

Review

Efficacy and Safety of Natalizumab and Vedolizumab in the Treatment of Crohn's Disease: A Systematic Review and Meta-Analysis

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Abstract: Background — This study compared the effectiveness and safety of natalizumab and vedolizumab in managing Crohn's disease (CD), focusing on clinical remission, response to therapy, and adverse events.

Material and Methods — A systematic review conducted using the PRISMA guidelines included 11 studies (9 randomized controlled trials and 2 cohort studies). Quality was assessed using the Risk of Bias 2 (RoB 2) tool and the Newcastle-Ottawa Scale (NOS). Outcomes were analyzed using Review Manager 5.4 using odds ratios (OR), 95% confidence intervals (CI), and p-values.

Results — Natalizumab improved clinical response (OR=2.14; 95% CI: 1.68-2.71, p<0.00001) and remission (OR=2.47; 95% CI: 1.12-5.42, p=0.02) compared with placebo. Vedolizumab also improved response (OR=1.60; 95% CI: 1.28-1.99, p<0.0001) and remission (OR=1.86; 95% CI: 1.42-2.43, p<0.00001). Both drugs demonstrated similar safety profiles to placebo in terms of infections, fatigue, and serious adverse events.

Conclusion — Natalizumab and vedolizumab effectively improve clinical outcomes in CD, with comparable safety profiles, supporting their therapeutic use.

Keywords: Crohn's disease, natalizumab, vedolizumab.

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Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract that affects all layers of the intestinal wall, primarily the small and large intestines [1, 2]. It belongs to the category of inflammatory bowel diseases (IBD) and is characterized mainly by severe wasting, weight loss, prolonged diarrhea, and abdominal pain [3, 4]. Compared with other regions of the world, the prevalence of CD among Caucasians in North America and Europe is higher than in Asia. In Asian countries, the incidence ranges from 0.07 to 3.12 per 100,000 [5].

Although the exact cause of CD is unknown, it is closely related to a complex interaction of environmental factors, genetic factors, and an abnormal immune response to intestinal microbiota [6, 7]. Mutation in the nucleotide-binding oligomerization domain 2 (NOD2) gene is one of the risk factors for the development of CD [8]. Environmental factors such as smoking and high-fat diet are also known to aggravate the condition. Treatment options for CD primarily include corticosteroids, immunomodulators, and biologics such as tumor necrosis factor (TNF) inhibitors [9]. However, not all patients respond adequately to these treatments or achieve remission, creating a need for additional therapeutic approaches to improve efficacy and minimize side effects.

Natalizumab and vedolizumab are two drugs that act by inhibiting the adhesion of certain integrin molecules, thereby preventing the migration of immune cells into inflamed intestinal tissues [10]. According to a study [11], natalizumab administered three times during weeks 4, 8, and 12 successfully resulted in remission and clinical response in patients with CD. With a single administration of natalizumab (300 mg) at Week 4, the rate of remission failure was lower in the natalizumab group (76%) than in the placebo group (83%) [11]. Two infusions at Week 8 resulted in a lower rate of remission failure in the natalizumab group (66%) than in the placebo group (77%) [11]. Finally, three injections at Week 12 showed that the natalizumab group had a lower rate of remission failure (61%) than in the placebo group (73%), indicating that natalizumab is significantly more effective than placebo in inducing remission in CD [11].

In addition, vedolizumab is effective in inducing remission and maintaining response to therapy in patients with CD [12]. By Week 6 of the GEMINI II clinical trial, nearly 31% of patients receiving vedolizumab had a higher clinical response rate than 26% of patients in the placebo group [12]. Given that only 15% of patients receiving vedolizumab achieved remission compared to 7% in the

placebo group, vedolizumab is useful in helping patients achieve early remission in the induction phase [12].

Both natalizumab and vedolizumab are effective in the treatment of CD, but have different safety profiles and mechanisms of action. Although natalizumab inhibits lymphocyte migration into intestinal and central nervous system tissues by targeting $\alpha 4$ integrin, it also increases the risk of progressive multifocal leukoencephalopathy (PML); consequently, it is only used in patients who did not respond to other treatments. In contrast, vedolizumab specifically targets $\alpha 4$ integrin, which only affects the intestine, thereby reducing the risk of PML and making it safer for long-term use.

However, several previous studies have shown mixed results to date, and there have been no recent meta-analyses of the efficacy and safety of natalizumab and vedolizumab in the treatment of CD. The previous meta-analysis was conducted in 2015 and included a small number of studies. This meta-analysis presents more recent and updated studies, as well as various outcome measures including clinical response, clinical remission, and the incidence of adverse events including nasopharyngitis,

arthralgia, nausea, abdominal pain, fatigue, headache, pyrexia, upper respiratory tract infection, vomiting, and serious adverse events compared with placebo. Therefore, we aimed to compare these two drugs to determine the most appropriate treatment option based on the safety profile, efficacy, and needs of patients with CD.

Material and Methods

This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. Ethical approval was not required because the study relies solely on data from previously published research. We did not use artificial intelligence to assist in writing the manuscript. In the process of compiling the meta-analysis, we used search engines to search for literature, data analysis applications such as Review Managers, and Grammarly to check the correctness of English grammar. This study has been registered with PROSPERO (CRD42024624052).

Table 1. Characteristics of the natalizumab (NAT) study for the treatment of Crohn's disease (CD)

Study, year	Study design	Country	Sample size	Male		Female		Age				Intervention	Follow-up	Baseline CDAI (mean CDAI score)		NOS
				NAT	PLACEBO	NAT	PLACEBO	NAT	PLACEBO	Mean	Range			Mean	Range	
Ghosh, 2003 (1) [14]	RCT	England	248	27	30	41	33	36	18-66	34	18-68	Natalizumab 3 mg/kg: 1 intravenous infusion; placebo intravenous infusion	Weeks 2, 4, 6, 8, 12	8.4	8.9	-
Ghosh, 2003 (2) [14]	RCT	England	248	30	30	36	33	36	19-64	34	18-68	Natalizumab 3 mg/kg: 2 intravenous infusions; placebo intravenous infusion	Weeks 2, 4, 6, 8, 12	8.1	8.9	-
Ghosh, 2003 (3) [14]	RCT	England	248	25	30	26	33	35	19-62	34	18-68	Natalizumab 6 mg/kg: 2 intravenous infusions; placebo intravenous infusion	Weeks 2, 4, 6, 8, 12	7.8	8.9	-
Gordon, 2001 [15]	RCT	England	30	7	5	11	7	34.4	N/A	36	N/A	Natalizumab 3 mg/kg: 1 intravenous infusion; placebo intravenous infusion	Weeks 2, 4	258	273	-
Kane, 2012 [16]	Cohort	Minnesota USA	30	9	N/A	21	N/A	35	20-63	N/A	N/A	Natalizumab infusions	N/A	N/A	N/A	8
Sandborn, 2005 (1) [17]	RCT	France	905	311	73	413	108	38	26-50	39	25-53	Natalizumab 300 mg intravenous infusion, placebo intravenous infusion; treatment was administered during weeks 0, 4, 8	Weeks 10, 12	302±60	303±65	-
Sandborn, 2005 (2) [17]	RCT	France	339	77	59	91	94	37	24-50	37	25-49	Natalizumab 300 mg intravenous infusion, placebo intravenous infusion; treatment was administered every four weeks (during weeks 12 through 56)	Every four weeks during weeks 12-60	118±57	105±54	-
Targan, 2007 [18]	RCT	California, USA	509	105	102	154	148	38.1	N/A	37.7	N/A	Natalizumab 300 mg intravenous infusion, placebo intravenous infusion; treatment was administered every four weeks (weeks 0, 4, 8)	Week 12	303.9±64.80	299.5±63.19	-

Table 2. Characteristics of the vedolizumab (VEDO) study for the treatment of Crohn's disease (CD)

