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Differential Efficacy of Advanced Therapies in Inducing Remission in Ulcerative Colitis Based on Prior Exposure to TNF Antagonists

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Abstract

Background and Aims: We sought to ascertain how prior exposure to TNF antagonists impacts treatment response with various classes of advanced therapies in patients with ulcerative colitis (UC), through a systematic review and meta-analysis.

Methods: Through a systematic review of multiple databases through June 30, 2024, we identified 17 RCTs in 8871 adults with moderate-severe UC who were treated with different advanced therapies vs. placebo, and reported efficacy in induction of clinical remission, stratified by prior exposure to TNF antagonists. We calculated the ratio of odds ratio of achieving remission with active drug vs. placebo, in TNF antagonist-naïve vs. TNF antagonist-exposed patients. We grouped advanced therapies based on primary mechanism of action: lymphocyte trafficking inhibitors (anti-integrins and sphingosine-1 phosphate [S1P] receptor modulators), anti-interleukins (interleukin-12/23 antagonist and selective IL-23 antagonists) and Janus kinase inhibitors.

Results: Lymphocyte trafficking inhibitors were more efficacious in TNF antagonist-naïve vs. exposed patients (five trials; ratio of OR, 1.88 [95% CI, 1.02–3.49]), whereas JAK inhibitors were less efficacious in TNF antagonist-naïve vs. exposed patients (six trials; ratio of OR, 0.47 [0.22–1.01]). No significant difference was observed in efficacy of selective IL-23 antagonists vs. placebo in TNF antagonist-naïve vs. exposed patients (six trials; ratio of OR, 1.07 [0.64–1.80]). There was minimal heterogeneity across analyses.

Conclusion: There is significant heterogeneity of treatment efficacy with different advanced therapies in inducing remission in patients with UC based on prior exposure to TNF antagonists, with plausible potentiation of JAK inhibitors and attenuation of lymphocyte trafficking inhibitors. Future studies on the mechanistic basis for these observations are warranted.

Keywords

Upadacitinib; risankizumab; infliximab; biologics; inflammatory bowel diseases

INTRODUCTION

Treatment options for patients with moderate-severe ulcerative colitis (UC) have increased in the last decade with the availability of six different classes of medications.¹ These medications have diverse mechanisms of action, targeting different pathways of inflammation, including neutralizing cytokines that promote inflammation (tumor necrosis factor- α [TNF] antagonists) or drive the differentiation and function of specialized immune subsets (interleukin [IL]-12/23 antagonists or selective IL-23 antagonists); blocking signal transduction cascades downstream of these pathways (Janus Kinase inhibitors [JAK inhibitors]); or modulating lymphocyte trafficking (anti- $\alpha 4\beta 7$ integrin antibodies such as vedolizumab and sphingosine-1-phosphate [S1P] receptor modulators such as ozanimod and etrasimod).^{2, 3} There is wide inter-individual variability in response to specific medications, and drivers of this heterogeneity of treatment effect are critical to understand to be able to choose the best therapy for each individual patient. For newer advanced therapies, one key biologic driver of this heterogeneity is prior exposure to TNF antagonists.⁴ In clinical trials, certain classes of medications such as lymphocyte trafficking inhibitors appear to have a smaller placebo-adjusted treatment effect in patients with prior exposure to TNF antagonists compared with TNF antagonist-naïve patients, whereas these effects are not readily apparent for other therapies.⁵ It is conceivable that exposure to TNF antagonists may “reprogram” the immune system, altering responsiveness to subsequent therapies in a manner that is dependent on the second drug’s mechanism-of-action.

While absolute rates of achieving clinical remission are higher in TNF antagonist-naïve patients compared with TNF antagonist-exposed treated with advanced therapies, so is the placebo response rate. In order to examine how prior exposure to TNF antagonists modifies placebo-adjusted treatment effect of different classes of advanced therapies, we conducted a systematic review and meta-analysis of phase 2 and 3 RCTs of approved advanced therapies vs. placebo, comparing treatment effect in patients with TNF antagonist-naïve patients vs. those with prior exposure to TNF antagonists, accounting for corresponding placebo remission rates. Since prior exposure to TNF antagonists was a stratification variable in all these trials, they preserved the benefits of randomization in subgroup analysis.

METHODS

This systematic review was performed using an *a priori* established protocol and is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).⁶

Study Selection

We identified phase 2 or 3 randomized controlled trials (RCTs) that met the following inclusion criteria: (1) Patients: adults (age ≥ 18 years) with moderately-to-severely active UC (Mayo Clinic Score [MCS] 6–12, with an endoscopic subscore of 2 or 3) who were either TNF antagonist-naïve or previously exposed to TNF antagonist therapy; (2) Intervention: advanced therapies including vedolizumab, S1P receptor modulators (ozanimod, etrasimod), JAK inhibitors (tofacitinib, upadacitinib, filgotinib), IL-12/23 antagonists (ustekinumab), or IL-23 antagonists (mirikizumab, risankizumab, guselkumab), with a minimum duration of

therapy of 14 days; (3) Comparator: placebo; (4) Outcome: induction of clinical remission (MCS ≤ 2 with no individual subscore of >1). From these RCTs, we specifically included studies which reported efficacy of active intervention vs. placebo, stratified by prior exposure to TNF antagonists.

