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Original Article

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Comparing the Efficacy and Safety of Adalimumab and Vedolizumab in Treating Moderate to Severe Crohn's Disease and Ulcerative Colitis

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Abstract

Background: Numerous patients with inflammatory bowel disease (IBD) do not respond to conventional or biological therapy. Adalimumab (ADA) and vedolizumab (VDZ), according to certain research, may be a useful alternative treatment for these people. The purpose of this study was to assess the effectiveness and safety of using ADA and VDZ to treat moderate to severe IBD: Crohn's disease (CD) and ulcerative colitis (UC).

Methods: We searched PubMed, Medline, Web of Science, Scopus, the Cochrane Library, Embase, Google Scholar, CINAHL, Clinicaltrials.gov, and WHO trials registry (ICTRP). Randomized controlled trials (RCTs) comparing ADA or VDZ with placebo in participants with active CD or UC were included. The primary outcomes were the clinical response and remission at induction and maintenance phases and mucosal healing. The secondary outcome was the incidence of profound negative events. The research used Comprehensive Meta-Analysis version 3 (Biostat Inc., USA).

Results: Eighteen RCTs were incorporated, in which 11 studies described the usefulness and safeness of ADA or VDZ in CD patients, and seven studies investigated the efficacy and safety of ADA or VDZ in UC patients. The meta-analysis revealed that both ADA and VDZ treatments were superior to placebo for producing clinical remission and eliciting clinical response at induction and maintenance phases in individuals with moderately to severely active CD or UC. Interestingly, we found that ADA was superior to VDZ as first-line treatment for patients with CD, but not UC.

Conclusion: ADA and VDZ are effective and safe in CD and UC patients. However, RCTs of a larger number of patients are still required for better assessing the safety profile of ADA and VDZ.

Keywords: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Vedolizumab; Adalimumab; PRISMA

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Introduction

Inflammatory bowel disease (IBD) is a chronic intestinal inflammation that develops in a genetically vulnerable person as a result of host-microbial interactions. IBDs are autoimmune diseases that are characterized by inflammation of both the small and large intestines and by immune system attacks on digestive system components [1]. The two classes of IBD, Crohn's disease (CD) and ulcerative colitis (UC), both commonly start in early adulthood; however, they can start at any age, starting in early childhood [2]. Although CD and UC can develop at any age beginning in early infancy, they typically do so in early adulthood [3]. Both CD and UC have numerous extraintestinal symptoms outside of the gastrointestinal tract. While the illnesses can be identified in the majority of patients, in at least 10% of patients, the features are so similar that it is first impossible to distinguish between the two conditions [4]. Both conditions have a genetic propensity; they are both incurable and have a significant morbidity. And lastly, both raise the chance of colorectal cancer [5]. IBD has no known medicinal or surgical treatment options. Anti-inflammatory medications are used to treat the illness, which can help keep the disease in remission and dramatically lessen its symptoms.

For CD, clinical remission denotes a Crohn's Disease activity index (CDAI) score under 150, reflecting an absence of primary symptoms like abdominal pain and diarrhea, with normalized inflammatory markers. In UC, it is gauged by a Mayo score of 0 - 2 or a simple clinical colitis activity index (SCCAI) score of ≤ 2, signifying normalized bowel habits without

blood presence. Conversely, a clinical response in CD means a 100-point or more decrease in the CDAI score, indicating symptom improvement, while for UC, it is marked by a notable drop in the Mayo score and reduced rectal bleeding. Anti-inflammatory medications, including 5-aminosalicylic acid, and immunomodulators, like azathioprine, mercaptopurine, methotrexate, infliximab, adalimumab (ADA), certolizumab, vedolizumab (VDZ) and natalizumab, are used to treat the symptoms of IBD [6]. ADA is a completely human IgG1 monoclonal antibody against tumor necrosis factor-α (TNF-α) that has also been demonstrated to achieve the clinical remission and maintain clinical response in patients with active inflammatory CD and UC [7]. Despite the widespread use of TNF-α antibodies in clinical practice, a sizable minority of patients are unable to establish or sustain remission while receiving treatment [8]. Patients with IBD who had an insufficient response to, lost response to, or were intolerable to either conventional therapy or a TNF-α antibody may benefit from the use of VDZ, a humanized anti-α4b7 integrin monoclonal antibody [9]. VDZ's gut-selective mechanism is thought to be safer than the anti-TNF-α antibodies currently used to treat IBD [10]. For the purpose of choosing a course of treatment, comparative clinical data comparing various treatments are crucial. Due to the lack of data directly comparing VDZ with ADA at this time, an indirect comparison may be an alternate way to investigate the relative efficacy of both biologicals. This systematic review and meta-analysis will synthesize the available evidence on the efficacy and safety of ADA and VDZ for the treatment of moderate to severe IBD.

Materials and Methods

This systematic review and meta-analysis adhered to the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Additionally, our meta-analysis was conducted in alignment with the standards of A MeaSurement Tool to Assess systematic Reviews (AMSTAR) [11].

The meta-analysis research involves synthesizing and comparing data from multiple previously published studies rather than collecting primary, new data from human participants. Given that it is a secondary analysis of existing public data, and no further data are being collected directly from participants, there is no direct interaction or intervention with human subjects. As a result, Institutional Review Board (IRB) approval, which primarily ensures the protection of the rights and welfare of human research participants, is not usually required for network meta-analyses.

Search strategy

A comprehensive examination of databases such as PubMed, Medline, Web of Science, Scopus, the Cochrane Library, Embase, Google Scholar, CINAHL, Clinicaltrials.gov, and the WHO trials registry (ICTRP) was carried out from their inception to April 2023 to find suitable studies. The search encompassed these term combinations: "Adalimumab" OR "ADA" OR "Vedolizumab" OR "VZB" with "Inflammatory Bowel Disease" OR "ulcerative colitis" OR "Crohn's disease" and also included "randomized controlled trial". The bibliography sections of pertinent studies and overview papers were hand-reviewed to detect additional essential works. Two investigators separately executed this search procedure.

Inclusion and exclusion criteria

We screened relevant articles by title and abstract after removing duplicates. Studies were eligible for inclusion if they addressed the efficacy and safety of ADA or VDZ in patients with UC or CD. The full text of the remaining studies was then examined to confirm eligibility.

The inclusion criteria were as follows: 1) randomized controlled trials (RCTs) reporting the efficacy and safety of ADA or VDZ in patients with UC or CD; 2) participants of any age diagnosed with CD or UC, as defined by conventional clinical, radiological, endoscopic, or histological criteria; 3) interventions that involve ADA or VDZ versus placebo or a control therapy; 4) publications reporting sufficient data to establish statistical analysis; and 5) studies published as original articles. The exclusion criteria were as follows: 1) full text not electronically accessible; 2) publication in a language other than English; 3) observational studies, comments, letters, editorials, protocols, guidelines, and review papers; and 4) studies with insufficient outcome data.

Outcomes

The primary outcomes were the clinical response and remission at induction and maintenance phases as well as mucosal healing. Regarding CD, clinical remission is defined as a CDAI score of < 150 and clinical response is defined as a decrease in CDAI score from baseline by ≥ 70 points and by ≥ 100 points. Regarding UC, clinical remission is defined as Mayo score ≤ 2 with no individual sub-score exceeding 1 point and clinical response was defined as a decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding sub-score of at least 1 point or an absolute rectal bleeding sub-score of 0 or 1. Mucosal healing was defined as Mayo endoscopy sub-score of 0 or 1. Secondary outcome was the incidence of serious adverse events.

Data collection

Two independent authors retrieved information from the eligible articles following the application of inclusion and exclusion criteria. We collected the following information using standardized data sheet: 1) study ID (name of first author, year of publication), 2) location, 3) period, 4) design, 5) study phase, 6) name of trial, 7) population, 8) sample size, 9) intervention, 10) mean age, 11) male sex (%), 12) trial duration (weeks), and 13) outcomes. Characteristics of included studies are summarized in Table 1 [12-29].