Study, year	Study design	Country	Sample size	Age		Male		Female		Intervention	Follow-up	Baseline CDAI (mean CDAI score)	
				VEDO	PLACEBO	VEDO	PLACEBO	VEDO	PLACEBO				
Feagan, 2008 (1) [19]	RCT	Canada	185	36.0±12.67	34.5±11.26	25	30	37	28	Vedolizumab 0.5 mg/kg intravenously vs. an identical-appearing placebo; treatment was administered on days 1 and 29	57 days	288.0±45.83	288.0±48.63
Feagan, 2008 (2) [19]	RCT	Canada	185	38.5±13.07	34.5±11.27	31	30	34	28	Vedolizumab 2.0 mg/kg intravenously vs. an identical-appearing placebo; treatment was administered on days 1 and 29	57 days	288.0±45.84	296.6±55.37
Sandborn, 2005 [17]	RCT	USA	1115	35.7±11.9	38.6±13.2	451	69	79	517	Vedolizumab 300 mg intravenous infusion vs. placebo intravenous infusion; treatment was administered on weeks 0 and 2	6 weeks – induction phase	323±68	325±78
Vermeire, 2022 [20]	RCT	USA	409	38.2	36.1	157	66	118	68	Vedolizumab 300 mg intravenous infusion vs. placebo intravenous infusion; treatment was administered on weeks 0, 2, 6	N/A	318.0	309.0
Sand, 2014 [21]	RCT	Canada	416	36.9 (20-69)	34.8 (19-77)	91	89	118	118	Vedolizumab 300 mg intravenous infusion vs. placebo intravenous infusion; treatment was administered on weeks 0, 2, 6	10-week treatment	313.9	301.3
Watanabe, 2019 (1) [22]	RCT	Japan	157	33.9	32.6	51	52	28	26	Vedolizumab 300 mg intravenous infusion vs. placebo intravenous infusion; treatment was administered on weeks 0, 2, 6	10-week treatment	303.9	295
Watanabe, 2019 (2) [22]	RCT	Japan	157	36.7	35.2	6	9	6	3	Vedolizumab 300 mg intravenous infusion vs. placebo intravenous infusion; treatment was given on weeks 0, 2, 6	10-week treatment	319.8	303.3

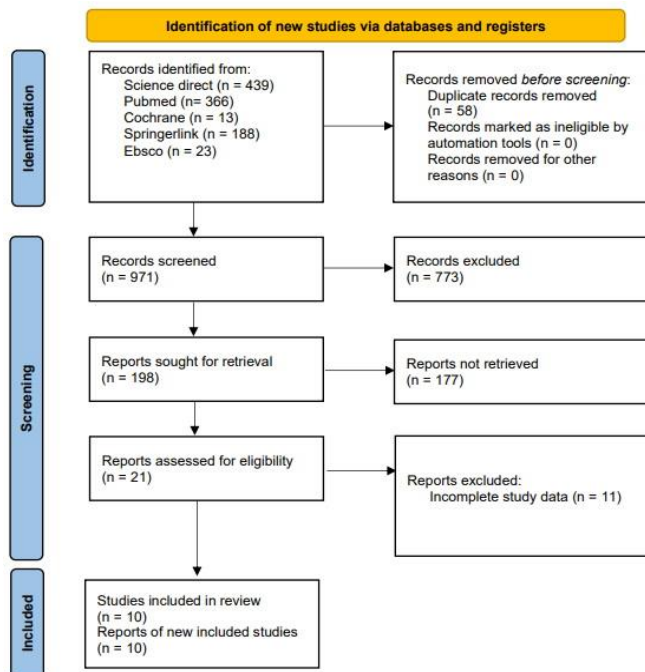


Figure 1. PRISMA flowchart.

Selection of publications

Literature searches were conducted in PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and EB

SCO databases to identify relevant studies up to July 2024, using the following keywords: “Crohn’s disease” OR “Inflammatory

Bowel Disease” OR “IBD” AND “Natalizumab” AND “Vedolizumab” AND “Efficacy” AND “Safety”.

Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were as follows: (1) selected studies were randomized controlled trials (RCT) with or without blinding, published in English, either domestically or internationally, while observational studies (prospective and retrospective cohorts, case-control, or cross-sectional) were also eligible; (2) selected studies compared natalizumab and vedolizumab; (3) selected studies involved adult patients (18 years or older) diagnosed with CD who met relevant diagnostic criteria; and (4) outcome indicators included clinical response, clinical remission, and incidence of side effects. The exclusion criteria were as follows: (1) duplicate publications; (2) absence of a control group; and (3) conference abstracts and case reports.

Study quality assessment

Three main components of study design were assessed using the modified Newcastle-Ottawa Scale (NOS), which is used to evaluate the quality of RCTs: outcome assessment, comparability of groups, and selection of study groups. This scale has an overall quality score ranging from 0 to 9 pts. However, the Cochrane Risk of Bias Tool (version 2) for RCTs is primarily concerned with assessing the quality of study methodologies. The choice of reported outcomes, handling of missing outcome data, precision of outcome measures, adherence to reported interventions, and randomization method are the five main components of study design that are assessed by this tool.

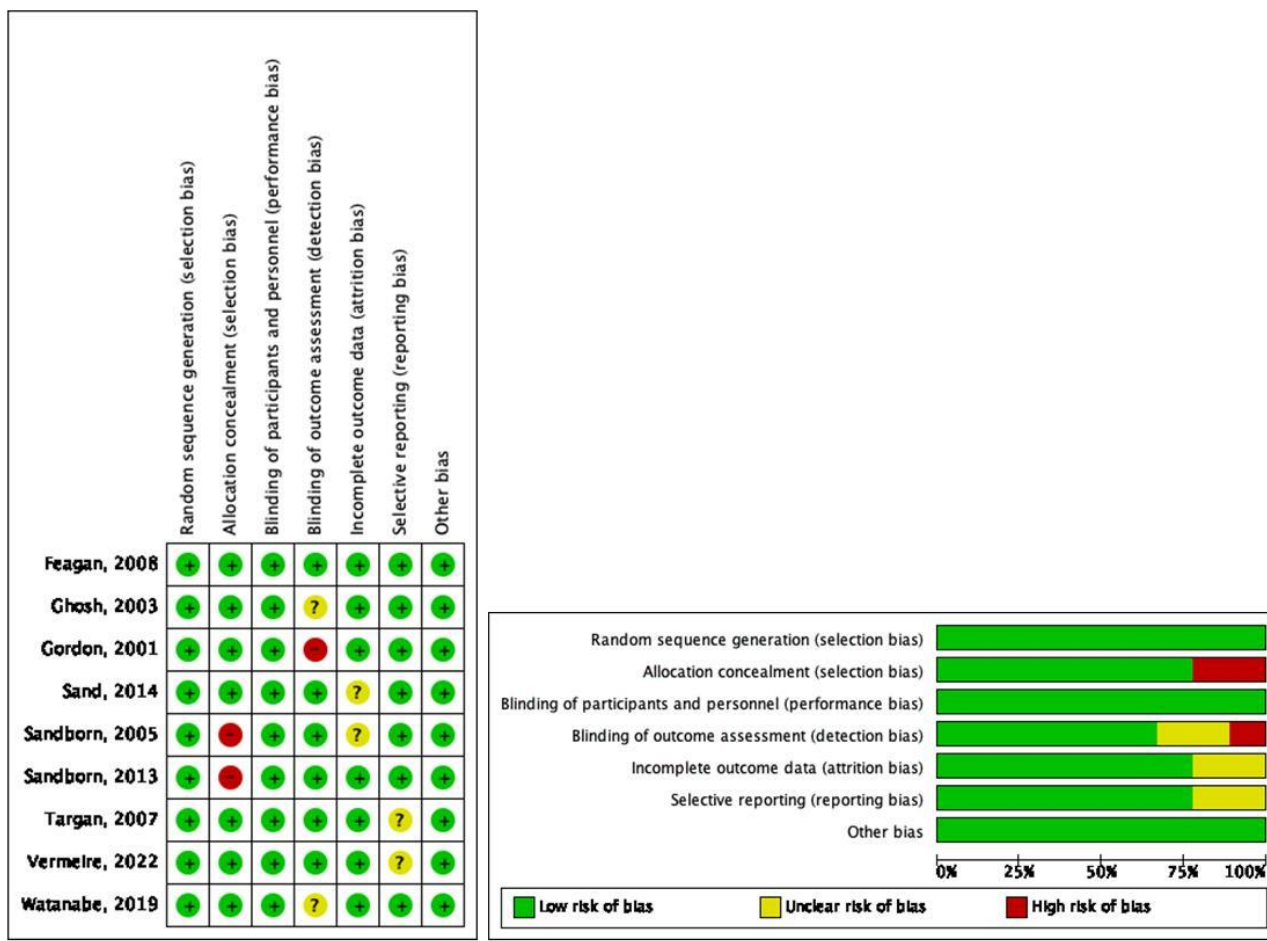


Figure 2. Quality assessment of each study.