We excluded the following studies: (1) trials where results were not stratified by prior exposure to biologic therapy, (2) trials of advanced therapies that have not yet been, and are unlikely to be approved by the United States Food and Drug Administration or European Medicines Agency, based on registration trials (e.g., etrolizumab, AJM300, ontamalimab), (3) trials of novel agents (e.g., PRA023, olamkicept) or novel approaches (combination therapy of advanced therapies) in development but without phase 3 RCT data yet, (4) head-to-head trials without a placebo arm since efficacy of drug vs. placebo could not be estimated, (5) pediatric studies, or (6) trials conducted in patients hospitalized with acute severe UC.

Search Strategy, Data Abstraction and Risk of Bias Assessment

We conducted a comprehensive search of multiple electronic databases through November 21, 2023, with no language restrictions; the search for MEDLINE was updated on June 30, 2024. The databases included Ovid MEDLINE, Ovid EMBASE, and Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, as well as clinical trial registries. The search strategy was designed and implemented by an experienced medical librarian, using controlled vocabulary supplemented with keywords, for RCTs of biologic therapy and small molecules in patients with IBD. Details of the search strategy are shown in the online supplement. We searched the bibliographies of these selected articles, systematic reviews, and clinical trial registries (www.clinicaltrials.gov) to identify any additional studies. We also conducted a manual search of abstracts from major gastroenterology conferences (Digestive Disease Week, American College of Gastroenterology annual meeting, European Crohn's and Colitis Organization annual meeting, and United European Gastroenterology Week) from 2021 to 2024 to identify additional abstracts on the topic. Finally, we contacted experts in the field to identify other unpublished studies. Two sets of investigators independently reviewed the title and abstract of studies identified in the search to exclude studies that did not address the research question of interest based on pre-specified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information. Conflicts in study selection at this stage were resolved by consensus.

Data on study-, participant-, disease- and treatment-related characteristics were abstracted onto a standardized form, by two sets of investigators independently, and discrepancies were resolved by consensus. Two sets of study investigators independently rated the quality of included trials using the Cochrane Risk of Bias Tool version 2.0.⁷

Outcomes

The primary efficacy outcome was induction of clinical remission (defined as MCS ≤ 2 with no individual subscore of >1). The timing of outcome assessment with induction trials was up to 14 weeks; when outcomes at multiple time points were reported, we used outcomes at

week 8 or 6. When data for multiple doses of the same medication was available, for agents that have received regulatory approval, only data for the approved dose and administration was considered. The denominator used in all trials was based on intention-to-treat analysis, and all dropouts were assumed to be treatment failures for the primary outcome of clinical remission. Post-hoc, we included induction of endoscopic improvement (MES 0 or 1) as a secondary outcome.

We grouped advanced therapies based on primary mechanism of action: lymphocyte trafficking inhibitors (anti-integrins and S1P receptor modulators), anti-interleukins (IL-12/23 antagonist and selective IL-23 antagonists) and JAK inhibitors. We performed subgroup analysis by class of advanced therapies.

Data Synthesis and Statistical Analysis

We first calculated odds ratio (OR) and 95% confidence intervals (CI) for active drug vs. placebo for each trial, within a stratum of TNF antagonist-naïve patients, and TNF antagonist-exposed patients. Subsequently, we calculated the ratio of odds ratio, by dividing OR of (drug vs. placebo) in TNF antagonist-naïve patients by OR of drug vs. placebo in TNF antagonist-exposed patients.

Subsequently, we performed random-effects meta-analysis using the DerSimonian and Laird approach to calculate the ratio of ORs and corresponding 95% CI for each class of advanced therapies.⁸ We estimated heterogeneity of treatment efficacy by examining the interaction between efficacy of drug vs. placebo by advanced therapy class. In this analysis, a p-value for differences between subgroups of <0.10 was considered statistically significant. We assessed heterogeneity between study-specific estimates using the inconsistency index (I^2), and used cut-offs of 0–40%, 30–60%, 50–90% and 75–100% to suggest minimal, moderate, substantial and considerable heterogeneity, respectively.⁹ Due to the small number of included studies, we did not perform statistical assessment for publication bias.¹⁰ All analyses were performed using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

RESULTS

Our search strategy yielded 5,350 unique studies. From this, we included 17 RCTs of advanced therapies vs. placebo that reported induction of clinical remission, stratified by prior biologic exposure. These included five RCTs of lymphocyte trafficking inhibitors (two RCTs of vedolizumab; three RCTs of S1P receptor modulators),^{11–14} six RCTs of anti-interleukins (one RCT of IL12/23 antagonist; five RCTs for selective IL-23 antagonists)^{15–20} and six RCTs of JAK inhibitors (two RCTs of tofacitinib; four RCTs of JAK1 inhibitors).^{21–24} Details of these trials are shown in Table 1. Overall, these trials included 8871 patients of whom 66% were treated with advanced therapies, and 48% had prior exposure to biologics, >90% of whom were exposed to TNF antagonists with or without exposure to other advanced therapies. U-ACHIEVE, U-ACCOMPLISH, and INSPIRE trials stratified their outcomes by prior advanced therapy without specifying which prior advanced therapies patients received. All trials were deemed to be at low risk of bias.

