Differential efficacy of medical therapies for ulcerative colitis according to disease extent: patient-level analysis from multiple randomized controlled trials

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Summary

Background Disease extent in Ulcerative Colitis (UC) has prognostic implications for disease course. It is unclear whether the efficacy of medical therapies for moderate to severely active UC vary according to disease extent at enrollment.

Methods We analyzed patient level data from 11 Phase 2 and 3 clinical trials of advanced therapies in patients with moderate-to-severe UC to assess modifications of advanced therapy effects by disease extent. Primary outcome was clinical response and secondary outcomes were clinical remission, endoscopic response/remission and endoscopic improvement, and Mayo clinic subscore for both induction and maintenance studies. Binary and continuous outcomes were analyzed using the modified Poisson regression model and the mixed-effects model, respectively, adjusting for age, sex, disease duration, concomitant steroid use and prior anti-TNF use. Effect modifications with binary outcomes were quantified by ratios of risk ratio for left-sided to that for extensive colitis while effect modifications with the Mayo subscores were quantified by differences of the differences between mean scores of the left-sided and extensive colitis. Results were presented with point estimates and 95% confidence intervals as well as p-values.

Findings Eleven clinical trials enrolling 5450 UC patients (infliximab = 2, adalimumab = 2, golimumab = 2, vedolizumab = 2, tofacitinib = 3) were included. In induction trials, there was evidence to suggest effect modification by disease extent for clinical response with tofacitinib (the ratio of RRs 0.67, 95% CI [0.45, 0.99], p = 0.049) and clinical remission with infliximab (ratio of RRs 0.33, 95% CI [0.13, 0.85], p = 0.020) favoring patients with extensive colitis. There was no evidence to suggest effect modification for endoscopic improvement and clinical outcomes. There was evidence to suggest effect modification by disease extent for clinical remission with tofacitinib (ratio of RRs 0.44, 95% CI [0.22, 0.89], p = 0.020) favoring patients with extensive colitis. For symptom subscores from the Mayo Clinic score, tofacitinib was associated with a greater reduction in both stool frequency (difference of differences 0.37, 95% CI [0.08, 0.65], p = 0.012) and rectal bleeding scores (difference of differences 0.25, 95% CI [0.03, 0.47], p = 0.026) in patients with extensive colitis compared to left sided.

Interpretation These findings underscore the possibility of differential efficacy of medical therapies according to disease distribution. These results warrant further exploration in forthcoming trials to better inform treatment strategies and consideration of disease distribution as a baseline stratification factor in clinical trials.

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Research in context

Evidence before this study

We searched PubMed, conference proceedings, trial registries and unpublished data for previously published meta-analysis on advanced therapies for moderate-to-severe ulcerative colitis (UC) using the search terms 'ulcerative colitis', 'extent' or 'distribution'. No prior meta-analysis assessed efficacy of advanced therapies according to disease extent.

Added value of this study

The study includes 11 RCTs (5450 participants) comparing five different drugs for induction and maintenance of clinical and endoscopic outcomes in patients with moderate-to-severe UC, we were able to evaluate the comparative efficacy of several agents between left-sided colitis and extensive colitis. For induction studies, tofacitinib and infliximab had greater efficacy in inducing clinical response/remission in patients with extensive colitis compared to left-sided colitis. Analysis of symptom subscores from the Mayo Clinical Score was consistent with clinical outcomes. Similar observations were found with tofacitinib for maintenance of clinical outcomes. To the best of our knowledge this is the first study to explore differences in treatment efficacy of advanced therapies based on disease extent for moderate to severe UC.

Implications of all the available evidence

These results highlight the potential differences in efficacy between various medical treatments for patients with left-sided colitis and extensive colitis. These findings warrant additional investigation in future trials to provide more insights for treatment strategies and to consider disease location as a stratification factor in clinical trials.

Introduction

Ulcerative colitis (UC) phenotypically is sub classified into ulcerative proctitis (E1-limited to rectum), left-sided (E2) and extensive colitis (E3).[1] According to pooled analysis of 17 population based cohort studies, approximately 40% of patients with UC have left-sided colitis, 30% have extensive colitis[2] and 30% have proctitis at diagnosis. Furthermore, 20% of patients with left-sided colitis at diagnosis will progress to extensive colitis over the subsequent 10 years of their disease course.[3] Left-sided colitis and extensive colitis differ not only in the extent of disease distribution, but also in terms of long-term prognosis. Several observational studies have reported a higher risk of colectomy in patients with extensive colitis compared to left-sided colitis.[4–6] Similarly long-term follow-up studies demonstrated that the risk of colorectal cancer was higher in patient with extensive colitis compared to left-sided colitis.[7,8] In addition, differential gene expression profiles have been reported between patients with extensive colitis versus left-sided colitis, suggesting differences in inflammatory process between these phenotypes.[9] Allelic variations of genes such as the multi drug resistance (MDR) gene were shown to be associated with extensive colitis indicating genetic differences might exist between these two clinical phenotypes.[10] There may also be differential patterns of healing in the colon after medical therapy, based on the concept that the colon heals from right to left. Furthermore, it is plausible that symptom burden may also differ; for example, symptoms such as tenesmus and urgency may be dominant in left-sided disease. Despite these differences in underlying pathophysiology and long-term prognosis, it is unclear whether there is a differential response to treatment according to disease distribution. In a study of 5-aminosalycilic acid (5-ASA), patients with extensive colitis had shorter time to relapse compared to left-sided colitis.[11] However, studies evaluating the efficacy of advanced therapies according to different distribution are scarce. In a single center observational study, left-sided colitis was associated with superior clinical remission rates compared to extensive colitis after treatment with vedolizumab.[12]

In clinical trials for moderate to severe UC, patients with isolated proctitis have historically been excluded. Among the recruited patients, typically two-thirds have left-sided disease and one-third extensive disease at baseline; however, disease location is not used as a stratification factor. Given that patients with extensive versus left-sided colitis have different prognosis and inflammatory burden, it is plausible that response to treatment could vary. Thus, we undertook an individual patient level data meta-analysis from multiple clinical trials of advanced therapies in UC to investigate whether clinical outcomes were influenced by disease distribution. By identifying the impact of disease distribution on treatment efficacy, the results may help to inform treatment recommendations as well as the design of future clinical trials.