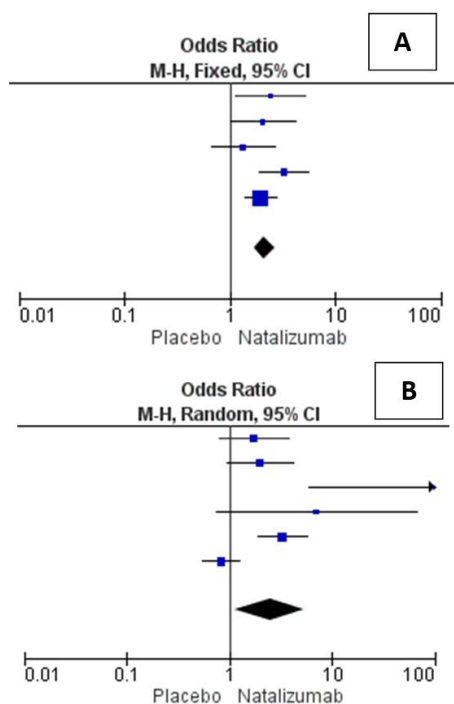


Figure 3. Forest plot of the meta-analyses of the efficacy natalizumab vs. placebo for clinical response (A) and clinical remission (B).

Table 3. Forest plot of the meta-analyses of the efficacy natalizumab vs. placebo for clinical response

Study or Subgroup	Natalizumab Events	Natalizumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ghosh, 2003 (1)	33	51	27	63	9.2%	2.44 [1.14, 5.23]
Ghosh, 2003 (2)	40	66	27	63	11.7%	2.05 [1.02, 4.14]
Ghosh, 2003 (3)	34	68	27	63	15.1%	1.33 [0.67, 2.66]
Sandborn, 2005	59	168	24	170	16.6%	3.29 [1.93, 5.62]
Targan, 2007	155	258	109	250	47.5%	1.95 [1.37, 2.77]
Total (95% CI)		611		609	100.0%	2.14 [1.68, 2.71]
Total events	321		214			

Heterogeneity: $\text{Chi}^2=4.71$, $\text{df}=4$ ($P=0.32$); $I^2=15\%$. Test for overall effect: $Z=6.24$ ($P<0.00001$).

Table 4. Forest plot of the meta-analyses of the efficacy natalizumab vs. placebo for clinical remission

Study or Subgroup	Natalizumab Events	Natalizumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Ghosh, 2003 (1)	20	51	17	63	19.9%	1.75 [0.79, 3.85]
Ghosh, 2003 (2)	28	66	17	63	20.4%	1.99 [0.95, 4.18]
Ghosh, 2003 (3)	19	19	17	63	5.8%	103.63 [5.93, 1810.28]
Sandborn, 2005	7	18	1	12	8.2%	7.00 [0.73, 66.80]
Targan, 2007	55	168	22	170	22.2%	3.27 [1.89, 5.69]
Total (95% CI)	97	258	63	150	23.4%	0.83 [0.55, 1.25]
Total events	226	580	137	521	100.0%	2.47 [1.12, 5.42]

Heterogeneity: $\text{Tau}^2=0.65$, $\text{Chi}^2=27.27$; $\text{df}=5$ ($P<0.0001$); $I^2=82\%$. Test for overall effect: $Z=2.24$ ($P=0.02$).

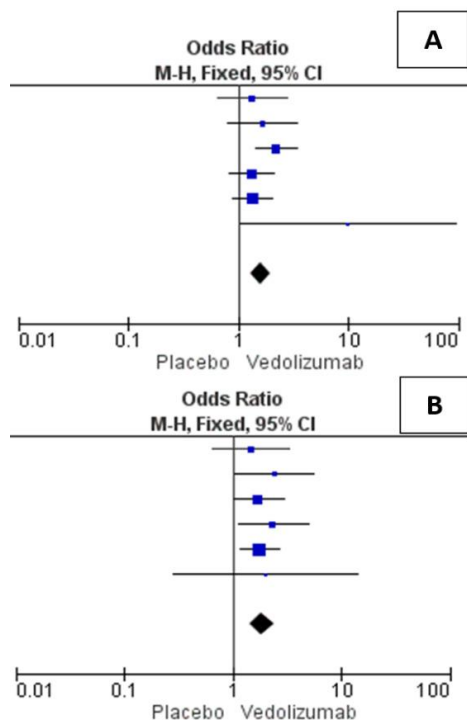


Figure 4. Forest plot of the meta-analyses of the efficacy vedolizumab vs. placebo for clinical response (A) and clinical remission (B).

Table 5. Forest plot of the meta-analyses of the efficacy vedolizumab vs. placebo for clinical response

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Feagan, 2008 (1)	30	62	24	58	10,4%	1.33 [0.65, 2.73]
Feagan, 2008 (2)	35	65	24	58	9,5%	1.65 [0.81, 3.38]
Sand, 2014	82	209	47	207	23,2%	2.20 [1.43, 3.37]
Sandborn, 2013	69	220	38	148	25,2%	1.32 [0.83, 2.11]
Vermeire, 2022	143	275	60	134	31,3%	1.34 [0.88, 2.02]
Watanabe, 2019	5	7	2	10	0,4%	10.00 [1.05, 95.46]
Total (95% CI)		838		615	100,0%	1.60 [1.28, 1.99]
Total events	364		195			

Heterogeneity: $\text{Chi}^2=6.28$, $\text{df}=5$ ($P=0.28$); $I^2=20\%$. Test for overall effect: $Z=4.11$ ($P<0.0001$).

Table 6. Forest plot of the meta-analyses of the efficacy vedolizumab vs. placebo for clinical remission

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Feagan, 2008 (1)	19	69	12	58	11.6%	1.46 [0.64, 3.33]
Feagan, 2008 (2)	24	62	12	58	9.4%	2.42 [1.07, 5.47]
Sand, 2014	40	209	25	207	25.0%	1.72 [1.00, 2.96]
Sandborn, 2013	32	220	10	148	12.6%	2.35 [1.12, 4.94]
Vermeire, 2022	132	275	46	134	39.6%	1.77 [1.15, 2.71]
Watanabe, 2019	4	8	3	9	1.7%	2.00 [0.28, 14.20]
Total (95% CI)		843		614	100.0%	1.86 [1.42, 2.43]
Total events	251		108			

Heterogeneity: $\text{Chi}^2=1.25$, $\text{df}=5$ ($P=0.94$); $I^2=0\%$. Test for overall effect: $Z=4.54$ ($P<0.00001$).

Data extraction

The following data were extracted from each study: author's name, publication year, country, study design, sample size, gender distribution, and age. The primary outcome for this meta-analysis was clinical response and clinical remission. Odds ratios (ORs), 95%

confidence intervals (CIs), and p-values were also collected from the selected studies. The 95% CI was included as one of the components of this analysis when presenting the data as a survival plot using the Kaplan-Meier curve.

Statistical analyses

RevMan 5.4 software was used for statistical analysis in this study. 95% CI and ORs were determined when calculating the data. To examine the heterogeneity between studies, χ^2 and I^2 tests were employed in this meta-analysis. Fixed effects model analysis was performed when $P>0.1$ or $I^2<50\%$ indicated no statistical heterogeneity between studies. This suggests statistical heterogeneity between studies. Further investigation of the causes of heterogeneity was required. After eliminating obvious heterogeneity, random effects model was used for analysis. Publication bias analysis and subgroup analysis based on the type of included studies were performed using funnel plots. The test threshold was: $\alpha=0.05$.

Results

Selection of publications

PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and EBSCO were among the online databases that yielded 1,029 studies throughout the relevant study search process. After screening for titles and abstracts, 971 studies were found that could be evaluated for eligibility. Ten studies were included after 773 were eliminated due to their non-compliance with the inclusion and exclusion criteria. A flowchart that summarizes the entire literature search procedure in accordance with PRISMA Guidelines 2022 is shown in [Figure 1](#).

Characterization of included studies

Ten studies (9 RCTs and 1 cohort study) were included in our meta-analysis ([Tables 1](#) and [2](#)). In terms of the design of the included studies evaluating the efficacy and safety of vedolizumab in patients with CD, most of them used an RCT design. In terms of the country, most studies were from England. The total sample size was 2,557 patients. The lowest mean age was 34.4 years, and the highest mean age was 38.1 years. Based on the included studies evaluating the efficacy and safety of vedolizumab in patients with CD, most studies used an RCT design. Based on the country, most studies were from the United States, Canada, and Japan. The total sample size was 2,624 patients. The lowest mean age was 33.9 years, and the highest mean age was 38.2 years. The quality assessment of the cohort studies yielded the NOS score of 8 pts implying good quality. The assessment of bias in RCT studies is presented in [Figure 2](#).