Lymphocyte trafficking inhibitors

In five RCTs of trafficking inhibitors (2046 patients, 787 [38%] with prior TNF antagonist exposure),^{11–14} the magnitude of benefit with drug vs. placebo was significantly higher in TNF antagonist-naïve patients (OR, 3.20 [95% CI, 2.23–4.60]) compared with TNF antagonist-exposed patients (OR, 1.68 [95% CI, 1.02–2.76]) (p-value for difference between subgroups = 0.04) (Figure 1). There was minimal heterogeneity for both analyses ($I^2=0\%$).

Comparing the difference in the magnitude of efficacy of drug vs. placebo by prior TNF antagonist exposure status, the ratio of odds ratio suggested that lymphocyte trafficking inhibitors had 88% higher odds of achieving remission in TNF antagonist-naïve patients compared with TNF antagonist-exposed patients (ratio of OR of TNF antagonist-naïve vs. TNF antagonist-exposed: 1.88 [95% CI, 1.02–3.49]) with minimal heterogeneity ($I^2=0\%$) (Figure 2). Similar estimates were observed for endoscopic improvement outcome, though did not reach statistical significance (3 trials; ratio of OR of TNF antagonist-naïve vs. TNF antagonist-exposed: 1.50 [95% CI, 0.88–2.58]) (Supplementary Figure 1). There was no difference in the magnitude of this increased efficacy in TNF antagonist-naïve patients in trials of vedolizumab (ratio of OR, 2.17 [95% CI, 0.68–6.91]) and S1P receptor modulators (ratio of OR, 1.78 [95% CI, 0.86–3.69]) (p-value for difference between groups = 0.78).

IL-12/23 antagonists and IL-23 antagonists

In six RCTs of anti-interleukins (3810 patients, 1924 [50%] with prior TNF antagonist exposure),^{15–20} the magnitude of benefit with drug vs. placebo was similar in TNF antagonist-naïve patients (OR, 2.98 [95% CI, 2.13–4.18]) and TNF antagonist-exposed patients (OR, 3.23 [95% CI, 2.15–4.84]) (p-value for difference between subgroups = 0.77) (Figure 3). There was minimal heterogeneity for both analyses ($I^2=0\%$ for TNF antagonist-exposed and $I^2=30\%$ for TNF antagonist-naïve).

Comparing the difference in the magnitude of efficacy of drug vs. placebo by prior TNF antagonist exposure status, the ratio of odds ratio suggested that selective IL-23 antagonists had similar magnitude of efficacy in TNF antagonist-naïve patients compared with TNF antagonist-exposed patients (ratio of OR of TNF antagonist-naïve vs. TNF antagonist-exposed: 1.07 [95% CI, 0.64–1.80]), with minimal heterogeneity ($I^2=0\%$) (Figure 2). However, prior TNF antagonist exposure significantly increased the efficacy of ustekinumab in patients with moderate-severe UC (ratio of OR of TNF antagonist-naïve vs. TNF antagonist-exposed: 0.16 [95% CI, 0.03–0.80]). Similar estimates were observed for endoscopic improvement outcome (6 trials; ratio of OR of TNF antagonist-naïve vs. TNF antagonist-exposed: 1.11 [95% CI, 0.78–1.57]) (Supplementary Figure 1).

Janus kinase inhibitors

In six RCTs of JAK inhibitors (3015 patients, 1607 [53%] with prior TNF antagonist exposure),^{21–24} the magnitude of benefit with drug vs. placebo was lower in TNF antagonist-naïve patients (OR, 3.56 [95% CI, 1.92–6.58]) compared with TNF antagonist-exposed patients (OR, 8.53 [95% CI, 3.49–20.83]), though this difference in efficacy was of borderline statistical significance (p-value for difference between subgroups = 0.11) (Figure

4). There was moderate heterogeneity for all analyses ($I^2=29\%$ for TNF antagonist-exposed and $I^2=62\%$ for TNF antagonist-exposed).

Comparing the difference in the magnitude of efficacy of drug vs. placebo by prior TNF antagonist exposure status, the ratio of odds ratio suggested that JAK inhibitors had 53% lower odds of achieving remission in TNF antagonist-naïve patients compared with TNF antagonist-exposed patients (ratio of OR of TNF antagonist-naïve vs. TNF antagonist-exposed: 0.47 [95% CI, 0.22–1.01]), with minimal heterogeneity ($I^2=0\%$) (Figure 2). Similar estimates were observed for endoscopic improvement outcome (6 trials; ratio of OR of TNF antagonist-naïve vs. TNF antagonist-exposed: 0.66 [95% CI, 0.38–1.16]) (Supplementary Figure 1).

There was no difference in the magnitude of this decreased efficacy in TNF antagonist-naïve patients in trials of tofacitinib (ratio of OR, 0.18 [95% CI, 0.03–1.06]), upadacitinib (ratio of OR, 0.46 [95% CI, 0.11–1.88]) and filgotinib (ratio of OR, 0.67 [95% CI, 0.23–1.93]) (p-value for difference in groups = 0.46).

