Review Article

Introducing Vedolizumab to Clinical Practice: Who, When, and How?

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Abstract

Vedolizumab (VDZ), a humanized monoclonal antibody that selectively targets $\alpha_4\beta_7$ integrin, is approved for use in inflammatory bowel disease (IBD). Here we review the evidence for the safety and efficacy of VDZ in IBD, in order to identify patients likely to benefit from therapy and to integrate VDZ into clinical practice. A bibliographic search was performed of the online databases MEDLINE, EMBASE, PubMed, and the Cochrane Library, using the key words ‘inflammatory bowel diseases’ OR ‘ulcerative colitis’ OR ‘Crohn’s disease’ AND ‘vedolizumab’ OR ‘MLN0002’ OR ‘integrin alpha4beta7’ OR ‘anti-integrin’. Eight-nine articles were returned using the primary search. Eight randomized controlled trials, one Cochrane review, and two network meta-analyses were identified. VDZ is well tolerated with a low rate of adverse events (similar to placebo), and is associated with minimal systemic immunosuppression. VDZ is effective for induction and maintenance of remission in outpatients with moderate to severe ulcerative colitis (UC) or Crohn’s disease (CD) who have failed conventional and anti-tumor necrosis factor (anti-TNF) therapy. VDZ is also a first-line alternative to anti-TNF therapy in UC. The efficacy of VDZ is best assessed at, or beyond, 10 weeks of therapy. The safety, tolerability, and efficacy profile of VDZ place it as a new therapy in IBD, though further trials directly comparing VDZ with other biological agents as well as pragmatic studies to evaluate cost-effectiveness are necessary.

Keywords: Vedolizumab; inflammatory bowel disease; Crohn’s disease; ulcerative colitis

1. Introduction

Infiltration of the inflamed gastrointestinal tract by leucocytes involves a complex interaction of adhesion and signaling molecules on the surface of T lymphocytes with corresponding ligands on the gut endothelium.¹ Integrins are cellular adhesion transmembrane proteins integral to the process. The $\alpha_4\beta_7$ integrin mediates selective trafficking of gut-homing CD4+ T lymphocytes to the gut, where they bind to the addressin cell adhesion molecule 1 (MAdCAM-1), expressed on intestinal venules and up-regulated at sites of inflammation.¹⁻³

Vedolizumab (VDZ) selectively binds to the $\alpha_4\beta_7$ integrin.¹⁴ It has been approved for the treatment of ulcerative colitis (UC) and Crohn’s disease (CD) by both the European Medicines Agency and the US Food and Drug Administration (FDA), but its place among conventional therapies in treatment algorithms for inflammatory bowel disease (IBD) is not yet clear.³⁻⁴ We review the evidence for the efficacy and safety of VDZ in IBD in order to gain insight on how VDZ can be integrated into clinical practice.

2. Efficacy data

The GEMINI phase 3 studies were each of similar design (Table 1).⁵⁻¹¹ The induction phase of the trials randomized patients to receive intravenous VDZ 300 mg or placebo at weeks 0 and 2. A separate open-label group received the same induction regimen in order to provide sufficient patients to power the maintenance trial. Response to VDZ was assessed at week 6; responders were then randomly assigned to continue receiving VDZ (300 mg) every 8 weeks, every 4 weeks, or placebo, for up to 52 weeks. All groups included patients with active inflammation despite conventional therapy (corticosteroids, immunosuppressants, anti-TNF therapy) and were stratified accordingly.
The GEMINI I trial enrolled patients with active UC. The primary endpoint for induction was clinical response at week 6, defined as a reduction in the Mayo score of ≥3 points and a decrease of at least 30% from baseline, with a decrease of ≥1 point on the rectal bleeding subscale (absolute score 0–1). The primary endpoint for maintenance therapy was clinical remission at week 52. Of 374 patients randomized to VDZ or placebo, clinical response at week 6 was achieved in 47.1% of the VDZ group versus 25.5% of the placebo group (95% confidence interval [CI] 11.6–31.7, p < 0.001).

At week 52, 41.8% of patients assigned to VDZ 8-weekly, 44.8% of patients assigned to VDZ 4-weekly, and 15.9% of patients assigned to placebo were in clinical remission (8-weekly and 4-weekly compared with placebo, respectively: 95% CI 14.9–37.2, p < 0.001; 17.9–40.4, p < 0.001). A Cochrane systematic review on the efficacy of VDZ included 606 patients from four studies. After 4–6 weeks, 77% of VDZ-treated patients failed to enter clinical remission, compared with 92% receiving placebo (relative risk [RR] 0.86, 95% CI 0.80–0.91).\(^2\) After 6 weeks, 48% of VDZ-treated patients failed to

