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Lauren N. Cherry
Virginia Commonwealth University

Nancy S. Yunker
Virginia Commonwealth University

Erika R. Lambert
Virginia Commonwealth University

DaleMarie Vaughan
Virginia Commonwealth University

Denise K. Lowe
Virginia Commonwealth University, dlowe@mcvh-vcu.edu

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Lauren N. Cherry, Nancy S. Yunker, Erika R. Lambert, DaleMarie Vaughan and Denise K. Lowe

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***Abstract*:** Ulcerative colitis (UC) and Crohn's disease (CD) are chronic, relapsing inflammatory bowel diseases associated with significant morbidity. Conventional therapies for these diseases include corticosteroids, aminosalicylates, immunomodulators, and monoclonal antibodies. Over the years tumor necrosis factor (TNF)-α antagonists alone or in combination with other therapies have emerged as the cornerstone of treatment for induction and maintenance of remission of moderate to severe UC and CD. Unfortunately, some patients with moderate to severe UC and CD are unable to attain or maintain remission with TNF-α antagonist treatment. Vedolizumab, a humanized monoclonal antibody, is the first integrin receptor antagonist approved that selectively antagonizes α4β7 gastrointestinal integrin receptors. US Food and Drug Administration approval is for treatment of patients with moderate to severe active UC and CD who have inadequate response with, lost response to, or are intolerant to a TNF-α antagonist or an immunomodulator; or have inadequate response with, are intolerant to, or demonstrate dependence on corticosteroids. When administered according to approved dosing in patients with moderate to severe CD and UC, vedolizumab induces clinical response rates up to 31.4% and 47.1% at week 6, and clinical remission rates up to 39% and 41.8% at week 52, respectively. Serious adverse events reported with vedolizumab include serious infections, malignancies, and anaphylaxis. Since vedolizumab is gastrointestinal selective, to date, it has not shown evidence of causing progressive multifocal leukoencephalopathy; however, postmarketing studies monitoring for this adverse effect are ongoing. Further assessment of vedolizumab earlier in the course of these diseases and in combination with other therapies is warranted.

Keywords: Crohn's disease, inflammatory bowel disease, ulcerative colitis, vedolizumab

Correspondence to:
Denise K. Lowe, PharmD, BCPS
Virginia Commonwealth University Health System, and Virginia Commonwealth University School of Pharmacy, 401 North 12th Street, PO Box 980042, Richmond, VA 23298, USA
dlowe@mcvh-vcu.edu

Lauren N. Cherry, PharmD
Virginia Commonwealth University Health System, Richmond, VA, USA

Nancy S. Yunker, PharmD, FCCP, BCPS
Erika R. Lambert, PharmD
Virginia Commonwealth University School of Pharmacy, Richmond, VA, USA

DaleMarie Vaughan, PharmD
Virginia Commonwealth University Health System, Richmond, VA, USA

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic, relapsing inflammatory bowel diseases (IBDs) [Lichenstein *et al*. 2008; Kornbluth *et al*. 2010]. Differences between UC and CD include bowel wall involvement (mucosal *versus* transmural), patterns of inflammation (continuous *versus* noncontinuous), location of inflammation (primarily rectum and colon *versus* entire gastrointestinal tract), and absence or presence of fistulas. Common symptoms for these diseases include diarrhea, abdominal tenderness or pain, rectal bleeding, and possible weight loss [Lichenstein *et al*. 2008; Kornbluth *et al*. 2010; Cosnes *et al*. 2011; Danese *et al*. 2014]. In the United States, the incidence and prevalence rates for UC and CD have been increasing and are reported as 7.9 and 8.8 cases per 100,000 person years and 263 and 241 per 100,000 adults diagnosed with UC and CD, respectively [Kappelman *et al*. 2013; Long *et al*. 2014].

The exact causes of UC and CD are unknown. Evidence suggests that environmental factors, genetic predisposition, and changes in the gastrointestinal microbial flora may trigger an overly aggressive immune response leading to elevations of proinflammatory mediators [e.g. interferon γ, certain interleukins and tumor necrosis factor α (TNF-α)] [Abrahm and Cho, 2009]. These mediators recruit additional leukocytes, which results in a sustained inflammatory response and tissue

destruction [Abrahm and Cho, 2009; Zhang and Li, 2014]. Both UC and CD can be categorized as mild, moderate or severe, and characterized by exacerbations and remissions in most patients [Lichenstein *et al.* 2008; Kornbluth *et al.* 2010]. Treatment goals for patients with UC and CD include improving symptoms, inducing and maintaining remission, and minimizing drug toxicities [Lichenstein *et al.* 2008; Kornbluth *et al.* 2010; D'Haens *et al.* 2014].

