2015

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Vedolizumab: an $\alpha 4\beta 7$ integrin antagonist for ulcerative colitis and Crohn’s disease

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

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-$\alpha$) 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-$\alpha$ antagonist treatment. Vedolizumab, a humanized monoclonal antibody, is the first integrin receptor antagonist approved that selectively antagonizes $\alpha 4\beta 7$ 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-$\alpha$ 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

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 $\gamma$, certain interleukins and tumor necrosis factor $\alpha$ (TNF-$\alpha$)] [Abraham and Cho, 2009]. These mediators recruit additional leukocytes, which results in a sustained inflammatory response and tissue...
Both UC and CD can be categorized as mild, moderate or severe, and characterized by exacerbations and remissions in 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 monoclonal 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. 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. 2008; Kornbluth et al. 2010; Terdiman et al. 2013; Marinkovic et al. 2014].

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.

### 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 America Inc., 2014) 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
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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, 3) with treatment failure to glucocorticoids and immunomodulators (GEMINI 1, 2, 3). Each of these trials was 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 intravenous vedolizumab 300 mg every 4 weeks, intravenous vedolizumab 300 mg every 8 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 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].

<table>
<thead>
<tr>
<th>Medications</th>
<th>Proposed cell mediator targets</th>
</tr>
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<tbody>
<tr>
<td>Corticosteroids</td>
<td>COX-2, IL-1β, NF-κB, IL-1β, PG</td>
</tr>
<tr>
<td>Budesonide</td>
<td></td>
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<tr>
<td>Hydrocortisone</td>
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<tr>
<td>Methylprednisolone</td>
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<td>Prednisone</td>
<td></td>
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<tr>
<td>Aminosalicylates</td>
<td>COX-2, IL-8, PPAR-γ, PG, leukotrienes, NF-κB, TNF-α</td>
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<tr>
<td>Balsalazide</td>
<td></td>
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<tr>
<td>Mesalamine</td>
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<td>Olsalazine</td>
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<td>Sulfasalazine</td>
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<tr>
<td>Immunosuppressants</td>
<td>Chemokines, IL-8</td>
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<tr>
<td>6-Mercaptopurine</td>
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<tr>
<td>Azathioprine</td>
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<td>Cyclosporine</td>
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<td>Methotrexate</td>
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<td>TNF-α inhibitors</td>
<td>TNF-α</td>
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<tr>
<td>Adalimumab</td>
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<tr>
<td>Certolizumab pegol</td>
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<tr>
<td>Golimumab</td>
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<tr>
<td>Infliximab</td>
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</table>

COX, cyclooxygenase; IL, interleukin; NF, nuclear factor; PG, prostaglandin; PPAR, peroxisome proliferator activated receptor; TNF, tumor necrosis factor.
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 \( p < 0.001 \), respectively).

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Response endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GEMINI 1</strong></td>
<td>R, parallel</td>
<td>Moderate to severe UC* (n = 895)</td>
<td><strong>Induction</strong> Intra venous infusion on days 1, 15</td>
<td><strong>Induction</strong> Clinical response at week 6</td>
</tr>
<tr>
<td>[Feagan et al. 2013]</td>
<td>group, DB, PC</td>
<td>C1R1: VDZ 300 mg (n = 225)</td>
<td>47.1% C1R1 versus 25.5% C1R2 (( p &lt; 0.001 ))</td>
<td>16.9% C1R1 versus 5.4% C1R2 (( p = 0.001 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C1R2: PBO (n = 149)</td>
<td>44.3% C2</td>
<td>19.2% C2</td>
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<tr>
<td></td>
<td></td>
<td>C2: open label VDZ 300 mg (n = 521)</td>
<td></td>
<td>Mucosal healing at week 6</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>40.9% C1R1 versus 24.8% C1R2 (( p = 0.001 ))</td>
<td>40.9% C1R1 versus 24.8% C1R2 (( p = 0.001 ))</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>36.7% C2</td>
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<tr>
<td><strong>Induction</strong></td>
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<tr>
<td><strong>Maintenance</strong></td>
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<tr>
<td>R1: VDZ every 8</td>
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<tr>
<td>weeks (n = 122)</td>
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<tr>
<td>R2: VDZ every 4</td>
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<tr>
<td>weeks (n = 125)</td>
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<tr>
<td>PBO (n = 126)</td>
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<tr>
<td><strong>Maintenance</strong></td>
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<tr>
<td>Clinical remission at week 52</td>
<td>41.8% R1 and 44.8% R2 versus 15.9% PBO (( p &lt; 0.001 ) and ( p &lt; 0.001 ), respectively)</td>
<td>Mucosal healing at week 52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid-free remission</td>
<td>31.4% R1 and 45.2% R2 versus 13.9% PBO (( p = 0.01 ) and ( p &lt; 0.001 ), respectively)</td>
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</tr>
</tbody>
</table>

*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.
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 and placebo. The primary endpoint was clinical remission at week 6, and the secondary endpoints included CDAI-100 response and glucocorticoid-free remission. The results showed that vedolizumab was significantly more effective than placebo in achieving clinical remission and CDAI-100 response, with a clinically meaningful improvement in glucocorticoid-free remission.

GEMINI 3 [Sands et al. 2014] assessed the efficacy and safety of vedolizumab in a TNF-α antagonist failure population. The study included 416 patients with moderate to severe active CD and clinical remission at week 6. Patients were randomized to vedolizumab 300 mg (n = 209) or placebo (n = 207) for 6 weeks, followed by maintenance treatment at weeks 0, 2, 6, and 8. The primary endpoint was clinical remission at week 6, and the secondary endpoints included CDAI-100 response and clinical remission at week 10. The results showed that vedolizumab was significantly more effective than placebo in achieving clinical remission and CDAI-100 response, with a clinically meaningful improvement in clinical remission at week 10.

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Response endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GEMINI 2</strong> [Sandborn et al. 2013]</td>
<td>R, parallel group, DB, PC</td>
<td>Moderate to severe CD* (n = 1115)</td>
<td>Intravenous infusion on weeks 0, 2 C1R1: VDZ 300 mg (n = 220) C1R2: PBO (n = 148) C2: open label VDZ 300 mg (n = 747)</td>
<td>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</td>
</tr>
<tr>
<td><strong>GEMINI 3</strong> [Sands et al. 2014]</td>
<td>R, DB, PC</td>
<td>Moderate to severe CD* (n = 416)</td>
<td>Intravenous infusion on weeks 0, 2, 6 VDZ 300 mg (n = 209) PBO (n = 207)</td>
<td>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 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 &lt; 0.0001</td>
</tr>
</tbody>
</table>

*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.
R, randomized; R1, regimen 1; R2, regimen 2; C1, cohort 1; C2, cohort 2; CI, confidence interval; DB, double blind; PBO, placebo; PC, placebo controlled; VDZ, vedolizumab.
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 ≤ 150 points) and CDAI-100 response (=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 ≤ 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 (=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 I 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].

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.

Conclusion
Vedolizumab is an α4β7 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.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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

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