Table 1. Characteristics of Included Studies

Study	Location	Period	Design	Study phase	Name of trial	Sample size	Mean age, years	Male sex, %	Trial duration, weeks	Outcomes
Chen et al, 2020 [12]	15 sites in China	August 17, 2015 to December 15, 2017	Multicenter, phase III randomized trial (The study comprised an 8-week double-blind (DB) period followed by an 18-week open-label (OL) period)	Induction	-	205	32.9	68%	26	-Clinical remission at week 4. -Clinical response at week 4. -Adverse events
Colombel et al, 2007 [13]	92 sites in Europe, the United States, and Canada	July 2003 to September 2005	Multicenter, phase 3, randomized, double-blind, placebo-controlled trial	Maintenance	Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM)	854	37.1	11.9%	56	-Clinical response at weeks 26 and 56. -Clinical remission at weeks 26 and 56. -Adverse events
Hanauer et al, 2006 [14]	55 centers in Europe, the United States, and Canada	July 24, 2002 to December 18, 2003	Multicenter, randomized, double-blind, placebo-controlled trial	Induction	Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease (CLASSIC-I)	299	38	46%	4	-Clinical remission at week 4. -Clinical response at week 4. -Adverse events
Rutgeerts et al, 2012 [15]	19 sites in Europe, the United States, and Canada	August 2006 to September 2008	Randomized, double-blind, placebo-controlled, maintenance/withdrawal study of adalimumab	Induction and Maintenance	Extend the safety and efficacy of adalimumab through endoscopic healing (EXTEND)	129	37.1	37.2%	52	-Clinical remission at weeks 12 and 52. -Clinical response at weeks 12 and 52. -Mucosal healing at weeks 12 and 52. -Adverse events.
Sandborn et al, 2007a [16]	52 sites in the United States, Canada, and Europe	November 2004 to December 2005	Randomized, double-blind, placebo-controlled trial	Induction	-	325	38	35%	4	-Clinical remission at week 4. -Clinical response at week 4. -Adverse events.
Sandborn et al, 2007b [17]	Multi-countries	August 28, 2002 to January 12, 2005	Multi-center, randomized, double-blind, placebo-controlled trial	Maintenance	Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease (CLASSIC-II)	55	36	40%	56	-Clinical remission at week 56. -Clinical response at week 56. -Adverse events.

Table 1. Characteristics of Included Studies - *(continued)*

Study	Location	Period	Design	Study phase	Name of trial	Sample size	Mean age, years	Male sex, %	Trial duration, weeks	Outcomes
Watanabe et al, 2012 [18]	Japan	January 2007 to December 2008	Multicenter, randomized, double-blind, placebo-controlled trial	Induction and maintenance	-	90	31.1	59.9%	56	-Clinical remission at week 4 and 56. -Clinical response at week 4 and 56. -Adverse events.
Sandborn et al, 2013 [19]	285 medical centers in 39 countries	December 2008 to May 2012	Phase 3, randomized, parallel-group, double-blind, placebo-controlled study	Induction and maintenance	GEMINI 2	1115	36.1	46.6%	52	-Clinical remission at week 6 and 52. -Clinical response at week 6 and 52. -Adverse events.
Sands et al, 2014 [20]	107 sites in North America, Europe, Asia, Africa, and Australia	November 2010 to April 2012	Phase 3, randomized, placebo-controlled, double-blind, multinational, multicenter trial	Induction	GEMINI 3	315	35.8	56.5%	10	-Clinical remission at week 6 and 10. -Clinical response at week 6 and 10. -Adverse events.
Vermeire et al, 2022 [21]	169 sites in 30 countries	December 2015 to May 2019	Randomized, double-blind, placebo-controlled, phase 3 trial	Maintenance	VISIBLE 2	409	37	53.2%	52	-Clinical remission at week 52. -Clinical response at week 52. -Adverse events.
Watanabe et al, 2020 [22]	77 centers in Japan	January 28, 2014 to November 16, 2017	A prospective, multicenter, randomized, double-blind, placebo-controlled phase 3 trial	Induction and maintenance	-	157	34.6	64%	60	-Clinical remission at weeks 10 and 60. -Clinical response at weeks 10 and 60. -Adverse events.
Croft et al, 2021 [23]	24 hospitals in 10 countries	January 1, 2014 to December 22, 2020	A double-blind, placebo-controlled phase 3 trial	Induction and maintenance	ENVISION I	93	14.1	45%	52	-Clinical remission at weeks 8 and 52. -Clinical response at week 52. -Mucosal healing at week 52. -Adverse events.
Reinisch et al, 2011 [24]	94 centers in North America and Europe	August 2007 to February 2010	Phase III, multicenter, randomized, double-blind, placebo-controlled trial	Induction	-	390	37.5	62.3%	8	-Clinical remission at week 8. -Clinical response at week 8. -Mucosal healing at week 8. -Adverse events.

Table 1. Characteristics of Included Studies - *(continued)*

Study	Location	Period	Design	Study phase	Name of trial	Sample size	Mean age, years	Male sex, %	Trial duration, weeks	Outcomes
Sandborn et al, 2012 [25]	103 centers in North America, Europe, Australia, New Zealand, and Israel	November 2006 and March 2010	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial	Induction and maintenance	-	494	40.4	59.5%	52	-Clinical remission at weeks 8 and 52. -Clinical response at weeks 8 and 52. -Mucosal healing at weeks 8 and 52. -Adverse events.
Suzuki et al, 2014 [26]	Japan	February 2009 to May 2011	Phase II/III, randomized, double-blind, placebo-controlled study	Induction and maintenance	-	273	42.7	62.7%	52	-Clinical remission at weeks 8 and 52. -Clinical response at weeks 8 and 52. -Mucosal healing at weeks 8 and 52. -Adverse events.
Feagan et al, 2013 [27]	211 medical centers in 34 countries from 2008 to 2012	2008 to 2012	Phase 3, randomized, double-blind, placebo-controlled study	Induction and maintenance	-	895	40.3	58.7%	52	-Clinical remission at weeks 6 and 52. -Clinical response at week 6. -Mucosal healing at weeks 6 and 52. -Adverse events.
Motoya et al, 2019 [28]	86 sites in Japan	February 2014 to November 2015	Phase 3, randomized, double-blind, placebo-controlled study	Induction and maintenance	-	292	42.9	61.3%	60	-Clinical remission at weeks 10 and 60. -Clinical response at weeks 10 and 60. -Mucosal healing at weeks 10 and 60.
Sandborn et al, 2020 [29]	141 sites in 29 countries	December 18, 2015 to August 21, 2018	Phase 3, randomized, placebo-controlled, double-blind, double-dummy trial	Maintenance	VISIBLE 1	216	39.7	59.8%	52	-Clinical response at week 52. -Clinical remission at week 52. -Mucosal healing at week 52. -Adverse events.

Table 2. Methodological Quality of Included Studies

Study	The Jadad scores					Total score
	1	2	3	4	5	
Chen et al, 2020 [12]	1	0	1	1	1	4
Colombel et al, 2007 [13]	1	0	1	1	1	4
Hanauer et al, 2006 [14]	1	0	1	1	1	4
Rutgeerts et al, 2012 [15]	1	0	1	1	0	3
Sandborn et al, 2007a [16]	1	0	1	1	1	4
Sandborn et al, 2007b [17]	1	0	1	1	1	4
Watanabe et al, 2012 [18]	1	0	1	1	1	4
Sandborn et al, 2013 [19]	1	0	1	1	0	3
Sands et al, 2014 [20]	1	0	1	1	1	4
Vermeire et al, 2022 [21]	1	0	1	1	0	3
Watanabe et al, 2020 [22]	1	0	1	1	0	3
Croft et al, 2021 [23]	1	0	1	1	1	4
Reinisch et al, 2011 [24]	1	0	1	1	0	3
Sandborn et al, 2012 [25]	1	0	1	1	0	3
Suzuki et al, 2014 [26]	1	0	1	1	1	4
Feagan et al, 2013 [27]	1	0	1	1	0	3
Motoya et al, 2019 [28]	1	0	1	1	0	3
Sandborn et al, 2020 [29]	1	0	1	1	1	4

1: Was the study carried out using randomization? 2: Did the study provide a clear and suitable description of the randomization process? 3: Was the study characterized as double-blind? 4: Was the blinding procedure described meticulously and aptly? 5: Were details regarding withdrawals and dropouts included?

Quality assessment of the studies

The methodological integrity of the selected trials was evaluated based on the Jadad scale, focusing on aspects such as randomization, blinding, and participant withdrawals in the studies [30]. The grading scale spans from 0 to 5 points. Reports of lower quality score 2 or below, while those of higher quality attain a score of 3 or more [31]. Methodological quality of included studies is shown in Table 2 [12-29].

