JGH Open An open access journal of gastroenterology and hepatology
Open Access
JGHF Journal of Gastroenterology and Hepatology Foundation
doi:10.1002/jgh3.13056

REVIEW ARTICLE

Etrolizumab as an induction and maintenance therapy for ulcerative colitis: A systematic review and meta-analysis of randomized controlled trials

Othman Saleh,* Mohamed T. Abuelazm,† Islam Mohamed,‡ Alaa Ramadan,§ Mohammad Assaf,* Ahmad Alzoubi,* Majd M. AlBarakat¶ and Basel Abdelazeem‖,**

*Faculty of Medicine, The Hashemite University, Zarqa, ¶Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan, †Faculty of Medicine, Tanta University, Tanta, §Faculty of Medicine, South Valley University, Qena, Egypt, ‡Department of Internal Medicine, University of Missouri, Kansas City, Missouri, ‖Department of Cardiology, West Virginia University, Morgantown, West Virginia and **Department of Medicine, Michigan State University, East Lansing, Michigan, USA

Key words
colon, etrolizumab, inflammatory bowel disease, meta-analysis, review, ulcerative colitis.

Accepted for publication 14 March 2024.

Correspondence
Basel Abdelazeem, Department of Medicine, Michigan State University, East Lansing, MI, USA.
Email: ibrah126@msu.edu

Othman Saleh and Mohamed T. Abuelazm contributed equally to this work.

Declaration of conflict of interest: The authors declare no conflict of interest.

Author contribution: Mohamed T. Abuelazm conceived the idea. Mohamed T. Abuelazm and Othman Saleh designed the research workflow. Mohamed T. Abuelazm and Othman Saleh searched the databases. Mohammad Assaf and Ahmad Alzoubi screened the retrieved records, extracted relevant data, assessed the quality of evidence, and Othman Saleh resolved the conflicts. Alaa Ramadan performed the analysis. Mohammad Assaf, Othman Saleh, and Islam Mohamed wrote the final manuscript. Basel Abdelazeem supervised the project. All authors have read and agreed to the final version of the manuscript.

Abstract

Background and Aim: Etrolizumab is a gut-targeted anti-β7 integrin monoclonal antibody. However, the evidence of etrolizumab efficacy and safety in ulcerative colitis remains inconclusive. Therefore, we aim to evaluate the safety and efficacy of etrolizumab as an induction and maintenance therapy for active moderate to severe ulcerative colitis.

Methods: We synthesized randomized controlled studies (RCTs) from MEDLINE, Scopus, EMBASE, PubMed, Web of Science, and Cochrane Library until April 2023. The risk ratio (RR) for dichotomous outcomes with the corresponding 95% confidence interval (CI) was used. The study protocol was registered in PROSPERO with ID: CRD42023437040.

Results: Five RCTs with 1849 participants were included. The etrolizumab group had a significant clinical response (RR: 1.28 with 95% CI [1.08, 1.51], $P = 0.005$), clinical remission rates during the induction phase (RR: 2.47 with 95% CI [1.48, 4.11], $P = 0.0005$), compared with the placebo group in ulcerative colitis; however, there was no statistically significant difference between the two groups, regarding the corticosteroids-free remission rate (RR: 1.92 with 95% CI [0.94, 3.92], $P = 0.07$). Moreover, endoscopic improvement, endoscopic remission, and histologic remission rates were observed more in the etrolizumab group during both the induction and maintenance phases. For safety outcomes, etrolizumab was significantly safer, but any adverse event was higher in the etrolizumab group than in the placebo.

Conclusion: Etrolizumab shows its effectiveness as both an induction and maintenance therapy for moderate or severe UC. The findings demonstrate its positive impact on clinical, endoscopic, and histologic remission rates. Regarding safety, other than any side effects, etrolizumab showed a good safety than a placebo.

Introduction

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease characterized by chronic or recurrent inflammation of the colon and rectum linings. This inflammation significantly reduces the patient's quality of life, manifested by abdominal pain, diarrhea, rectal bleeding, or fatigue. The exact cause of UC remains unknown, highlighting the complexity of the condition.[1–4]

Various treatment options are available for treating moderate to severe active UC. Corticosteroids such as prednisone and budesonide are commonly used to reduce inflammation and relieve symptoms. However, long-term use is limited due to the possible side effects. Immunosuppressants such as azathioprine and mercaptopurine help regulate the immune response and prevent further damage to intestinal tissue, which are usually used when corticosteroids cannot induce or maintain remission.[5]

Targeted biological agents have revolutionized the treatment of UC. Tumor necrosis factor (TNF) is a pro-inflammatory cytokine involved in the disease process. So, one of the new synthesizing drugs is TNF inhibitors, such as infliximab, adalimumab, and golimumab which work by neutralizing TNF.

Moreover, etrolizumab, a gut-selective integrin antagonist, works to prevent immune cell trafficking and reduce inflammation in the gastrointestinal tract Ustekinumab, another biologic agent, targets interleukin-12 and interleukin-23, which are cytokines implicated in the immune response in UC. Tofacitinib, a Janus kinase (JAK) inhibitor, is an oral medication that inhibits the signaling pathways involved in inflammation.[1,5–7] Despite the availability of these therapeutic options, a significant proportion of patients with UC do not achieve durable clinical remission. This unmet need has prompted the exploration of novel treatment strategies.[1]

Therefore, a new approach involving anti-integrin therapies has gained attention due to their high specificity and favorable safety profile. Etrolizumab, a gut-targeted, anti-integrin biologic, selectively targets both α4β7 and αEβ7 integrins in contrast to vedolizumab, which targets α4β7 integrin only. Even though both vedolizumab and etrolizumab target the α4β7 integrin, Lichnog *et al*., showed that etrolizumab is more effective than vedolizumab in inducing β7 internalization, which suggests better clinical efficacy for etrolizumab.[8] By controlling immune cell trafficking and its inflammatory effects on the gut lining, etrolizumab aims to alleviate the symptoms of UC and induce clinical remission.[7,9,10] Clinical studies have shown promising results for etrolizumab in patients with moderately to severely active UC. In Phase II clinical trial, the induction regimen of etrolizumab was well tolerated and demonstrated significantly higher rates of clinical remission compared with a placebo.[11] In this systematic review and meta-analysis, we aim to evaluate the induction and maintenance efficacy and safety of etrolizumab compared with a placebo in patients with moderate to severe UC.

Methodology

Protocol registration. This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12] and the Cochrane Handbook of Systematic Reviews and Meta-Analysis.[13] The study's protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023437040.

Data sources and search strategy. Five databases (PubMed, Cochrane, WOS, SCOPUS, EMBASE) were systematically searched by O.S. and M.T. until 18 April 2023, without search limits. The search strategy included the following: ("Etrolizumab" OR "rhuMAb β7" OR "anti-β7" OR "PRO145223") AND ("ulcerative colitis" OR "UC" OR "inflammatory bowel disease" OR "IBD") (Table S1, Supporting information).

Eligibility criteria. We used the following PICOS criteria to include population (P): patients with moderately to severely active UC; intervention (I): etrolizumab as induction or maintenance therapy; control (C): placebo; and outcome (O): the primary outcome of this review is clinical remission at the end of treatment duration defined as Mayo clinic score (MCS) less than 2.[14] Secondary outcomes were any adverse event, any serious adverse event, adverse events leading to treatment discontinuation, infections, serious infection, and death. Study design (S) randomized controlled trials (RCTs).

Study selection. Three reviewers (A.Z., M.A., and O.S.) individually screened the titles and abstracts of the retrieved records via (Covidence) online software after excluding duplicates. Then, full-text screening was conducted by the same three reviewers using the previously stated eligibility criteria. Any conflicts were solved via discussion.

Data extraction. Two reviewers (O.S. and M.T.) pilot-tested and drafted an extraction sheet for the following data: summary characteristics (study design, country, center, total participants, etrolizumab dose, frequency of subcutaneous injection dose, treatment duration, remission definition, adjuvant intervention, duration of induction phase, main inclusion criteria, primary outcome, and follow-up duration); baseline characteristics (number of patients in each group, age, sex, body mass index [BMI], duration of disease in years, CRP, fecal calprotectin, MCS, disease extent, and baseline treatments); and efficacy outcomes data (clinical remission, corticosteroids-free remission, endoscopic improvement, clinical response, histologic remission, endoscopic remission, any adverse event [AEs], any serious AEs, infections, serious infections, AEs leading to treatment discontinuation, and death). Two reviewers (A.Z. and M.A.) separately extracted the previously mentioned data. Disagreements were resolved through discussion.