Efficacy of vedolizumab

Clinical response

When comparing patients with CD treated with vedolizumab with those treated with placebo, the clinical response was significantly higher in the former (OR=2.14; 95% CI: 1.68-2.71, $p<0.00001$). A fixed effects model was used to analyze clinical response, as there was no evidence of significant heterogeneity ($I^2=15\%$; $p=0.32$) ([Figure 3A](#), [Table 3](#)).

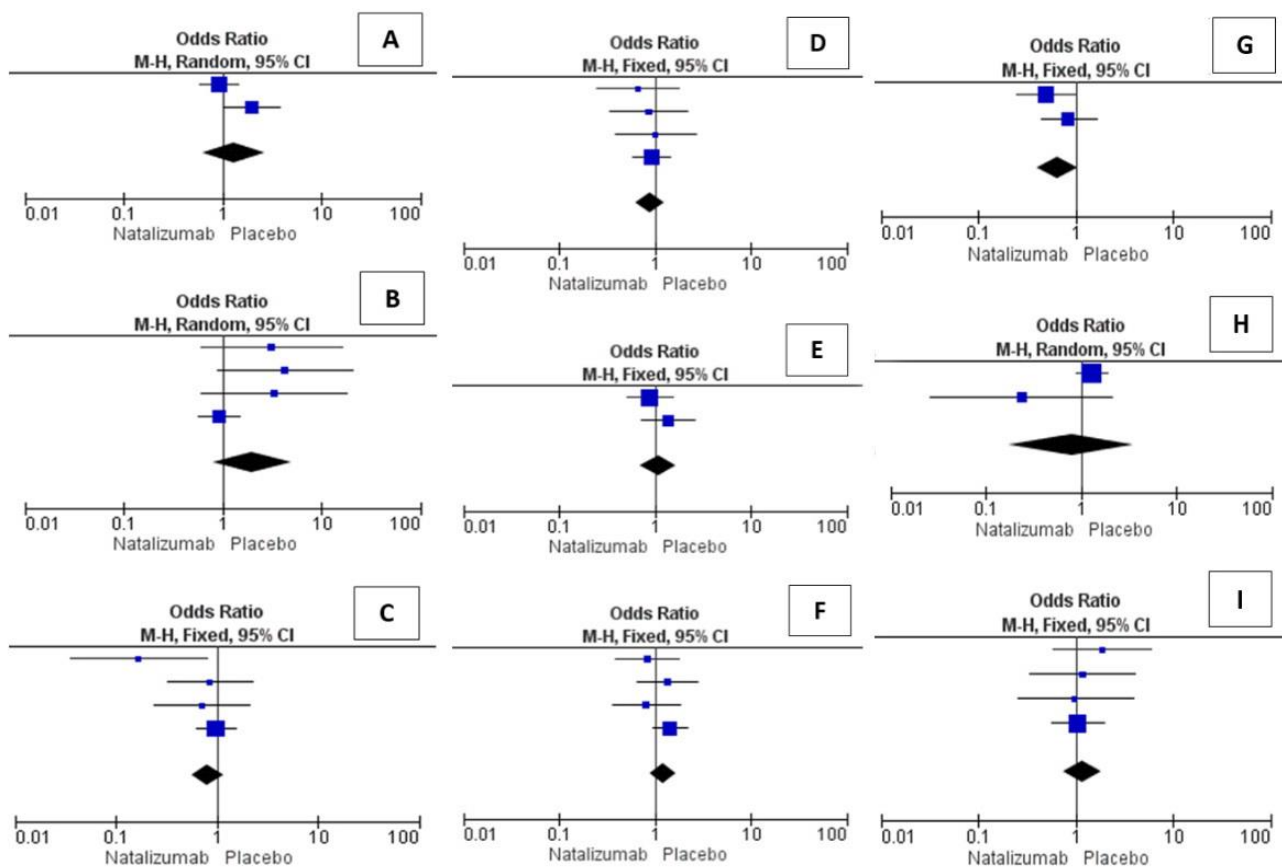


Figure 5. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for nasopharyngitis (A), arthralgia (B), nausea (C), abdominal pain (D), fatigue (E), headache (F), serious adverse events (G), infections (H) and pharyngitis (I).

Table 7. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for nasopharyngitis.

Study or Subgroup	Natalizumab		Placebo		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Sandborn, 2005	49	214	52	214	55.1%	0.93 [0.59, 1.45]
Targan, 2007	29	260	15	250	44.9%	1.97 [1.03, 3.76]
Total (95% CI)		474		464	100.0%	1.30 [0.62, 2.71]
Total events	78		67			

Heterogeneity: Tau²=0.20; Chi²=3.52, df=1 (P=0.06); I²=72%. Test for overall effect: Z=0.70 (P=0.49).

Table 8. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for arthralgia

Study or Subgroup	Natalizumab		Placebo		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Ghosh, 2003 (1)	6	65	2	63	19.1%	3.10 [0.60, 15.99]
Ghosh, 2003 (2)	8	65	2	63	19.8%	4.28 [0.87, 21.01]
Ghosh, 2003 (3)	5	51	2	63	18.5%	3.32 [0.62, 17.86]
Sandborn, 2005	42	214	45	214	42.7%	0.92 [0.57, 1.47]
Total (95% CI)		395		403	100.0%	1.99 [0.79, 5.00]
Total events	61		51			

Heterogeneity: Tau²=0.46; Chi²=6.43, df=3 (P=0.09); I²=53%. Test for overall effect: Z=1.46 (P=0.14).

Clinical remission

Patients with CD treated with natalizumab had a significantly higher rate of clinical remission (OR=2.47; 95% CI: 1.12-5.42, p=0.02) than patients treated with placebo. Due to high heterogeneity (I²=82%; p<0.0001), clinical response was analyzed using a random effects model (Figure 3B, Table 4).

Efficacy of vedolizumab

Clinical response

Vedolizumab demonstrated a better clinical response than placebo (OR=0.60; 95% CI: 1.28-1.99, p<0.0001). Due to the lack of evidence of statistically significant heterogeneity (I²=20%; p=0.28), clinical response was analyzed using a fixed effects model (Figure 4A, Table 5).

Clinical remission

Vedolizumab was superior to placebo in clinical remission (OR=1.86; 95% CI: 1.42-2.43, p<0.00001). Since no evidence of significant heterogeneity was observed, clinical response was analyzed using a fixed effects model (I²=0%; p=0.94) (Figure 4B, Table 6).

Safety of natalizumab

Natalizumab was safer than placebo regarding the incidence of nasopharyngitis (OR=1.30; 95% CI: 0.62-2.71, p=0.49), arthralgia (OR=1.99; 95% CI: 0.79-5.00, p=0.14), nausea (OR=0.08; 95% CI: 0.56-1.16, p=0.24), abdominal pain (OR=0.88; 95% CI: 0.62-1.26, p=0.50), fatigue (OR=1.08; 95% CI: 0.71-1.64, p=0.74), headache (OR=1.21; 95% CI: 0.90-1.63, p=0.22) and serious adverse events (OR=0.65; 95% CI: 0.41-1.05, p=0.08). Other adverse events, such as infections (OR=0.79; 95% CI: 0.18-3.55, p=0.76) and pharyngitis (OR=1.17; 95% CI: 0.73-1.86, p=0.51), were similar between natalizumab and placebo (Figure 5, Table 7-15).

Safety of vedolizumab

Vedolizumab was safer than placebo in terms of the incidence of nasopharyngitis (OR=1.23; 95% CI: 0.90-1.69, p=0.19), arthralgia (OR=1.02; 95% CI: 0.74-1.42, p=0.89), nausea (OR=1.26; 95% CI: 0.91-1.75, p=0.17), abdominal pain (OR=0.81; 95% CI: 0.60-1.10, p=0.17), exhaustion (OR=0.18; 95% CI: 0.02-2.13, p=0.18), headache (OR=0.97; 95% CI: 0.74-1.29, p=0.85) and serious adverse event (OR=1.06; 95% CI: 0.49-2.31, p=0.88). Additional adverse events comparable with placebo included vomiting (OR=0.81; 95% CI: 0.53-1.24, p=0.33), upper respiratory tract infection (OR=1.34; 95% CI: 0.87-2.07, p=0.18), and pyrexia (OR=1.04; 95% CI: 0.72-1.49, p=0.84 ([Figure 6, Tables 16-25](#))).

Assessing the risk of bias

This study also assessed a risk of bias in selected publications, which is presented in [Figures 7](#) and [8](#). The results of the analysis show that the clinical remission ([Figure 7B](#)) and arthralgia ([Figure 7D](#)) in the natalizumab vs. placebo, and the arthralgia ([Figure 8D](#)), fatigue ([Figure 8G](#)) and serious adverse events ([Figure 8I](#)) in the analysis of vedolizumab vs. placebo, may be subject to publication bias, one of the reasons for which is the study limitations associated with a relatively new research. However, most variables showed a symmetrical distribution in the funnel plots, indicating a low risk of bias.