Data analysis

The statistical evaluations were carried out using Comprehensive Meta-Analysis version 3 by Biostat Inc., USA. Based on the outcomes of the reviewed studies, ADA and VDZ were analyzed independently compared to placebos. Safety-related data were scrutinized from the safety population. Binary results, like clinical remission and clinical response, were gauged using the odds ratio (OR) alongside its 95% confidence intervals (CIs). Study variability was examined via the Cochrane Chi-squared test (Chi^2) and the I^2 inconsistency statistic. A P-value below 0.05 or an I^2 of 50% and above was a sign of noteworthy variability. When studies showcased pronounced consistency, a fixed-effects model was utilized. However, in cases of evident variability, a random-effects model was adopted [32]. Given the limited number of studies available for each comparison, funnel plots were not used to investigate publication bias. The analysis of results adhered to the intention-to-treat approach.

Results

Identification of studies

The search of the database yielded 607 studies for review. From these, 401 abstracts seemed potentially suitable, leading to a full-text examination. Only 18 of these articles satisfied the criteria, and they were incorporated into this systematic review and meta-analysis. Figure 1 displays the PRISMA flow diagram.

Characteristics of included studies

The included articles were published between 2006 and 2023. Among the included studies, 11 and six studies investigated CD and UC, respectively. Among CD studies, seven and four studies reported the efficacy and safety of ADA and VZB, respectively. For the treatment of UC, only four and three studies described the efficacy of ADA and VZB, respectively. Among included studies, 5/18 studies reported induction phase, 3/18

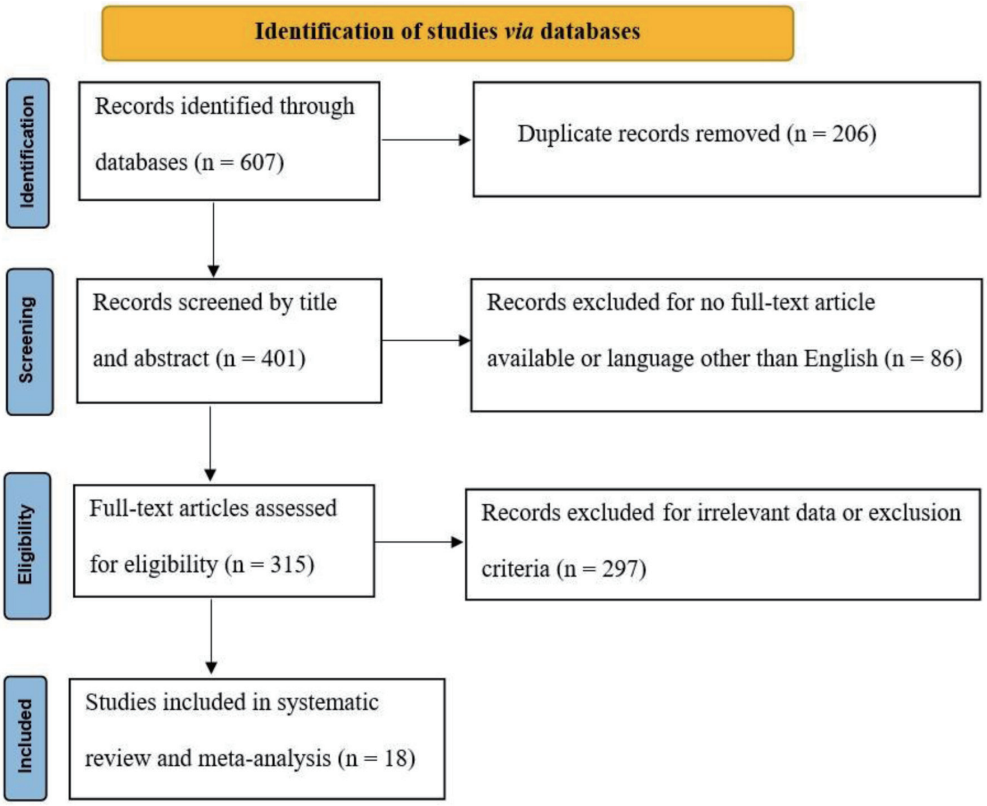

Figure 1. PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

studies described maintenance phase and 10 studies investigated both induction and maintenance phases. The sample size of the included articles varied from 55 to 115. The mean age of participants was ranged between 14.1 and 42.9 years. The majority of participants (> 50%) were male in 11 studies. Characteristics of included studies are summarized in Table 1.

Quality assessment

All RCTs were judged as being of high quality according to the Jadad scale (with 3 scores for eight studies and 4 scores for 10 studies). The reason for not receiving a full quality score was that the method of randomization and withdrawals/dropouts were not described.

Data analysis

Primary outcomes

1) CD

a) Induction phase

Clinical remission: The heterogeneity was low for both ADA ($Chi^2 = 9.579$, $P = 0.214$, $I^2 = 26.92\%$) and VDZ ($Chi^2 = 0.443$, $P = 0.801$, $I^2 = 0\%$) groups, so a fixed effect model was used. The forest plot analysis showed there was a significantly beneficial effect of ADA and VDZ for induction of remission with a superiority of ADA over VDZ (OR = 3.037, P = 0.000 and OR= 2.444, P = 0.000, respectively) (Fig. 2).

Clinical response: The heterogeneity was low for both ADA ($Chi^2 = 11.986$, $P = 0.101$, $I^2 = 41.59\%$) and VDZ ($Chi^2 = 2.545$, $P = 0.280$, $I^2 = 21.41\%$) groups, so a fixed effect model was used. The forest plot analysis showed there was a significantly beneficial effect of ADA and VDZ for induction of response with a slightly superiority of ADA over VDZ (OR = 2.601, P = 0.000 and OR = 2.254, P = 0.000, respectively) (Fig. 3).

b) Maintenance

Clinical remission: The heterogeneity was low for both ADA ($Chi^2 = 0.428$, $P = 0.995$, $I^2 = 0\%$) and VDZ ($Chi^2 = 1.016$, $P = 0.602$, $I^2 = 0\%$) groups, so a fixed effect model was used. Our meta-analysis on ADA and VDZ maintenance therapy showed that both ADA (OR = 4.808, P = 0.000) and VDZ (OR = 2.014, P = 0.000) were superior to the placebo in remission rates with a superiority of ADA over VDZ (Fig. 4).

Clinical response: The heterogeneity was low for both ADA ($Chi^2 = 3.360$, $P = 0.645$, $I^2 = 0\%$) and VDZ ($Chi^2 = 4.518$, $P = 0.104$, $I^2 = 55.37\%$) groups, so a fixed effect model

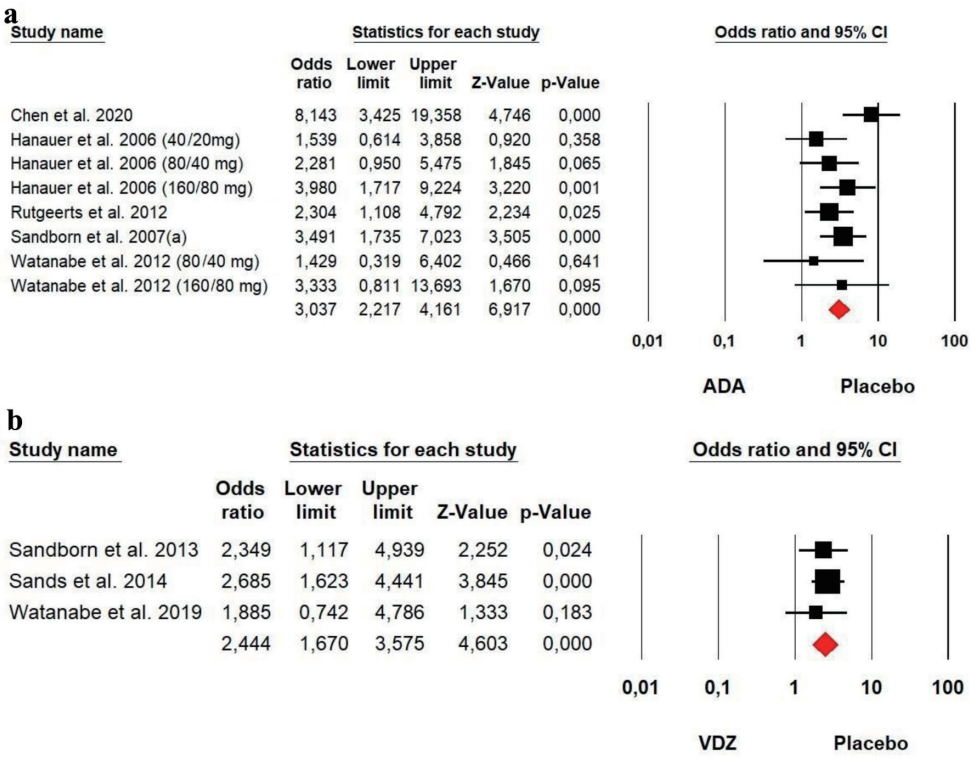

Figure 2. Forest plot for achieving clinical remission at induction phase in (a) ADA and (b) VDZ versus control group among CD patients. ADA: adalimumab; CD: Crohn's disease; VDZ: vedolizumab.