Conventional therapies for UC and CD target various cell mediators and include corticosteroids, aminosalicylates, immunomodulators, and monocolonal antibodies (Table 1) [Sharon *et al.* 1978; Horn *et al.* 1991; Poldosky, 2002; Rousseaux *et al.* 2005; Stolfi *et al.* 2008; Kornbluth *et al.* 2010; Terdiman *et al.* 2013; Marinkovic *et al.* 2014]. Over the years, TNF-α antagonists alone or in combination with other therapies have emerged as the cornerstone of treatment for induction and maintenance of remission of moderate to severe UC and CD. Unfortunately, more than 60% of patients with UC and CD evaluated in clinical trials were unable to attain or maintain remission at week 52 after TNF-α antagonist initiation [Hanauer *et al.* 2002; Rutgeerts *et al.* 2005; Colombel *et al.* 2007]. Moreover, it is documented that patients whose condition has failed to respond to one TNF-α antagonist have a markedly reduced response rate when treated with a second TNF-α antagonist [Sandborn, 2007; Sandborn *et al.* 2007]. For these reasons, newer agents are needed to treat patients with moderate or severe UC or CD that is unresponsive, refractory, or patients who are unable to tolerate traditional treatment options.

The integrin receptor and vedolizumab

Integrin receptors have emerged as targets for newer therapies to treat patients with IBD. Integrins are composed of two subunits, α and β, and are found on certain B and T lymphocytes. At least 24 unique integrins have been identified in various combinations of α and β subunits. Although not exclusive, those associated with cell migration into the gastrointestinal tissue include α2β2, α4β1, and α4β7. By antagonizing these receptors there is inhibition of lymphocyte migration to the gastrointestinal mucosa during the inflammatory process [Gosh and Panaccione, 2010; Jovani and Danese, 2013]. Natalizumab, the first integrin receptor antagonist approved by the US Food and Drug Administration (FDA), targets both the α4β1 and α4β7 integrins. Its initial US approval was for multiple sclerosis and later expanded to moderate to severe CD. Though deemed effective for CD, its use has been limited in this patient population because it can cause reactivation of the John Cunningham virus and possibly cause progressive multifocal leukoencephalopathy (PML), a serious central nervous system infection that often results in mortality [Center for Drug Evaluation and Research, 2011; Biogen Idec Inc., 2013].

Vedolizumab (Entyvio; Takeda Pharmaceuticals, Deerfield, IL, USA), also known as MLN0002, is a humanized monoclonal antibody that selectively antagonizes α4β7 gastrointestinal integrin receptors. It was approved by the FDA in May 2014, and is indicated for the treatment of patients with moderate to severe active UC and CD who have an inadequate response with, lost response to, or are intolerant to a TNF-α antagonist or an immunomodulator; or have an inadequate response with, are intolerant to, or demonstrate dependence on corticosteroids [Takeda Pharmaceuticals America Inc., 2014]. Because of vedolizumab's receptor selectivity and improved safety profile over natalizumab, it is considered as a new treatment option for patients with UC and CD. The purpose of this manuscript is to review the pharmacology, pharmacokinetics, efficacy, adverse effects (AEs), drug–drug interactions, dosage and administration, cost, and place in therapy of vedolizumab.

Pharmacology

Vedolizumab is a humanized, anti-α4β7 integrin, monoclonal antibody [Takeda Pharmaceuticals America Inc., 2014]. The α4β7 integrin is a cell-surface glycoprotein that is expressed on circulating B and T lymphocytes. It binds to adhesion molecules on gastrointestinal and other vascular endothelial cells to promote the influx of integrin binds specifically to the mucosal addressin cell adhesion molecule 1 and causes a decrease in gastrointestinal mucosal degradation and inflammation [Erle *et al.* 1994; Fedyk *et al.* 2012].