Table 9. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for nausea

Study or Subgroup	Natalizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Ghosh, 2003 (1)	2	65	10	63	15.3%	0.17 [0.04, 0.80]
Ghosh, 2003 (2)	9	65	10	63	13.6%	0.85 [0.32, 2.26]
Ghosh, 2003 (3)	6	51	10	63	12.2%	0.71 [0.24, 2.10]
Sandborn, 2005	48	214	49	214	58.9%	0.97 [0.62, 1.53]
Total (95% CI)		395		403	100.0%	0.80 [0.56, 1.16]
Total events	65		79			

Heterogeneity: Chi²=4.62, df=3 (P=0.20); I²=35%. Test for overall effect: Z=1.19 (P=0.24).

Table 10. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for abdominal pain

Study or Subgroup	Natalizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Ghosh, 2003 (1)	8	65	11	63	15.1%	0.66 [0.25, 1.78]
Ghosh, 2003 (2)	10	65	11	63	14.6%	0.86 [0.34, 2.19]
Ghosh, 2003 (3)	9	51	11	63	12.5%	1.01 [0.38, 2.67]
Sandborn, 2005	44	214	47	214	57.7%	0.92 [0.58, 1.46]
Total (95% CI)		395		403	100.0%	0.88 [0.62, 1.26]
Total events	71		80			

Heterogeneity: Chi²=0.43, df=3 (P=0.93); I²=0%. Test for overall effect: Z=0.68 (P=0.50).

Table 11. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for fatigue

Study or Subgroup	Natalizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Sandborn, 2005	26	214	29	214	60.6%	0.88 [0.50, 1.56]
Targan, 2007	25	260	18	250	39.4%	1.37 [0.73, 2.58]
Total (95% CI)		474		464	100.0%	1.08 [0.71, 1.64]
Total events	51		47			

Heterogeneity: Chi²=1.04, df=1 (P=0.31); I²=3%. Test for overall effect: Z=0.34 (P=0.74).

Table 12. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for headache

Study or Subgroup	Natalizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Ghosh, 2003 (1)	18	65	20	63	18.7%	0.82 [0.39, 1.76]
Ghosh, 2003 (2)	25	65	20	63	15.9%	1.34 [0.65, 2.78]
Ghosh, 2003 (3)	14	51	20	63	16.5%	0.81 [0.36, 1.83]
Sandborn, 2005	77	214	60	214	48.9%	1.44 [0.96, 2.17]
Total (95% CI)		395		403	100.0%	1.21 [0.90, 1.63]
Total events	134		120			

Heterogeneity: Chi²=2.70, df=3 (P=0.44); I²=0%. Test for overall effect: Z=1.24 (P=0.22).

Table 13. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for serious adverse events

Study or Subgroup	Natalizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Targan, 2007	13	260	24	250	54.7%	0.50 [0.25, 1.00]
Sandborn, 2005	18	214	21	214	45.3%	0.84 [0.44, 1.63]
Total (95% CI)		474		464	100.0%	0.65 [0.41, 1.05]
Total events	31		45			

Heterogeneity: Chi²=1.18; df=1 (P=0.28); I²=15%. Test for overall effect: Z=1.75 (P=0.08).

Table 14. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for infections

Study or Subgroup	Natalizumab		Placebo		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Sandborn, 2005	132	214	119	214	71.3%	1.29 [0.87, 1.89]
Targan, 2007	1	260	4	250	28.7%	0.24 [0.03, 2.14]
Total (95% CI)		474		464	100.0%	0.79 [0.18, 3.55]
Total events	133		123			

Heterogeneity: Tau²=0.78; Chi²=2.21, df=1 (P=0.14); I²=55%. Test for overall effect: Z=0.31 (P=0.76).

Table 15. Forest plot of the meta-analyses of the safety of natalizumab vs. placebo for pharyngitis

Study or Subgroup	Natalizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Ghosh, 2003 (1)	9	65	5	63	13.4%	1.86 [0.59, 5.91]
Ghosh, 2003 (2)	6	65	5	63	14.1%	1.18 [0.34, 4.08]
Ghosh, 2003 (3)	4	51	5	63	12.6%	0.99 [0.25, 3.88]
Sandborn, 2005	23	214	22	214	60.0%	1.05 [0.57, 1.95]
Total (95% CI)		395		403	100.0%	1.17 [0.73, 1.86]
Total events	42		37			

Heterogeneity: Chi²=0.80, df=3 (P=0.85); I²=0%. Test for overall effect: Z=0.66 (P=0.51).

This meta-analysis also conducted a quality assessment of each included study. The results of the assessment showed that the included studies were of moderate to high quality; hence, they provided accurate data for interpreting the results of this meta-analysis, as shown in [Figure 2](#).

Discussion

Based on the results of this meta-analysis, both natalizumab and vedolizumab are significantly more effective than placebo in the treatment of CD. Among patients receiving natalizumab, clinical response (OR=2.14; 95% CI: 1.68-2.71, p<0.00001) was significantly higher compared with placebo. In addition, natalizumab also demonstrated superiority over placebo in terms of clinical remission (OR=2.47; 95% CI: 1.12-5.42, p=0.02). This was supported by the ENACT-1 study, which demonstrated that

natalizumab could improve clinical response (56% vs. 49% in the placebo group) and clinical remission (37% vs. 30% in the placebo group) at Week 10, albeit these results were not statistically significant [14]. However, further analysis of the subpopulation of patients with elevated C-reactive protein (CRP) levels (>2.87 mg/L) showed more significant results in the natalizumab group [14]. At Week 12, the ENCORE study demonstrated that natalizumab was successful as an induction therapy with a clinical response rate of 48% vs. 32% in the placebo group ($p < 0.001$) and a clinical remission rate of 26% vs. 16% in the placebo group ($p = 0.002$) [14].

Among patients with CD, vedolizumab was similarly superior to placebo in achieving clinical response (OR=1.60; 95% CI: 1.28-1.99, $p < 0.0001$) and clinical remission (OR=1.86; 95% CI: 1.42-2.43, $p < 0.00001$). Of 4 studies with 1,126 participants, 19.8% of the

vedolizumab group achieved remission vs. 11.6% in the placebo group (RR 1.61; 95% CI 1.20-2.17). A number needed to treat (NNT) of 13 indicates high treatment efficacy [15]. Further evidence for this comes from a study that showed that patients who responded to vedolizumab had a higher rate of clinical remission (36–39%) at Week 52 during the maintenance phase than those in the placebo group (22%) [16]. Furthermore, compared with 30% in the placebo group, 44-46% of participants taking vedolizumab had a sustained clinical response [16]. Although it is unclear how this result was maintained from the early stages to Week 52, the GEMINI 1 study showed that vedolizumab successfully achieved corticosteroid-free clinical remission at Week 52 [17].

