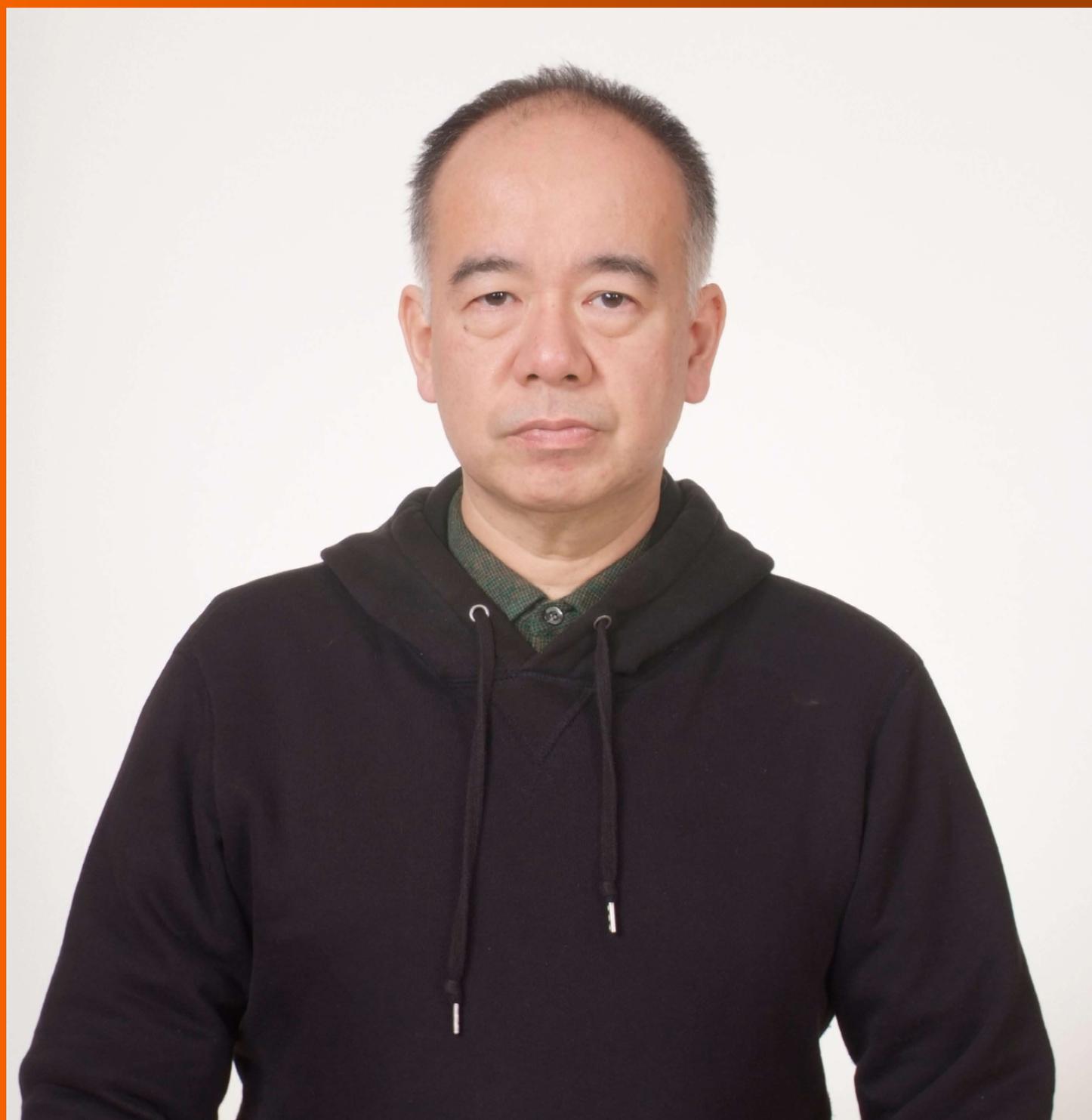


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Vedolizumab for inflammatory bowel disease: From randomized controlled trials to real-life evidence

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Abstract

The biologic antitumor necrosis factor alpha (anti-TNF α) agents have revolutionised the treatment of inflammatory

bowel disease (IBD). However, some patients experience primary nonresponse, loss of response, or intolerance. Therefore, introducing a newer class of therapy with a mechanism of action that acts on different inflammatory pathways involved in IBD pathogenesis is appealing. Vedolizumab is a fully humanised monoclonal antibody that selectively targets $\alpha 4\beta 7$ integrin. Based on the results of the pivotal clinical GEMINI trials, vedolizumab was approved for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD) refractory or intolerant to either conventional therapy or TNF α inhibitors. This review describes the efficacy, safety, and tolerability of vedolizumab reported in both randomized, controlled, clinical trials and from real-world experience in patients with UC and CD in order to identify its place in treatment algorithms for IBD.