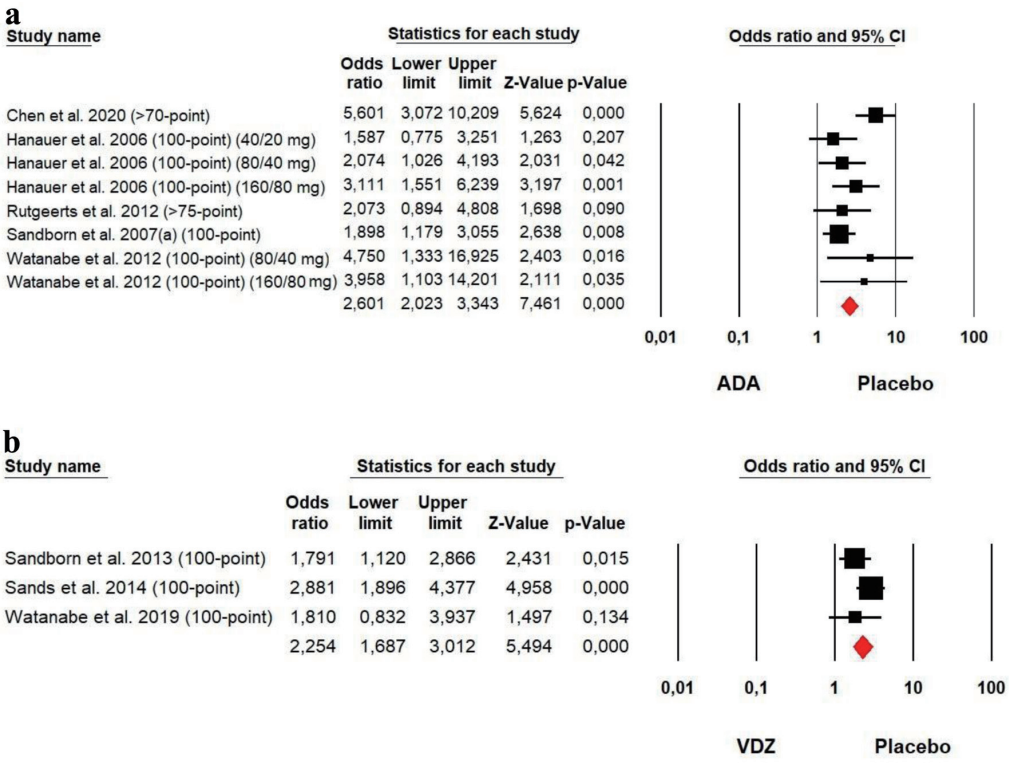

Figure 3. Forest plot for achieving clinical response at induction phase in (a) ADA and (b) VDZ versus control group among CD patients. ADA: adalimumab; CD: Crohn's disease; VDZ: vedolizumab.

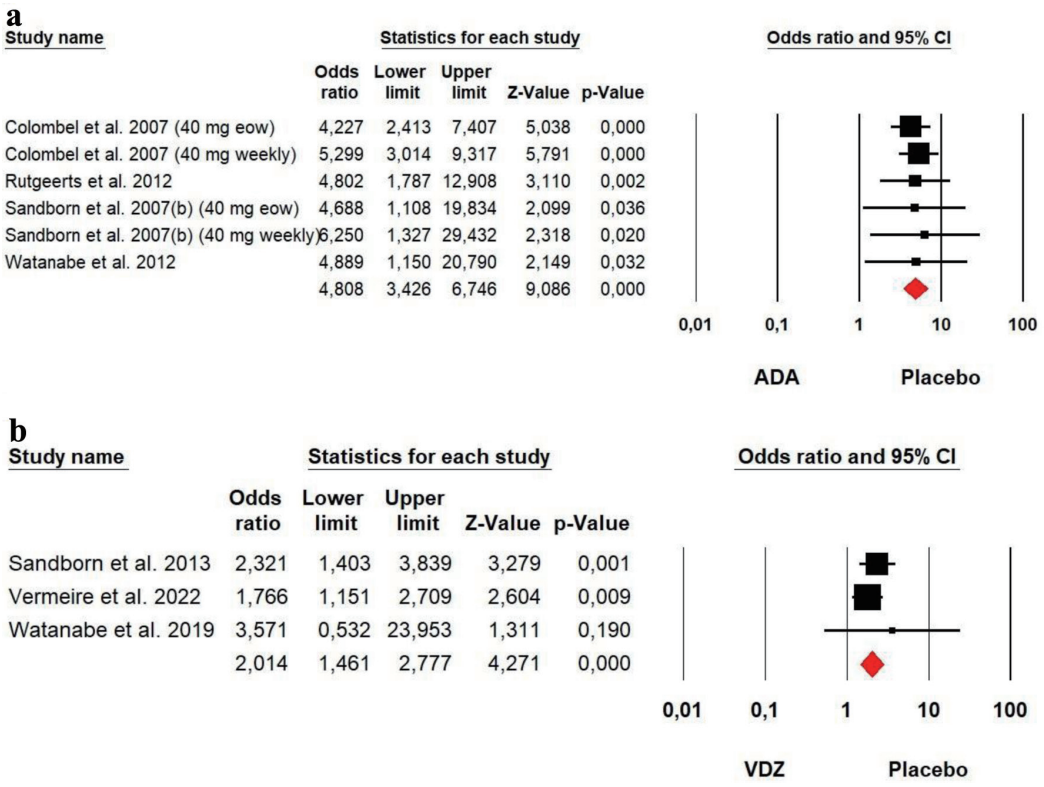

Figure 4. Forest plot for achieving clinical remission at maintenance phase in (a) ADA and (b) VDZ versus control group among CD patients. ADA: adalimumab; CD: Crohn's disease; VDZ: vedolizumab.

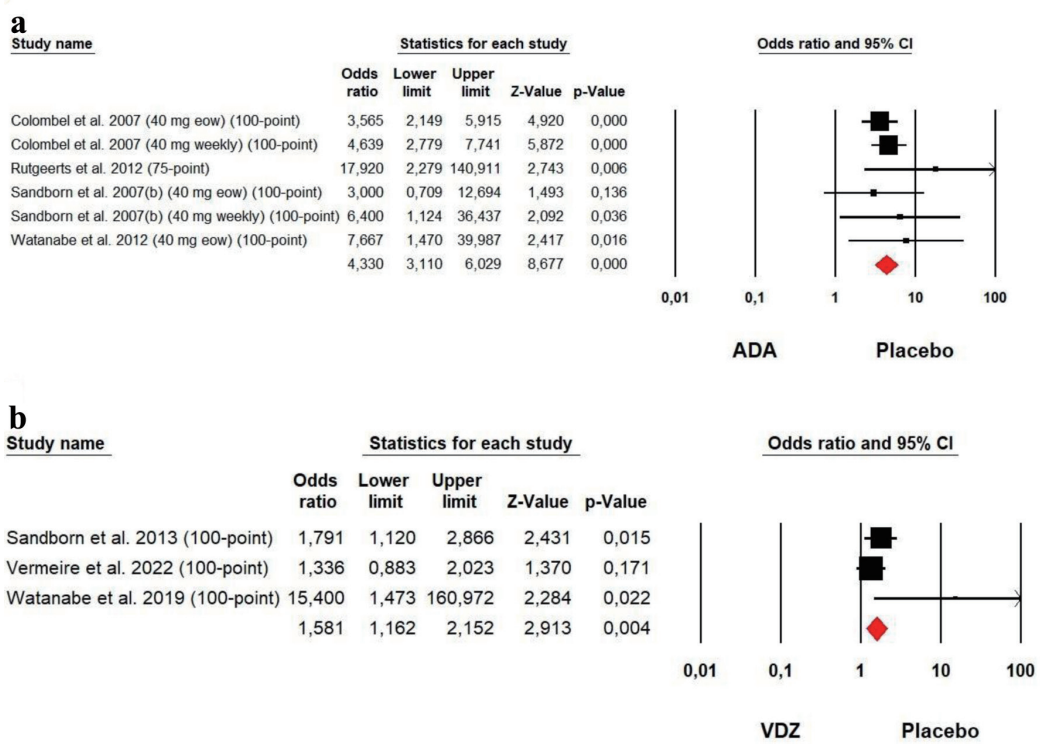

Figure 5. Forest plot for achieving clinical response at maintenance phase in (a) ADA and (b) VDZ versus control group among CD patients. ADA: adalimumab; CD: Crohn's disease; VDZ: vedolizumab.

