Table 2. Comparative Efficacy of Pharmacologic Agents for Induction of Clinical Remission and Endoscopic Improvement in Biologic-Naive Patients With Moderate–Severe Ulcerative Colitis Using Network Meta-Analysis

Induction of endoscopic improvement	Induction of clinical remission					
Ustekinumab 6 mg/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 10 mg 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

NOTE. 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. Numbers in bold are statistically significant. For induction of clinical remission, an odds ratio greater than 1 favors row-defining treatment. For induction of endoscopic improvement, an odds ratio greater than 1 favors column-defining treatment. Numbers in parentheses indicate 95% CI. b.d., twice daily.

methodologic characteristics). If direct and indirect estimates were similar (ie, coherent), then the higher 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) (Active Ulcerative Colitis Trials 1 and 2,[17] Jiang et al,[18] NCT01551290,[19] Ulcerative colitis Long-Term Remission and maintenance with Adalimumab 1 and 2,[20,21] Suzuki et al,[22] Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment phase 2 and phase 3 induction studies,[23] GEMINI I,[24] Motoya et al,[25] VARSITY, Oral Clinical Trials for tofAcitinib in ulceratiVE colitis (OCTAVE) 1 and 2,[26] and UNIFI), and 7 RCTs of second-line agents (in patients with prior exposure to TNFα antagonists) (Ulcerative colitis Long-Term Remission and maintenance with Adalimumab 2,[21] GEMINI I,[24] Motoya et al,[25] VARSITY,[6] OCTAVE 1 and 2,[26] UNIFI[7]) in patients with moderate–severe ulcerative colitis. Trials of infliximab (Active Ulcerative Colitis Trials 1 and 2,[17] Jiang et al,[18] NCT01551290[19]), adalimumab (Ulcerative colitis Long-Term Remission and maintenance with Adalimumab 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; Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment-M, Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment-J, and OCTAVE-Sustain reported outcomes for maintenance therapy with golimumab and tofacitinib, respectively.[26–28] From our previous analysis, 3 additional studies were included. The schematic diagram of study selection is shown in Supplementary Figure 1, and available direct comparisons and network of trials are shown in Figure 1.

Trial and patient characteristics are summarized in Table 1. Overall, the median average age of patients was 41 years (interquartile range, 40–42 y), and 60% (interquartile range, 56%–63%) were men. The median disease duration was 6.7 years (interquartile range, 6.0–7.8 y), and 49% (interquartile range, 46%–55%) of patients had extensive colitis. A median of 40% (interquartile range, 30%–50%) of 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 assessed uniformly based on the standard definition of the 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 weeks 30, 54, or 60 for maintenance therapy; endoscopy was read by blinded local

