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ORIGINAL RESEARCH

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Efficacy and safety of etrolizumab in treatment of moderate to severe ulcerative colitis: A systematic review and meta-analysis

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Abstract

Background: Etrolizumab is a promising drug for treating moderate to severe ulcerative colitis.

Aim: The aim of this study was to assess the efficacy and safety of etrolizumab for induction and maintenance of remission in moderate to severe ulcerative colitis.

Methods: We searched the following databases: PUBMED, Web of Science, OVID, and SCOPUS from inception to January 15. Inclusion criteria were any phase 2 and 3 clinical trials that compared etrolizumab with a placebo in treating moderate to severe ulcerative colitis, excluding case reports, animal studies, phase 1 trials, and conference abstracts due to duplication. We used RevMan software (5.4) for the meta-analysis.

Results: Five clinical trials were included in our meta-analysis. The total number of patients included in the study is 1248 patients, 860 patients in the etrolizumab group and 388 patients in the placebo group. In the induction phase, the pooled analyses showed a statistically significant association between etrolizumab and increased clinical remission, and endoscopic remission compared with placebo (risk ratio [RR] = 2.66, 95% confidence interval [CI] = 1.69–4.19, $p < 0.0001$), and (RR = 2.35, 95% CI = 1.52–3.65, $p = 0.0001$), respectively. In the maintenance phase, the pooled analyses showed a statistically significant association between etrolizumab and increased histologic remission and endoscopic remission (RR = 2.04, 95% CI = 1.40–2.98, $p = 0.0002$) and (RR = 1.92, 95% CI = 1.29–2.85, $p = 0.001$), respectively. No statistically significant difference was observed in adverse events between etrolizumab and placebo in the induction and maintenance phases.

Conclusion: Our results show that etrolizumab is an effective and safe drug for the induction and maintenance of clinical remission in moderate to severe ulcerative colitis patients, as proved by histologic and endoscopic findings. Future randomized trials are still needed to compare etrolizumab to the other agents and further establish its value for the practice.

KEYWORDS
biologic drugs, etrolizumab, ulcerative colitis

1 | INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that affects the colonic mucosa almost exclusively. It targets the rectum in most cases (40%–50%) and progresses proximally over time, and may be so extensive that it involves the whole colon (pancolitis) in 25%–30% of cases.[1] It is a global disease with its incidence increasing remarkably in recent years.[2] The highest annual incidence rate is 24.3 per 100,000 person-years in Europe and 19.2 per 100,000 person-years in North America, and it is far less common in Asia and the Middle East (5.0 per 100,000 person-years).[3] It presents mainly in young adulthood between 20 and 29 years with no specific gender prevalence, yet recently pediatric UC has been increasing remarkably and is associated with a more severe manifestation of the disease.[4–7]

Diagnosis of UC depends on the clinical manifestation, colonoscopy, and histopathologic evaluation. The main symptom suggestive of an acute attack of UC is the presence of bloody diarrhea with negative stool culture for any other infectious cause of diarrhea.[1,8] Other associated symptoms are abdominal pain and tenesmus.[1,8] The next step is a colonoscopy and a mucosal biopsy for histopathologic examination. The key microscopic findings are diffuse mucosal inflammation with basal plasmacytosis, cryptitis, and crypt abscess.[9] UC is associated with extraintestinal manifestation (EIM), such as arthritis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, and iritis/uveitis, in 20%–40% of patients.[10]

Although the exact etiology of UC is not well established, it is now believed that it is a combination of environmental, genetic, and immunologic factors.[1] The abnormal immunologic response is the key factor for the pathogenesis of UC. The cell-mediated immune response is released against commensal, intestinal flora due to decreased tolerance, which leads to massive neutrophil recruitment and release of cytokines like tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12), thus more inflammatory cells are recruited like macrophages with more destructive enzymes released that lead to tissue damage.[11,12]

The main goal of the management of UC is to induce remission of the acute attack and maintain this remission to decrease the frequency of the attacks as well as the risk of hospitalization and development of complications like toxic mega-colon. Medical treatment works on the modification of the immune response to decrease inflammation. Biologic therapy targeting leukocyte homing to the gut mucosa is a promising therapy. Etrolizumab is a humanized monoclonal antibody against the β_7-subunit that blocks the β_7-integrin-containing ($\alpha_4\beta_7$ and $\alpha_E\beta_7$) heterodimers, which are transmembrane glycoproteins of the intestinal lymphocytes.[13–16] This integrin interacts with mucosal cell adhesion molecule-1 (MAdCAM-1) that is present in intestinal vasculature to facilitate cell trafficking of inflammatory cells into the intestine to mediate inflammation.[17] Other novel drugs that target the integrins are natalizumab (anti-a4),[18] AJM300 (anti-a4),[19] and vedolizumab (anti-a4b7).[20] Drugs that target integrin receptors are also being developed, such as PF-00547659 (anti-MAdCAM).[21]

Recently, multiple phase 3 trials have tested the clinical efficacy and safety of etrolizumab for UC and the reported efficacy of the drug varied between reports. We aimed to determine the clinical effectiveness of etrolizumab for induction of remission in moderate and severe cases of UC by pooling data from phase 2 and phase

Highlights

- Our analysis showed that etroliozumab is an effective biologic drug in the induction and maintenance of moderate and severe cases of ulcerative colitis.
- Etrolizumab is generally a safe drug, as it rarely causes serious adverse effects that would result in the discontinuation of the drug.
- We did a comprehensive review on the comparison between etrolizumab and the most common biologic agents used in the treatment of moderate and severe ulcerative colitis (infliximab, adalimumab, and vedolizumab). However, our results are inconclusive and future studies should aim to make head-to-head comparisons with other biologic drugs for treatment of ulcerative colitis.
- This is the first meta-analysis to include phase 2 and phase 3 trials on etrolizumab efficacy versus placebo, so we provide the most recent evidence to affect future clinical decisions, and this article shall be a reference for all future studies.
- Our analysis included a large number of patients from multi-international centers, which allows for generalization and increases the credibility of our results.

3 randomized clinical trials. The remission will be determined by clinical, endoscopic, and histologic remission. We also aimed to assess the safety of the drug based on the results of the recently published trials and discuss the difference between etrolizumab and other immune-based therapies used for the treatment of UC. Also, we aimed to assess the efficacy of the intervention for long-term use for the maintenance of remission.

2 | METHODS

We followed the guidelines of the Cochrane Handbook of Systematic Reviews[22] and the regulations of Preferred Reporting Items for Systematic Reviews and Meta-analyses (the PRISMA 2020 update)[23,24] during the conduction of this review. (A filled form of the PRISMA 2020 checklist was submitted.)

2.1 | Search strategy

We used MeSH terms to form the following search strategy ("UC" OR "Ulcerative colitis" OR "colitis gravis" OR "Idiopathic Proctocolitis") AND ("etrolizumab" OR "rhuMAb Beta7" OR "ANTI-BETA7" OR "ANTI-. BETA.7" OR "RHUMAB. BETA.7" OR "PRO145223" OR "PRO-145223") to search four databases: PubMed, SCOPUS, Web of Science, and OVID from inception to January 15; for a further check, two authors performed a manual search by screening the references of included studies.

2.2 | Study selection

Our inclusion criteria were: All phase 2 and 3 clinical trials compared etrolizumab therapy with placebo in treating moderate to severe UC. A phase I study[25] was excluded due to a very low sample size compared with other included phase 2 and 3 trials. The main outcomes were induction of clinical remission in the induction phase and maintaining clinical remission in the maintenance phase. The accepted study design was randomized, placebo-controlled trials (RCTs). Thus, the PICO criteria for our review shall be:

Population: Patients with moderate to severe UC.

Intervention: Etrolizumab therapy.

Comparison: Placebo.

Outcome: Clinical remission, clinical response, endoscopic improvement, histologic remission, endoscopic remission, and adverse events in induction and maintenance phases.

We excluded case reports, animal studies, phase 1 trials, conference abstracts, and studies that did not report our desired outcomes. We have gone through two steps to select the eligible studies: (1) title and abstract screening and (2) full-text screening; the authors were grouped into two groups and each group performed the screening and data collection separately. The first author resolved the disputes and compared the results from the two groups.