Risk of bias and certainty of evidence. Two independent investigators (M.A. and M.M.) implemented the revised Cochrane Collaboration's tool for assessing the risk of bias in RCTs (ROB 2),[15] considering selection, performance, detection bias, attrition, reporting, and other potential sources of biases. Any disagreement was resolved through discussion or by a third reviewer (O.S.). Furthermore, two independent investigators (M.T. and B.A.) used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to evaluate the quality of the evidence.[16]

Statistical analysis. We performed the meta-analysis using Revman software version 5.4[17] to pool dichotomous outcomes using risk ratio (RR) and continuous outcomes using mean difference (MD), along with the corresponding 95% confidence interval (CI). We conducted pooled analysis using the random-effects model. In case of significant heterogeneity, the random-effects model was implemented. We evaluated heterogeneity using the chi-square test, and it was measured by the I^2 test. On an alpha level below 0.1, the chi-square test was considered significant, and heterogeneity was considered significant if the I^2 was >50%. To investigate the source of heterogeneity, sensitivity analysis was conducted by excluding one study at a time and rerunning the analysis. Finally, we did not investigate publication bias using funnel plots, as we included less than 10 RCTs.[18]

Results

Search results and study selection. Our search yielded 821 results across the different databases, with 608 records

remaining for abstract screening after omitting 213 duplicates. After screening abstracts and titles, 587 records were excluded, leaving 21 studies retrieved for full-text review. Of them, 16 were excluded and five were included in our review. The flow diagram records search and selection are depicted in Figure 1.

Characteristics of included studies. The summary characteristics of the five included studies are presented in Table 1. Three studies used etrolizumab as an induction therapy,[11,19] one as a maintenance therapy,[20] and another as an induction and maintenance therapy.[11] A total of 1208 patients (males = 859) were enrolled, with a mean age of 39.7 years old (SD = 13.6). Characteristics of the studies' participants are presented in Table 2.

Three trials revealed that most of the etrolizumab group received 5-aminosalicylic acid (5-ASA) and corticosteroids[19,20] as baseline therapies. Additionally, three studies[11,19] demonstrate that the majority of etrolizumab patients were taking both corticosteroids and immunosuppressants. Baseline treatments of the studies' participants are present in Table S2.

Risk of bias and quality of evidence. All five RCTs[19–21] exhibited a low overall risk of bias, indicating a high level of methodological rigor. The detailed risk of bias assessment is available in Figure 2. These reliable findings reinforce the validity of the studies and support evidence-based practice.

Efficacy outcomes. Etrolizumab was significantly associated with increased clinical response (RR: 1.28 with 95% CI [1.08, 1.51], $P = 0.005$) (moderate-quality evidence) (Fig. 3a, Table 3) and clinical remission rates during the induction phase (RR: 2.47 with 95% CI [1.48, 4.11], $P = 0.0005$) (high-quality evidence), but not during the maintenance phase (RR: 1.31 with 95% CI [0.93, 1.85], $P = 0.12$) (moderate-quality evidence) (Fig. 3b, Table 3). Etrolizumab was associated with increased endoscopic improvement rate during both inductions (RR: 1.44 with 95% CI [1.14, 1.83], $P = 0.003$) and maintenance phases (RR: 1.69 with 95% CI [1.24, 2.30], $P = 0.0008$) (moderate-quality evidence) (Fig. 4a, Table 3). Also, etrolizumab was associated with increased endoscopic remission rate during both induction (RR: 2.21 with 95% CI [1.41, 3.47], $P = 0.0005$) and maintenance phases (RR:

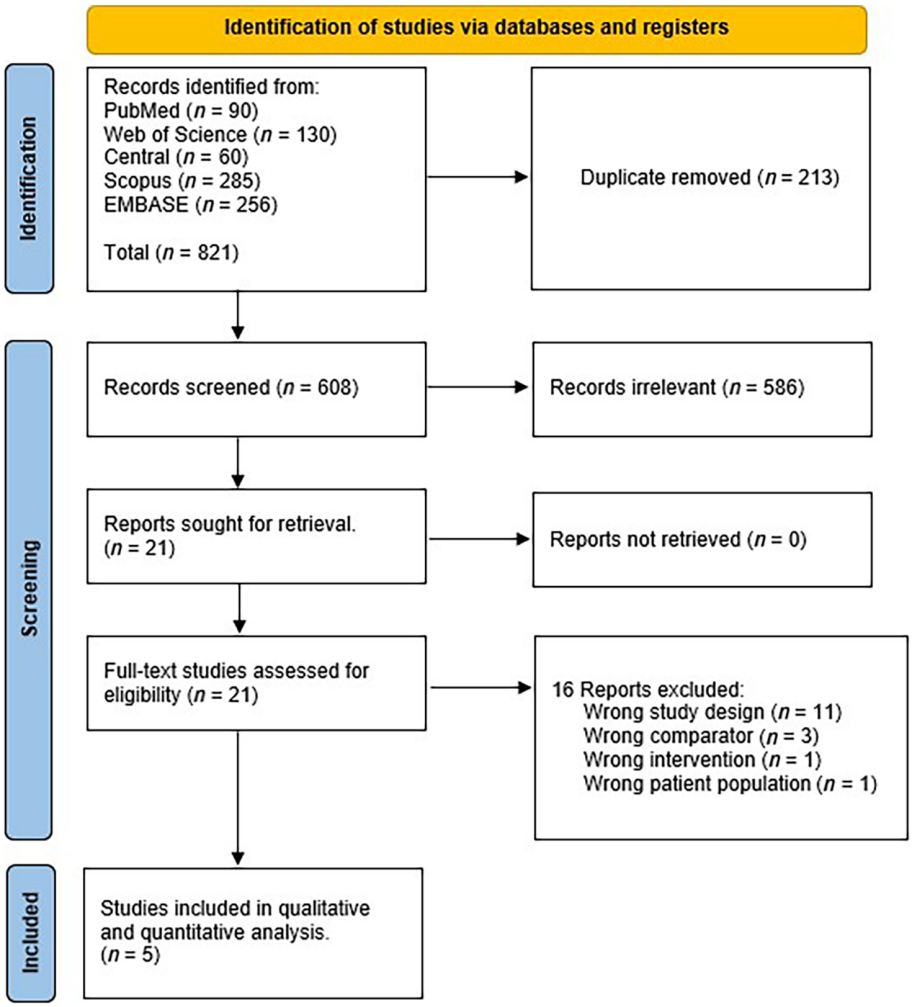


Figure 1 PRISMA flowchart of the screening process.

Table 1 Summary characteristics of the included RCTs

Study ID	Study design	Total participants	Ertolizumab intervention			Main inclusion criteria	Primary endpoint	Induction or maintenance	Follow-up duration
			Dose	Frequency of administration	Duration				
Vermeire et al. (2014)	Double-blinded, multicenter phase 2 RCT, study	124	100 mg	Q4W	10 weeks	Adult (18–75 years) patients with MCS of ≥5 (or ≥6 in USA); and disease extending 25 cm or more from anal verge	Clinical remission at week 10, defined as MCS of ≤2 (with no individual subscore of >1)	Induction	28 weeks
Vermeire et al. (2021) (LAUREL)	Double-blinded, phase 3 RCT, study	359	105 mg	Q4W	62 weeks	Patients between 18 and 80 years old who are diagnosed with moderate-to-severe UC with an MCS of 6–12	Adult (age 18–80 years) patients with moderately to severely active UC (MCS of 6–12 with an endoscopic subscore of ≥2, a rectal bleeding subscore of ≥1, and a stool frequency subscore of ≥1) who were naive to TNF inhibitors	Maintenance	62 weeks
Peyrin-Biroulet et al. (2021) (HICKORY)—induction	Double-blinded, phase 3 RCT, study	609	105 mg	Q4W	66 weeks	Adult (18–80 years) patients with moderately to severely active UC (MCS of 6–12 with an endoscopic subscore of ≥2, a rectal bleeding subscore of ≥1, and a stool frequency subscore of ≥1) previously treated with TNF inhibitors	Remission (MCS ≤2, with individual subscores of ≤1 and a rectal bleeding subscore of 0) at week 14, and remission at week 66 among patients with a clinical response (MCS with ≥3-point decrease and ≥30% reduction from baseline, plus ≥1 point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1) at week 14	Both	78 weeks
Peyrin-Biroulet et al. (2021) (HICKORY)—maintenance	Double-blinded, phase 3 RCT, study	259	105 mg	Q4W	52 weeks	Adult (18–80 years) with moderately to severely active UC (MCS of 6–12 with an subscore of ≥2, a rectal bleeding subscore of ≥1, and a	Remission at week 66 among patients with clinical response (MCS with ≥3-point decrease and ≥30% reduction from baseline, plus ≥1	Both	78 weeks

(*Continues*)

Table 1 (Continued)