Methods

This was a post hoc analysis of participant-level data from several clinical trials of adult patients (≥18 years) with moderate to severe UC. Data from phase 3 clinical trials evaluating the efficacy of biologics or small molecule agents, available on Yale University Open Data Access (YODA) Project and Vivli platforms (ID: 00007854) were accessed after approval by the respective data sharing committees. The primary objective was to assess whether the treatment effect of the intervention differs according to disease distribution (left-sided versus extensive disease) in induction and maintenance trials with moderate to severe UC patients, based on the rates of clinical response/remission and endoscopic response/remission. The secondary objectives were to examine the impact on the individual symptoms of stool frequency and rectal bleeding.

Study selection

Data from eleven clinical trials of patients with moderate to severe UC were used for this study (Tables 1 and 2). The clinical trials included studies on: Tofacitinib,[13] Golimumab,[14,15] Infliximab,[16] Adalimumab,[17,18] and Vedolizumab.[19,20] Data from four trials were obtained through Yale Open Data Access (YODA), with permissions from Johnson & Johnson (NCT00488774,

Patient characteristics	OCTAVE 1 (N = 614)	OCTAVE 2 (N = 547)	PURSUIT-IV (N = 291)	PURSUIT-SC (N = 1065)	ACT 1 (N = 364)	ACT 2 (N = 364)	GEMINI 1 (N = 895)	ULTRA 1 (N = 576)	ULTRA 2 (N = 518)
	Tofacitinib	Tofacitinib	Golimumab	Golimumab	Infliximab	Infliximab	Vedolizumab	Adalimumab	Adalimumab
Sex, n (%)									
Male	363 (59.1)	317 (58.0)	174 (59.8)	596 (56.0)	222 (61.0)	215 (59.1)	525 (58.7)	356 (61.8)	305 (58.9)
Female	251 (40.9)	230 (42.1)	117 (40.2)	469 (44.0)	142 (39.0)	149 (40.9)	370 (41.3)	220 (38.2)	213 (41.1)
Randomization									
Treatment	492 (80.1)	435 (79.5)	214 (73.5)	734 (68.9)	243 (66.8)	241 (66.2)	746 (83.35)	353 (61.3)	258 (49.8)
Placebo	122 (19.9)	112 (20.5)	77 (26.5)	331 (31.1)	121 (33.2)	123 (33.8)	149 (16.65)	223 (38.7)	260 (50.2)
Disease extent, n (%)									
Left-sided colitis	286 (46.7)	274 (50.3)	161 (55.3)	615 (57.8)	196 (54.4)	215 (60.1)	455 (50.8)	202 (35.1)	200 (38.6)
Extensive colitis	74 (12.1)	54 (9.9)	130 (44.7)	449 (42.2)	164 (45.6)	143 (39.9)	109 (12.2)	316 (54.9)	250 (48.3)
Pancolitis	253 (41.3)	216 (39.6)					331 (37.0)	58 (10.1)	68 (13.1)
Other		1 (0.2)							
Age (years), mean (SD)	41.4 (14.3)	40.8 (13.4)	41.0 (13.7)	40.0 (13.4)			40.3 (13.1)	39.7 (13.2)	40.63 (12.8)
Disease duration, n (%) mean									
<6 years	291 (47.4)	271 (49.5)	270 (93.8)	991 (93.1)	179 (49.2)	184 (50.7)	517 (57.9)	286 (49.7)	258 (49.8)
≥6 years	323 (52.6)	276 (50.5)	18 (6.3)	74 (6.9)	185 (50.8)	179 (49.3)	376 (42.1)	290 (50.3)	260 (50.2)
Ethnicity									
Hispanic	31 (5.2)	14 (2.7)					31 (3.5)	26 (4.5)	13 (2.5)
Not Hispanic	570 (94.8)	510 (97.3)					481 (53.7)	550 (95.5)	505 (97.5)
Race, n (%)									
White	505 (84.0)	424 (80.9)	239 (82.1)	874 (82.1)	340 (93.4)	344 (94.5)	734 (82.0)	528 (91.7)	494 (95.4)
Black	6 (1.0)	4 (0.8)	4 (1.4)	26 (2.4)	6 (1.7)	8 (2.2)	12 (1.3)	19 (3.3)	11 (2.1)
Asian	71 (11.8)	74 (14.1)	44 (15.1)	126 (11.8)	4 (1.1)	5 (1.37)	135 (15.1)	22 (3.8)	5 (1.0)
Other	19 (3.2)	22 (4.2)	4 (1.4)	39 (3.7)	14 (3.9)	7 (1.9)	14 (1.6)	7 (1.2)	8 (1.5)
Smoking status									
Ex-smoker	197 (32.1)	164 (30.0)			161 (44.2)	153 (42.0)	285 (31.8)	173 (30.2)	200 (38.5)
Never smoked	389 (63.4)	353 (64.5)			191 (52.5)	191 (52.5)	555 (62.0)	360 (62.5)	281 (54.1)
Smoker	28 (4.6)	30 (5.5)			12 (3.3)	20 (5.5)	55 (6.2)	39 (6.8)	38 (7.3)
Baseline BMI kg/mg^2, mean (SD)	24.7 (5.0)	25.1 (5.0)					25.1 (5.6)	25.5 (5.2)	25.5 (5.5)
Prior steroid treatment, n (%)	558 (90.9)	493 (90.1)	199 (68.4)	613 (57.6)	96 (26.4)	90 (24.7)	347 (38.8)		
Prior immunosuppressant treatment, n (%)	467 (76.1)	392 (71.7)	127 (43.6)	489 (45.9)	50 (13.7)	26 (7.14)	376 (42.1)		
Prior anti-TNF treatment, n (%)	327 (53.3)	303 (55.4)	0 (0.00)[a]	0 (0.00)[a]			431 (48.2)	0 (0.00)[c]	0 (0.00)[b]
Concomitant steroid treatment, n (%)	280 (45.6)	257 (47.0)			134 (36.8)	126 (34.6)	481 (53.7)		
Concomitant immunosuppressant[d] treatment, n (%)					154 (42.3)	125 (34.3)	308 (34.4)		

[a]Participants with previous exposure to biologic anti-tumor necrosis factor (TNF) agents were excluded from the study. [b]Participants with any prior exposure to Tysabri® (natalizumab), or Orencia® (abatacept) or any other biological therapy [other than Kineret® (anakinra) and anti-TNF agents] were excluded. [c]Participants who received infliximab or any other anti-TNF agent or any biological therapy in the past were excluded. [d]Immunosuppressants include azathioprine, mercaptopurine or methotrexate.

