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

Scribano ML. Vedolizumab for IBD

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**Abstract**

The biologic antitumor necrosis factor alpha (anti-TNFα) 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 α4β7 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 TNFα 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; Ulcerative colitis; Controlled trial; Real-world; Efficacy; 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-TNFα 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.

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**Introduction**

The introduction of biologic, antitumor necrosis factor alpha (anti-TNFα) 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, loose their response over time, or are intolerant to these treatments[4-6]. Additionally, the efficacy of a second anti-TNFα agent is lower in patients who have previously received an anti-TNFα 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 α4β7 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 TNFα 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-TNFα 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-TNFα therapy as well as those who were anti-TNFα therapy-naïve; however, slightly better outcomes were seen in patients who were TNFα-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 μg/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-TNFα 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 weeks 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 weeks or 8 weeks (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 TNFα 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 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 weeks, 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 weeks 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-TNFα 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-TNFα 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 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-TNFα agent, with 91% having failed two. Patients received vedolizumab 300 mg iv at weeks 0, 2, and 6 then every 8 weeks 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-TNFα 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 months 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 weeks in 64% and 60% of patients with UC and CD, respectively, 86% of whom had previously used TNFα inhibitors[19] (Table 2). Elevated CRP at baseline and prior use of anti-TNFα 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-TNFα 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 TNFα-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 months, respectively. Prior TNFα-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 months were observed in 63% and 26% of patients with CD, respectively. Patients with previous anti-TNFα 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 TNFα 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 (Figs. 2 and 3). 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-TNFα agents in the treatment of IBD**

The combination of vedolizumab and anti-TNFα 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-TNFα, 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 months (median 17 months) and at the end of the follow-up period all patients achieved clinical remission, and 8 out of 10 could stop the anti-TNFα treatment.

In 2 case reports previously published vedolizumab was successfully used in association with an anti-TNFα 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-TNFα 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 TNFα 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-TNFα 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 (≤ 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-TNFα 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 ≤ 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-TNFα therapy alone was observed in the small series of patients treated with a combination of vedolizumab and anti-TNFα 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 TNFα 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 et al, 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.

**References**

1 **Arnold M**, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017; **66**: 683-691 [PMID: 26818619 DOI: 10.1136/gutjnl-2015-310912]

2 **Eser S**, Chang J, Charalambous H, Silverman B, Demetriou A, Yakut C, Nimri O, Pavlou P, Özgür S, Ziogas A, Stevens L, Ward K, Anton Culver H. Incidence patterns of colorectal cancers in four countries of the Middle East Cancer Consortium (Cyprus, Jordan, Israel, and İzmir, Turkey) compared with those in the United States Surveillance, Epidemiology, and End Results Program. *Turk J Gastroenterol* 2018; **29**: 36-44 [PMID: 29391306 DOI: 10.5152/tjg.2018.17263]

3 **Moskal A**, Freisling H, Byrnes G, Assi N, Fahey MT, Jenab M, Ferrari P, Tjønneland A, Petersen KE, Dahm CC, Hansen CP, Affret A, Boutron-Ruault MC, Cadeau C, Kühn T, Katzke V, Iqbal K, Boeing H, Trichopoulou A, Bamia C, Naska A, Masala G, de Magistris MS, Sieri S, Tumino R, Sacerdote C, Peeters PH, Bueno-de-Mesquita BH, Engeset D, Licaj I, Skeie G, Ardanaz E, Buckland G, Castaño JM, Quirós JR, Amiano P, Molina-Portillo E, Winkvist A, Myte R, Ericson U, Sonestedt E, Perez-Cornago A, Wareham N, Khaw KT, Huybrechts I, Tsilidis KK, Ward H, Gunter MJ, Slimani N. Main nutrient patterns and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition study. *Br J Cancer* 2016; **115**: 1430-1440 [PMID: 27764841 DOI: 10.1038/bjc.2016.334]

