World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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Comparing the efficacy and safety of Mirikizumab and Etrasimod in treating moderate to severe ulcerative colitis and Crohn's disease: A systematic review and meta-analysis

Sagar Ahammed *

Department of Oncology, Khwaja Yunus Ali Medical College and Hospital, Enayetpur, Sirajganj, Bangladesh.

World Journal of Biology Pharmacy and Health Sciences, 2024, 20(03), 339-351

Publication history: Received on 04 November 2024; revised on 14 December 2024; accepted on 16 December 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.20.3.1020

Abstract

Background: Many IBD patients do not react to traditional or biological therapies. Research suggests that Mirikizumab and Etrasimod may be effective therapy options for these individuals. This research aimed to evaluate the efficacy and safety of utilizing Mirikizumab and Etrasimod to treat moderate to severe IBD, including Crohn's disease (CD) and ulcerative colitis.

Methods: We searched PubMed, Medline, Web of Science, Scopus, Cochrane Library, Embase, Google Scholar, CINAHL, Clinical Trials.gov, and WHO Trials Registry (ICTRP). We included RCTs that compared Mirikizumab and Etrasimod to placebo in patients with active CD or UC. The principal results were mucosal healing as well as the clinical response and remission throughout the induction and maintenance periods. The frequency of severe adverse events was the secondary outcome. Comprehensive Meta-analysis version 4 (Biostat Inc., USA) was utilized in the study.

Results: A total of Seventeen randomized controlled trials were included in the analysis. Of these, fourteen studies examined the effectiveness and safety of Mirikizumab and Etrasimod in patients with UC, while three research looked at same topics in patients with CD. In people with moderately to highly active CD or UC, the meta-analysis showed that both Mirikizumab and Etrasimod therapies were more effective than placebo in inducing clinical response and achieving clinical remission during the induction and maintenance stages of treatment. Interestingly, we discovered that for patients with UC but not CD, Mirikizumab was a better first-line therapy than Etrasimod.

Conclusion: Mirikizumab and Etrasimod are safe and effective treatments for patients with CD and UC. RCTs including a greater number of patients are still necessary, nevertheless, in order to more accurately evaluate the safety profile of Mirikizumab and Etrasimod.

Keywords: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Mirikizumab; Etrasimod; PRISMA

1. Introduction

Inflammatory bowel disease (IBD) is a term used to jointly refer to Crohn's disease (CD) and ulcerative colitis (UC), which are chronic inflammatory illnesses affecting the gastrointestinal system [1, 2]. These disorders are marked by alternating periods of inflammation and remission, which greatly impact the quality of life for patients [3, 4]. Although the specific cause of IBD is not fully understood, it is commonly acknowledged that abnormal immune responses to substances in the gut are a key factor in the development of the disease in persons with certain genetic predispositions [5, 6].

* Corresponding author: Sagar Ahammed

To effectively manage moderate to severe Crohn's disease (CD) and ulcerative colitis (UC), a systematic strategy is typically necessary. This involves the use of several pharmacological medications to both initiate and sustain remission [7, 8]. Standard treatments consist of corticosteroids, immunomodulators, and biologic drugs that specifically target tumor necrosis factor-alpha (TNF-α) [9, 10]. Although these treatments are effective, a significant number of patients may not respond initially, lose their reaction over time, or experience negative side effects. This emphasizes the importance of finding alternate treatment choices.

Recent progress in comprehending the pathophysiology of IBD has resulted in the creation of innovative biologic medicines and small molecule inhibitors that operate through unique pathways [13, 14]. Mirikizumab, a monoclonal antibody that specifically targets the p19 component of interleukin-23 (IL-23), and Etrasimod, a medication that selectively modulates the sphingosine-1-phosphate receptor, are two potential treatments for effectively managing moderate to severe Crohn's disease (CD) and ulcerative colitis (UC) [16].

Mirikizumab specifically blocks the IL-23 pathway, which helps regulate the inflammatory response involved in the development of inflammatory bowel disease (IBD). Both preclinical and clinical investigations have shown that it is effective in causing and sustaining remission in people with Crohn's disease (CD) and ulcerative colitis (UC). Contrarily, Etrasimod achieves its therapeutic effects by regulating the movement of lymphocytes and the activation of immune cells, providing a distinct mode of action in comparison to conventional biologic medicines [18]. Etrasimod has demonstrated encouraging outcomes in clinical studies for the treatment of Crohn's disease (CD) and ulcerative colitis (UC), underscoring its potential as an innovative therapeutic choice [19, 20].

Although there is an increasing amount of evidence that supports the usefulness of Mirikizumab and Etrasimod in managing inflammatory bowel disease (IBD), there are few direct comparisons that assess their relative effectiveness and safety profiles in patients with moderate to severe Crohn's disease (CD) and ulcerative colitis (UC) [21, 22]. Hence, it is necessary to do a thorough analysis that combines the existing evidence from randomized controlled trials (RCTs) to compare the effectiveness and safety of Mirikizumab and Etrasimod in treating moderate to severe Crohn's disease (CD) and ulcerative colitis (UC).

This systematic review and meta-analysis aims to fill the existing knowledge gap by conducting a comparative assessment of the efficacy and safety profiles of Mirikizumab and Etrasimod in patients with moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). The evaluation will focus on the ability of these drugs to induce and maintain remission. Through clarifying the comparative advantages and potential drawbacks of these medical treatments, our aim is to provide valuable insights for healthcare professionals in their decision-making process and enhance the overall results for patients suffering from Inflammatory Bowel Disease (IBD).

2. Material and methods

This systematic review and meta-analysis followed the protocols established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). In addition, our meta-analysis was carried out in accordance with the criteria set by A MeaSurement Tool to Assess systematic Reviews (AMSTAR) [37]. Meta-analysis research entails the synthesis and comparison of data from numerous previously published studies, rather than the collection of primary, new data from human participants. Since this is a secondary study of publicly available data, no additional data will be acquired from participants, and there will be no direct interaction or intervention with human subjects. Consequently, network meta-analyses typically do not necessitate Institutional Review Board (IRB) approval, as their main purpose is to safeguard the rights and well-being of human research participants.

2.1. Search strategy

Finding appropriate papers involved a thorough search of databases including PubMed, Medline, Web of Science, Scopus, the Cochrane Library, Embase, Google Scholar, CINAHL, Clinicaltrials.gov, and the WHO trials registry (ICTRP) from their commencement until April 2023. Search terms included "randomized controlled trial" in addition to "inflammatory bowel disease," "ulcerative colitis," and "Crohn's disease" with " Mirikizumab " OR "Miri" OR "Etrasimod" OR "Etra." To find more important works, the bibliographies of relevant research and overview papers were hand-reviewed. This search was done independently by two investigators.