Table 1: **Baseline characteristics of induction studies.**

Patient characteristics	OCTAVE Sustain (N = 594)	ACT 2 (N = 364)	ACT 1 (N = 364)	GEMINI 1 (N = 837)	VISIBLE 1 (N = 216)
	Tofacitinib	Infliximab	Infliximab	Vedolizumab	Vedolizumab
Sex, n (%)					
Male	330 (55.6)	215 (59.1)	222 (61.0)	492 (58.78)	130 (60.19)
Female	264 (44.4)	149 (40.9)	142 (39.0)	345 (41.22)	86 (39.81)
Randomization					
Treatment	395 (66.50)	241 (66.2)	243 (66.8)	576 (68.82)	160 (74.07)
Placebo	198 (33.33)	123 (33.8)	121 (33.2)	261 (31.18)	56 (25.93)
Disease extent, n (%)					
Left-sided colitis	277 (46.9)	215 (60.1)	196 (54.4)	422 (50.42)	120 (55.81)
Extensive colitis	67 (11.3)	143 (39.9)	164 (45.6)	104 (12.43)	18 (8.37)
Pancolitis	247 (41.8)			311 (37.16)	77 (35.81)
Other					
Age (years), mean (SD)	42.8 (14.1)			40.29 (13.20)	39.33 (13.05)
Disease duration, n (%) mean					
<6 years	279 (47.0)	184 (50.7)	179 (49.2)	480 (57.35)	
≥6 years	315 (53.0)	179 (49.3)	185 (50.8)	357 (42.65)	
Ethnicity					
Hispanic	19 (3.3)				1 (0.46)
Not hispanic	556 (96.7)				21 (9.72)
Race, n (%)					
White	473 (82.3)	344 (94.5)	340 (93.4)	688 (82.20)	181 (83.80)
Black		8 (2.2)	6 (1.7)	11 (1.31)	2 (0.93)
Asian	74 (12.8)	5 (1.37)	4 (1.1)	126 (15.05)	32 (14.81)
Other	23 (4.0)	7 (1.9)	14 (3.9)	12 (1.43)	1 (0.46)
Smoking status					
Ex-smoker	186 (31.3)	153 (42.0)	161 (44.2)	268 (32.02)	54 (25.00)
Never smoked	383 (64.5)	191 (52.5)	191 (52.5)	519 (62.01)	141 (65.28)
Smoker	25 (4.2)	20 (5.5)	12 (3.3)	50 (5.97)	21 (9.72)
Baseline BMI kg/mg^2, mean (SD)	25.5 (4.9)			25.10 (5.59)	24.76 (5.12)
Prior steroid treatment, n (%)	541 (91.1)	90 (24.7)	96 (26.4)	316 (37.75)	
Prior immunosuppressant treatment, n (%)	428 (72.1)	26 (7.14)	50 (13.7)	352 (42.05)	
Prior anti-TNF treatment, n (%)	284 (47.8)			405 (48.39)	80 (37.04)
Concomitant steroid treatment, n (%)	298 (50.2)	126 (34.6)	134 (36.8)	459 (54.84)	90 (41.67)
Concomitant immunosuppressant[a] treatment, n (%)		125 (34.3)	154 (42.3)	286 (34.17)	70 (32.41)

[a]Immunosuppressants include azathioprine, mercaptopurine or methotrexate.

Table 2: **Baseline characteristics of maintenance studies.**

NCT00487539, NCT00096655, NCT00036439). The remaining seven trials were obtained through Vivli and were used with permissions from Pfizer (NCT01465763, NCT01458951, NCT01458574), AbbVie (NCT00408629, NCT00385736), and Takeda (NCT00783718, NCT02611830) (Tables 1 and 2).

Participants

Tofacitinib

Data from phase 3, double blind, placebo controlled randomized controlled trials (RCTs) (OCTAVE induction 1 and 2 trials and OCTAVE sustain maintenance trial) assessing efficacy of tofacitinib were included. Eligible patients in OCTAVE 1 (n = 598) and 2 (n = 541) trials were adults (≥18 years) with moderate to severely active UC (Mayo clinic score of 6–10 with a rectal bleeding subscore of 1–3 and centrally assessed endoscopic subscore of 2 or 3) who failed or intolerant to glucocorticoids or immunomodulators or infliximab or adalimumab. Patients who completed the OCTAVE Induction 1 or 2 trial and had a clinical response during the induction trial were eligible to participate in the OCTAVE Sustain trial (n = 593). Patients in induction trials were randomized in 4:1 ratio received 10 mg twice daily tofacitinib or placebo for 8 weeks. Whereas patients in maintenance trial, patients were randomized in 1:1:1 ratio to tofacitinib 5 mg twice daily, 10 mg twice daily and placebo until week 52.

Infliximab

Two phase 3, double blind, placebo controlled RCTs (ACT 1 and 2 trials) evaluated efficacy of infliximab for induction and maintenance therapy in adult patients with active UC (Mayo clinic score between 6 and 12 and

Mayo endoscopic subscore of at least 2). Patients in ACT 1 trial (n = 364) were required to have active disease and concurrent treatment with corticosteroids alone or in combination with immunomodulators, whereas patients in ACT 2 (n = 364) had to fail concurrent corticosteroids alone or in combination with immunomodulators and 5-aminosalicylates. Eligible patients were randomly assigned in a 1:1:1 ratio to receive 5 mg/kg or 10 mg/kg of infliximab or placebo intravenously at weeks 0, 2, and 6 and then every 8 weeks up to week 46 in ACT 1 and week 22 in ACT 2.

Adalimumab

ULTRA 1 (n = 576), a phase 3, double blind, placebo controlled RCT evaluated efficacy of subcutaneous adalimumab in patients within adult patients with active UC (Mayo clinic score between 6 and 12 and Mayo endoscopic subscore of at least 2) despite concurrent treatment with corticosteroids and/or immunomodulators. Initially patients were randomized to receive placebo or adalimumab 160 mg at week 0, 80 mg at week 2 followed by 40 mg at week 4 and 6. Protocol was later amended to include another arm where patients received 80 mg at week 0, 40 mg at week 2, 4 and 6. Whereas, ULTRA 2 trial (n = 518) evaluated efficacy of adalimumab for induction and maintenance phases. Inclusion criteria were similar to that of ULTRA 1 study. Patients were randomly assigned in a 1:1 ratio to receive subcutaneous adalimumab at doses of 160 mg at week 0, 80 mg at week 2 followed by 40 mg alternate week from week 4, or placebo. Outcomes were assessed at week 8 and week 52. Data of only induction phase of ULTRA 2 trial was available for the analysis of present study.