2.3 | Data extraction

We extracted the data from the included studies in two Excel sheets. In the first one, two authors extracted a summary of the studies and baseline characteristics of the eligible patients: age, disease location, duration of the disease, the Mayo clinic score (MCS), baseline treatment, and so on, and the other contained outcomes measurement. We divided the main outcomes into (a) primary outcome: clinical remission (*n*) in induction and maintenance phases and (b) secondary outcomes: clinical response (*n*), endoscopic improvement (*n*), histologic remission (*n*), endoscopic remission (*n*), and adverse events (*n*) in induction and maintenance phases.

Clinical remission was defined as MCS of 2 or less, with individual subscores of 1 or less and rectal bleeding subscores of 0. Clinical response (defined as MCS with ≥3-point decrease and with a 30% reduction from the baseline, plus ≥1-point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1), endoscopic improvement (defined as Mayo endoscopic subscore of ≤1), endoscopic remission (defined as Mayo endoscopic subscore of 0), histological remission (defined as Nancy histological index [NHI] of ≤1 among patients with histological inflammation at the baseline).

2.4 | Risk of bias assessment

We used the Cochrane tool (ROB 2) to assess the risk of bias in RCTs. The following items were assessed (overall bias, selection of the reported result, measurement of the outcome, the missing outcome data, deviations from intended interventions, and randomization process).

2.5 | Data analysis

We used the Review Manager Software version 5.4 to perform the meta-analysis; the dichotomous outcomes were presented as risk ratios (RRs) with a 95% confidence interval (CI). In case of heterogeneity (χ^2 $p < 0.1$), a random effect model was adopted; otherwise, a fixed-effect model was employed, in general; the results were considered significant if the p value was less than 0.05.

3 | RESULTS

3.1 | Literature search

After a complete search of the literature, 405 publications resulted, of these 261 publications were eligible for the title and abstract screening after removing duplicates. Of the 261, 247 were irrelevant and 14 studies were eligible for full-text screening. Finally, six studies were included for the systematic review and four studies, including five trials, were included in the meta-analysis after the full-text screening, as two clinical trials were reported in one study,[26] as

shown in the PRISMA in Figure 1. The summary of the studies is shown in Table 1.

3.2 | Characteristics

The results were reported based on two phases, the induction phase at 10 or 14 weeks and the maintenance phase at 62 or 64 weeks. Efficacy and safety outcomes were pooled in both phases with doses of 100 or 105 mg every 4 weeks. Clinical remission, clinical response, endoscopic improvement, histologic remission, and endoscopic remission were reported as induction efficacy outcomes in four, four, three, three, and four studies, respectively. Clinical remission in patients with remission at 10 or 14 weeks, clinical remission in patients with the clinical response at 10 or 14 weeks, endoscopic improvement, histologic remission, and endoscopic remission as maintenance efficacy outcomes were all reported in two studies. Any adverse events, severe adverse events, discontinuation due to adverse events, UCs, and headaches were reported in four studies in the induction phase and two in the maintenance phase. The overall risk of bias was low in the included studies, as shown in Figure 2. We found no significant bias in overall bias, selection of the reported results, measurement of the outcome, missing outcome data, deviations from intended interventions, and randomization process domains. (Details of risk of bias are found in Supporting Infomation: Materials).)

3.3 | Patients characteristics

The total number of patients included in the study is 1248 patients, 860 patients in the etrolizumab group and 388 patients in the placebo group. The mean age of patients in the intervention group was 40.1 years and of the patients in the control group was 39.7 years. The mean duration of the disease in the intervention group

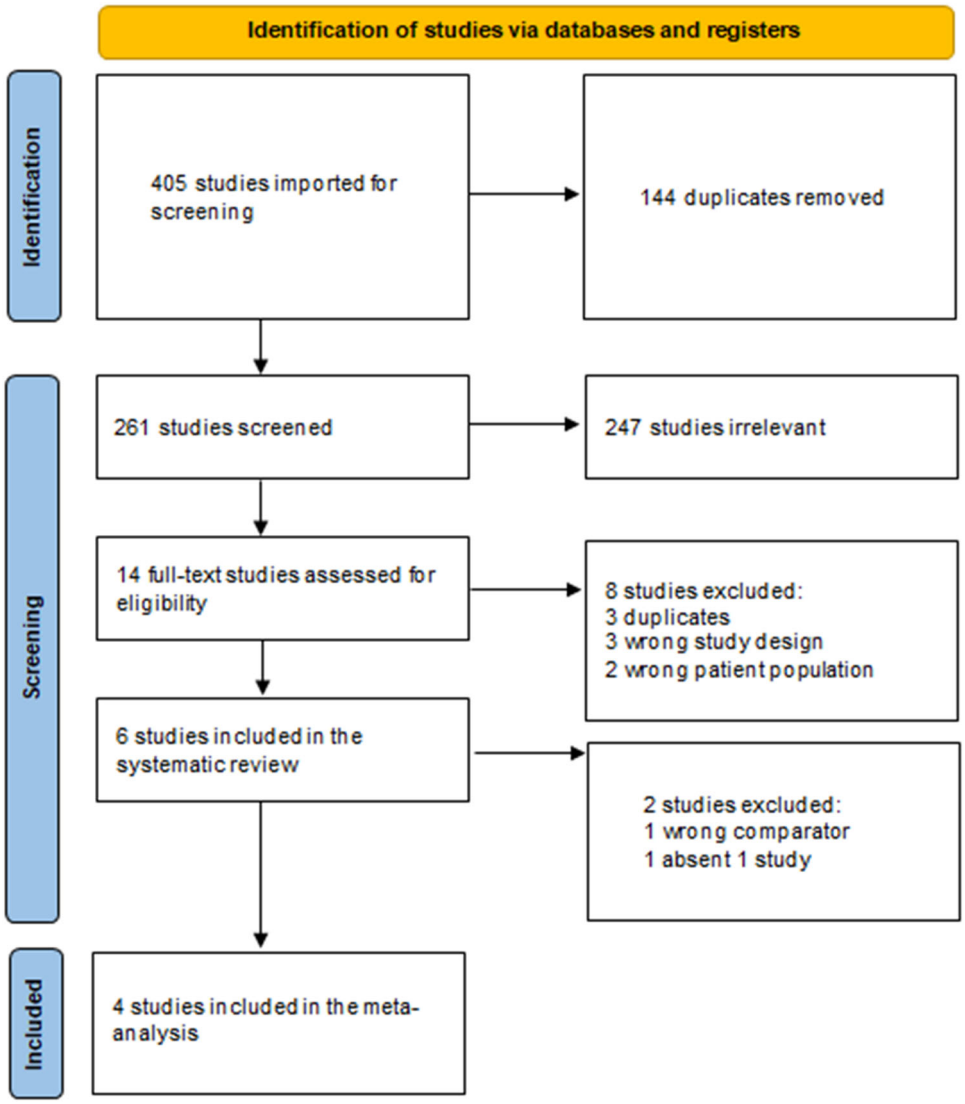

FIGURE 1 PRISMA flow diagram.

TABLE 1 Summary of the included studies.

ID	NCT	Design	Duration	Study arms	Efficacy outcomes	Safety outcomes	Conclusion
HIBISCUS1.2021[26]	2163759	Phase 3, randomized, double-blind, placebo-controlled, and active-controlled studies of etrolizumab, adalimumb, and placebo	A double-blind treatment period of up to 14 weeks and a 12-week safety follow-up period	Etrolizumab, *n* = 144; adalimumab, *n* = 142; placebo, *n* = 72	In HIBISCUS I, 28 (19.4%) of 144 patients in the etrolizumab group and five (6.9%) of 72 patients in the placebo group were in remission at Week 10, with an adjusted treatment difference of 12.3% (95% CI: 1.6–20.6, *p* = 0.017) in favor of etrolizumab. Etrolizumab was not superior to adalimumb for induction of remission, endoscopic improvement, clinical response, histological remission, or endoscopic remission; however, similar numerical results were observed	In HIBISCUS I, 50 (35%) of 144 patients in the etrolizumab group reported any adverse event, compared with 61 (43%) of 142 in the adalimumb group and 26 (36%) of 72 in the placebo group	Etrolizumab was superior to placebo for induction of remission. Etrolizumab was also well tolerated
HIBISCUS2.2021[26]	2171429	Phase 3, randomized, double-blind, placebo-controlled, and active-controlled studies of etrolizumab, adalimumb, and placebo	A double- blind treatment period of up to 14 weeks and a 12-week safety follow-up period	Etrolizumab, *n* = 143; adalimumab, *n* = 143; placebo, *n* = 72	In HIBISCUS II, 26 (18.2%) of 143 patients in the etrolizumab group and eight (11.1%) of 72 patients in the placebo group were in remission at Week 10, with an adjusted treatment difference of 7.2% (95% CI: −3.8 to 16.1, *p* = 0.17) Etrolizumab was not superior to adalimumb for induction of remission, endoscopic improvement, clinical response, histological remission, or endoscopic remission; however, similar numerical results were observed in both groups	In HIBISCUS II, 63 (44%) of 143 patients in the etrolizumab group reported any adverse event, as did 62 (43%) of 143 in the adalimumb group and 33 (46%) in the placebo group	Etrolizumab was not superior to placebo for induction of remission. Etrolizumab, however, was well tolerated
LAUREL.2021[27]	2165215	A randomized, placebo-controlled, double-blind, phase 3 study	62 weeks	Etrolizumab *n* = 108 or placebo, *n* = 106	At Week 62, 32 (29.6%) of 108 patients in the etrolizumab group and 21 (20.6%) of 102 in the placebo group were in remission (adjusted treatment difference 7.7%, 95% CI: −4.2 to 19.2, *p* = 0.19)	A greater proportion of patients reported one or more adverse events in the placebo group (82 [80%] of 102) than in the etrolizumab group (70 [65%] of 108) The most common adverse event in both groups was UC (16 [15%]	No significant differences were observed between the maintenance of etrolizumab and placebo in the primary endpoint of remission at Week

