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PRODUCT REVIEW

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A product review of vedolizumab in inflammatory bowel disease

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ABSTRACT

Vedolizumab is a monoclonal antibody to the α4β7 integrin that selectively reduces intestinal lymphocyte trafficking, thereby providing a safe and effective treatment option for patients with inflammatory bowel disease (IBD). This product review outlines the unique mechanism of vedolizumab in addition to efficacy, safety, pharmacokinetic and pharmacodynamic data from clinical trials, observational studies and meta-analyses. Vedolizumab has been shown to be effective as a first- or second-line induction and maintenance therapy in both ulcerative colitis (UC) and Crohn's disease (CD). Prolonged induction therapy may increase efficacy, particularly in tumor necrosis factor-alpha-exposed CD patients. To date, no drug-specific safety signals have been identified. In addition to the presence of an apparent exposure-response relationship, vedolizumab has demonstrated consistent pharmacodynamic effects on α4β7, mucosal vascular addressin cell adhesion molecule 1 and other cell adhesion molecules. Future efforts should focus on identifying predictive biomarkers capable of guiding personalized IBD treatment with vedolizumab.

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Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic idiopathic inflammatory bowel diseases (IBD). In North America, UC has an incidence of up to 23.1 per 100,000 person-years and a prevalence of 139.8 to 286.3 per 100,000 persons.[1] Patients typically present with rectal bleeding, diarrhea and abdominal pain. Despite the best available pharmacotherapy, up to 25% of patients experience a refractory disease course.[2] Given that long-term, uncontrolled inflammation is associated with an increased risk of colorectal cancer, approximately 30% of these patients ultimately require colectomy.[3]

The annual incidence and prevalence of CD in North America have been reported to be as high as 23.8 per 100,000 person-years and 318.5 per 100,000 persons, respectively.[1] While inflammation is limited to the mucosa of the large bowel in UC, any location in the gastrointestinal tract can be affected by CD and transmural involvement is common. Consequently, CD patients are predisposed to develop penetrating complications such as strictures and fistulas.[4–6] Surgery is required in up to 80% of CD patients due to lack of response and management of disease-related complications.[7]

Clinical symptoms of IBD vary according to disease phenotype and location. For example, inflammatory disease often manifests as diarrhea and bleeding, strictures may cause bowel obstructions with abdominal pain, and perianal fistulas are frequently associated with leakage, pain, and abscess formation. Extra-intestinal manifestations (EIMs), including arthralgias, aphthous stomatitis, and uveitis can occur in both UC and CD, although they are more common in the latter.[8,9]

Moderate-to-severe UC is often treated with a tumor necrosis factor-alpha (TNF-α) antagonist (infliximab, adalimumab and golimumab) – administered either as monotherapy or in combination with an immunosuppressant (thiopurines or methotrexate) – or the Janus kinase (JAK) 1/3 inhibitor tofacitinib. Similarly, in moderate-to-severe CD, TNF-α antagonist (infliximab, adalimumab and certolizumab pegol) monotherapy, combination therapy or the interleukin (IL) 12/23 antagonist ustekinumab are utilized. Corticosteroids are effective for inducing clinical remission, however it is recommended that they be reserved for short-term rescue therapy.[10]

Unfortunately, IBD patients receiving TNF-α antagonists, ustekinumab and tofacitinib are prone to experience either primary non-response or secondary loss of response.[11] Since a substantial proportion of patients require alternative therapeutic options, coupled with the fact that these drugs increase the risk of developing serious infection, there is a need for novel IBD therapies with improved safety profiles.

Vedolizumab (Entyvio, Takeda Pharmaceutical Company Ltd, Japan; previous versions: LDP02, MLN02, and MLN0002) is a humanized IgG_1 monoclonal antibody directed against the α4β7 integrin that selectively blocks leukocyte binding to gut endothelium. Approved for the treatment of moderate-to-severe UC and CD by the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) in 2014, vedolizumab may be used as a first-line biologic agent or in patients who are refractory to TNF-α antagonist therapy.[12,13] This product review outlines the unique mechanism of action of vedolizumab, and summarizes clinical, pharmacokinetic, and pharmacodynamic data from clinical trials and real-world cohorts.