Golimumab

PURSUIT-IV (n = 291) and PURSUIT-SC (n = 1064) were phase 2/3, double blind, dose finding/dose confirming, placebo controlled RCTs that evaluated efficacy of golimumab for induction phase in adult patients with moderate to severely active UC (Mayo score of 6–12 and endoscopic subscore ≥2). In phase 2 of PURSUIT-IV, patients were randomized in 1:1:1:1 ratio to receive a single dose of 1 mg/kg or 2 mg/kg or 4 mg/kg golimumab or placebo intravenously. This was followed by phase 3 in which patients were randomized in 1:1:1 ratio to receive 2 mg/kg or 4 mg/kg golimumab or placebo intravenously. In PURSUIT-SC trial, patients were given subcutaneous golimumab at an initial dose of 100 mg followed by 50 mg (phase 2 only), or 200 mg followed by 100 mg, or 400 mg followed by 200 mg, 2 weeks apart. Outcomes were assessed at week 6 for both studies.

Vedolizumab

Two phase 3, double blind, placebo controlled, RCTs, GEMINI 1 (n = 895) and VISIBLE 1 (n = 216) evaluated efficacy of intravenous vedolizumab and subcutaneous vedolizumab respectively. GEMINI 1 trial assessed vedolizumab efficacy in both induction and maintenance phases. Eligible participants were adults aged between 18 and 80 years, with active ulcerative colitis (Mayo score of 6–12 and endoscopic subscore ≥2) who failed or were intolerant to one or more glucocorticoids, immunomodulators or anti-TNF therapy. In induction phase patients were randomized in 3:2 ratio to receive a dose of 300 mg vedolizumab or placebo intravenously at day 1 and day 15. Patients who had clinical response at week 6 were re-randomized in 1:1:1 ratio to received 300 mg vedolizumab intravenously every 8 weeks or 4 weeks or placebo up to week 52. VISIBLE 1 trial was phase 3, double blind, placebo controlled RCT where patients with moderate to severely UC (Mayo score of 6–12 and endoscopic subscore ≥2) received open label induction therapy with intravenous vedolizumab (300 mg) at week 0, 2 and at week patients with clinical response were randomized in 2:1:1 ratio to subcutaneous vedolizumab (108 mg vedolizumab subcutaneous every 2 weeks along with intravenous placebo every 8 weeks), intravenous vedolizumab (300 mg every 8 weeks along with subcutaneous placebo every 2 weeks), or placebo (subcutaneous placebo every 2 weeks and intravenous placebo every 8 weeks) up to week 52.

Outcomes

The primary outcome was the rate of clinical response according to disease distribution and secondary outcomes were clinical remission, endoscopic improvement, individual symptoms of stool frequency and rectal bleeding for both induction and maintenance trials. Clinical response was defined as a decrease from baseline in total Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the rectal bleeding sub score of at least 1 point or an absolute rectal bleeding sub score of 0 or 1. Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual sub score exceeding 1 point. Endoscopic improvement (termed "mucosal healing" at the time these trials were conducted") was defined as a Mayo endoscopic sub score of 0 or 1.

Ethical approval

Local research ethics review was not required because the data was already previously collected and deidentified data were being used, and no informed consent was required.

Statistical analysis

Appropriate descriptive statistics are presented for demographic and baseline characteristics for both the entire study sample and according to each study treatment arm (active or placebo) according to disease distribution (left-sided disease versus extensive disease). Those studies which reported extensive colitis and

pancolitis separately, data were combined into single category of extensive colitis and compared with left sided colitis.

Binary outcomes such as clinical response, and remission as well as endoscopic improvement were analyzed using the modified Poisson regression to quantify modification of drug effects by disease distribution on the risk ratio (RR) scale.[21] Study-specific estimates and the 95% two-sided confidence intervals were obtained for outcomes of interest (clinical and endoscopic outcomes). To obtain overall estimates and 95% confidence intervals of all studies, we applied the extended modified Poisson regression model[22] with studies being considered as clusters. The model contained main effects of drug, distribution of disease, their product term, and potential confounders available including age, sex, disease duration, concomitant steroid use and prior anti-TNF use. The parameter of interest is the ratio of the RR for left-sided disease to the RR for extensive disease. The values of <1, 1, and >1 indicate that the drug had smaller, equal, and large effects, respectively, for left-sided disease as compared to extensive disease. Continuous outcomes such as the Mayo clinical score (MCS) and its components as well as their changes from baselines were analyzed with mixed-effect model with study as random effect to accounting for potential heterogeneity of study-specific effects. Each model included independent variables including drug, disease distribution, and their interaction, adjusting for available potential confounders. The focus of this analysis is the coefficient estimation for the interaction term, which quantified drug effects modified by disease location. Primary estimates are expressed as the difference between treatment effects on left-sided colitis and that of extensive colitis.

Results are presented as point estimates, 2-sided 95% confidence intervals and associated p values. Statistical significance was claimed when the 2-sided p-value < 0.05. All analyses were done using SAS V9.4 (SAS Institute, Cary, NC, USA).

Role of the funding source

This study did not receive any financial support. All authors had full access to all data in the study and accept responsibility for the decision to submit for publication.

Results

Baseline characteristics of included studies

Baseline characteristics of included studies are presented in Tables 1 and 2. A total of eleven studies (infliximab = 2, adalimumab = 2, golimumab = 2, vedolizumab = 2, tofacitinib = 3)[13–20] were included in the analysis. Among them outcome data for the induction phase were extracted from six studies,[13–15,17,18] for maintenance phase from two[13,20] and for both phases from three studies.[16,19] Induction outcomes were available for all five drugs whereas maintenance outcomes were available for only infliximab, vedolizumab and tofacitinib.

A total of 5450 patients with active UC participated in the included trials combined. The proportion of patients with left-sided colitis ranged from 35% to 60.1% and none of the studies included patients with proctitis. Male participants ranged from 56% to 61.8% and the mean age ranged from 39.7 yrs to 41.4 yrs. Outcome assessment for induction studies was done between 6 and 9 weeks, whereas for maintenance studies it ranged between 30 and 52 weeks. Tofacitinib (OCTAVE) and vedolizumab (GEMINI-I) trials allowed prior anti-TNF exposure (approximately 50%) and studies assessing anti-TNF agents included biologic naïve participants. The definitions of clinical response, clinical remission, and endoscopic improvement outcomes were the same across the included studies. Endoscopic improvement was defined as Mayo endoscopic sub score of 0 or 1 (All outcome definitions are listed in footnotes of tables).