DISCUSSION

Biologic drivers of heterogeneity of treatment effect are important to understand for personalized medicine in patients with IBD.²⁵ One consistent adverse prognostic factor for treatment efficacy in patients with UC is prior failure of TNF antagonists. However, prior exposure to TNF antagonists may variably modify treatment efficacy of subsequent advanced therapies. In this systematic review and meta-analysis, we made several key observations by methodically examining the efficacy of different classes of advanced therapies based on prior TNF antagonist exposure status. We confirmed prior observations that exposure to TNF antagonists significantly reduces the efficacy of lymphocyte trafficking inhibitors in inducing remission, including both vedolizumab and S1P receptor modulators, by approximately 50%. In contrast, prior exposure to TNF antagonists was associated with a significant increase in the efficacy of JAK inhibitors in inducing remission, with two-fold higher efficacy in TNF antagonist-exposed vs. TNF antagonist-naïve patients. Prior exposure to TNF antagonist did not modify the efficacy of selective IL-23 antagonists; in contrast, in the UNIFI trial the efficacy of IL-12/23 antagonist, ustekinumab was significantly increased with prior exposure to TNF antagonists. These observations were similar for induction of endoscopic improvement endpoint. Clinically, these findings reassure positioning of JAK inhibitors after exposure to TNF antagonists; while these recommendations from the FDA were driven by safety concerns with JAK inhibitors,²⁶ our findings suggest that prior exposure to TNF antagonists may potentiate the efficacy of JAK inhibitors.

With availability of several different treatment options, optimal therapeutic sequencing is critical to understand. There are limited studies in patients with IBD that have examined treatment sequencing. Observational comparative effectiveness studies in patients with UC have shown that tofacitinib is more efficacious than vedolizumab in patients with prior failure of TNF antagonists.^{27–29} However, these same studies have not examined comparative effectiveness of these therapies in TNF antagonist-naïve patients, and importantly, have not been able to discern changes in the effectiveness of vedolizumab

or tofacitinib following exposure to TNF antagonists. While trials of therapeutic sequencing are limited in IBD, such trials have been conducted in other immune-mediated diseases, such as rheumatoid arthritis. In the SELECT-COMPARE trial in patients with rheumatoid arthritis with inadequate response to methotrexate, clinical remission was achieved in 29% upadacitinib- vs. 16% adalimumab-treated patients.^{30, 31} At week 26, patients with inadequate response to upadacitinib or adalimumab were switched to the other therapy. After this switch, a significantly higher proportion of patients who switched to upadacitinib after failure of adalimumab achieved clinical remission compared with those who switched to adalimumab after failure of upadacitinib (35% vs. 21%). These published findings, together with the observation in this study that exposure to TNF antagonists augments the efficacy of JAK inhibitors, support the potentially paradigm-shifting concept that exposure to one drug may differentially influence subsequent efficacy of a second drug.

It is critical to understand mechanistic insights into these observations which need further biologic characterization. We propose that exposure to TNF antagonists could durably change the immune system in patients with UC. Indeed, it has been previously demonstrated that infectious exposures can result in lasting consequences to the immune system. For example, a single acute gastrointestinal infection was shown to disrupt the communication between the immune system and the tissue, causing an “immunological scar” that compromised tissue immunity and homeostasis in the long-term.³² Further, non-infectious exposures can have lasting effects on the immune system. Smoking was shown to exert a transient effect on innate immune responses, but an enduring effect on adaptive immunity that persisted well beyond smoking cessation.³³ Thus, the current findings raise the intriguing possibility that exposure to TNF antagonists could result in lasting effects on the immune system that differentially alter responsiveness to therapies with distinct mechanisms of action. TNF α -blockade reduces leukocyte trafficking and decreased leukocyte trafficking may contribute to a reduction in response rates to lymphocyte trafficking therapies.^{34, 35} The possible potentiation of JAK inhibitors in those with prior exposure to TNF antagonists could be due to the IL-6/JAK/STAT pathway that is initially suppressed (~2 weeks) but later increases in some patients starting at week 8.³⁶ Moreover, drugs can cause changes in gene expression that persist long after the drug has been discontinued, through both direct and indirect mechanisms.^{37, 38} In a recent study, using a network transcriptomic approach to predict efficacy of drug targets in *in silico* trials agrees with the findings we report. In this study, JAK inhibitors were significantly more likely to upregulate a 34-gene signature of molecular remission in patients with prior exposure to TNF antagonists, whereas vedolizumab and S1P receptor modulators upregulated only a small subset of these genes.³⁹ These findings suggest epigenetic rewiring and a foundational impact on gene regulatory networks that impact gene expression after exposure to TNF antagonists.

Another provocative observation in the current study is that exposure to TNF antagonists enhanced subsequent efficacy of IL-12/23 antagonists, but not selective IL-23 antagonists. IL-12 was once considered to be the primary driver of autoimmune and immune-mediated diseases, including IBD, but the discovery of IL-23 led to a paradigm shift whereby IL-23 and Type 17 immunity are now thought to be far more critical.⁴⁰ Nonetheless, IL-12 may still play an important role in the pathogenesis of chronic intestinal inflammation by playing

an early role in disease development relative to IL-23, which may play a temporally distinct role in controlling disease chronicity.⁴¹ We speculate that treatment with TNF antagonists may reshape the Type 17 immune-driven nature of UC into a more Type 1 immune-biased disease, providing a potential explanation for enhanced efficacy of therapies that target IL-12. Indeed, TNF is known to inhibit IL-12 production by macrophages;^{42, 43} hence, TNF blockade may lead to de-repressed (increased) IL-12 production, resulting in a Type 1 immunity-dominant microenvironment that is more responsive to IL-12 antagonism.

