Efficacy and safety of vedolizumab in the treatment of patients with inflammatory bowel disease: A systematic review and meta-analysis of randomized controlled trials

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Abstract. Few studies have thoroughly assessed the efficacy and safety of vedolizumab (VDZ) in the treatment of inflammatory bowel disease (IBD). Therefore, this systematic review and meta-analysis was performed to further evaluate this association. PubMed, Embase, and the Cochrane databases were searched until April 2022. Randomized controlled trials (RCTs) evaluating the efficacy and safety of VDZ in the treatment of IBD were included. The risk ratio (RR) and 95% confidence intervals (CI) were estimated for each outcome using a random effects model. A total of 12 RCTs, including 4,865 patients, met the inclusion criteria. In the induction phase, VDZ was more effective than placebo for patients with ulcerative colitis and Crohn's disease (CD) in clinical remission (RR=2.09; 95% CI=1.66-2.62) and clinical response (RR=1.54; 95% CI=1.34-1.78). In the maintenance therapy group, VDZ reached higher clinical remission (RR=1.98; 95% CI=1.58-2.49) and clinical response (RR=1.78; 95% CI=1.40-2.26) rates compared with the placebo group. VDZ particularly improved clinical remission (RR=2.07; 95% CI=1.48-2.89) and clinical response (RR=1.84; 95% CI=1.54-2.21) in patients with TNF antagonist failure. In terms of corticosteroid-free remission, VDZ was also more effective than placebo in patients with IBD (RR=1.98; 95% CI=1.51-2.59). In Crohn's patients, VDZ was more effective than placebo in terms of mucosal healing (RR=1.78; 95% CI=1.27-2.51). With respect to adverse events, VDZ significantly reduced the risk of IBD exacerbation compared with the placebo (RR=0.60; 95% CI=0.39-0.93; P=0.023). However, when compared with the placebo, VDZ increased the risk of nasopharyngitis in patients with CD (RR=1.77; 95% CI=1.01-3.10; P=0.045). No significant differences in other adverse events were observed. Although there might be underlying risk, such as selection bias, in the present study it can be safely concluded that VDZ is a safe and effective biological agent for IBD, particularly for patients with TNF antagonist failure.

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Introduction

Inflammatory bowel disease (IBD) results from the interaction between genetic and environmental factors, which may influence immune responses. Crohn's disease (CD) and ulcerative colitis (UC), the two main forms of IBD (1), consist of manifestations of chronic inflammation of the gastrointestinal tract. However, the inflammatory and symptom burden between patients and within the same individual displays considerable heterogeneity over time (2). In the past two to three decades, the incidence and prevalence of IBD have increased rapidly around the world. IBD not only seriously affects patients' quality of life, but also has the potential to induce serious complications. For example, CD can cause an intestinal fistula, and skin and biliary stones, while UC is associated with osteoporosis and possibly colon cancer if it lasts over 8-10 years (1).

Conventional treatments for IBD include 5-aminosalicylates, corticosteroids, azathioprine, or 6-mercaptopurine. Novel anti-TNF-α biologics, such as infliximab and adalimumab, have been used as the basis for moderate-to-severe IBD treatment (3). However, >30% of patients do not respond to initial anti-TNF-α therapy, and up to 45% of patients show a decreased response over time (4). In addition, anti-TNF-α agents are associated with serious adverse events, such as infusion response, neutropenia, and systemic infections. Therefore, it is important to identify novel therapies for IBD. Vedolizumab (VDZ), specifically expressed by gastrointestinal T lymphocytes, is an integrin antagonist that binds to α4β7 integrin. VDZ alleviates intestinal inflammation by selectively inhibiting interactions between integrin α4β7 and mucosal addressin cell adhesion molecule-1, thereby blocking lymphocyte migration to the intestinal tract, thus playing an effective role in moderate-to-severe IBD (5).

In recent years, VDZ has been approved for the treatment of moderate-to-severe active UC and CD patients with at least one conventional treatment failure. There are multiple randomized controlled trials (RCTs) on the use of VDZ for the treatment of IBD, whose findings on efficacy and adverse reactions differ. Therefore, this systematic review and meta-analysis was conducted to thoroughly evaluate the therapeutic value of VDZ for the treatment of IBD by selecting high-quality RCTs and providing an objective basis for its clinical application.

Materials and methods

The present systematic review and meta-analysis was registered in PROSPERO (https://www.crd.york.ac.uk/prospero) under CRD42022335987 and was performed in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (6). The PICO format (population, intervention, comparison, outcome) was used to answer the research question: 'Is VDZ effective and safe for the treatment of IBD?' The population included IBD patients with UC or CD, and the intervention included VDZ or placebo. The primary outcomes were clinical remission and clinical response during induction and maintenance therapy. Secondary outcomes included clinical remission and clinical response in patients with TNF antagonist failure, corticosteroid-free remission, mucosal healing in CD patients, IBD exacerbation, and adverse event rate.

Search strategy. PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com), and the Cochrane databases (https://www.cochranelibrary.com) in English were searched until April 2022. The search terms used were as follows: 'IBD' or 'UC' or 'Crohn's disease' or 'IBD' or 'UC' or 'CD' and 'VDZ' or 'α4β7 integrin', and 'TNF-α' or 'TNF antagonist failure', and 'RCTs'. Titles and abstracts were independently screened by two reviewers (HJT and LLZG) to exclude irrelevant articles. A secondary search was made for references for the literature review. Duplicates were excluded and full texts were then retrieved to assess eligibility.

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Adults (age, >18 years) with moderate-to-severe UC or CD (confirmed endoscopically and/or histopathologically, with a partial Mayo score of 1-12 at screening) who were either treatment-naive, previously exposed to anti-TNF agents, or had failed TNF antagonist therapy; ii) randomized, double-blinded, placebo-controlled studies to evaluate the efficacy and safety of VDZ in the treatment of IBD; iii) available studies reporting the risk estimates with their corresponding 95% confidence interval (CI) or original data allowing us to compute them; and iv) if the published studies reported data for specific subgroups, results for the whole population were considered.