Clinical outcomes at the end of induction phase

Clinical response

On pooled analysis adjusted for age, sex, disease duration, concomitant steroid usage, anti-TNF therapy and treatment arm, all drugs were superior to placebo for induction of clinical response in patients with left-sided colitis and extensive colitis, except adalimumab which was not statistically effective for left-sided colitis (RR 1.20, 95% CI [0.96, 1.50], p = 0.109) but effective for extensive colitis (RR 1.28, 95% CI [1.08, 1.53], p = 0.004) compared to placebo. Adjusting for the potential confounders, the pooled analysis of induction studies comparing efficacy of advanced therapies showed that the effect of tofacitinib was significantly modified by disease distribution, with the effect for patients with extensive colitis larger than that of patients with left-sided disease (the ratio of RRs 0.67, 95% CI [0.45, 0.99], p = 0.049). However, there was no difference in treatment effect for infliximab (ratio of RRs 1.09, 95% CI [0.74, 1.60], p = 0.673). Similarly, there was no difference in treatment effect when left-sided colitis was compared with extensive colitis with all anti-TNF drugs combined or other advanced therapies (Table 3).

Clinical remission

On pooled analysis adjusted for confounding factors, all drugs were superior to placebo in induction of clinical remission for patients with left-sided colitis and extensive colitis, while adalimumab was marginally effective in patients with left-sided colitis (RR 1.71, 95% CI [0.92, 3.15], p = 0.088) and statistically effective in patients with extensive colitis (RR 1.69, 95% CI [1.05, 2.71], p = 0.031). Similar analysis showed that there was statistically significant difference in treatment effect for induction of clinical remission with infliximab favoring

Outcomes	Left sided colitis		Extensive colitis		Ratio of RRs	
	Risk ratio	p value for RR = 1	Risk ratio	p value for RR = 1	Ratio of risk ratios	p-value for effect modification
Tofacitinib [Week 9]						
Clinical response[a] (N = 1074)	1.57 (1.22, 2.02)	<0.001	2.34 (1.74, 3.16)	<0.001	0.67 (0.45, 0.99)	0.049
Clinical remission[b] (N = 1077)	2.08 (1.78, 3.67)	<0.001	6.43 (2.10, 19.71)	<0.001	0.32 (0.09, 1.14)	0.078
Endoscopic improvement[c] (N = 1077)	1.94 (1.29, 2.92)	0.001	2.64 (1.59, 4.40)	<0.001	0.73 (0.38, 1.41)	0.347
Golimumab [week 6]						
Clinical response[a] (N = 1282)	1.30 (1.09, 1.56)	0.004	1.65 (1.30, 2.10)	<0.001	0.79 (0.58, 1.07)	0.120
Clinical remission[b] (N = 1280)	2.25 (1.42, 3.56)	<0.001	2.06 (1.20, 3.54)	0.009	1.09 (0.54, 2.22)	0.811
Endoscopic improvement[c] (N = 1280)	1.25 (1.02, 1.52)	0.031	1.60 (1.22, 2.10)	0.001	0.78 (0.56, 1.09)	0.142
Infliximab [week 8]						
Clinical response[a] (N = 634)	1.61 (1.26, 2.06)	<0.001	1.48 (1.10, 1.99)	0.010	1.09 (0.74, 1.60)	0.673
Clinical remission[b] (N = 633)	1.74 (1.18, 2.55)	0.005	5.29 (2.22, 12.65)	<0.001	0.33 (0.13, 0.85)	0.021
Endoscopic improvement[c] (N = 643)	1.51 (1.22, 1.87)	<0.001	1.58 (1.20, 2.10)	0.001	0.95 (0.67, 1.36)	0.776
Adalimumab [week 8]						
Clinical response[a] (N = 858)	1.20 (0.96, 1.50)	0.109	1.28 (1.08, 1.53)	0.004	0.94 (0.71, 1.24)	0.664
Clinical remission[b] (N = 859)	1.71 (0.92, 3.15)	0.088	1.69 (1.05, 2.71)	0.031	1.01 (0.47, 2.20)	0.980
Endoscopic improvement[c] (N = 859)	1.11 (0.87, 1.41)	0.397	1.23 (1.00, 1.52)	0.050	0.90 (0.65, 1.24)	0.523
Anti-TNFs combined [Weeks 6–8]						
Clinical response[a] (N = 2774)	1.34 (1.19, 1.51)	<0.001	1.42 (1.25, 1.61)	<0.001	0.94 (0.79, 1.12)	0.487
Clinical remission[b] (N = 2772)	1.98 (1.51, 2.60)	<0.001	2.37 (1.73, 3.27)	<0.001	0.84 (0.55, 1.27)	0.414
Endoscopic improvement[c] (N = 2782)	1.28 (1.13, 1.45)	0.001	1.42 (1.24, 1.64)	<0.001	0.90 (0.75, 1.08)	0.257
Vedolizumab [weeks 6]						
Clinical response[a] (N = 860)	3.28 (1.24, 8.69)	0.017	3.21 (1.21, 8.50)	0.019	1.02 (0.26, 4.07)	0.977
Clinical remission[b] (N = 860)	1.44 (0.97, 2.13)	0.070	1.49 (0.97, 2.28)	0.069	0.97 (0.54, 1.73)	0.918
Endoscopic improvement[c] (N = 860)	3.28 (1.24, 8.69)	0.017	3.21 (1.21, 8.50)	0.019	1.02 (0.26, 4.07)	0.977

[a]Decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the rectal bleeding sub score of at least 1 point or an absolute rectal bleeding sub score of 0 or 1. [b]Total Mayo score of 2 points or lower, with no individual sub score exceeding 1 point. [c]Mayo endoscopic sub score of 0 or 1.

Table 3: **Comparative efficacy of pharmacotherapies for induction phase in patients with left sided, extensive colitis and effect modification by disease extend, adjusted for sex, age, disease duration, concomitant corticosteroid use, prior-anti TNF exposure, and treatment arm (pooled analysis).**

extensive colitis (ratio of RRs 0.33, 95% CI [0.13, 0.85], p = 0.020). There was marginal evidence of a difference in treatment effect with tofacitinib (ratio of RRs 0.32, 95% CI [0.09, 1.14], p = 0.078). There was no evidence to show difference in treatment effect when left-sided colitis was compared with extensive colitis with other advanced therapies or with all anti-TNF drugs combined (Table 3).