4 **Godos J**, Bella F, Torrisi A, Sciacca S, Galvano F, Grosso G. Dietary patterns and risk of colorectal adenoma: a systematic review and meta-analysis of observational studies. *J Hum Nutr Diet* 2016; **29**: 757-767 [PMID: 27412573 DOI: 10.1111/jhn.12395]

5 **Feng YL**, Shu L, Zheng PF, Zhang XY, Si CJ, Yu XL, Gao W, Zhang L. Dietary patterns and colorectal cancer risk: a meta-analysis. *Eur J Cancer Prev* 2017; **26**: 201-211 [PMID: 26945285 DOI: 10.1097/CEJ.0000000000000245]

6 **van Meer S**, Leufkens AM, Bueno-de-Mesquita HB, van Duijnhoven FJ, van Oijen MG, Siersema PD. Role of dietary factors in survival and mortality in colorectal cancer: a systematic review. *Nutr Rev* 2013; **71**: 631-641 [PMID: 24032367 DOI: 10.1111/nure.12042]

7 **Kushi LH**, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T; American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin* 2012; **62**: 30-67 [PMID: 22237782 DOI: 10.3322/caac.20140]

8 **Lee DH**, Keum N, Giovannucci EL. Colorectal Cancer Epidemiology in the Nurses' Health Study. *Am J Public Health* 2016; **106**: 1599-1607 [PMID: 27459444 DOI: 10.2105/AJPH.2016.303320]

9 **Ekmekcioglu C**, Wallner P, Kundi M, Weisz U, Haas W, Hutter HP. Red meat, diseases, and healthy alternatives: A critical review. *Crit Rev Food Sci Nutr* 2018; **58**: 247-261 [PMID: 27128451 DOI: 10.1080/10408398.2016.1158148]

10 **Miccadei S**, Masella R, Mileo AM, Gessani S. ω3 Polyunsaturated Fatty Acids as Immunomodulators in Colorectal Cancer: New Potential Role in Adjuvant Therapies. *Front Immunol* 2016; **7**: 486 [PMID: 27895640 DOI: 10.3389/fimmu.2016.00486]

11 **Yao Y**, Suo T, Andersson R, Cao Y, Wang C, Lu J, Chui E. Dietary fibre for the prevention of recurrent colorectal adenomas and carcinomas. *Cochrane Database Syst Rev* 2017; **1**: CD003430 [PMID: 28064440 DOI: 10.1002/14651858.CD003430.pub2]

12 **Zamora-Ros R**, Barupal DK, Rothwell JA, Jenab M, Fedirko V, Romieu I, Aleksandrova K, Overvad K, Kyrø C, Tjønneland A, Affret A, His M, Boutron-Ruault MC, Katzke V, Kühn T, Boeing H, Trichopoulou A, Naska A, Kritikou M, Saieva C, Agnoli C, Santucci de Magistris M, Tumino R, Fasanelli F, Weiderpass E, Skeie G, Merino S, Jakszyn P, Sánchez MJ, Dorronsoro M, Navarro C, Ardanaz E, Sonestedt E, Ericson U, Maria Nilsson L, Bodén S, Bueno-de-Mesquita HB, Peeters PH, Perez-Cornago A, Wareham NJ, Khaw KT, Freisling H, Cross AJ, Riboli E, Scalbert A. Dietary flavonoid intake and colorectal cancer risk in the European prospective investigation into cancer and nutrition (EPIC) cohort. *Int J Cancer* 2017; **140**: 1836-1844 [PMID: 28006847 DOI: 10.1002/ijc.30582]

13 **Printz C**. Vegetarian diet associated with lower risk of colorectal cancer. *Cancer* 2015; **121**: 2667 [PMID: 26249116 DOI: 10.1002/cncr.29582]

14 **Harmon BE**, Wirth MD, Boushey CJ, Wilkens LR, Draluck E, Shivappa N, Steck SE, Hofseth L, Haiman CA, Le Marchand L, Hébert JR. The Dietary Inflammatory Index Is Associated with Colorectal Cancer Risk in the Multiethnic Cohort. *J Nutr* 2017; **147**: 430-438 [PMID: 28179489 DOI: 10.3945/jn.116.242529]