Study ID	Study design	Total participants	Ertolizumab intervention			Main inclusion criteria	Primary endpoint	Induction or maintenance	Follow-up duration
			Dose	Frequency of administration	Duration				
						stool frequency subscore of ≥1) previously treated with TNF inhibitors	point decrease in bleeding subscore or absolute rectal bleeding score of 0 or 1) at week 14		
Rubin et al. (2021) (HIBISCUS I)	Double-blinded, phase 3 RCT, study	358	105 mg	Q4W	14 weeks	Adult (18–80 years) patients with moderately to severely active UC (MCS of 6–12 with an endoscopic subscore of ≥2, a rectal bleeding subscore of ≥1, and a stool frequency subscore of ≥1) who were naive to TNF inhibitors	Induction of remission at week 10 (MCS of ≤2, with individual subscores of ≤1, and rectal bleeding subscores of 0) with etrolizumab compared with placebo	Induction	26 weeks
Rubin et al. (2021) (HIBISCUS II)	Double-blinded, phase 3 RCT, study	358	105 mg	Q4W	14 weeks	Adult (18–80 years) patients with moderately to severely active UC (MCS of 6–12 with an endoscopic subscore of ≥2, a rectal bleeding subscore of ≥1, and a stool frequency subscore of ≥1) who were naive to TNF inhibitors	Induction of remission at week 10 (MCS of ≤2, with individual subscores of ≤1, and rectal bleeding subscore of 0) with etrolizumab compared with placebo	Induction	26 weeks

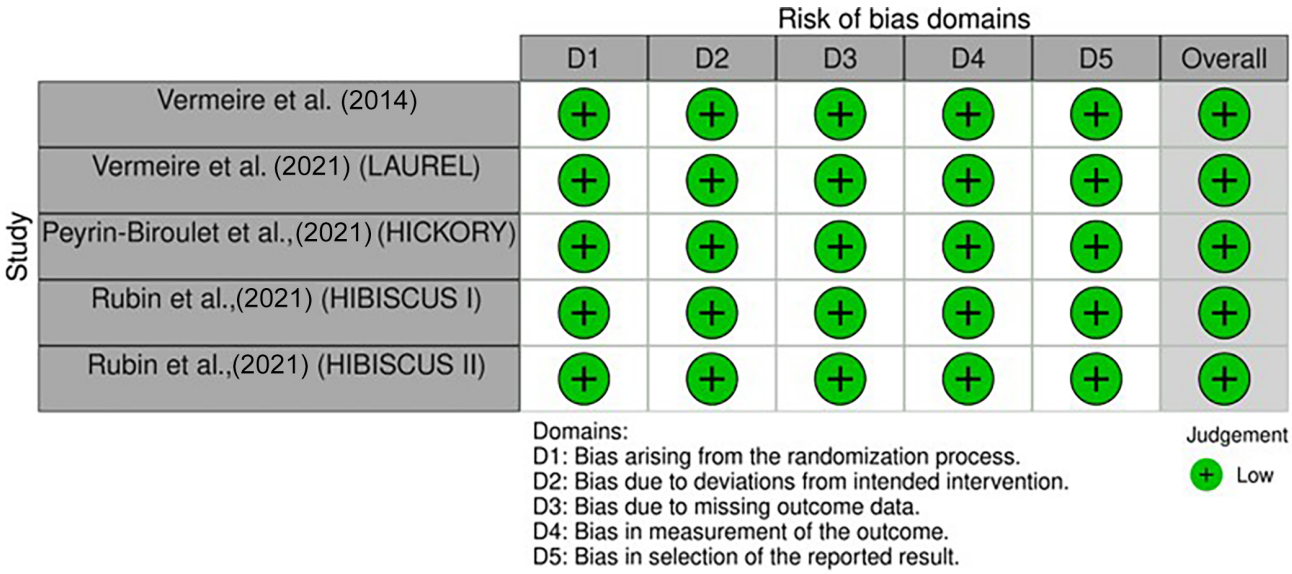
MCS, Mayo Clinic score; Q4W, every 4 weeks; RCT, randomized controlled trial; TNF, tumor necrosis factor; US, ulcerative colitis.

Table 2 baseline characteristics of the participants

	Age (years), mean (SD)		Gender (male), *n* (%)		BMI, mean (SD)		Disease duration in years, mean (SD)		Fecal calprotectin, mean (SD)	
Study	Etrolizumab	Placebo	Etrolizumab	Placebo	Etrolizumab	Placebo	Etrolizumab	Placebo	Etrolizumab	Placebo
Vermeire et al. (2014)	44.4 (13.9)	37.5 (12.8)	28 (68%)	37.5 (12.8)	NR	NR	9.2 (8.3)	9.8 (8.4)	1547.0 (1808.5)	1087.8 (1118.1)
Vermeire et al. (2021) (LAUREL)	36 (14.75)	38 (12.75)	60 (56%)	52 (49%)	24 (16.75)	25 (7.75)	5.4 (10.85)	5.9 (10.025)	814 (301.5)	1517 (578.25)
Peyrin-Biroulet et al. (2021) (HICKORY) (Induction)	40.7 (13.3)	38.8 (13.9)	224 (58%)	54 (57%)	24.3 (11.9)	24.4 (7.6750)	7.1 (10.85)	"7.36 (10.025)"	"1675.5 (802.875)"	"1634 (588)"
Peyrin-Biroulet et al. (2021) (HICKORY) (maintenance)	—	40.0 (12.9)	60 (51%)	72 (63%)	25.1 (11.5)	24.6 (5.425)	7.19 (10.77)	7.85 (10.05)	1620.667 (1665.601)	"1942 (1988.794)"
Rubin et al. (2021) (HIBISCUS I)	40.1 (13.4)	38.4 (13.3)	74 (51.4%)	39 (54.2%)	22.7 (4.65)	23.2 (6.25)	3.4 (10.375)	4.7 (10.125)	1776 (1957.501)	1544.333 (2150.723)
Rubin et al. (2021) (HIBISCUS II)	41.1 (14.4)	40.3 (12.5)	84 (58.7%)	38 (52.8%)	25 (8.125)	23.7 (7.225)	3.6 (14.625)	4 (6.275)	1768.333 (1815.968)	1498 (1365.479)

	MCS, mean (SD)		CRP, mean (SD)		Disease extent, *n* (%)					
					Left-sided colitis (%)		Extensive colitis *n* (%)		Pancolitis *n* (%)	
Study	Etrolizumab	Placebo	Etrolizumab	Placebo	Etrolizumab	Placebo	Etrolizumab	Placebo	Etrolizumab	Placebo
Vermeire et al. (2014)	9.3 (1.5)	9.1 (1.9)	1.4 (2.4)	1.4 (1.9)	14 (34)	17 (40)	15 (37)	13 (30)	NR	NR
Vermeire et al. (2021) (LAUREL)	8.48 (1.36)	8.62 (1.44)	2.57 (1.805)	3.92 (1.988)	62 (57%)	65 (61%)	14 (13%)	12 (11%)	32 (30%)	29 (27%)
Peyrin-Biroulet et al. (2021) (HICKORY) (Induction)	8.95 (1.61)	9.02 (1.51)	4.93 (2.755)	6.4 (2.9)	197/383 (51%)	47 (50%)	53/383 (14%)	13 (14%)	133/383 (35%)	35 (37%)
Peyrin-Biroulet et al. (2021) (HICKORY) (maintenance)	8.75 (1.58)	8.90 (1.67)	4.877 (5.787)	5.713 (7.388)	63/116 (54%)	56 (49%)	16/116 (14%)	15 (13%)	37/116 (32%)	44 (38%)
Rubin et al. (2021) (HIBISCUS I)	8.9 (1.3)	8.7 (1.6)	4.4 (6.066)	4.433 (6.203)	89 (62%)	44 (61%)	22 (15%)	10 (14%)	33 (23%)	18 (25%)
Rubin et al. (2021) (HIBISCUS II)	8.8 (1.4)	8.8 (1.6)	5.367 (6.515)	4.34 (6.339)	86 (60%)	48 (67%)	11 (8%)	7 (10%)	46 (32%)	17 (24%)

BMI, body mass index; CRP, C-reactive protein; MCS, Mayo Clinic score.



