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Safety and efficacy of ontamalimab in inflammatory bowel disease: A systematic review and dose-response meta-analysis

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ABSTRACT

Inflammatory bowel diseases (IBDs), such as Crohn's disease and ulcerative colitis, involve chronic inflammation of the digestive tract. The incidence of IBD has been increasing globally, posing a growing burden despite advancements in treatment. Novel therapies targeting adhesion molecules such as MAdCAM-1 show promise by specifically inhibiting lymphocyte infiltration into the gut, potentially offering safer and more effective treatment options. This meta-analysis and systematic review were conducted to provide efficacy and safety analysis of ontamalimab for IBD treatment. Dose-response (DRMA), network (NMA), and random effect meta-analysis were conducted to extract clinical response, clinical remission, biomarker change, and adverse events of ontamalimab. Studies were retrieved from PubMed, Cochrane, and EMBASE to describe the pooled risk ratio (RR) and heterogeneity was determined if I^2 >50%. RoB2 tool and ROBINS-I were used to assess risk of bias in RCT and clinical trial studies, respectively. The result was considered significant if p<0.05. A total of 670 studies were screened, resulting in 8 multicentre studies. There were significant differences in clinical response (RR: 1.39; 95%CI: 1.12–1.73; p = 0.003; I^2= 35%), clinical remission (RR: 1.72; 95%CI: 1.17–2.53; p=0.006; I^2= 26%), mean change of FC (RR: 624.29; 95%CI: 543.28-705.29; p<0.001; I^2= 0%), mean change of CRP serum (RR: 9.71; 95%CI: 7.12–12.3; p<0.001), and mean MAdCAM-1 serum level (RR: 235.57; 95%CI: 203.80–267.33; p <0.001) between ontamalimab 75 mg and placebo after 12 wk of treatment. Meanwhile, adverse events from both groups were similar to those observed in patients treated with either placebo or ontamalimab. This study concluded that ontamalimab 75mg demonstrated significant efficacy in treating IBD, achieving superior outcomes in clinical response and clinical remission compared to placebo. Importantly, no cases of PML and significant adverse events were detected, indicating a favorable safety profile relative to other anti-MAdCAM-1 therapies.

ABSTRAK

Inflammatory bowel diseases (IBDs), penyakit radang usus, seperti penyakit Crohn dan kolitis ulseratif, menyebabkan peradangan kronis pada saluran pencernaan. Insiden IBD meningkat secara global, menimbulkan beban yang semakin besar meskipun ada kemajuan dalam pengobatan. Terapi target yang berfokus pada molekul adesi, seperti MAdCAM-1, memberi harapan baru dalam menghambat infiltrasi limfosit ke lumen usus, menawarkan pilihan pengobatan yang lebih aman dan efektif. Tinjauan sistematis dan meta-analisis ini dilakukan untuk mengevaluasi efektivitas dan keamanan ontamalimab sebagai terapi pada IBD. *Dose-response* (DRMA), *network* (NMA), dan meta-analisis efek random dirancang untuk menganalisa respon klinis, remisi klinis, perubahan biomarker, dan efek samping ontamalimab. Studi diambil dari PubMed, Cochrane, dan EMBASE untuk menjabarkan *pooled risk ratio* (RR) dan heterogenitas ditetapkan jika I^2 >50%. RoB2 dan ROBINS-I digunakan untuk

Keywords:
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menelaah risiko bias dari studi RCT dan uji klinis. Hasil dinyatakan signifikan jika p<0.05. Sebanyak 670 studi disaring dan diperoleh 8 studi multicenter yang memenuhi kriteria. Terdapat perbedaan yang bermakna pada respon klinis (RR: 1,39; 95% CI: 1,12–1,73; p=0,003; I^2=35%), remisi klinis (RR: 1,72; 95% CI: 1,17–2,53; p=0,006; I^2=26%), perubahan rerata kadar *fecal calprotectin*/FC (RR: 624,29; 95%CI: 543,28–705,29; p<0,001; I^2=0%), perubahan rerata kadar serum CRP (RR: 9,71; 95%CI: 7,12–12,31; p<0,001), serta kadar serum MAdCAM-1 (RR: 235,57; 95%CI: 203,80–267,33; p<0,001) antara ontamalimab 75 mg dibandingkan dengan plasebo setelah 12 minggu pemberian. Sementara itu, kejadian efek samping pada kedua kelompok serupa dengan yang ditemukan pada pasien yang mendapatkan plasebo maupun ontamalimab. Studi ini menyimpulkan bahwa ontamalimab 75 mg menunjukkan efektivitas yang signifikan dalam penatalaksanaan IBD, dengan hasil respon klinis dan remisi klinis yang lebih baik dibandingkan plasebo. Selain itu, tidak ditemukan kasus PML maupun efek samping berat, menunjukkan profil keamanan yang baik dibandingkan dengan terapi anti-MAdCAM-1 lainnya.

INTRODUCTION

Inflammatory bowel disease (IBD) is a broad term used to describe chronic inflammation of the intestines, encompassing ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis. The exact cause of IBD is not fully understood, but potential factors believed to influence its development include bacterial presence, immune system alterations, and genetic factors.[1] There was an almost 50% increase in IBD cases in the span of 29 yr globally, from 3.32 million to 4.90 million in 2019. This study also reports the US (245.3 cases per 100.00 people) and China (66.9 cases per 100.00 people) are the top two countries with the most cases.[2] In Southeast Asia, the average annual increase and mean annual growth in the incidence of IBD were reported as the second highest (1.45% and 1.58%, respectively) after East Asia, leading to significant concern in IBD healthcare.[3] The prevalence of IBD in Indonesia is approximately 0.55 per 100,000 for UC and CD at 0.33 per 1,000,000.[4]

Despite advancements in treatment, many patients do not tolerate or respond to conventional therapies like 5-aminosalicylic acid, thiopurines, and corticosteroids. Furthermore, the long-term use of glucocorticoids poses greater risks than benefits. Adhesion molecules, crucial for guiding lymphocytes to inflamed gut sites, hold significant promise as treatment targets for IBD. Mucosal addressin cell adhesion molecule-1 (MAdCAM-1) receptor, which is elevated in IBD and is responsible for lymphocyte migration into gut tissue, presents a promising new target for therapy in UC and CD.[5-9] Ontamalimab, an anti-inflammatory human immunoglobulin G2 monoclonal antibody, also known as PF-00547659, selectively binds with high affinity to MAdCAM-1, thereby inhibiting the binding of α4β7+ lymphocytes to MAdCAM-1 receptor sites.[9] Chu *et al.*,[10] PF-00547659 demonstrated significantly greater efficacy than infliximab (OR=6.36; 95%CI 1.09–37.21) and azathioprine (OR=4.22; 95%CI 1.93–9.22) in inducing clinical remission.