Key words: Vedolizumab; Crohn's disease; Real-world; Efficacy; Ulcerative colitis; Controlled trial; Effectiveness; Safety

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Core tip: Vedolizumab represents an interesting new therapeutic option for the treatment of patients with moderate-to-severe ulcerative colitis and Crohn's disease that are refractory or intolerant to either conventional treatments or anti-TNF α agents. This review describes the efficacy, safety, and tolerability of vedolizumab demonstrated in the clinical GEMINI trials. In addition, the paper reviews the effectiveness and the safety of vedolizumab in the real-world studies in order to identify its place in treatment algorithms for patients with inflammatory bowel disease.

Scribano ML. Vedolizumab for inflammatory bowel disease: From randomized controlled trials to real-life evidence. *World J*

INTRODUCTION

The introduction of biologic, antitumor necrosis factor alpha (anti-TNF α) therapies has transformed the management of patients with moderate-to-severe, active inflammatory bowel diseases (IBD) that are refractory to conventional treatments^[1-3]. However, a proportion of patients do not respond to these drugs, lose their response over time, or are intolerant to these treatments^[4-6]. Additionally, the efficacy of a second anti-TNF α agent is lower in patients who have previously received an anti-TNF α drug^[7]. Therefore, the advent of a newer class of therapy, characterized by a different mode of action, is an attractive option for patients with IBD.

Vedolizumab is a fully humanised monoclonal IgG-1 antibody that selectively inhibits the interaction between $\alpha 4\beta 7$ integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). It prevents lymphocyte translocation from the blood into the inflamed gut tissue, resulting in a reduction in local inflammation^[8,9] (Figure 1).

The efficacy of vedolizumab for the induction and maintenance of remission in patients with IBD was demonstrated in the pivotal phase III GEMINI studies^[10-12]. Based on the results of these randomized, double-blind, placebo-controlled trials, vedolizumab was approved for the treatment of adult patients with moderate-to-severe active ulcerative colitis (UC) and Crohn's disease (CD) who had an inadequate response to either standard therapies or TNF α antagonists by both the European Medicines Agency and the US Food and Drug Administration.

However, all randomized controlled trials (RCTs) have restrictive enrolment criteria and, in order to include a highly selected and homogeneous population, tend to exclude several groups of patients^[13]. This limits the generalisation of RCT results to patients commonly seen in general practice.

Patients in real-world cohorts tend to have more complicated diseases, multiple comorbidities, variable treatment regimens applied with flexibility, and follow-up controls that are not fixed. In addition, the goals of therapy in clinical practice are variable and are specific for the single patient ("treat to target")^[14]. Therefore, evaluating biologic therapies is highly relevant in the clinical practice setting.

To date, several real-world studies on the effectiveness and safety of vedolizumab in patients with moderate-to-severe, active UC and CD have been published^[15-26]. This paper reviews the efficacy of vedolizumab for the treatment of IBD from the randomized controlled clinical

trials (GEMINI program) and in the GEMINI long-term safety (LTS) study^[27,28], the effectiveness of vedolizumab in the real-world studies, and the drug's safety profile.

EFFICACY OF VEDOLIZUMAB FROM RCTS

Vedolizumab in UC

The efficacy of vedolizumab for inducing and maintaining remission in patients with UC was demonstrated in the GEMINI 1 study, a trial involving more than 800 patients with moderate-to-severe UC, defined as a Mayo score^[29] of 6-12, with an endoscopic subscore ≥ 2 ^[10]. The trial consisted of two induction cohorts; a double-blind cohort including 374 patients randomized to receive vedolizumab 300 mg intravenous (iv) or placebo at weeks 0 and 2, and a second additional cohort of 521 patients receiving open-label vedolizumab aimed to generate the needed number of responders to fulfil sample-size requirements for the maintenance phase. Eligible patients had no response to or unacceptable adverse events from steroids, immunosuppressive drugs, or anti-TNF α therapy.

In the first cohort, a significantly higher rate of patients treated with vedolizumab achieved clinical response, clinical remission, and mucosal healing after 6 wk compared to placebo. The primary outcome of the induction phase, clinical response at week 6, was achieved by 47.1% of patients treated with vedolizumab vs 25.5% of patients in the placebo group ($P < 0.001$) (Table 1).

Patients from both cohorts achieving clinical response to vedolizumab at 6 wk were randomized to receive vedolizumab 300 mg iv every 4 wk or 8 wk, or to receive placebo in the maintenance phase for up to 52 wk. The results of the maintenance phase were as impressive as those in the induction phase. The rates of clinical remission at week 52, the primary outcome of the maintenance phase, were significantly higher in patients treated with vedolizumab than in those treated with placebo (44.8% in the vedolizumab 4-weekly group, 41.8% in the vedolizumab 8-weekly group, and 15.9% in the placebo group; $P < 0.001$). Durable clinical remission (defined as remission at week 6 and week 52) was also reported by significantly more patients in the vedolizumab groups (24.0% in the vedolizumab 4-weekly group, 20.5% in the vedolizumab 8-weekly group, and 8.7% in the placebo group; $P = 0.001$ and $P = 0.008$, respectively, vs placebo). Vedolizumab was also associated with greater mucosal healing rates ($P < 0.001$ for both vedolizumab groups vs placebo) and significantly higher rates of steroid-free remission ($P < 0.001$ for both vedolizumab groups vs placebo) (Table 1).