### Table 1. Comparative randomized placebo-controlled trials of moderate to severe ulcerative colitis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial, year</th>
<th>Patients</th>
<th>Prior TNF</th>
<th>Regime, time of assessment</th>
<th>End-points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remission induction</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Vedolizumab (VDZ)</td>
<td>GEMINI I</td>
<td>374</td>
<td>42%</td>
<td>VDZ 300 mg IV (Weeks 0, 2) 6 weeks</td>
<td>Clinical response(^1)</td>
<td>47.1 vs. 25.5% (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Clinical remission(^2)</td>
<td>38 vs. 8% (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Mucosal healing(^3)</td>
<td>40.9 vs. 24.8% (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical response</td>
<td>69 vs. 61 vs. 37% (5 mg/kg, 10 mg/kg, PBO) (p &lt; 0.001 both)</td>
</tr>
<tr>
<td>Infliximab (IFX)</td>
<td>ACT1</td>
<td>364</td>
<td>0%</td>
<td>IFX IV 5–10 mg/kg (Weeks 0, 2, 6) 8 weeks</td>
<td>Clinical response</td>
<td>18.5 vs. 9.2% (p = 0.031)</td>
</tr>
<tr>
<td>Adalimumab (ADA)</td>
<td>ULTRA 1</td>
<td>186</td>
<td>0%</td>
<td>ADA SC 160/80/40 mg (Weeks 0, 2, 6) 8 weeks</td>
<td>Clinical response</td>
<td>16.5 vs. 9.3% (p &lt; 0.005)</td>
</tr>
<tr>
<td></td>
<td>ULTRA 2</td>
<td>494</td>
<td>40%</td>
<td>GLM SC 200/100 mg or 400/200 mg (Weeks 0, 2) 6 weeks</td>
<td>Clinical response</td>
<td>50.4 vs. 34.6% (p &lt; 0.005)</td>
</tr>
<tr>
<td>Golimumab (GLM)</td>
<td>PURSUIT-SC</td>
<td>774</td>
<td>0%</td>
<td>GLM 50 or 100 mg 2-weekly 54 weeks</td>
<td>Clinical response</td>
<td>41.1 vs. 31.7% (p &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td>(Phase 3)</td>
<td></td>
<td></td>
<td></td>
<td>Clinical remission</td>
<td>51 vs. 54.9 vs. 30.3% (200/100 mg vs. 400/200 mg vs. PBO) (p &lt; 0.001 both)</td>
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<td></td>
<td>Mucosal healing</td>
<td>17.8 vs. 17.9 vs. 6.4% (200/100 mg vs. 400/200 mg vs. PBO) (p &lt; 0.01 both)</td>
</tr>
<tr>
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<td></td>
<td>Steroid-free remission</td>
<td>42.3 vs. 45.1 vs. 28.7% (200/100 mg vs. 400/200 mg vs. PBO) (p = 0.0014, p &lt; 0.001 respectively)</td>
</tr>
</tbody>
</table>

**Remission maintenance**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial, year</th>
<th>Patients</th>
<th>Prior TNF</th>
<th>Regime, time of assessment</th>
<th>End-points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vedolizumab (VDZ)</td>
<td>GEMINI I 42%</td>
<td>373</td>
<td></td>
<td>VDZ 300 mg IV (4- or 8-weekly) 52 weeks</td>
<td>Clinical response(^4)</td>
<td>41.8 vs. 44.8 vs. 15.9% (8-, 4-weekly, PBO) (both p &lt; 0.001)</td>
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<td>Durable response(^5)</td>
<td>56.6 vs. 42. vs. 23.8% (8-, 4-weekly, PBO) (both p &lt; 0.01)</td>
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<td></td>
<td>Durable remission(^5)</td>
<td>20.5 vs. 24 vs. 8.7% (8-, 4-weekly, PBO) (both p &lt; 0.008)</td>
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<tr>
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<td></td>
<td>Mucosal healing</td>
<td>51.6 vs. 56 vs. 19.8% (8-, 4-weekly, PBO) (both p &lt; 0.001)</td>
</tr>
<tr>
<td>Infliximab (IFX)</td>
<td>ACT1 trial</td>
<td>364</td>
<td>0%</td>
<td>IFX 5–10 mg/kg IV (8-weekly) 54 weeks</td>
<td>Clinical response</td>
<td>44 vs. 45 vs. 20% (5 mg/kg, 10 mg/kg, PBO) (p &lt; 0.001 all comparisons)</td>
</tr>
<tr>
<td>Adalimumab (ADA)</td>
<td>ULTRA 2</td>
<td>494</td>
<td>40%</td>
<td>ADA SC 160/80 mg induction (Weeks 0, 2) then 40 mg 2-weekly 54 weeks</td>
<td>Clinical response</td>
<td>17.3 vs. 8.5% (p = 0.004)</td>
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<td></td>
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<td>Clinical remission</td>
<td>47 vs. 49.7 vs. 31.2% (50 mg vs. 100 mg vs. PBO) (p &lt; 0.01, p &lt; 0.001 respectively)</td>
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<td></td>
<td>Mucosal healing</td>
<td>23.2 vs. 27.8 vs. 15.6% (50 mg vs. 100 mg vs. PBO) (p &lt; 0.004 vs. PBO)</td>
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<td></td>
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<td></td>
<td>Steroid-free remission</td>
<td>42.4 vs. 41.7 vs. 26.6% (50 mg vs. 100 mg vs. PBO) (p &lt; 0.002 vs. PBO)</td>
</tr>
</tbody>
</table>

**IV,** intravenously; **SC,** subcutaneously; **TNF,** TNF-α antagonist.

\(^1\)Clinical response defined as decrease in Mayo score of ≥3 points and ≥30%, accompanying decrease in the subscore for rectal bleeding of ≥1 point or an absolute rectal bleeding subscore of 0 or 1.