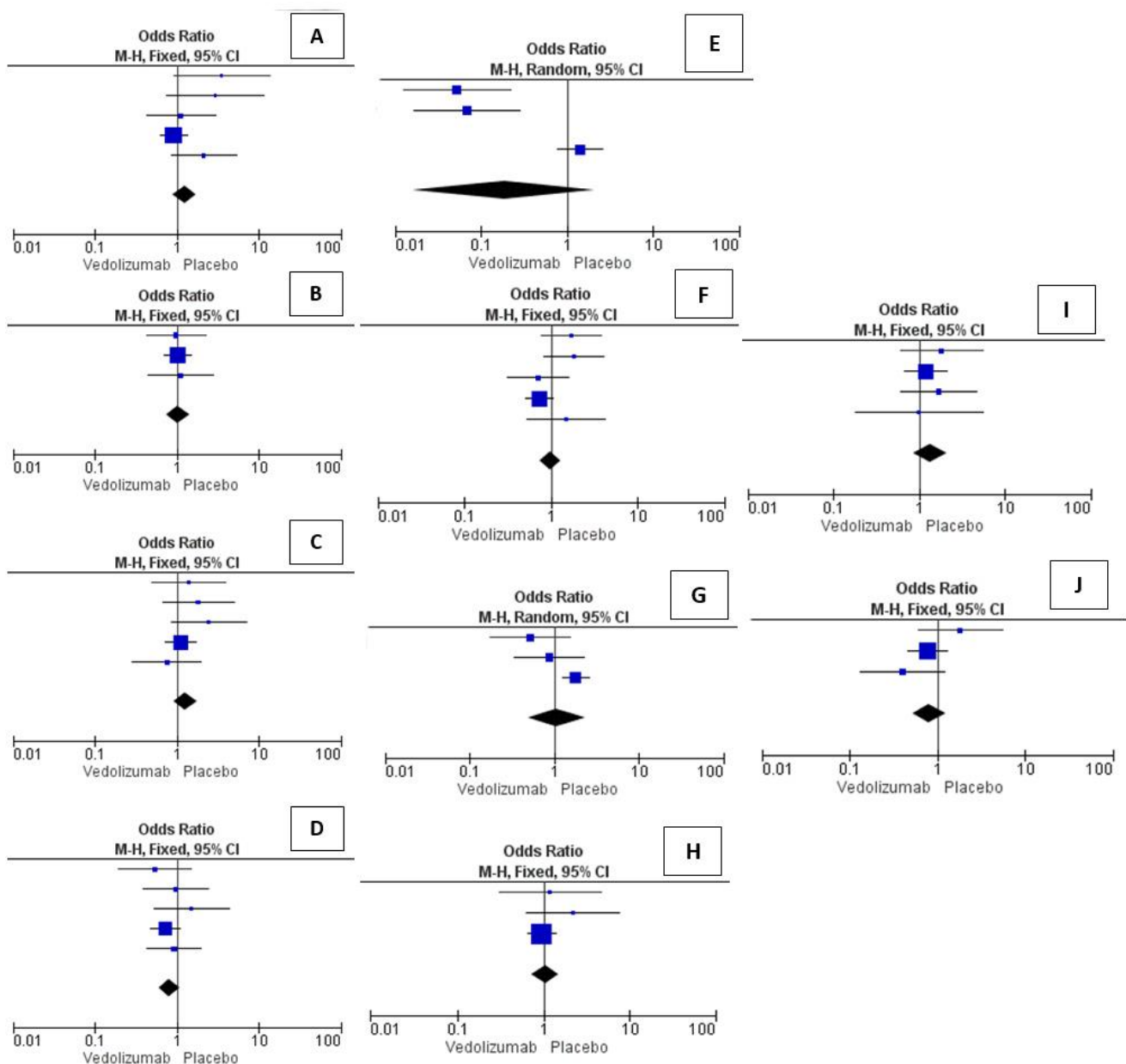


Figure 6. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for nasopharyngitis (A), arthralgia (B), nausea (C), abdominal pain (D), fatigue (E), headache (F), serious adverse events (G), pyrexia (H), upper respiratory tract infections (I), and vomiting (J).

Table 16. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for nasopharyngitis

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Feagan, 2008 (1)	10	62	3	58	3.6%	3.53 [0.92, 13.53]
Feagan, 2008 (2)	9	65	3	58	3.8%	2.95 [0.76, 11.46]
Sand, 2014	9	209	8	207	10.7%	1.12 [0.42, 2.96]
Sandborn, 2013	100	814	40	301	71.6%	0.91 [0.62, 1.35]
Vermeire, 2022	25	275	6	134	10.2%	2.13 [0.85, 5.33]
Total (95% CI)		1425		758	100.0%	1.23 [0.90, 1.69]
Total events	153		60			

Heterogeneity: Chi²=7.57, df=4 (P=0.11); I²=47%. Test for overall effect: Z=1.30 (P=0.19).

Table 17. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for arthralgia

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Vermeire, 2022	18	275	9	134	16.1%	0.97 [0.42, 2.23]
Sandborn, 2013	110	814	40	301	71.7%	1.02 [0.69, 1.50]
Sand, 2014	10	209	9	207	12.2%	1.11 [0.44, 2.78]
Total (95% CI)		1298		642	100.0%	1.02 [0.74, 1.42]
Total events	138		58			

Heterogeneity: Chi²=0.04, df=2 (P=0.98); I²=0%. Test for overall effect: Z=0.13 (P=0.89)

Table 18. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for nausea

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Feagan, 2008 (1)	10	62	7	58	9.4%	1.40 [0.50, 3.97]
Feagan, 2008 (2)	13	65	7	58	9.1%	1.82 [0.67, 4.93]
Sand, 2014	12	209	5	207	7.3%	2.46 [0.85, 7.11]
Sandborn, 2013	90	814	30	301	60.2%	1.12 [0.73, 1.74]
Vermeire, 2022	11	275	7	134	14.0%	0.76 [0.29, 2.00]
Total (95% CI)		1425		758	100.0%	1.26 [0.91, 1.75]
Total events	136		56			

Heterogeneity: Chi²=3.42, df=4 (P=0.49); I²=0% Test for overall effect: Z=1.37 (P=0.17).

Table 19. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for abdominal pain

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Feagan, 2008 (1)	7	62	11	58	11.2%	0.54 [0.20, 1.51]
Feagan, 2008 (2)	12	65	11	58	10.5%	0.97 [0.39, 2.40]
Sand, 2014	9	209	6	207	6.4%	1.51 [0.53, 4.31]
Sandborn, 2013	79	814	39	301	56.9%	0.72 [0.48, 1.09]
Vermeire, 2022	21	275	11	134	15.1%	0.92 [0.43, 1.98]
Total (95% CI)		1425		758	100.0%	0.81 [0.60, 1.10]
Total events	128		78			

Heterogeneity: Chi²=2.49, df=4 (P=0.65); I²=0%. Test for overall effect: Z=1.37 (P=0.17).

Table 20. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for fatigue

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Feagan, 2008 (1)	10	62	11	14	32.2%	0.05 [0.01, 0.22]
Feagan, 2008 (2)	13	65	11	14	32.3%	0.07 [0.02, 0.28]
Sandborn, 2013	53	814	14	301	35.5%	1.43 [0.78, 2.61]
Total (95% CI)		941		329	100.0%	0.18 [0.02, 2.13]
Total events	76		36			

Heterogeneity: Tau²=4.29; Chi²=27.92, df=2 (P<0.00001); I²=93%. Test for overall effect: Z=1.36 (P=0.18).

Table 21. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for headache

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Feagan, 2008 (1)	22	62	14	58	9.4%	1.73 [0.78, 3.83]
Feagan, 2008 (2)	24	65	14	58	9.4%	1.84 [0.84, 4.03]
Sand, 2014	11	209	15	207	14.3%	0.71 [0.32, 1.59]
Sandborn, 2005	97	814	47	301	60.6%	0.73 [0.50, 1.07]
Vermeire, 2022	15	275	5	134	6.4%	1.49 [0.53, 4.19]
Total (95% CI)		1425		758	100.0%	0.97 [0.74, 1.29]
Total events	169		95			

Heterogeneity: Chi²=7.99, df=4 (P=0.09); I²=50%. Test for overall effect: Z=0.19 (P=0.85).

Table 22. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for serious adverse events

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Feagan, 2008 (1)	6	62	10	58	25.5%	0.51 [0.17, 1.52]
Feagan, 2008 (2)	10	65	10	58	28.6%	0.87 [0.33, 2.28]
Sandborn, 2013	199	814	46	301	45.8%	1.79 [1.26, 2.55]
Total (95% CI)		941		417	100.0%	1.06 [0.49, 2.31]
Total events	215		66			

Heterogeneity: Tau²=0.31; Chi²=5.97, df=2 (P=0.05); I²=66%. Test for overall effect: Z=0.15 (P=0.88).

Table 23. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for pyrexia

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Feagan, 2008 (1)	5	62	4	58	6.5%	1.18 [0.30, 4.64]
Feagan, 2008 (2)	9	65	4	58	6.2%	2.17 [0.63, 7.47]
Sandborn, 2013	103	814	40	301	87.3%	0.95 [0.64, 1.40]
Total (95% CI)		941		417	100.0%	1.04 [0.72, 1.49]
Total events	117		48			

Heterogeneity: Chi²=1.62, df=2 (P=0.44); I²=0%. Test for overall effect: Z=0.20 (P=0.84).

Table 24. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for upper respiratory tract infections

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Sand, 2014	9	209	5	207	13.0%	1.82 [0.60, 5.52]
Sandborn, 2013	54	814	17	301	62.7%	1.19 [0.68, 2.08]
Vermeire, 2022	17	275	5	134	17.1%	1.70 [0.61, 4.71]
Watanabe, 2019	4	12	4	12	7.2%	1.00 [0.18, 5.46]
Total (95% CI)		1310		654	100.0%	1.34 [0.87, 2.07]
Total events	84		31			

Heterogeneity: Chi²=0.79, df=3 (P=0.85); I²=0%. Test for overall effect: Z=1.33 (P=0.18).