(Continues)

TABLE 1 (Continued)

ID	NCT	Design	Duration	Study arms	Efficacy outcomes	Safety outcomes	Conclusion
						patients in the etrolizumab group and 37 [36%] in the placebo group). Ten (9%) patients in the etrolizumab group and eight (8%) in the placebo group reported one or more serious adverse events. No deaths were reported in either treatment group	62 among patients who had a clinical response at Week 10 Etrolizumab was well tolerated in this population and no new safety signals were identified
HICKORY.2021[28]	2100696	Multicenter, phase 3, double-blind, placebo-controlled study	14 weeks for the induction phase and 12 weeks for safety follow-up	One hundred and thirty patients were included in cohort 1. In the cohort, 2479 patients were randomly assigned to the induction phase (etrolizumab, $n = 384$, placebo; $n = 95$). Two-hundred and thirty-two patients were randomly assigned to the maintenance phase (etrolizumab to etrolizumab, $n = 117$; etrolizumab to placebo, $n = 115$)	At Week 14, 71 (18.5%) of 384 patients in the etrolizumab group and six (6.3%) of 95 patients in the placebo group achieved the primary induction endpoint of remission ($p = 0.0033$) No significant difference between etrolizumab and placebo was observed for the primary maintenance endpoint of remission at Week 66 among patients with a clinical response at Week 14 (27 [24.1%] of 112 vs. 23 [20.2%] of 114, $p = 0.50$)	Four patients in the etrolizumab group reported treatment-related adverse events leading to treatment discontinuation. The proportion of patients reporting at least one adverse event was similar between treatment groups for induction (etrolizumab 253 [66%] of 384; placebo 63 [66%] of 95) and maintenance (etrolizumab to etrolizumab 98 [88%] of 112; etrolizumab to placebo 97 [85%] of 114). The most common adverse event in both groups was UC flare Most adverse events were mild or moderate. During induction, the most common serious adverse event was UC flare (etrolizumab 10 [3%] of 384; placebo 2 [2%] of 95). During maintenance, the most common serious adverse event in the etrolizumab to etrolizumab group was appendicitis (2 [2%] of 112) and the most common serious adverse events in the etrolizumab to the placebo group were UC flare (2 [2%] of 114) and anemia (2 [2%] of 114)	HICKORY demonstrated that a significantly higher proportion of patients with moderately to severely active UC who had been previously treated with an anti-TNF agent were able to achieve remission at Week 14 when treated with etrolizumab compared with placebo; however, there was no significant difference between groups in remission at Week 66 among patients with a clinical response at Week 14

TABLE 1 (Continued)

ID	NCT	Design	Duration	Study arms	Efficacy outcomes	Safety outcomes	Conclusion
Vermeire.2014[29]	1336465	Double-blind, placebo-controlled, randomized trial	10 weeks	Control arm: 43 assigned and received placebo Study arms: 41 assigned and received etrolizumab 100 mg Forty assigned and received etrolizumab 300 mg plus LD	One hundred and twenty-four patients were randomly assigned, of whom five had an endoscopic subscore of 0 or 1 and were excluded from the mITT population, leaving 39 patients in the etrolizumab 100 mg group Thirty-nine in the etrolizumab 300 mg plus LD group, and 41 were in the placebo group for the primary analyses. No patients in the the placebo group had clinical remission at Week 10, compared with eight (21%, 95% CI: 7–36) patients in the etrolizumab 100 mg group ($p = 0.0040$) and four (10%, 95% CI: 0.2–24) patients in the 300 mg plus LD group ($p = 0.048$)	Adverse events occurred in 25 (61%) of 41 patients in the etrolizumab (100 mg) group (5 [12%] of which were regarded as serious), 19 (48%) of 40 patients in the etrolizumab 300 mg plus LD group (2 [5%] serious), and 31 (72%) of 43 patients in the placebo group (5 [12%] serious)	Etrolizumab was more likely to lead to clinical remission at Week 10 than was placebo. Therefore, blockade of both α4β7 and αEβ7 might provide a unique therapeutic approach for the treatment of UC
Rutgeerts.2012[25] "excluded from analysis"	694980	A randomized, placebo-controlled, double-blind within-cohort study	In SAD, patients were followed for 18 weeks after the single dose of the study drug was administered. The MD parallel stage was commenced ~10 weeks after dosing was completed for the last patient treated in cohort E of the SAD stage	In the SAD stage, etrolizumab (0.3, 1.0, 3.0, 10 mg/kg intravenous, 3.0 mg/kg sc, or placebo) was administered 4:1 ($n = 25$) in each cohort. In the MD stage, new patients received monthly etrolizumab (0.5 mg/kg sc ($n = 4$), 1.5 mg/kg sc ($n = 5$), 3.0 mg/kg sc ($n = 4$), 4.0 mg/kg intravenous ($n = 5$)), or placebo ($n = 5$)	A clinical response was observed in 12/18 patients, and clinical remission in 3/18 patients treated with etrolizumab in the MD stage, compared with 4/5 and 1/5 placebo patients, respectively	In the SAD stage, there were no dose-limiting toxicities, infusion, or injection site reactions. Two impaired wound healing serious adverse events occurred in two patients receiving etrolizumab. In the MD stage, there were no dose-limiting toxicities and no infusion or injection site reactions. Headache was the most common adverse event, occurring more often in etrolizumab patients. Anti-etrolizumab antibodies were detected in two subjects. The duration of β7 receptor full occupancy was dose-related	Etrolizumab is well tolerated in moderate to severe UC

(Continues)

TABLE 1 (Continued)

ID	NCT	Design	Duration	Study arms	Efficacy outcomes	Safety outcomes	Conclusion
GARDENIA. 2021[30] "excluded from analysis"	2136069	A randomized, double-blind, double-dummy, parallel-group, phase 3 study	45 weeks	Etrolizumab group (n = 199) Infliximab group (n = 198)	Seven hundred and thirty patients were screened for eligibility and 397 were enrolled and randomly assigned to etrolizumab (n = 199) or infliximab (n = 198). Ninety-five (48%) patients in the etrolizumab group and 103 (52%) in the infliximab group completed the study through Week 54 At Week 54, 37 (18.6%) of 199 patients in the etrolizumab group and 39 (19.7%) of 198 in the infliximab group met the primary endpoint (adjusted treatment difference—0.9%, 95% CI: −8.7 to 6.8; p = 0.81)	The number of patients reporting one or more adverse events was similar between treatment groups (154 [77%] of 199 in the etrolizumab group and 151 [76%] of 198 in the infliximab group); the most common adverse event in both groups was UC (55 [28%] patients in the etrolizumab group and 43 [22%] in the infliximab group). More patients in the etrolizumab group reported serious adverse events (including serious infections) than did those in the infliximab group (32 [16%] vs. 20 [10%]); the most common serious adverse event was UC (12 [6%] and 11 [6%]). There was one death during follow-up, in the infliximab group due to a pulmonary embolism, which was not considered to be related to the study treatment	This trial is the first phase 3 maintenance study in moderately to severely active UC to use infliximab as an active comparator. Although the study did not show statistical superiority for the primary endpoint, etrolizumab performed similarly to infliximab from a clinical viewpoint

Abbreviations: CI, confidence interval; LD, loading dose; MD, multiple dose; mITT, modified intention to treat; SAD, single ascending dose; sc, subcutaneous; UC, ulcerative colitis.