15 **Saetang J**, Sangkhathat S. Diets link metabolic syndrome and colorectal cancer development (Review). *Oncol Rep* 2017; **37**: 1312-1320 [PMID: 28098913 DOI: 10.3892/or.2017.5385]

16 **Rosato V**, Guercio V, Bosetti C, Negri E, Serraino D, Giacosa A, Montella M, La Vecchia C, Tavani A. Mediterranean diet and colorectal cancer risk: a pooled analysis of three Italian case-control studies. *Br J Cancer* 2016; **115**: 862-865 [PMID: 27537381 DOI: 10.1038/bjc.2016.245]

17 **Menotti A**, Keys A, Blackburn H, Kromhout D, Karvonen M, Nissinen A, Pekkanen J, Punsar S, Fidanza F, Giampaoli S, Seccareccia F, Buzina R, Mohacek I, Nedeljkovic S, Aravanis C, Dontas A, Toshima H, Lanti M. Comparison of multivariate predictive power of major risk factors for coronary heart diseases in different countries: results from eight nations of the Seven Countries Study, 25-year follow-up. *J Cardiovasc Risk* 1996; **3**: 69-75 [PMID: 8783033]

18 **Dinu M**, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *Eur J Clin Nutr* 2018; **72**: 30-43 [PMID: 28488692 DOI: 10.1038/ejcn.2017.58]

19 **Sofi F**, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr* 2014; **17**: 2769-2782 [PMID: 24476641 DOI: 10.1017/S1368980013003169]

20 **Medina-Remón A**, Kirwan R, Lamuela-Raventós RM, Estruch R. Dietary patterns and the risk of obesity, type 2 diabetes mellitus, cardiovascular diseases, asthma, and neurodegenerative diseases. *Crit Rev Food Sci Nutr* 2018; **58**: 262-296 [PMID: 27127938 DOI: 10.1080/10408398.2016.1158690]

21 **Cottet V**, Bonithon-Kopp C, Kronborg O, Santos L, Andreatta R, Boutron-Ruault MC, Faivre J; European Cancer Prevention Organisation Study Group. Dietary patterns and the risk of colorectal adenoma recurrence in a European intervention trial. *Eur J Cancer Prev* 2005; **14**: 21-29 [PMID: 15677892]

22 **Whalen KA**, McCullough M, Flanders WD, Hartman TJ, Judd S, Bostick RM. Paleolithic and Mediterranean diet pattern scores and risk of incident, sporadic colorectal adenomas. *Am J Epidemiol* 2014; **180**: 1088-1097 [PMID: 25326623 DOI: 10.1093/aje/kwu235]

23 **Dixon LB**, Subar AF, Peters U, Weissfeld JL, Bresalier RS, Risch A, Schatzkin A, Hayes RB. Adherence to the USDA Food Guide, DASH Eating Plan, and Mediterranean dietary pattern reduces risk of colorectal adenoma. *J Nutr* 2007; **137**: 2443-2450 [PMID: 17951483]

24 **Singh PN**, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol* 1998; **148**: 761-774 [PMID: 9786231]

25 **Keys A**. Mediterranean diet and public health: personal reflections. *Am J Clin Nutr* 1995; **61**: 1321S-1323S [PMID: 7754982]

26 **Martinez-Gonzalez MA**, Martin-Calvo N. Mediterranean diet and life expectancy; beyond olive oil, fruits, and vegetables. *Curr Opin Clin Nutr Metab Care* 2016; **19**: 401-407 [PMID: 27552476 DOI: 10.1097/MCO.0000000000000316]

27 **Widmer RJ**, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. *Am J Med* 2015; **128**: 229-238 [PMID: 25447615 DOI: 10.1016/j.amjmed.2014.10.014]