The promising novel treatment of IBD needs to be assessed further. Several randomized controlled trials (RCTs) have been conducted to assess the efficacy and safety of ontamalimab, including the TOSCA,[11] OPERA,[12] and TURANDOT[13] studies, which evaluated these outcomes in both UC and CD individually. These trials were followed by maintenance studies, OPERA II[14] and TURANDOT II,[15]

that further investigated these indicators over the long term. Meanwhile, there are only a few systematic review or meta-analysis evaluating the efficacy and safety of ontamalimab in treating IBD. The previous meta-analysis by Awad *et al.*,[16] included only the 25, 75, and 225 mg doses in their study. Other doses reported in different RCTs were not examined, thereby limiting the evaluation of dose variability. In contrast, the present DRMA meta-analysis incorporates a broader range of doses. Moreover, it does not perform a NMA meta-analysis as conducted in the present study, that also have not been previously undertaken. This study was conducted to complement previous studies and represents the first DRMA and meta-analysis to evaluate the efficacy and safety of ontamalimab in the management of IBD.

MATERIAL AND METHODS

Search strategy

A comprehensive search was conducted using PubMed, Cochrane, and Scopus from the earliest available date until June 19th, 2024. The search was using keywords "Ontamalimab" OR "SHP647" OR "Monoclonal Antibody Against Mucosal Addressin Cell Adhesion Molecule-1" OR "MAdCAM-1" OR "PF-00547659" AND "Inflammatory bowel disease" OR "Ulcerative colitis" OR "Crohn disease". This study was registered in PROSPERO with registration number [CRD42024600868].

Study selection

Inclusions of the study were as follows 1) Population: patients diagnosed with moderate-to-severe IBD, including CD and UC, based on American Gastroenterological Association; 2) Intervention: patients treated with Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1) or ontamalimab or PF-00547659, whereas the control group was treated with placebo. Meanwhile, interventional studies that included additional treatments alongside ontamalimab and non-English language studies were excluded to ensure consistency in data extraction and interpretation. We compared various doses of ontamalimab (7.5; 22.5; 25; 75; and 225 mg) using the DRMA method; 3) Outcome: Clinical response, clinical remission, biomarker change including change in mean serum MAdCAM-1 level, mean FC concentration, mean serum CRP concentration, and adverse events. Further information on clinical response and remission can be found in TABLE 1.

Data extraction

Three review authors independently extracted data from each selected study utilizing a structured and standardized form that was created by discussion. First authors' names and publication year, study design, country of origin, center of the study, grouping, sample size, UC/CD Grade, intervention protocol, follow-up period, patients' mean age, clinical remission, clinical response, mean serum MAdCAM-1 level, mean FC concentration, mean serum CRP concentration, and adverse events were assesed and extracted into the form.

Quality assessment

Three review authors assessed the quality of the studies independently through the risks of bias from each included study, utilizing the Cochrane risk of bias tool for five randomized trials (RoB ver.2)[17] and ROBINS-I for two non-randomized trials[18]. The certainty of evidence was evaluated using the GRADE approach, which considers domains including risk of bias, inconsistency, indirectness, and imprecision, with the overall quality rated as 'high', 'moderate', 'low', or 'very low'. Additionally, funnel

plot analysis was performed to assess the potential presence of publication bias. Any conflicts were resolved by discussion until concurrence was reached.

Statistical analysis

Network meta-analysis and DRMA were performed in R Studio with the "netmeta" and "dosresmeta" packages, respectively. The DRMA meta-analysis was assessed using the Greenland & Longnecker method, which estimated the outcome based on the reported effect size across multiple dose levels within each study.[19] Meanwhile, the random-effect model was expressed using Revman 5.4. The pooled risk ratio (RR) with 95% CI was computed for clinical response, clinical remission, and adverse events, meanwhile mean difference (MD) with 95% CI was used to calculate the effect size for biomarker change. Random effect models were used to perform all meta-analysis with statistically significant heterogeneity if $p<0.05$ or $I^2 >50\%$.

RESULTS

Search results

The systematic search identified 670 records through database searches. Following the removal of duplicates, 570 records remained for screening. Subsequently, 83 articles were sought for full-text retrieval after the initial screening of titles and abstracts. Among these, 65 were excluded during the screening process due to inappropriate population (such as conditions other than UC or CD), unsuitable study designs, irrelevant outcomes unrelated to efficacy, biomarker changes, or adverse events, and use of interventions other than ontamalimab, as detailed in FIGURE 1. A total of 8 studies were included in the final analysis.