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Mechanism of action and mechanistic rationale

Natalizumab (Tysabri, Biogen, Cambridge, MA), a humanized monoclonal antibody that inhibits leukocyte migration to the gut by binding to the α4 subunit of α4β1- and α4β7-integrins on T cells, was the first approved anti-integrin therapy for IBD. While effective in treating moderate-to-severe CD,[14,15] clinical application of natalizumab has been limited by an increased risk of progressive multifocal leukoencephalopathy (PML). A rare but fatal disease, PML occurs when α4β1-vascular cell adhesion molecule 1 (VCAM-1) interactions are impaired. This process disrupts immune surveillance in the kidney, blocks T-cell trafficking to the brain, and ultimately leads to reactivation of the John Cunningham virus.[16–18]

Another anti-integrin therapy, vedolizumab is a humanized IgG_1 monoclonal antibody that recognizes a conformational epitope of the α4β7 integrin heterodimer. A transmembrane cell adhesion protein, α4β7 is expressed on naïve T and B cell lymphocytes as well as on innate immune cells.[19,20] The ligand for α4β7 (mucosal vascular addressin cell adhesion molecule 1 [MAdCAM-1]) is found primarily in endothelial cells within the gastrointestinal track and gut-associated lymph tissue.[21] Thus, the effect of vedolizumab is restricted to these areas. Since vedolizumab has no affinity for the α4 subunit, α4β1-VCAM-1 interactions remain uninhibited and there is no theoretical risk of PML.[22–25]

Pre-clinical development of vedolizumab

Pre-clinical studies initially evaluated murine antibodies targeting various cell adhesion molecules in the cotton top tamarin (CTT), a primate known to spontaneously develop a disease resembling ulcerative colitis. In a randomized, blinded trial in CTTs, the anti-a4 integrin monoclonal antibody was shown to significantly reduce histologic disease activity compared to placebo ($P = 0.005$).[26] Similarly, another CTT study found that a murine monoclonal antibody to α4β7 significantly reduced diarrhea and histologic disease activity within seventy-two hours compared to placebo. Furthermore, no toxicity was observed in this study at day 20. Neither liver function, renal function nor leukopenia were observed. A trend toward lymphocytosis was observed in CTTs on therapy compared to placebo.[27] Long-term safety studies in animals have not been performed.

Clinical development of vedolizumab

The clinical development of vedolizumab began with a phase 1b/2a proof-of-concept randomized controlled trial (RCT) in which 29 patients with moderate-to-severe UC received single doses of LPD-02 (0.15 mg/kg subcutaneously, or 0.15, 0.5, or 2.0 mg/kg intravenously), a humanized monoclonal antibody to α4β7 derived from an NS0 mouse myeloma cell line, or placebo (Table 1). Forty percent of patients who received 0.5 mg/kg of LPD-02 achieved deep remission.[28] Conversely, none of the placebo patients achieved this outcome. This trial did not demonstrate any signal for adverse events.

A phase 2 RCT of was initiated in 181 UC patients using the same LPD-02 compound. Patients with moderate-to-severe disease received MLN02 0.5 mg/kg, 2.0 mg/kg, or placebo intravenously on days 1 and 29.[29] Six weeks after starting therapy, higher rates of clinical (0.5 mg/kg: 33%, 19/58; 2 mg/kg: 32%, 19/60; placebo: 14%, 9/63, $p = 0.03$) and endoscopic (0.5 mg/kg: 28%, 16/58; 2 mg/kg: 12%, 7/60; placebo: 8%, 5/63, $p = 0.007$) remission were observed in all treatment groups compared to placebo. However, a substantial proportion of patients (44%, 52/118) formed anti-drug antibodies (ADAs) by week eight, with the majority of ADA-positive patients demonstrating high titers (54%, 28/52). The presence of ADAs was associated with reduced drug concentration and clinical remission rates similar to placebo. To reduce the immunogenic potential of MLN-02, a new formulation (vedolizumab) was developed using a Chinese hamster ovary (CHO) cell-based expression system. The idiotype of the original molecule was unaffected by this change; and a highly similar *in vitro* potency of the product was observed with the novel processing technology.[30] Nevertheless, manufacturing changes in the production of monoclonal antibodies can influence pharmacologic properties *in vivo*. For example, modifications to the glycosylation pattern may affect immunogenic chracteristics.[35] Therefore, a dose-ranging clinical trial in UC patients was conducted to study the clinical

Table 1. Randomized, placebo-controlled trials of vedolizumab.