The exclusion criteria were as follows: i) Not RCTs; ii) animal studies; iii) studies on children and pregnant women; iv) non-original papers; v) duplicate reports and abstracts; vi) comparison of VDZ with other biological agents; and vii) full-text or complete data were not available.

Data extraction and quality assessment. The data extracted from each study included the name of the first author, publication year, location, sample size (number of cases and total number of participants), type of IBD, categories of efficacy indicators, and types of adverse reactions. Three investigators (LLZG, LXZ, and HJT) independently extracted the data, and discrepancies were resolved by consensus.

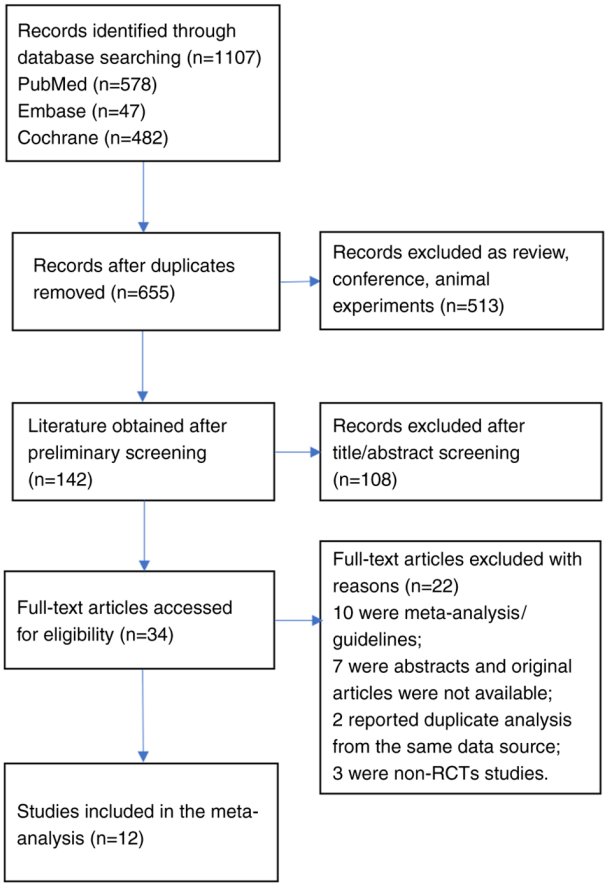

Figure 1. Flow diagram of the assessment of studies identified by the literature search for inclusion.

The clinical response of CD patients was defined as CD Activity Index (CDAI)-100 response. Mucosal healing was determined using a sub-score of 0 or 1 on the Mayo endoscopic component. Adverse events included serious adverse events, such as infusion reaction and delayed hypersensitivity that led to discontinuation of the drug, headaches, nasopharyngitis, upper respiratory tract infection, arthralgia, abdominal pain, and vomiting.

The methodological quality of the included RCTs was evaluated based on the Cochrane Collaboration's risk of bias tool (7), which consists of selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other (bias source); and together are used to evaluate the risk of bias. The results of methodological quality were interpreted as 'low-risk bias', 'high-risk bias', and 'unclear' for each item according to the risk assessment criteria of bias. The study quality was assessed independently by two investigators (LXZ and CQB), and any discrepancies were addressed by a joint reevaluation of the original article.

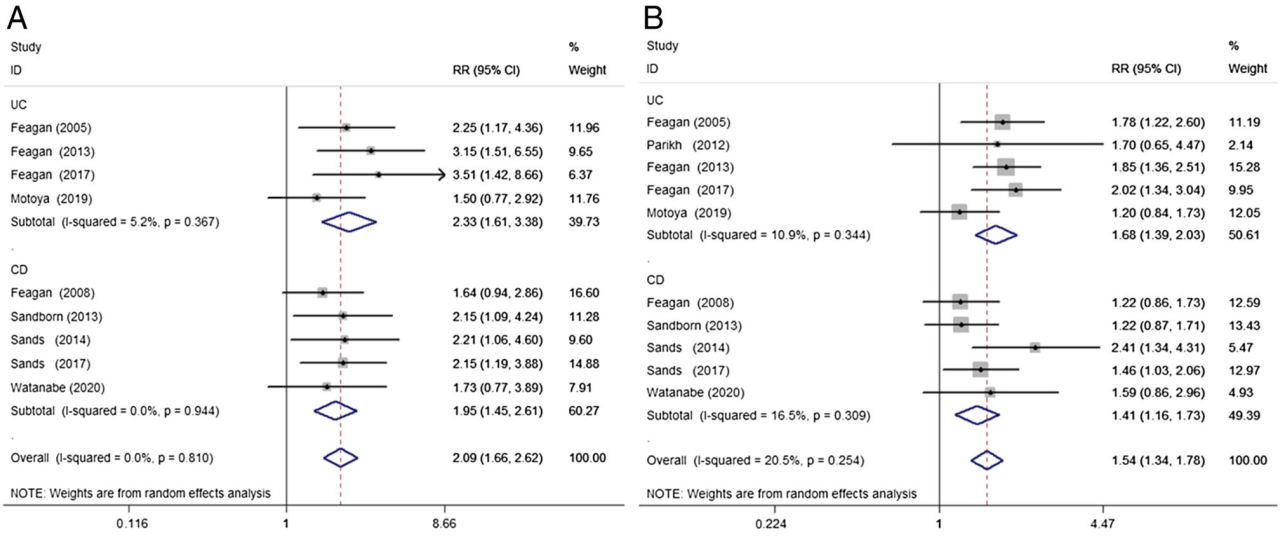

Figure 2. Randomized effects meta-analysis of the efficacy of vedolizumab treatment in the induction phase. (A) Clinical remission and (B) clinical response. UC, ulcerative colitis; CD, Crohn's disease; RR, risk ratio; CI, confidence interval.