Mayo clinic symptom sub scores for induction phase

On comparison of treatment effect of drugs on symptom sub scores of MCS between left-sided and extensive colitis, tofacitinib was associated with greater reduction in stool frequency (difference of differences 0.37, 95% CI [0.08, 0.65], p = 0.012), rectal bleeding scores (difference of differences 0.25, 95% CI [0.03, 0.47], p = 0.026), and total Mayo score (difference of differences 1.16, 95% CI [0.34, 1.99], p = 0.006) in patients with extensive colitis compared to left-sided colitis. There was no difference between extensive colitis and left-sided colitis in stool frequency or bleeding scores with other therapies or combined anti-TNF antagonists (Table 4).

Endoscopic outcomes at the end of induction

On pooled analysis adjusted for confounding factors, all drugs were effective for both left-sided colitis and extensive colitis for induction of endoscopic improvement except adalimumab which was not effective for left-sided colitis (RR 1.11, 95% CI [0.87, 1.41], p = 0.397) but there was little evidence to suggest that adalimumab may be effective for extensive colitis (RR 1.23, 95% CI [1.00, 1.52], p = 0.050). On comparison of left-sided versus extensive colitis for difference in treatment effects adjusted confounding factors, there was no statistically significant difference with any of the drugs (Table 3).

Clinical outcomes at the end of maintenance

Maintenance outcome data were available for infliximab,[16] vedolizumab[19,20] and tofacitinib[13] from five trials. On comparison of left-sided and extensive colitis after adjusting for confounding factors, there was no statistically significant difference for induction of clinical response with any of the three drugs. However, for maintenance of clinical remission, there was statistically significant difference with tofacitinib (ratio of RR 0.44,

Outcomes	Left sided colitis		Extensive colitis		Difference of differences	
	Difference of placebo—drug	p value for difference = 0	Difference of placebo—drug	p value for difference = 0	Difference of differences	p-value for difference of differences = 0
Tofacitinib [Week 9]						
Total MCS (N = 1091)	0.92 (0.18, 1.66)	0.015	−0.24 (−0.61, 0.13)	0.204	1.16 (0.34, 1.99)	0.006
Rectal bleeding score (N = 1089)	0.12 (−0.08, 0.32)	0.240	−0.13 (−0.23, −0.03)	0.011	0.25 (0.03, 0.47)	0.026
Stool frequency score (N = 1089)	0.30 (0.05, 0.56)	0.019	−0.07 (−0.19, 0.06)	0.253	0.37 (0.08, 0.65)	0.012
Golimumab [Week 6]						
Total MCS (N = 1280)	0.06 (−0.31, 0.44)	0.751	0.41 (−0.17, 0.99)	0.166	−0.35 (−1.04, 0.34)	0.320
Rectal bleeding score (N = 1286)	−0.05 (−0.16, 0.06)	0.373	0.02 (−0.15, 0.19)	0.818	−0.06 (−0.27, 0.14)	0.575
Stool frequency score (N = 1286)	0.04 (−0.09, 0.17)	0.546	0.18 (−0.02, 0.39)	0.078	−0.15 (−0.39, 0.09)	0.221
Infliximab [Week 8]						
Total MCS (N = 624)	0.20 (−0.59, 0.99)	0.620	0.39 (−0.13, 0.90)	0.142	−0.18 (−1.13, 0.76)	0.710
Rectal bleeding score (N = 634)	−0.16 (−0.38, 0.06)	0.154	0.09 (−0.05, 0.23)	0.208	−0.25 (−0.51, 0.01)	0.059
Stool frequency score (N = 634)	0.25 (−0.02, 0.52)	0.070	0.13 (−0.04, 0.31)	0.134	0.11 (−0.21, 0.44)	0.500
Adalimumab [Week 8]						
Total MCS (N = 859)	0.37 (−0.21, 0.94)	0.211	0.13 (−0.36, 0.63)	0.603	0.23 (−0.52, 0.99)	0.548
Rectal bleeding score (N = 868)	0.03 (−0.16, 0.23)	0.757	−0.05 (−0.22, 0.12)	0.564	0.08 (−0.18, 0.34)	0.546
Stool frequency score (N = 868)	−0.001 (−0.20, 0.20)	0.999	0.05 (−0.13, 0.22)	0.586	−0.05 (−0.31, 0.22)	0.706
Anti-TNFs combined [Weeks 6–8]						
Total MCS (N = 2763)	0.08 (−0.28, 0.44)	0.663	0.15 (−0.11, 0.41)	0.258	−0.07 (−0.52, 0.37)	0.760
Rectal bleeding score (N = 2788)	0.05 (−0.06, 0.16)	0.373	0.09 (0.01, 0.17)	0.027	−0.04 (−0.18, 0.10)	0.575
Stool frequency score (N = 2788)	0.19 (0.06, 0.31)	0.004	0.11 (0.02, 0.20)	0.017	0.08 (−0.08, 0.23)	0.327

Table 4: **Effects of biologics on Mayo clinic subscore for induction phase in patients with left sided, extensive colitis, and effect modification by disease extent, adjusted for sex, age, disease duration, concomitant corticosteroid use, prior-anti TNF exposure, and treatment arm.**

95% CI [0.22, 0.89], p = 0.020) favoring extensive colitis (Table 5).

Mayo clinic sub scores for maintenance phase

On analysis of Mayo clinic sub scores, there was significant difference in stool frequency (difference of differences –0.92, 95% CI [–1.35, –0.49], p < 0.001), bleeding scores (difference of differences –0.74, 95% CI [–1.04, –0.44], p < 0.001) and total Mayo scores (difference of differences –1.87, 95% CI [–3.24, –0.50], p = 0.007) for left-sided colitis when compared to extensive colitis with vedolizumab (GEMNI 1) favoring left-sided colitis. However, similar results were not observed with vedolizumab from VISIBLE 1 study or with infliximab (ACT1 and ACT2) (Table 6).

Endoscopic outcomes at the end of maintenance

On comparing left-sided colitis with extensive colitis for maintenance of endoscopic improvement after adjusting for confounding factors, effect of tofacitinib (OCTAVE sustain) was significantly modified by the disease distribution with effect for patients with extensive colitis larger than that of patients with left sided colitis (ratio of RR 0.55, 95% CI [0.31, 0.98], p = 0.041). Similar observation was noted for infliximab (ACT 1) with effect for patients with extensive colitis larger than left sided colitis (ratio of RR 0.63, 95% CI [0.39, 1.01], p = 0.059). Endoscopic response and remission outcomes were available for only tofacitinib and there was no statistically significant difference when left-sided colitis was compared with extensive colitis for both outcomes.

