

## REVIEW

### Vedolizumab in the treatment of inflammatory bowel disease: evolving paradigms

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#### Abstract

Inflammatory bowel diseases, comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing and remitting immune-mediated inflammatory diseases affecting the gastrointestinal tract. Vedolizumab is the first licensed drug in a group of 'gut-selective' biological agents used to treat inflammatory bowel diseases. The GEMINI registrational trials established the efficacy of vedolizumab for the induction and maintenance of remission in both CD and UC, with the most favourable results in tumour necrosis factor (TNF)-antagonist-naïve patients. In recent years, a wealth of 'real-world' data has emerged supporting positive clinical, endoscopic and histological outcomes in patients treated with vedolizumab (VDZ) as well as reassuring safety data. More recently, the results of the first head-to-head trials of VDZ and TNF antagonists have been reported, as well as the results of a number of studies exploring the role of therapeutic drug monitoring

with VDZ. This review brings together data reported on VDZ to date, including from the GEMINI trials, real-world data and emerging studies regarding therapeutic drug monitoring and immunogenicity. The safety profile of VDZ is also reviewed. Evolving treatment paradigms are explored, including data regarding the role of VDZ in perianal CD, post-operative complications and recurrence, extraintestinal manifestations and pregnancy.

**Keywords:** Crohn's disease, inflammatory bowel diseases, mucosal healing, safety, therapeutic drug monitoring, ulcerative colitis, vedolizumab.

#### Citation

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#### Introduction

Inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and ulcerative colitis (UC) are chronic, relapsing and remitting immune-mediated inflammatory diseases affecting the gastrointestinal tract.<sup>1,2</sup> Conventional management has included use of broad-spectrum anti-inflammatory drugs such as aminosalicylates and corticosteroids or immunosuppressants such as thiopurines or methotrexate, often in a step-up manner, aiming to relieve symptoms and to an extent prevent long-term complications.<sup>3</sup> The advent of anti-tumour necrosis factor (anti-TNF) therapy, showing efficacy in the induction and maintenance of remission, corticosteroid-sparing effects, mucosal healing and reduced rates of hospitalisation and surgery, has redefined meaningful disease control, providing much-needed impetus to the development of other biological therapies.<sup>3,4</sup> Anti-TNF therapies are not universally effective, with up to 30% of patients demonstrating primary non-responsiveness and with 50% of patients showing secondary

loss of response due to intolerance, immunogenicity or mechanistic failure.<sup>5,6</sup> Furthermore, there is a risk of infectious complications attributable to non-specific TNF-mediated inhibition.<sup>4,7</sup>

Meanwhile, evolution of our understanding of T-lymphocyte biology orchestrating gut inflammation has led to the development of several agents directed against trafficking of effector T lymphocytes towards the gut mucosa.<sup>8</sup> The premise for this development was the recognition that tissue injury in CD and UC occurs in areas where activated lymphocytes produce an array of inflammatory mediators. These cells are recruited from the bloodstream as a result of increased expression of adhesion molecules on the intestinal vascular endothelium and integrins on lymphocytes and excessive production of chemokines within the inflammatory microenvironment.<sup>8</sup> Inhibition of leukocyte recruitment to the gut mucosa during the inflammatory process is a novel therapeutic target. Vedolizumab (VDZ) is the first and currently

only licensed drug in this group of ‘gut-selective’ biological agents.<sup>9–12</sup> The aim of this review is to summarise the current literature regarding the mechanism of action of VDZ, data from registrational trials on safety and efficacy, including open-label extension (OLE), observational and emerging real-world evidence on its effectiveness in the treatment of IBD, and evolving paradigms with VDZ. A thorough literature search was conducted using PubMed to identify all relevant articles published until August 2019.

## Mechanism of action

As leukocytes travel through the bloodstream, a highly coordinated sequential adhesion pathway is activated, involving tethering, rolling, activation, adhesion and migration through the vascular wall. Infiltrating leukocytes secrete pro-inflammatory cytokines, leading to endothelial cell activation and up-regulation of adhesion molecules with enhancement of inflammatory cell recruitment.<sup>13</sup> Adhesion molecules belong to the integrin family (leukocyte cell-surface adhesion molecules), which allow them to stop rolling and start migration through the vascular wall. Integrins involved in T-cell migration are leukocyte function-associated antigen 1 (LFA-1 or  $\alpha 2\beta 2$ ) and the two  $\alpha 4$ -integrins ( $\alpha 4\beta 1$  and  $\alpha 4\beta 7$ ).<sup>13,14</sup> The subunit  $\alpha$  is connected to specificity, and subunit  $\beta$  relates to signalling. Integrins bind to specific ligands on the endothelium called addressins or adhesion molecules. The integrin  $\alpha 4\beta 7$  is expressed on lymphocytes in gut-associated lymphoid tissue, which interacts with mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1). This class of biological agents includes the integrins  $\alpha 4\beta 1$ ,  $\alpha 4\beta 7$  and  $\alpha 2\beta 2$ , which interact with vascular cell adhesion molecule 1 (VCAM-1), MAdCAM-1 and intercellular adhesion molecule 1 (ICAM-1), respectively.<sup>14</sup> These are monoclonal antibodies natalizumab (anti- $\alpha 4$  integrin), VDZ (anti- $\alpha 4\beta 7$  integrin), AMG181 (anti- $\alpha 4\beta 7$  integrin) and etrolizumab (anti- $\beta 7$  integrin targeting both  $\alpha 4\beta 7$  and  $\alpha E\beta 7$  integrin). Others in this class are AJM-300 (inhibits the  $\alpha 4$  integrin subunit) and alicaforsen, an antisense nucleotide against ICAM-1 messenger RNA. The interaction between  $\alpha 4\beta 7$  and MAdCAM-1 activates the gut-specific migration of lymphocytes to Peyer’s patches.<sup>14</sup>

VDZ is a humanized immunoglobulin (Ig) G1 monoclonal antibody, which binds to  $\alpha 4\beta 7$ . It does not involve  $\alpha 4\beta 1$ –VCAM interactions or T-cell trafficking to the brain or kidney. As such, it is not directly linked with risk of progressive multifocal leukoencephalopathy (PML), which is a rare viral disease associated with high mortality.<sup>15,16</sup> VDZ received regulatory approval (The US Food and Drug Administration [FDA] and the European Medicines Agency) for the treatment of patients with moderate-to-severe UC and CD, in 2014.<sup>9–11</sup>