Pharmacokinetics

Similar pharmacokinetic parameters of vedolizumab have been reported in patients with UC and CD. In a dose-ranging study, 36 patients with UC were administered vedolizumab as a 30–60 min intravenous infusion at doses of 2, 6, or 10

Table 1. Ulcerative colitis (UC) and Crohn's disease (CD) therapies and proposed targets [Sharon *et al.* 1978; Horn *et al.* 1991; Poldosky 2002; Rousseaux *et al.* 2005; Stolfi *et al.* 2008; Terdiman *et al.* 2013; Marinkovic *et al.* 2014].

Medications	Proposed cell mediator targets
Corticosteroids	COX-2, IL-1β, NF-κB, IL-1β, PG
Budesonide	
Hydrocortisone	
Methylprednisolone	
Prednisone	
Aminosalicylates	COX-2, IL-8, PPAR-γ, PG, leukotrienes, NF-κB, TNF-α
Balsalazide	
Mesalamine	
Olsalazine	
Sulfasalazine	
Immunomodulators	Chemokines, IL-8
6-Mercaptopurine	
Azathioprine	
Cyclosporine	
Methotrexate	
TNF-α inhibitors	TNF-α
Adalimumab	
Certolizumab pegol	
Golimumab	
Infliximab	

COX, cyclooxygenase; IL, interleukin; NF, nuclear factor; PG, prostaglandin; PPAR, peroxisome proliferator activated receptor; TNF, tumor necrosis factor.

mg/kg at weeks 0, 2, and 4 (induction phase) and week 12 (maintenance phase). With each of these doses, maximum serum concentration and area under the curve were considered dose dependent. Serum concentrations declined in a linear manner when concentrations ranged from 1 to 10 μg/mL, with a nonlinear decline thereafter. Across all doses, the mean half-life ranged from 15–22 days [Parikh *et al.* 2012]. These pharmacokinetic parameters were confirmed in phase III trials, when 300 mg of vedolizumab was administered as a 30 min intravenous infusion at weeks 0, 2, 6, and then every 4 or 8 weeks thereafter to patients with UC and CD. Trough serum concentrations declined in a linear fashion from week 6 to week 46 from 26.3 to 11.2 μg/ml (UC) and from 27.4 to 13 μg/ml (CD), and the serum half life was determined to be nearly 25 days. Further analysis of these data showed a linear clearance of 0.157 L/day and a volume of distribution of approximately 5 L [Feagan *et al.* 2013; Sandborn *et al.* 2013; Takeda Pharmaceuticals America Inc., 2014].

Clinical efficacy

The FDA approval of vedolizumab for UC and CD was based on results from three prospective, randomized, multicenter, phase III trials (GEMINI 1, GEMINI 2, and GEMINI 3). GEMINI 1 and 2 were integrated trials with similar study design and methodology and consisted of both induction and maintenance studies for UC and CD, respectively, while GEMINI 3 was an induction only study for CD [Feagan *et al.* 2013; Sandborn *et al.* 2013; Sands *et al.* 2014]. In each of these trials, patients had moderate to severe disease (defined in Tables 2 and 3) with treatment failure to glucocorticoids and immunomodulators (GEMINI 1, 2) or TNF-α inhibitors (GEMINI 1, 2, 3). Each of these trials is summarized below and further detailed in Tables 2 and 3 [Feagan *et al.* 2013; Sandborn *et al.* 2013; Sands *et al.* 2014].

Ulcerative colitis

GEMINI 1 evaluated the efficacy and safety of vedolizumab for induction and maintenance in 895 adults with moderately to severely active UC [Feagan *et al.* 2013]. The induction study was divided into two cohorts. In cohort 1 patients were randomized to intravenous vedolizumab 300 mg (n = 225) or placebo (n = 149) at weeks 0 and 2 while cohort 2 patients received open-label vedolizumab 300 mg (n = 521) at the same time intervals. Patients from cohorts 1 and 2 who had a clinical response at week 6 (i.e. a 3-point or more reduction in the Mayo Clinic score and a 30% or more reduction from the baseline score, along with a 1-point or more decrease on the rectal bleeding subscale or a score of 0 or 1 for absolute rectal bleeding) were allowed to move into the maintenance study. In this study patients were randomized to one of three treatment arms: intravenous vedolizumab 300 mg every 8 weeks, intravenous vedolizumab 300 mg every 4 weeks, or placebo. The primary efficacy endpoints for the induction and maintenance studies were clinical response at week 6 and clinical remission at week 52, respectively. Other outcomes assessed included durable clinical response and remission (both at weeks 6 and 52), mucosal healing, and corticosteroid-free remission (both at week 52). When reporting results, all endpoint differences were adjusted for concomitant use or no use of

Table 2. Summary of vedolizumab phase III studies in patients with active UC.