Discussion

Although one third of patients with left-sided colitis on endoscopy may progress to extensive colitis over their lifetime, the majority of patients have stable disease extent.[2] Generally extensive disease is considered to be associated with greater severity compared to left-sided colitis with increased risk of long-term colectomy and risk of dysplasia.[23] Through access to patient level data and adjustments for important confounders from induction studies, we found that tofacitinib and infliximab exhibited greater effectiveness in patients with extensive colitis compared to those with left-sided colitis. On face value, these findings may be counterintuitive since less extensive disease may seem inherently easier to treat than more extensive disease owing to inflammatory burden. However, several possible explanations should be considered. It is well known that embryological, functional, immunological differences exist between left and right sided colon in healthy humans. A single cell RNA sequencing study showed that there is distinct T helper cell distribution along the colon length, with TH17 cells predominating in cecum and TH1 cells in sigmoid colon in deceased transplant donors.[24] In another study, site-specific patterns of leukocyte

Outcomes	Adjusted					
	Left sided colitis		Extensive colitis		Ratio of RRs	
	Risk ratio	p value for RR = 1	Risk ratio	p value for RR = 1	Ratio of ratios	p-value for effect modification
Tofacitinib (OCTAVE) [Week 53]						
Clinical response[a] (N = 285)	1.15 (0.93, 1.41)	0.188	1.28 (1.04, 1.58)	0.020	0.90 (0.67, 1.21)	0.485
Clinical remission[b] (N = 285)	1.00 (0.72, 1.38)	0.999	2.28 (1.23, 4.23)	0.009	0.44 (0.22, 0.89)	0.020
Endoscopic improvement[c] (N = 285)	1.02 (0.76, 1.37)	0.895	1.85 (1.13, 3.04)	0.014	0.55 (0.31, 0.98)	0.041
Endoscopic remission[d] (N = 285)	1.00 (0.51, 1.98)	0.999	3.67 (0.92, 14.69)	0.065	0.27 (0.06, 1.28)	0.094
Vedolizumab (VISIBLE 1) [week 52]						
Clinical response[a] (N = 147)	1.53 (1.04, 2.27)	0.031	2.40 (1.20, 4.84)	0.013	0.64 (0.29, 1.42)	0.271
Clinical remission[b] (N = 147)	2.29 (1.08, 4.82)	0.031	3.41 (0.91, 12.79)	0.069	0.67 (0.15, 3.07)	0.603
Endoscopic improvement[c] (N = 147)	1.70 (1.00, 2.86)	0.050	3.80 (1.02, 14.10)	0.047	0.45 (0.11, 1.83)	0.266
Infliximab (ACT 1) [week 30]						
Clinical response[a] (N = 253)	1.03 (0.81, 1.30)	0.807	1.12 (0.84, 1.49)	0.440	0.92 (0.63, 1.34)	0.665
Clinical remission[b] (N = 250)	1.32 (0.84, 2.08)	0.230	1.53 (0.89, 2.61)	0.124	0.87 (0.43, 1.75)	0.697
Endoscopic improvement[c] (N = 265)	0.96 (0.74, 1.25)	0.760	1.53 (1.02, 2.26)	0.040	0.63 (0.39, 1.01)	0.059
Infliximab (ACT 2) [week 30]						
Clinical response[a] (N = 248)	1.43 (1.04, 1.97)	0.028	1.09 (0.78, 1.53)	0.614	1.31 (0.82, 2.09)	0.258
Clinical remission[b] (N = 249)	2.31 (1.22, 4.38)	0.010	1.62 (0.67, 3.90)	0.284	1.43 (0.48, 4.24)	0.520
Endoscopic improvement[c] (N = 264)	1.26 (0.94, 1.68)	0.119	0.99 (0.70, 1.42)	0.955	1.26 (0.80, 1.99)	0.320
Vedolizumab (GEMINI 1) [week 52]						
Clinical response[a] (N = 375)	1.55 (1.17, 2.05)	0.002	1.12 (0.88, 1.42)	0.357	1.39 (0.96, 2.01)	0.081
Clinical remission[b] (N = 375)	1.53 (1.04, 2.27)	0.031	1.26 (0.80, 1.99)	0.319	1.21 (0.67, 2.21)	0.531
Endoscopic improvement[c] (N = 375)	1.42 (1.07, 1.89)	0.015	1.22 (0.88, 1.70)	0.233	1.16 (0.75, 1.80)	0.506

[a]Decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the rectal bleeding sub score of at least 1 point or an absolute rectal bleeding sub score of 0 or 1. [b]Total Mayo score of 2 points or lower, with no individual sub score exceeding 1 point. [c]Mayo endoscopic sub score of 0 or 1. [d]Mayo endoscopic sub score of 0.

Table 5: **Comparative efficacy of pharmacotherapies for maintenance phase in patients with left sided, extensive colitis, and effect modification by disease extent, adjusted for sex, age, disease duration, concomitant corticosteroid use, prior-anti TNF exposure, and treatment arm.**

localization were observed with predominantly CD8+ T cells proximal colon, CD4+ T cells in distal colon and increased abundance of both γδT cells and NK cells.[25] These studies indicate that different segments of colon are immunologically different in healthy individuals. Whereas in UC, phenotypic differences in the immune pathways predominantly driving inflammation are poorly explored. Several genetic susceptibility studies have clearly shown that left sided colitis and extensive colitis have association with different HLA susceptibility loci.[26–29] In a study from Spanish group, allelic variant of IKBL gene (inhibitor of KB like gene), (IKBL+738(C), was associated with extensive colitis but not left sided colitis. The IKBL protein regulates the nuclear localization of NFkB, a nuclear factor that stimulates the transcription of TNF and other cytokines.[27] In the largest genotype-phenotype study which included 30,000 patients with IBD genetic susceptibility loci are distinct between extensive and non-extensive colitis.[30] These findings indicate that extensive colitis and left sided colitis are genetically distinct and it is biologically plausible that the immune pathways driving inflammation are also different for patients with different disease distributions thereby the treatment response to different targeted therapies.

In this study, even though pooled analysis indicated the overall effectiveness of all drugs for both left-sided colitis and extensive colitis, treatment with infliximab and tofacitinib demonstrated superiority for extensive colitis for clinical outcomes. These findings could be related to a greater inflammatory disease burden in extensive colitis and the ability of more systemically acting agents to treat this, in comparison to more gut specific agents. There were notable differences among the anti-TNF therapies, where only infliximab exhibited statistically significant differences between left-sided and extensive colitis, while other anti-TNF therapies did not. Although the mechanism of action remains the same, variations in efficacy can be observed among anti-TNF agents. For instance, infliximab is ranked higher than adalimumab for ulcerative colitis on network meta-analysis.[31] A study conducted by Scarozza et al., which assessed the efficacy of vedolizumab, reported superior clinical remission in patients with left-sided colitis compared to those with extensive colitis.[12] These findings align with the observations from our study, since analysis of GEMINI-I study demonstrated that vedolizumab had greater efficacy in left-sided colitis compared to extensive colitis.