Table 25. Forest plot of the meta-analyses of the safety of vedolizumab vs. placebo for vomiting

Study or Subgroup	Vedolizumab		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Sand, 2014	9	209	5	207	10.5%	1.82 [0.60, 5.52]
Sandborn, 2013	49	814	23	301	69.2%	0.77 [0.46, 1.29]
Vermeire, 2022	6	275	7	134	20.2%	0.40 [0.13, 1.23]
Total (95% CI)		1298		642	100.0%	0.81 [0.53, 1.24]
Total events	64		35			

Heterogeneity: Chi²=3.56, df=2 (P=0.17); I²=44%. Test for overall effect: Z=0.97 (P=0.33).

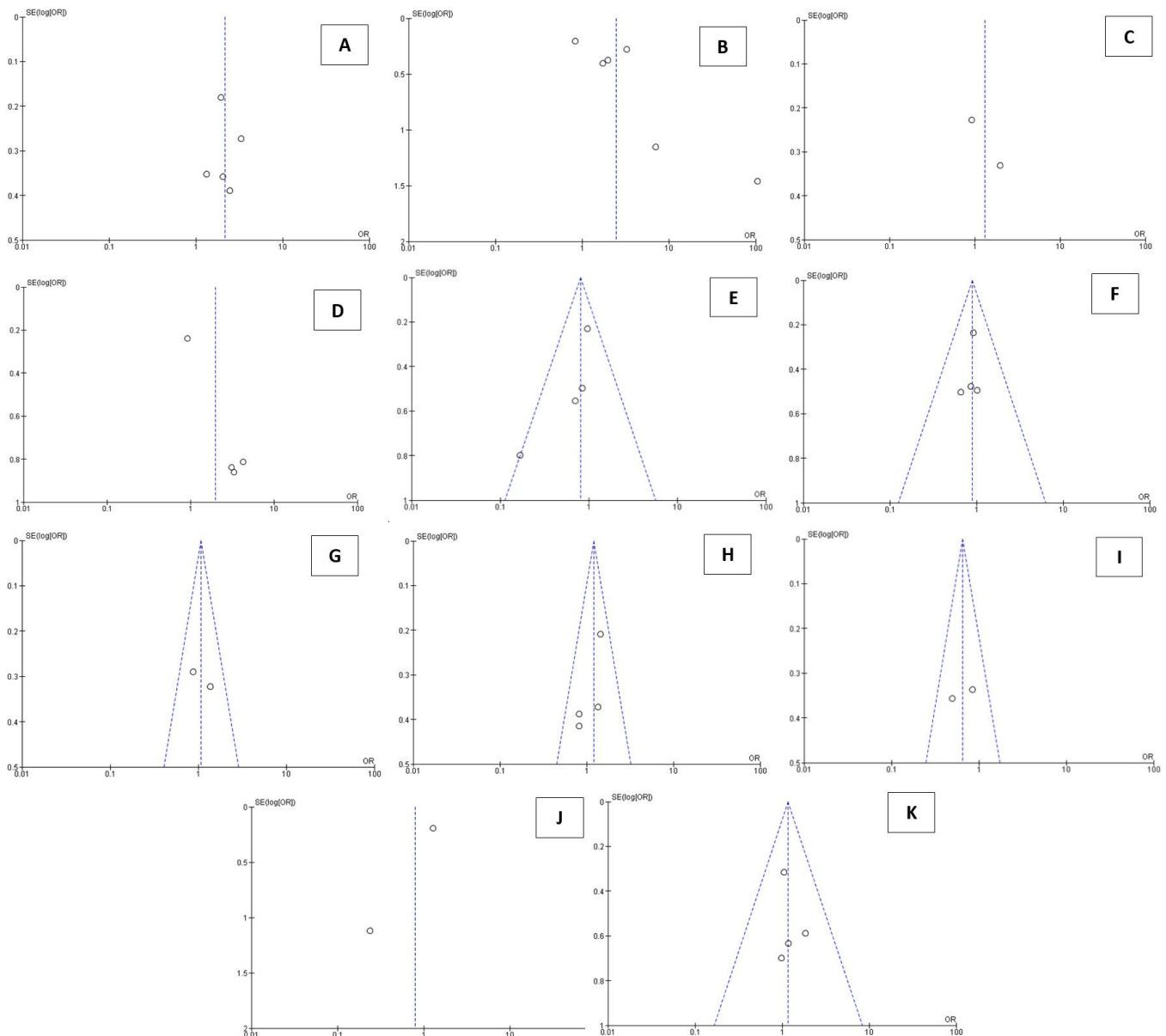


Figure 7. Funnel plots of natalizumab vs. placebo for clinical response (A), clinical remission (B), nasopharyngitis (C), arthralgia (D), nausea (E), abdominal pain (F), fatigue (G), headache (H), serious adverse events (I), infections (J) and pharyngitis (K).

In terms of safety, natalizumab carries a higher risk of nasopharyngitis, arthralgia, and fatigue. Although serious side effects are generally lower with natalizumab than with placebo, PML remains a serious concern due to its potential to induce PML [14]. One study found that natalizumab use in patients with CD may increase the risk of PML, a rare but serious brain infection. PML is caused by reactivation of the JC polyomavirus (JCV) in the central nervous system of patients with weakened immune systems [18]. Natalizumab works by inhibiting the $\alpha 4$ integrin molecule, which is essential for lymphocyte migration into inflamed tissue. However, inhibition of this integrin also affects the brain, increasing the risk of PML because immune cells are less capable of protecting against JCV reactivation [19]. Therefore, patients taking natalizumab should be closely monitored for neurological symptoms and should be enrolled in the TOUCH

registry to monitor the risk of PML and improve early detection [20].

Vedolizumab, on the other hand, has a better safety profile, with adverse events such as nasopharyngitis, arthralgia, and headache not significantly different from placebo. Serious adverse events were also similar to placebo, and to date, no cases of PML have been reported in patients taking vedolizumab [21]. This is further supported by a study that suggests that although vedolizumab has a similar mechanism of action to natalizumab, it selectively targets the $\alpha 4\beta 7$ integrin on lymphocytes, directing them to the gastrointestinal tract [22]. Unlike natalizumab, which targets the central nervous system (CNS)-associated $\alpha 4$ subunit ($\alpha 4\beta 1$ integrin), vedolizumab is considered to be less prone to disruption of immune surveillance in the CNS, thereby reducing the potential risk of developing PML compared to natalizumab [15, 22].