Recent research has indicated that VDZ may also have an effect through modulation of innate immunity, particularly macrophage populations, and this activity correlates with clinical efficacy.<sup>17</sup>

## VDZ in CD

The registrational GEMINI 2 trial included patients with moderately to severely active CD and evidence of inflammation (C-reactive protein [CRP] >2.87 mg/L, faecal calprotectin >250  $\mu\text{g/g}$  stool and evidence of ulcers at colonoscopy and imaging).<sup>10</sup> It has two co-primary endpoints at week 6, namely clinical remission (Crohn’s disease activity index [CDAI]  $\leq 150$  points) and a CDAI-100 response ( $\geq 100$ -point decrease in CDAI; Table 1). For maintenance therapy, the primary endpoint was clinical remission at week 52. A total of 368 patients were randomized; 14.5% achieved remission on VDZ as opposed to 6.8% on placebo ( $p=0.02$ ), and a CDAI-100 response was achieved by 31.3% treated with VDZ versus 25.7% on placebo ( $p=0.23$ ). Clinical remission was achieved at week 52 in 39% receiving VDZ 8-weekly, 36.4% receiving VDZ 4-weekly and 21.6% receiving placebo.<sup>10</sup>

The GEMINI 3 trial had a 10-week induction period and enrolled 416 patients with moderately to severely active CD; the majority (76%) had previously failed anti-TNF therapy.<sup>11</sup> The primary endpoint was clinical remission at week 6. Clinical remission at week 10 and a CDAI-100 response at week 6 and week 10 were secondary endpoints. There were 315 CD patients with anti-TNF intolerance or failure, of whom 15.2% treated with VDZ and 12.1% on placebo achieved clinical remission at week 6 ( $p=0.433$ ). Clinical remission was achieved at week 10 by 26.6% patients treated with VDZ as against 12.1% on placebo (95% confidence interval [CI]: 1.3–3.6;  $p<0.001$ ).<sup>11</sup> VDZ was found to be more effective than placebo for induction of remission in anti-TNF-naïve patients (35.3 versus 16.0%,  $p=0.025$ ) in a subgroup analysis.<sup>11</sup> A Cochrane systematic review also found that for the induction of remission, VDZ was superior to placebo (relative risk [RR]=0.86, 95% CI: 0.80–0.91).<sup>12</sup>

In a further analysis of patients enrolled in GEMINI 2 and GEMINI 3, of 516 anti-TNF-naïve and 960 anti-TNF-exposed patients, clinical remission in anti-TNF-naïve patients at week 6 (22.7 versus 10.6%, 95% CI: 3.7–21.4) and week 10 (26.6 versus 15.4%, 95% CI: 1.5–21.1) were noted.<sup>18</sup> Higher rates of clinical remission were achieved by patients naïve to anti-TNF therapy at week 52, compared with placebo (48.9 versus 26.8%, 95% CI: 8.9–35.4). Among patients previously unresponsive to anti-TNF agents, clinical remission with VDZ and placebo at week 6 were comparable (13.3 versus 9.7%, 95% CI: –1.6–9.8). Clinical remission rates at week 10, however, were higher in VDZ-treated patients (21.8 versus 11.0%, 95% CI: 4.5–18.6).<sup>18</sup>

During maintenance also, clinical remission was higher for VDZ-treated patients with prior anti-TNF failure against placebo at week 52 (27.7 versus 12.8%, 95% CI: 4.7–25.0). Taken together, the data suggest that prior anti-TNF antagonist failure is associated with more refractoriness to induction therapy possibly requiring a relatively longer treatment period to demonstrate benefit. In contrast, responders to VDZ have a durable treatment benefit irrespective of prior TNF antagonist exposure.<sup>18</sup>

**Table 1. GEMINI studies summary.**

| Study   | n   | Endpoint                                       | Week 6   | Week 52  |
|---|---|--|--|--|
| GEMINI I<br>RCT<br>Feagan et al. <sup>9</sup>     | <b>Induction</b><br>n=374 (UC)<br>(225 VDZ, 149 placebo)                  | Clinical response                              | <b>47% VDZ versus 26% placebo (p&lt;0.001)<sup>a</sup></b> |  |
|   |   | Clinical remission                             | 17% VDZ versus 5% placebo (p=0.001) <sup>b</sup>           | <b>42% VDZ q8 versus 45% VDZ q4 versus 16% placebo<sup>a</sup></b> |
|   | <b>Maintenance</b><br>n=373 (UC)<br>(125 VDZ q4, 122 VDZ q8, 126 placebo) | Mucosal healing                                | 41% VDZ versus 25% placebo (p=0.001) <sup>b</sup>          | 52% VDZ q8 versus 56% VDZ q4 versus 20% placebo <sup>b</sup>       |
| GEMINI II<br>RCT<br>Sandborn et al. <sup>10</sup> | <b>Induction</b><br>n=368 (CD)<br>(220 VDZ, 148 placebo)                  | Clinical response                              | <b>31% VDZ versus 26% placebo (p=0.23)<sup>a</sup></b>     | 44% VDZ q8 versus 46% VDZ q4 versus 30% placebo <sup>b</sup>       |
|   |   | Clinical remission                             | <b>15% VDZ versus 7% placebo (p=0.02)<sup>a</sup></b>      | <b>39% VDZ q8 versus 36% VDZ q4 versus 22% placebo<sup>a</sup></b> |
| GEMINI III<br>RCT<br>Sands et al. <sup>11</sup>   | n=416 (CD)<br>(209 VDZ, 207 placebo)                                      | Clinical response (anti-TNF failure subgroup)  | 39% VDZ versus 22% placebo (p=0.001) <sup>b</sup>          | 47% VDZ versus 25% placebo (p<0.001) <sup>b</sup>                  |
|   |   | Clinical response (all-comers)                 | 39% VDZ versus 23% placebo (p=0.0002) <sup>b</sup>         | 48% VDZ versus 24% placebo (p<0.0001) <sup>b</sup>                 |
|   |   | Clinical remission (anti-TNF-failure subgroup) | <b>15% VDZ versus 12% placebo (p=0.443)<sup>a</sup></b>    | 27% VDZ versus 12% placebo (p=0.001) <sup>b</sup>                  |
|   |   | Clinical remission (all-comers)                | 29% VDZ versus 13% placebo (p<0.0001) <sup>b</sup>         | 19% VDZ versus 12% placebo (p=0.048) <sup>b</sup>                  |

<sup>a</sup>study primary endpoint (in bold text); <sup>b</sup>study secondary endpoint.