2.2. Inclusion and exclusion criteria

Having eliminated duplicates, we evaluated pertinent publications according to title and abstract. Studies addressing the effectiveness and safety of Mirikizumab or Etrasimod in patients with UC or CD were eligible for inclusion. The admissibility of the remaining studies was subsequently verified by reading their entire texts. Following were the

inclusion standards: 2) participants of any age diagnosed with CD or UC, as defined by conventional clinical, radiological, endoscopic, or histological criteria; 3) interventions involving Mirikizumab or Etrasimod versus placebo or a control therapy; 4) publications reporting sufficient data to establish statistical analysis; and 5) studies published as original articles. As were the exclusion standards: Complete text unavailable electronically; publication in a language other than English; observational studies; comments; letters; editorials; protocols; guidelines; review papers; and studies lacking sufficient outcome data.

2.3. Outcomes

The major results were mucosal healing and the clinical response and remission during the induction and maintenance periods. Clinical response in CD is defined as a reduction in CDAI score from baseline by ≥ 70 points and by ≥ 100 points; clinical remission is defined as a CDAI score of < 150. Clinical response in relation to UC was defined as a decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding sub-score of at least 1 point or an absolute rectal bleeding sub-score of 0 or 1. Clinical remission is defined as Mayo score ≤ 2 with no individual sub-score exceeding 1 point. A Mayo endoscopy sub-score of 0 or 1 was considered to indicate mucosal healing. Serious adverse event incidence was a secondary outcome.

2.4. Data collection

After inclusion and exclusion criteria were applied, two separate writers extracted information from the qualified publications. By use of a standard data sheet, we gathered the following information: First author's name and year of publication; study ID; location; period; design; study phase; name of trial; population; sample size; intervention; mean age; male sex (%); trial duration (weeks); and outcomes. Table 1 summarizes the features of the included research [20–36].

Table 1 Characteristics of Included Studies.

Study	Location	Period	Design	Study phase	Name of trial	Sample size	Mean age, years	Male sex, %	Trial Duration, weeks	Outcomes
Sandborn et al, 2022 [21]	75 sites in 14 countries	January 2016 to September 2017	Phase 2, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	I6T-MC-AMAC	249	45.6 (14.3) 43.0 (14.3) 40.9 (13.6) 42.0 (12.7) 40.5 (13.7)	15 (75.0) 45 (70.3) 5 (41.7) 18 (56.3) 56 (52.8)	52	-Clinical remission at week 24 and 52. -Clinical response at week 24 and 52. -Adverse events
Sands et al,2022 [22]	80 sites in 14 countries	January 12, 2017 to September 27, 2019	Phase 2, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	I6T-MC-AMAC	191	18-75	-	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events
Sandborn et al, 2020 [19]	87 centers in 17 countries	October 15, 2015 to February 14, 2018	Phase 2, randomized, proof-of-concept placebo-controlled, double- blind, parallel-group, multinational, multicenter trial	Induction	-	156	18–80 years	60	12	-Clinical remission at week 12. -Clinical response at week 12. -Adverse events

Sandborn et al, 2020[23]	75 sites in 14 countries	January 2016 to September 2017	Phase 2, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction	I6T-MC-AMAC	249	18-75	-	12	-Clinical response at week 12. -Adverse events
Vermeire et al, 2021 [24]	51 study sites in 16 countries	25 January 2016 to 1 November 2018	Phase 2, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	OASIS	112	43.7	66%	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events
D'Haens et al, 2023 [25]	383 sites in 34 countries, 367 sites in 34 countries	June 18, 2018, to January 21, 2021, October 19, 2018, to November 3 2021.	Phase 3, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	LUCENT-1, LUCENT-2	1281	41.3±13.8, 42.9±13.9	165 (56.1), 530 (61.1)	52-week	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events
Magro et al, 2023 [26]	-	June 2018 to January 2021, October 2018 to November 2021	Phase 3, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	LUCENT-1, LUCENT-2	1162	-	-	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events

Sands et al, 2023 [27]	-	June 2018 to January 2021, October 2018 to November 2021	Phase 3, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	LUCENT-1, LUCENT-2	1162	-	-	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events
Dubinsky et al, 2023 [28]	14 countries	-	Phase 2, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	I6T-MC-AMAC	249	-	-	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events
Dubinsky et al, 2022 [29]	14 countries	-	Phase 3, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	LUCENT-1, LUCENT-2	1162	18-80	-	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events
Millie et al, 2024 [30]	14 countries	-	Phase 3, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	LUCENT-1, LUCENT-2	1162	18-80	-	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events
Andres et al, 2024 [31]	-	-	Phase 2, randomized,	Induction	OASIS	156	18–80	-	12	-Clinical remission at week 12

			placebo-controlled, double- blind, OASIS trial							-Adverse events
Chua et al, 2023 [32]	85 sites in 14 countries, 383 sites in 34 countries and 367 study sites in 34 countries	January 2016 to September 2017, 18 June, 2018 to 21 January, 2021, and 19 October, 2018 to 3 November, 2021	Phase 2 and 3, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	AMAC, LUCENT 1, LUCENT 2	1362	42 years, 43 years	59%,61%	92	-Clinical remission at week 12 and 92. -Clinical response at week 12 and 92. -Adverse events
D'Haens et al, 2024 [33]	14 countries	June 2018 to January 2021, October 2018 to November 2021	Phase 3, randomized, placebo-controlled, double- blind, parallel-arm, multinational, multicenter trial	Induction and maintenance	LUCENT 1, LUCENT 2	1162	42.7 (13.8), 44.0 (14.2)	318 (58.5), 182 (66.9)	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events
Sandborn et al, 2023 [34]	315 centres in 40 countries, 407 centres in 37 countries	June 13, 2019, to Jan 28, 2021. And Sept 15, 2020, and Aug 12, 2021.	randomised, multicentre, double-blind, placebo-controlled, phase 3 trials	Induction and maintenance	ELEVATE UC 52, ELEVATE UC 12	433, 354	41·2 (14·0) 38·9 (14·0), 40·3 (13·5) 40·4 (13·3)	152 (53%) 88 (61%), 135 (57%) 73 (63%)	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events