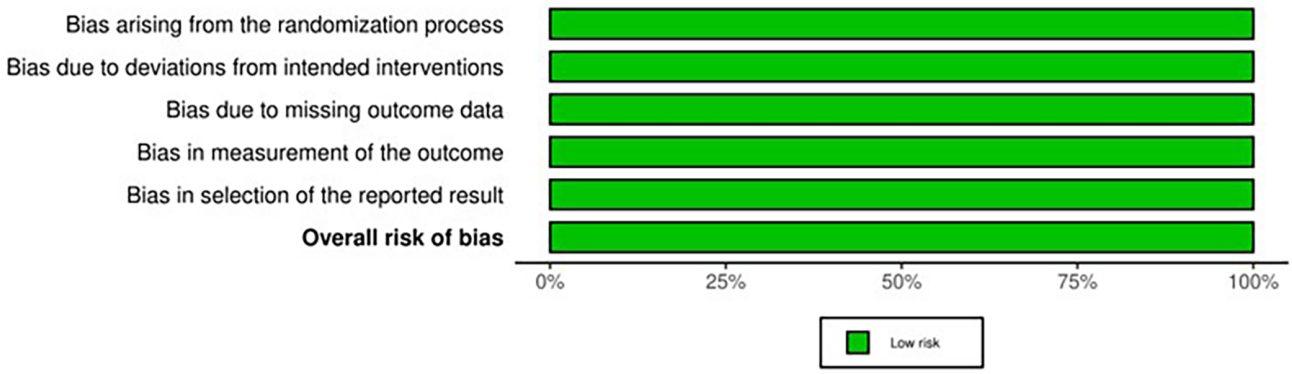


Figure 2 Quality assessment of the risk of bias in the included trials.

1.92 with 95% CI [1.29, 2.85], $P = 0.001$) (moderate-quality evidence) (Fig. 4b, Table 3). Etrolizumab was associated with increased histologic remission rate during both induction (RR: 1.60 with 95% CI [1.01, 2.52], $P = 0.05$) and maintenance phases (RR: 2.04 with 95% CI [1.40, 2.98], $P = 0.0002$) (moderate-quality evidence) (Fig. 5a, Table 3). Finally, there was no difference between etrolizumab and placebo regarding corticosteroid-free remission rate (RR: 1.92 with 95% CI [0.94, 3.92], $P = 0.07$) (Very low-quality evidence) (Fig. 5b, Table 3).

Studies were homogenous in clinical response ($P = 0.66$, $I^2 = 0\%$), clinical remission ($P = 0.13$, $I^2 = 42\%$), endoscopic improvement ($P = 0.60$, $I^2 = 0\%$), endoscopic remission ($P = 0.89$, $I^2 = 0\%$), histologic remission ($P = 0.19$, $I^2 = 35\%$), and corticosteroids-free remission ($P = 0.69$, $I^2 = 0\%$).

Safety outcomes. Any AEs were higher in the etrolizumab group than in the placebo group (RR: 0.90 with 95% CI [0.83, 0.98], $P = 0.01$) (high-quality evidence); however, there was no difference between etrolizumab and placebo regarding any serious AEs (RR: 1.10 with 95% CI [0.72, 1.67], $P = 0.66$) (low-quality evidence), any infection (RR: 0.94 with 95% CI [0.79, 1.13], $P = 0.53$) (moderate-quality evidence), serious infections (RR: 0.82 with 95% CI [0.36, 1.84], $P = 0.63$) (low-quality evidence), AEs leading to drug discontinuation (RR: 0.98 with 95% CI [0.57, 1.69], $P = 0.95$) (Low-quality evidence), and death (RR: 0.87 with 95% CI [0.34, 2.27], $P = 0.78$) (low-quality evidence) (Fig. 6, Table 3).

Studies were homogenous in safety ($P = 0.99$, $I^2 = 0\%$), any AE ($P = 0.66$, $I^2 = 0\%$), any serious adverse events ($P = 0.87$, $I^2 = 0\%$), any infection ($P = 0.94$, $I^2 = 0\%$), serious infections ($P = 0.90$, $I^2 = 0\%$), adverse events leading to drug discontinuation ($P = 0.25$, $I^2 = 26\%$), and death ($P = 0.86$, $I^2 = 0\%$).

Discussion

To the best of our knowledge, this meta-analysis is the first in the literature to comprehensively examine the efficacy of

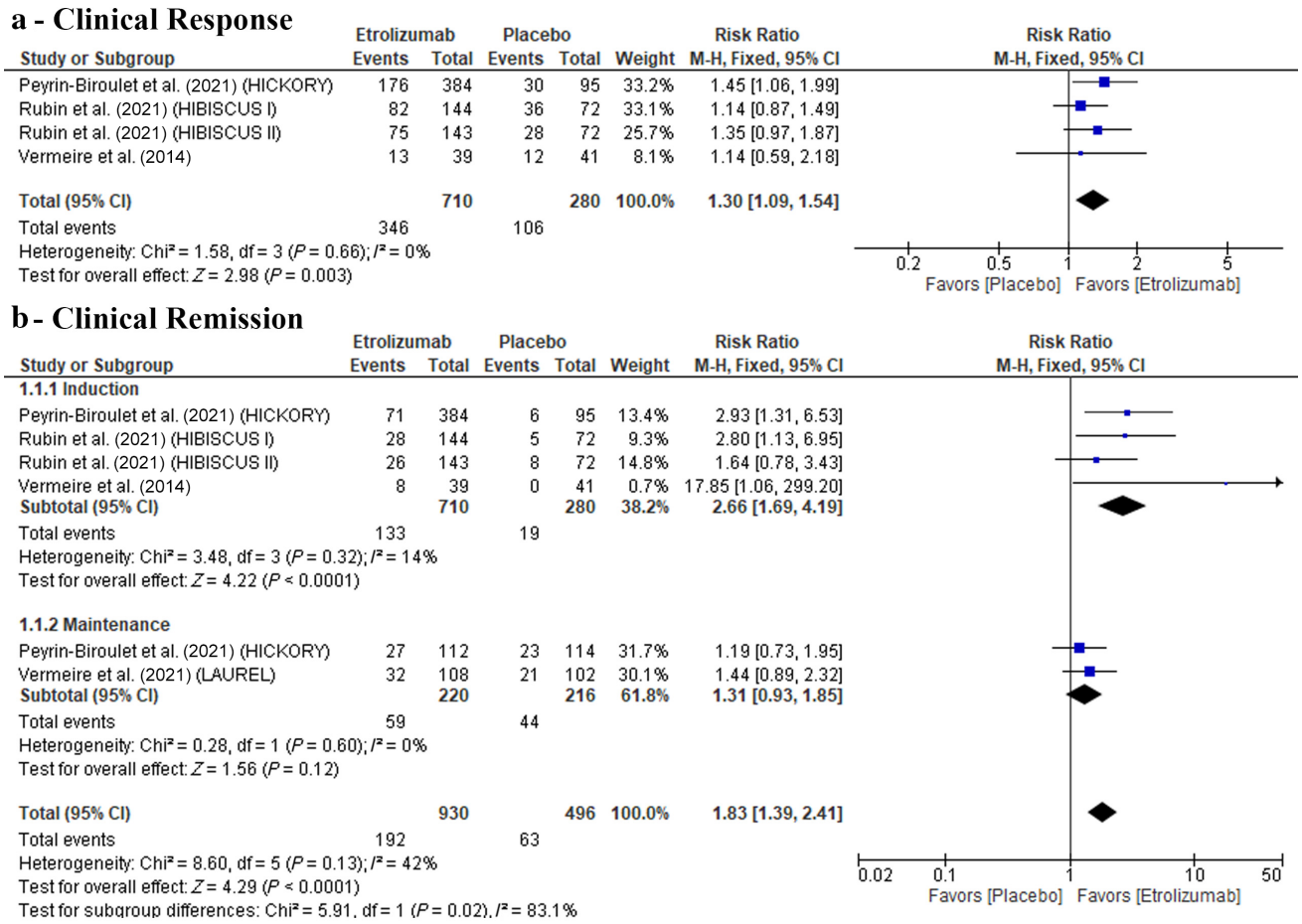


Figure 3 Forest plot of the efficacy outcomes (a—clinical response, b—clinical remission). CI, confidence interval; RR, risk ratio.

etrolizumab as an induction and maintenance therapy for active UC. Our results showed that etrolizumab was associated with increased clinical response, endoscopic improvement, endoscopic remission, and histologic remission rates during both the induction and maintenance phases, while improvement in clinical remission rates was observed during the induction phase only. However, there was no significant difference in corticosteroid-free remission rates compared with placebo. In terms of safety, etrolizumab had a lower risk of adverse events compared with placebo, and there was no significant difference in serious adverse events, infections, adverse events leading to drug discontinuation, and death.

Available treatments. To tailor treatment for patients with UC, an initial assessment of disease severity is essential at the time of diagnosis. This evaluation can be done using the MCS or the Montreal classification.[22,23] This helps determine the disease's severity at its onset and aids in monitoring disease progression in response to various therapies. The current treatment options for moderate to severe UC include corticosteroids, immunosuppressants, and targeted therapies such as tumor necrosis factor inhibitors (anti-TNFs), vedolizumab, ustekinumab, and tofacitinib.[24,25] However, despite the availability of these treatment options, many patients do not achieve a sustained response to these therapies.[26] Therefore, there is a need for targeted therapies that have a favorable safety profile and the ability to induce remission and prevent long-term complications. Anti-integrin therapies have been developed as potential treatment options for patients with UC due to their high selectivity and minimal side effects.[27] One such therapy is etrolizumab, which is a gut-targeted, anti-integrin, biological therapeutic.