CD, Crohn's disease; q4, 4-weekly; q8, 8-weekly; RCT, randomized controlled trial; TNF, tumour necrosis factor; UC, ulcerative colitis; VDZ, vedolizumab.

The GEMINI OLE study followed clinical responders from the randomized trials who completed at least 52 weeks of treatment. Sixty-one of 146 patients had 248 weeks of therapy.<sup>19</sup> Of these, 95 and 89% of patients maintained clinical response and remission, respectively, with consistent treatment benefits through weeks 52 and 248.<sup>19</sup>

Finally, the prevailing notion that therapies targeting lymphocyte trafficking are slow to act has been challenged by post hoc analysis of the GEMINI trials, which reported significant improvements in patient-reported outcomes of abdominal pain and stool frequency as early as 2 weeks.<sup>20</sup>

## 'Real-world' experience in CD

Real-world data provide greater insights into the effectiveness of therapy in a heterogeneous and more

complex patient population representative of clinical practice (Table 2). A growing body of evidence from real-world data for VDZ provides credible evidence for its effectiveness and safety. In a systematic review of data from 994 participants, clinical response and remission rates at week 6 were 54% (95% CI: 41–66%) and 22% (95% CI: 13–35%), with similar rates at week 14.<sup>21</sup> Remission was noted in 32% (95% CI: 12–62%) of patients at week 52.<sup>21</sup> The results were similar to the GEMINI studies although the proportion of anti-TNF-naïve patients in the real-world data was very small (8.5%) as compared to GEMINI II (38.2%).<sup>10,21</sup> Another recent systematic review with meta-analysis of real-world data noted 30% of CD patients to be in clinical remission by week 14 (95% CI: 25–34%) and at 12 months (95% CI: 20–42%), with higher rates in bio-naïve patients achieving clinical remission in 48% of patients at week 14

**Table 2. Real-world studies for vedolizumab.**

| Study  | n                                       | Endpoint                          | Week 6                 | Week 14                | Week 26                | Week 52                                 | Week 104                                     |
|--|---|-----------------------------------|------------------------|------------------------|------------------------|---|--|
| Engel et al. <sup>21</sup>   | n=1565<br>(994 CD, 571 UC)              | CD clinical response              | 56%                    | 49%                    |                        | 45%                                     |  |
| Systematic review and pooled analysis                              |   | UC clinical response              | 43%                    | 51% (week 12–22)       |                        | 48%                                     |  |
|  |   | CD clinical remission             | 22%                    | 32%                    |                        | 32%                                     |  |
|  |   | UC clinical remission             | 25%                    | 30% (week 12–22)       |                        | 39%                                     |  |
|  |   |                                   |                        |                        |                        |   |  |
| Schreiber et al. <sup>22</sup>                                     | n=9486<br>(4532 CD, 3216 UC, 1738 IBDU) | CD clinical response              |                        | 58% <sup>b</sup>       |                        | 49% <sup>b</sup>                        |  |
| Systematic review and meta-analysis                                |   | UC clinical response              |                        | 56% <sup>b</sup>       |                        | 52% <sup>b</sup>                        |  |
|  |   | CD clinical remission             | <b>24%<sup>a</sup></b> | <b>30%<sup>a</sup></b> | <b>26%<sup>a</sup></b> | <b>30%<sup>a</sup></b>                  |  |
|  |   | UC clinical remission             | <b>24%<sup>a</sup></b> | <b>32%<sup>a</sup></b> | <b>39%<sup>a</sup></b> | <b>46%<sup>a</sup></b>                  |  |
|  |   | CD CFCR                           |                        |                        |                        | 31% <sup>b</sup>                        |  |
|  |   | UC CFCR                           |                        |                        |                        | 42% <sup>b</sup>                        |  |
| Kopylov et al. <sup>23</sup>                                       | n=184 (anti-TNF naive)                  | CD clinical response              |                        | <b>84%<sup>a</sup></b> |                        | 77% <sup>b,c</sup>                      |  |
| Multicentre retrospective study                                    | (50 CD, 134 UC)                         | UC clinical response              |                        | <b>79%<sup>a</sup></b> |                        | 77% <sup>b,c</sup>                      |  |
|  |   | CD clinical remission             |                        | 64% <sup>b</sup>       |                        | 69% <sup>b,c</sup>                      |  |
|  |   | UC clinical remission             |                        | 40% <sup>b</sup>       |                        | 67% <sup>b,c</sup>                      | Data from last follow-up (i.e. not 52 weeks) |
|  |   | CD mucosal healing                |                        |                        |                        | 46% <sup>b,c</sup>                      |  |
|  |   | UC mucosal healing                |                        |                        |                        | 59% <sup>b,c</sup>                      |  |
|  |   | CD CFCR                           |                        | 52% <sup>b</sup>       |                        | 60% <sup>b,c</sup>                      |  |
|  |   | UC CFCR                           |                        | 37% <sup>b</sup>       |                        | 59% <sup>b,c</sup>                      |  |
| Lenti et al. <sup>24</sup>   | n=203<br>(135 CD, 68 UC)                | CD clinical response or remission |                        | <b>79%<sup>a</sup></b> |                        | <b>64%<sup>a</sup></b>                  |  |
| <b>The Cross Pennine Study:</b><br>Multicentre retrospective study |   | UC clinical response or remission |                        | <b>91%<sup>a</sup></b> |                        | <b>83%<sup>a</sup></b>                  |  |
| Bressler et al. <sup>25</sup>                                      | n=419 (CD)<br>(biologic naive)          | Clinical response                 |                        |                        |                        | 74.5% VDZ<br>versus 73.4% anti-TNF (ns) |  |
| <b>EVOLVE:</b><br>Multicentre retrospective study                  | (177 VDZ,<br>242 anti-TNF)              | Clinical remission                |                        |                        |                        | 69.7% VDZ<br>versus 66.4% anti-TNF (ns) |  |
|  |   | Mucosal healing                   |                        |                        |                        | 100% VDZ<br>versus 90.1% anti-TNF (ns)  |  |
|  |   |                                   |                        |                        |                        |   |  |

(Continued)