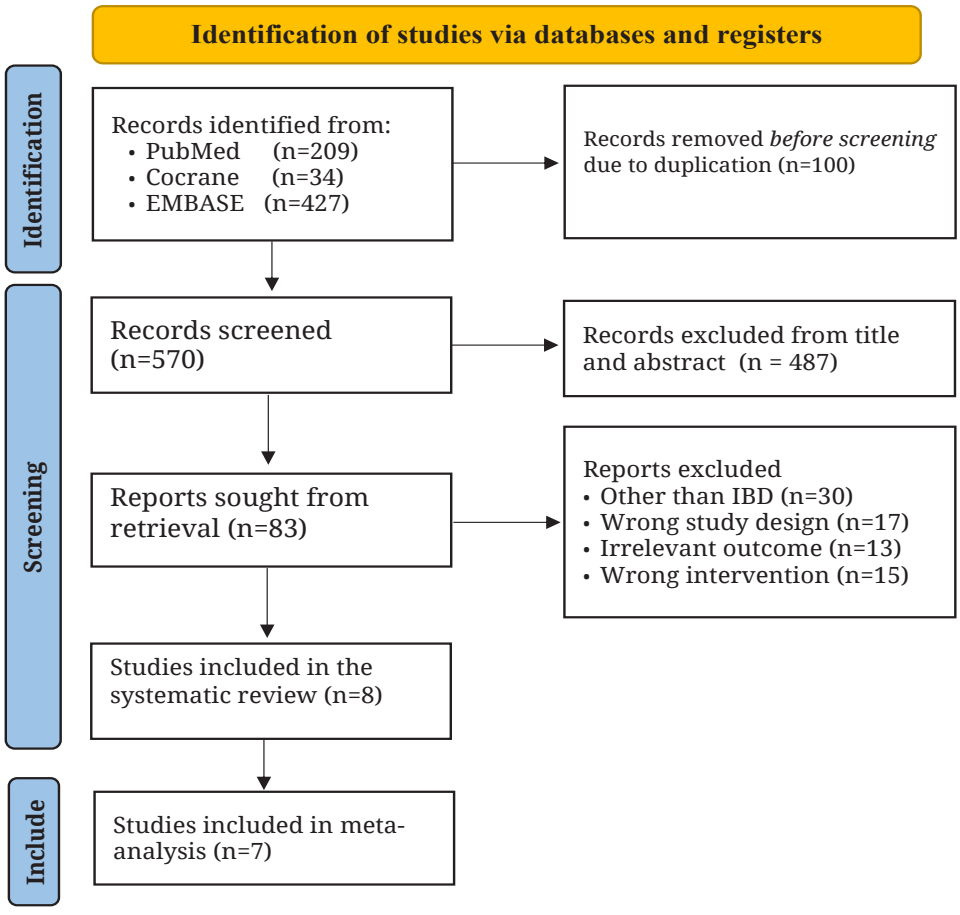


FIGURE 1. PRISMA flow chart for the selected studies

Study characteristics

Eight studies were finally included in this systematic review (TABLE 1). Six multicenter randomized double-blind placebo-controlled trials and two open-label extensions assessing the long-term safety and efficacy of ontamalimab were included in this systematic review, which included a total of 957 patients. Of these, 563 patients were treated with ontamalimab or equivalent therapies, while 394 patients were given a placebo or standard therapy as the control group. These studies were conducted across multiple countries, including Italy, Spain, Japan, Korea, and the USA, and targeted patients with moderate-to-severe CD or UC who were refractory to conventional treatments such as corticosteroids, immunosuppressants, or anti-TNF agents.[12,14,15,20,21]

The intervention protocols included subcutaneous administration of ontamalimab at doses of 22.5; 75; or 225 mg every 4 wk in 5 studies.[12–15,20] One study incorporated a dose-escalation approach for patients with inadequate responses to the initial dose, while another study employed intravenous administration of single or multiple doses.[11,13] The follow-up periods ranged from 12 to 144 wk. Standard therapies across the studies included corticosteroids, anti-inflammatory agents, and vitamin supplements, providing a baseline for comparison with the ontamalimab-treated groups.[14,20]

Clinical remission was a key outcome assessed, defined by disease-specific indices such as the Harvey-Bradshaw index (HBI) for CD and the Mayo score for UC. For CD, clinical remission (HBI < 5) was achieved in 49/115 patients (42.6%) by Week 4 and 45/110 patients (40.9%) by Week 8 in a phase II extension study.[20] Similarly, in UC, remission rates based on the Mayo score were reported as 24/153 patients (15.7%) for the 25 mg dose group and 45/151 patients (29.8%) for the 75 mg dose group in a phase III RCT.[21]

Clinical response, defined as a reduction in disease activity indices (e.g., HBI reduction ≥3 points or a Mayo score reduction ≥3 and ≥30%), showed substantial improvements in intervention groups. For instance, in CD, clinical response rates by Week 4 were 117/177 patients (66.1%) and 93/157 patients (59.2%) by Week 8 in a long-term study.[20] For UC, clinical response rates in an RCT were 67/111 patients (60.4%) for the 25 mg dose and 64/112 patients (57.1%) for the 75 mg dose by Week 12.[21]

Endoscopic Improvement was another critical endpoint, assessed through either centrally-read or local endoscopy scores. In a study on UC, 32/71 patients (45.1%) receiving 75 mg ontamalimab achieved significant improvement by Week 12 compared to 21/73 patients (28.8%) in the placebo group.[13] Biomarkers such as serum CRP, fecal calprotectin (FC), and serum MAdCAM-1 levels provided additional evidence of clinical improvement. In one study, serum CRP levels decreased from a baseline of 20.5 mg/L (95% CI: 16.2–25.3) to 13.4 mg/L (95% CI: 10.0–17.0) by Week 12 for the 75 mg ontamalimab group.[20] Fecal calprotectin levels also showed reductions, with geometric mean levels decreasing from 848 μg/g to 300 μg/g by Week 12.[15]

Safety profiles were evaluated across all studies. Treatment-emergent adverse events (TEAEs) were reported in 249/268 patients (92.9%) in one long-term study, with 10/268 patients (3.7%) experiencing serious adverse events (SAEs) related to the therapy. Discontinuation due to adverse events was relatively low, with rates of 15/268 patients (5.6%) in the treatment period and 0/194 patients in the follow-up period.[15,20]