A clear difference in efficacy between the 4- and 8-weekly vedolizumab regimens was not observed. Efficacy was reported by both patients with previous exposure to anti-TNF α therapy as well as those who

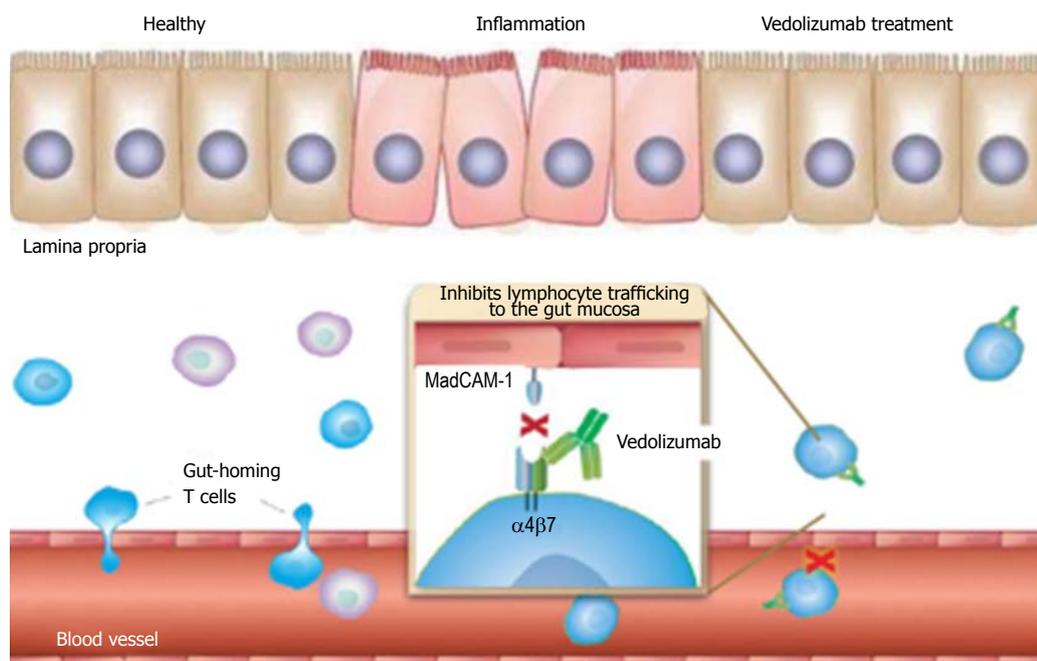


Figure 1 Vedolizumab targets the $\alpha 4\beta 7$ integrin, preventing leucocyte translocation from the blood into the inflamed gut tissue. MadCAM-1: Mucosal addressin cell adhesion molecule.

were anti-TNF α therapy-naïve; however, slightly better outcomes were seen in patients who were TNF α -inhibitor-naïve.

Vedolizumab in CD

The efficacy of vedolizumab in patients with moderately to severely active CD was demonstrated in the GEMINI 2 and GEMINI 3 clinical trials^[11,12]. In GEMINI-2, 368 patients were randomized to receive either vedolizumab 300 mg iv or placebo at week 0 and week 2^[11]. Additionally, as in the GEMINI 1 trial, a second cohort of 747 subjects was treated with vedolizumab in an open-label fashion. All patients enrolled had active disease defined by a Crohn's Disease Activity Index (CDAI)^[30] of 220-450, and had one of the following: serum C-reactive protein (CRP) > 2.87 mg/L or colonoscopic documentation showing ≥ 3 large ulcers or ≥ 10 aphthous ulcers, or faecal calprotectin concentrations > 250 $\mu\text{g/g}$ in conjunction with computed tomography or magnetic resonance enterography, small-bowel radiography, or capsule endoscopy revealing Crohn's ulcers. Eligible patients had no response to or unacceptable adverse events from steroids, immunosuppressive drugs, or anti-TNF α drugs.

Two coprimary endpoints in the induction trial, clinical remission and CDA-100 response, were evaluated at week 6. A significantly greater proportion of patients receiving vedolizumab achieved clinical remission at 6 wk with respect to the placebo group (14.5% vs 6.8%; $P = 0.02$) (Table 1). However, the CDAI-100 response rate was comparable to the placebo (31.4% vs 25.7%; $P = 0.23$).