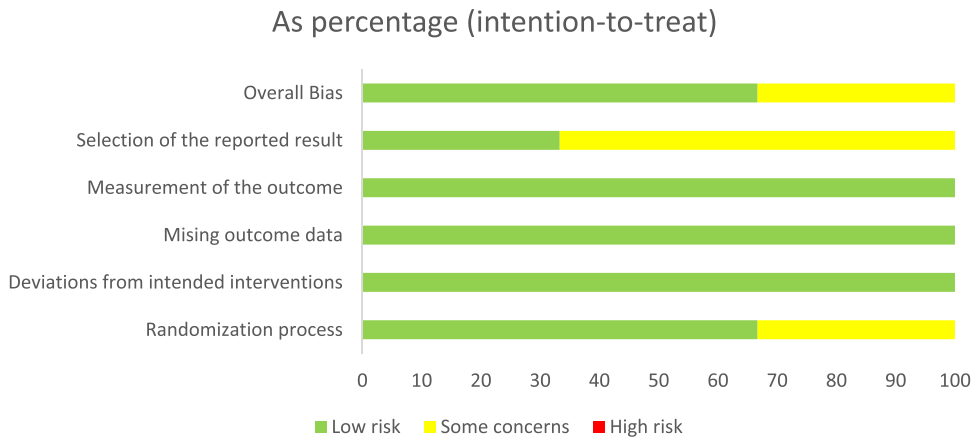

FIGURE 2 Risk of bias assessment.

was 15.84 years, while in the control group it was 13.32 years. Other baseline data of the included patients are shown in Table 2}

3.4 | Efficacy

Our analysis outcomes are designed to classify the intervention's efficacy and safety according to the desired effect into two main categories: either for the induction of remission in the patients under current attack (induction phase 10–14 weeks) or for the maintenance of remission in symptom-free patients who had a recent attack (maintenance phase 62–66 weeks)

3.4.1 | Induction phase at 10–14 weeks

Clinical remission (determined by MCS of 2 or less, with individual subscores of 1 or less and rectal bleeding subscores of 0).

The pooled effect showed a statistically significant association between etrolizumab and increased clinical remission compared with placebo (RR = 2.66, 95% CI = 1.69–4.19, $p < 0.0001$). We observed no statistically significant heterogeneity among studies ($p = 0.32$, $I^2 = 14\%$) (Figure 3).

Clinical response (determined by MCS with ≥3-point decrease and with a 30% reduction from the baseline, plus ≥1-point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1).

The pooled effect showed a statistically significant association between etrolizumab and increased clinical response compared with placebo (RR = 1.30, 95% CI = 1.10–1.54, $p = 0.003$). We observed no statistically significant heterogeneity among studies ($p = 0.65$, $I^2 = 0\%$) (Figure 3).

Endoscopic improvement (determined by Mayo endoscopic subscore of ≤1).

The pooled effect showed a statistically significant association between etrolizumab and increased endoscopic improvement compared with placebo (RR = 1.43, 95% CI = 1.13–1.81, $p = 0.003$). We observed no statistically significant heterogeneity among studies ($p = 0.50$, $I^2 = 0\%$) (Figure 3).

Histologic remission (determined by NHI of ≤1 among patients with histological inflammation at the baseline).

The pooled effect showed a statistically significant association between etrolizumab and increased histologic remission compared with placebo (RR = 1.57, 95% CI = 1.17–2.10, $p = 0.002$). We observed no statistically significant heterogeneity among studies ($p = 0.10$, $I^2 = 57\%$) (Figure 3).

Endoscopic remission (determined by Mayo endoscopic subscore of 0).

The pooled effect showed that etrolizumab significantly increased endoscopic remission rates compared with placebo (RR = 2.35, 95% CI = 1.52–3.65, $p = 0.0001$). We observed no statistically significant heterogeneity among studies ($p = 0.62$, $I^2 = 0\%$), Figure 3.

3.4.2 | Maintenance phase at 62–66 weeks

Maintenance of remission in patients who achieved remission at 10–14 weeks

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 1.25, 95% CI = 0.82–1.91, $p = 0.30$) (Figure 4). We observed no statistically significant heterogeneity ($p = 0.45$, $I^2 = 0\%$) (Figure 4).

Maintenance of remission in patients who achieved clinical response at 10–14 weeks

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 1.31, 95% CI = 0.93–1.85, $p = 0.12$) (Figure 4). We observed no significant heterogeneity ($p = 0.60$, $I^2 = 0\%$) (Figure 4).

Endoscopic improvement in patients who achieved clinical response at 10–14 weeks

The pooled effect showed a statistically significant association between etrolizumab and increased endoscopic improvement

TABLE 2 Baseline characteristics of the included studies.

ID		Study arms		Number of patients in each group		Age (years)		Sex (*n*)			
								Intervention		Control	
		Intervention (the route of adminis-tration)	Control (placebo or another drug)	Intervention	Control	Intervention	Control	Female	Male	Female	Male
Rubin1. 2021[26]		Subcutaneous	Placebo	144	72	44.5 (45.7)	44.3 (44.6)	70 (49%)	74 (51%)	33 (46%)	39 (54%)
Rubin2. 2021[26]		Subcutaneous	Placebo	143	72	44.7 (44.2)	40.8 (37.8)	59 (41%)	84 (59%)	34 (47%)	38 (53%)
Vermeire. 2022[27]		Subcutaneous	Placebo	108	106	43.7 (44.3)	41.7 (38.3)	48 (44%)	60 (56%)	54 (51%)	52 (49%)
Biroulet. 2021[28]	Induction	Subcutaneous	Placebo	384	95	44.3 (43.2)	44.3(43.7)	160 (42%)	224 (58%)	41 (43%)	54 (57%)

Disease location		Duration of disease (years) (mean)		MCS (mean, SD)		Baseline treatment	
Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Left-sided colitis: 89 (62%) Extensive colitis: 22 (15%) Pancolitis: 33 (23%)	Left-sided colitis: 44 (61%) Extensive colitis: 10 (14%) Pancolitis: 18 (25%)	15.2 (31)	15.3 (30.6)	8.9 (1.3)	8.7 (1.6)	No corticosteroid or immunosuppressant: 45 (31%) Corticosteroid, no immunosuppressant: 50 (35%) Immunosuppressant, no corticosteroid: 32 (22%) Corticosteroid and immunosuppressant: 17 (12%)	No corticosteroid or immunosuppressant: 24 (33%) Corticosteroid, no immunosuppressant: 25 (35%) Immunosuppressant, no corticosteroid: 15 (21%) Corticosteroid and immunosuppressant: 8 (11%)
Left-sided colitis: 86 (60%) Extensive colitis: 11 (8%) Pancolitis: 46 (32%)	Left-sided colitis: 48 (67%) Extensive colitis: 7 (10%) Pancolitis: 17 (24%)	20.9 (43.8)	9.6 (18.2)	8.8 (1.4)	8.8 (1.6)	No corticosteroid or immunosuppressant: 55 (39%) Corticosteroid, no immunosuppressant: 40 (28%) Immunosuppressant, no corticosteroid: 28 (20%) Corticosteroid and immunosuppressant: 20 (14%)	No corticosteroid or immunosuppressant: 27 (38%) Corticosteroid, no immunosuppressant: 23 (32%) Immunosuppressant, no corticosteroid: 14 (19%) Corticosteroid and immunosuppressant: 8 (11%)
Left-sided colitis: 62 (57%) Extensive colitis: 14 (13%) Pancolitis: 32 (30%)	Left-sided colitis: 65 (61%) Extensive colitis 12 (11%) Pancolitis 29 (27%)	16.7 (32.6)	15.5 (30.1)	8.48 (1.36)	8.62 (1.44)	5-Aminosalicylic acid: 89 (82%) No corticosteroid or immunosuppressant: 37 (34%) Corticosteroid, no immunosuppressant: 44 (41%) Immunosuppressant, no corticosteroid: 16 (15%) Corticosteroid and immunosuppressant: 13 (12%), 11 (10%)	5-Aminosalicylic acid: 80 (75%) No corticosteroid or immunosuppressant: 37 (35%) Corticosteroid, no immunosuppressant: 40 (38%) Immunosuppressant, no corticosteroid: 16 (15%) Corticosteroid and immunosuppressant: 13 (12%), 11 (10%)
Left-sided colitis: 197/383 (51%) Extensive colitis: 53/383 (14%) Pancolitis: 133/383 (35%)	Left-sided colitis: 47 (50%) Extensive colitis: 13 (14%) Pancolitis: 35 (37%)	17.2 (32.3)	16.4 (30.2)	8.95 (1.61)	9.02 (1.51)	5-Aminosalicylate use: 232 (60%) No corticosteroid or immunosuppressant: 134 (35%) Corticosteroid, no immunosuppressant: 138 (36%) Immunosuppressant, no corticosteroid: 68 (18%) Corticosteroid and immunosuppressant: 44 (11%)	5-Aminosalicylate use: 52 (55%) No corticosteroid or immunosuppressant: 34 (36%) Corticosteroid, no immunosuppressant: 35 (37%) Immunosuppressant, no corticosteroid: 17 (18%) Corticosteroid and immunosuppressant: 9 (10%)