Table 2. (Continued)

| Study   | n   | Endpoint  | Week 6                  | Week 14          | Week 26                 | Week 52                                    | Week 104                             |
|---|---|---|-------------------------|------------------|-------------------------|--|--------------------------------------|
|   |   | Treatment persistence                                   |                         |                  |                         | 85.6% VDZ versus 76% anti-TNF ( $p=0.02$ ) | 71.4% VDZ versus 70.7% anti-TNF (ns) |
| Dulai et al. <sup>26</sup>  | $n=212$ (CD)  | Clinical remission                                      | <b>11%</b> <sup>a</sup> |                  | <b>18%</b> <sup>a</sup> | <b>35%</b> <sup>a</sup>                    |                                      |
| <b>US VICTORY Consortium:</b><br>Multicentre retrospective cohort study |   | Mucosal healing   |                         |                  | <b>20%</b> <sup>a</sup> | <b>63%</b> <sup>a</sup>                    |                                      |
|   |   | Deep remission (clinical remission and mucosal healing) |                         |                  |                         | 26% <sup>b</sup>                           |                                      |
| Danese et al. <sup>30</sup>   | $n=101$ (CD)  | Clinical response                                       |                         |                  | 60% <sup>b</sup>        | 59% <sup>b</sup>                           |                                      |
| <b>VERSIFY:</b><br>Phase 3b, open-label, single-group prospective study |   | Clinical remission                                      |                         | 34% <sup>b</sup> | 42% <sup>b</sup>        | 50% <sup>b</sup>                           |                                      |
|   |   | Endoscopic response                                     |                         |                  | 25% <sup>b</sup>        | 54% <sup>b</sup>                           |                                      |
|   |   | Endoscopic remission                                    |                         |                  | <b>12%</b> <sup>a</sup> | 18% <sup>b</sup>                           |                                      |
|   |   | Complete mucosal healing                                |                         | 12% <sup>b</sup> | 15% <sup>b</sup>        | 18% <sup>b</sup>                           |                                      |
| Lowenberg et al. <sup>31</sup>  | $n=110$ (CD)  | Clinical response                                       |                         |                  | 38%                     | 35%  |                                      |
|   |   | CFCR  |                         |                  | 29%                     | 31%  |                                      |
| <b>LOVE-CD:</b><br>Open-label, prospective study                        |   | Endoscopic response                                     |                         |                  | 40%                     | 45%  |                                      |
|   |   | Endoscopic remission                                    |                         |                  | 33%                     | 36%  |                                      |
|   |   | Histological remission                                  |                         |                  | 64% (GS), 66% (RHI)     |  |                                      |
| Narula et al. <sup>33</sup>   | $n=321$ (UC)  | Clinical response                                       |                         |                  | 54% <sup>b</sup>        | 75% <sup>b</sup>                           |                                      |
| <b>US VICTORY Consortium:</b><br>Multicentre retrospective cohort study |   | Clinical remission                                      |                         |                  | <b>36%</b> <sup>a</sup> | <b>51%</b> <sup>a</sup>                    |                                      |
|   |   | Endoscopic remission                                    |                         |                  | <b>18%</b> <sup>a</sup> | <b>41%</b> <sup>a</sup>                    |                                      |
|   |   | CFCR  |                         |                  | 21% <sup>b</sup>        | 37% <sup>b</sup>                           |                                      |
| Yarur et al. <sup>34</sup>  | $n=527$ (UC) (biologic naive) (325 VDZ, 202 anti-TNF) | Clinical response                                       |                         |                  |                         |  | 90.8% VDZ versus 85.7% anti-TNF (ns) |
| <b>EVOLVE:</b><br>Multicentre retrospective study                       |   | Clinical remission                                      |                         |                  |                         |  | 79% VDZ versus 66.2% anti-TNF (ns)   |
|   |   | Mucosal healing   |                         |                  |                         |  | 92% VDZ versus 84.4% anti-TNF (ns)   |

(Continued)

**Table 2. (Continued)**

| Study  | n                             | Endpoint               | Week 6 | Week 14 | Week 26 | Week 52  | Week 104                                     |
|--|-------------------------------|------------------------|--------|---------|---------|--|--|
|  |                               | Treatment persistence  |        |         |         |  | 75.1% VDZ versus 53.8% anti-TNF ( $p<0.01$ ) |
| Sands et al. <sup>37</sup>                           | n=769 (UC) (383 VDZ, 386 ADA) | Clinical remission     |        |         |         | <b>31% VDZ versus 23% ADA (<math>p=0.006</math>)<sup>a</sup></b> |  |
| <b>VARSITY:</b><br>Phase 3b randomized control trial |                               | Endoscopic improvement |        |         |         | 40% VDZ versus 28% ADA ( $p<0.001$ ) <sup>b</sup>                |  |
|  |                               | CFCR                   |        |         |         | 13% VDZ versus 22% ADA (ns) <sup>b</sup>                         |  |

<sup>a</sup>study primary endpoint (in bold text); <sup>b</sup>study secondary endpoint; <sup>c</sup>data from last follow-up (i.e. not 52 weeks).

ADA, adalimumab; CD, Crohn's disease; CFCR, corticosteroid free clinical remission; GS, Geboes score; IBDU, inflammatory bowel disease unspecified; LOVE-Cd, LOw Countries Vedolizumab in CD Study; ns, not significant; RHI, Robert's histopathology index; TNF, tumour necrosis factor; UC, ulcerative colitis; US VICTORY Consortium, US VICTORY (Vedolizumab for Health Outcomes in Inflammatory Bowel Diseases) Consortium; VDZ, vedolizumab.