\(^2\)Clinical remission defined as Mayo score ≤2 with endoscopic subscore ≤1.

\(^3\)Mucosal healing defined as endoscopic subscore of 0 or 1.

\(^4\)Durable clinical response defined as a response at both week 6 and week 52.

\(^5\)Durable clinical remission defined as remission at both week 6 and week 52.
achieve a clinical response, compared with 72% receiving placebo (RR 0.68, 95% CI 0.59–0.78). Mucosal healing was a secondary outcome for UC: after 4–6 weeks of therapy, failure to achieve endoscopic remission was 68% on VDZ compared with 82% on placebo (RR 0.82, 95% CI 0.75–0.91). During maintenance therapy, 54% on VDZ relapsed compared with 84% on placebo (RR 0.67, 95% CI 0.59–0.77).

The GEMINI II trial enrolled patients with moderate to severely active CD with objective evidence of inflammation (C-reactive protein [CRP] >2.87 mg/L, colonoscopic ulceration, or fecal calprotectin >250 μg/g stool plus evidence of ulcers on imaging). The two primary endpoints for induction were clinical remission (Crohn’s Disease Activity Index [CDAI] ≤150 points) and a CDAI-100 response (≥100-point decrease in CDAI) at week 6, with alpha error set at \( p < 0.05 \) for both endpoints or \( p < 0.025 \) for either of the individual endpoints. The primary endpoint for maintenance therapy was clinical remission at week 52 (Table 2). Of 368 patients randomized to induction, clinical remission was achieved in 14.5% on VDZ versus 6.8% on placebo (\( p = 0.02 \)). A CDAI-100 response was achieved in 31.4% on VDZ versus 25.7% on placebo (\( p = 0.23 \)). Following induction there was no significant difference in CRP between the groups. At week 52, 39% receiving VDZ 8-weekly, 36.4% receiving VDZ 4-weekly, and 21.6% receiving placebo were in clinical remission (4-weekly and 8-weekly compared with placebo: \( p < 0.001 \) and \( p = 0.004 \) respectively).

The GEMINI III trial enrolled patients with moderately to severely active CD, most of whom (76%) had failed anti-TNF therapy. The primary endpoint was clinical remission at week 6.
in the anti-TNF failure subgroup. Secondary endpoints were clinical remission at week 10 and a CDAI-100 response at week 6 and week 10. Of 315 patients with CD and anti-TNF intolerance or failure, 15.2% on VDZ versus 12.1% on placebo achieved clinical remission at week 6 (p = 0.433). At week 10 however, more patients on VDZ achieved remission compared with placebo (26.6% versus 12.1%, 95% CI 1.3–3.6, p < 0.001). Taken together, these three trials indicate that VDZ is moderately effective both for UC and CD in a group of patients refractory to conventional therapy including anti-TNF agents, but the onset of action is relatively slow, often requiring 10 weeks or more of therapy.

3. Safety data

Safety data from all GEMINI trials show an overall rate of adverse events similar to placebo (Tables 3 and 4). A Cochrane systematic review of VDZ for UC (four studies, 606 patients) reported no significant differences between VDZ and placebo for any adverse event (RR 0.99, 95% CI 0.93–1.07) or serious adverse event (RR 1.01, 95% CI 0.72–1.42). Minor infections (43% in the VDZ group versus 42%/35% in the intention-to-treat [ITT] and non-ITT placebo groups respectively) were most prevalent and infusion reactions occurred in 4% given VDZ. Potential drug-induced hepatitis was reported in four patients on VDZ; although causality was not established, potential drug-induced liver injury has also been reported with natalizumab.

Preliminary data from a VDZ extension study (GEMINI-LTS) have reported the long-term safety of VDZ therapy (exposure ≥6 months in 1334 patients, ≥12 months in 1149 patients and ≥24 months in 502 patients) as of July 2012. The rate of drug-related adverse events is similar between UC and CD. Headache (6%), nasopharyngitis (4%), nausea (4%), arthralgia (4%), upper respiratory tract infection (URT I) (3%), and fatigue (3%) indicate that VDZ is generally well tolerated. The incidence of serious infection is <1%, with the exception of perianal abscess in CD (2%). Malignancy has been reported in <1% (two cases of colon cancer and two of melanoma).