28 **Schwingshackl L**, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. *Cancer Med* 2015; **4**: 1933-1947 [PMID: 26471010 DOI: 10.1002/cam4.539]

29 **Alam MN**, Almoyad M, Huq F. Polyphenols in Colorectal Cancer: Current State of Knowledge including Clinical Trials and Molecular Mechanism of Action. *Biomed Res Int* 2018; **2018**: 4154185 [PMID: 29568751 DOI: 10.1155/2018/4154185]

30 **Abenavoli L**, Milic N, Peta V, Alfieri F, De Lorenzo A, Bellentani S. Alimentary regimen in non-alcoholic fatty liver disease: Mediterranean diet. *World J Gastroenterol* 2014; **20**: 16831-16840 [PMID: 25492997 DOI: 10.3748/wjg.v20.i45.16831]

31 **Little CH**, Combet E, McMillan DC, Horgan PG, Roxburgh CS. The role of dietary polyphenols in the moderation of the inflammatory response in early stage colorectal cancer. *Crit Rev Food Sci Nutr* 2017; **57**: 2310-2320 [PMID: 26066365 DOI: 10.1080/10408398.2014.997866]

32 **Tosti V**, Bertozzi B, Fontana L. Health Benefits of the Mediterranean Diet: Metabolic and Molecular Mechanisms. *J Gerontol A Biol Sci Med Sci* 2018; **73**: 318-326 [PMID: 29244059 DOI: 10.1093/gerona/glx227]

33 **Bultman SJ**. Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer. *Mol Nutr Food Res* 2017; **61**: [PMID: 27138454 DOI: 10.1002/mnfr.201500902]

34 **Alemán JO**, Eusebi LH, Ricciardiello L, Patidar K, Sanyal AJ, Holt PR. Mechanisms of obesity-induced gastrointestinal neoplasia. *Gastroenterology* 2014; **146**: 357-373 [PMID: 24315827 DOI: 10.1053/j.gastro.2013.11.051]

35 **Smith RA**, Andrews K, Brooks D, DeSantis CE, Fedewa SA, Lortet-Tieulent J, Manassaram-Baptiste D, Brawley OW, Wender RC. Cancer screening in the United States, 2016: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin* 2016; **66**: 96-114 [PMID: 26797525 DOI: 10.3322/caac.21336]

36 **Whiteman DC**, Wilson LF. The fractions of cancer attributable to modifiable factors: A global review. *Cancer Epidemiol* 2016; **44**: 203-221 [PMID: 27460784 DOI: 10.1016/j.canep.2016.06.013]

37 **Lieberman DA**, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2012; **143**: 844-857 [PMID: 22763141 DOI: 10.1053/j.gastro.2012.06.001]

38 **Levin B**, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, Dash C, Giardiello FM, Glick S, Levin TR, Pickhardt P, Rex DK, Thorson A, Winawer SJ; American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American College of Radiology Colon Cancer Committee. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008; **58**: 130-160 [PMID: 18322143 DOI: 10.3322/CA.2007.0018]

39 **Israel. Central Bureau of Statistics**. Population in Israel, by marital status, sex and age, aged 15-54, 1987. *Mon Bull Stat U N Stat Off* 1989; **40**: 17-50 [PMID: 12233657]

40 **Schwingshackl L**, Hoffmann G. Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. *J Acad Nutr Diet* 2015; **115**: 780-800.e5 [PMID: 25680825 DOI: 10.1016/j.jand.2014.12.009]

41 **Jacobs S**, Harmon BE, Ollberding NJ, Wilkens LR, Monroe KR, Kolonel LN, Le Marchand L, Boushey CJ, Maskarinec G. Among 4 Diet Quality Indexes, Only the Alternate Mediterranean Diet Score Is Associated with Better Colorectal Cancer Survival and Only in African American Women in the Multiethnic Cohort. *J Nutr* 2016; **146**: 1746-1755 [PMID: 27511927 DOI: 10.3945/jn.116.234237]