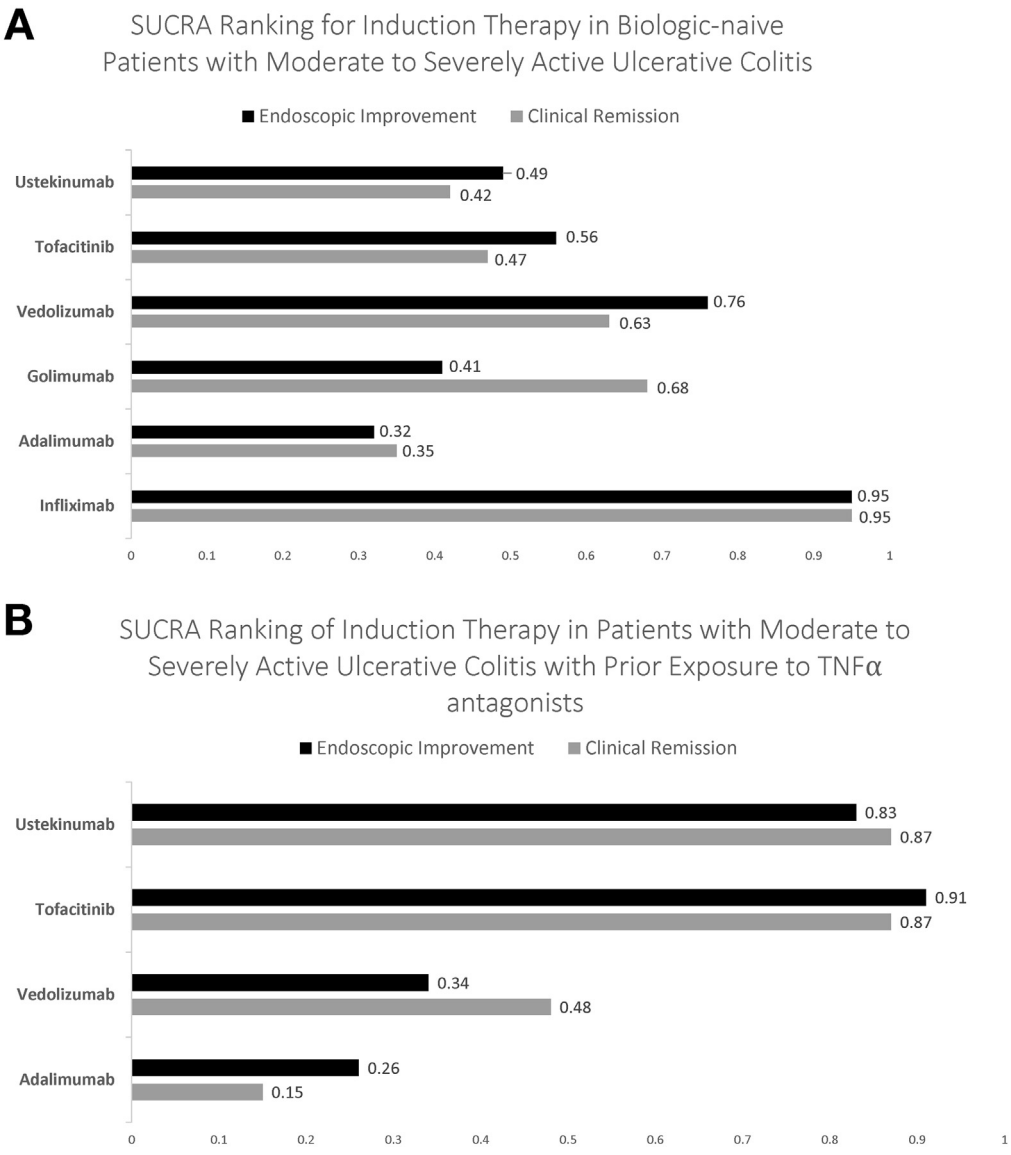

Figure 2. (*A*) Relative efficacy of different interventions for induction of clinical remission and endoscopic improvement in biologic-naïve patients with moderate to severely active ulcerative colitis. (*B*) Relative efficacy of different interventions for induction of clinical remission and endoscopic improvement in patients with moderate to severely active ulcerative colitis with prior exposure to tumor necrosis factor (TNF)α antagonists. SUCRA, surface under the cumulative ranking.

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; 1 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; 95% CI, 1.53–6.26), with minimal to moderate heterogeneity across estimates ($I^2 < 35\%$) (Supplementary Figure 2*A*). On network meta-analysis, compared with 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 was rated down owing to imprecision caused by a 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 2*A*). With an estimated placebo rate of achieving remission of 10% in included trials, we anticipate that 31.1%, 17.7%, 23.7%, 22.0%,

Table 3. Comparative Efficacy of Pharmacologic 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

	Induction of clinical remission				
Induction of endoscopic improvement	Ustekinumab 6 mg/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 10 mg 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

NOTE. Comparisons should be read from left to right. The odds ratio for comparisons are in the cell in common between the column-defining and row-defining treatment. Numbers in bold are statistically significant. For induction of clinical remission, an odds ratio greater than 1 favors row-defining treatment. For induction of endoscopic improvement, an odds ratio greater than 1 favors column-defining treatment. Numbers in parentheses indicate 95% CI.
b.d., twice daily.

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 ($I^2 = 0\%$) (Supplementary Figure 2*B*). On network meta-analysis, compared with 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 was rated down owing to imprecision caused by a 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 2*A*). 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 analyses 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 to TNFα antagonists who 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% to 58% of patients had inadequate response to a TNFα antagonist, and in trials of ustekinumab, 13% to 18% patients had prior exposure to both vedolizumab and TNFα antagonists. These data were 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 (Supplementary Figure 3*A*), 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 2*B*). 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

Table 4. Comparative Safety of Pharmacologic Agents During Maintenance Therapy in Patients With Moderate–Severe Ulcerative Colitis Using Network Meta-Analysis

	Risk of serious adverse events					
Risk of infections	Ustekinumab 90 mg 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 5 mg 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

NOTE. Comparisons should be read from left to right. The odds ratio for comparisons are in the cell in common between the column-defining and row-defining treatment. Numbers in bold are statistically significant. For serious adverse events, an odds ratio less than 1 favors row-defining treatment. For risk of infections, an odds ratio less than 1 favors column-defining treatment. Numbers in parentheses indicate 95% CI.
b.d., twice daily; q8w, every 8 weeks.

across estimates ($I^2 < 30\%$) (Supplementary Figure 3*B*). On network meta-analysis, compared with 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 2*B*). 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. Supplementary Table 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 the overall event rate for important safety outcomes was low; hence, a formal network meta-analysis was not performed. Overall, the median rate of serious adverse events with active intervention was 4.7% (interquartile range, 3.6%–6.9%). The median rate of serious infections in induction trials with active intervention was 0.6% (interquartile range, 0.1%–1.8%).

Maintenance Therapy

Efficacy. Because of differences in trial design, trials of infliximab and adalimumab (treat straight-through) and of golimumab, tofacitinib, and ustekinumab (rerandomization of responders to induction therapy) were analyzed 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 (Supplementary Table 2A; Supplementary Figure 4); 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, respectively), followed by

infliximab (0.63 and 0.67, respectively). Similarly, on network meta-analysis of trials in which responders to induction therapy were rerandomized to active intervention or placebo, golimumab, vedolizumab, tofacitinib, and ustekinumab were superior to placebo for maintenance of clinical remission and endoscopic improvement (Supplementary Figure 5, Supplementary Table 2B). No significant differences 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). Although the maintenance trial of golimumab was conducted only in 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. Supplementary Table 3 summarizes the 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 significantly worse than placebo in rates of serious adverse events (Table 4, Supplementary Figure 6), which may be related to effective disease control. Among active interventions, rates of serious adverse events were lower with vedolizumab and infliximab compared with golimumab. The rate of serious infections was low and was not deemed amenable to network meta-analysis; hence, the risk of overall infections was used as a surrogate safety outcome. On network meta-analysis, golimumab and tofacitinib were associated with increased risk of infections compared with placebo (Table 4, Supplementary Figure 7). On comparing active interventions, the rate of serious infection was lower with vedolizumab compared with 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 detect publication bias reliably.

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, although 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 of 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, which limits inference on their efficacy if used in the setting of prior TNFα antagonist exposure. Third, vedolizumab was ranked safest, with the lowest rate of infections among active interventions, followed by ustekinumab. As compared with previous estimates, this updated analysis has key strengths with inclusion of a head-to-head trial comparing vedolizumab and adalimumab, which forms a more connected network, and provides more robust and statistically and clinically significant results on the comparative efficacy of second-line pharmacotherapy in patients with prior exposure to TNFα antagonists. Notable new findings are the relative lowering efficacy of vedolizumab as a first-line agent for induction of remission than prior estimates, and the 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 inform clinical practice and guidelines directly 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 differences in pharmacokinetics and bioavailability with different dosing schema (weight-based vs fixed dose) and route of administration. The recent Study to Evaluate the Safety and Efficacy of Two Drug Regimens in Subjects With Moderate to Severe Ulcerative Colitis-UC trial comparing standard- vs high-dose adalimumab in patients with moderate–severe ulcerative colitis failed to show the 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 the VICTORY consortium that vedolizumab is more effective than adalimumab for long-term maintenance of clinical remission; over 8 to 12 weeks of induction therapy, however, no differences were observed between the 2 agents.[6,32] Moreover, we did not observe any differences in the efficacy of vedolizumab and infliximab in the 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 the high rates of primary nonresponse 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 because these trials did not always mirror clinical practice. For example, current trials did not use therapeutic drug monitoring to understand the plausible mechanism of failure of initial biologic intervention. Given the potential differences in the efficacy of second-line interventions depending on the underlying reason for discontinuation of prior TNFα antagonists (primary nonresponse 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 reported consistently. It is conceivable that because 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 antagonist; 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 before clinical trial intervention, and inherently may be difficult to treat. However, trials of ustekinumab were conducted following approval of vedolizumab, and a subset of patients in these trials failed multiple TNFα antagonists and vedolizumab, conceivably making it a more refractory patient population. Despite this, we observed the superiority of ustekinumab over vedolizumab, suggesting the effect likely is real and not confounded by treatment refractoriness.