Clinical response and remission. Etrolizumab showed increased clinical response and clinical remission rates during the induction phase, suggesting that etrolizumab effectively induces a positive response and remission in patients with UC. These results align with previous studies that have shown the therapeutic potential of etrolizumab in managing moderate to severe UC symptoms[28,29] The significant associations observed in this meta-analysis provide robust evidence supporting the efficacy of etrolizumab in achieving favorable clinical outcomes. These positive clinical outcomes align with improved medication compliance, as patients are more likely to adhere to their prescribed treatment regimens when they experience favorable clinical improvement.[30]

Table 3 GRADE evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With (comparison)	With (intervention)	Relative effect (95% CI)	Risk with (comparison)	Risk difference with (intervention)
Clinical response											
990 (4 RCTs)	Not serious	Not serious	Not serious	Serious[†]	None	⨁⨁⨁◯ Moderate	106/280 (37.9%)	346/710 (48.7%)	RR 1.30 (1.09 to 1.54)	379 per 1000	114 more per 1000 (from 34 more to 204 more)
Clinical remission—induction											
990 (4 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ High	19/280 (6.8%)	133/710 (18.7%)	RR 2.66 (1.69–4.19)	68 per 1000	113 more per 1000 (from 47 more to 216 more)
Clinical remission—maintenance											
436 (2 RCTs)	Not serious	Not serious	Not serious	Serious[†]	None	⨁⨁⨁◯ Moderate	44/216 (20.4%)	59/220 (26.8%)	RR 1.31 (0.93–1.85)	204 per 1000	63 more per 1000 (from 14 fewer to 173 more)
Endoscopic improvement—induction											
990 (4 RCTs)	Not serious	Not serious	Not serious	Serious[†]	None	⨁⨁⨁◯ Moderate	62/280 (22.1%)	247/710 (34.8%)	RR 1.48 (1.17–1.87)	221 per 1000	106 more per 1000 (from 38 more to 193 more)
Endoscopic improvement—maintenance											
436 (2 RCTs)	Not serious	Not serious	Not serious	Serious[†]	None	⨁⨁⨁◯ Moderate	47/216 (21.8%)	81/220 (36.8%)	RR 1.69 (1.24–2.30)	218 per 1000	150 more per 1000 (from 52 more to 283 more)
Endoscopic remission—induction											
910 (3 RCTs)	Not serious	Not serious	Not serious	Serious[‡]	None	⨁⨁⨁◯ Moderate	20/239 (8.4%)	124/671 (18.5%)	RR 2.23 (1.43–3.49)	84 per 1000	103 more per 1000 (from 36 more to 208 more)
Endoscopic remission—maintenance											
436 (2 RCTs)	Not serious	Not serious	Not serious	Serious[‡]	None	⨁⨁⨁◯ Moderate	30/216 (13.9%)	59/220 (26.8%)	RR 1.92 (1.29–2.85)	139 per 1000	128 more per 1000 (from 40 more to 257 more)
Histologic remission—induction											
742 (3 RCTs)	Not serious	Not serious	Not serious	Serious[†]	None	⨁⨁⨁◯ Moderate	43/204 (21.1%)	176/538 (32.7%)	RR 1.57 (1.17–2.10)	211 per 1000	120 more per 1000 (from 36 more to 232 more)
Histologic remission—maintenance											
346 (2 RCTs)	Not serious	Not serious	Not serious	Serious[‡]	None	⨁⨁⨁◯ Moderate	30/170 (17.6%)	64/176 (36.4%)	RR 2.04 (1.40–2.98)	176 per 1000	184 more per 1000 (from 71 more to 349 more)
Corticosteroids-free remission											
214 (2 RCTs)	Not serious	Not serious	Not serious	Extremely serious[§]	None	⨁◯◯◯ Very low	10/105 (9.5%)	20/109 (18.3%)	RR 1.94 (0.95–3.94)	95 per 1000	90 more per 1000 (from 5 fewer to 280 more)
Safety—any adverse event											
1430 (5 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ High	332/498 (66.7%)	559/932 (60.0%)	RR 0.90 (0.83–0.98)	667 per 1000	67 fewer per 1000 (from 113 fewer to 13 fewer)
Safety—any serious adverse event											
1430 (5 RCTs)	Not serious	Not serious	Not serious	Very serious[§]	None	⨁⨁◯◯ Low	32/498 (6.4%)	61/932 (6.5%)	RR 1.10 (0.72–1.67)	64 per 1000	6 more per 1000 (from 18 fewer to 43 more)

(*Continues*)

Table 3 (Continued)

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With (comparison)	With (intervention)	Relative effect (95% CI)	Risk with (comparison)	Risk difference with (intervention)
Safety—any infection											
1346 (4 RCTs)	Not serious	Not serious	Not serious	Serious[‡]	None	⨁⨁⨁◯ Moderate	127/455 (27.9%)	233/891 (26.2%)	RR 0.94 (0.79–1.13)	279 per 1000	17 fewer per 1000 (from 59 fewer to 36 more)
Safety—serious infections											
1430 (5 RCTs)	Not serious	Not serious	Not serious	Very serious[§]	None	⨁⨁◯◯ Low	9/498 (1.8%)	14/932 (1.5%)	RR 0.82 (0.36–1.84)	18 per 1000	3 fewer per 1000 (from 12 fewer to 15 more)
Safety—adverse events leading to drug discontinuation											
1489 (4 RCTs)	Not serious	Not serious	Not serious	Very serious[§]	None	⨁⨁◯◯ Low	20/598 (3.3%)	33/891 (3.7%)	RR 0.98 (0.57–1.69)	33 per 1000	1 fewer per 1000 (from 14 fewer to 23 more)
Safety—death											
1430 (5 RCTs)	Not serious	Not serious	Not serious	Very serious[§]	None	⨁⨁◯◯ Low	7/498 (1.4%)	7/932 (0.8%)	RR 0.87 (0.34–2.27)	14 per 1000	2 fewer per 1000 (from 9 fewer to 18 more)

[†]Confidence interval does not exclude the risk of appreciable benefit/harm.

[‡]The number of events is less than 300 event.

[§]Confidence interval does not exclude the risk of appreciable benefit/harm and the number of events is less than 300 event.

CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio.