While the findings are intriguing, there are important limitations that should be considered. First, we combined classes of therapies based on similarity of putative mechanism of action, such as lymphocyte trafficking inhibitors and S1P receptor modulators, even though their exact mechanism of blocking trafficking is different with potential biologic effects. On subgroup analysis by class of advanced therapies, our findings were stable. Second, while we intended to examine the impact of prior exposure to TNF antagonists on heterogeneity of treatment efficacy, for some trials, these results were only available based on prior exposure to any biologic. In these trials, TNF antagonist was the primary biologic exposure in >90% of instances across trials, and in some trials, patients could also have been exposed to additional biologics. Third, among TNF antagonist-exposed patients, there is a subset of patients that have failed two or more types of advanced therapies, which may be negatively associated with therapeutic success.^{44,45} Unfortunately, we are unable to examine the impact of exposure to multiple cases of medications on treatment efficacy modification due to limited reporting of these data. Since they are definitively categorized as TNF-exposed, their impact on the analysis results is expected to be minimal. Fourth, we were unable to explicitly adjust for other potential confounding variables. However, since prior exposure to TNF antagonists was a stratification variable in trials, it preserved the benefits of randomization such that patients were randomly assigned to drug or placebo in each stratum.

In conclusion, through a meta-analysis of RCTs, we observed that there is significant heterogeneity of treatment efficacy for induction of remission with different advanced therapies in patients with moderate-severe UC based on prior exposure to TNF antagonists. Prior exposure to TNF antagonists appears to potentiate the efficacy of JAK inhibitors and IL-12/23 antagonists but may attenuate responsiveness to lymphocyte trafficking inhibitors. Future studies on the mechanistic insight for these intriguing observations are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Lymphocyte trafficking inhibitors vs. placebo, by prior TNF antagonist exposure

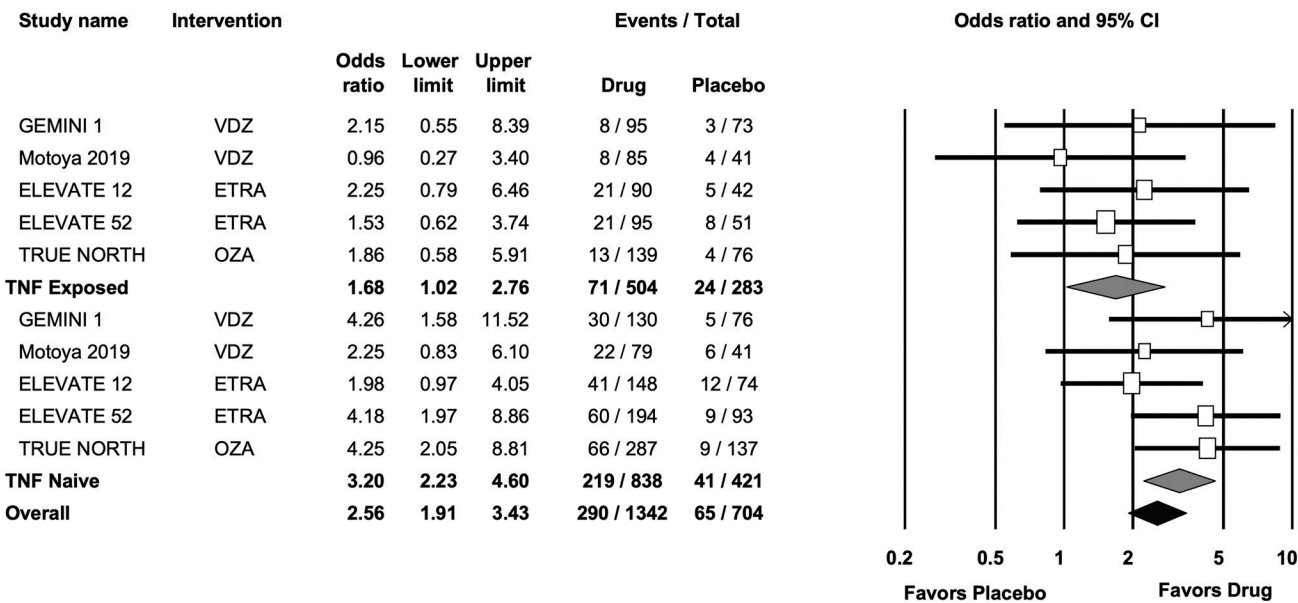


Figure 1. Efficacy of lymphocyte trafficking inhibitors vs. placebo, stratified by prior exposure to TNF antagonists, in patients with moderate-severe ulcerative colitis. There was minimal heterogeneity for both analyses ($I^2=0\%$).