Statistical analysis. All statistical analysis was performed using STATA version 12.0 (StataCorp LLC). The results are presented as the risk ratio (RR) and 95% CI for the comparison of VDZ and placebo treatment in IBD. A random effects model was used to calculate the pooled estimates. Statistical heterogeneity between studies was examined using the I^2 value, and I^2>50% was considered to indicate statistically significant heterogeneity (8). Subgroup analysis based on study design, IBD category, and type of adverse reaction was conducted to explore the source of heterogeneity in this study. Sensitivity analysis was further performed to examine the reliability of the results by omitting one study at a time. Publication bias was assessed using a Begg's test and funnel plots if ≥10 studies were available, and it was considered to exist when P<0.05. The trim-and-fill method was used to reduce the potential influence of publication bias (9).

Results

Fig. 1 shows a flow diagram of the detailed selection process. A total of 1,107 potentially relevant articles were initially retrieved, 452 duplicate articles were excluded, and 513 were articles were excluded due to being reviews, conference abstracts, and animal experiments. After screening the title and abstract, 34 articles remained for full-text review. Among them, 22 were excluded (10 were meta-analyses/guideline articles, 7 were abstracts whose original articles were not available, 2 reported duplicate analysis from the same data source and three were not RCTs). Thus, a total of 12 eligible articles (10-21) were included in this meta-analysis. Of these studies, 5 were conducted in the United States (11,15,17-19), 4 in Canada (10,12,13,16), 2 in Japan (14,20), and 1 in Belgium (21). Table I shows the primary characteristics of the included studies. All 12 studies were assessed as having a low or moderate risk of bias. Table SI shows the study quality and risk of bias in each domain of the included studies.

As shown in Table II, a total of 12 RCTs were included to discuss the efficacy and safety of VDZ compared with that of a placebo for the treatment of IBD patients. All outcomes were uniformly assessed according to the standard-defined Mayo Clinic Score on weeks 6-10 of induction therapy and weeks 52-60 of maintenance therapy.

Induction therapy

Induction of clinical remission. A total of 9 studies (9,11-13,15-19) were included to compare the clinical remission of IBD during induction therapy with VDZ vs. placebo. VDZ significantly improved clinical remission during induction therapy when compared with the placebo (RR=2.09; 95% CI=1.66-2.62; P<0.001; I^2=0%; P=0.81). This positive association was also seen in the subgroup analysis of both UC (RR=2.33; 95% CI=1.61-3.38; P<0.001; I^2=5.2%, P=0.37) and CD (RR=1.95; 95% CI=1.45-2.61; P<0.001; I^2=0%; P=0.94; Fig. 2A).

Induction of clinical response. A total of 10 studies (9-13,15-19) were included to compare the clinical response of IBD to VDZ/placebo during induction therapy. Begg's test results showed no publication bias (P=0.363) in the 10 included studies. The funnel plots are presented in Fig. S1. When compared with the placebo, VDZ significantly improved the clinical response of IBD (RR=1.54; 95% CI=1.34-1.78; P<0.001; I^2=20.5%; P=0.25), UC (RR=1.68; 95% CI=1.39-2.03; P<0.001; I^2=10.9%; P=0.34) and CD (RR=1.41; 95% CI=1.16-1.73; P=0.001; I^2=16.5%; P=0.31) during induction therapy (Fig. 2B).

Maintenance therapy

Maintenance of clinical remission. A total of 7 studies (11,13,14,16,18-20) were included to compare the clinical remission of IBD with VDZ/placebo during maintenance therapy. Compared with the placebo, VDZ had significant benefits for the clinical remission of IBD (RR=1.98; 95% CI=1.58-2.49; P<0.001; I^2=43.9%; P=0.09) during maintenance therapy. This positive association was also seen in the subgroup analysis of both UC (RR=2.55; 95% CI=1.93-3.35;

Table I. Detailed information on the included studies.

First author, year	Country	Diagnosis	Intervention measures and administration methods of VDZ group	No. of patients	Female (%)	Outcomes	Follow-up	(Refs.)
Feagan *et al*, 2005	Canada	UC	Induction Phase:			Induction Phase:	8 weeks	(10)
			VDZ(0.5 mg/2.0 mg/kg, iv)	118	-	Clinical response, clinical remission		
			Placebo	63	-	Adverse events		
Parikh *et al*, 2012	USA	UC	Induction Phase:			Clinical response; clinical remission	253 days	(11)
			VDZ (2 mg/kg, 6 mg/kg, 10 mg/kg, iv)	37	57			
			Placebo	9	67			
Feagan *et al*, 2013	Canada	UC	Induction Phase:			Induction Phase:	6 weeks	(12)
			VDZ (300 mg, iv)	225	41.3	Clinical response, clinical remission		
			Placebo	149	38.3			
			Maintenance Phase:			Maintenance Phase:	52 weeks	
			VDZ (300 mg iv, Q4/Q8W)	247	-	Clinical response, clinical remission		
			Placebo	126	-			
Feagan *et al*, 2017	Canada	UC	Induction Phase:			Induction Phase:	6 weeks	(13)
			TNF-naïve: VDZ (300 mg, iv)	130	47.0	Clinical response, clinical remission		
			Placebo	76	38.2	TNF-failure: clinical response,	6 weeks	
			TNF-failure: VDZ (300 mg, iv)	82	39.0	clinical remission		
			Placebo	63	44.4			
Motoya *et al*, 2019	Japan	UC	Induction Phase:			Induction Phase:	10 weeks	(14)
			VDZ: 300 mg iv	164	39.6	Clinical response, clinical remission		
			Placebo	82	32.9	Maintenance Phase:	60 weeks	
			MaintenancePhase:			Clinical response, clinical remission		
			VDZ300 mg iv (Q8W)	41	-	Adverse events		
			Placebo	42	-			
Sandborn *et al*, 2020	USA	UC	Maintenance Phase:			Maintenance Phase:	52 weeks	(15)
			VDZ (108 mg, SC, Q2W)	106	38.7	Clinical response, clinical remission		
			VDZ (300 mg, iv, Q8W)	54	42.6	Adverse events	52 weeks	
			Placebo	56	39.3			
Feagan *et al*, 2008	Canada	CD	Induction Phase:			Induction Phase:	57 days	(16)
			VDZ (0.5 mg/2.0 mg/kg, iv)	127	56.0	Clinical response, clinical remission		
			Placebo	58	48.3	Adverse events		

Table I. Continued.