(95% CI: 28–68%) and 44% of patients at 12 months (95% CI: 18–75%), respectively.<sup>22</sup>

Kopylov and colleagues evaluated the efficacy of VDZ in 184 anti-TNF-naïve patients from 23 centres across Europe.<sup>23</sup> In patients with CD, clinical response and remission at week 14 were observed in 84 and 64% of patients, respectively. Of those who continued with maintenance treatment, 68.6% were in clinical remission at last follow-up, with 60% in corticosteroid-free clinical remission (CFCR). About 94.5% of CD patients receiving an additional week 10 dose demonstrated clinical response.<sup>23</sup> In a multicentre UK study involving 203 patients with IBD treated with VDZ steroid, free remission at week 14 for CD was 38.3%, with 39.5% of patients ( $p=0.0021$ ) in CFCR by week 52.<sup>24</sup>

The recently presented EVOLVE study was a multicentre retrospective study, which assessed the effectiveness and safety of VDZ compared with anti-TNF agents in a real-world cohort of biologic-naïve patients with CD.<sup>25</sup> At 24 months, cumulative rates of clinical response, clinical remission, mucosal healing and dose escalation were similar in both cohorts. Treatment persistence was significantly ( $p<0.05$ ) greater at 12 (86 versus 76%) and 18 (79 versus 70%) months for VDZ versus anti-TNF patients, respectively, but did not differ at 24 months (71 versus 71%). VDZ proved equally effective in a first-line biologic setting for CD over 24 months.<sup>24</sup>

The US VICTORY (Vedolizumab for Health Outcomes in Inflammatory Bowel Diseases) Consortium included 212

patients with moderate-to-severe CD. Twelve-month cumulative rates of clinical remission, mucosal healing and deep remission (clinical remission and mucosal healing) were 35, 63, and 26%, respectively. Individuals with prior TNF antagonist exposure (hazard ratio (HR): 0.40; 95% confidence interval (CI): 0.20–0.81), smoking history (HR: 0.47; 95% CI: 0.25–0.89), active perianal disease (HR: 0.49; 95% CI: 0.27–0.88) and severe disease activity (HR: 0.54; 95% CI: 0.31–0.95) were less likely to achieve clinical remission.<sup>26</sup> In a subsequent publication from the same group, after adjusting for disease-related factors, including previous exposure to TNF antagonists, patients with early-stage CD (<2 years) were significantly more likely than patients with later-stage CD to achieve clinical remission (adjusted hazard ratio [aHR]: 1.59; 95% CI: 1.02–2.49), CFCR (aHR, 3.39; 95% CI: 1.66–6.92) and endoscopic remission (aHR, 1.90; 95% CI: 1.06–3.39).<sup>26</sup>

Taken together, 'real-world' studies suggest that predictors of a poor response include extensive and severe disease,<sup>21,23,26–28</sup> active perianal disease,<sup>21,26,28</sup> smoking history,<sup>21,26,28</sup> prior anti-TNF exposure,<sup>21,26,28</sup> prior surgery,<sup>27</sup> high CRP,<sup>21,27,28</sup> lack of clinical response at week 6<sup>29</sup> and corticosteroid use at induction.<sup>29</sup>

The recently reported VERSIFY study was the first prospective study of endoscopic, radiologic and histologic healing in 101 patients who received VDZ therapy for moderately severe CD (CDAI 220–450), had a simple endoscopic score for CD (simple endoscopic score for Crohn's disease [SES-CD]) of 7 or

more and experienced failure of conventional therapy.<sup>30</sup> The primary endpoint was endoscopic remission (SES-CD score  $\leq 4$ ) at week 26, achieved by 11.9% of patients (95% CI: 6.3–9.8). By week 52, 17.9% of the patients were in endoscopic remission (95% CI: 8.9–30.4). Higher proportions of patients naive to TNF antagonists achieved endoscopic remission than patients with TNF antagonist failure at weeks 26 and 52. Higher proportion of patients with moderate CD (SES-CD scores, 7–15) achieved endoscopic remission at weeks 26 and 52 than patients with severe CD (SES-CD scores above 15). Remission was detected by magnetic resonance enterography in 21.9% of patients at week 26 (95% CI: 9.3–40.0) and in 38.1% at week 52 (95% CI: 18.1–61.6). At week 52, 20.5% of patients had a histologic response in the colon (95% CI: 9.8–35.3), and 34.3% of patients had a histologic response in the ileum (95% CI: 19.1–52.2).<sup>30</sup>

The ability of VDZ to induce endoscopic and histological remission was also reported in a recent phase 4 open-label study from Europe.<sup>31</sup> In addition to standard induction, patients received an additional infusion at week 10 if their CDAI score had not decreased by  $\geq 70$  points. At weeks 26 and 52, 36 patients (29%) and 34 patients (31%), respectively, were in CFCR. Endoscopic remission (SES-CD score  $< 4$ ) was achieved by 36 patients (33%) and 40 patients (36%) at weeks 26 and 52. Histologic remission at week 26 was observed in 43 (64%) of 67 patients based on Geboes score and 37 (66%) of 56 patients based on Robarts histopathology index scores in analyses of paired biopsies with inflammation at baseline. Serum concentrations of VDZ above 10  $\mu\text{g/mL}$  at week 22 were associated with endoscopic remission at week 26.<sup>31</sup>

## VDZ in UC

In the GEMINI I study, patients with active UC were treated with VDZ (Table 1).<sup>9</sup> The primary endpoint was clinical response at week 6 (defined by a reduction in the Mayo score of  $\geq 3$  points and a decrease of at least 30% from baseline, with a decrease of  $\geq 1$  point on the rectal bleeding subscore (absolute score 0–1). For maintenance therapy, the primary endpoint was clinical remission at week 52. Among 374 patients randomized to VDZ or placebo, 47.1% achieved clinical response at week 6 in the VDZ group as compared with 25.5% in the placebo group (95% CI: 11.6–31.7;  $p < 0.001$ ). By week 52, 41.8% of patients treated with VDZ 8-weekly, 44.8% treated with VDZ 4-weekly, and 15.9% of patients receiving placebo achieved clinical remission. A Cochrane systematic review noted that VDZ was superior to placebo for clinical response (RR=0.82, 95% CI: 0.75–0.91), induction of remission (RR=0.86, 95% CI: 0.80–0.91), endoscopic remission (RR=0.82, 95% CI: 0.75–0.91) and remission at 52 weeks in week 6 responders (RR=2.73, 95% CI: 1.78–4.18).<sup>12</sup>

The GEMINI OLE included patients with at least 248 weeks of cumulative VDZ treatment ( $n=154$ ). Of patients responding to induction therapy and who completed the maintenance study,

40.9% of patients had 248 weeks of treatment; 98% achieved clinical response and 90% had clinical remission. Improvements in health-related quality of life were noted.<sup>32</sup>

Post hoc analysis of the GEMINI trials reported significant improvements in patient reported outcomes of reduction in rectal bleeding and stool frequency as early as 2 weeks.<sup>20</sup>