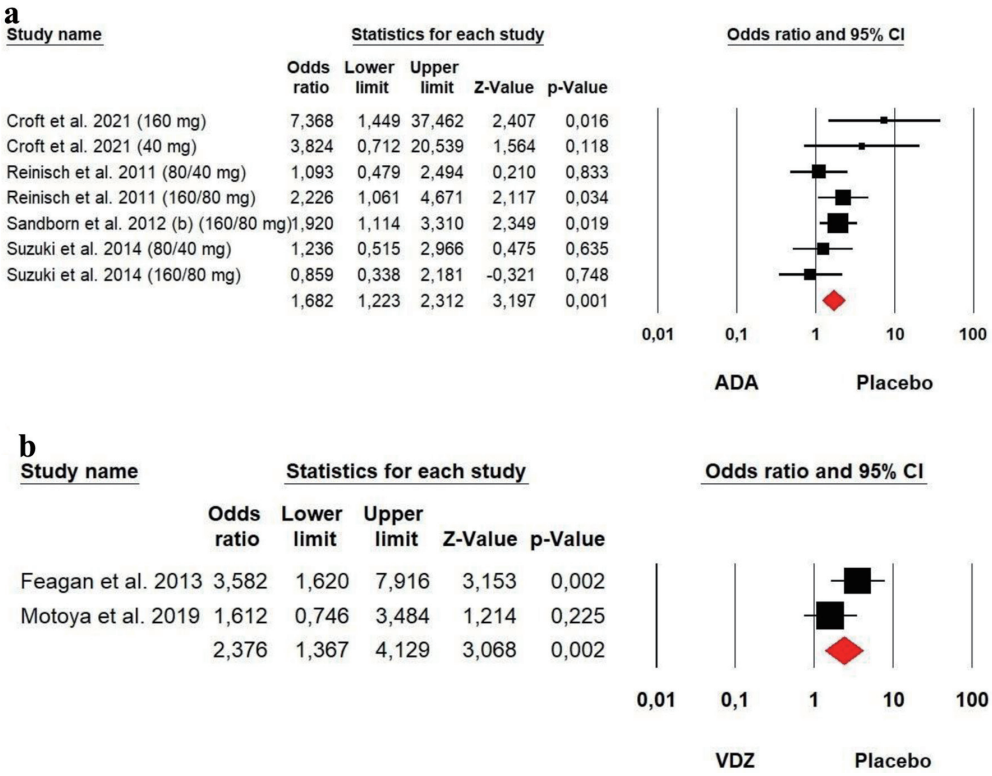

Figure 6. Forest plot for achieving clinical remission at induction phase in (a) ADA and (b) VDZ versus control group among UC patients. ADA: adalimumab; UC: ulcerative colitis; VDZ: vedolizumab.

was used. Our meta-analysis on ADA and VDZ maintenance therapy showed that both ADA (OR = 4.330, P = 0.000) and VDZ (OR = 1.581, P = 0.004) were superior to the placebo in response rates with a superiority of ADA over VDZ (Fig. 5).

2) UC

a) Induction phase

Clinical remission: The heterogeneity was low for both ADA (Chi^2 = 8.389, P = 0.211, I^2 = 28.48%) and VDZ (Chi^2 = 2.002, P = 0.157, I^2 = 50.03%) groups, so a fixed effect model was used. The forest plot analysis showed there was a significantly beneficial effect of ADA and VDZ for induction of remission with a superiority of VDZ over ADA (OR = 1.682, P = 0.001 and OR = 2.376, P = 0.002, respectively) (Fig. 6).

Clinical response: The heterogeneity was low for both ADA (Chi^2 = 2.170, P = 0.705, I^2 = 0%) and VDZ (Chi^2 = 3.308, P = 0.069, I^2 = 69.77%) groups, so a fixed effect model was used. The forest plot analysis showed there was a significantly beneficial effect of ADA and VDZ for induction of response with a slightly superiority of VDZ over ADA (OR = 1.616, P = 0.000 and OR = 1.998, P = 0.000, respectively) (Fig. 7).

Mucosal healing: The heterogeneity was high for ADA (Chi^2 = 33.214, P = 0.000, I^2 = 87.95%), so a random effect model was used. However, a low heterogeneity was detected for VDZ (Chi^2 = 1.564, P = 0.211, I^2 = 36.06%) groups, so a fixed effect model was used. The forest plot analysis showed there was a significantly beneficial effect of VDZ for induction of mucosal (OR = 1.744, P = 0.002). However, no significant difference was detected between ADA and placebo (OR = 1.039, P = 0.736) (Fig. 8).

b) Maintenance phase

Clinical remission: The heterogeneity was low for both ADA (Chi^2 = 1.424, P = 0.700, I^2 = 0%) and VDZ (Chi^2 = 1.025, P = 0.906, I^2 = 0%) groups, so a fixed effect model was used. Our meta-analysis on ADA and VDZ maintenance therapy showed that both ADA (OR = 2.675, P = 0.000) and VDZ (OR = 4.057, P = 0.000) were superior to the placebo in remission rates with a superiority of VDZ over ADA (Fig. 9).

Clinical response: The heterogeneity was low for both ADA (Chi^2 = 3.266, P = 0.352, I^2 = 8.13%) and VDZ (Chi^2 = 1.741, P = 0.783, I^2 = 0%) groups, so a fixed effect model was used. Our meta-analysis on ADA and VDZ maintenance therapy showed that both ADA (OR = 2.191, P = 0.000) and VDZ (OR = 4.142, P = 0.000) were superior to the placebo in response rates with a superiority of VDZ over ADA (Fig. 10).

Mucosal healing: The heterogeneity was low for both ADA (Chi^2 = 1.801, P = 0.615, I^2 = 0%) and VDZ (Chi^2 = 0.291, P = 0.865, I^2 = 0%) groups, so a fixed effect model was used. Our meta-analysis on ADA and VDZ maintenance therapy showed

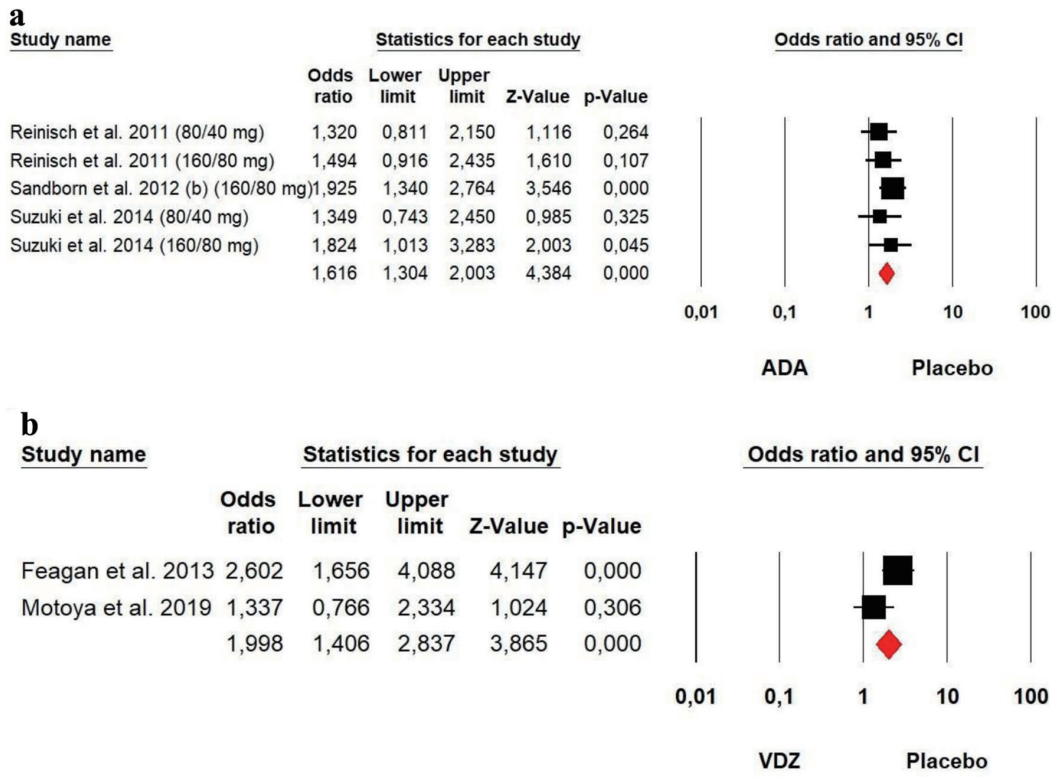

Figure 7. Forest plot for achieving clinical response at induction phase in (a) ADA and (b) VDZ versus control group among UC patients. ADA: adalimumab; UC: ulcerative colitis; VDZ: vedolizumab.