First author, year	Country	Diagnosis	Intervention measures and administration methods of VDZ group	No. of patients	Female (%)	Outcomes	Follow-up	(Refs.)
Sandborn *et al*, 2013	USA	CD	Induction Phase:			Induction Phase:	6 weeks	(17)
			VDZ (300 mg, iv)	220	52.3	Clinical response, clinical		
			Placebo	148	53.4	remission		
			Maintenance Phase:			Maintenance Phase:	52 weeks	
			VDZ (300 mg, iv, Q4/8W)	308	-	Clinical response, clinical remission		
			Placebo	153	-			
Sands *et al*, 2014	USA	CD	Induction Phase:			Induction Phase:	10 weeks	(18)
			TNF-naïve:	51	55.0	Clinical response, clinical remission		
			VDZ (300 mg, iv)	50	46.0	TNF-failure: clinical response,	6 weeks	
			Placebo			clinical remission. Adverse reactions		
			TNF-failure:					
			VDZ (300 mg, iv)	158	57.0			
			Placebo	157	61.0			
Sands *et al*, 2017	USA	CD	Induction Phase:			Induction Phase:	6 weeks	(19)
			VDZ (300 mg, iv)	154	48.7	Clinical response, clinical remission		
			Placebo	123	47.2			
			Maintenance Phase:			Maintenance Phase:	52 weeks	
			VDZ (300 mg, iv, Q4/8W)	137	-	Clinical response, clinical remission		
			Placebo	71	-	TNF-failure: clinical response,	6 weeks	
			TNF-failure:			clinical remission		
			VDZ (300 mg, iv)	263	56.7			
			Placebo	227	60.0			
Watanabe *et al*, 2020	Japan	CD	Induction Phase:			Induction Phase:	10 weeks	(20)
			VDZ (300 mg, iv)	79	35.4	Clinical response, clinical remission		
			Placebo	78	33.3		60 weeks	
			Maintenance Phase:			Maintenance Phase:		
			VDZ (300 mg, iv, Q8W)	12	50.0	Clinical response, clinical remission		
			Placebo	12	25.0	Adverse events		
Vermeire *et al*, 2022	Belgium	CD	Maintenance Phase:			Maintenance Phase:	52 weeks	(21)
			VDZ (108 mg, SC, Q2W)	275	42.9	Clinical response, clinical remission		
			Placebo	134	50.7	Adverse events.		

SC, subcutaneous injection; IV, intravenous injection; VDZ, vedolizumab.

Table II. Summary of results.

Treatment	Outcome	Subgroups	No. of studies	Pooled RR (95% CI)	P-value	Heterogeneity I^2 (%)	Heterogeneity P_h
Induction therapy	Clinical remission	IBD	9	2.09 (1.66-2.62)	<0.001	0.0	0.810
		UC	4	2.33 (1.61-3.38)	<0.001	5.20	0.367
		CD	5	1.95 (1.45-2.61)	<0.001	0.0	0.944
	Clinical response	IBD	10	1.54 (1.34-1.78)	<0.001	20.5	0.254
		UC	5	1.68 (1.39-2.03)	<0.001	10.9	0.344
		CD	5	1.41 (1.16-1.73)	0.001	16.5	0.309
Maintenance therapy	Clinical remission	IBD	8	1.98 (1.58-2.49)	<0.001	43.9	0.086
		UC	4	2.55 (1.93-3.35)	<0.001	0.0	0.482
		CD	4	1.59 (1.32-1.91)	<0.001	0.0	0.566
	Clinical response	IBD	8	1.78 (1.40-2.26)	<0.001	68.7	0.002
		UC	4	2.23 (1.82-2.73)	<0.001	0.0	0.807
		CD	4	1.38 (1.10-1.74)	0.006	45.3	0.140
Failure of TNF antagonists	Clinical remission	All studies	5	2.07 (1.48-2.89)	<0.001	10.2	0.348
		Induction therapy	3	1.85 (1.30-2.65)	0.001	0.0	0.601
		Maintenance therapy	2	3.29 (1.06-10.15)	0.039	58.2	0.122
	Clinical response	All studies	5	1.84 (1.54-2.21)	<0.001	0.0	0.820
		Induction therapy	3	1.83 (1.50-2.23)	<0.001	0.0	0.951
		Maintenance therapy	2	1.97 (1.17-3.31)	0.010	29.6	0.233
Corticosteroid-free remission/glucocorticoid free remission		IBD	8	1.98 (1.51-2.59)	<0.001	17.4	0.293
		UC	4	2.79 (1.84-4.21)	<0.001	0.0	0.876
		CD	4	1.58 (1.21-2.07)	0.001	0.0	0.461
Mucosal healing	UC	All studies	4	1.78 (1.27-2.51)	0.001	68.4	0.023
		Induction therapy	2	1.43 (1.05-1.95)	0.022	35.1	0.215
		Maintenance therapy	2	2.35 (1.66-3.34)	<0.001	26.5	0.243
Adverse event							
Headache		IBD	9	1.09 (0.81-1.47)	0.567	0.0	0.561
		UC	4	0.98 (0.60-1.58)	0.921	0.0	0.837
		CD	5	1.08 (0.63-1.86)	0.769	35.7	0.198
		Induction therapy	5	1.05 (0.71-1.55)	0.805	17.0	0.307
		Maintenance therapy	4	1.13 (0.58-2.21)	0.720	0.0	0.603
Nasopharyngitis		IBD	7	1.43 (0.98-2.08)	0.062	31.0	0.191
		UC	4	1.28 (0.76-2.16)	0.350	49.2	0.116
		CD	3	1.77 (1.01-3.10)	0.045	0.0	0.421
		Induction therapy	4	1.49 (0.95-2.34)	0.084	0.0	0.600
		Maintenance therapy	3	1.38 (0.64-2.97)	0.416	70.0	0.036
Upper respiratory tract infection		IBD	7	1.30 (0.85-2.00)	0.223	0.0	0.643
		UC	3	1.60 (0.43-5.99)	0.488	38.9	0.195
		CD	4	1.30 (0.81-2.09)	0.281	0.0	0.793
		Induction therapy	3	1.11 (0.64-1.94)	0.706	0.0	0.468
		Maintenance therapy	4	1.63 (0.84-3.16)	0.149	0.0	0.569
Arthralgia		IBD	5	1.15 (0.71-1.86)	0.561	0.0	0.841
		UC	3	1.46 (0.63-3.39)	0.373	0.0	0.630
		CD	2	1.03 (0.57-1.84)	0.927	0.0	0.839
		Induction therapy	3	1.16 (0.61-2.19)	0.652	0.0	0.968
		Maintenance therapy	2	1.31 (0.45-3.84)	0.625	27.7	0.239
Abdominal pain		IBD	4	0.90 (0.61-1.33)	0.590	0.0	0.726
		UC	1	0.73 (0.31-1.73)	0.480	NA	NA
		CD	3	0.95 (0.61-1.47)	0.807	0.0	0.592
		Induction therapy	3	0.88 (0.55-1.41)	0.608	0.0	0.521
		Maintenance therapy	1	0.93 (0.46-1.87)	0.839	NA	NA