Reference	Design	Population	Treatment	Response endpoints	
				Primary	Secondary
GEMINI 1 [Feagan *et al.* 2013]	R, parallel group, DB, PC	Moderate to severe UC* (n = 895)	**Induction** Intravenous infusion on days 1, 15 C1R1: VDZ 300 mg (n = 225) C1R2: PBO (n = 149) C2: open label VDZ 300 mg (n = 521)	**Induction** Clinical response$ at week 6 47.1% C1R1 *versus* 25.5% C1R2 ($p <$ 0.001) 44.3% C2	**Induction** Clinical remission‡ at week 6 16.9% C1R1 *versus* 5.4% C1R2 (p = 0.001) 19.2% C2 Mucosal healing§ at week 6 40.9% C1R1 *versus* 24.8% C1R2 (p = 0.001) 36.7% C2
			Maintenance R1: VDZ every 8 weeks (n = 122) R2: VDZ every 4 weeks (n = 125) PBO (n = 126)	**Maintenance** Clinical remission‡ at week 52 41.8% R1 and 44.8% R2 *versus* 15.9% PBO ($p < 0.001$ and $p <$ 0.001, respectively)	**Maintenance** Mucosal healing§ at week 52 51.6% R1 and 56% R2 *versus* 19.8% PBO ($p < 0.001$ and $p <$ 0.001, respectively) Glucocorticoid-free remission‖ 31.4% R1 and 45.2% R2 *versus* 13.9% PBO (p = 0.01 and $p <$ 0.001, respectively)

*Moderate to severe active disease: baseline Mayo Clinical Score (MCS) of at least 6 points and endoscopy subscore of at least 2 points.
$Clinical response: decrease of at least 3 points in MCS and decrease of at least 30% of baseline MCS, with a decrease of at least 1 point on the rectal bleeding subscale or a score of 0 or 1 for absolute rectal bleeding.
‡Clinical remission: MCS up to 2 points with no subscore greater than 1 point.
§Mucosal healing: score of 0 or 1 for endoscopic subscore.
‖Glucocorticoid-free remission assessed in patients receiving oral corticosteroids at baseline.
DB, double blind; C1R1, cohort 1 regimen 1; C1R2, cohort 1 regimen 2; C2, cohort 2; PBO, placebo; PC, placebo controlled, R, randomized; R1, regimen 1; R2, regimen 2; VDZ, vedolizumab.

corticosteroids and concomitant use or prior use of immunomodulators or TNF-α antagonists. In the induction study, clinical response was achieved at week 6 by 47.1% of vedolizumab-treated patients compared with 25.5% of placebo-treated patients [adjusted difference 21.7%, 95% confidence interval (CI) 11.6–31.7, $p < 0.001$, number needed to treat (NNT) = 4.6]. Other significant differences found between cohort 1 groups at week 6 included the rate of clinical remission [vedolizumab (16.9%) *versus* placebo (5.4%); p = 0.001] and rate of mucosal healing [vedolizumab (40.9%) *versus* placebo (24.8%); p = 0.001]. For patients who received open-label vedolizumab (cohort 2), clinical response, remission, and mucosal healing rates were 44.3%, 19.2%, and 36.7%, respectively. Of those who moved on to the maintenance study, vedolizumab-treated patients had a better clinical remission compared with placebo-treated patients at week 52 (every 8-week group: 41.8% *versus* 15.9%, adjusted difference 26.1%; 95% CI 14.9–37.2, $p < 0.001$, NNT = 3.8; and every 4-week group: 44.8% *versus* 15.9%, adjusted difference 29.1%; 95% CI 17.9–40.4, $p < 0.001$, NNT = 3.4). Additionally, patients who received vedolizumab every 8 weeks and every 4 weeks compared with placebo were more likely to achieve a durable clinical response (56.6% and 52% *versus* 23.8%, $p < 0.001$ and $p < 0.001$, respectively) durable clinical remission (20.5% and 24% *versus* 8.7%, p = 0.008 and p = 0.001, respectively), mucosal healing (51.6% and 56% *versus* 19.8%, $p < 0.001$ and $p < 0.001$, respectively) and corticosteroid-free remission (31.4% and 45.2% *versus* 13.9%, p = 0.01 and $p < 0.001$) at week 52. Limitations to this study exist. Unfortunately, the induction study only lasted 6 weeks. Extension of the induction study would have allowed for identifying the optimal time to induction instead of limiting it to the 6-week time period. Likewise, the minimal effective dose regimen was not determined since both regimens, though not directly compared, had similar efficacy. Finally, by using a placebo instead of an active comparator the exact placement of vedolizumab in the treatment algorithm for the management of moderate to severe active UC is unknown.