During the maintenance phase, 461 patients

who were vedolizumab responders were randomized to receive vedolizumab 300 mg iv administered at either 4- or 8-weekly intervals up to week 52. Clinical remission at week 52, the primary endpoint of this phase, was significantly greater in patients assigned to vedolizumab therapy every 4 wk or 8 wk (36.4% and 39.0%) than in the placebo group (21.6%; $P = 0.004$ and $P < 0.001$, respectively, vs placebo). The rates of steroid-sparing remission were also significantly higher among patients treated with vedolizumab ($P = 0.04$ and $P < 0.02$, respectively, vs placebo), while the rates of durable clinical remission showed no significant differences (Table 1).

Similar results were observed in the GEMINI 3 trial, which evaluated the efficacy of vedolizumab in 315 patients with moderately to severely active CD and inadequate response, loss of response, or intolerance to previous TNF α antagonists^[12]. Patients were assigned randomly to receive vedolizumab 300 mg iv or placebo at weeks 0, 2, and 6. Clinical remission at week 6 was observed in 15.2% of vedolizumab patients compared to 12.1% in the placebo group ($P = 0.4$) (Table 1). Therefore, the primary endpoint of the study was not met. However, the rates of clinical remission at week 10 were significantly higher in patients treated with vedolizumab (26.6% vs 12.1% in the placebo group; $p = 0.001$). The benefit in this population was therefore observed at week 10, suggesting a delayed response in obtaining clinical remission. In clinical practice, there is an opportunity for a fourth induction dose at week 10 in patients with CD, with insufficient response to the first three administrations of vedolizumab.

A meta-analysis pooling data from the phase II

Table 1 Phase III randomized controlled trials of vedolizumab in patients with ulcerative colitis and Crohn's disease

Study	n (patients)	Setting of trial	Treatment arms	Clinical response (%)	Clinical remission (%)	CS-free remission (%)	Mucosal healing (%)
GEMINI 1 ^[10] 2013	374	Induction	300 mg	47.1	16.9	-	40.9
			Placebo	25.5	5.4	-	24.8
		Maintenance	300 mg 4 weekly	-	44.8	45.2	56.0
			300 mg 8 weekly	-	41.8	31.4	51.6
GEMINI 2 ^[11] 2013	368	Induction	300 mg	31.4	14.5	-	-
			Placebo	25.7	6.8	-	-
		Maintenance	300 mg 4 weekly	45.5	36.4	28.8	-
			300 mg 8 weekly	43.5	39.0	31.7	-
GEMINI 3 ^[12] 2015	315	Induction	300 mg	-	15.2	-	-
			Placebo	30.1	21.6	15.9	-
			Placebo	-	12.1	-	-

Clinical response was defined as a reduction in the Mayo score of at least 3 points plus a decrease of at least 30% from the baseline score, with a decrease in the rectal bleeding subscore ≥ 1 , an absolute rectal bleeding subscore ≤ 1 (GEMINI 1), or as a ≥ 100 -point decrease in the CDAI score (GEMINI 2). Clinical remission defined as a Mayo score of ≤ 2 and no subscore > 1 (GEMINI 1) or as a CDAI score ≤ 150 points (GEMINI 2, GEMINI 3). CS: Corticosteroid.

and phase III randomized controlled studies involving patients with active CD showed that vedolizumab increased the rates of clinical remission and CDAI-100 response during the induction phase, although it failed to meet some of the primary endpoints of the GEMINI 2 and GEMINI 3 trials^[31].

LONG-TERM EFFICACY OF VEDOLIZUMAB IN IBD FROM CLINICAL TRIALS

An interim analysis of the efficacy data from the GEMINI LTS study was recently published^[27,28]. The GEMINI LTS study is an ongoing, open-label, extension trial in patients with UC and CD designed to investigate the long-term safety of vedolizumab in patients with IBD. In addition, an exploratory evaluation of long-term clinical efficacy was also performed. Patients were enrolled from the long-term, phase II, C13004 study and from the GEMINI 1, GEMINI 2, and GEMINI 3 trials. A remaining part of the population consisted of patients with IBD who were vedolizumab-naïve who were included directly into the GEMINI LTS trial. A total of 894 patients with UC and 1349 with CD were enrolled in the GEMINI LTS. All patients received vedolizumab 300 mg iv every 4 wk.

Populations evaluated during the efficacy analysis of the GEMINI LTS included only patients with moderate-to-severe UC (532/894) or CD (1297/1349); patients from the C13004 study were excluded because some patients with mild IBD were enrolled in this study.

Outcomes of clinical response and remission, evaluated using a partial Mayo score in UC and the Harvey-Bradshaw Index^[32] in CD, were assessed after up to 152 wk of therapy. The results showed that among patients with UC having a response to vedolizumab at week 6 in the GEMINI 1 study, 88% ($n = 120/136$) and 96% ($n = 70/73$) were in clinical

remission after 104 and 152 wk, respectively. Similarly, the rates of remission reported by the patients with CD who responded to the induction phase of the GEMINI 2 study were 83% ($n = 100/120$) and 89% ($n = 62/70$) at the same time points.