The safety profile of VDZ is attributable to its gut-specific mechanism of action, without systemic immunosuppression. This was elegantly demonstrated in a randomized trial showing reduced seroconversion from oral vaccination against cholera toxin, but no difference after parenteral hepatitis B vaccination, following a single 750-mg dose of VDZ in healthy subjects. Nevertheless, enteric infection occurred after VDZ but not placebo in the GEMINI trials (Clostridium difficile in six, Campylobacter spp. in three and Salmonella spp. in one). The principal concern has been for JC virus reactivation, the cause of progressive multifocal leukoencephalopathy (PML), provoked by natalizumab. Cerebrospinal fluid T-lymphocyte populations are not altered by VDZ in either humans or monkeys, in contrast to natalizumab. By February 2013, there were no cases of PML reported from almost 3000 patients treated with VDZ (median exposure 18.8 months), although 80% had previously received immunosuppressants and 900 had received VDZ for >24 months. Routine testing for Jacob Creutzfeldt (JC) virus antibodies was not performed in the GEMINI trials due to the lack of a validated, commercially available assay.

These data raise many questions for clinical practice. Put simply, who, when, and how?

4. WHO will benefit from VDZ?

4.1. Patients with CD or just UC?

The use of VDZ for UC is not only approved, but has attracted approval from the UK’s National Institute for Health and Care Excellence (NICE). Induction efficacy for CD over 6 weeks appears to be less (Tables 1 and 2). Although ‘clinical remission’ in CD was superior to placebo, there was no difference in CDAI-100 response or a biological measure (CRP) following induction. The GEMINI III trial suggests that detecting benefit was limited by the timing of assessment. At 10 weeks, but not at 6 weeks, VDZ was superior to placebo for inducing clinical remission among patients who had previously failed anti-TNF therapy. However, maintenance with VDZ in CD for achieving clinical remission at 52 weeks was also superior to placebo, and the magnitude of the effect was generally similarly to that seen with maintenance therapy in UC and was clearly clinically meaningful. Since this only emerged after 30 weeks, the message with VDZ is patience, as well as appropriate selection of patients and the use of bridging strategies to manage patients during the first 10 weeks or so of therapy, for instance co-induction with corticosteroids.

Direct comparisons between the efficacy and safety of VDZ with other drugs are challenging in the absence of head-to-head trials. Caution is particularly warranted in the context of CD, since patients enrolled into the GEMINI CD trials had objective evidence of inflammation, in contrast to registration trials of infliximab (IFX), adalimumab (ADA), or certolizumab pegol (Table 3). Results for VDZ in UC appear comparable to those for anti-TNF therapy, taking account of different trial populations and analyses.

In contrast, VDZ appears less effective than anti-TNF therapy for inducing remission of CD, though comparable for remission maintenance.

Bayesian network meta-analysis allows indirect comparison with a common comparator. Analysis is limited by unmeasured heterogeneity between trials. One network analysis of eight RCTs of biological therapy for UC found an odds ratio (OR) for inducing clinical remission with VDZ comparable to that with IFX (Table 3). Another network meta-analysis analyzed VDZ against other biologic and/or immunosuppressive therapies for inducing and maintaining remission in 39 RCTs of patients with CD. VDZ was superior to placebo for inducing remission (OR 2.0, 95% CI 1.2–3.3), with no significant differences between therapies. Although apparently less effective than ADA for maintaining remission (OR 0.42, 95% CI 0.22–0.85), such post hoc subgroup analysis should be regarded with caution, even if the message is consistent: VDZ is broadly comparable to anti-TNF therapy in this difficult-to-treat group of patients.

It is in safety that VDZ appears to have a potential advantage over others. A Cochrane review of VDZ in UC found no significant difference between VDZ and placebo and network analysis in UC found an even lower incidence of serious adverse events than with placebo. In CD, VDZ had fewer withdrawals due to adverse events than azathioprine, methotrexate, IFX, or IFX + azathioprine. Rates of malignancy and serious infection with VDZ are very low, so when faced with prescribing long-term therapy to a young (or elderly) patient with IBD, the excellent safety and tolerability profile potentially shift the paradigm towards VDZ.

Consequently, the efficacy and safety profile of VDZ position it as a potential first-line biologic therapy for induction and maintenance of remission in outpatients with moderate to severe UC who have failed or had inadequate response to corticosteroids or immunosuppressant therapy. Induction results in CD are less compelling, but patients who are able to be treated for 10 weeks or more can experience benefit in the longer term. Assuming that surgery is not desirable, VDZ is appropriate to induce remission for patients with CD who have failed anti-TNF therapy, as a first-line biologic therapy in patients where the focus is more on safety than efficacy, and is an alternative to anti-TNF therapy for maintenance of remission.
4.2. VDZ for acute severe colitis?