Table 3. Summary of vedolizumab phase III studies in patients with active Crohn's disease (CD).

Reference	Design	Population	Treatment	Response endpoints	
				Primary	Secondary
GEMINI 2 [Sandborn *et al*. 2013]	R, parallel group, DB, PC	Moderate to severe CD* (n = 1115)	**Induction** Intravenous infusion on weeks 0, 2 C1R1: VDZ 300 mg (n = 220) C1R2: PBO (n = 148) C2: open label VDZ 300 mg (n = 747)	**Induction** Clinical remission† at week 6 14.5% C1R1 vs. 6.8% C1R2, p = 0.02 17.7% C2 CDAI-100 response‡ at week 6 31.4% C1R1 vs. 25.7% C1R2, p = 0.23 34.4% C2	
			Maintenance R1: VDZ every 8 weeks (n = 154) R2: VDZ every 4 weeks (n = 154) PBO (n = 153)	**Maintenance** Clinical remission§ at week 52 39% R1 and 36.4% R2 *versus* 21.6% PBO 17.4, $p < 0.001$ and 14.8, p = 0.004, respectively	**Maintenance** CDAI-100 response‡ at week 52 43.5% R1 and 45.5% R2 *versus* 30.1% PBO 13.4, p = 0.01 and 15.4, p = 0.005, respectively Glucocorticoid-free remission§ 31.7% R1 and 28.8% R2 *versus* 15.9% PBO 15.8, p = 0.02 and 12.9, p = 0.04, respectively
GEMINI 3 [Sands *et al*. 2014]	R, DB, PC	Moderate to severe CD* (n = 416)	Intravenous infusion on weeks 0, 2, 6 VDZ 300 mg (n = 209) PBO (n = 207)	**TNF-α antagonist failure population** Clinical remission§ at week 6 15.2% VDZ *versus* 12.1% PBO 3.0 (95% CI −4.5 to 10.5), p = 0.433	**TNF-α antagonist failure population** CDAI-100 response‡ at week 6 39.2% VDZ *versus* 22.3% PBO 16.9 (95% CI 6.7–27.1), p = 0.001 Clinical remission§ at week 10 26.6% VDZ *versus* 12.1% PBO 14.4 (95% CI 5.7–23.1), p = 0.001 **Overall population** Clinical remission† at week 6 19.1% VDZ *versus* 12.1% PBO 6.9 (95% CI 0.1–13.8), p = 0.048 Clinical remission§ at week 10 28.7% VDZ *versus* 13.0% PBO 15.5 (95% CI 7.8–23.3), $p < 0.0001$

*Moderate to severe active disease: CD Activity Index (CDAI) score of 220–450.
§Clinical remission: CDAI score up to 150 points.
‡CDAI-100 response: decrease of at least 100 points in CDAI score.
§Glucocorticoid-free remission: clinical remission without corticosteroids at week 52.
C1R1, cohort 1 regimen 1; C1R2, cohort 1 regimen 2; C2, cohort 2; CI, confidence interval; DB, double blind; PBO, placebo; PC, placebo controlled; R, randomized; R1, regimen 1; R2, regimen 2; VDZ, vedolizumab.