Ratio of Treatment Effect (Drug vs. Placebo), in TNF antagonist-naïve vs. TNF antagonist-exposed patients in trials of different advanced therapies for moderate-severe ulcerative colitis

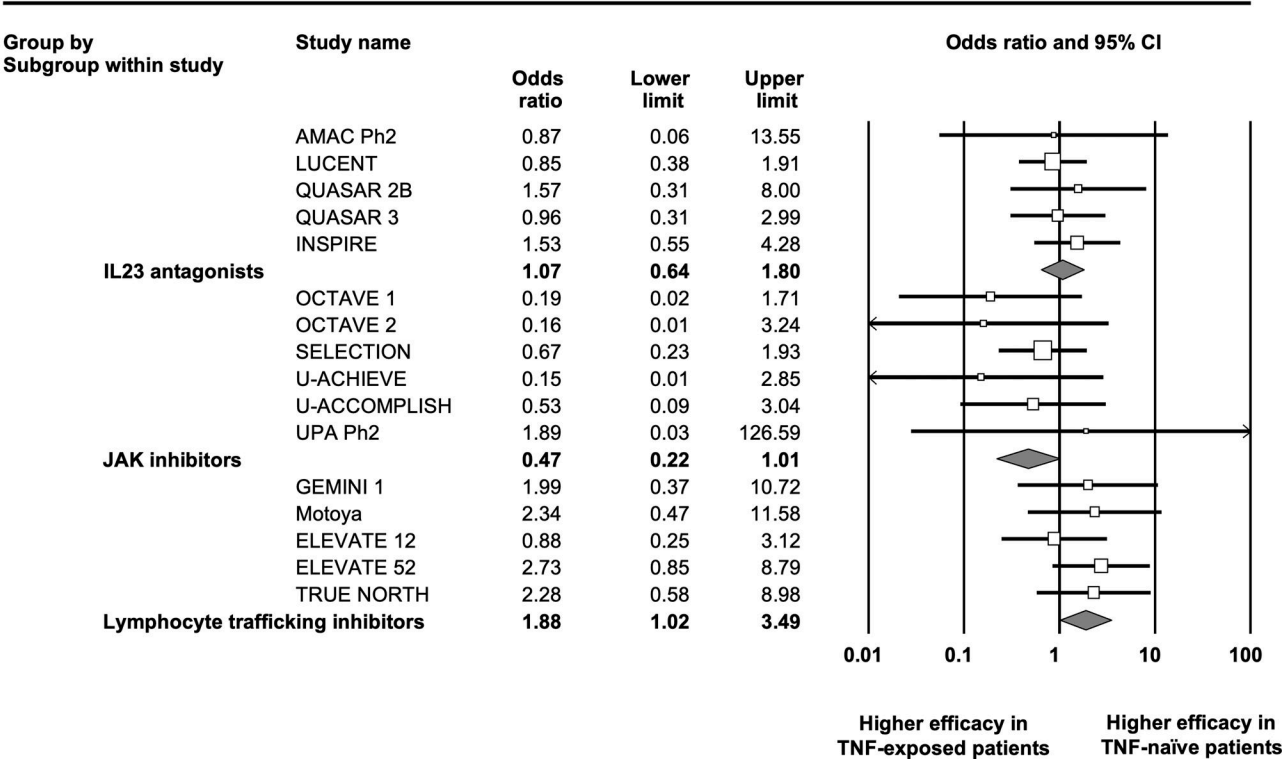


Figure 2. Heterogeneity of treatment efficacy – ratio of odds ratio of efficacy of drug vs. placebo in TNF antagonist-naïve and TNF antagonist-exposed patients in inducing clinical remission with different classes of advanced therapies in patients with moderate-severe ulcerative colitis. There was minimal statistical heterogeneity for all analyses ($I^2=0\%$).

Anti-interleukins vs. placebo, by prior TNF antagonist exposure

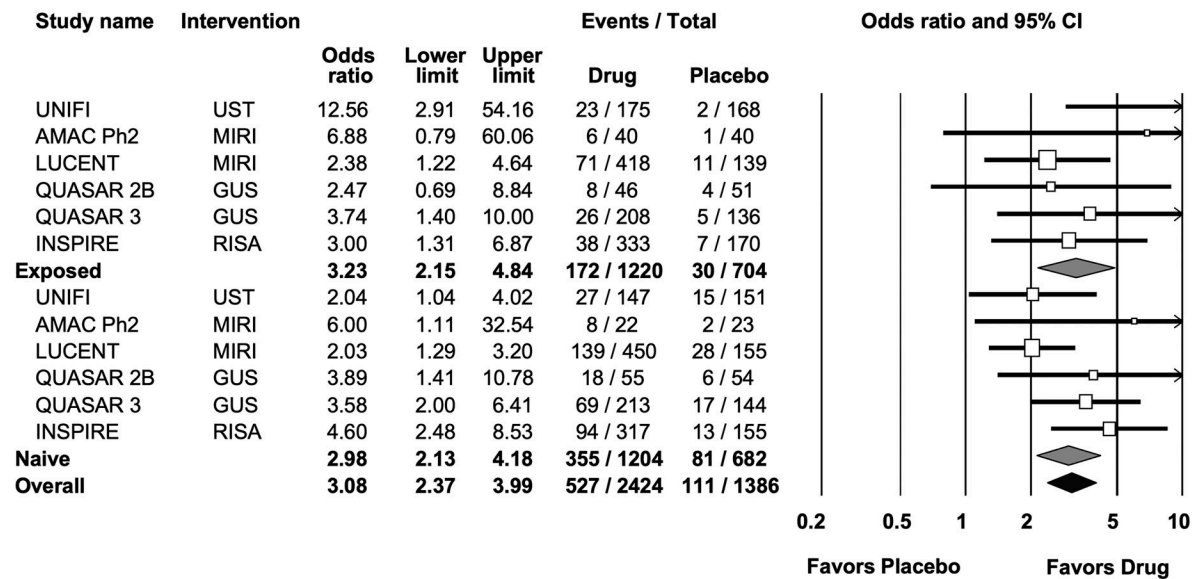


Figure 3.