Acute severe colitis (ASC) affects 25% of patients with UC. Despite advances in therapy, the colectomy rate in ASC remains 29%. There is no clinical experience with VDZ in ASC. Given the apparently slow onset of action and the absence of data for this treatment indication, VDZ cannot be recommended at the present time. Whether VDZ for outpatients with active UC prevents progression to ASC merits formal study, as do strategies where VDZ would be combined with an induction course of treatment with cyclosporine or tacrolimus.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Remission induction</th>
<th>Remission maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vedolizumab</td>
<td>Induction: 300 mg IV, Weeks 0, 2 Maintenance: 300 mg IV 8- or 4-weekly</td>
<td>4.51 (1.13–20.76) 5.19 (2.59–10.42)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Induction: 5 mg/kg IV at Weeks 0, 2, 6 Maintenance: 5 mg/kg IV 8-weekly</td>
<td>5.33 (2.28–13.63) 2.78 (1.75–4.41)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Induction: 160 mg SC at week 0, 80 mg at week 2, 40 mg at Week 4 Maintenance: 40 mg every other week</td>
<td>1.91 (0.98–3.72) 2.30 (1.37–3.86)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Induction: 200 mg SC at week 0, 100 mg at Week 2 Maintenance: 100 mg every 4 weeks</td>
<td>2.9 (1.19–6.54) 2.24 (1.41–3.56)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Induction: 400 mg SC at Weeks 0, 2, 4 Maintenance: 400 mg every 4 weeks</td>
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</table>

Data are from two systematic network meta-analyses. IV, intravenously; SC, subcutaneously; OR, odds ratio vs. placebo; CrI, credible interval.

UC clinical remission was defined as Mayo clinic score of ≤2, with an absolute rectal bleeding score subscore of 0 or 1; CD clinical remission was defined as CDAI <150 points.

Regimes used varied between trials included in the analysis and commonly used representative regimes presented. Trials were also heterogeneous with respect to prior anti-TNF-α therapy. Maintenance arms differed and some only included those who responded to induction therapy.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>ITT placebo (n = 279) (%)</th>
<th>Non-ITT placebo (n = 297) (%)</th>
<th>VDZ (n = 1434) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Infections</td>
<td>84</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>Overall Nasopharyngitis</td>
<td>42</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
<td>7</td>
<td>13</td>
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<tr>
<td>Sinusitis</td>
<td>7</td>
<td>6</td>
<td>7</td>
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<tr>
<td>Gastrointestinal infections</td>
<td>4</td>
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<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>4</td>
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<tr>
<td>Arthralgia</td>
<td>15</td>
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<tr>
<td>Nausea</td>
<td>13</td>
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<tr>
<td>Pyrexia</td>
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<td>Abdominal pain</td>
<td>11</td>
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<tr>
<td>Infusion-related reaction</td>
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<td>Nervous system disorders</td>
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<tr>
<td>Ulcerative colitis exacerbation</td>
<td>25</td>
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<tr>
<td>Crohn’s disease exacerbation</td>
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<td>Overall IBD-related</td>
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<td>Overall Infections</td>
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<td>Overall Anal abscess</td>
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<tr>
<td>Malignancy</td>
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<td>Gastrointestinal disorders</td>
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<tr>
<td>Ulcerative colitis</td>
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<tr>
<td>Death</td>
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<td>&lt;1</td>
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</tr>
</tbody>
</table>

* Adapted from Colombel et al. (2013).
4.3. VDZ for the young or the elderly?
There is a desire for IBD therapy in the young or elderly that does not cause systemic immunosuppression. Thiopurine therapy alone or in combination with anti-TNF therapy in young patients is associated with a small but real risk of hepatosplenic T-cell lymphoma. Among patients older than 65 years treated with anti-TNF therapy, 11% developed severe infections and 3% malignancy, and 10% died. The relative risk of opportunistic infection in patients with IBD older than 50 years is 3-fold that in younger patients, especially with combination immunosuppressive therapy. Nevertheless, there are few data on VDZ in paediatric or elderly populations. Given the safety data, VDZ may theoretically be particularly appropriate for such groups, but evidence is needed.

4.4. VDZ for patients at risk of or with a history of opportunistic infection?
Likewise, VDZ may appeal for IBD in patients with a history of opportunistic infections on conventional therapy. One caveat may be perianal sepsis, given the slightly higher rate in patients with CD treated with VDZ (see Table 4). Once again, evidence is needed, which can only be collated through international registries or patient cohorts. Nevertheless, VDZ targets gut-specific innate immunity, so recent or recurrent gastrointestinal infection with *Clostridium difficile* or endemic exposure when living or travelling in less developed countries should be regarded with caution.

4.5. Patients at risk of or with a history of prior malignancy?
VDZ has not been associated with an increased risk of malignancy, although long-term experience remains limited. Patients with a prior history of malignancy were excluded from trials. Diminished gastrointestinal immune surveillance remains a theoretical concern for colorectal cancer complicating UC or small intestinal adenocarcinoma in CD, since both are known to have an increased risk relative to the general population. Nevertheless, carcinogenesis is a likely consequence of inflammation, so control of inflammation by VDZ may reduce risk, as appears to be the case for azathioprine therapy for UC. This is another fertile area for study through international collective databases.