An increase in dosing frequency in patients who had withdrawn early from the GEMINI 1 and GEMINI 2 studies, treated every 8 wk to every 4 wk in the GEMINI LTS trial, resulted in remission rates of 28% and 32%, respectively, after 52 wk. Similar improvements were observed regardless of previous anti-TNF α therapy.

A retrospective evaluation of mucosal healing after treatment with vedolizumab in patients with IBD enrolled in the GEMINI LTS study at Leuven University Hospital was recently reported^[33]. A total of 58 patients (34 UC, 24 CD), previously exposed to anti-TNF α therapy, were endoscopically followed for a median duration of 3.2 years. Mucosal healing, corrected with non-responder imputation, was reported by 50% of patients with UC and 29% with CD. Additionally, 32.4% of patients with UC and 20.8% with CD achieved histological healing. A significant correlation between mucosal and histological healing was observed in both patients with UC and CD.

EFFECTIVENESS OF VEDOLIZUMAB IN PATIENTS WITH IBD FROM REAL-WORLD STUDIES

Several prospective and retrospective real-life studies of vedolizumab in patients with moderate-to-severe UC and CD have been published by authors from Europe and the United States^[15-26].

European real-life studies

To date, the French GETAID group (Groupe d' Etude Therapeutique des Affections Inflammatoires du tube Digestif) has published the largest real-world cohort

Table 2 Real-world studies on vedolizumab in patients with inflammatory bowel disease, Crohn's disease, or ulcerative colitis

Study author (country) years	IBD	CD	UC
Amiot <i>et al</i> ^[15,16] (France), 2016-2017	294	173	121
Eriksson <i>et al</i> ^[19] (Sweden), 2017	246	147	99 ¹
Baumgart <i>et al</i> ^[17] (Germany), 2016	212	97	115
Dulai <i>et al</i> ^[23] (United States, multicentre), 2016	212	212	-
Kopylov <i>et al</i> ^[20] (Israel), 2017	204	130	74 ¹
Shelton <i>et al</i> ^[24] (United States, Boston), 2015	172	107	65 ¹
Macaluso <i>et al</i> ^[22] (Italy, Sicily), 2018	163	84	79
Allegretti <i>et al</i> ^[26] (United States, Boston), 2017	136	96	40
Stallmach <i>et al</i> ^[18] (German Registry), 2016	127	67	60
Vivio <i>et al</i> ^[25] (United States, Saint Louis), 2016	102 (51) ²	30	21
Samaan <i>et al</i> ^[21] (United Kingdom), 2017	50	27	23 ¹
Total	1.918	1.170	697

¹UC + IBD unclassified; ²102 patients started vedolizumab, and 51 patients were followed prospectively. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis.