Table II. Continued.

Treatment	Outcome	Subgroups	No. of studies	Pooled RR (95% CI)	P-value	Heterogeneity I^2 (%)	Heterogeneity P_h
Vomiting		IBD	5	0.87 (0.42-1.83)	0.720	31.2	0.213
		UC	3	0.89 (0.32-2.48)	0.821	12.8	0.318
		CD	2	0.86 (0.21-3.58)	0.838	71.6	0.061
		Induction therapy	3	1.03 (0.45-2.37)	0.948	18.7	0.292
		Maintenance therapy	2	0.89 (0.13-6.00)	0.903	60.8	0.110
Serious adverse events		IBD	9	0.90 (0.67-1.20)	0.473	0.0	0.891
		UC	4	1.27 (0.77-2.11)	0.352	0.0	0.899
		CD	5	0.76 (0.54-1.08)	0.130	0.0	0.985
		Induction therapy	5	0.93 (0.64-1.34)	0.694	0.0	0.647
		Maintenance therapy	4	0.86 (0.54-1.36)	0.513	0.0	0.788

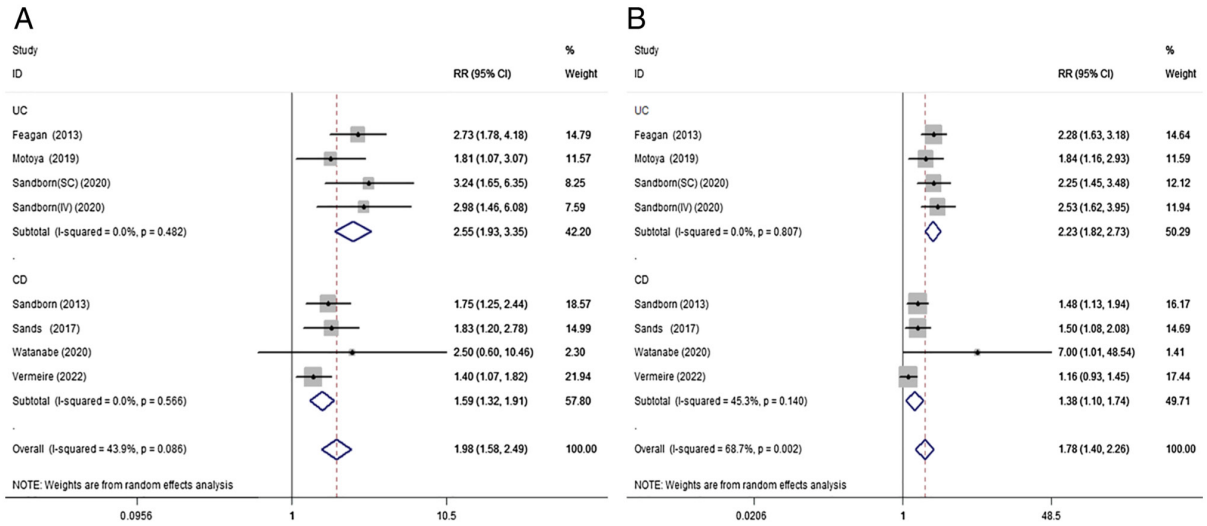

Figure 3. Randomized effects meta-analysis of the efficacy of vedolizumab treatment in the maintenance phase. (A) Clinical remission and (B) clinical response. UC, ulcerative colitis; CD, Crohn's disease; RR, risk ratio; CI, confidence interval.

P<0.001; I^2=0%; P=0.48) and CD (RR=1.59; 95% CI=1.32-1.91; P<0.001; I^2=0%; P=0.57; Fig. 3A).

Maintenance of clinical response. A total of 7 (11,13,14,16,18-20) studies were included to compare the clinical response of IBD to the VDZ/placebo during maintenance therapy. There was a positive association between VDZ induction treatment and clinical response compared with placebo during induction treatment (RR=1.78; 95% CI=1.40-2.26; P<0.001; I^2=68.7%; P=0.002). Subgroup analysis showed that VDZ had similar effects in both UC (RR=2.23; 95% CI=1.82-2.73; P<0.001; I^2=0%, P=0.81) and CD (RR=1.38; 95% CI=1.10-1.74; P=0.006; I^2=45.3%; P=0.14; Fig. 3B).