(Continues)

TABLE 2 (Continued)

ID		Study arms		Number of patients in each group		Age (years)		Sex (*n*)			
								Intervention		Control	
		Intervention (the route of adminis-tration)	Control (placebo or another drug)	Intervention	Control	Intervention	Control	Female	Male	Female	Male
	Mainte-nance	Subcutaneous	Placebo	117	115	43.7 (42.8)	44.7 (42)	57 (49%)	60 (51%)	43 (37%)	72 (63%)
Vermeire. 2014[29]	100 mg	Subcutaneous	Placebo	41	43	44.4 (13.9)	37.5 (12.8)	13 (32%)	28 (68%)	24 (56%)	19 (44%)
	300 mg + LD	Subcutaneous	Placebo	40	43	40.3 (13.4)	37.5 (12.8)	16 (40%)	24 (60%)	24 (56%)	19 (44%)

Abbreviations: LD, loading dose; MSC, Mayo clinic score.

compared with placebo (RR = 1.69, 95% CI = 1.24–2.30, $p = 0.0008$). We observed no statistically significant heterogeneity ($p = 0.98$, $I^2 = 0\%$) (Figure 4).

Histologic remission in patients with baseline histological inflammation (determined by the absence of inflammatory cells histologically)

The pooled effect showed a statistically significant association between etrolizumab and increased histologic remission compared with placebo (RR = 2.04, 95% CI = 1.40–.98, $p = 0.0002$). We observed no statistically significant heterogeneity ($p = 0.77$, $I^2 = 0\%$) (Figure 4).

Endoscopic remission in patients who achieved clinical response at 10–14 weeks

The pooled effect showed a statistically significant association between etrolizumab and increased endoscopic remission compared with placebo (RR = 1.92, 95% CI = 1.29–2.85, $p = 0.001$). We observed no statistically significant heterogeneity ($p = 0.80$, $I^2 = 0\%$) (Figure 4).

Disease location		Duration of disease (years) (mean)		MCS (mean, SD)		Baseline treatment	
Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Left-sided colitis: 63/116 (54%) Extensive colitis: 16/116 (14%) Pancolitis: 37/116 (32%)	Left-sided colitis: 56 (49%) Extensive colitis: 15 (13%) Pancolitis: 44 (38%)	34.4 (34.5)	26 (15.9)	8.75 (1.58)	8.90 (1.67)	5-Aminosalicylate use: 69 (59%) No corticosteroid or immunosuppressant: 42 (36%) Corticosteroid, no immunosuppressant: 41 (35%) Immunosuppressant, no corticosteroid: 20 (17%) Corticosteroid and immunosuppressant: 14 (12%)	5-Aminosalicylate use: 68 (59%) No corticosteroid or immunosuppressant: 43 (37%) Corticosteroid, no immunosuppressant: 43 (37%) Immunosuppressant, no corticosteroid: 16 (14) Corticosteroid and immunosuppressant: 13 (11%)
Rectosigmoid: 10 (24%) Left-sided: 14 (34%) Pancolitis or extensive: 15 (37%) Nonspecifi ed: 2 (5%)	Rectosigmoid: 13 (30%) Left-sided: 17 (40%) Pancolitis or extensive: 13 (30%) Nonspecified: 0	9.2 (8.3)	9.8 (8.4)	9.3 (1.5)	9.1 (1.9)	*Concomitant medication use*: Corticosteroids: 17 (41%); dose, mg/day 13.1 (6.0) Immunosuppressants: 17 (41%) Mesalazine: 28(68%) Previous anti-TNF therapy: 25 (61%) No response to previous anti-TNF therapy: 24 (59%) Unacceptable adverse event: 1 (2%)	*Concomitant medication use*: Corticosteroids: 20 (47%); dose, mg/day: 13.7 (6.6) Immunosuppressants: 16 (37%) Mesalazine :38(88%) Previous anti-TNF therapy: 27 (63%) No response to previous anti-TNF therapy: 26 (60%) Unacceptable adverse event: 1 (2%)
Rectosigmoid: 8 (20%) Left-sided: 14 (35%) Pancolitis or extensive: 18 (45%) Nonspecified: 0	Rectosigmoid: 13 (30%) Left-sided: 17 (40%) Pancolitis or extensive: 13 (30%) Nonspecified: 0	8.0 (7.1)	9.8 (8.4)	9.2 (1.6)	9.1 (1.9)	*Concomitant medication use*: Corticosteroids: 18 (45%); dose, mg/day: 14.5 (5.7) Immunosuppressants: 14 (35%) Mesalazine: 25(63%) Previous anti-TNF therapy: 28 (70%) No response to previous anti-TNF therapy: 26 (65%) Unacceptable adverse event: 2 (5%)	*Concomitant medication use*: Corticosteroids: 20 (47%); dose, mg/day: 13.7 (6.6) Immunosuppressants: 16 (37%) Mesalazine: 38(88%) Previous anti-TNF therapy: 27 (63%) No response to previous anti-TNF therapy: 26 (60%) Unacceptable adverse event: 1 (2%)

3.5 | Safety

3.5.1 | Induction phase at 10–14 weeks

1. *Any adverse events*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 0.96, 95% CI = 0.85–1.09, $p = 0.53$) (Figure 5). We observed no statistically significant heterogeneity ($p = 0.84$, $I^2 = 0\%$) (Figure 5).

2. *Any severe adverse events*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 1.20, 95% CI = 0.66–2.16, $p = 0.55$), Figure 5). We observed no statistically significant heterogeneity ($p = 0.49$, $I^2 = 0\%$) (Figure 5).

3. *Discontinuation due to adverse events*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 1.15, 95% CI = 0.53–2.48, $p = 0.72$) (Figure 5). We observed no