Study	Formulation	Patients	Phase	Duration	Clinical Endpoints	Notes
Feagan 2000[28]	LDP-02	Moderate-severe UC N = 29	1b/2a	30 days	Mayo Clinic Score Endoscopic response Endoscopic remission	-Reported in abstract form only
Feagan 2005[29]	LDP-02/ MLN02	Moderate-severe UC N = 181	2	6 weeks	Clinical response Clinical remission Endoscopic response Endoscopic remission	-Patients had received no therapy or mesalamine prior to study
Parikh 2012[30]	Vedolizumab	Mild UC N = 47	2	253 days	Clinical response Fecal calprotectin	-Study not powered for efficacy
Feagan 2013[31] *GEMINI 1*	Vedolizumab	Moderate-severe UC N = 895	3	6 weeks 52 weeks	Clinical response Clinical remission Mucosal healing	-Integrated induction and maintenance trials -<50% patients TNF antagonist-exposed
Feagan 2008[32]	LDP-02/ MLN0002	Moderate-severe CD N = 185	2	57 days	Clinical response Clinical remission	-Concomitant mesalamine and antibiotics were permitted if patient was stable for 2 weeks prior to study
Sandborn 2013 *GEMINI 233*	Vedolizumab	Moderate-severe CD N = 1115	3	6 weeks 52 weeks	Clinical response Clinical remission	-Integrated induction and maintenance trials -<50% patients TNF antagonist-exposed
Sands 2014 *GEMINI 334*	Vedolizumab	Moderate-severe CD N = 416	3	10 weeks	Clinical response Clinical remission	-Patients had failure to respond/loss of response or intolerance to corticosteroids, immunosuppressants or TNF antagonists within 5 years

pharmacology, safety, and efficacy of CHO cell-derived vedolizumab, given at more frequent and higher doses than in previous studies. In this phase 2 study, patients with mild-to-moderate UC received either vedolizumab (2.0, 6.0, or 10.0 mg/kg) or placebo on days 1, 15, 29, and 85.[30] Clinical response rates in treatment groups exceeded 50% between day 29 and day 253, while clinical response rates ranged between 22% and 33% in the placebo group. Furthermore, clinical remission rates were numerically higher in vedolizumab- versus placebo-treated patients (53%-79% vs. 25%-50%, respectively). It should be noted that formal efficacy analyses were not performed as the study was designed to evaluate safety and immunogenicity. Immunogenicity rates were found to be low (11%, 4/37) and no infusion reactions were reported. Thirty-eight patients continued into an open-label extension (OLE) study comprised of 56 UC and 19 CD patients. High rates of clinical remission (88%) were observed at day 491.[36]

The GEMINI 1 trial assessed the efficacy and safety of vedolizumab as induction and maintenance therapy in moderate-to-severe UC.[31] A single dose of vedolizumab (300 mg IV) or placebo was administered at days 1 and 15. At week 6, there was a statistically significant difference in clinical response (47.1% vs. 25.5%, $p < 0.001$), clinical remission (16.9% vs. 5.4%, $p = 0.001$) and mucosal healing (40.9% vs. 24.8%, $p = 0.001$) rates between the vedolizumab and placebo groups. Week 6 clinical responders, in addition to patients who responded to open-label vedolizumab induction therapy, were enrolled in the maintenance trial and received placebo or vedolizumab every 4 or 8 weeks until week 52. The vedolizumab groups had superior clinical remission (every 8 weeks: 41.8%, $p < 0.001$; every 4 weeks: 44.8%, $p < 0.001$; placebo: 15.9%) and mucosal healing rates compared to placebo. A long-term OLE observed high clinical response (98%) and remission (90%) rates at week 248 among patients who finished the GEMINI 1 maintenance trial.[37]