In this study, by updating analyses with the inclusion of ustekinumab, accounting for dose change for tofacitinib, including a 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 the 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 a paucity of head-to-head trials to truly inform comparative efficacy and safety. However, it is important to note that across trials of induction therapy, key inclusion/exclusion criteria, outcome definitions, and patient and clinical characteristics, co-interventions were comparable across trials, which facilitated this network meta-analysis.

Besides inherent limitations of individual trials, there were limitations to our analyses. A thorough comparative analysis across all agents was limited to trials of induction therapy; because of differences in trial design of maintenance therapy, we had to conduct 2 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. In addition, the efficacy outcome in OCTAVE induction trials of tofacitinib were more robust, requiring a rectal bleeding subscore of 0.[26] There were differences in timing of outcomes assessment in induction studies (weeks 6–14), and time-dependent variability in efficacy could not be analyzed in detail. Although corticosteroid-free remission may be a more relevant clinical end point, this was reported inconsistently in the 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: inclusion of this trial with 3 active arms (including 1 arm of thiopurine monotherapy) would have resulted in a disconnected network, and the efficacy of thiopurine monotherapy as a separate intervention would have been hard to interpret and biased because other older trials of thiopurines for induction and maintenance, which systematically were different from contemporary trials, were being excluded. This trial has suggested that 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] Although

comparative analysis of maintenance trials has suggested higher safety with vedolizumab, rates of important events such as serious infections was low and other serious events such as malignancy could not be evaluated thoroughly. Moreover, differences in study design of maintenance therapy (treat straight-through vs rerandomization of responders), as well as lack of information on safety stratified by prior TNFα antagonist exposure status, potentially may bias safety results. Postmarketing surveillance studies of these different agents may better inform the relative safety of these agents. Safety of tofacitinib seems to be dose-dependent, and in instances in which a higher 10-mg twice-per-day dose of tofacitinib is used for long-term maintenance, safety concerns should be discussed adequately with patients.

Integrating findings from this meta-analysis and other studies, current evidence favors infliximab or vedolizumab as the preferred first-line agents for moderate–severe ulcerative colitis. In patients who fail infliximab, ustekinumab and tofacitinib likely would 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 dermatologic diseases, and so forth), clinical judgment and experience of the treating physicians, values and preferences of patients (dosing route, regimen, acceptability of risk–benefit trade-offs, and so forth), as well as the costs/resources available, are important to facilitate shared decision making, in developing a personalized treatment strategy for each patient, and shape health care policy on positioning different agents. Pragmatic head-to-head trials in both biologic-naïve and biologic-exposed patients are warranted to optimally inform the relative positioning of newly available agents in clinical practice.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.01.008.

References

1. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2018;390:2769–2778.
2. Fumery M, Singh S, Dulai PS, et al. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. Clin Gastroenterol Hepatol 2018;16:343–356.
3. Vester-Andersen MK, Prosberg MV, Jess T, et al. Disease course and surgery rates in inflammatory bowel disease: a population-based, 7-year follow-up study in the era of immunomodulating therapy. Am J Gastroenterol 2014;109:705–714.
4. Bonovas S, Lytras T, Nikolopoulos G, et al. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther 2018;47:454–465.
5. Singh S, Fumery M, Sandborn WJ, et al. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Aliment Pharmacol Ther 2018;47:162–175.
6. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med 2019;381:1215–1226.
7. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019;381:1201–1214.
8. Puhan MA, Schunemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 2014;349:g5630.
9. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–784.
10. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health 2011;14:417–428.
11. Higgins JPT, Thomas J, Chandler J, eds. Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook. Accessed June 30, 2019.
12. Murad MH, Montori VM, Ioannidis JPA, et al. Advanced topics in systematic reviews: fixed-effects and random-effects models. McGraw Hill, New York, NY, 2014:507–514.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
14. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.
15. White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods 2012;3:111–125.
16. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–171.
17. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. [Erratum appears in N Engl J Med 2006;354:2200]. N Engl J Med 2005;353:2462–2476.
18. Jiang XL, Cui HF, Gao J, et al. Low-dose infliximab for induction and maintenance treatment in Chinese patients with moderate to severe active ulcerative colitis. J Clin Gastroenterol 2015;49:582–588.
19. Xian-Janssen. A study to evaluate the effectiveness and safety of infliximab in Chinese patients with active ulcerative colitis. 2015. Available from: https://clinicaltrials.gov/ct2/show/NCT01551290. Accessed June 5, 2017.
20. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011;60:780–787.

21. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012; 142:257–265.
22. Suzuki Y, Motoya S, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. J Gastroenterol 2014;49:283–294.
23. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85–95.
24. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699–710.
25. Motoya S, Watanabe K, Ogata H, et al. Vedolizumab in Japanese patients with ulcerative colitis: a phase 3, randomized, double-blind, placebo-controlled study. PLoS One 2019;14: e0212989.
26. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2017;376:1723–1736.
27. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014; 146:96–109.
28. Hibi T, Imai Y, Senoo A, et al. Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: a phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). J Gastroenterol 2017;52:1101–1111.
29. Singh S, Proudfoot JA, Dulai PS, et al. Efficacy and speed of induction of remission of infliximab vs golimumab for patients with ulcerative colitis, based on data from clinical trials. Clin Gastroenterol Hepatol 2020;18:424–431.
30. Singh S, Andersen NN, Andersson M, et al. Comparison of infliximab and adalimumab in biologic-naive patients with ulcerative colitis: a nationwide Danish Cohort Study. Clin Gastroenterol Hepatol 2017;15:1218–1225.
31. Panés J, Colombel JF, D'Haens GR, et al. High versus standard adalimumab induction dosing regimens in patients with moderately to severely active ulcerative colitis: results from the SERENE-UC induction study. United European Gastroenterology Week, 2019; Barcelona. United European Gastroenterol J 2019;7(Supple):118.
32. Faleck D, Shashi P, Meserve J, et al. Comparative effectiveness of vedolizumab and tumor necrosis factor-antagonist therapy in ulcerative colitis: a multicenter consortium propensity score-matched analysis. Gastroenterology 2018;154:S82.
33. Gisbert JP, Marin AC, McNicholl AG, et al. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther 2015;41:613–623.
34. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. Nat Rev Gastroenterol Hepatol 2015; 12:537–545.
35. Vickers AD, Ainsworth C, Mody R, et al. Systematic review with network meta-analysis: comparative efficacy of biologics in the treatment of moderately to severely active ulcerative colitis. PLoS One 2016;11:e0165435.
36. Cameron C, Ewara E, Wilson FR, et al. The importance of considering differences in study design in network meta-analysis: an application using anti-tumor necrosis factor drugs for ulcerative colitis. Med Decis Making 2017;37:894–904.
37. Bonovas S, Fiorino G, Allocca M, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. Clin Gastroenterol Hepatol 2016;14:1385–1397.

Reprint requests
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Siddharth Singh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest
These authors disclose the following: Siddharth Singh has received research grants from AbbVie and Janssen, and consulting fees from Pfizer; Mathurin Fumery has received consultant/lecture fees from AbbVie, Takeda, Ferring, MSD, Boehringer, Tillots, Gilead, Celgene, and Janssen; Parambir Dulai has received research support from Takeda, Pfizer, AbbVie, Janssen, Polymedco, ALPCO, and Buhlmann, and consulting fees from Takeda, Pfizer, AbbVie, and Janssen; and William Sandborn has received research grants from Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, AbbVie, Janssen, Takeda, Lilly, Celgene/Receptos, Pfizer, and Prometheus Laboratories (now Prometheus Biosciences), consulting fees from AbbVie, Allergan, Amgen, Arena Pharmaceuticals, Avexegen Therapeutics, BeiGene, Boehringer Ingelheim, Celgene, Celltrion, Conatus, Cosmo, Escalier Biosciences, Ferring, Forbion, Genentech, Gilead Sciences, Gossamer Bio, Incyte, Janssen, Kyowa Kirin Pharmaceutical Research, Landos Biopharma, Lilly, Oppilan Pharma, Otsuka, Pfizer, Progenity, Prometheus Biosciences (merger of Precision IBD and Prometheus Laboratories), Reistone, Ritter Pharmaceuticals, Robarts Clinical Trials (owned by Health Academic Research Trust), Series Therapeutics, Shire, Sienna Biopharmaceuticals, Sigmoid Biotechnologies, Sterna Biologicals, Sublimity Therapeutics, Takeda, Theravance Biopharma, Tigenix, Tillotts Pharma, UCB Pharma, Ventyx Biosciences, Vimalan Biosciences, and Vivelix Pharmaceuticals, and stock or stock options from BeiGene, Escalier Biosciences, Gossamer Bio, Oppilan Pharma, Prometheus Biosciences (merger of Precision IBD and Prometheus Laboratories), Progenity, Ritter Pharmaceuticals, Ventyx Biosciences, and Vimalan Biosciences. The remaining author discloses no conflicts.