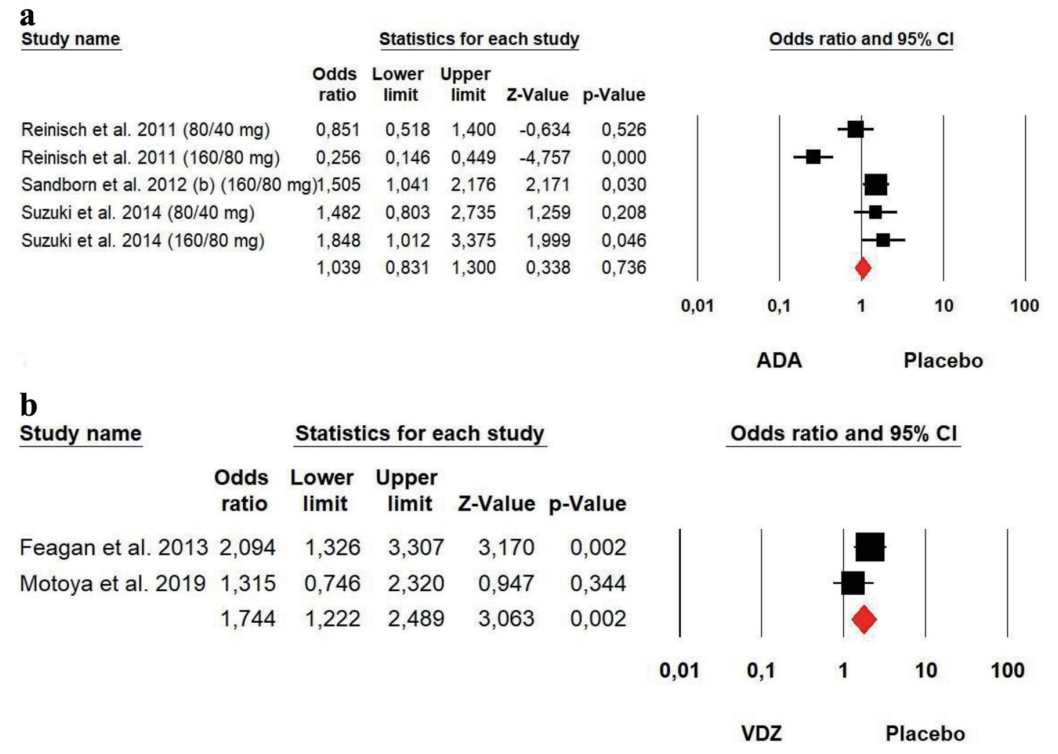

Figure 8. Forest plot for achieving mucosal healing at induction phase in (a) ADA and (b) VDZ versus control group among UC patients. ADA: adalimumab; UC: ulcerative colitis; VDZ: vedolizumab.

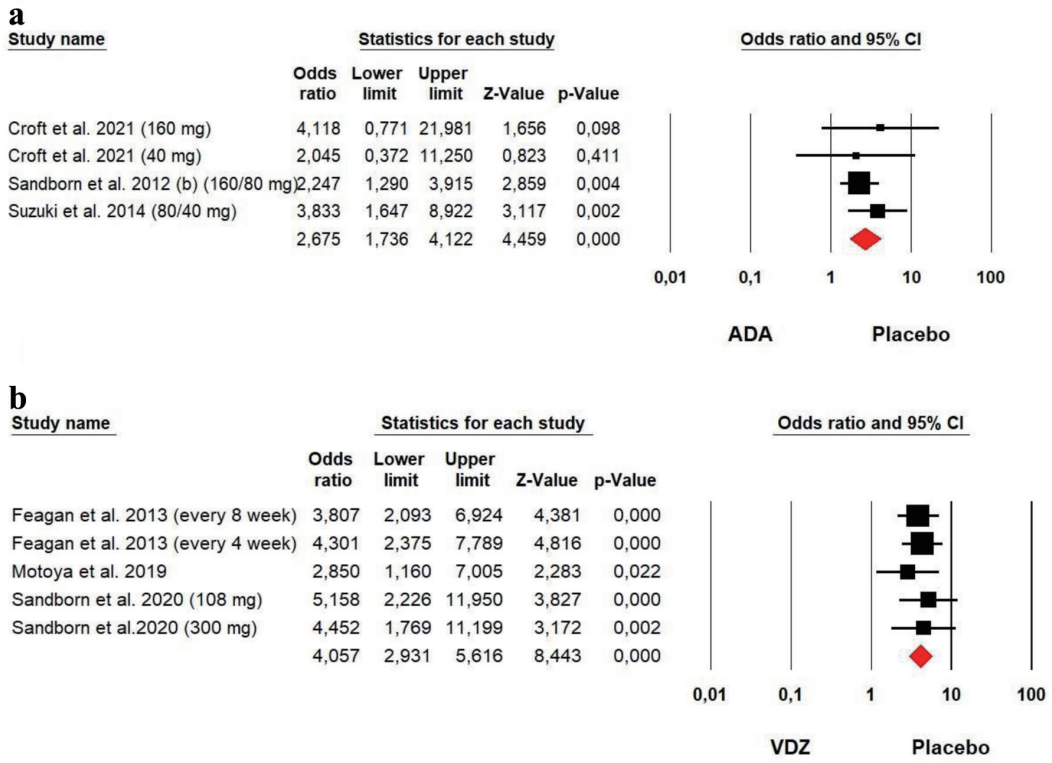

Figure 9. Forest plot for achieving clinical remission at maintenance phase in (a) ADA and (b) VDZ versus control group among UC patients. ADA: adalimumab; UC: ulcerative colitis; VDZ: vedolizumab.

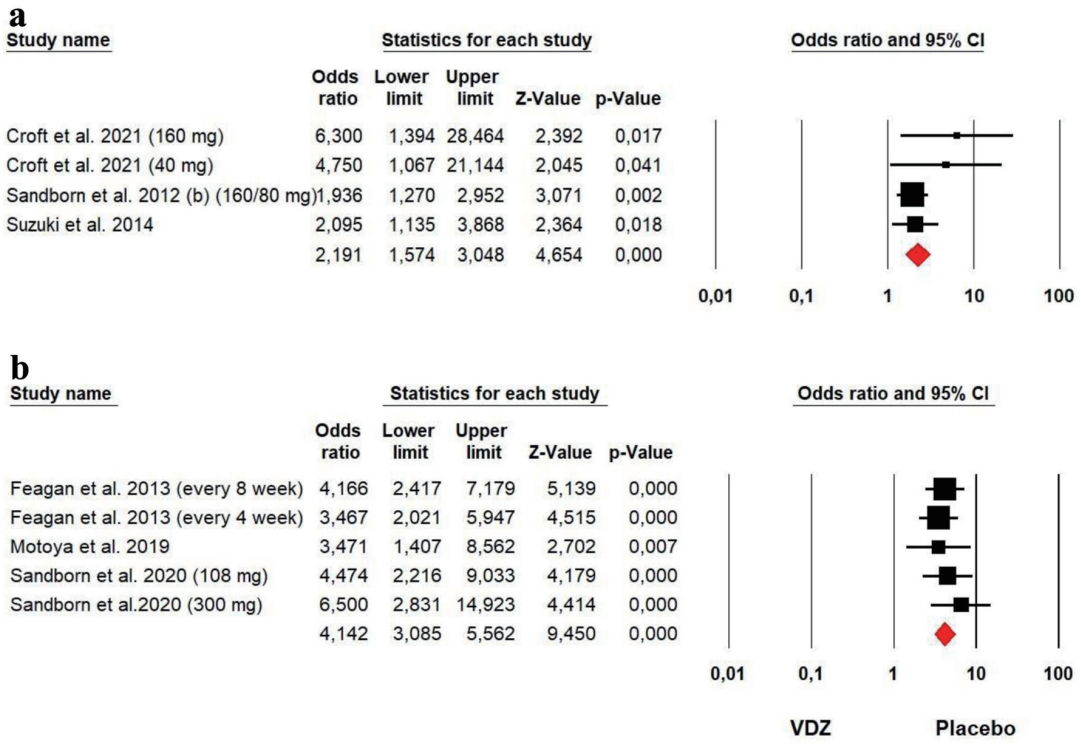

Figure 10. Forest plot for achieving clinical response at maintenance phase in (a) ADA and (b) VDZ versus control group among UC patients. ADA: adalimumab; UC: ulcerative colitis; VDZ: vedolizumab.

that both ADA (OR = 2.069, P = 0.000) and VDZ (OR = 4.216, P = 0.000) were superior to the placebo in mucosal healing rates with a superiority of VDZ over ADA (Fig. 11).