## ‘Real-world’ experience in UC

A growing body of evidence from real-world data provides further credible evidence for effectiveness and safety of VDZ (Table 2). Efficacy data from 9 open-label cohorts, from 571 UC patients, noted overall week 6 response and remission rates of 43% (95% CI 37–49%) and 25% (95% CI 12–45%), respectively.<sup>21</sup> The US VICTORY Consortium reported outcomes from 321 VDZ-treated UC patients, 71% of whom had failed anti-TNF treatment.<sup>33</sup> Clinical and endoscopic remission was achieved at 12 months by 51 and 41% of patients, respectively. Previous anti-TNF exposure was associated with lower rates of clinical (HR: 0.53, 95% CI: 0.38–0.75) and endoscopic remission (HR: 0.51, 95% CI: 0.29–0.88).<sup>33</sup>

The EVOLVE study for UC retrospectively assessed the safety and effectiveness of VDZ compared with anti-TNF agents in a real-world cohort of biologic naive patients.<sup>34</sup> At 24 months, cumulative rates of clinical response (91 *versus* 86%), clinical remission (79 *versus* 66%) and mucosal healing (92 *versus* 84%) were high in VDZ and anti-TNF patients, respectively, and did not differ significantly between groups. Higher treatment persistence (75 *versus* 54%;  $p < 0.01$ ) occurred in VDZ *versus* anti-TNF patients,<sup>34</sup> and dose escalation was more common in the anti-TNF group (25 *versus* 31%;  $p < 0.05$ ).

Kopylov and colleagues evaluated the efficacy of VDZ in 184 anti-TNF-naive patients from 23 centres across Europe.<sup>23</sup> Among 134 UC patients, 116 (79.1%) had a clinical response to treatment by week 14, including 53 (39.5%) in clinical remission; 49/134 (36.6%) achieved CFCR. At last follow-up (42.5 weeks; interquartile range: 30–52 weeks), 79/103 (76.7%) patients had a clinical response, 69/103 (67.0%) were in clinical remission, and 61/103 (59.2%) were in CFCR. Adverse effects were reported in 20 (11%) of patients, leading to treatment discontinuation in 6 (3.3%).<sup>23</sup> Taken together, real-world experience suggests that VDZ probably is more effective in anti-TNF-naive UC patients although a significant proportion of anti-TNF-exposed patients are able to attain clinical and endoscopic remission over time.

With an expanding therapeutic armamentarium, the inevitable question and challenge for clinicians and patients is choosing between treatment classes. Recently reported systematic reviews with network meta-analysis reported that VDZ and infliximab ranked highest for induction of clinical remission in biologic-naive UC patients<sup>35</sup> and that VDZ was associated with the lowest risk of serious adverse events (SAEs) and infections.<sup>36</sup> The VARSITY trial was the first head-to-head comparison, which compared intravenous infusions

of VDZ with subcutaneous adalimumab in a double-blind, double-dummy, randomized controlled trial.<sup>37</sup> Clinical remission at week 52 occurred in a significantly higher percentage of patients who received VDZ than in those who received adalimumab (31.3 *versus* 22.5%), as did endoscopic improvement (39.7 *versus* 27.7%). The percentage of patients who had CFCR at week 52 (a key secondary endpoint) was higher in the adalimumab group than in the VDZ group (21.8 *versus* 12.6%). More adverse events were reported in the adalimumab group than with VDZ. Notably, previous anti-TNF exposure was allowed (albeit capped at 25%), and dose escalation was not permitted, raising questions on if and how these might have impacted the results.<sup>38</sup> Nonetheless, it sets the scene for other head-to-head comparisons, which may better inform treatment choices in real-world practice.

In the light of the VARSITY trial outcomes, clinicians, who may have previously had more familiarity with prescribing anti-TNF medications as a first-line biologic in moderate-to-severe UC, can perhaps have increased confidence with choosing VDZ. In fact, the study results suggest that it may well be preferential to prescribe VDZ first line, over adalimumab, in such patients. However, while efficacy and safety data are paramount, convenience to patients, as well as cost, must also be considered. The VARSITY trial compares intravenous VDZ against subcutaneous adalimumab, and as such, the convenience to patients of the different modalities of delivery, as well as the costs involved, may factor in decisions regarding drug choice. The recently published results from the VISIBLE trial, demonstrating the efficacy and favourable safety profile of subcutaneous VDZ, will almost certainly impact upon both the cost and convenience of VDZ when considering it as a first-line biologic.<sup>39</sup> Further head-to-head studies are now required to compare subcutaneous VDZ to the other available options.

Limited data exist on the cost effectiveness of VDZ as a first-line biologic treatment in patients with moderate-to-severe UC. The outcomes of the available studies are inconsistent with some favouring anti-TNF medications<sup>40,41</sup> and others suggesting VDZ may be at least as cost-effective as other biologic treatment options.<sup>42–44</sup> A significant limitation of these studies is that they frequently do not consider the anti-TNF biosimilars, which are now widely available, and whose use would inevitably impact upon any cost analyses.<sup>42,44</sup>

## Safety profile

Gut specificity with VDZ without systemic immunosuppression is particularly attractive. In a Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID) study, reporting on patients with active IBD (CD=173 and UC=121), who had an inadequate or loss of response to conventional therapy, or at least one anti-TNF agent, received standard induction and maintenance doses of VDZ.<sup>29</sup> Prior treatment

with corticosteroids, thiopurines or methotrexate was permitted. CFCR was achieved by 31% of patients at week 14 and clinical response in 51% patients. In patients with UC, CFCR and response rates were 36 and 50%, respectively. Severe adverse events were noted in 24 patients (8.2%); this led to VDZ discontinuation in 15 (5.1%) patients (including pulmonary tuberculosis in 1 and rectal adenocarcinoma in another patient).<sup>29</sup> Integrated long-term safety data (2009–2013) from 2830 patients with 4811 patient-years (PYs) of VDZ exposure (median exposure range, 1–1977 days) showed no signals of increased risk associated with VDZ. Sepsis, tuberculosis and Clostridial infections were uncommon ( $\leq 0.6\%$  of patients). Previous anti-TNF failure and use of narcotic analgesia use were noted to be independent risk factors for serious infection in UC, and for CD, these were corticosteroid and narcotic use and younger age. Cancer diagnoses were reported in <1% VDZ-treated (18) patients and these were colon, breast, renal, liver, lung and non-melanoma skin cancer and malignant melanoma. All (but one with renal cancer) had prior azathioprine and/or anti-TNF exposure.<sup>45</sup> There was no significant increase in opportunistic infections or malignancy with anti-integrin antibodies as compared to placebo in a recent systematic review.<sup>46</sup> In the GEMINI OLE study, adverse events (AEs) were reported in 137 patients, of which 17 patients discontinued treatment. Forty-four SAEs were reported, with seven considered drug-related.<sup>32</sup> In a systematic review and meta-analysis of *randomized controlled trials* (RCTs) of 1122 UC patients, SAEs between the VDZ and placebo-treated groups were similar (12% [97/775] *versus* 12% [43/347]; RR: 1.02, 95% CI: 0.73–1.42).<sup>12</sup>