4.6. Pregnancy and lactation?
Intentional VDZ during pregnancy or lactation has (of course) not yet been evaluated. The few data available from unplanned pregnancies during RCTs (all patients were promptly withdrawn from studies) are, however, reassuring. Among 24 VDZ-treated patients (or their partners) who became pregnant as of July 2013, spontaneous abortion occurred in three and live births in nine; the others had therapeutic abortion. A single report of congenital anomaly (agenesis of the corpus callosum with left frontal polymicrogyria) occurred in the baby of a 28-year-old woman after a single dose of 2 mg/kg VDZ. Animal studies have not shown fetotoxicity or drug-related teratogenic effects with doses up to 100 mg/kg in rabbits or monkeys (identifying VDZ as an FDA category B drug). Thus, theoretically, VDZ could be continued during pregnancy, as is often done with anti-TNF agents. However, there are some caveats. The half-lives of anti-TNF biologics are 10 days for IFX and 14 days for ADA and golimumab (GLM). Given that there is increased transplacental transfer during the third trimester of pregnancy, the general strategy is to stop anti-TNF dosing during the third trimester, a strategy that reduces anti-TNF drug concentrations in the newborn and allows drug clearance within a few months. In contrast, the half-life of VDZ is much longer (25 days), and so a strategy of withholding dosing during the third trimester would still result in substantial VDZ concentrations in the mother as the third trimester starts, and thus theoretically result in substantial concentration of VDZ in the fetus prior to delivery, leading to prolonged drug clearance in the newborn infant that could extend to 6–12 months. The consequences of this prolonged drug exposure in the infant are unknown. For these reasons, the intentional use of VDZ during pregnancy will require careful consideration on a case-by-case basis, and extensive discussion with the parents regarding the uncertainties described above. Post-natal vaccination strategies need to take these considerations into account. Vaccination against enteric infection with rotavirus is administered at 6 months; whether the baby is at increased risk of rotavirus, or vaccination is best avoided, would be informed by measurement of neonatal circulating levels of VDZ. Fortunately, devastating consequences of anti-TNF therapy to the mother after live (BCG) vaccination in the baby are improbable.

It is not known whether VDZ is excreted in human milk. Low levels (<300 μg/L) of VDZ were detected 1 month post partum in the milk of 3/11 cynomolgus monkeys treated with 100 mg/kg of vedolizumab every 2 weeks, though not in any animals that received 10 mg/kg. Based on these data, as well as experience with anti-TNF agents, breast-feeding while taking VDZ is probably reasonable, but will require discussion with the individual.

4.7. VDZ for perianal disease?
The GEMINI II trial included 57 patients with draining fistulae at baseline. At 52 weeks, 41.2% of the VDZ 8-weekly group achieved fistula closure compared with 22.7% of the VDZ 4-weekly group and 11.1% of the placebo group (p = 0.03, p = 0.32 versus placebo respectively). Conservative interpretation of this borderline significance is warranted, due to small numbers and post hoc analysis. Preliminary data from the GEMINI-LTS extension study reports a higher incidence (2%) of new perianal abscess formation amongst VDZ-treated patients with CD. Similar cautions regarding small numbers and post hoc analyses apply. Consequently, no definitive recommendations regarding the use of VDZ for the treatment of perianal CD can be made at present.

4.8. What about patients with extra-intestinal manifestations?
There are no data evaluating VDZ for extra-intestinal manifestations of IBD. Given the gut-specific mechanism of VDZ, it may seem unlikely that patients with extra-intestinal manifestations might derive benefit from VDZ, but some (erythema nodosum, episcleritis) are associated with active luminal disease. These might be assumed to benefit from VDZ. It is an area for study, especially in the neutrophilic dermatoses, where mechanisms of inflammation are similar to IBD.

4.9. What about VDZ for primary sclerosing cholangitis?
Although speculative, VDZ holds theoretical promise for the treatment of primary sclerosing cholangitis (PSC), which affects 3–10% of patients with IBD. In PSC, hepatic inflammation driven by TNF-α and methylamines in the portal circulation results in aberrant hepatic expression of MadCAM1 and the chemokine CCL25. Expression of MadCAM1 leads to enhanced recruitment of α4β7 and the CCL25 receptor CCR9. Randomized trials
of VDZ in patients with IBD–PSC are under way (clinicaltrials.gov NCT00783692 and NCT01316939).

5. WHEN to use VDZ?

5.1. Is VDZ best used before or after anti-TNF therapy?

In GEMINI I (VDZ for UC), 55% of patients were naive and 39% had failed anti-TNF therapy. VDZ was incrementally more effective in inducing a response in those who had only failed corticosteroids \((n = 67, 59.5\% \text{ versus } 20.0\% \text{ for placebo, } p < 0.001)\), in contrast to those failing immunosuppressives \((n = 150, 49\% \text{ versus } 34.5\%, p = 0.08)\), although significant for previous anti-TNF therapy \((n = 145, 39\% \text{ versus } 20.6\%, p = 0.01)\). GEMINI I did not show differences in the maintenance arm. NICE has recommended VDZ for patients with UC naive to or intolerant of anti-TNF therapy. Inexplicably, NICE proposals advise against VDZ for patients failing anti-TNF therapy.22 For UC, therefore, VDZ is well placed as the next step after failure of steroids/immunosuppressives and before anti-TNF therapy, and, despite the NICE recommendations, for patients who have also failed anti-TNF therapy.