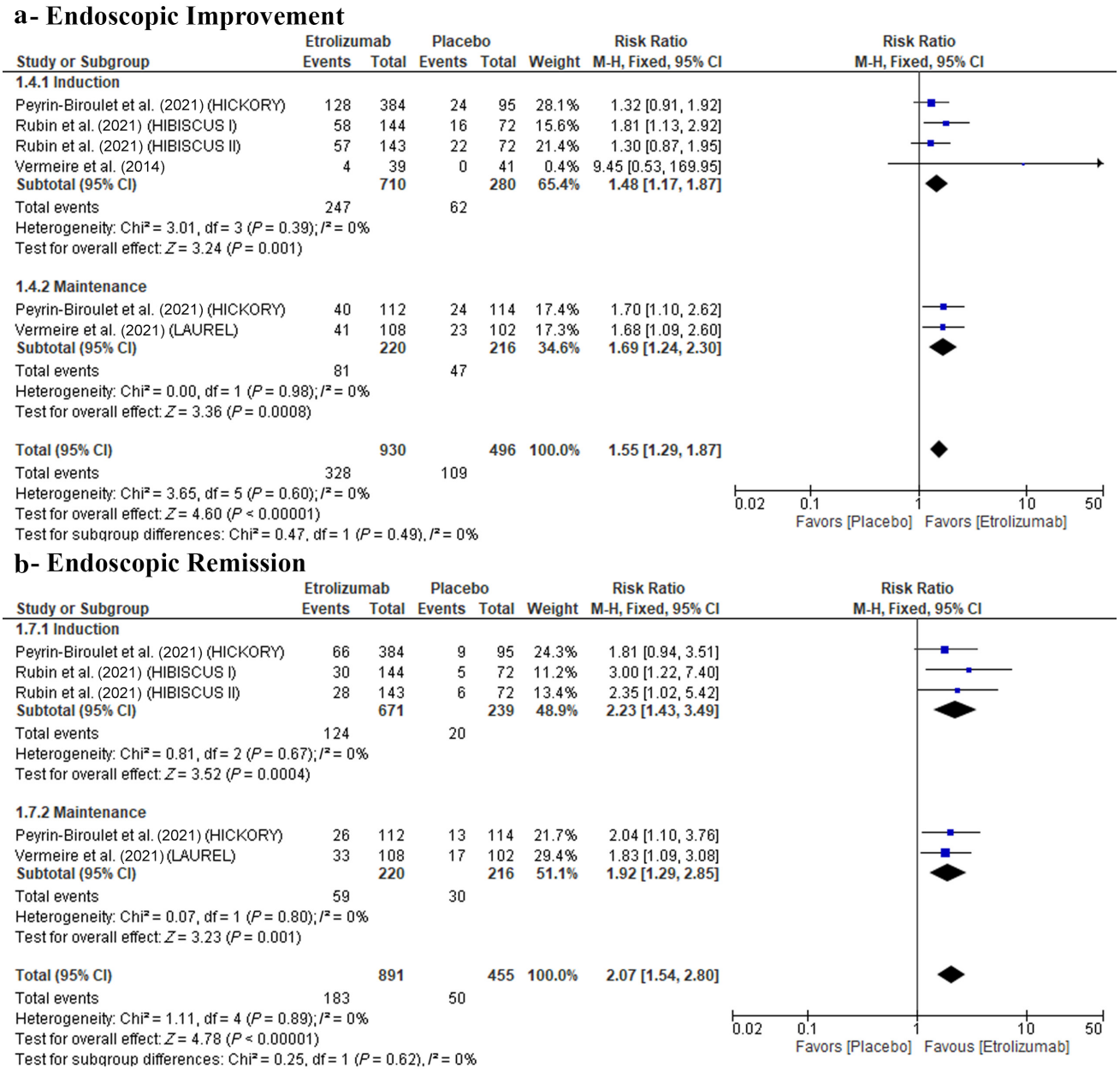


Figure 4 Forest plot of the efficacy outcomes (a—Endoscopic improvement, b—Endoscopic remission). CI, confidence interval; RR, risk ratio.

Endoscopic improvement and remission. Achieving endoscopic improvement and remission are crucial in the treatment of UC, as they signify the restoration of mucosal health and enhanced disease management.[31] Endoscopic improvement has demonstrated associations with decreased risks of relapse, hospitalization, dysplasia, cancer, and the necessity for colectomy.[32–36] 36 The significance of endoscopic improvement as a treatment objective has been underscored by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative initiated by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD).[37] The outcomes of this study provide valuable insights by demonstrating that etrolizumab is significantly associated with increased rates of endoscopic improvement and remission, both during the induction and maintenance phases. These findings highlight the effectiveness of etrolizumab in targeting the underlying inflammatory mechanisms implicated in the development of UC.[38] By effectively modulating these processes, etrolizumab promotes mucosal healing and facilitates long-term remission of the disease.

Histologic remission. Histologic remission, which evaluates the microscopic healing of the colonic mucosa, serves as a vital measure of treatment success in UC.[39] Recent studies have shown that, in UC patients, achieving histological healing

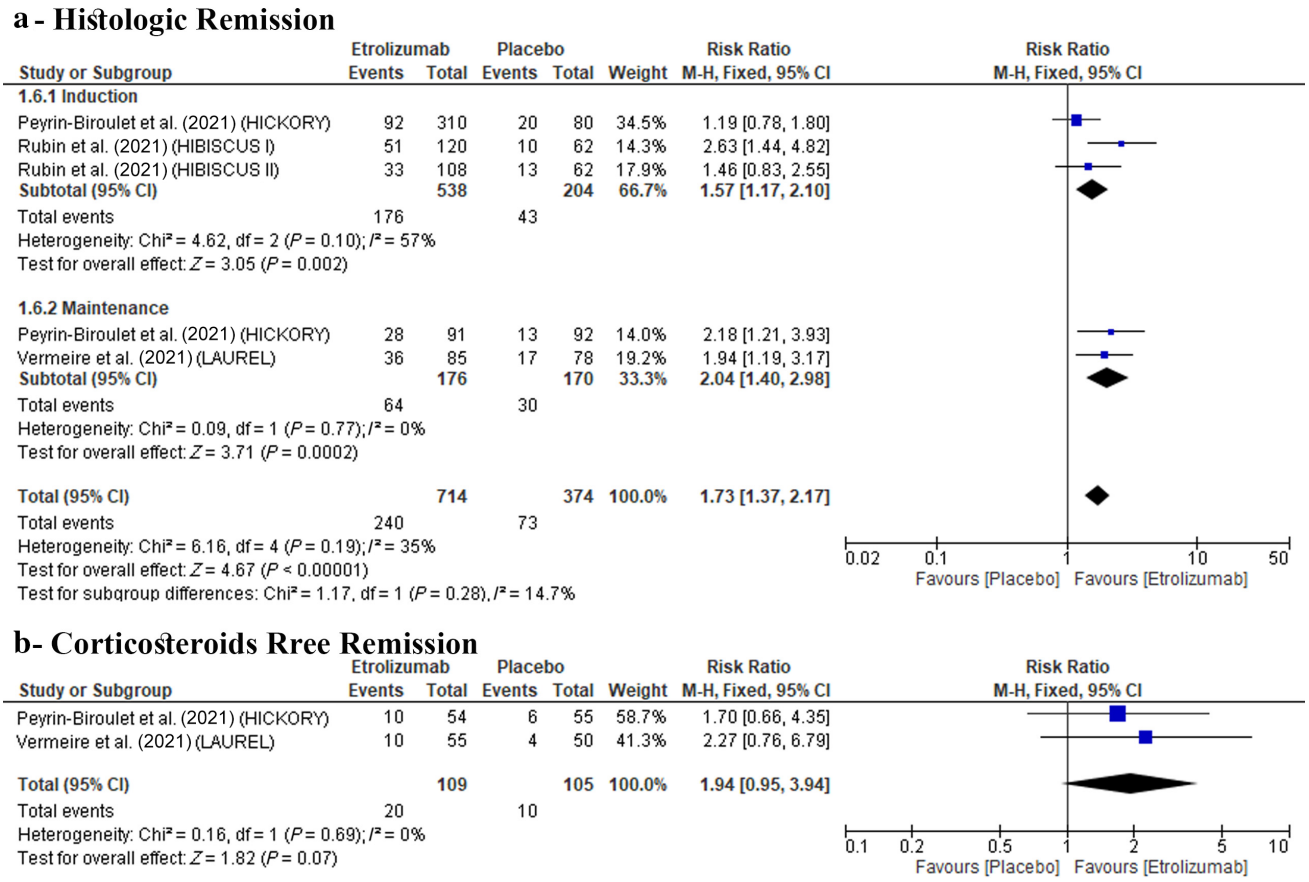


Figure 5 Forest plot of the efficacy outcomes (a—Histologic remission, b—Corticosteroids-free remission). CI, confidence interval; RR, risk ratio.

(healing at a microscopic level) in addition to endoscopic mucosal healing (healing visible during endoscopy) can lead to better outcomes. Histological inflammation in UC increases the risk of colorectal neoplasia (abnormal tissue growth),[40,41] while histological healing can prevent clinical relapses, reduce the use of steroids, and lower hospitalization rates.[42,43] Notably, even when UC patients achieve endoscopic mucosal healing, nearly 40% of them still have ongoing microscopic inflammation.[44] Our results establish a significant association between the use of etrolizumab and increased rates of histologic remission during both the induction and maintenance phases. These results signify the comprehensive therapeutic impact of etrolizumab, as it not only improves clinical and endoscopic outcomes but also plays a crucial role in resolving microscopic inflammation.

Corticosteroid-free remission rates. A fundamental treatment objective in managing UC is to achieve and subsequently maintain clinical remission without the need for corticosteroids. This strategy permits short-term corticosteroid use, mitigating safety concerns associated with their prolonged usage.[45,46] Our analysis of corticosteroid remission included just two eligible studies. Our findings revealed an improvement in steroid clinical remission rates compared with a placebo, with a relative risk (RR) of 1.94 (95% CI: 0.95–3.94). However, the pooled *P* value was 0.07, indicating no statistical significance. This suggests that etrolizumab demonstrates a trend toward clinical remission without the need for corticosteroids. To enhance the power of our study, further RCTs comparing corticosteroid-free remission between etrolizumab and a placebo are necessary.

Comparison between anti-TNF and etrolizumab. In terms of comparative efficacy to anti-TNFs, a head-to-head meta-analysis was conducted, comparing etrolizumab with infliximab for the treatment of moderate to severe UC.[47] It incorporated data from seven RCTs, representing the first meta-analysis with comparison between these two novel medications. Notably, there were no significant differences observed in terms of clinical remission and serious AEs between etrolizumab and infliximab. Also, the comparative efficacy between anti-TNFs is similar, but the meta-analysis showed a trend toward lower adverse events profile for etrolizumab *versus* infliximab. In a different RCT, the efficacy of etrolizumab was compared with another anti-TNF: adalimumab.[19] The pooled analysis revealed that etrolizumab did not exhibit superiority over adalimumab in inducing remission, achieving endoscopic improvement or remission, eliciting a clinical response, or attaining histological remission.