Efficacy of anti-interleukins (ustekinumab and selective IL-23 antagonists) vs. placebo, stratified by prior exposure to TNF antagonists, in patients with moderate-severe ulcerative colitis. There was minimal heterogeneity for both analyses ($I^2=0\%$ for TNF antagonist-exposed and $I^2=30\%$ for TNF antagonist-exposed).

JAK inhibitors vs. placebo, by prior TNF antagonist exposure

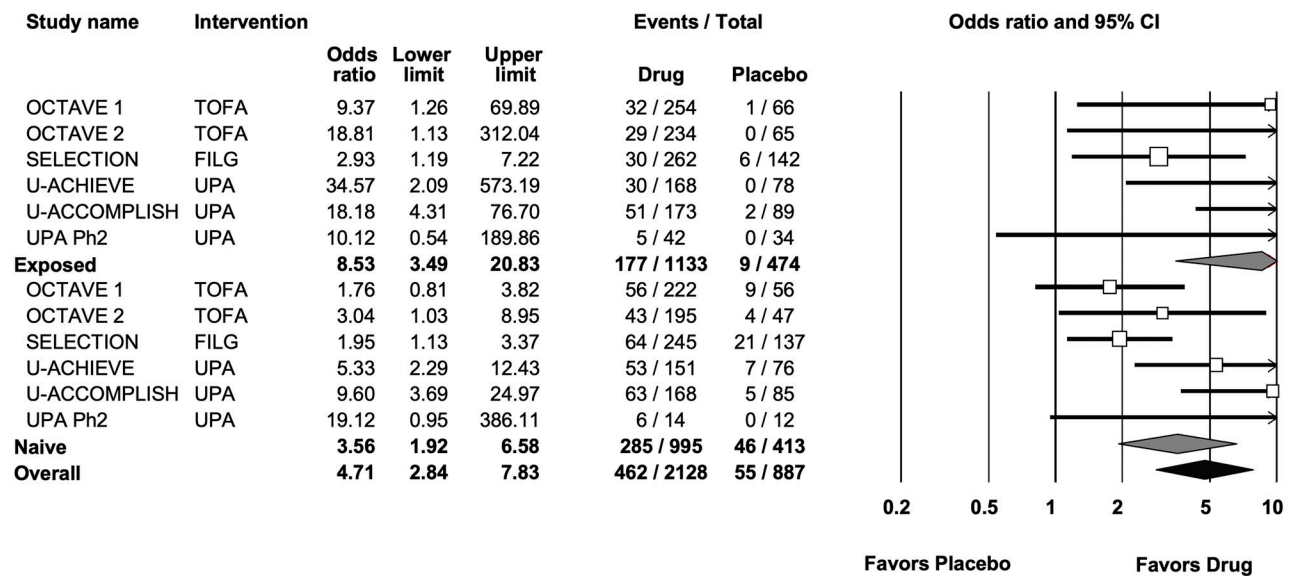


Figure 4.

Efficacy of JAK inhibitors vs. placebo, stratified by prior exposure to TNF antagonists, in patients with moderate-severe ulcerative colitis. There was moderate heterogeneity for both analyses ($I^2=29\%$ for TNF antagonist-exposed and $I^2=62\%$ for TNF antagonist-exposed).

Table 1.

Trial and patient characteristics included in the synthesis

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (SD); Sex (% male)	Mean Disease duration (y) (SD); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (SD)	Prior exposure to: TNF antagonist (%); vedolizumab (%); tofacitinib (%)	Clinical Remission rate in placebo arm (%)
					IMM (%)	Corticosteroids (%)			
Lymphocyte trafficking inhibitors									
GEMINI I	211 sites, 2008–12; P: 149; I: Vedolizumab 300mg, w0,2 – 746	MCS≤2 with no score >1; W6	P: 41 (13); 62 I: 40 (13); 58	7.1 (7.2); 46 6.8 (6.2); 50	29.5 35.4	56.3 53.2	NR	49/0/0 48/0/0	5
Motoya et al	100 sites, 2014–18; P: 82; I: Vedolizumab 300mg, w0,2,6 – 164	MCS≤2 with no score >1; W10	P: 44 (16); 67 I: 42 (14); 60	8.6 (8.0); 62 7.2 (6.2); 62	52.5 48.8	30.5 31.7	>3mg/L; 39 >3mg/L; 54	50/0/0 51/0/0	12
TRUE NORTH	285 sites; 2015–20; P: 216; I: Ozanimod 1 mg qday – 429	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W10	P: 42 (14); 66 I: 41 (14); 57	6.8 (7.0); 38 I: 6.9 (6.6); 38	0 0	32.4 27.7	5.0 (2.0–12.0) 4.0 (1.0–9.0)	30.1/17.6/1.9 30.3/16.6/0.7	18
ELEVATE 12	407 sites; 2020–2021; P: 116; I: Etrasimod 2mg qday – 238	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W12	P: 40 (13); 63 I: 40 (14); 57	7.7 (7.3); 35 7.3 (6.6); 32	0 0	33 33	8.1 (15.7) 7.5 (12.6)	25/9/8 24/14/6	15
ELEVATE 52	315 sites; 2019–2021; P: 144 I: Etrasimod 2mg qday – 289	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W12	P: 39 (14); 61 I: 41 (14); 53	5.9 (5.5); 33 7.5 (8.0); 32	0 0	32 33	10.8 (18.1) 9.6 (15.5)	22/13/6 21/10/7	12
	Janus kinase inhibitors								
OCTAVE 1	144 sites, 2012–15; P: 122; I: Tofacitinib 10 mg po b.d. – 476	MCS≤2, with RBS 0; W8	P: 42 (15); 63 I: 41 (14); 58	6.0 (0.5–36.2) ♦; 54 6.5 (0.3–42.5) ♦; 53	NA	47.5 45.0	4.7 (0.1–82.5) ♦ 4.4 (0.1–208.4) ♦	53.3/0/0 53.4/0/0	8
OCTAVE 2	169 sites, 2012–15; P: 112; I: Tofacitinib 10mg po b.d. – 429	MCS≤2, with RBS 0; W8	P: 40 (13); 49 I: 41 (14); 60	6.2 (0.4–27.9) ♦; 51 6.0 (0.4–39.4) ♦; 49	NA	49.1 46.2	5.0 (0.2–205.1) ♦ 4.6 (0.2–156.0) ♦	58.0/0/0 54.5/0/0	4