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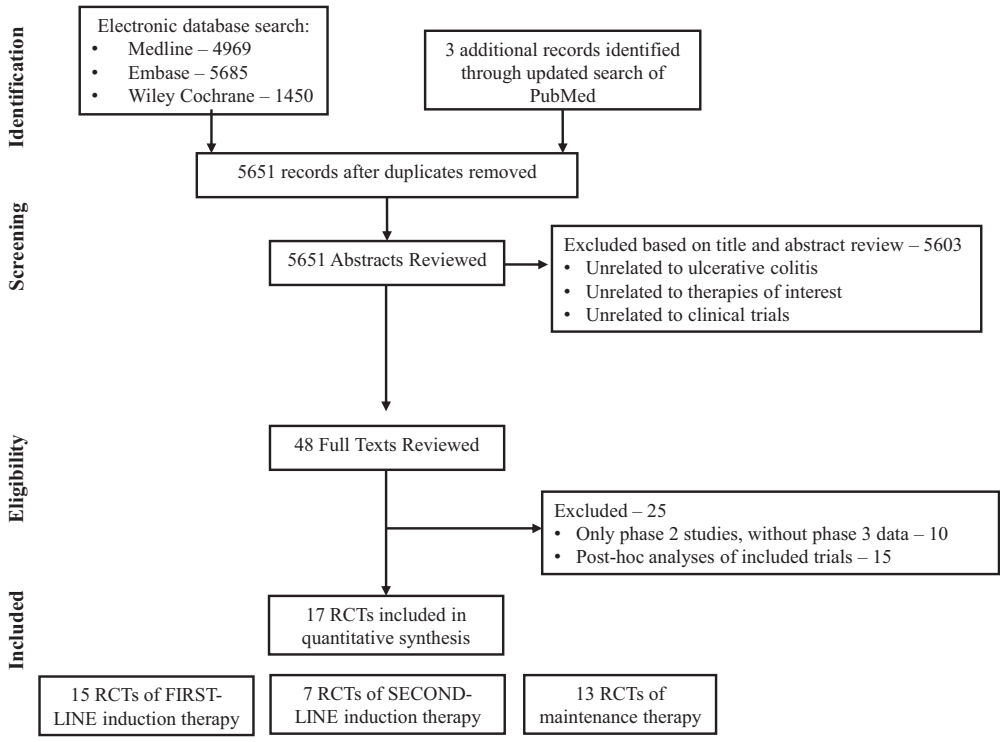
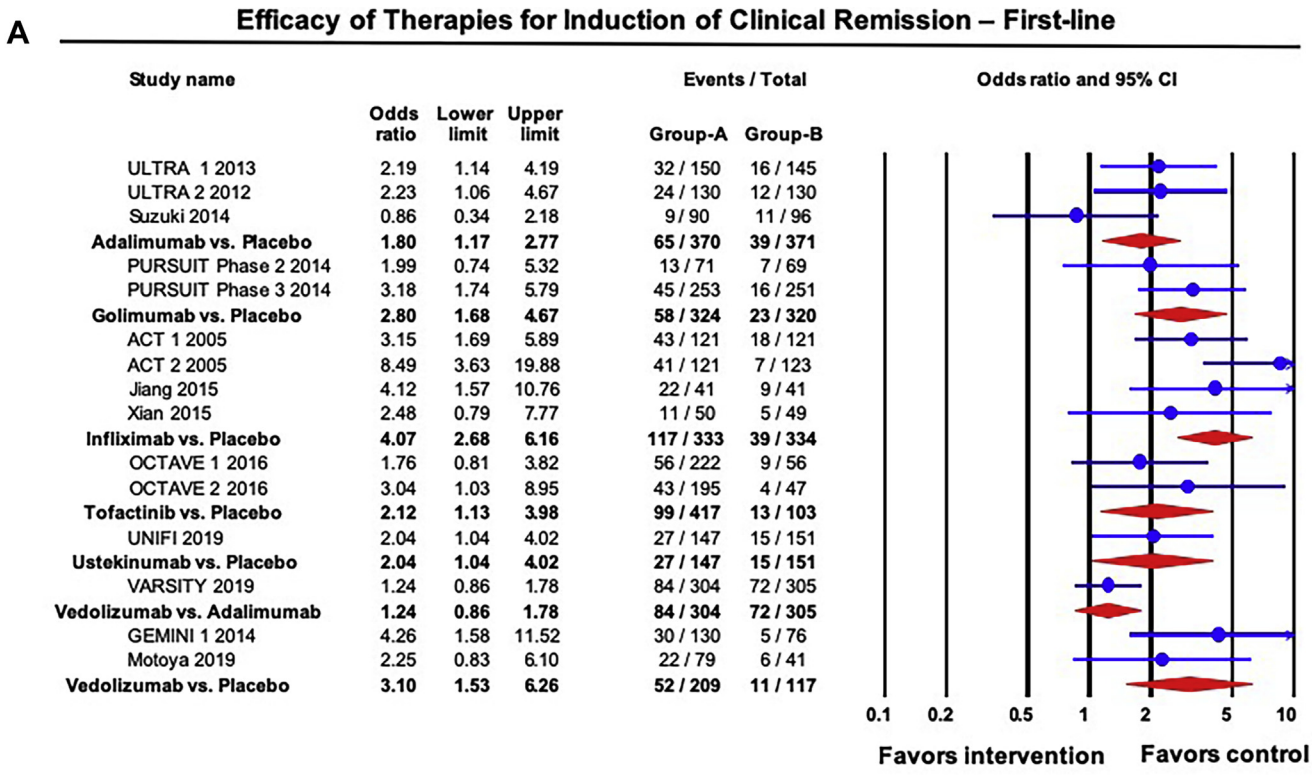
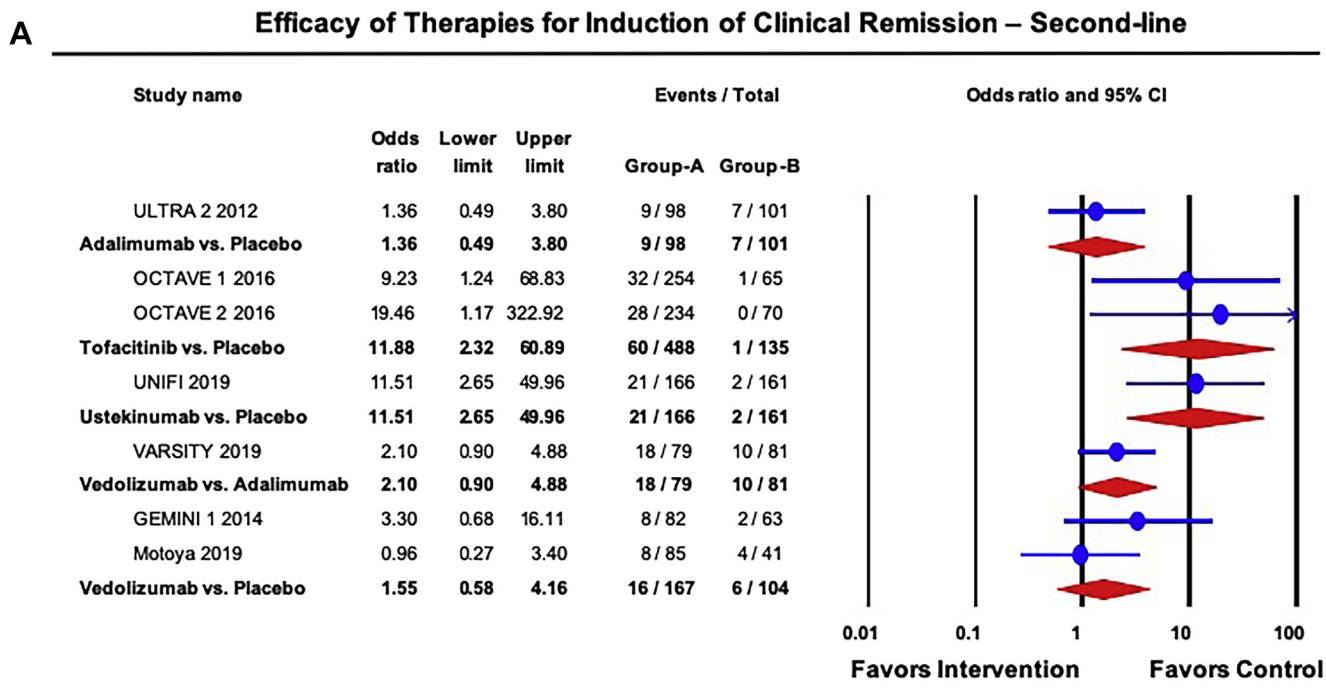
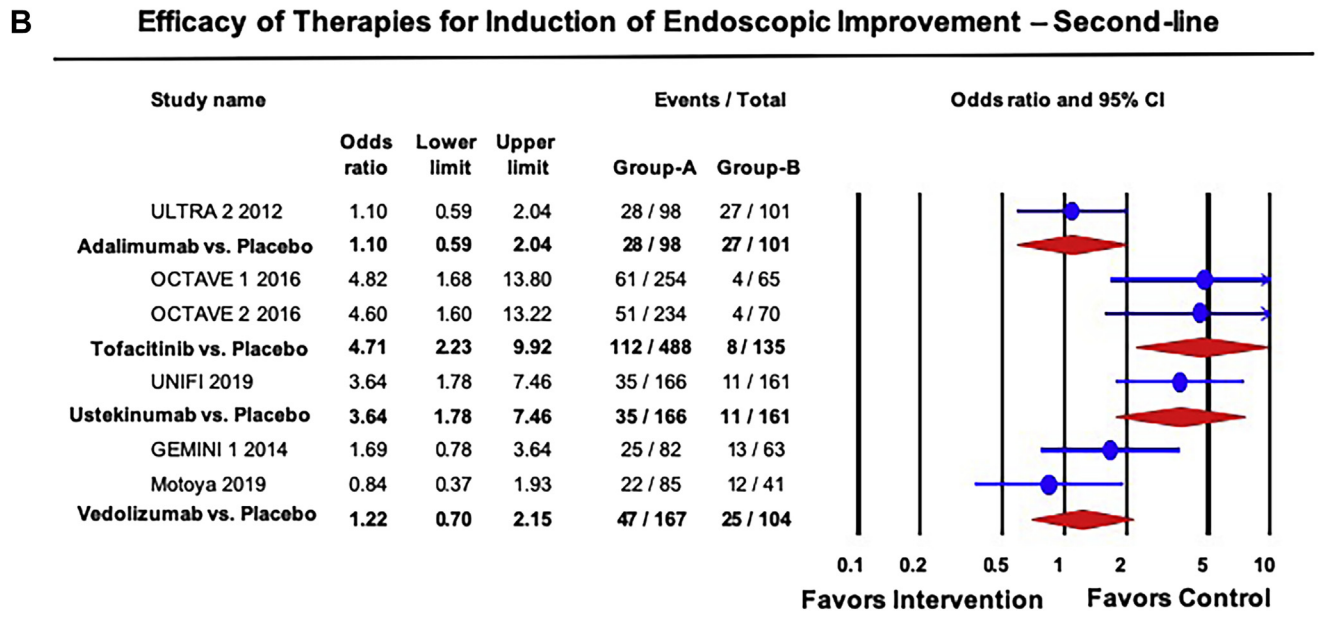