Secondary outcomes: serious adverse events

1) CD

The heterogeneity was low for both ADA (Chi^2 = 5.060, P = 0.887, I^2 = 0%) and VDZ (Chi^2 = 9.395, P = 0.052, I^2 = 57.42%) groups, so a fixed effect model was used. Our meta-analysis showed that placebo presented more serious adverse events than ADA among CD patients (OR = 0.514, P = 0.000). However, no significant difference was detected between VDZ and placebo (OR = 1.284, P = 0.076) (Fig. 12).

2) UC

The heterogeneity was low for both ADA (Chi^2 = 4.757, P = 0.190, I^2 = 36.93%) and VDZ (Chi^2 = 0.703, P = 0.951, I^2 = 0%) groups, so a fixed effect model was used. Our meta-analysis showed that no significant difference was detected between ADA and VDZ versus placebo in terms of serious adverse events among UC patients (OR = 0.890, P = 0.512 and OR = 0.979, P = 0.904, respectively) (Fig. 13).

Discussion

In this meta-analysis, we have shown that ADA treatment was superior to placebo for producing clinical remission and eliciting clinical response at induction phase in individuals with moderately to severely active CD. For example, participants in the biologic-naive CLASSIC I trial had a remission rate of 36% in the ADA group at induction phase compared to 12% in the placebo group [14]. Remission rates that were comparable were seen in the other investigations. The 160 mg/80 mg dose group is frequently utilized, and it was shown that it may be most beneficial in bringing about clinical remission and a clinical response [14, 18]. ADA was also investigated in four studies to maintain remission and clinical response in CD patients. These studies evaluated the long-term effectiveness of ADA [14, 15, 17, 18]. Both ADA groups (40 mg weekly and 40 mg every other week) exhibited significantly greater efficacy in the maintenance of clinical remission and response than the placebo group. The overall incidence of serious adverse events in ADA group during double-blind period was lower than that in the placebo group, and the overall safety profile observed was similar to those observed among other studies [33]. There are five further systematic review and meta-analysis studies that evaluated the effectiveness and security of ADA in CD patients. All of these reviews reached the same conclusion as revealed by us and showed that ADA was effective and significantly improved the life quality of CD participants [34-38].

VDZ is currently used in an emerging group of patients with IBD due to high efficacy and good safety profile. In this systematic review and meta-analysis of four RCTs of VDZ treatment in adults with CD, we made several key observations. First, we confirmed that VDZ treatment was superior to placebo for producing clinical remission and eliciting clinical response at induction and maintenance phase in individuals with moderately to severely active CD [19-22]. Second, the overall incidence of serious adverse events in VDZ group was similar to that in the placebo group.

On the other side, there are four further systematic review and meta-analysis studies that assessed the efficacy of VDZ in CD patients. VDZ was found to have a favorable efficacy and safety profile in bio-naive patients with CD, as reported by Attauabi et al [39]. Chandar et al revealed that natalizumab and VDZ were effective in inducing remission and response in patients with CD, with similar efficacy in anti-TNF-naive and anti-TNF-exposed patients [40], while Peyrin-Biroulet demonstrated that infliximab had better efficacy in the induction phase and comparable efficacy during the maintenance phase and overall safety profile compared to VDZ [41]. In the same context, Parrot et al showed that ustekinumab and VDZ were similarly effective in induction, but as maintenance treatment, ustekinumab appears to be more effective than VDZ [42].

To the best of our knowledge, there are presently no effectiveness or safety profile comparisons between ADA and VDZ in CD patients, in the literature. The positioning of ADA and VDZ in the therapeutic paradigm of CD patients should be based on indirect comparisons for clinical efficacy (clinical response, induction and maintenance of remission), as well as for safety profile, due to the lack of direct clinical comparisons. In this meta-analysis, we showed that ADA was superior to VDZ for producing both clinical remission and response at induction phase. Similarly, ADA was proven to be more effective than VDZ in the maintenance of clinical remission and response. On the other hand, we revealed that VDZ presented more serious adverse events than ADA. All these findings reveal that ADA seems to be more effective than VDZ to treat CD patients. However, there are no previous studies that confirm this conclusion.

Regarding UC, meta-analysis studies about the effectiveness of ADA and VDZ are limited [43-45]. Our meta-analysis proved that both ADA and VDZ treatments were superior to placebo for producing clinical remission and eliciting clinical response at induction and maintenance phases in individuals with moderately to severely active UC [23, 25-27]. However, we revealed that VDZ was superior to ADA with respect to achievement of clinical remission and response as well as mucosal healing contrary to CD patients. However, no significant difference was detected between ADA and VDZ versus placebo in terms of serious adverse events among UC patients. Similar results have been mentioned by Sands et al. Indeed, a comparison between VDZ and ADA for moderate to severe UC showed that VDZ presented higher efficacy than ADA in terms of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission [46]. However, an indirect comparison between VDZ and ADA for biologic-naive patients with UC demonstrated that VDZ has comparable efficacy to ADA [45]. Additional well-designed RCTs are needed to confirm these results.

In our study, ADA demonstrated a superior efficacy in managing CD, particularly in induction of remission and mucosal healing. This suggests that patients with CD might derive great-

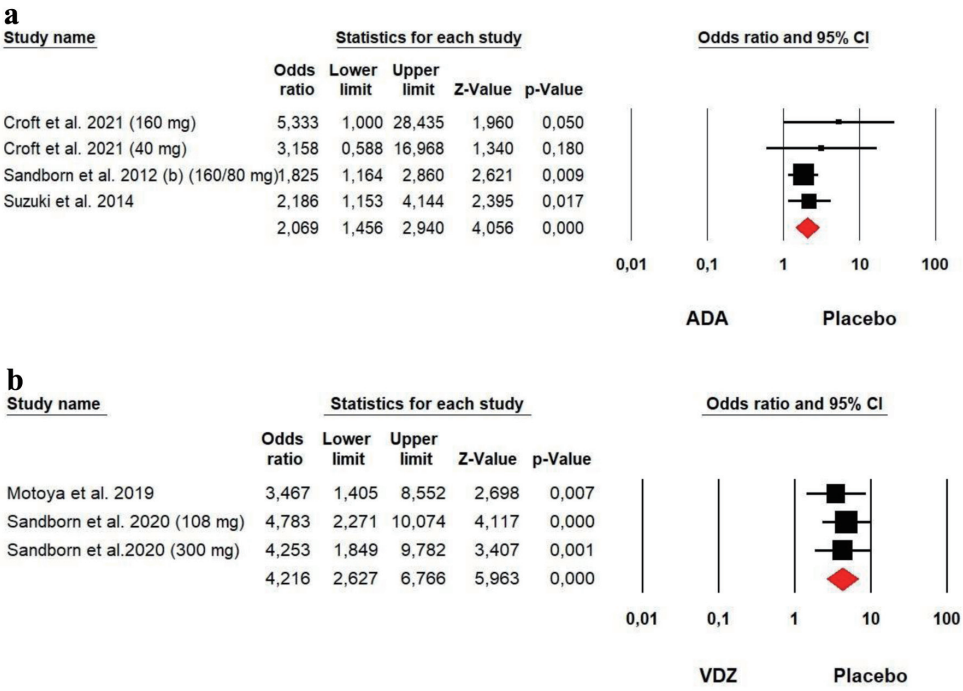

Figure 11. Forest plot for achieving mucosal healing at maintenance phase in (a) ADA and (b) VDZ versus control group among UC patients. ADA: adalimumab; UC: ulcerative colitis; VDZ: vedolizumab.