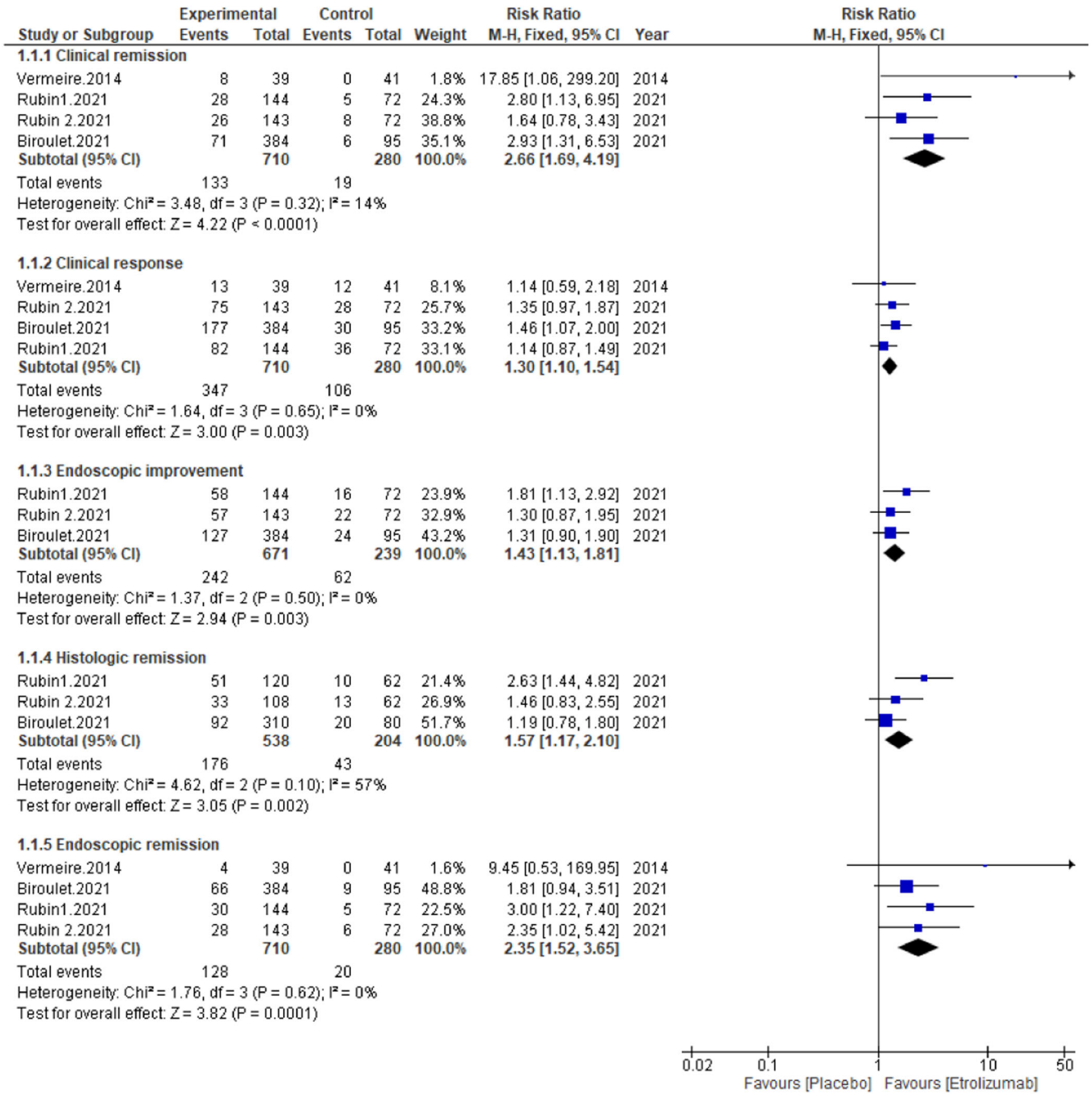

FIGURE 3 Forest plots of induction efficacy outcomes. CI, confidence interval; df, degrees of freedom; M–H, Mantel–Haenszel. Blue square and blue circle represent the effect estimate for each study.while the black rhomboid represents the overall estimate when you combine and average all the individual studies together.

statistically significant heterogeneity ($p = 0.38$, $I^2 = 3\%$) (Figure 5).

4. *UC flares*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 0.81, 95% CI = 0.54–1.20, $p = 0.29$) (Figure 5). We observed no statistically significant heterogeneity ($p = 0.66$, $I^2 = 0\%$) (Figure 5).

5. *Headache*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 0.88, 95% CI = 0.47–1.64, $p = 0.69$) (Figure 5). We observed no statistically significant heterogeneity ($p = 0.38$, $I^2 = 2\%$) (Figure 5).

6. *The upper respiratory tract infection*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 0.84, 95%

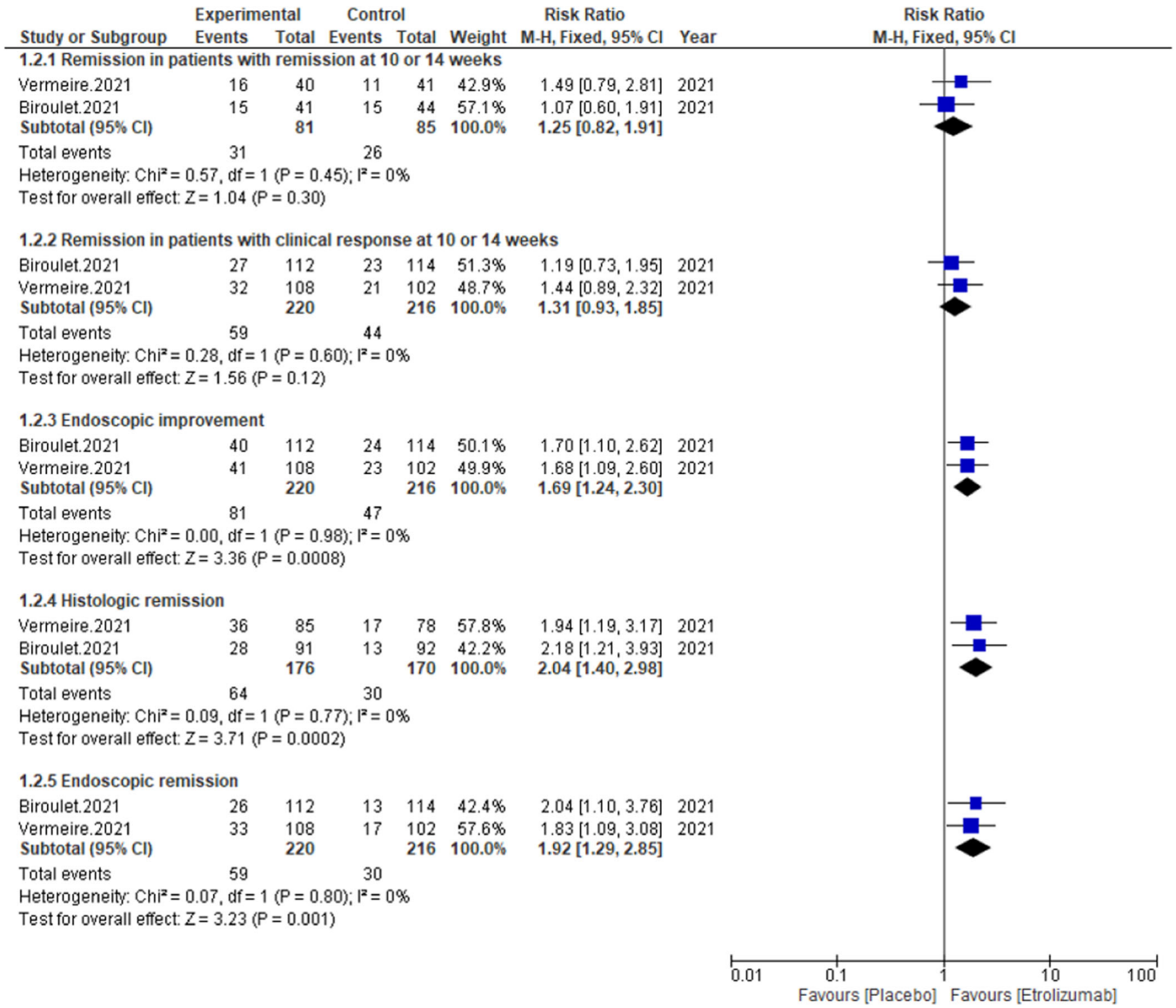

FIGURE 4 Forest plots of maintenance efficacy outcomes. CI, confidence interval; df, degrees of freedom; M–H, Mantel–Haenszel.

CI = 0.27–2.65, $p = 0.77$) (Figure 5). We observed no statistically significant heterogeneity ($p = 0.23$, $I^2 = 31\%$) (Figure 5).

7. *Arthralgia*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 1.27, 95% CI = 0.66–2.44, $p = 0.47$), Figure 5). We observed no statistically significant heterogeneity ($p = 0.68$, $I^2 = 0\%$) (Figure 5).

3.5.2 | Maintenance phase at 62–66 weeks

1. *Any adverse events in patients with clinical response at 10–14 weeks*.

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 0.92, 95% CI = 0.71–1.18, $p = 0.51$) (Figure 6). We observed a statistically significant heterogeneity ($p = 0.01$, $I^2 = 85\%$) (Figure 6).

2. *Any severe adverse events in patients with clinical response at 10–14 weeks*.

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 1.37, 95% CI = 0.72–2.59, $p = 0.33$) (Figure 6). We observed no statistically significant heterogeneity ($p = 0.64$, $I^2 = 0\%$) (Figure 6).

3. *Discontinuation due to adverse events in patients with clinical response at 10–14 weeks*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 0.82, 95% CI = 0.39–1.73, $p = 0.60$) (Figure 6). We observed no statistically significant heterogeneity ($p = 0.27$, $I^2 = 18\%$) (Figure 6).