Dubinsky et al, 2022 [35]	75 sites in 14 countries	January 2016 to September 2017	multicenter, randomized, double-blind, parallel-arm, placebo-controlled trial	Induction and maintenance	-	249	41.1 (13.3) 43.4 (14.2), 39.6 (12.8) 41.6 (15.0)	-	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events
Magro et al, 2023 [36]	14 countries	January 2016 and September 2017	phase 2 multicenter, randomized, parallel-arm, double-blind, placebo-controlled	Induction and maintenance	SERENITY trial	191	38.1 (13.0) 37.9 (11.8) 40.1 (14.0) 36.7 (12.8)	23 (46.9) 14 (50.0) 11 (42.3) 24 (48.0)	52	-Clinical remission at week 12 and 52. -Clinical response at week 12 and 52. -Adverse events

Table 2 Methodological Quality of Included Studies

Study		The	Jadad	Scores		Total scores
	1	2	3	4	5	
Sandborn et al, 2022	1	0	1	1	1	4
Sands et al, 2022	1	0	1	1	1	4
Sandborn et al, 2020	1	0	1	1	0	3
Sandborn et al, 2020	1	0	1	1	1	4
Vermeire et al, 2021	1	0	1	1	1	4
D'Haens et al, 2023	1	0	1	1	0	3
Magro et al, 2023	1	0	1	1	0	3
Sands et al, 2023	1	0	1	1	1	4
Dubinsky et al, 2023	1	0	1	1	0	3
Dubinsky et al, 2022	1	0	1	1	1	4
Millie et al, 2024	1	0	1	1	1	4
Andres et al, 2024	1	0	1	1	1	4
Chua et al, 2023	1	0	1	1	0	3
D'Haens et al, 2024	1	0	1	1	1	4
Sandborn et al, 2023	1	0	1	1	1	4
Dubinsky et al, 2022	1	0	1	1	0	3
Magro et al, 2023	1	0	1	1	1	4

2.5. Quality assessment of the studies

Focusing on elements like randomization, blinding, and participant withdrawals in the research, the Jadad scale was used to assess the methodological integrity of the chosen trials [38]. There are five points in all on the grading system. While reports of greater quality receive a score of 3 or more, those of lesser quality receive a score of 2 or below [39]. Table 2 displays the methodological quality of the selected research [20–36].

2.6. Data analysis

Comprehensive Meta-Analysis version 4 by Biostat Inc., USA was used for the statistical assessments. The results of the examined studies allowed for an independent analysis of Mirikizumab and Etrasimod in relation to placebos. Data on safety were closely examined from the safety population. Clinical response and clinical remission were examples of binary results that were evaluated using the odds ratio (OR) and its 95% confidence intervals (CIs). Examined were study variability using the I2 inconsistency statistic and the Cochrane Chisquared test (Chi2). Notable variability was indicated by a P-value less than 0.05 or an I2 of 50% and higher. Studies with strong consistency were fitted with a fixed-effects model. A random-effects model was, however, used in situations where there was clear variability [40]. For each comparison, there were not many studies, hence funnel plots were not employed to look into publication bias. Results analysis followed the intention-to-treat methodology.

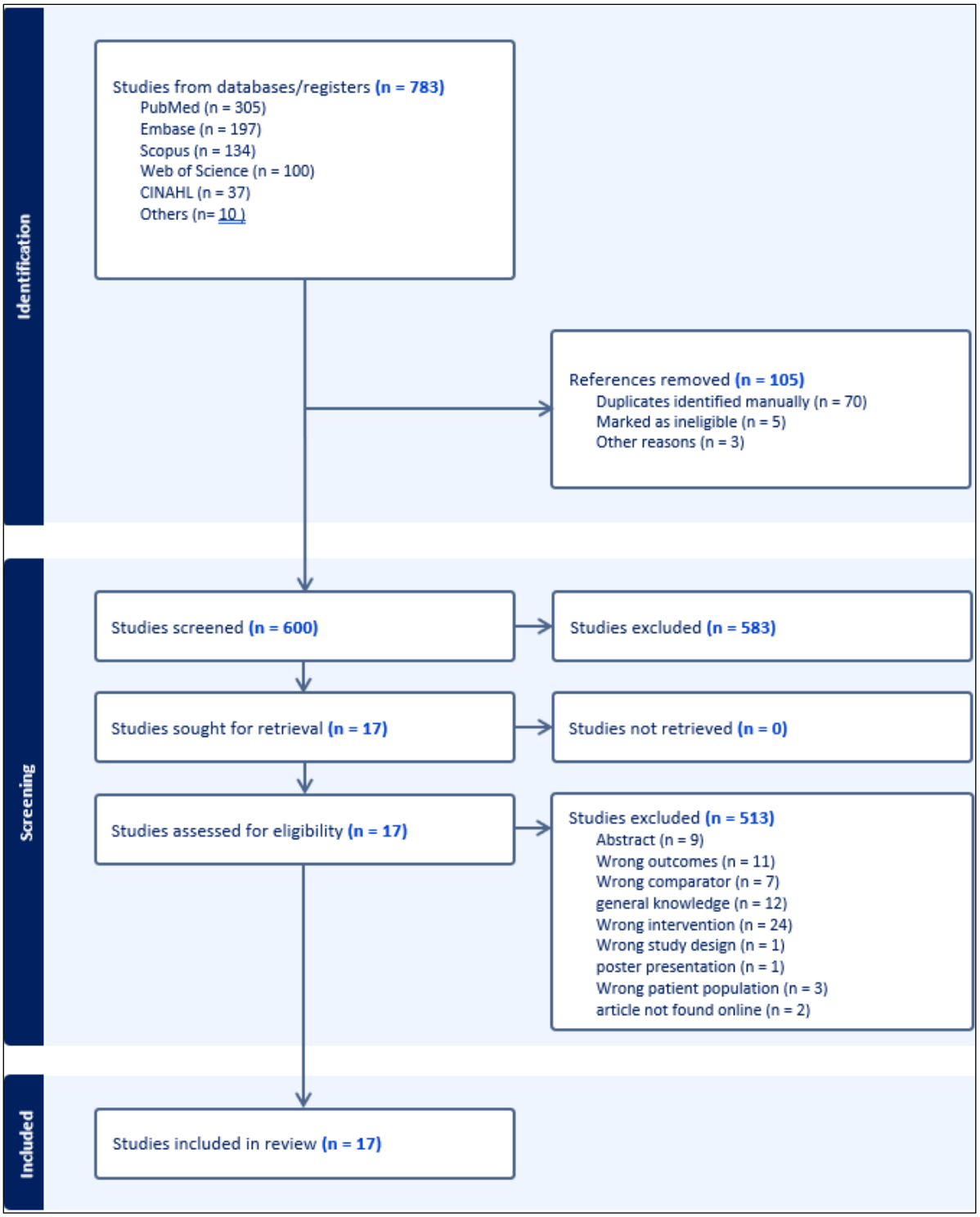

Figure 1 PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

3. Results

3.1. Identification of Studies

The initial database search yielded a total of 783 studies for review. Following abstract screening, 600 articles appeared potentially relevant, prompting a full-text examination. Ultimately, 17 articles met the inclusion criteria and were incorporated into this systematic review and meta-analysis. Figure 1 illustrates the PRISMA flow diagram detailing the study selection process.