42 **Schwingshackl L**, Bogensberger B, Hoffmann G. Diet Quality as Assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension Score, and Health Outcomes: An Updated Systematic Review and Meta-Analysis of Cohort Studies. *J Acad Nutr Diet* 2018; **118**: 74-100.e11 [PMID: 29111090 DOI: 10.1016/j.jand.2017.08.024]

43 **Park SY**, Boushey CJ, Wilkens LR, Haiman CA, Le Marchand L. High-Quality Diets Associate With Reduced Risk of Colorectal Cancer: Analyses of Diet Quality Indexes in the Multiethnic Cohort. *Gastroenterology* 2017; **153**: 386-394.e2 [PMID: 28428143 DOI: 10.1053/j.gastro.2017.04.004]

44 **Bloomfield HE**, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on Health Outcomes of a Mediterranean Diet With No Restriction on Fat Intake: A Systematic Review and Meta-analysis. *Ann Intern Med* 2016; **165**: 491-500 [PMID: 27428849 DOI: 10.7326/M16-0361]

45 **Schwingshackl L**, Schwedhelm C, Galbete C, Hoffmann G. Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis. *Nutrients* 2017; **9**: [PMID: 28954418 DOI: 10.3390/nu9101063]

46 **Chan DS**, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, Norat T. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *PLoS One* 2011; **6**: e20456 [PMID: 21674008 DOI: 10.1371/journal.pone.0020456]

47 **Tárraga López PJ**, Albero JS, Rodríguez-Montes JA. Primary and secondary prevention of colorectal cancer. *Clin Med Insights Gastroenterol* 2014; **7**: 33-46 [PMID: 25093007 DOI: 10.4137/CGast.S14039]

48 **Carr PR**, Walter V, Brenner H, Hoffmeister M. Meat subtypes and their association with colorectal cancer: Systematic review and meta-analysis. *Int J Cancer* 2016; **138**: 293-302 [PMID: 25583132 DOI: 10.1002/ijc.29423]

49 **Domingo JL**, Nadal M. Carcinogenicity of consumption of red meat and processed meat: A review of scientific news since the IARC decision. *Food Chem Toxicol* 2017; **105**: 256-261 [PMID: 28450127 DOI: 10.1016/j.fct.2017.04.028]

50 **Kobayashi M**, Tsubono Y, Otani T, Hanaoka T, Sobue T, Tsugane S; JPHC Study Group. Fish, long-chain n-3 polyunsaturated fatty acids, and risk of colorectal cancer in middle-aged Japanese: the JPHC study. *Nutr Cancer* 2004; **49**: 32-40 [PMID: 15456633 DOI: 10.1207/s15327914nc4901\_5]

51 **Yu XF**, Zou J, Dong J. Fish consumption and risk of gastrointestinal cancers: a meta-analysis of cohort studies. *World J Gastroenterol* 2014; **20**: 15398-15412 [PMID: 25386090 DOI: 10.3748/wjg.v20.i41.15398]

52 **Orlich MJ**, Singh PN, Sabaté J, Fan J, Sveen L, Bennett H, Knutsen SF, Beeson WL, Jaceldo-Siegl K, Butler TL, Herring RP, Fraser GE. Vegetarian dietary patterns and the risk of colorectal cancers. *JAMA Intern Med* 2015; **175**: 767-776 [PMID: 25751512 DOI: 10.1001/jamainternmed.2015.59]

53 **Pot GK**, Majsak-Newman G, Geelen A, Harvey LJ, Nagengast FM, Witteman BJ, van de Meeberg PC, Timmer R, Tan A, Wahab PJ, Hart AR, Williams MP, Przybylska-Phillips K, Dainty JR, Schaafsma G, Kampman E, Lund EK; FISHGASTRO Study Group. Fish consumption and markers of colorectal cancer risk: a multicenter randomized controlled trial. *Am J Clin Nutr* 2009; **90**: 354-361 [PMID: 19553301 DOI: 10.3945/ajcn.2009.27630]