4. *UC flares in patients with clinical response at 10–14 weeks*

The pooled effect showed a statistically significant association

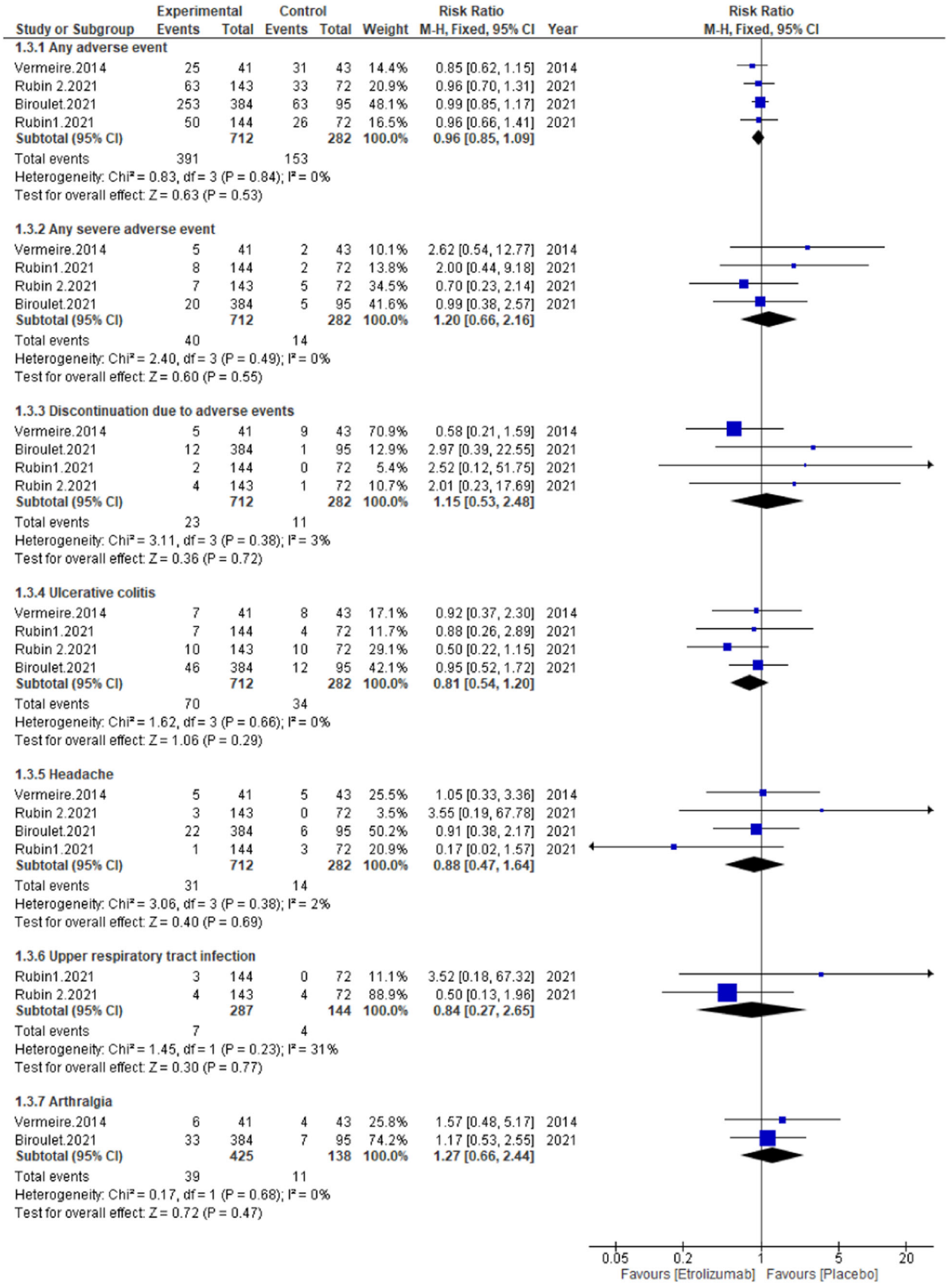

FIGURE 5 Forest plots of induction safety outcomes. CI, confidence interval; df, degrees of freedom; M–H, Mantel–Haenszel.

between etrolizumab and decreased UC compared with placebo (RR = 0.55, 95% CI = 0.33–0.90, $p = 0.02$) (Figure 6). We observed no statistically significant heterogeneity ($p = 0.11$, $I^2 = 60\%$) (Figure 6).

5. *Headache in patients with clinical response at 10–14 weeks*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 1.12, 95% CI = 0.57–2.18, $p = 0.74$), Figure 6). We observed no

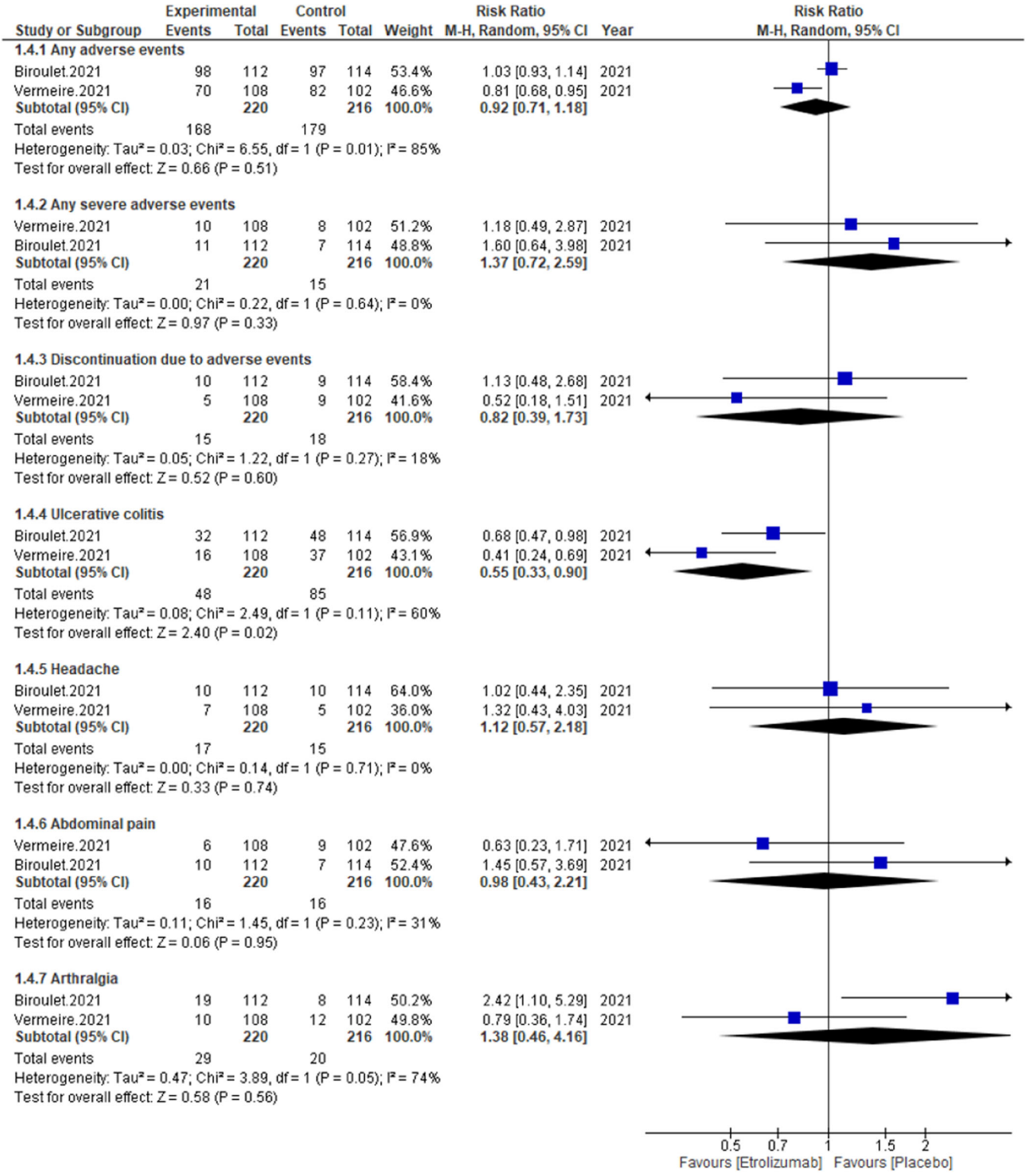

FIGURE 6 Forest plots of maintenance safety outcomes.

statistically significant heterogeneity ($p = 0.71$, $I^2 = 0\%$) (Figure 6).

6. *Abdominal pain in patients with clinical response at 10 –14 weeks*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 0.98, 95% CI = 0.43–2.21, $p = 0.95$), Figure 6). We observed no statistically significant heterogeneity ($p = 0.23$, $I^2 = 31\%$) (Figure 6).