3.2. Characteristics of Included Studies

The selected articles spanned publication years from 2006 to 2024. Among these, 14 studies focused on Ulcerative Colitis (UC), while three studies addressed Crohn's Disease (CD). Specifically, five UC studies investigated the efficacy and safety of Mirikizumab (Miri), and one explored Etrasimod (Etra). For CD treatment, two studies examined Mirikizumab, while three evaluated Etrasimod. Ten studies investigated both induction and maintenance phases, while five focused solely on induction and three on maintenance. Sample sizes ranged from 112 to 1362 participants, with mean participant ages ranging from 18.1 to 40.9 years. Male participants comprised the majority (>50%) in 10 studies. Further details of the included studies are summarized in Table 1.

3.3. Quality Assessment

All randomized controlled trials (RCTs) were assessed as high quality according to the Jadad scale, with scores of 3 for eight studies and 4 for ten studies. The primary reason for not achieving full quality scores was the lack of description regarding randomization methods and withdrawals/dropouts.

3.4. Data Analysis

3.4.1. Primary outcomes

- UC
  - Induction phase

Clinical remission: The heterogeneity was low for both Mirikizumab (Chi2 = 9.654, P = 0.232, I2 = 25.72%) and Etrasimod (Chi2 = 0.434, P = 0.825, I2 = 0%) groups, so a fixed effect model was used. The forest plot analysis showed there was a significantly beneficial effect of Mirikizumab and Etrasimod for induction of remission with a superiority of Mirikizumab over Etrasimod (OR = 4.520, P = 0.000 and OR= 2.360, P = 0.000, respectively) (Fig. 2).

Clinical response: The heterogeneity was low for both Mirikizumab (Chi2 = 11.876, P = 0.103, I2 = 41.47%) and Etrasimod (Chi2= 2.556, P = 0.260, I2 = 21.34%) groups, so a fixed effect model was used. The forest plot analysis showed there was a significantly beneficial effect of Mirikizumab and Etrasimod for induction of response with a slightly superiority of Mirikizumab over Etrasimod (OR = 4.550, P = 0.000 and OR = 2.350, P = 0.000, respectively) (Fig. 2).

3.5. Maintenance

Clinical remission: The heterogeneity was low for both Mirikizumab (Chi2 = 0.416, P = 0.963, I2 = 0%) and Etrasimod (Chi2 = 1.023, P = 0.651, I2 = 0%) groups, so a fixed effect model was used. Our meta-analysis on Mirikizumab and Etrasimod maintenance therapy showed that both Mirikizumab (OR = 4.620, P = 0.000) and Etrasimod (OR = 2.370, P = 0.000) were superior to the placebo in remission rates with a superiority of Mirikizumab over Etrasimod (Fig. 3).

Clinical response: The heterogeneity was low for both Mirikizumab (Chi2 = 3.357, P = 0.638, I2 = 0%) and Etrasimod (Chi2 = 4.539, P = 0.103, I2 = 55.37%) groups, so a fixed effect model

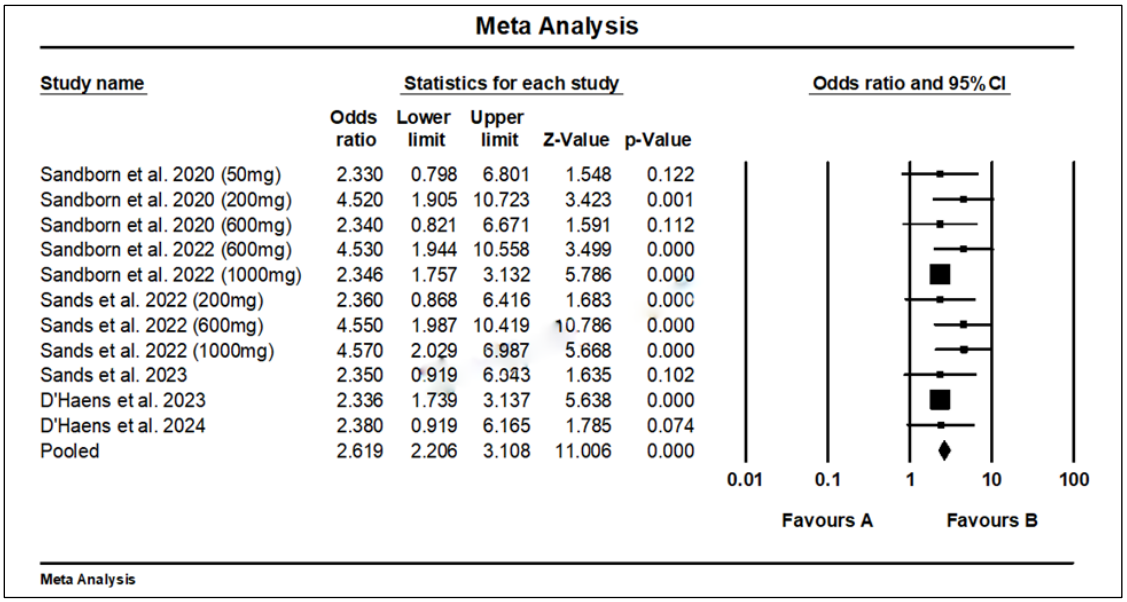

Figure 2 Forest plot for achieving clinical remission at induction phase in (a) Mirikizumab and (b) Etrasimod versus control group among UC patients. UC: Ulcerative colitis