54 **Zhang X**, Albanes D, Beeson WL, van den Brandt PA, Buring JE, Flood A, Freudenheim JL, Giovannucci EL, Goldbohm RA, Jaceldo-Siegl K, Jacobs EJ, Krogh V, Larsson SC, Marshall JR, McCullough ML, Miller AB, Robien K, Rohan TE, Schatzkin A, Sieri S, Spiegelman D, Virtamo J, Wolk A, Willett WC, Zhang SM, Smith-Warner SA. Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. *J Natl Cancer Inst* 2010; **102**: 771-783 [PMID: 20453203 DOI: 10.1093/jnci/djq107]

55 **Xu J**, Ye Y, Wu H, Duerksen-Hughes P, Zhang H, Li P, Huang J, Yang J, Wu Y, Xia D. Association between markers of glucose metabolism and risk of colorectal cancer. *BMJ Open* 2016; **6**: e011430 [PMID: 27354075 DOI: 10.1136/bmjopen-2016-011430]

56 **Vigneri PG**, Tirrò E, Pennisi MS, Massimino M, Stella S, Romano C, Manzella L. The Insulin/IGF System in Colorectal Cancer Development and Resistance to Therapy. *Front Oncol* 2015; **5**: 230 [PMID: 26528439 DOI: 10.3389/fonc.2015.00230]

57 **Abenavoli L**, Milic N, Luzza F, Boccuto L, De Lorenzo A. Polyphenols Treatment in Patients with Nonalcoholic Fatty Liver Disease. *J Transl Int Med* 2017; **5**: 144-147 [PMID: 29164049 DOI: 10.1515/jtim-2017-0027]

58 **Aune D**, Chan DS, Lau R, Vieira R, Greenwood DC, Kampman E, Norat T. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2011; **343**: d6617 [PMID: 22074852 DOI: 10.1136/bmj.d6617]

59 **Tantamango YM**, Knutsen SF, Beeson WL, Fraser G, Sabate J. Foods and food groups associated with the incidence of colorectal polyps: the Adventist Health Study. *Nutr Cancer* 2011; **63**: 565-572 [PMID: 21547850 DOI: 10.1080/01635581.2011.551988]

60 **Leenders M**, Siersema PD, Overvad K, Tjønneland A, Olsen A, Boutron-Ruault MC, Bastide N, Fagherazzi G, Katzke V, Kühn T, Boeing H, Aleksandrova K, Trichopoulou A, Lagiou P, Klinaki E, Masala G, Grioni S, Santucci De Magistris M, Tumino R, Ricceri F, Peeters PH, Lund E, Skeie G, Weiderpass E, Quirós JR, Agudo A, Sánchez MJ, Dorronsoro M, Navarro C, Ardanaz E, Ohlsson B, Jirström K, Van Guelpen B, Wennberg M, Khaw KT, Wareham N, Key TJ, Romieu I, Huybrechts I, Cross AJ, Murphy N, Riboli E, Bueno-de-Mesquita HB. Subtypes of fruit and vegetables, variety in consumption and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2015; **137**: 2705-2714 [PMID: 26077137 DOI: 10.1002/ijc.29640]

61 **Song M**, Garrett WS, Chan AT. Nutrients, foods, and colorectal cancer prevention. *Gastroenterology* 2015; **148**: 1244-60.e16 [PMID: 25575572 DOI: 10.1053/j.gastro.2014.12.035]

62 **Kaluski DN**, Goldsmith R, Arie OM, Mayer C, Green M. The first Israeli national health and nutrition survey (MABAT) as a policy maker. *Public Health Rev* 2000; **28**: 23-26 [PMID: 11411274]

63 **Zelber-Sagi S**, Lotan R, Shlomai A, Webb M, Harrari G, Buch A, Nitzan Kaluski D, Halpern Z, Oren R. Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. *J Hepatol* 2012; **56**: 1145-1151 [PMID: 22245895 DOI: 10.1016/j.jhep.2011.12.011]