TABLE 1. Study characteristic of publication included

Author	Study design	Population included	Intervention groups	Total patients assigned to treatment	Follow up period	Mean age (SD)	Effect Measure	
							Clinical remission definition	Clinical response definition
D'Haens *et al.*[20]	Phase 2 extension trial	Moderate to severe CD	-	Onta 75mg: 268	24 wk	36.5 (11.7)	HBI score of < 5	Decrease of ≥3 in HBI score from the baseline value
Vermeire *et al.*[21]	Parallel cilincal trial	Moderate to severe UC (n=380) or CD (n=29)	Induction study 1	UC Placebo: 76 Onta 25mg: 153 Onta 75mg: 151	12 wk	Placebo: 38.3 (13.33); Onta 25mg: 39.4 (13.90); Onta 75mg: 41.2 (14.75)	SF subscore of 0 or 1 with at least a 1-point change from baseline, RB subscore of 0, and endoscopic subscore of 0 or 1 reported by patients using daily e-diary and centrally read endoscopy	Decrease from baseline ≥2 points and ≥30% change, with decrease in the subscore for RB ≥1 point or a subscore for RB ≤1 without rescue therapy and discontinuation; or Decrease from baseline of MCS ≥3 with ≥30% change, accompanied by ≥1 point decrease or absolute score of ≤1 in RB subscore
		Moderate to severe UC (n=279) or CD (n=34)	Induction study 2	UC Placebo: 56 Onta 25mg: 111 Onta 75mg: 112	12 wk	Placebo: 41.6 (13.50); Onta 25mg: 43.5 (14.16); Onta 75mg: 43.9 (13.08)		
Saruta *et al.*[12]	RCT	Moderate to severe CD	-	Placebo: 63 Onta 22,5mg: 66 Onta 75mg:65 Onta 225mg: 68	12 wk	Placebo: 34.4 (11.1); Onta 22,5mg: 37.3 (13.0); Onta 75mg: 34.4 (10.7); Onta 225mg: 35.9 (11.0)	CDAI score < 150	Decrease from baseline in the CDAI score ≥ 70 points
Sandborn *et al.*[14]	RCT	Moderate to severe CD	-	Placebo: 63 Onta 22.5mg: 66 Onta 75mg:65 Onta 225mg: 68	12 wk	Placebo: 34.4 (11.1); Onta 22,5mg: 37.3 (13.0); Onta 75mg: 34.4 (10.7); Onta 225mg: 35.9 (11.0)	CDAI <150	Decrease from baseline in CDAI ≥100 points
Vermeire *et al.*[13]	RCT	Moderate to severe UC	-	Placebo: 73 Onta 7.5mg: 71 Onta 22,5mg: 72 Onta 75mg: 71 Onta 225mg: 70	12 wk	Placebo: 38.6 (12.7); Onta 7.5:41.3 (12.5) Onta 22.5; 42.1(14.7); Onta 75:37.7 (12.4); Onta 225: 41.3 (13.2)	Mayo score ≤2 with no individual subscore >1 and RB subscore ≤1	Decrease from baseline of MCS ≥3 with ≥30% change, accompanied by ≥1 point decrease or absolute score of ≤1 in RB subscore
D'Haens *et al.*[22]	RCT	Moderate to severe CD	Cohort 1 (pilot)	Onta 225mg: 10	12 wk	40.9 (15.9)	HBI score < 5 points	Reduction in HBI score from baseline by ≥ 3 points
			Cohort 2 (interventional)	Onta 225mg: 39	12 wk	37.4 (10.6)		
Reinisch, *et al.*[15]	Open label trial	Moderate to severe UC	Open Label-1	Onta 75 mg no escalation = 70 Onta 75mg escalated to 225mg= 94 Onta 225 mg = 166	72 wk	Onta 75: 40.5 (12.75); Onta 225: 41.1; (13.68)	Mayo score ≤2 with no individual subscore >1 and a RB sub-score of ≤1	Decrease from baseline of ≥3 points with ≥30% change in total MCS, accompanied by a ≥1-point decrease in RB subscore or an absolute RB subscore of ≤1
Vermeire *et al.*[11]	RCT	Moderate to severe UC	single dose phase and multiple dose phase	Ontamalimab: 60 Placebo: 20	4 & 12 wk	Onta: 45.1 (13.1); Placebo: 47.9 (14.8)	Mayo score ≤2 points with no individual subscore exceeding 1 point	Decrease from baseline of ≥3 points with ≥30% change in total MCS, accompanied by a ≥1-point decrease in RB subscore or an absolute RB subscore of ≤1

Onta: Ontamalimab; RCT: randomized controlled trial; UC: ulcerative colitis; CD: Chron's disease; HBI: Harvey-Bradshaw index; CDAI: Chron's disease activity index; RB: rectal bleeding; MCS: Mayo clinical score

A. Risk of bias domains

Study	D1	D2	D3	D4	D5	Overall
Vermeire[21]	+	+	+	+	+	+
Saruta[12]	+	+	+	+	−	+
Sandborn[13]	+	+	+	+	−	+
Vermeire[13]	+	+	+	−	+	+
D'Haens[22]	+	+	−	+	−	−

Judgement:

+ : Low − : Some concerns

Domains:

D1; Bias arising from the randomisation process, D2: Bias due to derivations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in measurement of the outcome, D5: Bias in selection of the reported result

B. Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	Overall
D'Haens[20]	+	+	+	+	−	−	+	+
Reinisch[15]	+	+	+	+	−	−	−	−

Judgement:

+ : Low − : Moderate

Domains:

D1; Bias due to confounding, D2: Bias due to selection of participants, D3: Bias in classification of interventions, D4: Bias in due to deviations from intended interventions, D5: Bias due to missing data, D6: Bias in measurement of outcomes, D7: Bias in selection of the reportes result

FIGURE 2. Risk of bias assessment. A) RoB tools for RCT, and B) ROBINS-I for non-randomized trials.

Risk of bias assessment

Cochrane risk of bias tool (RoB ver.2) and ROBINS-I were used to assess the risk of bias in five randomized trials and two non-randomized trials (FIGURE 2A and B). D'Haens *et al.*[22] showed some concerns in two domains, resulting in moderate risk, following Reinisch *et al.*[15] with four moderate risk domains. Summary findings table for the GRADE approach can be found in supplementary TABLE 1.

Efficacy outcomes

Five studies consisting of 3 moderate-to-severe CD and 2 moderate-to-severe UC were assessed.[12-14,21] The result showed that ontamalimab 75mg significantly increased clinical response (RR: 1.39; 95% CI: 1.12–1.73; p = 0.003; I^2= 35%) and clinical remission (RR: 1.72; 95%CI: 1.17–2.53; p=0.006; I^2= 26%) in comparison to placebo (FIGURE 3A and 3B). Other than that, in comparison to placebo, ontamalimab 75mg both showed the highest OR in clinical response and clinical remission among other doses (OR 2.08; 95% CI 1.12-3.87, OR 2.39; 95% CI 1.48-3.85, respectively) (FIGURE 4A and 4B). The NMA compared clinical response and clinical remission among 5 doses of ontamalimab (7.5; 22.5; 25; 75; and 225 mg) and placebo (FIGURE 6A and 6B). Both clinical response and clinical remission outcomes included 29 pairwise comparisons across 6 trials. Funnel plot analysis revealed no apparent asymmetry, suggesting a low risk of publication bias influencing the overall findings (FIGURE 5A and B). This result indicates ontamalimab 75mg as the most reliable therapeutic benefit both in clinical response and clinical remission compared to placebo, while other doses showed less consistent effect.