Failure of TNF antagonists

Clinical remission of TNF antagonist failure. Three studies (12,17,18) were included to compare VDZ and placebo treatment in clinical remission of IBD patients with a history of TNF antagonist failure. VDZ significantly increased the clinical remission of IBD with TNF antagonist failure when compared with the placebo (RR=2.07; 95% CI=1.48-2.89; P<0.001; I^2=10.2%; P=0.35). This positive association was also observed following subgroup analysis of both induction (RR=1.85; 95% CI=1.30-2.65; P=0.001; I^2=0%; P=0.60) and maintenance therapy (RR=3.29; 95% CI=1.06-10.15; P=0.039; I^2=58.2%; P=0.12; Fig. 4A).

Clinical response of TNF antagonist failure. A total of 3 studies (12,17,18) were included to compare VDZ and placebo in terms of clinical response of IBD in patients with a history of TNF antagonist failure. When compared with the placebo, VDZ significantly increased the clinical response of IBD patients with TNF antagonist failure (RR=1.84; 95% CI=1.54-2.21; P<0.001; I^2=0%; P=0.82) during both induction (RR=1.83; 95% CI=1.50-2.23; P<0.001; I^2=0%; P=0.95) and maintenance (RR=1.97; 95% CI=1.17-3.31; P=0.010; I^2=29.6%; P=0.23) therapy (Fig. 4B).

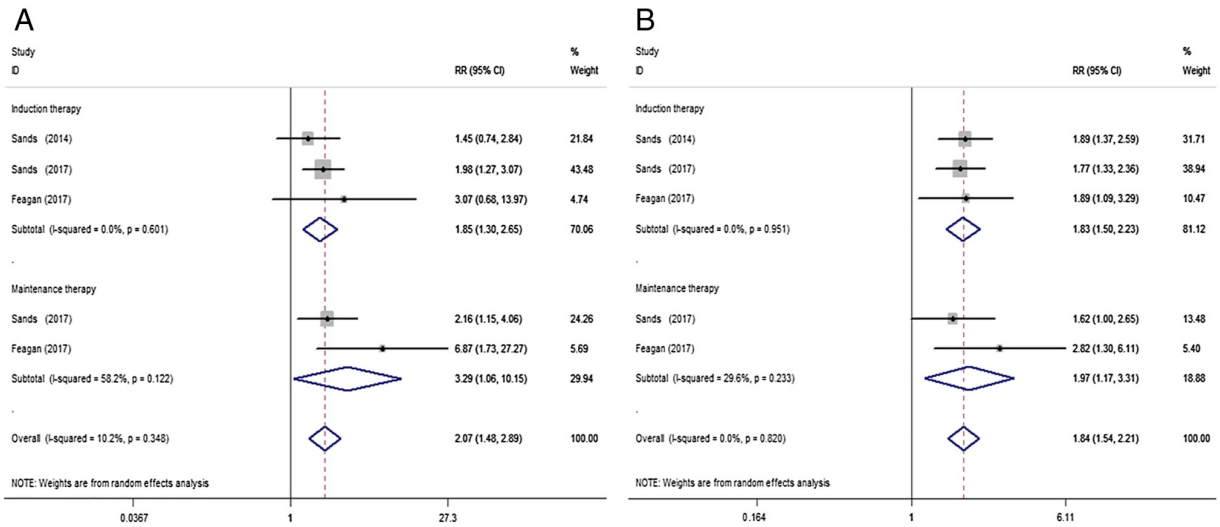

Figure 4. Random-effect meta-analysis of VDZ in IBD patients with a history of TNF antagonist failure. (A) Clinical remission and (B) clinical response. VDZ, vedolizumab; IBD, irritable bowel disease; RR, risk ratio; CI, confidence interval.

Corticosteroid-free remission. A total of 7 studies (11,13,14,16,18-20) were included to compare VDZ and placebo in terms of corticosteroid-free remission of IBD. VDZ improved corticosteroid-free remission compared with the placebo (RR=1.98; 95% CI=1.51-2.59; P<0.001; I^2=17.4%; P=0.29). This positive association was also observed in the subgroup analysis of both UC (RR=2.79; 95% CI=1.84-4.21; P<0.001; I^2=0%; P=0.88) and CD (RR=1.58; 95% CI=1.21-2.07; P=0.001; I^2=0%; P=0.46) (Fig. S2).

Mucosal healing. A total of 2 studies (11,13) were included to compare VDZ and placebo in terms of mucosal healing in UC. VDZ significantly improved the mucosal healing of UC compared with the placebo (RR=1.78; 95% CI=1.27-2.51; P=0.001; I^2=68.4%; P=0.02). This positive association was also observed in the subgroup analysis of both induction (RR=1.43; 95% CI=1.05-1.95; P=0.022; I^2=35.1%; P=0.22) and maintenance (RR=2.35; 95% CI=1.66-3.34; P<0.001; I^2=26.5%; P=0.24; Fig. S3) therapy.

IBD exacerbation. A total of 7 studies (9,13-15,17,19,20) were included to compare IBD exacerbation following VDZ and placebo treatment. VDZ significantly reduced the risk of IBD exacerbation compared with the placebo (RR=0.60; 95% CI=0.39-0.93; P=0.023; I^2=64.6%; P=0.004). In the subgroup analysis, evidence in favor of the aforementioned association was weaker in induction therapy (RR=0.62; 95% CI=0.30-1.28; P=0.20; I^2=75.7%; P=0.001) when compared with maintenance therapy (RR=0.56; 95% CI=0.37-0.87; P=0.009; I^2=22.0%; P=0.28). The placebo increased the risk of exacerbation in patients with CD when compared with VDZ (RR=0.51; 95% CI=0.27-0.99; P=0.047; I^2=63.9%; P=0.03), while there was no association between exacerbation and VDZ in UC patients (RR=0.69; 95% CI=0.34-1.41; P=0.31; I^2=71.6%; P=0.01).