For CD, the jury is still out. In GEMINI III, there was significant benefit for induction of clinical remission in CD at 12 weeks compared with placebo \((p = 0.01)\). Amongst those naive to TNF therapy, a larger proportion achieved clinical remission in GEMINI III at 12 weeks \((35.3\% \text{ versus } 16.0\% \text{ for placebo, } p = 0.025)\). The GEMINI II trial did not show significant differences between VDZ as either induction or maintenance therapy compared with placebo for anti-TNF-naive patients \((17.1\% \text{ versus } 10\% \text{ for placebo, } p = 0.24)\); 44.4% for VDZ 4-weekly versus 32.7% for placebo, \(p = 0.22\). Consequently, VDZ for remission induction and maintenance in CD shows efficacy in anti-TNF-naive patients, albeit perhaps somewhat less than with anti-TNF therapy, and after anti-TNF failure it has modest efficacy, but remains an option for patients with active inflammatory disease.

5.2. What about VDZ before immunosuppressive (azathioprine/methotrexate) therapy?

Cochrane meta-analyses of generally poor quality data report azathioprine to be superior to placebo for remission maintenance in UC \((RR 0.68, 95\% CI 0.54–0.86)\); however, data on induction are even more limited.52,53 Methotrexate appears no better than placebo.44 Almost one in five patients discontinue thiopurine or methotrexate due to adverse effects.55 VDZ is better tolerated and may have greater efficacy in UC. Immunosuppressive therapy costs around €235 for 8 weeks of therapy, whereas VDZ costs around €2670/2 for every 2 months \(300\text{mg}\) dose in the European Union. NICE has approved VDZ for patients with moderate or severely active UC refractory to steroids or immunosuppressives, but (currently) not for failure of anti-TNF therapy. Data for CD are less compelling. Azathioprine early in the course of CD does not induce sustained clinical remission compared with placebo.56,57 Although cost is a substantive factor, powerful arguments in favour of VDZ in jurisdictions where cost does not dominate decision-making. Selecting VDZ for patients with steroid-dependency who are intolerant of thiopurines or methotrexate is clearly appropriate. It is too early to say that VDZ should precede immunosuppressives, although this can be justified when there is particular concern about the risk of systemic infection or previous malignancy.

5.3. How about VDZ for early disease?

Disease duration appeared not to matter in GEMINI I and II. Such data are, however, gleaned from subgroup analyses, which the trial was inadequately powered to assess. Early anti-TNF therapy for CD, with or without immunosuppressives, improves outcomes of hospitalization, surgery, or corticosteroid requirement.58–60 Suppression of inflammation early in the course of disease to avoid disease progression works in other inflammatory conditions.61–63 The biology of VDZ supports early use, which is the current direction of IBD therapy. Early treatment trials with VDZ are necessary.

5.6. What role for VDZ in peri-operative disease or post-operative prophylaxis?

There are no data on the peri-operative safety of VDZ in either UC or CD. This is important, especially for emergency surgery, with regard to bacterial translocation and gut-related infection. Maintenance of surgically induced remission is also important, given that around 50% of patients will require intestinal resection within 10 years of diagnosis.64 The mechanism of action of VDZ, preventing the early stages of inflammation, suggests likely benefit in reducing post-operative relapse. Trials are warranted. The tolerability and safety profile of VDZ is attractive.

6. HOW best to use VDZ?

6.1. What about therapeutic drug monitoring, antibodies, or and dose intensification?

Vedolizumab is a highly specific humanized monoclonal IgG1 antibody to the human integrin α4β7. During the development of VDZ, a mouse myeloma cell line preparation (MLN02, MLN002) induced anti-drug antibodies in 38% of patients.65,66 When this changed to a Chinese hamster ovary cell line,67 antibody-dependent cell-mediated or complement-dependent cytotoxicity diminished. In the GEMINI trials, transient anti-drug antibodies occurred in 1.0–4.1% of patients (tested every 12 weeks), and overall <1% had persistently positive anti-drug antibodies, consistent with subsequent experience.68 Concurrent immunosuppressive therapy is protective against the formation of anti-drug antibodies to VDZ, particularly in the setting of discontinuous use. Persistently positive anti-drug antibodies were present in 12% of those randomized to placebo as maintenance therapy without concurrent immunosuppressive therapy in the GEMINI trials, whereas no patients developed anti-drug antibodies when maintained with VDZ and concomitant immunosuppressive therapy. The ELISA assay used to measure anti-drug antibodies, coupled with the long half-life of VDZ, may lead to underestimation of levels in the context of detectable drug.65,66,70 Amongst patients randomized to the 8-weekly VDZ maintenance arm, anti-drug antibodies were evident in only 3% of patients whilst on therapy, rising to 15% once VDZ was ceased for 16 weeks.70 Dose-ranging studies (2, 6, and 10 mg/kg) demonstrate that VDZ maximally saturates α4β7 receptors on peripheral lymphocytes.71,72 Furthermore, 300 mg, either 4- or 8-weekly, saturated more than 95% of the target receptors in almost all patients. However, there was an association between higher VDZ concentrations and greater clinical efficacy, suggesting that the VDZ concentrations required for efficacy may exceed the concentrations required to achieve saturation of target receptors in peripheral blood.5,10
6.2. Speed of action?
Vedolizumab appears to act more slowly than anti-TNF therapy. The lack of a plateau in the mean partial Mayo score after induction in GEMINI I means that it is likely to be beyond 6 weeks. Efficacy in CD was inconsistently evident at 6 weeks in GEMINI II and III, but clearly demonstrated after 10 weeks in GEMINI III. It seems reasonable to assess the efficacy of VDZ at 10 weeks or later, before deciding whether to continue therapy, although longer may be necessary. Predictors of early or later response need exploring.