In the GEMINI 2 study, infection risk was more frequent in VDZ-treated patients compared to placebo. SAEs were more common (24.4%) in patients treated with VDZ compared with placebo (15.3%).<sup>10</sup> Four patients died in the VDZ group and one in the placebo group. One patient had breast cancer reported during VDZ induction. In the maintenance study, tuberculosis, appendiceal carcinoid tumour, squamous cell carcinoma and basal cell skin carcinoma occurred in one patient each. In GEMINI 3, AEs were comparable between VDZ- ( $n=209$ ) and placebo-treated ( $n=207$ ) patients (56 *versus* 60%), respectively. No deaths were reported.<sup>18</sup> In the CD GEMINI OLE study, AEs were reported in 134 patients, SAEs in 41 patients and 3 were possibly drug related. After follow-up lasting 248 weeks, only 15 patients stopped treatment following an AE.<sup>19</sup>

The gut specificity of VDZ was demonstrated in a randomized trial wherein reduced seroconversion occurred following oral cholera vaccination. The response to parenteral hepatitis B vaccination was not attenuated following VDZ injection.<sup>47</sup> In the GEMINI trials, intestinal infections (1 *Salmonella*, 3 *Campylobacter* and 6 *Clostridium difficile*) occurred after VDZ, but not placebo.<sup>9,10,18</sup> As per the FDA label, patients who receive VDZ should receive live vaccines only if benefits are outweighed by potential risks. A case report of successful vaccination against measles virus while on VDZ has been

reported in a patient with Crohn's ileocolitis.<sup>48</sup> Although successful live vaccination on VDZ therapy is plausible, this needs further study. In keeping with expectations from its gut-specificity, PML has not been reported in trials or long-term extension studies.<sup>45,49</sup> Finally, *C. difficile* infections in randomized trials and postmarketing studies for VDZ- and placebo-treated patients are similar, and in fact lower than from large health population databases.<sup>26,45,49</sup>

## Evolving concepts

Although response to VDZ in IBD is promising, lack of response, as with conventional treatments, is seen in some patients. Reasons for lack of efficacy are likely multifactorial, including the heterogeneity of disease potentially rendering VDZ's mechanism of action ineffective and failure to achieve therapeutic drug levels. This raises the importance of establishing biomarkers to predict therapeutic response as well as to obtain a better understanding of therapeutic drug levels and potential dose intensification with VDZ. These evolving concepts will now be covered.

## Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) involves measuring drug and antidrug antibody levels with adjustment of dosing on the premise that drug exposure rather than drug dose is associated with response.<sup>50</sup> Although TDM-based dose adjustment is rapidly gaining momentum with anti-TNF therapies, its role with VDZ is less clear. Registrational trials for VDZ have however demonstrated an exposure–efficacy relationship.<sup>9,10,51</sup> Post hoc analysis of GEMINI trials demonstrated that higher trough levels correlated with higher rates of clinical remission.<sup>51</sup> Induction trough levels of <17µg/mL for UC and <16µg/mL for CD were associated with remission rates similar to placebo.<sup>51</sup> In a subsequently published propensity score-based case-matched analysis of UC patients from the GEMINI study, adjusting for confounders affecting trough levels, target levels of 37.1µg/mL at week 6 during induction, 18.4µg/mL at week 14 and 12.7µg/mL during maintenance were suggested.<sup>52</sup>

Data from the largest available real-world cohorts also confirm the relationship between higher trough levels and improved outcomes.<sup>53–55</sup> In a retrospective Belgian study, VDZ trough levels >30 µg/mL at week 2, >24 µg/mL at week 6 and >14 µg/mL during maintenance therapy, correlated with higher clinical and endoscopic effectiveness endpoints.<sup>53</sup> In a cross-sectional study from the United States, patients in CFCR and biologic remission had significantly higher VDZ trough levels than those who were not.<sup>55</sup> Furthermore, data from France showed that VDZ trough levels below 18.5 µg/mL at week 6 were associated with the need for additional doses during the first 6 months of therapy.<sup>56</sup> Higher VDZ levels have also been associated with histological remission, a rapidly evolving target.<sup>57–59</sup> Pooled population data from the GEMINI studies

(supported by subsequent data from real-world studies) have identified low serum albumin and a high body mass index as being associated with low VDZ trough levels and worse therapeutic outcomes.<sup>53,60</sup> Thus, low serum albumin, high CRP, and a low haemoglobin reflecting more severe disease activity are associated with a lower likelihood of achieving desired therapeutic outcomes with VDZ.<sup>28,51,53,61</sup>

Immunogenicity appears reassuringly low with a pooled analysis of GEMINI data detecting anti-drug antibodies (ADAs) in 4% of patients.<sup>49</sup> Notably, the assay used to detect ADAs in the GEMINI program was not drug tolerant. Real-world studies have however confirmed low immunogenicity with drug-resistant assays.<sup>62,63</sup> This probably corroborates with the observation that the addition of an immunomodulator neither enhances drug levels nor improves therapeutic response,<sup>64</sup> and the ability to use VDZ as monotherapy may be advantageous in certain patient groups.