Crohn's disease

GEMINI 2 assessed the efficacy and safety of vedolizumab for induction and maintenance in 1115 adults with moderate to severe active CD [Sandborn *et al*. 2013]. Similar to GEMINI 1, the induction study consisted of two cohorts. In cohort 1 patients were randomized to intravenous vedolizumab 300 mg (n = 220) or placebo (n = 148) at weeks 0 and 2 while patients in cohort 2 received open-label vedolizumab 300 mg (n = 747) also at weeks 0 and 2. All patients from cohorts 1 and 2 moved onto the maintenance phase and were followed through week 52, yet they were divided into two groups based on clinical response [i.e. ⩾70-point reduction in the CD Activity Index (CDAI) at week 6]. Patients who were considered 'clinical responders' were randomized equally to vedolizumab 300 mg every 8

weeks, vedolizumab 300 mg every 4 weeks, or placebo, while those who were considered 'clinical nonresponders' received vedolizumab 300 mg every 4 weeks. The primary efficacy outcomes for these studies were clinical remission (CDAI score $\leqslant$ 150 points) and CDAI-100 response ($\geqslant$100-point decrease in the CDAI score) at week 6 (induction) and clinical remission at week 52 (maintenance). Secondary outcomes measured at week 6 for the induction study were a change in mean C-reactive protein levels from baseline and at week 52 for the maintenance study, a CDAI-100 response, glucocorticoid-free remission (i.e. no corticosteroid at week 52 use while in clinical remission), and durable clinical remission (i.e. clinical remission at 80% or more of study visits that included the final visit). In cohort 1 of the induction study, more patients receiving vedolizumab treatment achieved clinical remission at week 6 compared with patients receiving placebo (14.5% *versus* 6.8%, $p = 0.02$, respectively). However, no significant difference in CDAI-100 response [vedolizumab (31.4%) *versus* placebo (25.7%); $p = 0.23$] or changes in mean C-reactive protein levels from baseline were detected at week 6. Of the patients in cohort 2, 17.7% (132/747) achieved clinical remission and 34.4% (257/747) had a CDAI-100 response at week 6. In the maintenance study, a greater percentage of patients who received vedolizumab achieved clinical remission at week 52 [every 8 weeks (39.0%), every 4 weeks (36.4%) compared with placebo (21.6%), $p < 0.001$ and $p = 0.004$, respectively]. Additionally, when patients who received vedolizumab treatment were compared with those receiving placebo there was a significant difference between groups for CDAI-100 response [every 8 weeks (43.5%), every 4 weeks (45.5%), placebo (30.1%); $p = 0.01$ and $p = 0.005$, respectively] and glucocorticoid-free remission [every 8 weeks (31.7%), every 4 weeks (28.8%), placebo (15.9%), $p = 0.02$ and $p = 0.04$, respectively]. There was no difference between groups for durable clinical remission. This study may be limited by its study population. The majority of enrolled patients had extremely refractory and complicated disease with nearly half of patients having a history of surgery or fistulizing disease and 15% of patients having active, draining fistulas at enrollment. This population has not been included in previous trials with TNF-α inhibitors and may have confounded the response rates reported for vedolizumab.

In an effort to examine subpopulations that may benefit from vedolizumab therapy in active CD, the GEMINI 3 study was conducted to determine the efficacy of vedolizumab induction specifically in those with moderately or severely active CD whose condition previously failed to respond to TNF-α antagonists [Sands *et al.* 2014]. Patients were randomized to receive intravenous vedolizumab 300 mg ($n = 209$) or placebo ($n = 207$) at weeks 0, 2, and 6. Randomization was stratified based on previous TNF-α antagonist status, concomitant corticosteroid use, and concomitant immunosuppressive use. The majority of patients (76%, 315/416) had disease that failed to respond to previous TNF-α antagonist therapy and this was considered the primary efficacy analysis population. The primary efficacy outcome was clinical remission (CDAI $\leqslant$ 150 points) at week 6 in patients whose condition failed to respond to prior TNF-α antagonist treatment. Secondary efficacy outcomes for the TNF-α antagonist failure population included CDAI-100 response ($\geqslant$100-point decrease from baseline in CDAI) at week 6 and clinical remission at week 10 and for the overall population included clinical remission at weeks 6 and 10. There was no significant difference between treatment groups for the proportion of patients achieving clinical remission at week 6 [vedolizumab (15.2%) *versus* placebo (12.1%); $p = 0.433$]. Since the primary outcome was not statistically significant, analysis of secondary outcomes was only completed for characterization purposes. In the TNF-α antagonist-failure population, patients who received vedolizumab treatment had a greater CDAI-100 response compared with placebo at week 6 (39.2% *versus* 22.3%, $p = 0.001$) and clinical remission was achieved in more patients treated with vedolizumab at week 10 compared with those receiving placebo (26.6% *versus* 12.1%, $p = 0.001$). In the overall population, a greater proportion of patients who received vedolizumab achieved clinical remission at week 6 [vedolizumab (19.1%) *versus* placebo (12.1%); $p = 0.048$] and at week 10 [vedolizumab (28.7%) *versus* placebo (13.0%); $p < 0.0001$]. Despite the insignificant results of the primary efficacy outcome, the authors state that the collective primary and secondary results suggest that the full effects of vedolizumab on clinical remission may not be realized until after week 6 of treatment, specifically in patients whose condition failed to respond to prior TNF-α antagonist therapy.