64 **Gemming L**, Ni Mhurchu C. Dietary under-reporting: what foods and which meals are typically under-reported? *Eur J Clin Nutr* 2016; **70**: 640-641 [PMID: 26669571 DOI: 10.1038/ejcn.2015.204]

65 **Khalesi S**, Doshi D, Buys N, Sun J. Validation of a short food frequency questionnaire in Australian adults. *Int J Food Sci Nutr* 2017; **68**: 349-357 [PMID: 27744752 DOI: 10.1080/09637486.2016.1240763]

66 **Nix E**, Wengreen HJ. Social approval bias in self-reported fruit and vegetable intake after presentation of a normative message in college students. *Appetite* 2017; **116**: 552-558 [PMID: 28572071 DOI: 10.1016/j.appet.2017.05.045]

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|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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  Placebo | 47.1%  25.5% | 16.9%  5.4% | \_\_ | 40.9%  24.8% |
| Maintenance | 300 mg 4 weekly  300 mg 8 weekly  Placebo | \_\_ | 44.8%  41.8%  15.9% | 45.2%  31.4%  13.9% | 56.0%  51.6%  19.8% |
| GEMINI 2[11]  2013 | 368 | Induction | 300 mg  Placebo | 31.4%  25.7% | 14.5%  6.8% | \_\_ | \_\_ |
| Maintenance | |  | | --- | | 300 mg 4 weekly  300 mg 8 weekly  Placebo | | 45.5%  43.5%  30.1% | |  | | --- | | 36.4%  39.0%  21.6% | | 28.8%  31.7%  15.9% | |  | | --- | | \_\_ | |
| GEMINI 3[12]  2015 | 315 | Induction | |  | | --- | | 300 mg  Placebo | | \_\_ | 15.2%  12.1% | \_\_ | \_\_ |

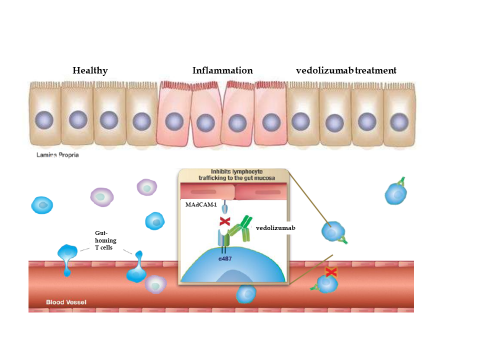
**Table 1 Phase III randomized controlled trials** **of vedolizumab in patients with ulcerative colitis and Crohn’s disease**

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.

**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 *et al*[15,16] (France), 2016-2017 | 294 | 173 | 121 |
| Eriksson *et al*[19] (Sweden), 2017 | 246 | 147 | 991 |
| Baumgart *et al*[17] (Germany), 2016 | 212 | 97 | 115 |
| Dulai *et al*[23] (United States, multicentre), 2016 | 212 | 212 | - |
| Kopylov *et al*[20] (Israel), 2017 | 204 | 130 | 741 |
| Shelton *et al*[24] (United States, Boston), 2015 | 172 | 107 | 651 |
| Macaluso *et al*[22] (Italy, Sicily), 2018 | 163 | 84 | 79 |
| Allegretti *et al*[26] (United States, Boston), 2017 | 136 | 96 | 40 |
| Stallmach *et al*[18] (German Registry), 2016 | 127 | 67 | 60 |
| Vivio *et al*[25] (United States, Saint Louis), 2016 | 102 (51)2 | 30 | 21 |
| Samaan *et al*[21] (United Kingdom), 2017 | 50 | 27 | 231 |
| 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 1 Vedolizumab targets the α4β7 integrin, preventing leucocyte translocation from the blood into the inflamed gut tissue.** MadCAM-1: mucosal addressin cell adhesion molecule.

A

B

**Figure 2 Real-world studies with vedolizumab in patients with ulcerative colitis (A) and Crohn’s disease (b): results at week 14.**