Safety. The safety profile of etrolizumab was evaluated in comparison with a placebo in our study. Our findings indicate

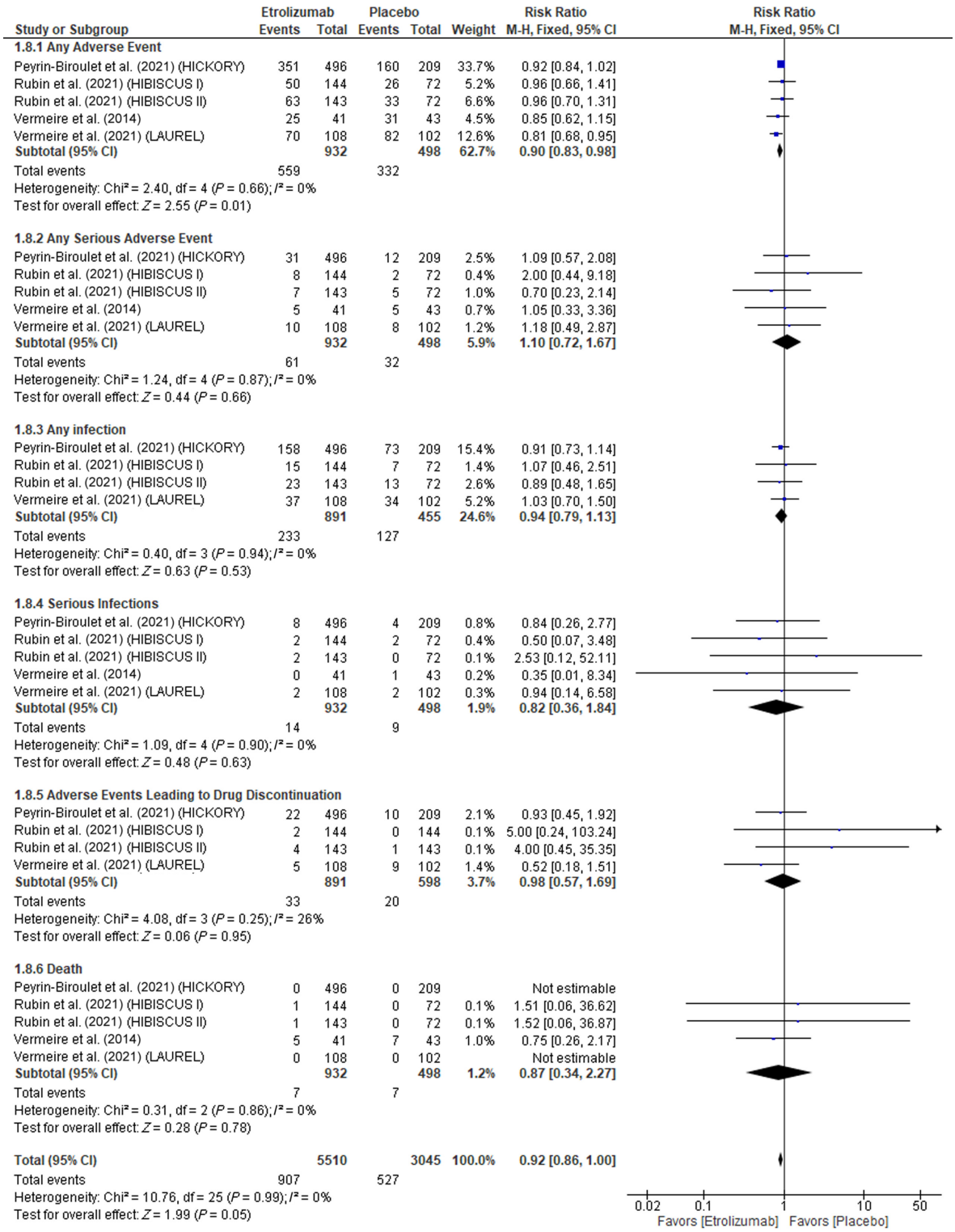


Figure 6 Forest plot of the safety outcomes (a—any adverse event, b—any serious adverse event, c—any infection, d—serious infection, e—adverse event leading to drug discontinuation, f—death). CI, confidence interval; RR, risk ratio.

that the etrolizumab group exhibited a higher risk of AEs, as supported by high-quality evidence. However, there were no significant differences in terms of serious AEs, any infections, serious infections, AEs leading to drug discontinuation, and death. While etrolizumab demonstrated a greater likelihood of AEs, the lack of significant differences in serious AEs and other

critical safety parameters is noteworthy, providing valuable insights into its safety profile and potential clinical utility.

Strengths. The analysis conducted in this article demonstrates a robust evaluation of the efficacy outcomes of etrolizumab in treating UC. Various outcome measures were assessed, including clinical response, clinical remission, endoscopic improvement, endoscopic remission, and histologic remission.

The safety outcomes of etrolizumab were also evaluated in this article, providing valuable insights into the adverse event profile of the treatment. The analysis compared the proportion of patients experiencing adverse events in the etrolizumab group *versus* the placebo group. Including safety data enhances the comprehensiveness of the analysis and provides clinicians with important information for making treatment decisions.

Overall, the strengths of this article lie in its rigorous methodology, comprehensive evaluation of efficacy and safety outcomes, and detailed reporting of study characteristics. These strengths contribute to the reliability and validity of the findings, making them a valuable resource for clinicians and researchers in the field of UC treatment.

Limitations. It is important to acknowledge several limitations in this study. First, the focus on short-term outcomes during the induction and maintenance phases limits our understanding of the long-term efficacy and safety of etrolizumab in UC treatment. Future studies with extended follow-up periods are needed to assess the durability of treatment effects and identify potential late-onset adverse events. Second, potential confounding factors and interactions with other concurrent medications were not explicitly accounted for in the analysis. These factors could influence treatment response and safety outcomes, and their impact should be addressed in future investigations to obtain a more comprehensive understanding of etrolizumab's effects.

Furthermore, the analysis primarily compared etrolizumab with a placebo, which restricts direct comparisons with other active treatments for UC. Conducting research that compares etrolizumab with commonly used therapies would provide valuable insights into its relative efficacy and safety in relation to existing treatment options.

Finally, the sample sizes and event rates in the safety analysis may have been inadequate to detect rare adverse events accurately or estimate the overall safety profile of etrolizumab. Conducting larger studies or utilizing post-marketing surveillance data would enable the capture of a broader range of safety events and enhance the reliability of safety assessments.

Implication for future research. The findings of this study have important implications for future research in the field of UC treatment. First, it is crucial to conduct long-term studies to assess the durability of the observed treatment effects. The manuscript primarily focused on short-term outcomes during the induction and maintenance phases, and the long-term efficacy and safety of etrolizumab were not thoroughly evaluated. Extended follow-up periods are needed to determine the sustainability of the treatment benefits and to identify any late-onset adverse events that may arise.

Additionally, future studies should consider potential confounding factors and interactions with other concurrent medications. The analysis did not account for these factors, which could influence treatment response and safety outcomes. Understanding the impact of these variables on the effectiveness and safety of etrolizumab is essential for optimizing its use in clinical practice.

Furthermore, comparative research comparing etrolizumab with other commonly used therapies for UC is warranted. The current analysis primarily focused on comparing etrolizumab with a placebo, limiting the ability to draw direct comparisons with other active treatments. Conducting head-to-head trials or meta-analyses that directly compare etrolizumab with other established therapies will provide a more comprehensive understanding of its relative efficacy and safety.

Finally, larger studies or post-marketing surveillance data are needed to capture a broader range of safety events and enhance the reliability of safety assessments. The sample sizes and event rates in the current analysis may have been insufficient to detect rare adverse events accurately. Increasing the sample size and conducting real-world studies will provide a more accurate estimation of the overall safety profile of etrolizumab. Addressing these implications for future research will help strengthen the evidence base for using etrolizumab in the treatment of UC and guide clinicians in making informed decisions about its use in clinical practice.

Conclusion

This study provides evidence supporting the effectiveness of etrolizumab as both an induction and maintenance therapy for moderate or severe UC. The findings demonstrate its positive impact on clinical, endoscopic, and histologic remission rates. However, further research is needed to establish the optimal position of etrolizumab in UC management guidelines. Specifically, head-to-head comparisons with other well-established drugs, such as vedolizumab, would be valuable in assessing its comparative efficacy and safety. These comparative studies would contribute to a more comprehensive understanding of etrolizumab's role in treating UC and aid in making informed clinical decisions.