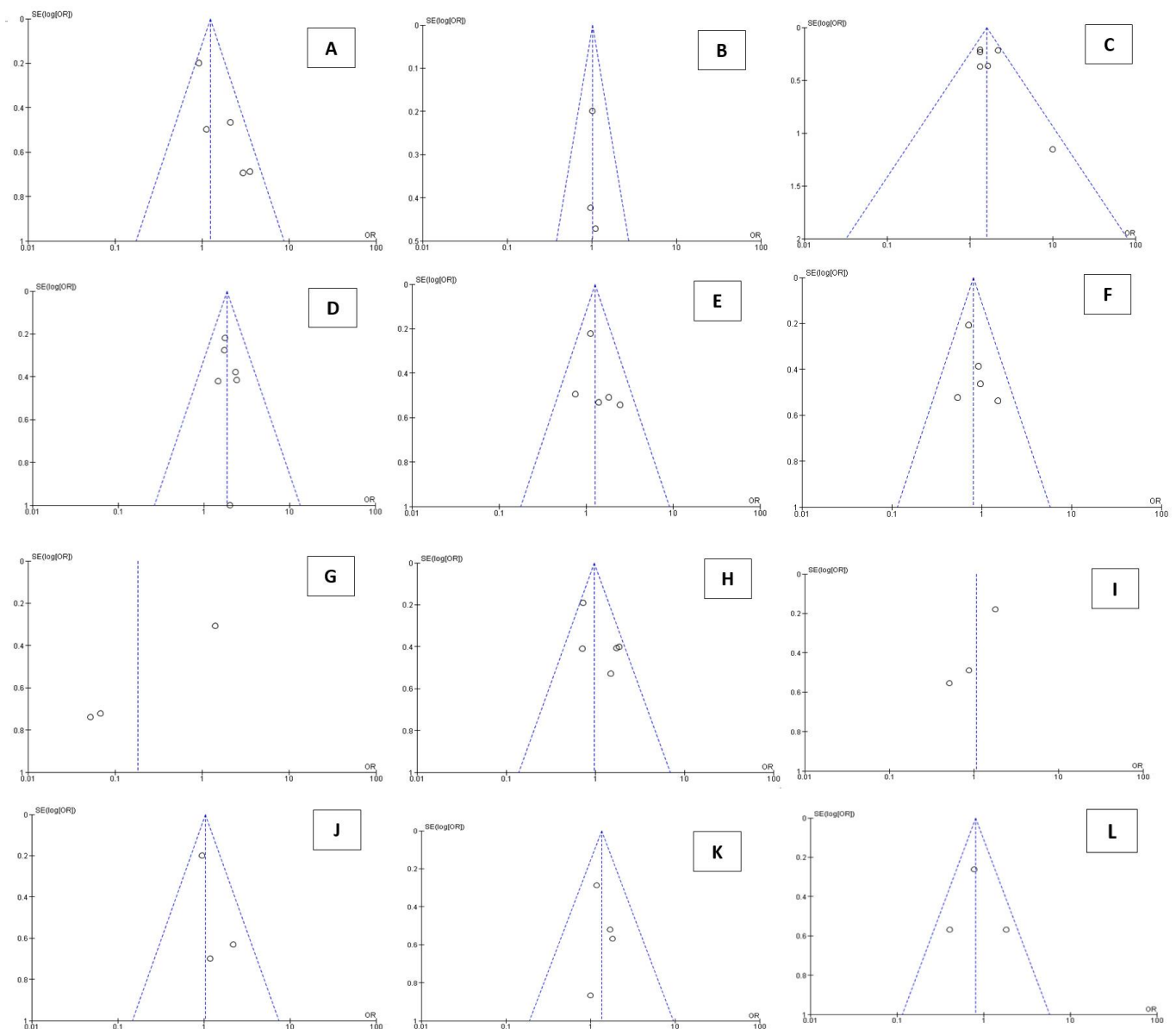


Figure 8. Funnel plots of vedolizumab vs. placebo for clinical response (A), clinical remission (B), nasopharyngitis (C), arthralgia (D), nausea (E), abdominal pain (F), fatigue (G), headache (H), serious adverse events (I), pyrexia (J), upper respiratory tract infections (K), and vomiting (L).

Limitations of this meta-analysis include the variability in the time frame of the included studies, spanning from 2008 to 2022. Such a long period may lead to differences in treatment standards and clinical approaches, which may affect the overall results. Additionally, although all analyzed studies were RCTs, which are considered the gold standard of clinical research, differences in patient population characteristics and variability in treatment duration may lead to heterogeneity in the results.

Conclusion

Both natalizumab and vedolizumab have proven their efficacy in the treatment of Crohn’s disease, demonstrating significant benefits over placebo in terms of clinical response and remission. Natalizumab shows high efficacy as an induction therapy, especially in the subpopulation of patients with elevated CRP levels, but poses a significant risk of PML requiring close

monitoring. In contrast, vedolizumab has a better safety profile, with adverse events comparable to placebo and no cases of PML reported, making it a safer option for long-term use. However, differences in study design and duration are limitations of this meta-analysis that should be considered when applying the results to clinical practice.

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Conflict of interest

No conflicts of interest declared by the authors.

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References

- Dotson JL, Boyle B. Crohn Disease. In: Wyllie R, Hyams JS, Kay M. Pediatric Gastrointestinal and Liver Disease, 6th Ed, Elsevier. 2021: 461-473.e8. <https://doi.org/10.1016/B978-0-323-67293-1.00042-6>.
- McDowell C, Farooq U, Haseeb M. Inflammatory Bowel Disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2025. <https://pubmed.ncbi.nlm.nih.gov/29262182>.
- Seyedian SS, Nokhostin F, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. *J Med Life* 2019; 12(2): 113-122. <https://doi.org/10.25122/jml-2018-0075>.
- Nóbrega VG, Silva IN de N, Brito BS, Silva J, da SILVA MCM, Santana GO. The onset of clinical manifestations in inflammatory bowel disease patients. *Arq Gastroenterol* 2018; 55(3): 290-295. <https://doi.org/10.1590/s0004-2803.201800000-73>.
- Permpoon V, Pongpirul K, Anuras S. Five-year clinical outcomes of Crohn's disease: A report of 287 multiethnic cases from an International Hospital in Thailand. *Clin Exp Gastroenterol* 2019; 12: 203-208. <https://doi.org/10.2147/ceg.s197255>.
- Goethel A, Croitoru K, Philpott DJ. The interplay between microbes and the immune response in inflammatory bowel disease. *J Physiol* 2018; 596(17): 3869-3882. <https://doi.org/10.1113/JP275396>.
- Jarmakiewicz-Czaja S, Zielińska M, Sokal A, Filip R. Genetic and Epigenetic Etiology of inflammatory bowel disease: An update. *Genes (Basel)* 2022; 13(12): 2388. <https://doi.org/10.3390/genes13122388>.
- Lauro ML, Burch JM, Grimes CL. The effect of NOD2 on the microbiota in Crohn's disease. *Curr Opin Biotechnol* 2016; 40: 97-102. <https://doi.org/10.1016/j.copbio.2016.02.028>.
- Mukim M, Chaturvedi M, Patel R, Roy S, Sharma P, Chaturvedi V, et al. Crohn's disease: A review on epidemiology, diagnosis and therapeutic management. *Indian Drugs* 2022; 59(9): 16-28. <https://doi.org/10.53879/id.59.09.12577>.
- Slack RJ, Macdonald SJF, Roper JA, Jenkins RG, Hatley RJD. Emerging therapeutic opportunities for integrin inhibitors. *Nat Rev Drug Discov* 2022; 21(1): 60-78. <https://doi.org/10.1038/s41573-021-00284-4>.
- Nelson SML, Nguyen TM, McDonald JWD, Macdonald JK. Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2018; 8(8): CD006097. <https://doi.org/10.1002/14651858.CD006097.pub3>.
- Ha C, Kornbluth A. Vedolizumab as a treatment for Crohn's disease and ulcerative colitis. *Gastroenterol Hepatol (N Y)* 2014; 10(12): 793-800. <https://pubmed.ncbi.nlm.nih.gov/27524947>.
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71. <https://doi.org/10.1136/bmj.n71>.
- Ghosh S, Goldin E, Gordon FH, Malchow HA, Rask-Madsen J, Rutgeerts P, et al. Natalizumab for Active Crohn's Disease. *N Engl J Med* 2003; 348: 24-32. <https://doi.org/10.1056/nejmoa020732>.
- Gordon FH, Lai CWY, Hamilton MI, Allison MC, Srivastava ED, Fouweather MG, et al. A randomized placebo-controlled trial of a humanized monoclonal antibody to $\alpha 4$ integrin in active Crohn's disease. *Gastroenterology* 2001; 121: 268-274. <https://doi.org/10.1053/gast.2001.26260>.
- Kane S V., Horst S, Sandborn WJ, Becker B, Neis B, Moschandrew M, et al. Natalizumab for moderate to severe Crohn's disease in clinical practice: The Mayo Clinic Rochester experience. *Inflamm Bowel Dis* 2012; 18: 2203-2208. <https://doi.org/10.1002/ibd.22943>.
- Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, et al. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005; 353: 1912-1925. <https://doi.org/10.1056/nejmoa043335>.
- Targan SR, Feagan BG, Fedorak RN, Lashner BA, Panaccione R, Present DH, et al. Natalizumab for the treatment of active Crohn's disease: Results of the ENCORE trial. *Gastroenterology* 2007; 132: 1672-1683. <https://doi.org/10.1053/j.gastro.2007.03.024>.
- Feagan BG, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JWD, et al. Treatment of Active Crohn's Disease With MLN0002, a Humanized Antibody to the $\alpha 4 \beta 7$ Integrin. *Clin Gastroenterol Hepatol* 2008; 6: 1370-1377. <https://doi.org/10.1016/j.cgh.2008.06.007>.
- Vermeire S, D'Haens G, Baert F, Danese S, Kobayashi T, Loftus E V., et al. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's disease: Results from the VISIBLE 2 randomised trial. *J Crohn's Colitis* 2022; 16: 27-38. <https://doi.org/10.1093/ecco-icc/ijab133>.
- Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014; 147(3): 618-627. <https://doi.org/10.1053/j.gastro.2014.05.008>.
- Watanabe K, Motoya S, Ogata H, Kanai T, Matsui T, Suzuki Y, et al. Effects of vedolizumab in Japanese patients with Crohn's disease: a prospective, multicenter, randomized, placebo-controlled Phase 3 trial with exploratory analyses. *J Gastroenterol* 2020; 55: 291-306. <https://doi.org/10.1007/s00535-019-01647-w>.

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