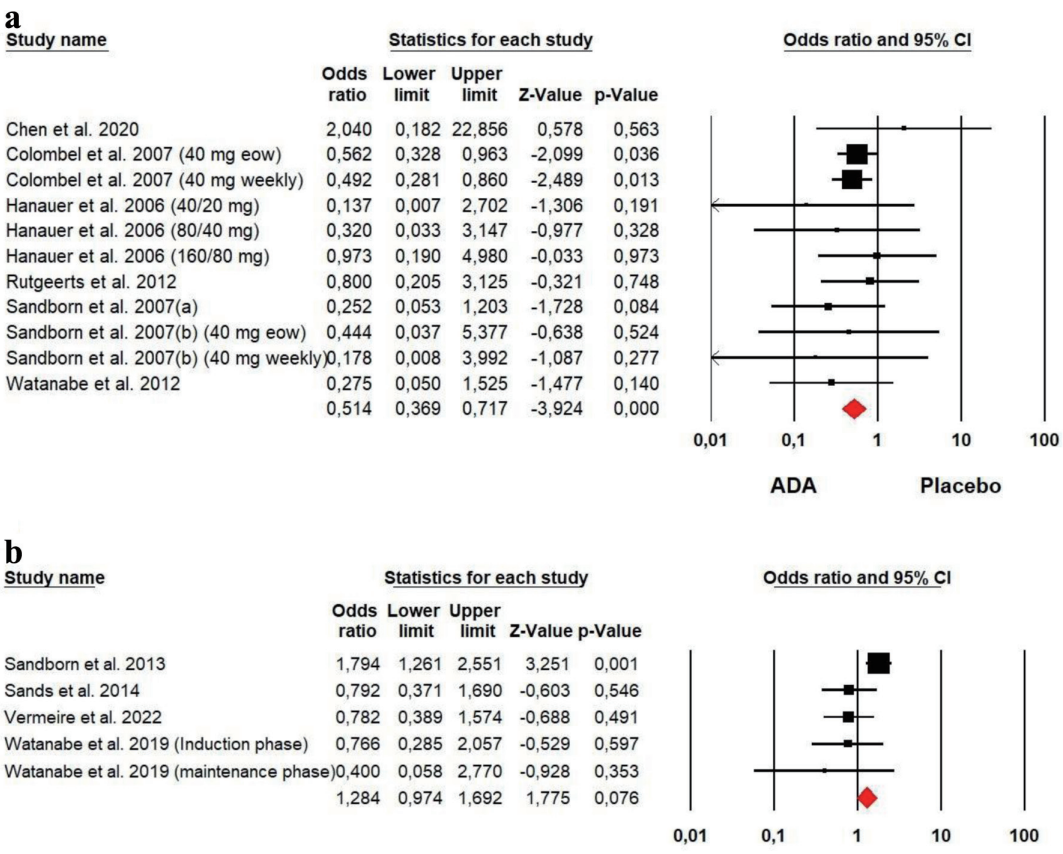

Figure 12. Forest plot for serious adverse events in (a) ADA and (b) VDZ versus control group among CD patients. ADA: adalimumab; CD: Crohn's disease; VDZ: vedolizumab.

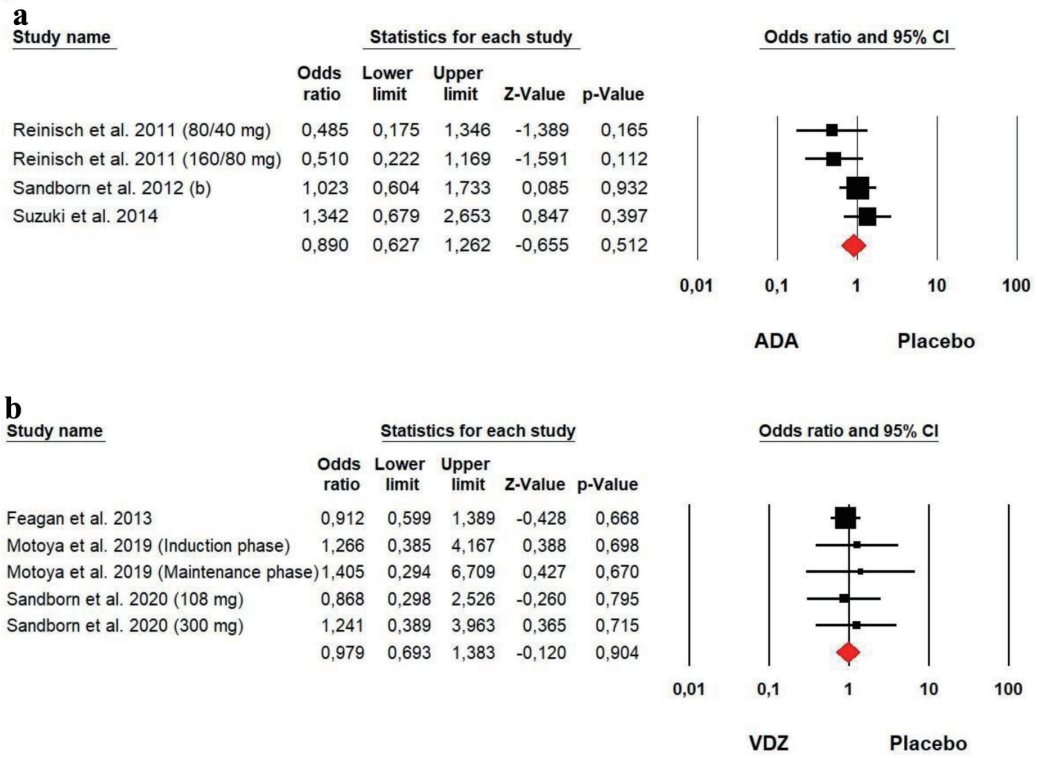

Figure 13. Forest plot for serious adverse events in (a) ADA and (b) VDZ versus control group among UC patients. ADA: adalimumab; UC: ulcerative colitis; VDZ: vedolizumab.

er benefits from ADA, especially in cases resistant to conventional therapies. On the other hand, VDZ exhibited pronounced effectiveness in UC patients, showing better maintenance of remission and a more favorable safety profile. This implies that for UC patients, especially those with moderate to severe forms or those who have previously failed other biological treatments, VDZ might be a more suitable therapeutic option. Clinicians and researchers should consider these differential impacts when choosing the most appropriate treatment for CD and UC.

This research has its constraints. Since the meta-analysis relied on data from published works, there is a chance that publication bias might have led to underrepresentation of non-significant findings. Moreover, undertaking a meta-analysis on ADA and VDZ poses challenges because of dose differences. The limited quantity of studies further exacerbated the problem. These constraints impeded the direct comparison of varied research findings, thereby complicating the aggregated analysis and contributing to discrepancies in the meta-analysis. As such, the inherent variability typical of meta-analysis studies can influence the interpretation of outcomes [47]. As a result, careful consideration must be given to the present work's findings.

Conclusion

Although there is no known treatment for IBD, there is now enough proof that a number of pharmacological substances can reduce intestinal inflammation. Our meta-analysis suggests that both ADA and VDZ are superior to placebo for induction and maintenance of clinical remission and response in patients with moderately to severely active CD and UC. Also, we noticed that serious adverse events were lower in ADA and VDZ participants compared with placebo. The low number of events raises questions about the impact of ADA and VDZ on serious adverse events. Therefore, no definitive conclusions about the safety of ADA and VDZ can be made. According to our findings, ADA seems to be superior to VDZ in CD patients, while VDZ has better efficacy compared to ADA in UC patients. Further studies, prospective, longer duration, with more participants are required to assess the long-term efficacy and safety of ADA in CD participants, and future RCTs should more clearly assess the serious adverse events.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

Manuscript writing and overview of published works: Kirthi Lilley, Mona Hassa, Nooraldin Merza, Omar Saab, Dushyant Singh Dahiya, and Safa Boujemaa. Database extraction, results, and statistics: Nooraldin Merza, Zohaib Ahmed, Yusuf Nawras, Dushyant Singh Dahiya, Kirthi Lilley, and Meghana Ranabothu. Manuscript preparation and editing: Mona Hassa, Nooraldin Merza, Zohaib Ahmed, Yusuf Nawras, Omar Saab, Meghana Ranabothu, and Abdallah Kobeissy. Final drafting, review, and approval: Nooraldin Merza, Kirthi Lilley, Abdallah Kobeissy, Safa Boujemaa, and Mona Hassan.

Data Availability

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

Abbreviations

ADA: adalimumab; CD: Crohn's disease; IBD: inflammatory bowel disease; IRB: Institutional Review Board; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; UC: ulcerative colitis; VDZ: vedolizumab

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