Other clinical trials evaluating vedolizumab in adults with moderate or severe active UC or CD are ongoing. Two of these trials are designed to assess clinical response and clinical remission at longer time periods than the previously published trials (i.e. induction therapy at week 10 and maintenance at week 60). One trial (GEMINI LTS) is focusing on long-term safety (i.e. up to 7 years) and another trial is evaluating vedolizumab when administered as a subcutaneous injection [ClinicalTrials.gov identifiers: NCT00790933, NCT02038920, NCT02039505, NCT0216342].

Adverse effects

Vedolizumab is generally well tolerated with an AE profile and tolerability being relatively similar among trials. AEs reported in 10% or more of patients receiving vedolizumab in these trials include upper respiratory infection, nasopharyngitis, abdominal pain, nausea, CD exacerbation, arthralgia, pyrexia, and headache [Feagan *et al*. 2013; Sandborn *et al*. 2013; Sands *et al*. 2014]. In the GEMINI 1 study, the incidence of serious AEs did not differ from placebo (12.4% *versus* 13.5%, respectively); however, in GEMINI 2, there was a higher incidence of serious infections and malignancies reported in patients receiving vedolizumab compared with those on placebo (serious infections: 5.5% *versus* 3.0%, respectively; and malignancies: 0.5% *versus* 0.3%, respectively) [Feagan *et al*. 2013; Sandborn *et al*. 2013; Takeda Pharmaceuticals America Inc., 2014]. Infusion-related reactions (up to 4% of patients) have been reported with vedolizumab administration. The most common infusion-related reaction symptoms include nausea, headache, pruritus, dizziness, fatigue, pyrexia, urticaria, and vomiting. Anaphylaxis has rarely (i.e. one patient in clinical trials) been reported with vedolizumab [Takeda Pharmaceuticals America Inc., 2014].

PML

More than 3000 patients received vedolizumab in clinical studies for a median of 313 days with no cases of PML reported [ClinicalTrials.gov identifier: NCT00790933; Feagan *et al*. 2013; Sandborn *et al*. 2013; Sands *et al*. 2014]. Prior to FDA approval, an independent adjudication committee of the FDA conducted a risk assessment and minimization for the association of PML with vedolizumab and no cases of PML were identified [FDA, 2013]. Thus, vedolizumab was FDA approved without a risk evaluation minimization strategy. However, to ensure patient safety, the manufacturer of vedolizumab must conduct a prospective, observational cohort study that compares vedolizumab with other treatments for IBD with a primary outcome of serious infections and secondary outcomes including PML. The expected completion date for the study is 2021 [Gingery, 2014]. Additionally, an open-label phase III trial to determine the long-term safety of vedolizumab in patients with UC and CD (GEMINI LTS), with safety evaluations including PML, is ongoing and due to be completed in March 2016 [ClinicalTrials.gov identifier: NCT00790933].

Immunogenicity

An early formulation of vedolizumab (MLN002) was derived from mouse myeloma cell lines and caused human anti-human antibodies (HAHA) development in up to 44% of patients [Feagan *et al*. 2005; Parikh *et al*. 2012]. In an effort to reduce immunogenicity, a new formulation of vedolizumab derived from a Chinese hamster ovary cell based system was developed [Parikh *et al*. 2012]. This new formulation was evaluated in the GEMINI 1, 2, and 3 studies and resulted in 1–4.1% of patients being positive for anti-vedolizumab antibodies at any time point and 0.4–1% of patients being persistently positive throughout the trials [Feagan *et al*. 2013; Sandborn *et al*. 2013; Sands *et al*. 2014].

Drug–drug interactions

Concomitant administration of vedolizumab with TNF-α antagonists and natalizumab should be avoided because of increased infection risk and PML, respectively. Additionally, live vaccines should only be given to patients receiving vedolizumab if the benefit clearly outweighs the risk [Takeda Pharmaceuticals America Inc., 2014].