	Trial and Intervention Characteristics	Definition and Timing of Outcome (CRem)	Mean age (y) (SD); Sex (% male)	Mean Disease duration (y) (SD); Disease extent (% extensive colitis)	Concomitant medications		Mean CRP (mg/L) (SD)	Prior exposure to: TNF antagonist (%); vedolizumab (%); tofacitinib (%)	Clinical Remission rate in placebo arm (%)
					IMM (%)	Corticosteroids (%)			
U-ACHIEVE	199 sites, 2016–18 P: 154; I: Upadacitinib 45 mg qday – 319	Adapted Mayo score ≤2, SFS≤1 and not greater than baseline, RBS=0, MES ≤1 without friability; W8	P: 45 (23); 63 I: 43 (23); 62	6.0 (10.0); 52 6.6 (9.6); 50	2 1	40 39	4.7 (12.5) 4.1 (8.1)	Any prior advanced therapy: P: 51 I: 53	5
U-ACCOMPLISH	204 sites, 2016–18 P: 174; I: Upadacitinib 45 mg qday – 341	Adapted Mayo score ≤2, SFS≤1 and not greater than baseline, RBS=0, MES ≤1 without friability; W8	P: 42 (24); 61 I: 40 (24); 63	4.9 (7.4); 49 5.6 (7.5); 52	2 <1	41 35	4.7 (10.0) 3.8 (8.0)	Any prior advanced therapy: P: 51 I: 50	4
Sandborn Ph2	142 sites, 2016–18; P: 46 I: Upadacitinib 45 mg qday – 56	Adapted Mayo score ≤2, SFS≤1, RBS=0, MES ≤1; W8	P: 40 (21–67); 63 I: 37 (19–74); 66	5.2 (0.4–30.8); 58.7 6.5 (0.4–23.9); 53.6	P: 0 I: 0	P: 54.3 I: 50.0	5.4 (0.35–41.2) ♦ 6.3 (0.2–67) ♦	71.7/50/0 69.6/41.1/0	0
SELECTION A	341 sites, 2016–20; P: 137; I: Filgotinib 200 mg qday – 245	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W10	P: 41 (13); 64 I: 42 (13); 50	P: 6.4 (7.4); NR I: 7.2 (6.9); NR	24.1 21.6	24.8 22.0	5.8 (7.6) 8.6 (16.3)	0.0/0 0.0/0	15
SELECTION B	341 sites, 2016–20; P: 142; I: Filgotinib 200 mg qday – 262	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W10	P: 44 (15); 61 I: 43 (14); 57	10.2 (8.2); NR 9.8 (7.6); NR	14.8 13.0	35.9 35.9	14.0 (24.3) 12.2 (14.9)	91.5/59.9/0 92.4/62.6/0	4
Interleukin-12/23 antagonists (Ustekinumab)									
UNIFI	244 sites, 2015–18 P: 319 I: IV ustekinumab 6mg/kg, w0 – 322	MCS ≤2 with no subscore >1; W8	P: 41 (14); 62 I: 42 (14); 61	8.0 (7.2); 47 8.2 (7.8); 47	27.9 27.6	49.2 52.2	4.7 (1.4–10.) 4.8 (1.8–13.7)	51/0/0 52/0/0	12
Selective interleukin-23 antagonists									
AMAC Ph2	75 sites, 2016–2017 P: 63 I: IV mirikizumab 200mg w0/4/8 – 62	Adapted Mayo score ≤2, SFS≤1 and at least 1 point decrease from baseline, RBS=0, MES ≤1 without friability; W12	P: 43 (14); 57 I: 43 (15); 60	9.5 (9.6); NR 9.0 (9.0); NR	39.7 29.0	52.4 40.3	3.9 (1.1–11.2) 3.6 (1.4–13.7)	Any prior advanced therapy: P: 27 I: 43.5	5

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

♦ Median (range)

[Abbreviations: CRP-C-reactive protein, 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; W-Week]