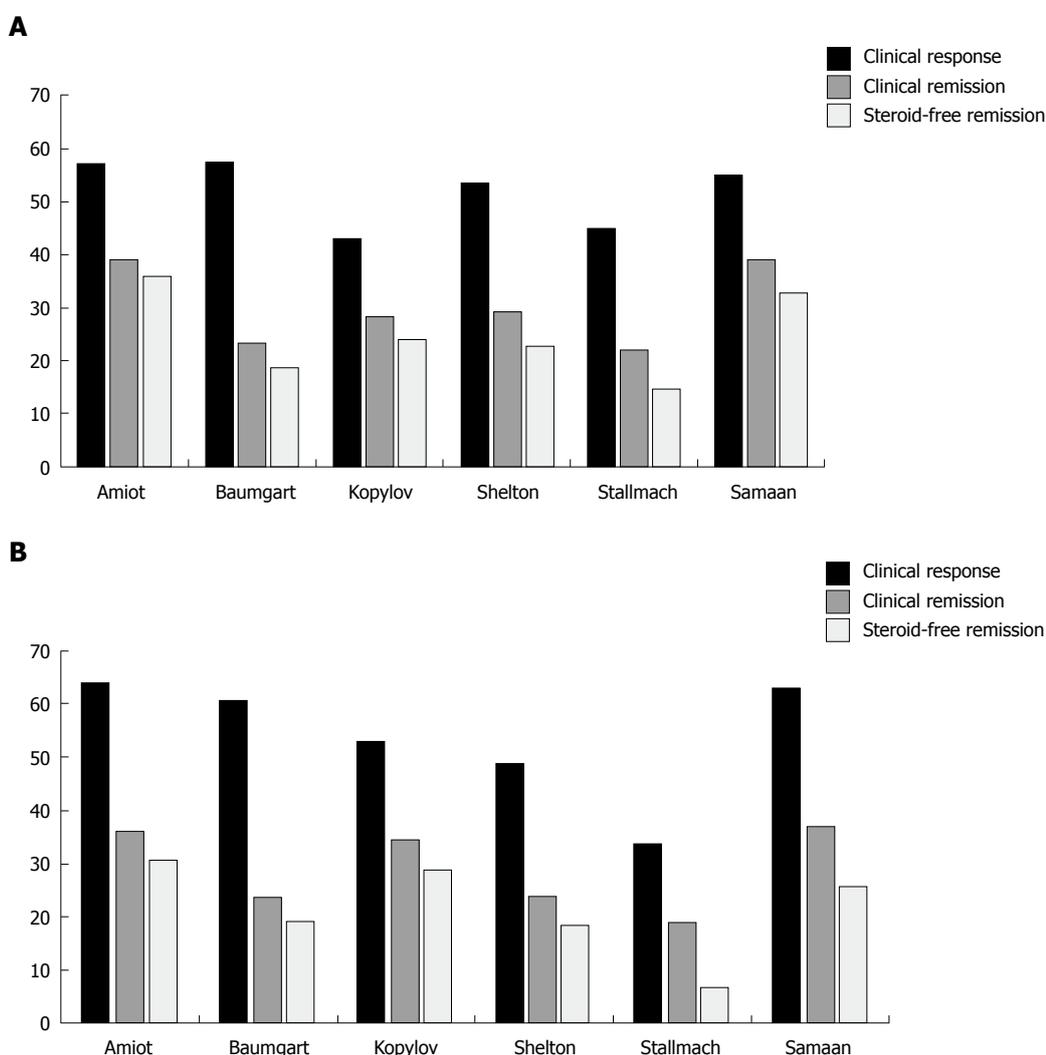


Figure 2 Real-world studies with vedolizumab in patients with ulcerative colitis (A) and Crohn's disease (B): Results at week 14.

comprising 294 patients with moderately to severely active IBD who were followed prospectively until week 54^[15,16] (Table 2). Almost all patients had previously failed at least one anti-TNF α agent, with 91% having failed two. Patients received vedolizumab 300 mg iv

at weeks 0, 2, and 6 then every 8 wk afterward up to week 52. At week 6, 32% of patients with UC and 31% with CD were in clinical remission. The primary outcome of the induction study, steroid-free clinical remission at week 14, was reported by 36% and 31%

of patients with UC and CD, respectively^[15] (Figure 2A and B). At week 54, steroid-free clinical remission rates were 40.5% in patients with UC and 27.2% in patients with CD^[16]. Mucosal healing, assessed between weeks 30 and 54, occurred in 54.8% of patients with UC and 29.8% with CD. However, it was evaluated in only a small proportion of the population, and it is possible that patients with active disease were reassessed less frequently. A significant number of patients experienced inadequate response or loss of response during the year of treatment, and vedolizumab therapy was optimized (300 mg every 4 wk) in 54% of patients. Dose optimization induced or restored clinical response in 41% of patients, of whom 30% achieved clinical remission.

Predictors of clinical effectiveness were assessed by the authors, who found that a clinical response at week 6, baseline CRP > 20 mg/L, and a higher baseline disease activity were predictive of steroid-free remission at week 14 in both groups^[15]. In addition, patients with UC and CD who achieved a clinical response at week 6 were more likely to achieve steroid-free clinical remission at week 54 ($P < 0.001$)^[16].

A German National cohort study prospectively included 212 patients with IBD, most of whom were anti-TNF α experienced^[17] (Table 2). The results showed that clinical remission at week 6 was reached by 11.3% and 15.5%, and at week 14 by 23.5% and 23.7%, of patients with UC and CD, respectively (Figure 2A and B). This group identified a low HBI at baseline and hospitalization in the past 12 mo as independent predictors of clinical remission at week 14 in patients with CD.

These data were followed by a longer-term study that included some patients from the previous German induction cohort as well as additional patients with IBD^[18] (Table 2). Based on nonresponding imputation analysis, clinical remission was observed in 22% and 19% of patients with UC and CD, respectively, at week 14 (Figure 2A and B). Clinical remission at week 54 was reported by 15/60 (25%) patients with UC and 14/67 (21%) patients with CD. Nonresponse status at week 14 was an indicator of a low likelihood of clinical response and remission at week 54 in patients with both diseases. In addition, the reduction of CRP at week 14 in patients with UC and CD, and of faecal calprotectin in patients with UC, was predictive of clinical remission at week 54.

More recently, a large prospective cohort based on the Swedish National Quality Registry for IBD (SWIBREG), evaluating the data at week 12, 52 and the last follow-up, reported that clinical remission was obtained with vedolizumab after 52 wk in 64% and 60% of patients with UC and CD, respectively, 86% of whom had previously used TNF α inhibitors^[19] (Table 2). Elevated CRP at baseline and prior use of anti-TNF α were associated with a higher risk of vedolizumab

discontinuation.

The large, Israeli, real-world study in patients with IBD who had high rates of previous anti-TNF α therapy, showed similar efficacy of vedolizumab in patients with UC and CD^[20] (Table 2; Figure 2A and B). A retrospective cohort of 50 patients with IBD from the UK demonstrated similar rates of effectiveness compared to the other real-world studies^[21] (Table 2; Figure 2A and B).