6.3. Will combination therapy help?
A singular asset of VDZ is its lack of systemic immunosuppression. Why then add or continue an immunosuppressive when immunogenicity is limited? No difference in efficacy between VDZ monotherapy and combination therapy was identified in the GEMINI studies but, like the ACCENT and ACT trials, they were not powered for detection and were likely subject to significant confounding by indication. As discussed above, combination therapy does protect against immunogenicity, which would be expected to improve efficacy. It should be noted that with anti-TNF therapy, prospective trials in which patients were randomized to monotherapy versus combination therapy were required to demonstrate the profound benefits of combination therapy. Monotherapy with VDZ has appreciable appeal, which will find favour with patients and clinicians. However, it appears probable that, like anti-TNF therapy, monotherapy will be associated with higher rates of immunogenicity and lower efficacy. Clinical trials are needed to clarify this issue.

7. Is the cost prohibitive?
Drug costs are high, but pharmacoeconomic modeling appears favorable for UC. Markov modeling simulated clinical progression of moderate to severely active UC during maintenance therapy over 10 years. This was compared with conventional therapy and surgery and anti-TNF therapies in anti-TNF-naive patients. Modeling found VDZ less costly than surgery in patients who had previously failed or were naive to anti-TNF therapy. The incremental cost-effectiveness ratio (ICER) for VDZ compared with conventional therapy was £33,297 per quality-adjusted life year (QALY) gained. For the anti-TNF-naive, the cost-effectiveness of VDZ was £4682 compared with conventional therapy and £6634 compared with adalimumab for UC. In patients who had failed anti-TNF therapy, however, the ICER for VDZ was £64,999 per QALY gained compared with conventional therapy.

8. Conclusions
The lack of systemic immunosuppression and tolerability combined with efficacy make VDZ appealing. VDZ is well placed to be a first-line biologic treatment for remission induction and maintenance in outpatients with moderate or severely active UC who have failed conventional therapy. For CD, VDZ is effective for induction in biologic-naive patients, albeit perhaps less so than anti-TNF therapy, and it is effective for maintenance in this patient population. GEMINI III makes VDZ appealing for patients who have failed anti-TNF therapy, as long as the time to response (>10 weeks) is acceptable. VDZ is potentially an effective option for subgroups, including patients predisposed to infection or malignancy, and treatment of early disease in the young or elderly, though further data are needed (Figure 1). Head-to-head comparisons between VDZ and other biologic agents should be a research priority, as are also pragmatic studies to evaluate cost-effectiveness.

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Conflict of interest

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References
Vedolizumab in practice


Appendix 1
Supplementary Methods

A bibliographic search for relevant studies from inception to 10 December 2014 was performed of the online databases MEDLINE, EMBASE, PubMed, and the Cochrane Library. Also searched was the ISI Web of Science and conference abstracts (Digestive Diseases Week and European Crohn’s Colitis Organisation Congress, 2005 to present). Each database was searched for Medical Library Subject heading (MeSH) terms and key words: (‘inflammatory bowel diseases’ OR ‘Crohn disease’ OR ‘ulcerative colitis’ OR ‘colitis’) AND (‘vedolizumab’ OR ‘MLN0002’ OR ‘anti-integrin’ OR ‘integrin alpha4beta7’). Randomized studies, case-controlled studies, cohort studies, meta-analyses, and review articles were included. Case reports, non-English articles, and studies pertaining to non-human subjects were excluded. Citations, abstracts, and retrieved full-text publications of all eligible articles were reviewed and screened for relevance by authors.

A total of 89 articles were returned using the initial search and, after application of exclusion criteria, 56 articles were screened for relevance and a recursive search of articles referenced in the bibliographies of retrieved articles was performed.

There were four RCTs\textsuperscript{9,66,72,75} and a single Cochrane review\textsuperscript{12} comparing the use of VDZ with placebo in patients with UC. There were four RCTs comparing the use of VDZ with placebo in patients with CD.\textsuperscript{9,11,65,76}