Supplementary Figure 1. Study selection flowsheet. RCT, randomized controlled trial.



Supplementary Figure 2. Pair-wise meta-analysis. Efficacy of pharmacologic agents in biologic-naïve patients with moderate–severe ulcerative colitis for induction of (*A*) clinical remission, and (*B*) endoscopic improvement.

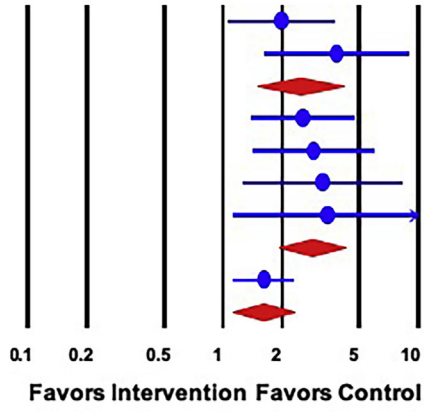




Supplementary Figure 3. Pair-wise meta-analysis. Efficacy of pharmacologic agents for moderate–severe ulcerative colitis in patients with prior exposure to TNFα antagonists for induction of (*A*) clinical remission, and (*B*) endoscopic improvement.

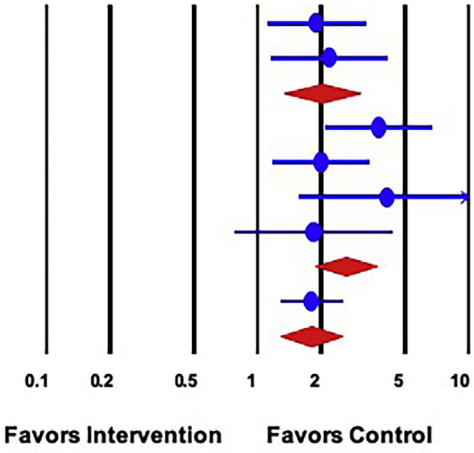
A **Efficacy of Therapies for Maintenance of Clinical Remission – Treat-straight-through**

Study name	Odds ratio	Lower limit	Upper limit	Events / Total Group-A	Events / Total Group-B
ULTRA 2 2013	1.99	1.06	3.72	33 / 150	18 / 145
Suzuki 2014	3.83	1.65	8.92	41 / 177	7 / 96
Adalimumab vs. Placebo	**2.51**	**1.52**	**4.15**	**74 / 327**	**25 / 241**
ACT 1 2005	2.59	1.41	4.76	41 / 121	20 / 121
ACT 2 2005	2.91	1.44	5.90	31 / 121	13 / 123
Jiang 2015	3.25	1.27	8.33	21 / 41	10 / 41
Xian 2015	3.42	1.13	10.41	14 / 50	5 / 49
Infliximab vs. Placebo	**2.89**	**1.96**	**4.25**	**107 / 333**	**48 / 334**
VARSITY 2019	1.62	1.14	2.31	104 / 304	74 / 305
Vedolizumab vs. Adalimumab	**1.62**	**1.14**	**2.31**	**104 / 304**	**74 / 305**