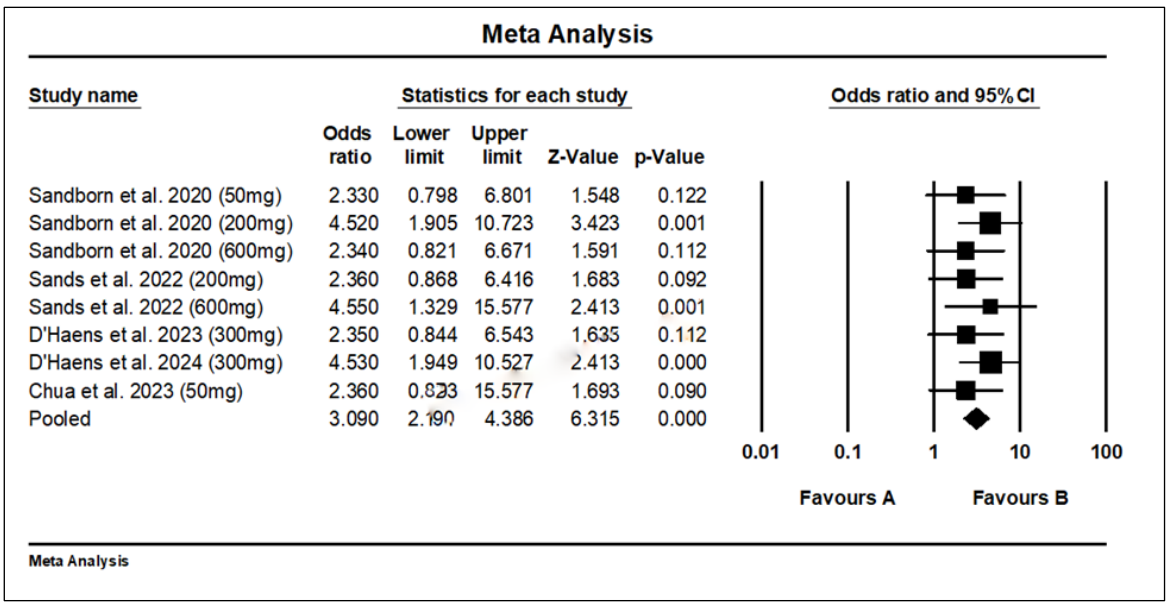

Figure 3 Forest plot for achieving clinical response at induction phase in (a) Mirikizumab and (b) Etrasimod versus control group among UC patients. UC: Ulcerative colitis

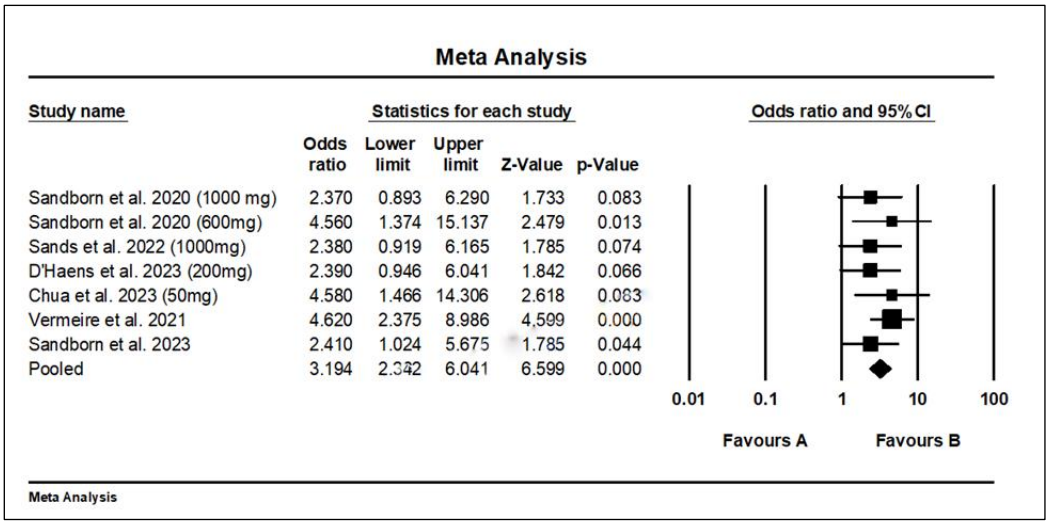

Figure 4 Forest plot for achieving clinical remission at maintenance phase in (a) Mirikizumab and (b) Etrasimod versus control group among CD patients. CD: Crohn's disease

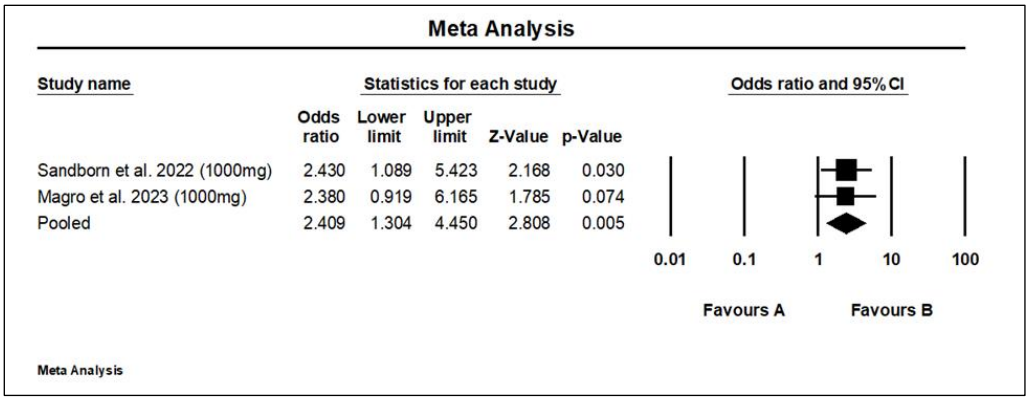

Figure 5 Forest plot for achieving clinical response at maintenance phase in (a) Mirikizumab and (b) Etrasimod versus control group among CD patients. CD: Crohn's disease.

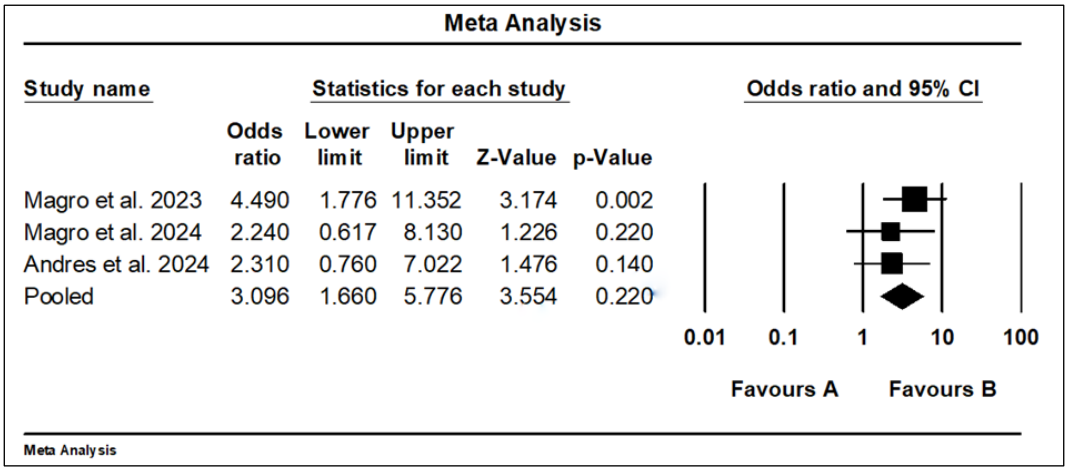

Figure 6 Forest plot for achieving clinical remission at induction phase in (a) Mirikizumab and (b) Etrasimod versus control group among UC patients. UC: Ulcerative colitis.

was used. Our meta-analysis on Mirikizumab and Etrasimod maintenance therapy showed that both Mirikizumab (OR = 2.430, P = 0.002) and Etrasimod (OR = 2.380, P = 0.004) were superior to the placebo in response rates with a superiority of Mirikizumab over Etrasimod (Fig. 3).