Dosing and administration

Before starting vedolizumab therapy, patients should be considered for tuberculosis screening, have baseline liver enzyme tests drawn, and brought up to date with all routine vaccinations. If vaccinations need to be given while a patient is receiving vedolizumab then inactivated vaccines may be given when indicated (though lower seroconversion rates may or may not occur), yet live vaccines should only be given after risk–benefit considerations. To date, no reports of secondary

transmission of infection by live vaccines in patients receiving vedolizumab exist [Takeda Pharmaceuticals America Inc., 2014].

Initial dose-finding studies for vedolizumab used weight-based dosing with doses ranging from 0.15 to 10 mg/kg administered as single doses or at different dosing intervals (e.g. weeks 0 and 4 or weeks 0, 2, 4, and 12) [Feagan *et al*. 2000, 2005, 2008; Parikh *et al*. 2012]. In phase III trials, vedolizumab dosing was standardized to a 300 mg intravenous infusion given at weeks 0, 2, for induction and then every 4 or 8 weeks for maintenance. This standardized dose corresponded to a mean dose of 4.1 mg/kg (UC) and 4.3 mg/kg (CD), with induction primarily achieved by week 6 and similar clinical outcomes when maintenance doses were given every 4 or 8 weeks [Feagan *et al*. 2013; Sandborn *et al*. 2013]. These results led to the FDA-approved dosing regimen of 300 mg as a 30 min intravenous infusion on weeks 0, 2, and 6, and then every 8 weeks thereafter for both UC and CD [Takeda Pharmaceuticals America Inc., 2014]. Product labeling recommends that vedolizumab treatment be discontinued if patients do not show signs of response by week 14 [Takeda Pharmaceuticals America Inc., 2014].

Due to the risk of hypersensitivity reactions, including anaphylaxis, vedolizumab must be administered by a healthcare provider equipped to respond to such reactions. Additionally, patients must be monitored for these possible infusion-type reactions throughout the 30 min infusion period [Takeda Pharmaceuticals America Inc., 2014]. If patients have a non-life-threatening infusion reaction history then administration of acetaminophen, antihistamines, or corticosteroids should be considered before the start of the infusion [Takeda Pharmaceuticals America Inc., 2014]. However, if a serious hypersensitivity reaction occurs during vedolizumab administration, vedolizumab should be immediately discontinued and medications for treating the reaction administered to the patient (e.g. epinephrine, antihistamines, corticosteroids).

Cost considerations

The average wholesale cost of a 300 mg vial of vedolizumab in the US is $5782.80 [*The Redbook (On Line)*, 2014]. Based on the recommended dosing of 300 mg on weeks 0, 2, 6, and then every 8 weeks thereafter, the cost of vedolizumab for the initial year of treatment is approximately $52,000 and for subsequent years approximately $34,700. To account for individual drug reimbursement, vedolizumab should generally be administered in an outpatient infusion clinic setting. The manufacturer of vedolizumab does provide support for copayment assistance for those with private insurance, identification of independent patient support foundations for possible financial assistance for those with Medicare/Medicaid, and determination of patient assistance qualification for those without insurance [Entyvio Connect, 2015]. To date, cost-effectiveness analyses comparing vedolizumab with other therapies approved for UC and CD have not been performed.

Conclusion

Vedolizumab is an $\alpha 4\beta 7$ integrin antagonist approved for use in patients with moderate to severe UC or CD who are considered non-responders, have relapsing disease, or are unable to tolerate TNF-α antagonists or who or have an inadequate response with, are intolerant to, or demonstrate dependence on corticosteroids. When administered according to approved dosing in patient with moderate to severe CD and UC, vedolizumab induces clinical response rates up to 31.4% and 47.1% at week 6 and clinical remission rates at week 52 up to 39% and 41.8%. Unlike other FDA approved integrin antagonists, vedolizumab is gastrointestinal selective and has not shown evidence of causing PML; however, postmarketing studies are ongoing to ensure patient safety for this serious AE. Other serious AEs reported in trials with vedolizumab include serious infections, malignancies, and anaphylaxis. Further assessment of vedolizumab earlier in the course of these diseases and in combination with other therapies is warranted.

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Conflict of interest statement

The authors do not have any conflicts of interest related to the subject matter.

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