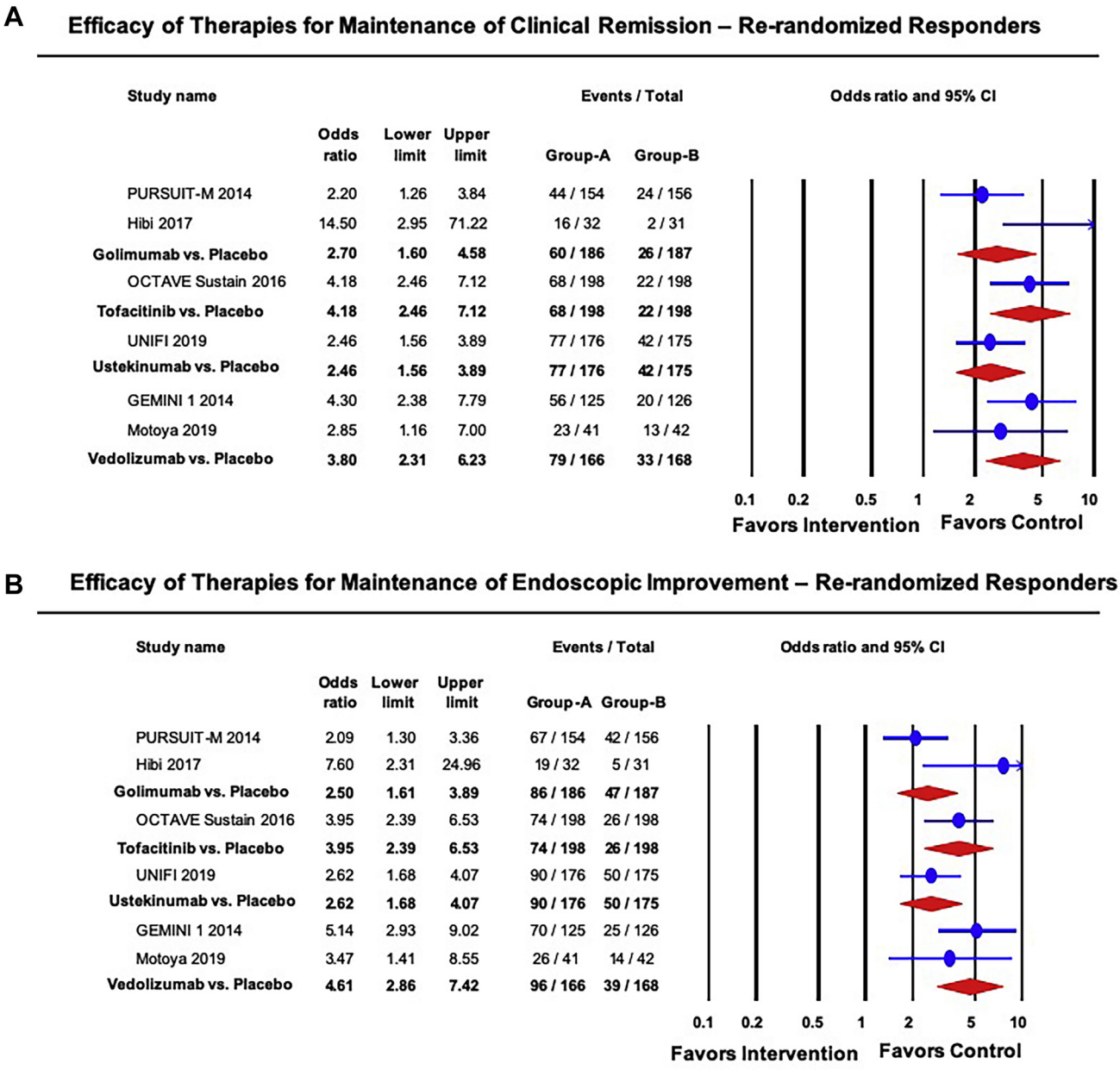


B **Efficacy of Therapies for Maintenance of Endoscopic Improvement – Treat-straight-through**