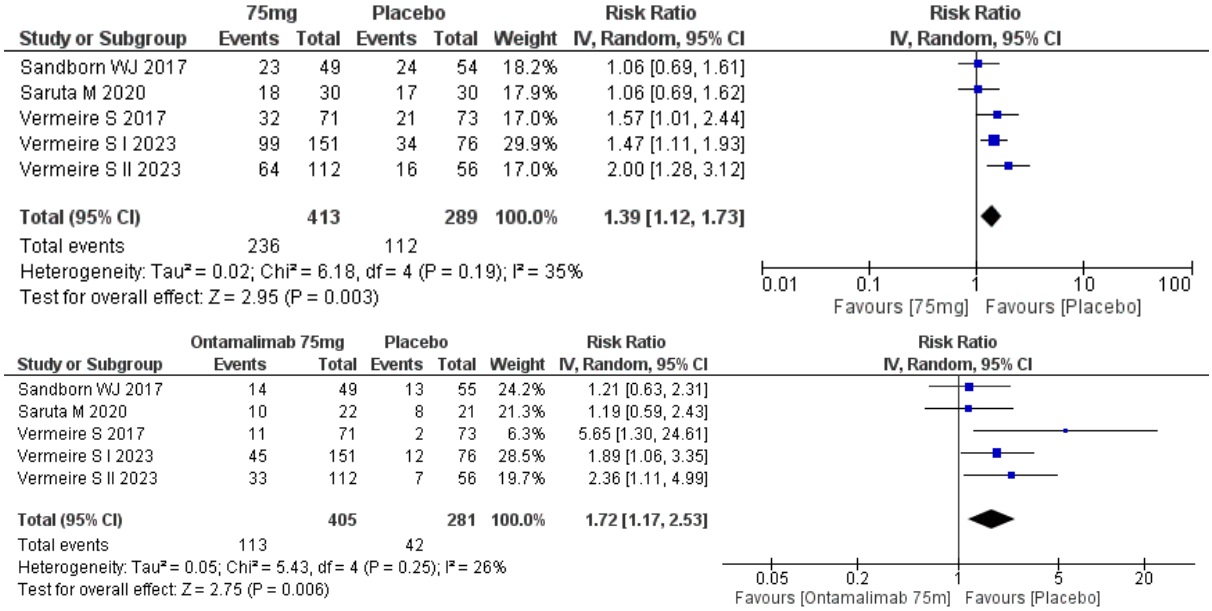


FIGURE 3. Meta-analysis of Ontamalimab 75mg in comparesion to placebo (A) Clinical Response (B) Clincal remission

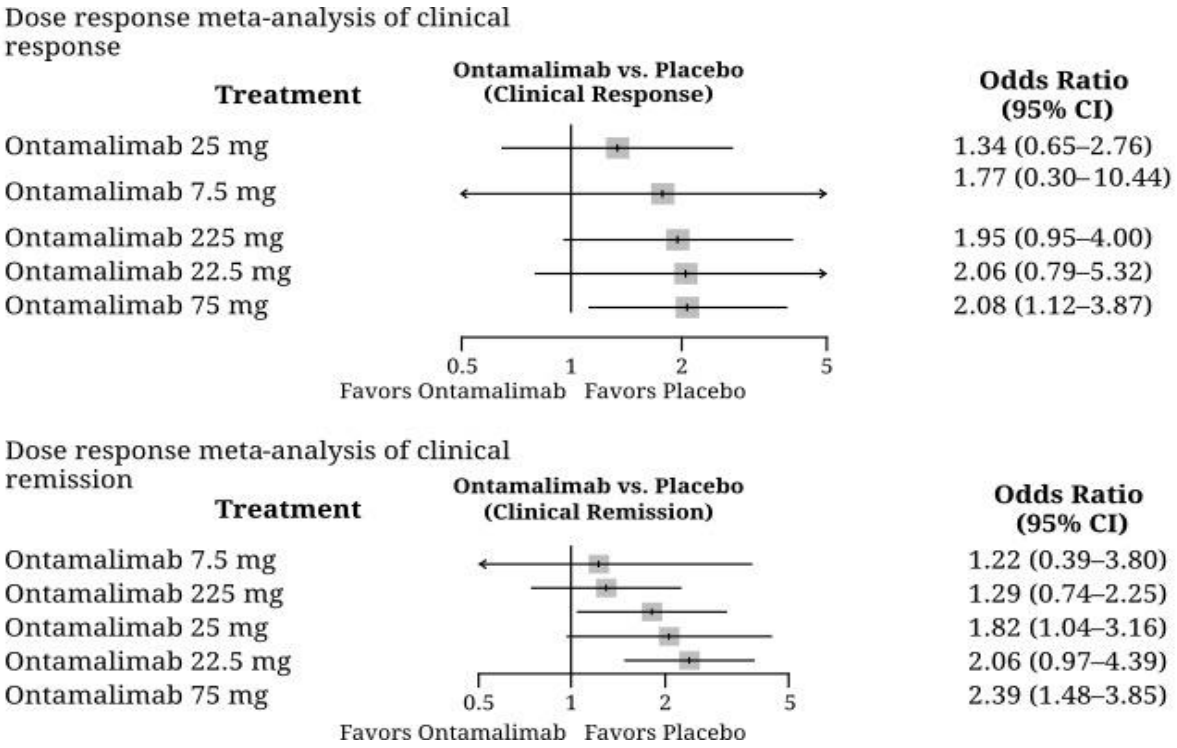


FIGURE 4. Dose Response Meta-analysis of five doses of Ontamalimab (A) Clinical response (B) Clinical remission