Adverse events. The safety results of VDZ compared with those of the placebo in IBD are shown in Table II.

Serious adverse events. A total of seven studies (9,13-15,17,19,20) were included to compare serious adverse events of VDZ/placebo treatment for IBD. No significant differences in serious adverse events were observed between the VDZ and placebo treatment groups (RR=0.90; 95% CI=0.67-1.20; P=0.473; I^2=0%; P=0.89). There were no significant differences in the subgroup analysis.

Headache. A total of 7 studies (9,13-15,17,19,20) were included to compare the occurrence of headache caused by VDZ and placebo treatment for IBD; no significant differences were observed between the two treatments (RR=1.09; 95% CI=0.81-1.47; P=0.567; I^2=0%; P=0.56).

Nasopharyngitis. A total of 6 studies (9,13-15,17,20) were included to compare the correlation between nasopharyngitis and VDZ/placebo treatment. No significant differences were observed between VDZ and placebo (RR=1.43; 95% CI=0.98-2.08; P=0.062; I^2=31.0%; P=0.19). In the subgroup analysis, VDZ increased the risk of nasopharyngitis in patients with CD when compared with the placebo (RR=1.77; 95% CI=1.01-3.10; P=0.045; I^2=0%; P=0.42), while there was no association between nasopharyngitis and VDZ in UC patients (RR=1.28; 95% CI=0.76-2.16; P=0.350; I^2=49.2%; P=0.12). There was also no association between nasopharyngitis and VDZ/placebo treatment in either induction or maintenance therapy.

Upper respiratory tract infection. A total of 5 studies (13,14,17,19,20) were included to compare the association between VDZ/placebo and upper respiratory tract infection in IBD. No significant differences were observed between the VDZ and placebo treatment groups (RR=1.30; 95% CI=0.85-2.00; P=0.223; I^2=0%; P=0.64). No significant differences were observed in the subgroup analysis either.

Arthralgia. A total of 5 studies (9,13,14,17,20) were included to compare the association between VDZ/placebo treatment and arthralgia in IBD; no significant differences were observed between the VDZ and placebo treatment groups (RR=1.15; 95% CI=0.71-1.86; P=0.561; I^2=0%; P=0.84).

Abdominal pain. A total of 4 studies (9,15,17,20) were included to compare the association between VDZ/placebo treatment and abdominal pain in IBD. No significant differences were observed between the VDZ and placebo treatment

groups (RR=0.90; 95% CI=0.61-1.33; P=0.590; I^2=0%; P=0.73). No significant differences were observed following subgroup analysis either.

Vomiting. A total of 4 studies (9,13,17,20) were included to compare the association between VDZ/placebo and vomiting in IBD and no significant differences were identified (RR=0.87; 95% CI=0.42-1.83; P=0.720; I^2=31.2%; P=0.21).

Sensitivity analysis. Sensitivity analysis was conducted to evaluate the influence of a single study on the overall risk estimate by omitting one study at a time (Table SII). In the analysis of clinical response during the maintenance phase, the heterogeneity decreased from 68.7 to 41.1% when omitting the study by Vermeire *et al* (21). In the analysis of IBD exacerbation, the risk ratio showed little change, which means that the result was stable. In the analysis of UC exacerbation, the heterogeneity was markedly decreased from 71.6 to 10.8% when omitting the study by Feagan *et al* (10). In the analysis of CD exacerbation, the heterogeneity decreased from 63.9 to 46.6% when omitting the study by Watanabe *et al* (20) (induction therapy). In the analysis of IBD exacerbation (induction therapy), the results were stable. In the analysis of nasopharyngitis (maintenance), the study by Sandborn *et al* (15) contributed to most of the heterogeneity. In the analysis of mucosal healing (UC), the heterogeneity decreased from 68.4 to 20.3% when omitting the study by Feagan *et al* (12) (maintenance therapy).

Discussion

In the present meta-analysis, 12 high-quality published RCTs assessing IBD patients were identified by searching several English databases to review relevant articles. The results showed that VDZ was superior to placebo for the treatment of IBD during both induction and maintenance therapy, especially for patients with TNF antagonist failure. VDZ also showed significant efficacy in IBD patients with regard to corticosteroid-free remission compared with the placebo. In terms of mucosal healing, VDZ had significant effects on UC patients during both induction and maintenance therapy. It was also found that VDZ significantly reduced the risk of IBD exacerbation when compared with the placebo groups. In subgroup analysis, evidence in favor of the association was weaker among induction therapy when compared with maintenance therapy. Placebo increased the risk of exacerbation in patients treated with CD compared with those treated with VDZ. These results fully demonstrate the effectiveness of VDZ in the induction and maintenance of IBD treatment.

Adverse reactions are very common in the treatment of biological agents. The most common adverse reactions in the VDZ treatment group were headache, nasopharyngitis, upper respiratory tract infection, and arthralgia. VDZ increased the risk of nasopharyngitis in patients with CD when compared with the placebo, but these symptoms quickly improved with symptomatic treatment. Concerning the incidence of serious adverse events and the other assessed adverse reactions, there were no significant differences between VDZ and placebo. Therefore, VDZ was shown to be a relatively safe biological agent in the treatment of IBD.

IBD is a chronic inflammatory disease of the gastrointestinal tract, which consists of two major subtypes, CD and UC (22). This disease is characterized by alternating periods of clinical relapse and remission (23). The etiology and pathogenesis of IBD remain unclear. Increasing evidence shows that persistent intestinal infections, mucosal barrier defects, mucosal immune dysregulation, and genetic and environmental factors are involved in the process of the disease (24,25). Among these, the genetic dysfunction of the mucosal immune system of susceptible hosts to intestinal microbiota plays an important role in the pathogenesis of IBD (26). The primary clinical manifestations of IBD are abdominal pain, diarrhea, stool with mucous, bloody stool, weight loss, perianal abscess, and anal fistula (27). In the 20th century, IBD was predominantly prevalent in Western countries such as North America, Europe, and Oceania. However, IBD began to emerge as a global disease at the beginning of the 21st century, accelerating in incidence in newly industrialized countries such as Asia, South America, and Africa (28).