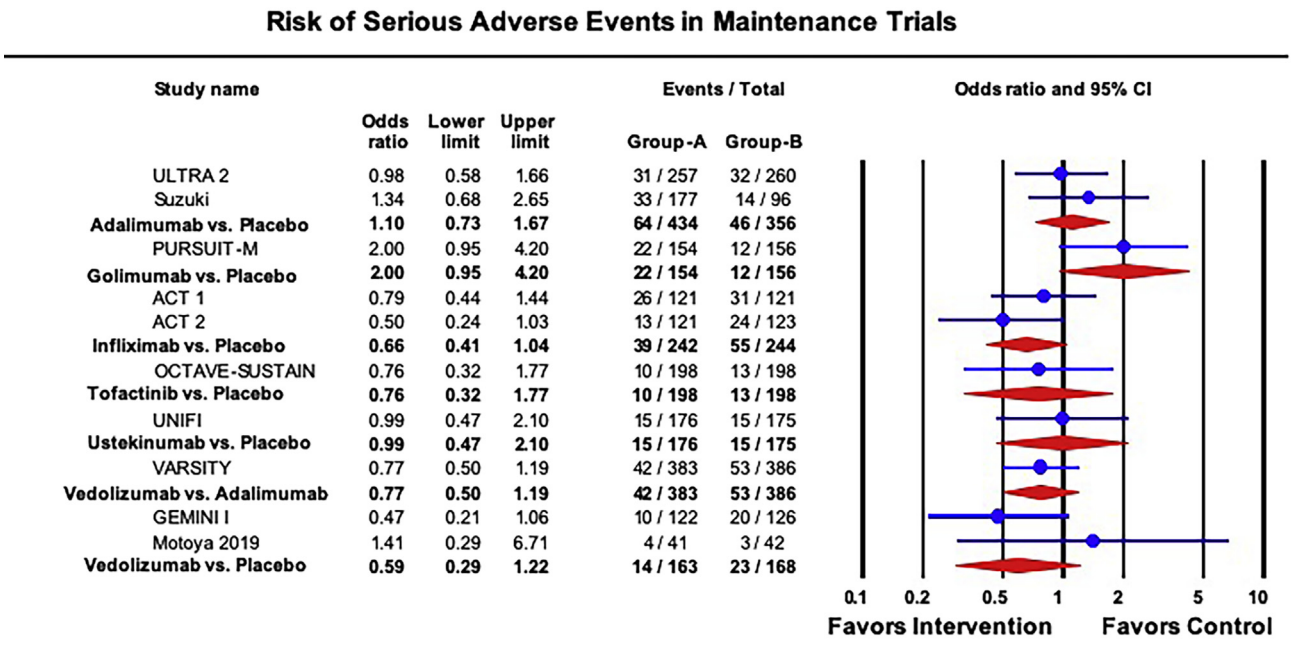
Study name	Odds ratio	Lower limit	Upper limit	Events / Total Group-A	Events / Total Group-B
ULTRA 2 2013	1.91	1.11	3.26	47 / 150	28 / 145
Suzuki 2014	2.19	1.15	4.14	51 / 177	15 / 96
Adalimumab vs. Placebo	**2.02**	**1.34**	**3.05**	**98 / 327**	**43 / 241**
ACT 1 2005	3.75	2.09	6.73	55 / 121	22 / 121
ACT 2 2005	2.00	1.18	3.39	56 / 121	37 / 123
Jiang 2015	4.12	1.57	10.76	22 / 41	9 / 41
Xian 2015	1.85	0.79	4.32	20 / 50	13 / 49
Infliximab vs. Placebo	**2.64**	**1.89**	**3.69**	**153 / 333**	**81 / 334**
VARSITY 2019	1.81	1.29	2.53	131 / 304	90 / 305
Vedolizumab vs. Adalimumab	**1.81**	**1.29**	**2.53**	**131 / 304**	**90 / 305**



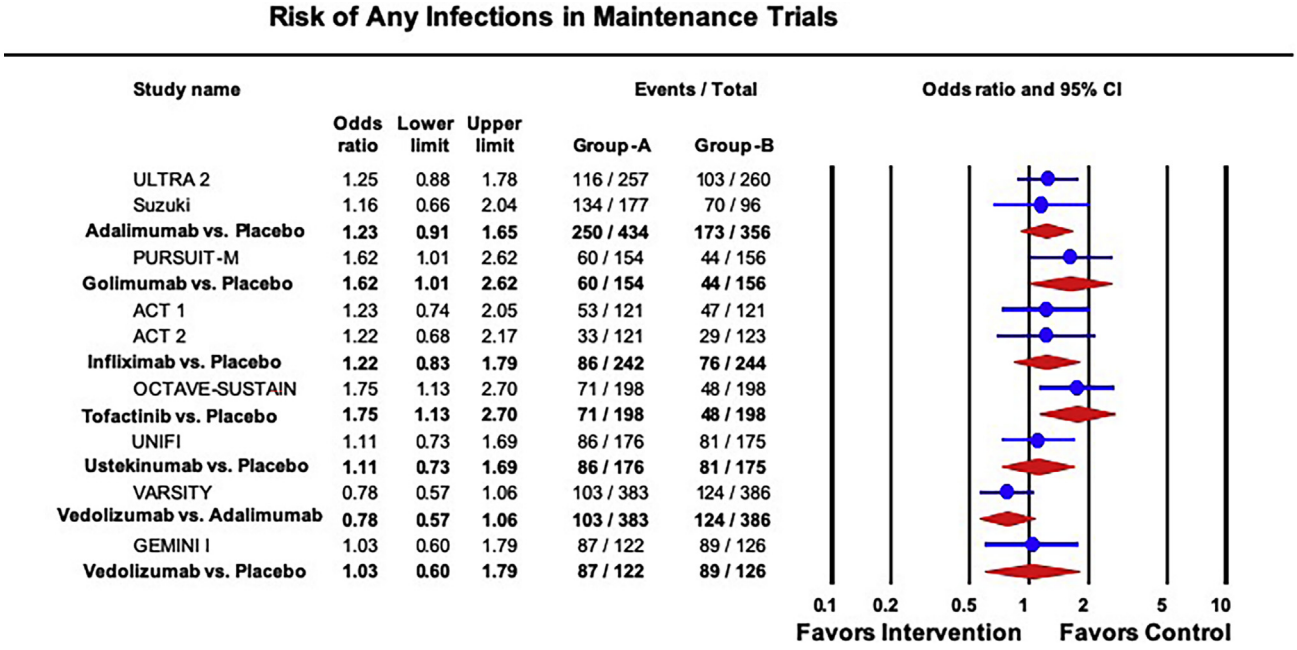
Supplementary Figure 4. Pair-wise meta-analysis. Efficacy of pharmacologic agents for moderate–severe ulcerative colitis for maintenance of (*A*) clinical remission, and (*B*) endoscopic improvement, in treat straight-through trial design.



Supplementary Figure 5. Pair-wise meta-analysis. Efficacy of pharmacologic agents for moderate–severe ulcerative colitis for maintenance of (*A*) clinical remission, and (*B*) endoscopic improvement, in rerandomization of responders trial design.



Supplementary Figure 6. Pair-wise meta-analysis. Risk of serious adverse events with pharmacologic agents for moderate–severe ulcerative colitis in maintenance trials.



Supplementary Figure 7. Pair-wise meta-analysis. Risk of any infections with pharmacologic agents for moderate–severe ulcerative colitis in maintenance trials.