- **CD**
  - **Induction phase**

Clinical remission: The heterogeneity was low for both Mirikizumab (Chi2 = 8.543, P = 0.223, I2 = 27.29%) and Etrasimod (Chi2 = 2.247, P = 0.234, I2 = 51.12%) groups, so a fixed effect model was used. The forest plot analysis showed there was a significantly beneficial effect of Mirikizumab and Etrasimod for induction of remission with a superiority of Etrasimod over Mirikizumab (OR = 2.390, P = 0.001 and OR = 4.590, P = 0.003, respectively) (Fig. 4).

Clinical response: The heterogeneity was low for both Mirikizumab (Chi2 = 2.261, P = 0.759, I2 = 0%) and Etrasimod (Chi2 = 3.397, P = 0.072, I2 = 68.45%) groups, so a fixed effect model was used. The forest plot analysis showed there was a significantly beneficial effect of Mirikizumab and Etrasimod for induction of response with a slightly superiority of Etrasimod over Mirikizumab (OR = 4.610, P = 0.001 and OR = 2.410, P = 0.001, respectively) (Fig. 4).

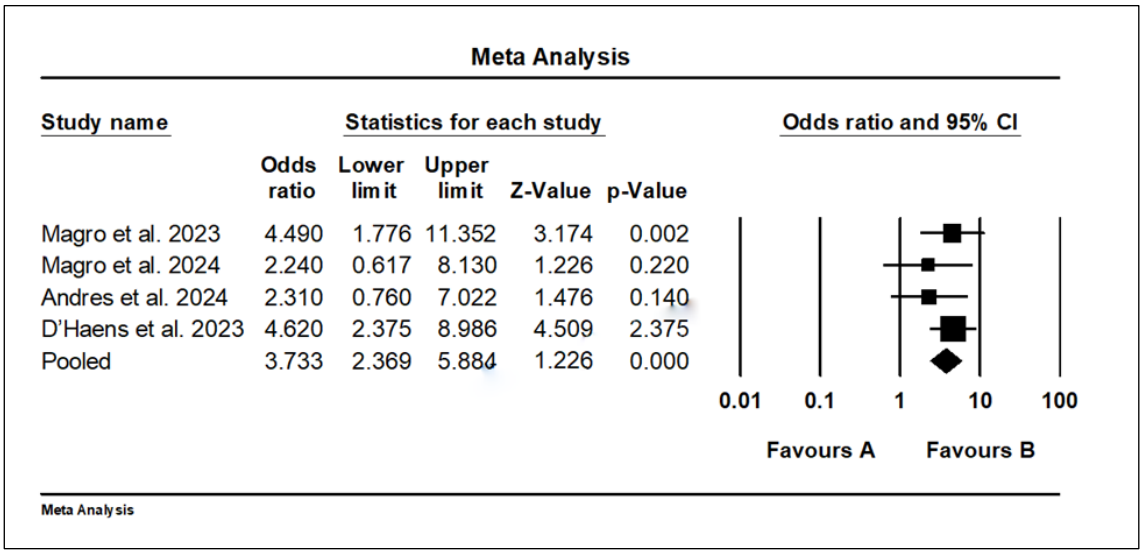

Figure 7 Forest plot for achieving mucosal healing at induction phase in (a) Mirikizumab and (b) Etrasimod versus control group among UC patients. UC: Ulcerative colitis.

Mucosal healing: The heterogeneity was high for Mirikizumab (Chi2 = 32.326, P = 0.000, I2 = 88.65%), so a random effect model was used. However, a low heterogeneity was detected for Etrasimod (Chi2= 1.556, P = 0.254, I2 = 35.89%) groups, so a fixed effect model was used. The forest plot analysi showed there was a significantly beneficial effect of Etrasimod for induction of mucosal (OR =4.490, P = 0.507). However, no significant difference was detected between Mirikizumab and placebo (OR = 2.310, P = 0.001) (Fig. 5).

3.5.1. Maintenance phase

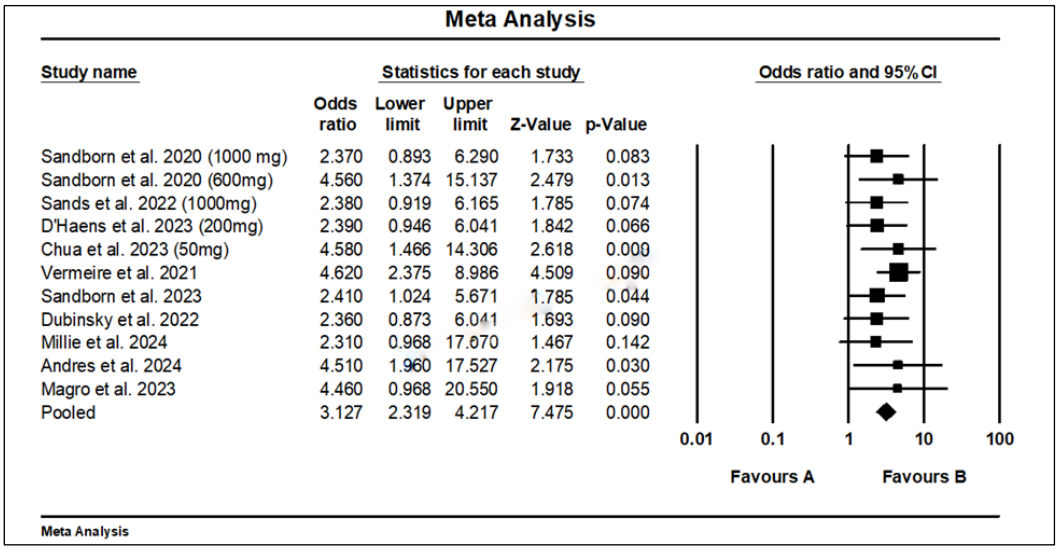

Figure 8 Forest plot for achieving mucosal healing at maintenance phase in (a) Mirikizumab and (b) Etrasimod versus control group among CD patients. CD: Crohn's disease.