Anti-TNF-α is the first-line treatment for the management of moderate-to-severe IBD at present (29). TNF-α is a type of cytokine that can trigger and amplify the intestinal inflammatory process and prevent inflammatory response by binding to proteins or cells, playing an important role in the inflammatory cascade and decreasing inflammation by inducing apoptosis (30). Relieving clinical symptoms of IBD patients is helpful for better controlling the disease, reducing disease complications, and improving the quality of life of patients with IBD (31). However, a large proportion of patients do not respond to TNF therapy; termed primary non-responders (32). In the present meta-analysis, 30-50% of patients initially responded to treatment but subsequently lost their response which coincided with the onset of symptoms. For these patients, a higher drug dose, use of alternative drugs, or surgical intervention was needed (33). In the past few decades, a variety of biological agents have been developed for the treatment of IBD. Due to the different treatment periods and adverse reactions associated with these drugs, the optimal treatment for IBD remains contested. Circulating leukocyte migration to the gastrointestinal tract is hypothesized to play a role in the pathogenesis of IBD. Integrins are expressed on immune cells and may interact with cell adhesion molecules (CAM) to block leukocyte transportation to the gastrointestinal tract. Therefore, this specific therapy provides an alternative treatment for the systemic immunosuppression of IBD (34). α4β1 Integrin, which plays a role in memory and effector T lymphocytes homing to the brain and inflamed intestinal tissue (35), has also been shown to be potentially effective in the management of moderate-to-severe Crohn's disease. However, subsequent clinical studies found a significantly increased risk of progressive multifocal leukoencephalopathy (PML) following the use of α4β1 integrin in patients previously exposed to the John Cunningham virus (34,36). VDZ is a humanized IgG1 monoclonal antibody that targets the α4β7 heterodimer. This antibody selectively inhibits the adhesion of α4β7-expressing cells to mucosal addressin cell adhesion molecule-1 and fibronectin, thereby preventing leukocyte adhesion to the intestinal endothelium without affecting α4β1. VDZ does not inhibit vascular CAM-1 (VCAM-1) and therefore does not lead to PML (37). VDZ is also recommended by 2021 IBD clinical guidelines for patients with UC that have not been treated with biological therapy and for UC

or CD patients with failure of conventional or anti-TNF-α therapy (38).

The present study had some limitations. First, although all included studies were assessed as having a low or moderate risk of bias, there was a slight heterogeneity among individual outcome indicators, which may have biased the results to a certain extent. Secondly, due to the limitation of existing studies, further subgroup analysis was not performed. For example, all included RCTs were published abroad. Although the research data from Asia (Japan) were updated and included, there was no domestic data. Furthermore, there were no RCTs evaluating the mucosal healing of UC patients following VDZ treatment. With regard to different types of VDZ administration, there were only 2 RCTs evaluating the efficacy and safety of the subcutaneous injection of VDZ in IBD patients. Dose-response analysis of VDZ treatment was also limited since a few studies reported the comparison among different dosages. In addition, research on the efficacy and safety of VDZ in the treatment of pediatric IBD remains incomplete. All included studies were conducted in adults, even though the incidence of pediatric IBD in industrialized or Western countries is increasing annually (39,40). Thirdly, the limitation of possible publication bias should be taken into consideration; it is easier to report studies with positive results, even though no publication bias was observed by the Begger's test.

The present meta-analysis is an updated and expanded version of a previous meta-analysis (38). The first meta-analysis conducted by Wang *et al* (41) showed that VDZ was more effective than the placebo as induction and maintenance therapies for IBD. However, VDZ was found to be associated with a higher rate of serious adverse events (21.7 vs. 14.3%) in patients with CD. Furthermore, that study also included only 6 RCTs to evaluate the efficacy and safety of VDZ in IBD, whereas the present study included 12 RCTs with 4,865 patients, which may yield more convincing results. In addition, the previous study did not further evaluate corticosteroid-free remission, mucosal healing, and VDZ efficacy in IBD patients with TNF antagonist failure. Schreiber *et al* (42) reached similar conclusions to those of the present study, but none of the included studies met the randomized controlled double-blind criteria and instead included data from peer-reviewed full-text manuscripts and abstracts. Mosli *et al* (43) only included 4 RCTs, thus subgroup analysis was not performed to further evaluate the efficacy of VDZ in UC patients, and the adverse reactions of VDZ were not specifically evaluated.

This meta-analysis study also had several strengths. First, the heterogeneity between studies was low in most of the analyses. Secondly, the largest RCT studies so far were included, containing new data from Asian countries and other countries, which may provide a more comprehensive analysis of the efficacy of VDZ in the treatment of IBD patients. Thirdly, sensitivity analysis was performed to investigate the stability of the results. Finally, most of the present meta-analyses did not analyze the common adverse reactions of IBD patients treated with VDZ in specific subgroups. The data on common adverse effects were summarized, and subgroup analysis showed that placebo increased the risk of exacerbation in patients with CD when compared with VDZ.

Although the present study clarified the effective role of VDZ in the treatment of IBD patients, several questions still need to be addressed in future studies. Large domestic RCTs with long-term follow-ups are required to further compare different types of administration and different dosages of VDZ in both adult and pediatric patients.

In conclusion, this meta-analysis comprehensively evaluated the efficacy and safety of VDZ in IBD patients. It was found that VDZ is a safe and effective biological agent for IBD, particularly for patients with TNF antagonist failure.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

HT, LG, and CB designed the study. ST performed the literature search and screened the articles for relevancy. LG, LZ and HT abstracted the data. LZ and CB assessed the methodological quality of the studies. LG and HT performed the statistical analysis and drafted the manuscript. ST was responsible for revising the manuscript. HT, CB and LG confirm the authenticity of the data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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