The first trial to evaluate vedolizumab in CD was a phase 2 RCT in which patients with moderate-to-severe disease were treated with MLN0002 2.0 mg/kg, MLN0002 0.5 mg/kg, or placebo intravenously at days 1 and 29.[32] Although the time required to achieve clinical response was shorter in the 2 mg/kg treatment group compared to placebo (17 vs. 42 days, $p = 0.04$), clinical response rates in treatment groups were only higher at day 15 but not days 8, 29, 43, and 57. However, day 57 clinical response ($p = 0.05$) and clinical remission rates at days 15, 29 and 57 ($p = 0.009$, 0.047, and 0.049, respectively) were higher in the 2 mg/kg treatment group compared to placebo. In an OLE bridging study, a high proportion of CD patients achieved clinical remission (40%) and response (70%) by day 491.[36]

GEMINI 2, a phase 3 RCT of vedolizumab in moderately-to-severely active CD, had an analogous design to GEMINI 1.[33] Although the rate of clinical response (defined as a minimum 100-point decrease in CDAI score) was similar between the vedolizumab and placebo groups (31.4% vs. 25.7%, $p = 0.23$), clinical remission rates were significantly higher with vedolizumab (14.5% vs. 6.8%, $p = 0.02$). Likewise, clinical remission rates were higher in the treatment groups compared to placebo (every 8 weeks: 39%, $p < 0.001$, every 4 weeks: 36.4%, $p = 0.004$, placebo: 21.6%) during the maintenance trial.

Given that a similar proportion of patients in the vedolizumab and placebo groups experienced clinical response in the GEMINI 2 trial, GEMINI 3 was designed to evaluate the efficacy of induction therapy at a later time point (week 10), and the primary analysis was performed in patients who had failed or were intolerant to TNF-α antagonists.[34] The clinical remission rates was similar between groups at week 6 ($p = 0.433$), but higher in the vedolizumab groups by week 10 (26.6% vs. 12.1%, $p = 0.001$). Furthermore, patients treated with vedolizumab had higher week 6 ($p = 0.001$) and week 10 (46.8% vs. 24.8%, $p < 0.0001$) CDAI-100 response rates.

A secondary analysis in TNF-α antagonist naïve CD patients demonstrated that vedolizumab was statistically superior to placebo for induction of clinical remission at week 10 (35.3% vs. 16.0%, $p = 0.025$). A long-term OLE study in patients enrolled in the GEMINI 2 trial also found high clinical response (95%) and remission (89%) rates in those who finished the maintenance trial with a consistent benefit observed between weeks 52 and 248.[38]

Real-world use of vedolizumab

Clinical use of vedolizumab has been widespread in both UC and CD since regulatory approval in 2014, and data from multiple real-world cohorts are now available.[39] In UC, pooled efficacy data from nine open-label cohorts (n = 571) identified week 6 clinical response and remission rates of 43% (95% confidence interval [CI] 37–49%) and 25% (95% CI 12–45%), respectively.[40] Furthermore, the maintenance of clinical remission rate was approximately 40% at one year. However, evidence suggest that approximately 40% of patients discontinue vedolizumab therapy for a variety of reasons (e.g. loss of response, intolerance, patient or physician preference or access to medications).[41,42]

The Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif (GETAID) reported data from 121 patients in 41 centers in France. All patients had failed TNF-α antagonist therapy and the rate of corticosteroid-free clinical remission at week 14 was 36% after initiating vedolizumab therapy.[43]

A cohort study of 115 UC patients from Germany demonstrated week 6 and week 14 clinical remission rates of 11.3% and 23.5%, respectively.[44] Nearly three quarters of the patients were TNF-α antagonist naïve, and higher clinical remission rates were observed in these patients compared to those with prior TNF-α antagonist exposure (39.3 vs.18.5%, $p = 0.023$).

The VICTORY (Vedolizumab for Health Outcomes in Inflammatory Bowel Disease) consortium evaluated 321 vedolizumab-treated UC patients in the United States. Most patients (71%) in this cohort had previously failed TNF-α antagonist therapy. Cumulative rates of clinical and endoscopic remission were 51% and 41% at 12 months, respectively.[45] Prior TNF-α antagonist exposure was associated with lower clinical (hazard ratio [HR] 0.53, 95% CI 0.38–0.75) and endoscopic remission rates (HR 0.51, 95% CI 0.29–0.88).

In CD, a pooled analysis (n = 994) reported week 6 clinical response and remission rates of 54% (95% CI 41–66%) and 22% (95% CI 13–35%), respectively.[40] The pooled week 52 clinical remission rate was 32% (95% CI 12–62%).