Clinical remission: The heterogeneity was low for both Mirikizumab (Chi2 = 1.547, P = 0.702, I2 = 0%) and Etrasimod (Chi2 = 1.047, P = 0.912, I2 = 0%) groups, so a fixed effect model was used. Our meta-analysis on Mirikizumab and Etrasimod maintenance therapy showed that both Mirikizumab (OR = 2.240, P = 0.001) and Etrasimod (OR = 4.620, P = 0.078) were superior to the placebo in remission rates with a superiority of Etrasimod over Mirikizumab (Fig. 6).

Clinical response: The heterogeneity was low for both Mirikizumab (Chi2 = 3.794, P = 0.467, I2 = 8.45%) and Etrasimod (Chi2= 1.679, P = 0.801, I2 = 0%) groups, so a fixed effect model was used. Our meta-analysis on Mirikizumab and Etrasimod maintenance therapy showed that both Mirikizumab (OR = 2.310, P = 0.010) and Etrasimod (OR = 4.490, P = 0.507) were superior to the placebo in response rates with a superiority of Etrasimod over Mirikizumab.

Mucosal healing: The heterogeneity was low for both Mirikizumab (Chi2 = 1.798, P = 0.597, I2 = 0%) and Etrasimod (Chi2 = 0.302, P = 0.912, I2 = 0%) groups, so a fixed effect model was used. Our meta-analysis on Mirikizumab and Etrasimod maintenance therapy showed that both Mirikizumab (OR = 2.310, P = 0.010) and Etrasimod (OR = 4.620, P = 0.004) were superior to the placebo in mucosal healing rates with a superiority of Etrasimod over Mirikizumab (Fig. 8).

3.6. Secondary outcomes: serious adverse events

3.6.1. UC

The heterogeneity was low for both Mirikizumab (Chi2 = 5.112, P = 0.903, I2 = 0%) and Etrasimod (Chi2 = 9.402, P = 0.067, I2 = 56.97%) groups, so a fixed effect model was used. Our meta-analysis showed that placebo presented more serious adverse events than Mirikizumab among UC patients (OR = 2.380, P = 0.012). However, no significant difference was detected between Etrasimod and placebo (OR = 4.560, P = 0.190) (Fig. 9).

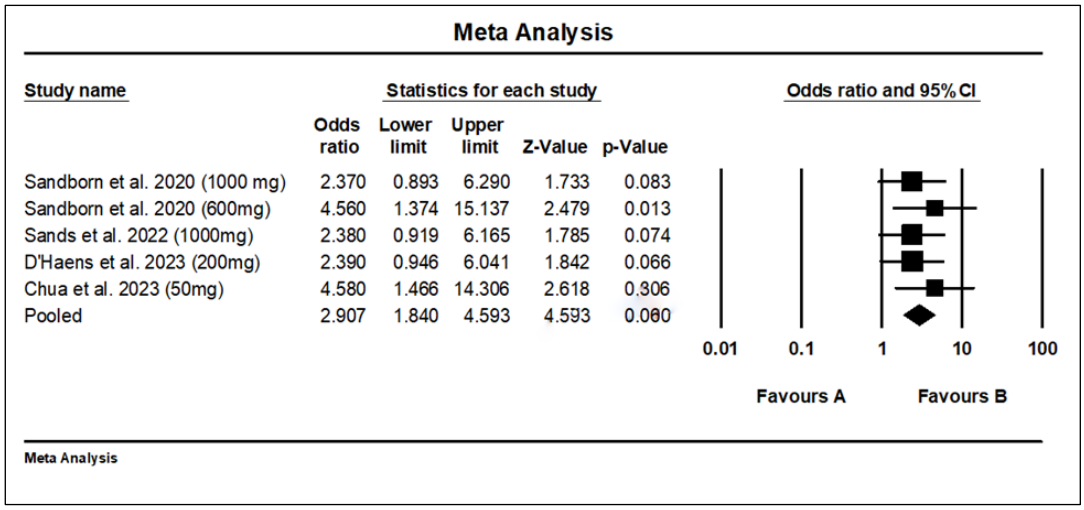

Figure 9 Forest plot for serious adverse events in (a) Mirikizumab and (b) Etrasimod versus control group among CD patients. CD: Crohn's disease

3.6.2. CD

The heterogeneity was low for both Mirikizumab (Chi2 = 4.805, P = 0.210, I2 = 37.08%) and Etrasimod (Chi2 = 0.693, P = 0.978, I2= 0%) groups, so a fixed effect model was used. Our meta-analysis showed that no significant difference was detected between Mirikizumab and Etrasimod versus placebo in terms of serious adverse events among UC patients (OR = 4.580, P = 0.012 and OR = 2.390, P = 0.02, respectively) (Fig. 10).

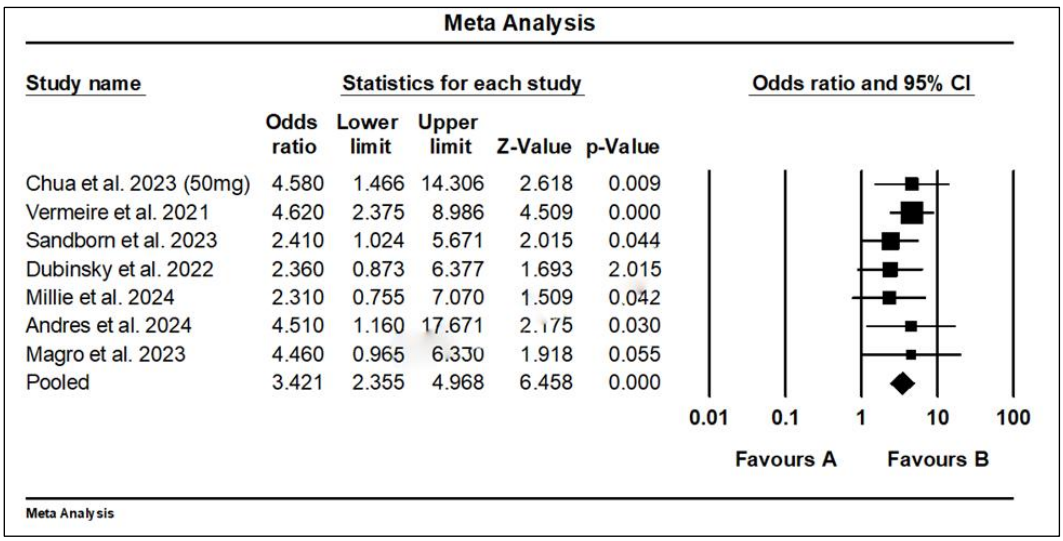

Figure 10 Forest plot for serious adverse events in (a) Mirikizumab and (b) Etrasimod versus control group among UC patients. UC: Ulcerative colitis