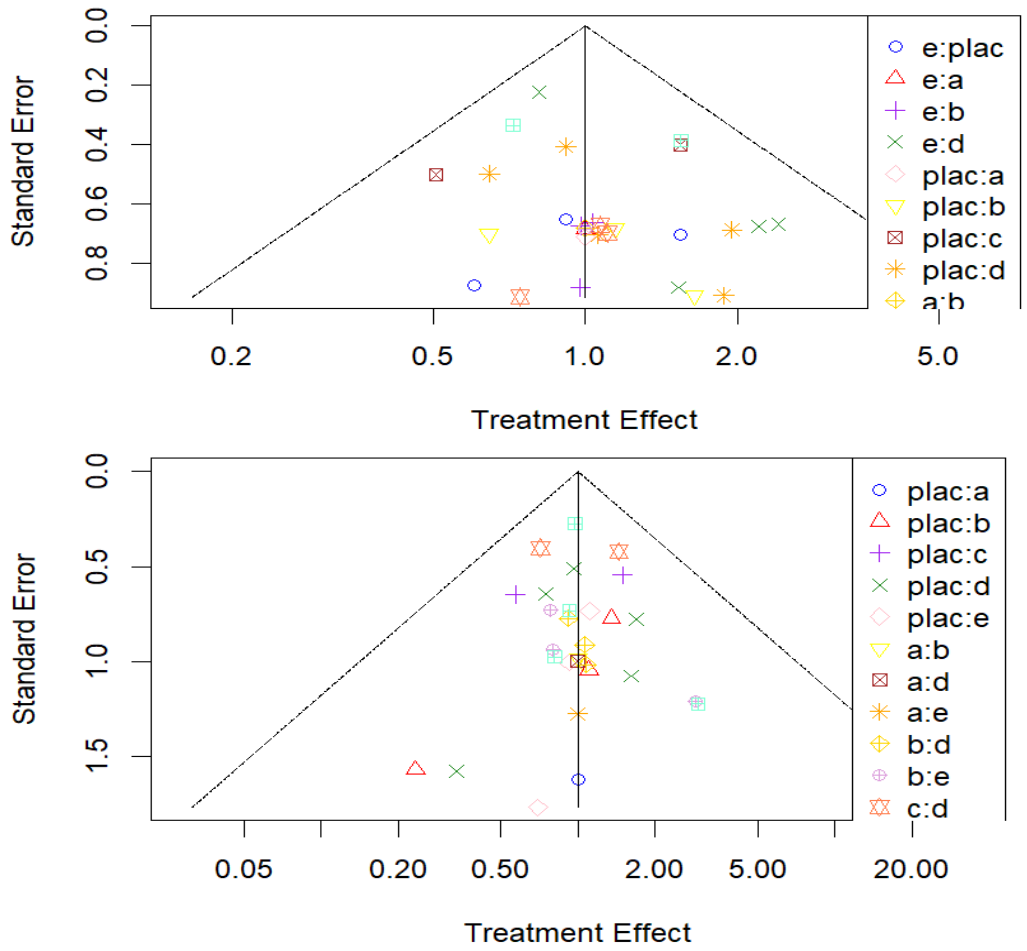
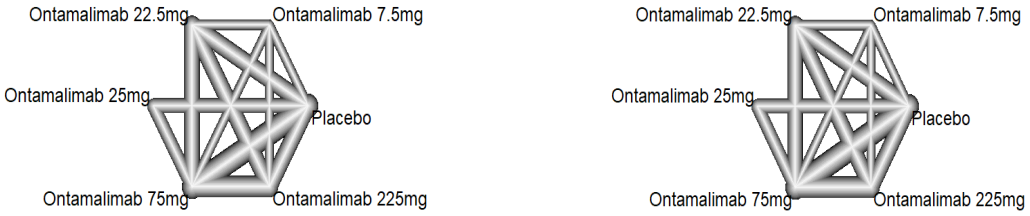


FIGURE 5. Funnel plot of (A) clinical response and (B) clinical remission (a: Ontamalimab 7.5 mg b: Ontamalimab 22.5mg c: Ontamalimab 25mg; d: Ontamalimab 75mg; e: Ontamalimab 225mg)



A B

FIGURE 6. Network meta-analysis of 5 doses of ontamalimab and placebo were assessed. Line thickness indicates the number of comparisons. (A). Clinical response (B). Clinical remission

Biomarker change

MadCAM-1 levels between ontamalimab 75 mg and placebo were significantly different after 12 wk of treatment. Two trials reported much lower levels of MadCAM-1 were demonstrated in ontamalimab 75 mg treatment (RR: 235.57; 95% CI: 203.80–267.33; I^2: 60%; p <0.001) compared to placebo after 12 week of treatment (FIGURE 8A).[21] Significantly low heterogeneity was reported from 3 trials in mean change of FC (RR: 624.29; 95% CI: 543.28—705.29.; I^2: 0%; p<0.001) (FIGURE 8B) and mean CRP levels between placebo and ontamalimab 75 mg after 12 week (RR: 3.29; 95% CI: 0.19–6.39; I^2: 0%; p=0.04) (FIGURE 8D).[13,21] Meanwhile change of CRP serum level (RR: 9.71; 95% CI: 7.12–12.31; I^2: 90%; p<0.001) FIGURE 8C between ontamalimab 75mg and placebo was significant after 12 wk of treatment despite substantial heterogeneity. This result supports the role of ontamalimab 75mg as targeted treatment to reduce MAdCAM-1 level, CRP, and FC levels in comparison to placebo.

Adverse events

No significant adverse events (AEs) were found when compared to placebo based on a meta-analysis conducted on the AE of ontamalimab at doses of 22.5-25 mg, 75 mg, and 225 mg, with RR 1.03 (95% CI 0.92-1.15), 0.96 (95% CI 0.85-1.08), and 0.96 (95% CI 0.84-1.11) respectively. FIGURE 9 This indicates that across various doses, ontamalimab did not show significant differences in side effects compared to the placebo, as reflected by the RR and 95%CI. With similar results, serious adverse events seen in the ontamalimab group at the doses of 22.5-25 mg, 75 mg, and 225 mg showed non-significant results compared to the placebo, with RR 1.07 (95% CI 0.58-1.95), RR 1.46 (95% CI 0.80-2.67), RR 1.76 (95% CI 0.77-4.01) respectively (FIGURE 7).