7. *Arthralgia in patients with clinical response at 10–14 weeks*

The pooled effect showed no statistically significant difference between etrolizumab and placebo (RR = 1.38, 95% CI = 0.46–4.16, $p = 0.56$) (Figure 6). We observed a statistically significant heterogeneity ($p = 0.05$, $I^2 = 74\%$) (Figure 6).

4 | DISCUSSION

Our pooled results showed that etrolizumab was associated with more induction of remission of UC symptoms compared with the placebo. The recorded improvement was statistically significant on clinical, endoscopic, and histologic assessments. Etrolizumab was also associated with endoscopic and histologic remission on 60 weeks of maintenance therapy protocol in patients who achieved clinical response at 10–14 weeks. However, etrolizumab did not show a superior effect over the control therapy in maintaining 60 weeks of remission in patients who achieved remission at 10–14 weeks. In addition, etrolizumab was associated with a decrease in UC flares after drug maintenance for 62 weeks.

Etroizumab is generally a safe drug. No statistically significant difference was observed in any of the adverse events in the induction phase (at 10 or 14 weeks), and it did not lead to significant drug discontinuation. Among the reported adverse events (UC flare, headache, upper respiratory tract infection, arthralgia), UC is the most serious one, and it is the most commonly reported in all the included studies[26–29] except the study by Rutgeerts et al.,[25] who reported that headache was the most common. On the other hand, in the maintenance phase (at 62 or 66 weeks), all the adverse events did not show a statistically significant difference except UC flare, which was reduced significantly due to the drug's long-term effect. Unlike other immunosuppressant agents, severe infections were generally less reported in all the included studies, except for mild pharyngitis, which was most commonly reported in the study by Biroulet et al.,[28] which is similar to other biologics like vedolizumab, with less common immune suppression compared with systemic immunosuppressive therapies.[20,31,32] Etrolizumab, like other biologics, is highly immunogenic and may lead to the formation of antidrug antibodies.[33] Studies at phase 3 showed a higher antibody titer compared to their results in phases 1 and 2,[26–28] but it did not affect the pharmacokinetic measures, nor did it have a significant effect on the efficacy and safety of the drug.

Our results agree with individual studies. All studies were comparable in their design (RCT), the age of included patients, and the severity of the disease. Three studies in phase 3[26–28] used the same dose (105 mg once every 4 weeks). In the phase 2 trial by Vermeire et al.,[29] they used another dose (420 mg loading dose [LD] + 300 mg) and compared it with the (105 mg) dose regarding efficacy and safety. Interestingly, they found that the higher dose had a lower clinical remission rate (10%) compared to the lower dose (21%), while both of them had no significant difference in safety profile compared with placebo. The phase 1 trial conducted by Rutgeerts et al.[34] used different doses with different routes of administration. They compared the use of a single ascending dose (SAD) (0.3, 1.0, 3.0, 10 mg/kg intravenous, 3.0 mg/kg subcutaneous [sc]) with the multiple dose (MD) strategy of monthly administration (0.5 mg/kg sc, 1.5 mg/kg sc, 3.0 mg/kg sc, and 4.0 mg/kg intravenous). They found no dose-related adverse events or infusion or injection site complications, but the small sample size of the included patients did not provide a reliable judgment over the dose-related effect; however, it showed a general tendency for a decrease in the MCS in sc low dose groups in both the SAD and MD methods. Although lower doses may be sufficient for inducing the desired clinical responses, higher doses had a more sustained effect due to the dose-dependent increase in the duration of etlolizumab occupancy of its targeted receptor.

The first drug used in mild and moderate UC is oral 5-aminosalicylic acid,[35] while IV corticosteroids are reserved for more severe attack.[36] Steroid-sparing agents, such as azathioprine and cyclosporine, are used in steroid-resistant patients, but they have long-term side effects and may be associated with increased risk of lymphoproliferative disorders[37–39] TNF-α antagonists, such as infliximab and adalimumab, are also effective in moderate to severe UC.[34,40] In the direct comparison between etrolizumab and adalimumab, there was no statistically significant difference between both drugs regarding clinical efficacy. Nevertheless, adalimumab had lower serious adverse events (2%) compared to etrolizumab (15%).[26]

In a recently published network meta-analysis, 3747 patients who received no biologic therapy before inclusion in the primary studies were included.[41] The authors compared five biologic agents, including infliximab, adalimumab, and vedolizumab. Their results showed that infliximab was the most likely biologic agent to induce clinical remission in moderate to severe UC patients compared to the placebo (odds ratio [OR] = 4.07, 95% CI: 2.68–6.16). By indirect comparison, etrolizumab is associated with lower induction of clinical remission than the reported efficacy of infliximab (OR = 3.04, 95% CI: 1.84–5.02), similar to vedolizumab (OR = 3.10, 95% CI: 1.53–6.26), and higher than adalimumab with no significant difference in safety profile among all drugs included. This contradicts the results of a previous meta-analysis that compared infliximab and etrolizumab using indirect comparison regarding the clinical efficacy and adverse events and reported that infliximab is similar to etrolizumab in the induction of remission and it carries a higher risk of serious adverse events to the patients.[42] The results of this previous study are unreliable because it is an indirect comparison that included only two trials on etrolizumab with a small sample size of patients in their comparison. In a phase 3 trial that compared infliximab to etrolizumab, the results showed that infliximab was similar to etrolizumab in induction of clinical remission in moderate to severe UC patients with similar safety profiles in both drugs.[30] The opposing

outcomes from these studies indicate that indirect analysis is insufficient to favor one biologic agent over the others and highlight the need for larger head-to-head comparisons in future randomized control trials.

The main strength of this review was that it was the first to discuss the safety and efficacy of etrolizumab for both induction and maintenance of UC symptoms and compare it with other biologic therapies proposed for UC patients. Also, our analysis pooled results from a relatively high number of participants (1248), and the included studies were multicenter international studies, which indicate that the results could be utilized to prove the safety and efficacy of the drug for future studies. In addition, the detected level of heterogeneity was low in most of the outcomes, and the primary randomized studies were similar in tested doses and population characteristics. Lastly, we used the Cochrane risk of bias assessment tool (ROB 2) to judge included studies and the overall risk of bias was low, which adds to the value of our results. However, our results had some limitations, such as the limited number of included articles and the fact that only two studies tested the drug use for maintenance of remission.

To conclude, etrolizumab is an effective biologic drug in the induction and maintenance of clinical remission in moderate to severe UC patients. It has limited adverse events that most probably do not lead to the discontinuation of the drug. Other biologics such as infliximab, adalimumab, and vedolizumab are also effective, but there is no reliable, current evidence, either by indirect meta-analyses or direct head-to-head trials, on the most effective drug to be used. The current report is intended to be used as a reference for etrolizumab's efficacy for future trials to build on. It also proves the efficacy of etrolizumab as a powerful choice for clinical practice with a comparable efficacy and safety to the standard treatment regimens. Thus, further multiarm studies need to be conducted with a larger sample size of patients to compare etrolizumab to the other biologic agents and decide the most effective agent for moderate and severe UC patients. We also recommend that future network meta-analyses compare the results of etrolizumab based on direct head-to-head primary reports.

AUTHOR CONTRIBUTIONS

Karam R. Motawea: Conceptualization; formal analysis. **Yomna A. Abdelghafar**: Writing—original draft; writing—review and editing. **Yossef H. AbdelQadir**: Writing—original draft; writing—review and editing. **Merna M. Aboelenein**: Writing—original draft; writing—review and editing. **Nancy Ibrahim**: Writing—original draft; writing—review and editing. **Mohamed M. Belal**: Writing—original draft; writing— review and editing. **Rowan H. Elhalag**: Data curation, writing—review and editing. **Lina T. Khairy**: Writing—original draft; writing—review and editing. **Agyad Bakkour**: Writing—original draft; writing—review and editing. **Ali H. H. Muwaili**: Writing—original draft; writing—review and editing. **Fatima A. A. Abdelmajid**: Writing—original draft; writing—review and editing. **Mhd K. Albuni**: Writing—review and editing. **Elias Battikh**: Writing—review and editing. **Bisher Sawaf**: Writing—original draft. **Eman M. S. Ahmed**: Writing—original draft; writing—review & editing. **Dhuha H. H. Muwaili**: Writing—original draft; Writing—review and editing. **Sarya Swed**: Data curation; validation; writing—original draft; writing—review and editing. All authors have read and approved the final version of the manuscript. Karam R. Motawea had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

TRANSPARENCY STATEMENT

The lead author Sarya Swed affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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