References

1 Danese S, Allez M, Van Bodegraven AA *et al*. Unmet medical needs in ulcerative colitis: an expert group consensus. *Dig. Dis.* 2019; **37**: 266–83.
2 Brown C, Gibson PR, Hart A *et al*. Long-term outcomes of colectomy surgery among patients with ulcerative colitis. *Springerplus*. 2015; **4**: 573.
3 Muller KR, Prosser R, Bampton P, Mountifield R, Andrews JM. Female gender and surgery impair relationships, body image, and sexuality in inflammatory bowel disease patient perceptions. *Inflamm. Bowel Dis.* 2010; **16**: 657–63.
4 Suilik HA, Jaber F, Abuelazm M *et al*. Sphingosine 1-phosphate (S1P) receptor modulators as an induction and maintenance therapy for ulcerative colitis: a systematic review and meta-analysis of randomized controlled trials. *Inflamm. Res.* 2023; **73**: 1–16.
5 McLean LP, Cross RK. Adverse events in IBD: to stop or continue immune suppressant and biologic treatment. *Expert Rev. Gastroenterol. Hepatol.* 2014; **8**: 223–40.

6 Papamichael K, Rivals-Lerebours O, Billiet T *et al*. Long-term outcome of patients with ulcerative colitis and primary non-response to infliximab. *J. Crohns Colitis*. 2016; **10**: 1015–23.
7 Stefanich EG, Danilenko DM, Wang H *et al*. A humanized monoclonal antibody targeting the β7 integrin selectively blocks intestinal homing of T lymphocytes. *Br. J. Pharmacol.* 2011; **162**: 1855–70.
8 Lichnog C, Klabunde S, Becker E *et al*. Cellular mechanisms of etrolizumab treatment in inflammatory bowel disease. *Front. Pharmacol.* 2019; **10**: 432762.
9 Tang MT, Keir ME, Erickson R *et al*. Review article: nonclinical and clinical pharmacology, pharmacokinetics and pharmacodynamics of etrolizumab, an anti-β7 integrin therapy for inflammatory bowel disease. *Aliment. Pharmacol. Ther.* 2018; **47**: 1440–52.
10 Dotan I, Allez M, Danese S, Keir M, Tole S, McBride J. The role of integrins in the pathogenesis of inflammatory bowel disease: approved and investigational anti-integrin therapies. *Med. Res. Rev.* 2020; **40**: 245–62.
11 Peyrin-Biroulet L, Hart A, Bossuyt P *et al*. Etrolizumab as induction and maintenance therapy for ulcerative colitis in patients previously treated with tumour necrosis factor inhibitors (HICKORY): a phase 3, randomised, controlled trial. *Lancet Gastroenterol. Hepatol.* 2022; **7**: 128–40.
12 Page MJ, McKenzie JE, Bossuyt PM *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021: 372.
13 Higgins JPT, Thomas J, Chandler J *et al*. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: John Wiley & Sons, 2019; 1–694.
14 Canadian Agency for Drugs and Technologies in Health. *Validity of outcome measures – Clinical review report: adalimumab (Humira) – NCBI Bookshelf*. 2016.
15 Sterne JAC, Savović J, Page MJ *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019: 366. Available from URL: https://www.bmj.com/content/366/bmj.l4898.
16 Guyatt GH, Oxman AD, Vist GE *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008; **336**: 924–6.
17 Twells LK. Evidence-based decision-making 1: critical appraisal. *Methods Mol. Biol.* 2015; **1281**: 385–96. Available from: http://www.jamaevidence.com.
18 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; **315**: 629–34. Available from URL: https://www.bmj.com/content/315/7109/629.
19 Rubin DT, Dotan I, DuVall A *et al*. Etrolizumab versus adalimumab or placebo as induction therapy for moderately to severely active ulcerative colitis (HIBISCUS): two phase 3 randomised, controlled trials. *Lancet Gastroenterol. Hepatol.* 2022; **7**: 17–27.
20 Vermeire S, Lakatos PL, Ritter T *et al*. Etrolizumab for maintenance therapy in patients with moderately to severely active ulcerative colitis (LAUREL): a randomised, placebo-controlled, double-blind, phase 3 study. *Lancet Gastroenterol. Hepatol.* 2022; **7**: 28–37.
21 Vermeire S, O'Byrne S, Keir M *et al*. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet*. 2014; **384**: 309–18.
22 Pabla BS, Schwartz DA. Assessing severity of disease in patients with ulcerative colitis. *Gastroenterol. Clin. North Am.* 2020; **49**: 671–88.
23 Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006; **55**: 749–53.
24 Trigo-Vicente C, Gimeno-Ballester V, García-López S, López-Del VA. Systematic review and network meta-analysis of treatment for moderate-to-severe ulcerative colitis. *Int. J. Clin. Pharmacol.* 2018; **40**: 1411–9.
25 Ferretti F, Cannatelli R, Monico MC, Maconi G, Ardizzone S. An update on current pharmacotherapeutic options for the treatment of ulcerative colitis. *J. Clin. Med.* 2022; **11**: 2302.
26 MacDermott RP, Green JA. Refractory ulcerative colitis treatment. *Gastroenterol. Hepatol. (N Y).* 2007; **3**: 64–9.
27 Gubatan J, Keyashian K, Rubin SJS, Wang J, Buckman CA, Sinha S. Anti-integrins for the treatment of inflammatory bowel disease: current evidence and perspectives. *Clin. Exp. Gastroenterol.* 2021; **14**: 333–42.
28 Danese S, Colombel JF, Lukas M *et al*. Etrolizumab versus infliximab for the treatment of moderately to severely active ulcerative colitis (GARDENIA): a randomised, double-blind, double-dummy, phase 3 study. *Lancet Gastroenterol. Hepatol.* 2022; **7**: 118–27.
29 Sandborn WJ, Panés J, Danese S *et al*. Etrolizumab as induction and maintenance therapy in patients with moderately to severely active Crohn's disease (BERGAMOT): a randomised, placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterol. Hepatol.* 2023; **8**: 43–55.
30 Kane SV. Overcoming adherence issues in ulcerative colitis. *Gastroenterol. Hepatol. (N Y).* 2007; **3**: 795–9.
31 Sharara AI, Malaeb M, Lenfant M, Ferrante M. Assessment of endoscopic disease activity in ulcerative colitis: is simplicity the ultimate sophistication? *Inflamm. Intest. Dis.* 2021; **7**: 7–12.
32 D'Haens G, Sandborn WJ, Feagan BG *et al*. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology*. 2007; **132**: 763–86.
33 Ardizzone S, Cassinotti A, Duca P *et al*. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *Clin. Gastroenterol. Hepatol.* 2011; **9**: 483–489.e3.
34 Lobatón T, Bessissow T, De Hertogh G *et al*. The Modified Mayo Endoscopic Score (MMES): a new index for the assessment of extension and severity of endoscopic activity in ulcerative colitis patients. *J. Crohn's Colitis*. 2015; **9**: 846–52.
35 Ikeya K, Hanai H, Sugimoto K *et al*. The ulcerative colitis endoscopic index of severity more accurately reflects clinical outcomes and long-term prognosis than the Mayo endoscopic score. *J. Crohn's Colitis*. 2016; **10**: 286–95.
36 Feuerstein JD, Isaacs KL, Schneider Y *et al*. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020; **158**: 1450–61.
37 Peyrin-Biroulet L, Sandborn W, Sands BE *et al*. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am. J. Gastroenterol.* 2015; **110**: 1324–38.
38 Ramos GP, Papadakis KA. Mechanisms of disease: inflammatory bowel diseases. *Mayo Clin. Proc.* 2019; **94**: 155–65.
39 Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? *Clin. Gastroenterol. Hepatol.* 2014; **12**: 929–934.e2.
40 Bopanna S, Roy M, Das P *et al*. Role of random biopsies in surveillance of dysplasia in ulcerative colitis patients with high risk of colorectal cancer. *Intest. Res.* 2016; **14**: 264–9.
41 Colman RJ, Rubin DT. Histological inflammation increases the risk of colorectal neoplasia in ulcerative colitis: a systematic review. *Intest. Res.* 2016; **14**: 202–10.
42 Bryant RV, Burger DC, Delo J *et al*. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. *Gut*. 2016; **65**: 408–14.
43 Zenlea T, Yee EU, Rosenberg L *et al*. Histology grade is independently associated with relapse risk in patients with ulcerative colitis in clinical remission: a prospective study. *Am. J. Gastroenterol.* 2016; **111**: 685–90.
44 Narang V, Kaur R, Garg B *et al*. Association of endoscopic and histological remission with clinical course in patients of ulcerative colitis. *Intest. Res.* 2018; **16**: 55–61.

45 Harbord M, Eliakim R, Bettenworth D *et al*. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J. Crohn's Colitis*. 2017; **11**: 769–84.
46 Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American college of gastroenterology, practice parameters committee. *Am. J. Gastroenterol.* 2010; **105**: 501–23.
47 Motaghi E, Ghasemi-Pirbaluti M, Zabihi M. Etrolizumab versus infliximab in the treatment of induction phase of ulcerative colitis: A systematic review and indirect comparison. *Pharmacol Res*. 2019; **139**: 120–5.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Search terms and results in different databases.
Table S2. Baseline treatments.
Table S3. Quality assessment of the risk of bias in the included trials.