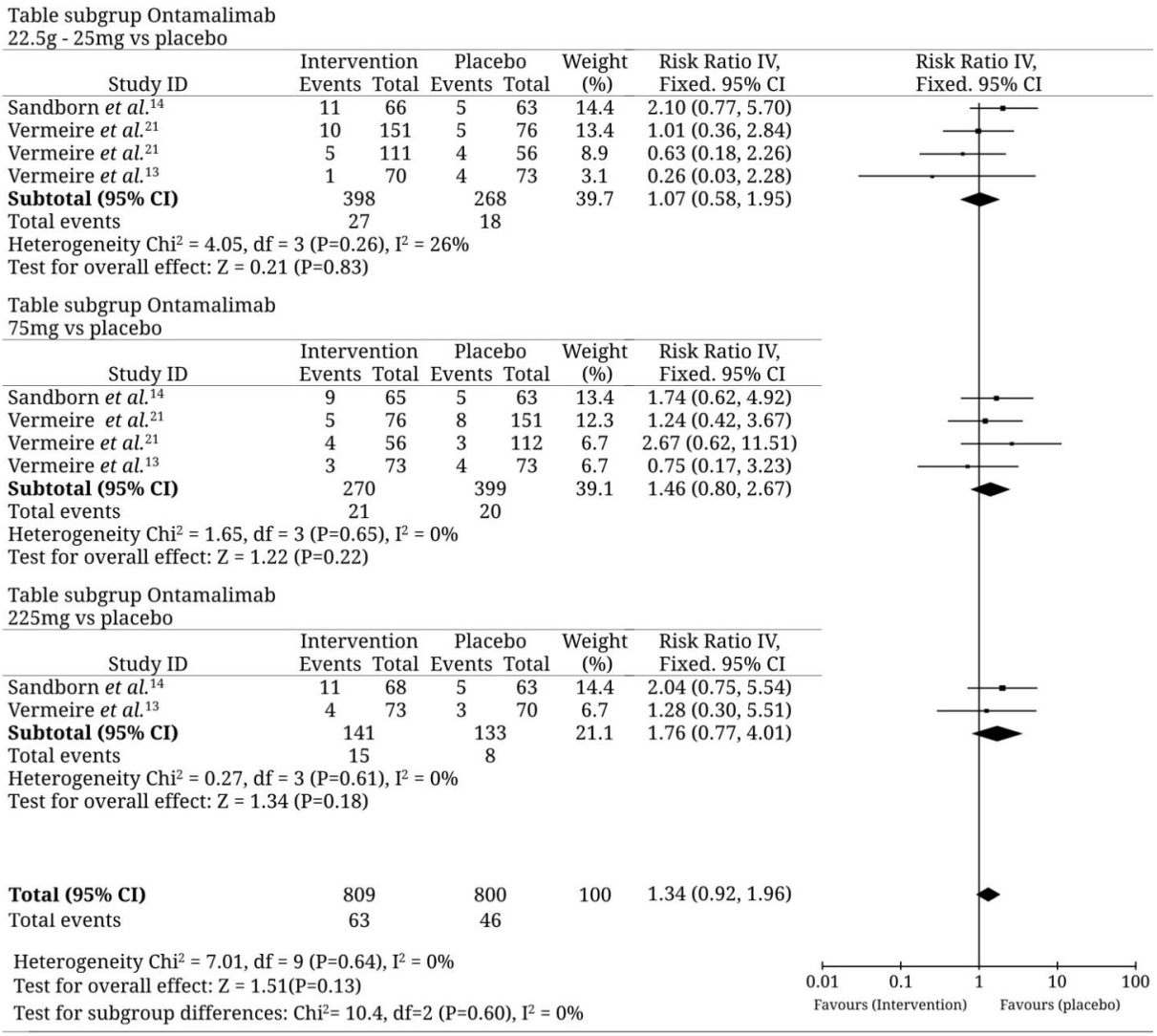


FIGURE 7. Comparison of serious AEs between 22.5-25 mg, 75 mg, and 225 mg ontamalimab vs placebo

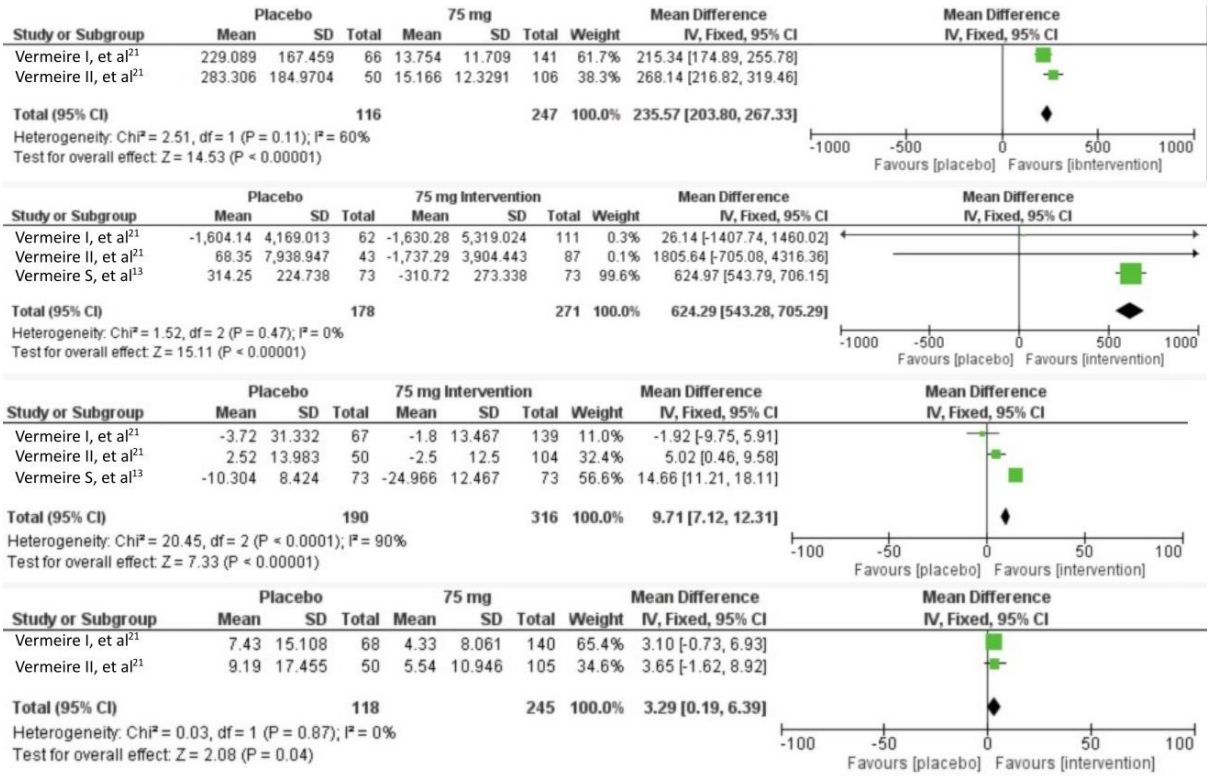


FIGURE 8 (A) Comparison of Mean CRP levels Between Placebo vs Ontamalimab 75 mg (B) Comparison of change FC levels Between Placebo vs Ontamalimab 75 mg (C) Comparison of change CRP levels Between Placebo vs Ontamalimab 75 mg (D) Comparison of Mean CRP levels Between Placebo vs Ontamalimab 75 mg