Outcomes	Left sided colitis		Extensive colitis		Effect modification	
	Difference of placebo—drug	p value for difference = 0	Difference of placebo—drug	p value for difference = 0	Difference of differences	p-value for difference of differences = 0
Vedolizumab (VISIBLE 1) [Week 52]						
Total MCS (N = 147)	1.67 (−0.44, 3.78)	0.121	−0.31 (−1.42, 0.81)	0.584	1.97 (−0.41, 4.35)	0.105
Rectal bleeding score (N = 159)	0.30 (−0.24, 0.83)	0.276	−0.13 (−0.43, 0.17)	0.396	0.42 (−0.19, 1.04)	0.177
Stool frequency score (N = 159)	0.54 (−0.06, 1, 13)	0.078	−0.16 (−0.49, 0.17)	0.342	0.70 (0.02, 1.37)	0.044
Infliximab (ACT 1) [Week 30]						
Total MCS (N = 250)	−0.20 (−1.10, 0.70)	0.663	0.04 (−1.38, 1.45)	0.956	−0.24 (−1.90, 1.43)	0.777
Rectal bleeding score (N = 257)	−0.06 (−0.28, 0.16)	0.593	−0.33 (−0.67, 0.01)	0.057	0.27 (−0.13, 0.67)	0.186
Stool frequency score \ (N = 257)	−0.07 (−0.37, 0.23)	0.647	0.09 (−0.38, 0.56)	0.707	−0.16 (−0.72, 0.39)	0.575
Infliximab (ACT 2) [Week 30]						
Total MCS (N = 254)	0.93 (0.05, 1.80)	0.038	−0.48 (−1.89, 0.94)	0.505	1.40 (−0.26, 3.07)	0.098
Rectal bleeding score (N = 259)	0.12 (−0.11, 0.35)	0.306	−0.11 (−0.47, 0.24)	0.549	0.24 (−0.19, 0.66)	0.274
Stool frequency score (N = 259)	0.09 (−0.20, 0.39)	0.543	0.04 (−0.42, 0.50)	0.865	0.06 (−0.49, 0.60)	0.831
Vedolizumab (GEMINI-I) [Week 52]						
Total MCS (N = 375)	−0.81 (−2.04, 0.41)	0.197	1.05 (0.42, 1.69)	0.001	−1.87 (−3.24, −0.50)	0.007
Rectal bleeding score (N = 375)	−0.57 (−0.83, −0.30)	<0.001	0.18 (0.04, 0.32)	0.012	−0.74 (−1.04, −0.44)	<0.001
Stool frequency score (N = 375)	−0.60 (−0.98, −0.21)	0.002	0.32 (0.12, 0.52)	0.002	−0.92 (−1.35, −0.49)	<0.001

Table 6: **The effects of biologics in maintenance phase on patient Mayo clinical subscore for patients with left sided disease, patients with extensive colitis, and effect modification by disease extent, adjusted for sex, age, disease duration, concomitant corticosteroid use, prior-anti TNF exposure, and treatment arm.**

The method of outcome measurement may also influence the observed differential efficacy in this study. The Mayo clinic score has been the standard scoring system utilized in clinical trials. While the endoscopic scoring component is objective, the remaining components, including stool frequency, blood in stools, and physician global assessment, are more subjective in nature.[32] Symptoms such as stool frequency and urgency are considered to be primarily influenced by inflammation in the left colon.[33] Consequently, clinical outcomes based on these symptoms could vary according to the extent of colonic involvement. Moreover, we also observed a correlation between the analysis of symptom sub scores and differences in clinical remission and response outcomes. In our analysis, differential efficacy of biologics was not observed for endoscopic outcomes which could be influenced by the standard practice of scoring the worst disease activity. In future studies this could be assessed by comparing cumulative burden of endoscopic disease activity across segments utilizing artificial intelligence-based scoring.

We acknowledge several limitations in our study. First, the original trials were not powered to detect treatment differences according to disease extent and therefore these results should be considered hypothesis generating and require prospective validation. Second, we did not include studies investigating newer biologics targeting IL-23, such as ustekinumab and risankizumab or more recently approved advanced small molecule therapies, including etrasimod which did include a small population of patients with isolated proctitis, since these were not available at the time the project was initiated. These exclusions may limit the comprehensiveness of our findings. Third, the limited availability of data prevented us from conducting a pooled analysis of maintenance studies. Fourth, outcome data were missing for approximately 10% of patients, although this is unlikely to have influenced the overall results given outcome data were available for the majority of participants. Patients randomized to low dose adalimumab in ULTRA1 study were not excluded from our analysis. However, these patients constitute only a small proportion of ULTRA1 and ULTRA2 patients combined, thus we feel it is unlikely that this would have led to a meaningful impact on the results. Finally, the analysis was not adjusted for concomitant immunosuppressants which could be a potential confounding factor. While majority of studies included in our analysis were done in anti-TNF naïve participants, only three included approximately 50% patients with prior anti-TNF exposure (OCTAVE 1 & 2, and GEMINI 1). However, further details on number of failed anti-TNF drugs were not available for analysis. Finally, baseline serological markers which could have influenced the results were not available to adjust.

To the best of our knowledge, this study represents the first comprehensive assessment of treatment efficacy between biological agents and oral small molecules based on disease extent for patients with moderate to severe UC. The findings of our study underscore the possibility of differential efficacy among medical therapies for patients with left-sided colitis and extensive colitis. Whilst these observations might be considered hypothesis generating, the findings warrant further

exploration in forthcoming trials to better inform treatment strategies and even consideration of disease extent as a baseline stratification factor.

Contributors

SK: Data interpretation, writing original draft and review of final manuscript.

CM: Review of final manuscript.

TN: Protocol development, data collection, data analysis, writing original draft and review of final manuscript.

GZ: Study design, data analysis, data interpretation, writing of original draft, and review of final manuscript.

LPB: Review of final manuscript.

SD: Review of final manuscript.

PSD: Review of final manuscript.

NN: Review of final manuscript.

SS: Review of final manuscript.

VJ: Conceptualization, study design, data interpretation, and review of final manuscript.

Data sharing statement

The data of the current study are available from the corresponding author on reasonable request.

Declaration of interests

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