Very recently, real-world data on the effectiveness of vedolizumab on gut and articular symptoms in 163 patients with IBD were reported by an Italian group^[22] (Table 2). Steroid-free remission was observed in 71 (43.6%; UC: 45.6%, CD: 41.7%) and 29 (40.8%; UC: 40.0%, CD: 41.7%) patients at weeks 10 and 22, respectively. At the same time points, a response on articular symptoms was achieved in 39.5% and 45.4% of patients with IBD who had active spondyloarthritis at baseline. The only factor associated with response on articular manifestations was the coexistence of a concomitant intestinal benefit at both weeks 10 and 22. These data suggest that the improvement of articular symptoms could be mainly related to the intestinal response.

United States real-world studies

A large real-world cohort in the United States was published by the US VICTORY (Vedolizumab for Health Outcomes in Inflammatory Bowel Diseases) consortium and included 212 patients with CD, 90% of whom were TNF α -antagonist exposed^[23] (Table 2). This retrospective study of seven medical centres from across the United States reported rates of clinical remission of 18%, 35%, and 54% at 6, 12 and 18 mo, respectively. Prior TNF α -inhibitor use, severe disease activity, active perianal disease, and smoking history were associated with a lower likelihood of achieving clinical remission. Cumulative rates of mucosal healing and "deep remission" (defined as a combination of clinical remission and mucosal healing) after 12 mo were observed in 63% and 26% of patients with CD, respectively. Patients with previous anti-TNF α treatment and severe disease activity were less likely to obtain mucosal healing.

In another study from the United States, two centres in Boston enrolled 172 patients with IBD, almost all with previous use of TNF α antagonist^[24] (Table 2). Similar rates of clinical response, clinical remission, and steroid-free remission at week 14 were reported by patients with UC and CD (Figure 2A and B). Early response at week 6 was a significant predictive factor of week 14 response/remission in patients with UC, with a trend toward significance in those with CD. Elevated CRP (> 8 mg/L) at baseline was associated with a lower likelihood of achieving clinical response/remission in patients with both diseases.

Vivio *et al*^[25] reported data on 102 patients with IBD, of whom 51 were followed prospectively (Table 2). At week 14, 55% of the patients with UC in the

prospective cohort achieved clinical remission. Rates of mucosal healing and endoscopic improvement after a median treatment duration of 22 wk were higher in patients with UC (69% and 76%) than in patients with CD (30% and 52%).

COMBINATION OF VEDOLIZUMAB AND ANTI-TNF α AGENTS IN THE TREATMENT OF IBD

The combination of vedolizumab and anti-TNF α drugs (infliximab or adalimumab) in the treatment of IBD was very recently reported by a case series of 6 patients with UC and 4 patients with CD^[34]. Before combination therapy, all patients were treated with anti-TNF α , however they still had an active disease even after the optimization of the dosage and/or the infusion interval. At the time of inclusion 4 patients received concomitant immunomodulators and 1 patient received systemic corticosteroid. The patients were prospectively followed for at least 12 mo (median 17 mo) and at the end of the follow-up period all patients achieved clinical remission, and 8 out of 10 could stop the anti-TNF α treatment.

In 2 case reports previously published vedolizumab was successfully used in association with an anti-TNF α drug for the treatment of a patient with chronic refractory pouchitis and axial spondylarthritis and a patient with CD and erythema nodosum^[35,36].

These data suggest that combination treatment of vedolizumab and anti-TNF α therapy might represent a therapeutic option in selected patients with IBD, however further larger studies are needed.

PREDICTORS OF RESPONSE TO VEDOLIZUMAB

Several factors have been evaluated as predictors of response and remission to vedolizumab and a recent review summarized the current data^[37]. Overall, patients with less disease activity (by clinical and inflammatory indices), naïve to TNF α inhibitors, and having higher vedolizumab trough levels at induction^[38-40] had a greater likelihood of responding to treatment in both disease groups.

Concomitant immunomodulatory treatment was not associated with improved results in the GEMINI 1 and 2 studies^[10,11]. However, the interpretation of these data is limited by the small sample size of patients receiving concomitant immunomodulators and their interruption during the maintenance period in both trials. In addition, the studies were not designed to address outcomes in patients on combination immunosuppressive therapy. No consistent benefit of adding an immunomodulatory agent to vedolizumab was observed in some real-world studies and in a small group of patients with

IBD^[15,20,23,24,41]. These data are in line with the finding that combination therapy did not lead to higher early vedolizumab trough levels^[38]. A potential explanation is the low immunogenic profile of vedolizumab, which differs from that of anti-TNF α agents^[42,43]. Currently, only a multicentre study and a recent case series showed that the addition of an immunomodulatory agent to vedolizumab was associated with an increased clinical response and remission in patients with CD and UC^[26,44]. Further studies are needed to better define this aspect.