## Treatment intensification

Data have shown that in CD, an additional infusion at week 10 could be beneficial in patients with a suboptimal response. A low threshold for this fourth infusion should be considered to achieve induction before progressing to the 8 weekly maintenance phase. In patients with a primary response to VDZ and losing response (secondary loss of response), dose intensification from the standard 8-weekly (Q8) to 4-weekly (Q4) dosing has been shown to be able to recapture response in some patients.<sup>65,66</sup> In clinical practice, empirical dose intensification may be required, particularly when TDM is not easily accessible and in order to make treatment decisions. This is particularly relevant as the majority of patients receiving VDZ for CD, in current clinical practice, will be 'anti-TNF failures', and therefore dose optimisation should be considered before a further switch in mechanistic class given further attrition with response as treatments fail patients and have to switch mechanism of action. In a recent systematic review and meta-analysis, Peyrin-Biroulet and colleagues showed that dose intensification restores responsiveness in over half of patients with UC and CD.<sup>65</sup> Further real-world data from Samaan and colleagues showed recapture of response in half of their mixed IBD cohort of 36 patients receiving dose escalation.<sup>66</sup>

## Candidate biomarkers predicting response to VDZ

Recent studies have explored the possibility of individual biomarkers, which may predict whether an individual patient is more likely to respond to VDZ. Pretreatment expression of α4β7 on multiple immune cell subsets is shown to be significantly higher in responders to VDZ as is trough α4β7 receptor saturation.<sup>67</sup> In another study, high pretreatment serum retinoic acid levels were predictive of achieving clinical remission with VDZ.<sup>68</sup> In the same study, undetectable

levels of soluble MAdCAM-1 (s-MAdCAM-1) in maintenance therapy were strongly associated with clinical remission.<sup>68</sup> Most recently, it has been shown that a number of potential biomarkers (soluble- $\alpha$ 4 $\beta$ 7, s-MAdCAM-1, soluble-vascular cell adhesion molecule and soluble-TNF) may help to predict the achievement of endpoints (clinical or endoscopic remission) at varying time points during treatment.<sup>69</sup> Such studies have started to pave the way towards personalized therapy for patients with IBD whereby clinicians may start to predict which treatment is likely to result in the optimal outcomes for any particular patient.

## VDZ in special situations

### Perianal CD

In GEMINI II, at 52 weeks, 41.2% of the VDZ 8-weekly group had fistula closure as compared to 22.7% receiving VDZ 4-weekly group and 11.1% in the placebo group ( $p=0.03$ ,  $p=0.32$  versus placebo, respectively).<sup>12</sup> In a postmarketing study of 35 patients who had active perianal disease, 12 patients had perianal fistula closure at 54 week follow-up.<sup>70</sup> The significance of this needs further investigation. Notably, a higher incidence of perianal abscesses was reported in the GEMINI OLE study.<sup>71</sup>

### Postoperative complications and recurrence risk

Although a number of retrospective studies have suggested an increase in postoperative complications<sup>72–75</sup> and surgical site infections with VDZ, this is not supported by meta-analysis.<sup>76</sup> In the GEMINI trials, rates of surgery (VDZ: 3.6%, 51/1434; placebo: 2.4%, 7/297), post-op complications (VDZ: 5.9%, 3/51; placebo: 14.3%, 1/7), serious postoperative complications (VDZ: 2.0%, 1/51; placebo: 14.3%, 1/7) were similar to placebo. It is likely that the differences in risk estimates suggesting the increased risk in observational studies were driven by inability to control for confounders such as corticosteroid exposure and disease activity.

The effectiveness in preventing postoperative recurrence is unknown. In a retrospective study of 203 patients who underwent a CD-related surgery, 22 patients received VDZ as postoperative treatment and 58, 38 and 16 patients received anti-TNF agents, immunomodulators and metronidazole, respectively, whereas 69 patients were monitored without any medication.<sup>77</sup> Rate of endoscopic remission at 6–12 months in the VDZ group was 25%, which was significantly lower compared to the anti-TNF group (66%,  $p=0.01$ ). The results were supported by a propensity score-matched analysis demonstrating lower rates of endoscopic remission (25 versus 69%,  $p=0.03$ ) in patients treated with VDZ as compared to anti-TNF agents.<sup>77</sup> Further studies are urgently needed.

## Extraintestinal manifestations

In post hoc analysis of the GEMINI data, patients with CD receiving VDZ in comparison to placebo had a lower risk of new or worsening arthralgia or arthritis (HR: 0.63, 95% CI: 0.44–0.89).<sup>78</sup> Arthritis or arthralgia was reported to the same extent in UC, for treatment and placebo.<sup>78</sup> A postmarketing study noted similar rates of extraintestinal manifestations (EIMs) in UC patients treated with VDZ and anti-TNF but more in VDZ-treated CD patients (adjusted incident rate ratio [IRR]: 1.28, 95% CI: 1.02–1.62) compared to anti-TNF patients. Notably, underlying disease activity and previous treatment were not adjusted for.<sup>79</sup> In a study of 173 CD and 121 UC patients over 54 weeks, 50 patients (17.2%) had EIMs at baseline. At week 54, 45.7% ( $n=46$ ) patients with arthropathy and 60% ( $n=5$ ) patients with dermatological manifestations were in complete remission of EIMs. New arthropathies were seen in 15.8% ( $n=32$ ) of patients, and dermatological manifestations were seen in 4.8% ( $n=14$ ) patients.<sup>70</sup>

### VDZ in pregnancy

There is limited safety data for VDZ use in pregnancy, a risk category B drug. Of 24 women exposed to VDZ in pregnancy in a case series, 12 live births, 5 elective abortions and 4 spontaneous abortions were reported.<sup>80</sup> Notably, with a half-life of 25 days, withholding VDZ in the third trimester may result in VDZ exposure to the foetus with prolonged drug clearance likely up to 6–12 months. The consequences of such foetal exposure are unknown. It is plausible that this may have implications for vaccination against intestinal infections such as rotavirus (which is an oral vaccine), but unlikely with parenteral agents that are administered in the first year of life. It is not possible to make evidence-based recommendations using current knowledge and any use in pregnancy should be discussed on an individual basis.<sup>81</sup> Data from retrospective studies from anti-TNF-exposed paediatric patients have shown remission of 100% at 14 weeks in three patients with UC, and 44% in 9 CD patients.<sup>82</sup> An ongoing phase 3 study of VDZ of patients aged 15 years and over will be reported in due course (ClinicalTrials.gov: NCT02039505).

## Conclusion

VDZ is a much-needed addition to the increasing armamentarium of IBD therapy, and its gut specificity is particularly appealing. VDZ has shown efficacy as a first-line agent for the induction and maintenance of remission in IBD. The safety profile is promising. Real-world data have supported its effectiveness and safety profile. Recent data on mucosal healing and histological healing appear promising. Data from patient populations such as pregnancy, extremes of age, prevention of postoperative recurrence, fistulising CD and pouchitis are now urgently needed and will further refine the approach to this particularly refractory group of patients.

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