A total of 212 patients with moderate-to-severe CD were analyzed by the VICTORY consortium.[46] Clinical remission, mucosal healing, and deep remission rates at 12 months were 35%, 63%, and 26%, respectively. In this cohort, prior TNF-α antagonist exposure had a HR of 0.40 (95% CI 0.20–0.81) for treatment response in comparison to TNF-α antagonist-naïve patients[44,47–49] which is consistent with results of other studies.[42,46,48,50]

Safety of vedolizumab

In GEMINI 1, the between-group differences in adverse events (AEs) and serious adverse events (SAEs) rates were not statistically significant. Of the 154 patients enrolled in the OLE study, 17 experienced AEs that led to discontinuation. While 44 SAEs were reported in the OLE, a minority (7/44) were considered to be drug-related.[37] In the GEMINI 2 trial SAEs occurred more often (24.4%) in vedolizumab-treated patients relative to placebo (15.3%).[33] Four deaths occurred in the vedolizumab group compared with one in the placebo group. However, it should be acknowledged that these rates were not exposure adjusted. In the GEMINI 3 trial[34] patients receiving vedolizumab and placebo experienced similar rates of AEs, with SAEs occurring in fewer than 1% of patients. While 41 CD patients in the GEMINI OLE study experienced SAEs, all but three of these were deemed drug-related.[38] In total, 15 patients discontinued treatment due to AEs.

A systematic review and meta-analysis of RCTs that included 1122 UC patients reported similar SAE rates for vedolizumab- and placebo-treated patients (12% [97/775] vs. 12% [43/347] RR = 1.02; 95% CI, 0.73–1.42).[51] Another pooled analysis of vedolizumab safety data based on six RCTs enrolling a total of 2830 UC and CD patients demonstrated lower exposure-adjusted incidence rates for AEs and SAEs in vedolizumab compared to placebo groups.[52] Prolonged exposure to vedolizumab did not appear to increase the AE and SAE rates. Furthermore, no between-group difference was observed with respect to infection and serious infection rates. Serious infections (including *Clostridium difficile* infection) occurred in less than 0.6% of patients. The VICTORY consortium reported safety data from 1087 patients (650 with CD and 437 with UC). The SAE rate was 5.9 per 100 patient years of exposure (PYE) while the infection rate was 7.9 per 100 PYE.[53] No cases of PML have been reported in any controlled trials or OLE studies. In July 2018, one HIV-positive CD patient receiving vedolizumab developed PML, which an adjudication committee attributed to HIV in combination with prolonged immunosuppressant medication use. A systematic review of safety data from six observational open-label cohorts[54] comprised of 1049 patients found a total non-infectious AE rate of 15.8%, with the most common individual AE being arthralgias (3.1%). These findings are consistent with data reported by the VICTORY consortium. Although observational studies suggest that vedolizumab use results in post-operative complications[55–58], safety analyses from the GEMINI trials and a meta-analysis of observational studies do not support this association.[59,60]

Subcutaneous formulation

Recently, a phase 3 RCT of a novel subcutaneous vedolizumab formulation was performed in UC (VISIBLE 1). After receiving an open-label IV vedolizumab induction dose identical to that in the GEMINI trials, 216 patients were randomized to vedolizumab 108 mg subcutaneously every 2 weeks, vedolizumab 300 mg IV every 8 weeks, or placebo for up to 52 weeks. Clinical remission rates at week 52 were higher with both subcutaneous vedolizumab (46.2%, 49/106) and IV vedolizumab (42.6%, 23/54) compared to placebo (14.3%, 8/56, $p < 0.001$). Additionally, mucosal healing rates were higher with subcutaneous vedolizumab (56.6%, 61/108) relative to placebo (21.4%, 12/56, $p < 0.001$). Consistent ADA rates were demonstrated with both SC (5.7%) and IV vedolizumab (5.6%).[61]

Immunogenicity

The first study to report immunogenicity rates associated with the current formulation of vedolizumab was the open-label "bridging" study. Four percent (3/72) of patients developed ADAs, and one patient experienced an infusion reaction.[36] In GEMINI 1, ADAs were detected in 3.7% of patient samples. However, only 1.0% of patients had persistently positive ADAs at a consecutive measurement. Concomitant immunosuppressive therapy was associated with decreased immunogenicity. Two patients experienced clinically-important infusion reactions that were ADA-related. The GEMINI 2 and 3 trials had comparably low ADA rates and effects of concomitant immunosuppressive therapy. Of note, these trials measured ADAs using assays that were not drug-tolerant, which have limited ADA detection in the presence of vedolizumab.[62]