SAFETY OF VEDOLIZUMAB FROM RANDOMIZED CONTROLLED TRIALS AND REAL-WORLD STUDIES

Safety data on vedolizumab have been evaluated from four double-blind and two open-label trials in an analysis that included over 2800 vedolizumab-exposed patients with IBD who were treated for up to 5 years^[45]. A very good safety profile and minimal immunogenicity were reported.

The risk of progressive multifocal leukoencephalopathy (PML) is a potential safety concern for drugs that block lymphocyte migration. More than 500 cases have occurred in natalizumab-treated patients^[46]. However, no cases of PML have been observed during treatment with vedolizumab according to the concept that the gut selectivity of vedolizumab is protective against the development of PML^[47].

Vedolizumab is not associated with an increased risk of serious or opportunistic infections, and few patients (< 1%) discontinued therapy because of infection. The most common events were upper respiratory tract infections, which accounted for approximately half of the total infections. Lower respiratory tract, lung infections, and abdominal and enteric infections were reported with similar rates as those in the placebo group. Serious infections including sepsis, *Clostridium difficile* infections, and tuberculosis occurred very rarely ($\leq 0.6\%$ of patients). Independent risk factors for serious infections were younger age (HR = 0.97) and concomitant steroid use (HR = 1.88) in patients with CD, and prior anti-TNF α failure (HR = 1.99) in patients with UC. Concomitant narcotic analgesic use was a risk factor for patients with both CD and UC (HR = 2.72 and HR = 2.68, respectively).

The rate of malignancy was consistent with that generally reported in patients with IBD.

A total of 23 hepatobiliary events were observed among vedolizumab-treated patients, most of which were hepatic steatosis and transaminase increases. Five hepatic events were considered serious and vedolizumab was interrupted. Appropriate treatment resulted in resolution or near resolution of the liver abnormalities.

Infusion-related reactions occurred in $\leq 5\%$ of

patients, and < 1% of patients discontinued the infusion or received an incomplete dose. Transient anti-drug antibodies were reported by 4% of subjects enrolled in the GEMINI 1 and GEMINI 2 trials, suggesting that loss of response related to the development of anti-drug antibodies may be a rare event.

Additionally, a post-hoc analyses of the GEMINI 1 and GEMINI 2 studies did not report any significant differences in infections or other adverse events amongst the age groups, confirming a good safety profile in older (> 55 years) patients^[48].

No higher rate of adverse events than the one expected with anti-TNF α therapy alone was observed in the small series of patients treated with a combination of vedolizumab and anti-TNF α agents.

The good safety profile of vedolizumab may be related to its mechanism of action, which is characterized by a gut-selectivity, without systemic action.

Cumulative evidence from real-world studies has not pointed out any relevant differences in infectious and noninfectious adverse events compared to those seen in the RCTs^[49]. Therefore, postmarketing data have confirmed the favourable safety profile of vedolizumab observed in the GEMINI program.

CONCLUSION

Vedolizumab represents an interesting new therapeutic option for the treatment of patients with UC and CD that are refractory to either conventional treatments or TNF α inhibitors^[50]. The efficacy and safety of vedolizumab in patients with IBD were demonstrated in the pivotal GEMINI studies. However, the stringent and restrictive inclusion and exclusion criteria in the study designs may limit the translation of clinical trial results into patients commonly seen in the clinic. In fact, patients enrolled in RCTs only partially represent the IBD population encountered during routine clinical practice^[13].

Real-world studies confirm the effectiveness of vedolizumab in the clinical practice setting and have also evaluated long-term data. Even though the interpretation of the data is limited by significant heterogeneity in the study designs, real-world experience series provide additional relevant evidence^[51]. A systematic review and pooled analysis on the effectiveness and safety of real-world studies has recently been published^[52].

Mucosal healing is a relevant therapeutic target in patients with IBD because it is associated with a reduction in hospitalization, IBD-related surgery, bowel damage, and risk of colonic dysplasia. There is increasing evidence that achieving mucosal healing can favourably alter the natural course of IBD^[53,54]. Therefore, the rates of long-term mucosal healing with vedolizumab reported by Noman, in keeping with the one-year mucosal healing data observed in the GEMINI 1 trial and in the real-world US VICTORY consortium study, appear very promising.

Safety data from all the GEMINI studies showed an

overall rate of adverse events similar to that reported in the placebo group. In addition, an increasing amount of real-world data has confirmed the reassuring safety profile of vedolizumab over an extended treatment period.

In conclusion, vedolizumab has demonstrated efficacy and safety in patients who failed TNF- α antagonists, and should therefore be considered a valid second-line induction and maintenance therapy for these patients. In addition, along with other biologic drugs, vedolizumab should be considered as a first-line treatment for steroid-dependent and steroid-refractory patients and for patients not responding or intolerant to immunosuppressant agents, thanks to its favourable safety profile. Although head-to-head prospective trials to compare the safety of biologic drugs are not available, in patients in whom it is preferable to avoid systemic immunosuppression (patients with high risk of opportunistic infections or the elderly^[55,56]), vedolizumab may be a safer alternative.

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