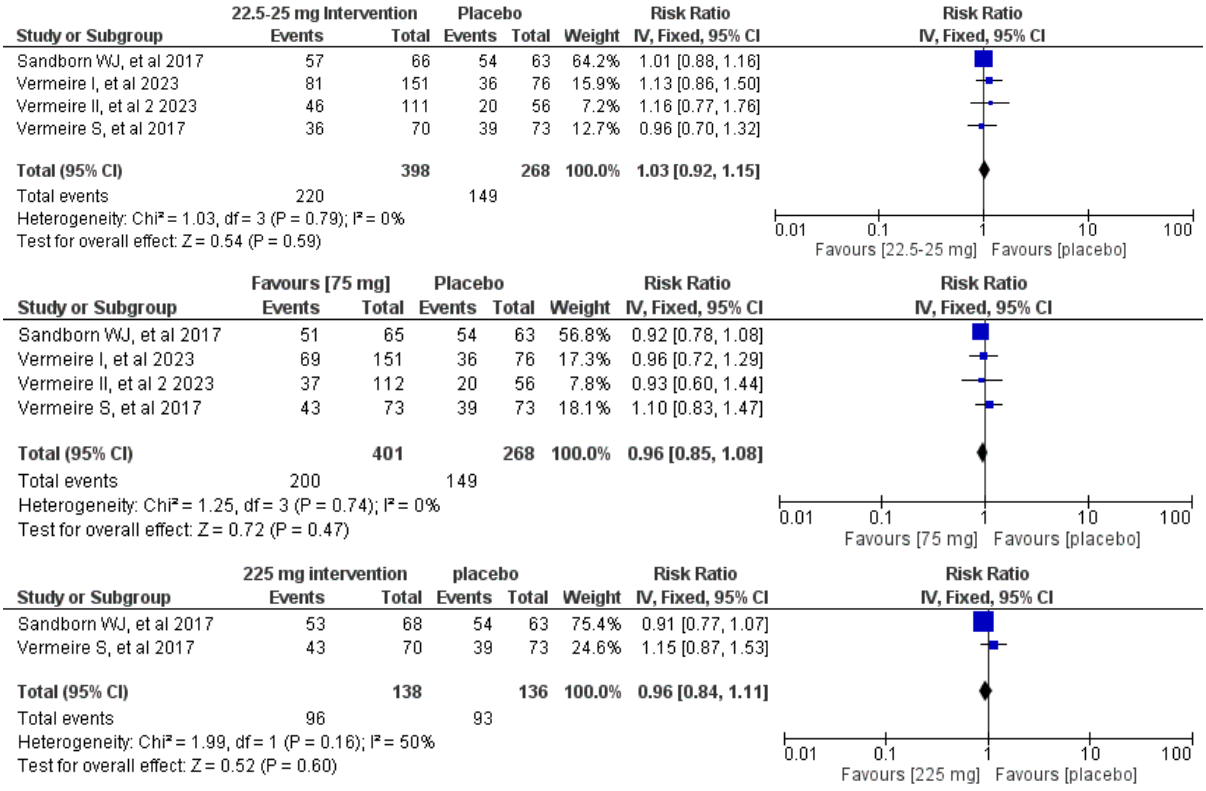


FIGURE 9. Comparison of Adverse Effect Between 22.25 -25 mg Ontamalimab vs Placebo

DISCUSSION

The study found that ontamalimab 75mg provides significantly greater clinical response and clinical remission amongst other doses in comparison to placebo to treat both UC and CD. This result aligns with a previous study that ontamalimab 25mg does not significantly increase outcomes.[16] Studies suggest that improvements in both response and remission are more closely associated with the duration of therapy rather than with increasing doses, as higher doses may lead to excessive depletion of regulatory T cells, potentially diminishing the therapeutic effect.[13,20] In addition, the placebo effect could be explained by the carryover effect of previous anti-TNFα treatment and high inflammation levels at baseline, giving better response and remission than low inflammation levels.

CRP and FC levels described systemic and local gastrointestinal inflammation, respectively. Significant diminished level of CRP and FC after 12 wk of ontamalimab 75 mg treatment, as well as signicantly lower CRP levels in ontamalimab 75 mg compared to placebo, was described as decreased inflammation that leads to remission rate improvement. Nevertheless, ontamalimab 225 mg has reversely more inflammation effects compared to ontamalimab 75 mg, which were demonstrated by higher FC levels. This could lead to more active disease and refractory treatment of the patients. Ontamalimab 75 mg was conclusively superior to ontamalimab 225 mg.[14,20] Moreover, MadCAM-1 levels wes studied as one of the specific markers of IBD, and it was significantly lower in patients with ontamalimab treatment compared to placebo in this meta-analysis. This demonstrated that ontamalimab 75 mg could be efficient in treating IBD.[14]

Ontamalimab was found to be safe and well-tolerated across all studies at all 3 dosage levels. These findings are consistent in the induction studies, including the TOSCA, TURANDOT, and a new phase 3 induction study by the same author of the TURANDOT study, which were analyzed in the forest plot above but showed no statistically significant differences. The drug also showed a good safety profile in the maintenance studies, such as OPERA II (encompassing both OPERA and TOSCA studies) and TURANDOT II. The most common AEs were linked to the underlying disease, with the worsening of UC being one of the primary concerns, along with arthralgia and upper respiratory tract infections. Adverse events that led to treatment discontinuation were typically related to the underlying condition itself. It is also notable to know that no cases of progressive multifocal leukoencephalopathy (PML) were observed in either the induction or maintenance studies, likely attributable to its selectivity, in contrast to natalizumab, a non-selective anti-α4 integrin antibody used in IBD that can affect the central nervous system and bone marrow, thereby increasing the risk of PML.[23] Most serious AEs were attributed to CD and were deemed unlikely to be related to the study drug. Withdrawals due to AEs were primarily due to complications of CD.

This study has several limitations, including a small number of included trials and limited sample sizes. Most of the studies had short durations, typically under 12 wk, as maintenance studies were not included. Additionally, the analysis primarily compares ontamalimab with placebo, limiting the ability to directly assess its efficacy and safety relative to other active treatments for IBD. Future research with larger sample sizes, longer head-to-head periods, and active comparator arms is needed to better understand ontamalimab's clinical utility. Although the meta-analysis revealed no statistically significant heterogeneity in efficacy or adverse outcome measures, this may be due to

the small number of included studies and the similarity in their characteristics. We addressed potential biases by ensuring homogeneity through careful review of study features, applying a fixed-effect model, and assessing evidence quality using the GRADE approach. The GRADE approach findings indicate moderate certainty of evidence for efficacy and safety outcomes, but low certainty for biomarker changes, primarily due to considerable heterogeneity and wide confidence intervals.

CONCLUSION

Ontamalimab, administered at a dose of 75 mg, demonstrated efficacy in the management of IBD, as evidenced by its superior clinical response rates and clinical remission outcomes when compared to placebo. Moreover, no significant AEs were observed during the study period, highlighting its favorable safety profile relative to other anti-MAdCAM-1 therapies. These findings underscore the potential of ontamalimab as an effective and safe therapeutic option for IBD. Nevertheless, while ontamalimab 75 mg shows promising efficacy and safety, longer-term head-to-head comparative trials with other biologics and other established treatments are warranted to confirm its clinical utility.

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