Therapeutic drug monitoring with vedolizumab

There is emerging evidence supporting an association between serum vedolizumab concentration and efficacy outcomes. In the GEMINI 1 and 2 trials, it was observed that increased vedolizumab serum concentrations were associated with higher clinical response and remission rates.[31,33] Detailed exposure-response analyses of these clinical studies found that the probability of achieving clinical remission, clinical response, and mucosal healing in patients with UC at week 6 increased by 31%, 34%, and 43% respectively, from concentration quartile 1 to 4.[63,64] A similar exposure-response for clinical remission was observed for patients with CD, although the trend was less pronounced in this population. Factors associated with a higher probability of clinical remission included higher serum albumin, lower fecal calprotectin (in patients with UC), lower C-reactive protein (CRP) concentrations (in patients with CD), and no prior TNF-α exposure.[63,64] The positive relationship between vedolizumab serum concentration and efficacy outcomes has been observed in several cohort studies.[65–71] In a study by Dreesen and colleagues that included 179 patients (66 UC, 113 CD), thresholds of >30.0 μg/mL at week 2, >24.0 μg/mL at week 6, and >14.0 μg/mL during maintenance therapy were associated with a higher probability of attaining effectiveness endpoints.[70] Similarly, in a study by Yacoub et al. (n = 82; 43 UC, 39 CD)

a vedolizumab serum concentration of >18 μg/mL at week 6 was associated with mucosal healing in the first year of therapy.[68] Since the aforementioned studies were retrospective, the causal relationship between exposure and response cannot be assessed. Furthermore, comparison of absolute concentrations across different studies is hampered by a lack of cross-comparative studies evaluating the operating characteristics of vedolizumab serum concentration assays.

Pharmacokinetics of vedolizumab

The pharmacokinetic (PK) profile of vedolizumab was evaluated in healthy volunteers and patients with IBD using a 2-compartment model with parallel components of linear and nonlinear elimination.[72] The linear elimination half-life of vedolizumab was estimated to be 25.5 days, with linear clearance values of 0.159 L/day and 0.155 L/day in patients with UC and CD, respectively. Interindividual variability was partly explained by differences between patients in albumin concentration and body weight. Since albumin and CRP were strongly correlated, any potential effect of CRP on linear vedolizumab clearance was already accounted for in the model by incorporating albumin. In contrast to observations for other monoclonal antibodies (i.e. infliximab)[73] use of concomitant immunosuppressants and presence of ADAs did not affect clearance, but inferences regarding this impact are limited by the low rate of ADAs observed in the GEMINI trials. Interindividual variabilities (% coefficient of variation [CV]) for the final population PK model were 35% for linear clearance and 19% for volume of distribution; residual variance was 24%.

Using a MAdCAM-1 assay, it was observed that α4β7 receptor occupation was maintained at serum vedolizumab concentrations considered to be subtherapeutic.[72] Full saturation is expected to occur at vedolizumab serum concentrations of 1 μg/mL, based on the EC_{50} estimate of 0.093 μg/mL from the population pharmacokinetic-pharmacodynamic model. This raises the question whether receptor occupation is necessary but not sufficient for efficacy. Future studies are needed to further examine receptor occupation and drug exposure in mucosal tissue.

Pharmacodynamics of vedolizumab

A substantial proportion of patients do not respond to vedolizumab. Thus, markers are needed to determine appropriate candidates for treatment initiation and continuation.[31,33,51,66,74–77] Understanding the pharmacodynamic effect of vedolizumab may help to identify predictive biomarkers capable of facilitating clinical decision making.