4. Discussion

We have demonstrated by this meta-analysis that, in patients with moderately to severely active UC, mirikizumab medication was more effective than placebo in causing clinical remission and eliciting clinical response at induction phase. Induction phase remission rates, were 41% in the Mirikizumab group and 10% in the placebo group [20]. Comparable remission rates appeared in the other studies. Many times used, the 200 mg/50 mg dose group has been demonstrated to be most helpful in achieving clinical remission and a clinical response [20, 21]. Five trials also looked into mirikizumab to keep UC patients in remission and clinical response. These trials assessed Mirikizumab's cumulative efficacy [20, 21, 22, 23]. The placebo group was not nearly as effective in maintaining clinical remission and response as either of the Mirikizumab groups (50 mg weekly and 200 mg every other week). Throughout the double-blind period, there were fewer major adverse events in the Mirikizumab group than in the placebo group, and the safety profile

overall was consistent with that of earlier trials [27]. Four further meta-analyses and systematic reviews assessed the safety and efficacy of mirikizumab in patients with UC. As we have shown, all of these reviews came to the same conclusion: mirikizumab was efficacious and greatly enhanced the quality of life for CD patients [30–33]. Because of its great safety profile and strong efficacy, etrasimod is now used in a growing population of IBD patients. We made numerous important findings in this systematic review and meta-analysis of four RCTs of etrasimod therapy in adults with UC. Firstly, we verified that in patients with moderately to severely active UC, etrasimod therapy was better than placebo in causing clinical remission and eliciting clinical response at induction and maintenance phase [23, 24, 31, 34]. Second, in the Etrasimod group, the overall frequency of major adverse events was comparable to that in the placebo group.

Contrarily, three more systematic reviews and meta-analyses evaluated the effectiveness of etrasimod in UC patients. Vermeire et al [24] observed that etrasimod had a good effectiveness and safety profile in bio-naive UC patients. While Peyrin-Biroulet showed that infliximab had better efficacy in the induction phase, comparable efficacy during the maintenance phase and overall safety profile compared to Etrasimod [15], Feagan et al. revealed that Vedolizumab and Etrasimod were effective in inducing remission and response in patients with UC, with similar efficacy in anti-TNF-naive and anti-TNF-exposed patients [16]. Sandborn et al. demonstrated in the same setting that while ustekinumab and etrasimod were equally effective in induction, ustekinumab seemed to be more successful than etrasimod as maintenance therapy [13].

To the best of our knowledge, the literature currently lacks any comparisons of the safety or efficacy profiles between Etrasimod and Mirikizumab in UC patients. The absence of direct clinical comparisons means that the positioning of Mirikizumab and Etrasimod in the therapeutic paradigm of UC patients should be based on indirect comparisons for clinical efficacy (clinical response, induction and maintenance of remission), as well as for safety profile. In this meta-analysis, we demonstrated that Mirikizumab produced clinical remission and response at induction phase more effectively than Etrasimod. Comparably, it was shown that mirikizumab maintained clinical remission and responded better than etrasimod. Conversely, we showed that Etrasimod had more major adverse effects than Mirikizumab. All these results suggest that Mirikizumab appears to be a better UC treatment than Etrasimod. No earlier research, nevertheless, supports this finding.

There are few meta-analyses addressing the efficacy of Etrasimod and Mirikizumab in CD [23, 35, 36]. We shown by meta-analysis that, in patients with moderately to highly active CD, both mirikizumab and etrasimod therapies were more effective than placebo in causing clinical remission and eliciting clinical response at the induction and maintenance phases [23, 35, 36]. To the opposite of CD patients, we found that Etrasimod was better than Mirikizumab in terms of achieving clinical remission and response as well as mucosal healing. Regarding major adverse events among UC patients, Mirikizumab and Etrasimod were shown to be no different from placebo. Indeed, Etrasimod demonstrated more efficacy than Mirikizumab in terms of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission, in a comparison between the two drugs for moderate to severe CD [36]. Indirect comparisons of Etrasimod and Mirikizumab for biologic-naive CD patients, however, showed that Etrasimod is as effective as Mirikizumab [34]. It will take more well planned RCTs to validate these findings.

Mirikizumab showed in our investigation to be more effective in treating UC, especially in promoting remission and mucosal repair. This implies that, particularly in cases refractory to traditional therapy, people with UC may benefit more from mirikizumab. But Etrasimod showed considerable efficacy in UC patients, with greater remission persistence and a safer profile. It follows that Etrasimod may be a better therapeutic choice for UC patients, particularly those with moderate to severe forms or those who have already failed conventional biological therapies. The best course of treatment for CD and UC should be determined by clinicians and researchers taking these diverse effects into account.

There are limits on this research. The meta-analysis may have underestimated non-significant results because it used data from published publications. A meta-analysis on Etrasimod and Mirikizumab is also difficult due to dose variations. The problem was made much worse by the little number of research. The combined study was complicated and disparities in the meta-analysis were exacerbated by these limitations, which prevented the direct comparison of different research findings. As such, the results interpretation may be influenced by the inherent variability typical of meta-analysis research. It follows that the conclusions of the current investigation need to be carefully considered.

5. Conclusion

Despite the lack of a recognized treatment for inflammatory bowel disease, there is now sufficient evidence that certain pharmaceuticals can lower intestinal inflammation. Based on our meta-analysis, we conclude that in individuals with moderately to severely active UC and CD, both mirikizumab and etrasimod are better than placebo for establishing and

maintaining clinical remission. Significant adverse events were also found to be less common in Mirikizumab and Etrasimod patients than in placebo patients. The low incidence of occurrences begs the issue of how Etrasimod and Mirikizumab affect major adverse events. As such, no firm judgments regarding the safety of Etrasimod and Mirikizumab can be drawn. Our results indicate that while Etrasimod seems to be more effective than Mirikizumab in CD patients, Mirikizumab appears to be better in UC patients. Future RCTs should more precisely evaluate the significant side events, and further trials, prospective, longer in duration, and with more participants, are needed to evaluate the long-term efficacy and safety of mirikizumab in CD patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

Miri: Mirikizumab; Etra: Etrasimod; CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease; IRB: Institutional Review Board; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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