Studies have assessed the effect of vedolizumab on its target, α4β7, and its ligand, s-MAdCAM1. Transmembrane α4β7 expression has been evaluated using flow cytometry on peripheral blood mononuclear cells (PBMCs) in vedolizumab-treated patients.[78,79] Importantly, transmembrane α4β7 has consistently demonstrated to have near-complete occupancy during both induction and maintenance therapy.[66] Studies have also demonstrated that vedolizumab therapy is associated with increased circulating lymphocytes.[26] Consistent with this finding and evidence that lymphocyte trafficking to the gut is mediated by α4β725 symptom reduction is associated with increased expression of α4β7.[79] Furthermore, a recent study in 32 UC patients found that soluble α4β7 consistently increased compared to baseline levels in all vedolizumab treated patients. Additionally, α4β7 concentration increased more rapidly and was higher in those achieving remission.[80] Another study utilizing flow cytometry in UC patients demonstrated that those achieving clinical response had higher baseline surface α4β7 expression on peripheral lymphocytes prior to therapy and more T cells in which transmembrane α4β7 was bound to vedolizumab.[78]

In the context of inflammatory pathways, TNF-α induces expression of transmembrane MAdCAM-1 in gastrointestinal tissue.[81,82] Based on flow cytometry, vedolizumab administration completely inhibits MAdCAM-1 binding to α4β7 in IBD patients.[30,83] Furthermore, pharmacodynamic changes in a soluble form of MAdCAM (s-MAdCAM-1) with therapy has been demonstrated. s-MAdCAM1 is detectable in serum and may provide an indirect measure of MAdCAM-1 expression.[84] In a randomized phase 2 study, a humanized monoclonal antibody against MAdCAM-1, PF-00547659, showed efficacy in the treatment of moderate to severely active ulcerative colitis with a dose-dependent reduction in s-MAdCAM1. There was 90–98% suppression of s-MAdCAM-1 at the higher treatment doses.[85] A retrospective study in both CD and UC patients treated with vedolizumab demonstrated that clinical remission was associated with undetectable s-MAdCAM-1 concentrations. s-MAdCAM-1 concentrations decreased in all patients, but baseline s-MAdCAM-1 concentrations were not associated with outcomes.[86] A recent study in UC patients showed similar findings but also demonstrated a more rapid decline in s-MAdCAM-1 those achieving remission.[80]

Several studies also support increased compensatory expression of alternative cell adhesion molecules with vedolizumab therapy. Vedolizumab-treated UC patients with worse outcomes have higher increases in α4β1+ on T cells.[79] Consistent with this, a recent study in UC patients demonstrated soluble transmembrane VCAM-1 and soluble intracellular adhesion molecule concentrations declined more rapidly in patients achieving remission.[80] In CD patients, α4β1 measurement increased in intestinal samples of patients receiving vedolizumab and in vivo homing of CD T cells to the ileum was not reduced by α4β7 blockade.[87]

Expert opinion

Vedolizumab is an effective therapy for achieving durable remission in both patients with UC and CD. Furthermore, it has a favorable safety profile. Although the efficacy of vedolizumab is affected by prior TNF antagonist exposure, future studies are needed to delineate the use of predictive biomarkers in guiding patient selection towards the most effective first-line or subsequent vedolizumab therapy. Furthermore, future research is needed to determine the effects of central compartment exposure in relation to target organ tissue, given the advent of locally-acting biologic medications.[88]

Conclusions

Vedolizumab has a unique, gut-specific mechanism of action that confers both a favorable efficacy and safety profile in UC and CD patients. A substantial amount of published data originating from both clinical trials and large real-world cohorts is available. Observed immunogenicity rates with vedolizumab are low, and an exposure-response relationship is apparent. Vedolizumab therapy has consistent pharmacodynamic effects on α4β7, MAdCAM-1 and other cell adhesion molecules, which may serve as biomarkers of response. and ultimately enable personalized vedolizumab management in patients with IBD.

Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
CD	Crohn's disease
CHO	Chinese hamster ovary cell
CI	Confidence interval
CRP	C-reactive protein
EIM	Extra-intestinal manifestation
EMA	European Medicines Agency
FDA	Food and Drug Administration
IBD	Inflammatory bowel disease
IL	Interleukin
JAK	Janus kinase
PML	Progressive multifocal leukoencephalopathy
MAdCAM-1	Mucosal vascular addressin cell adhesion molecule 1
PYE	Patient years of exposure
RCT	Randomized controlled trial
SAE	Serious adverse event
TNF-α	Tumor necrosis factor-alpha
UC	Ulcerative colitis
VCAM-1	vascular cell adhesion molecule 1

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