# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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## Reviewing the Use of Vedolizumab for the Treatment of Patients With Crohn's Disease

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### G&H What is the current indication for vedolizumab in patients with Crohn's disease?

**SH** Vedolizumab (Entyvio, Takeda) is currently indicated for the treatment of moderate to severe Crohn's disease in adult patients. Nonresponse to conventional therapy is not required as part of the indication.

### G&H How can moderate to severe Crohn's disease be best defined?

**SH** The concept of moderate to severe Crohn's disease originated with the initial clinical trials in Crohn's disease, such as the National Cooperative Crohn's Disease Study, which was conducted in the 1970s. That study was the first to utilize the Crohn's Disease Activity Index (CDAI), which is a composite index that includes a number of patient-reported symptoms, such as diarrhea and abdominal pain, as well as a number of laboratory parameters, such as hemoglobin, weight, the presence of an abdominal mass, and the presence of extraintestinal manifestations. From these factors, a scoring range was developed: less than 150 was considered to be in clinical remission, 150 to less than 250 mild disease, 250 to 400 moderate to severe disease, and greater than 400 severe disease. The moderate to severe disease group was selected for clinical trials of infliximab vs placebo in Crohn's disease because regulatory agencies did not have much experience with biologics and did not want to give new, potentially risky treatments to patients with mild disease.

However, in clinical practice, the definition of moderate to severe disease is not based on the CDAI. Groups such as the International Organization for the Study of Inflammatory Bowel Disease have developed guidelines for the treatment of patients with Crohn's disease that have divided patients not according to their disease activity (ie, how sick patients are today) but according to their disease severity (ie, the prognosis for patients to develop complications or need surgery). Factors for moderate to severe Crohn's disease are primarily clinical and have been agreed upon by gastroenterology societies. These factors include disease at young age, extensive disease, development of extraintestinal manifestations, presence of perianal disease, deep ulcerations, and need for corticosteroids. Any patient requiring corticosteroids is considered to have moderate to severe disease because 80% of patients who are started on corticosteroids become corticosteroid-dependent or -refractory. Therapy failure is not a requirement for moderate to severe disease, and patients can be diagnosed with it at presentation. Thus, the definition of moderate to severe Crohn's disease has evolved from initial clinical trials to practical definitions that are used in clinical practice.

### G&H How does the mechanism of action of vedolizumab compare with other lymphocyte trafficking agents?

**SH** There are now several mechanisms by which lymphocyte trafficking can be affected. The first lymphocyte trafficking agent approved for Crohn's disease was natalizumab (Tysabri, Biogen). Over a decade ago, natalizumab was shown to be effective at treating Crohn's disease by blocking the interaction of the α4 integrin with vascular

cell adhesion molecule and preventing inflammatory cells from entering tissue. However, because natalizumab also blocks lymphocyte migration into the brain, it impairs brain surveillance against viruses. An uncommon but lethal consequence was reactivation of human polyomavirus 2 (commonly referred to as the JC virus or John Cunningham virus), leading to progressive multifocal leukoencephalopathy. Thus, this agent is not commonly used for Crohn's disease at this time.

There is a unique integrin-addressin interaction involving a different integrin, the α4β7 integrin, which latches onto the mucosal addressin cell adhesion molecule that is present only within the gut (MadCAM). Vedolizumab blocks the α4β7 integrin on lymphocytes and prevents their attachment to MadCAM as well as their infiltration into the intestinal mucosa, making the drug gut selective. This mechanism has been effective in both Crohn's disease and ulcerative colitis.

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Another lymphocyte trafficking mechanism that has recently come into play relates to modulation of sphingosine-1 phosphate (S1P). Ozanimod (Zeposia, Bristol Myers Squibb) modulates S1P receptors on lymphocytes that allow these cells to migrate out of lymph nodes into the circulation and then into tissue. Essentially, vedolizumab blocks the exit ramps of the vascular highway into tissue, whereas ozanimod blocks the entrance ramps of lymphocytes so that they cannot enter the bloodstream and hence tissue. These are the 2 major ways of affecting lymphocyte trafficking that are currently available.

**G&H** What were the key studies that led to approval of vedolizumab for moderate to severe Crohn's disease?

**SH** The key studies that led to vedolizumab's approval by the US Food and Drug Administration in Crohn's disease are the GEMINI studies. The first GEMINI study randomized patients with moderate to severe Crohn's disease to receive vedolizumab 300 mg or placebo at 0, 2, and 6 weeks. Patients were assessed at 6 weeks and, in a subsequent study, at 10 weeks. Patients who improved were rerandomized to vedolizumab vs placebo every 4 weeks or every 8 weeks for 1 year. Thus, the induction studies lasted 6 and 10 weeks and the maintenance study 52 weeks. The investigators concluded that patients had increasing response rates between weeks 6 and 10 that continued to week 52 and demonstrated superiority of vedolizumab compared with placebo at 1 year.

The patient groups were subsequently divided into those who had been exposed to biologics, primarily tumor necrosis factor (TNF) blockers, vs patients naive to biologics. In both subgroups of patients, there was superior response with vedolizumab compared with placebo.

**G&H** Have both clinical and endoscopic responses been studied with vedolizumab in the setting of Crohn's disease?

**SH** The GEMINI studies primarily looked at patient-reported outcomes, and endoscopy was not a component. Thus, as manifest components of the CDAI, the patient-reported outcomes of abdominal pain and diarrhea improved in these patients.

Subsequently, a number of real-world experiences with vedolizumab, including a comparison with TNF blockers in the VICTORY Consortium, have confirmed the benefits of vedolizumab in Crohn's disease and extended the data to demonstrate not only clinical response but also endoscopic response.

**G&H** How soon can effects typically be seen with vedolizumab in patients who have moderate to severe Crohn's disease?

**SH** Clinical effects occur increasingly between 4 and 10 weeks and continue to accrue over time in patients up to at least 4 months. Thus, it is important not to give up on vedolizumab therapy for at least 4 to 6 months.

With that being said, there has been a common misconception that vedolizumab does not act quickly in Crohn's disease as well as ulcerative colitis. However, the VARSITY study, which compared vedolizumab with adalimumab in patients with ulcerative colitis, demonstrated that the onset of action of vedolizumab was equally as fast as that of TNF blockers. Subsequently, in the VICTORY Consortium, which compared vedolizumab with TNF blockers in both ulcerative colitis and Crohn's disease, the onset of action was again equally rapid with both mechanisms of action. Thus, the concept that vedolizumab was not as fast-acting or as effective in Crohn's disease based

on early experience is likely misconstrued. That notion was based on the fact that early on, the most refractory patients were the ones who received vedolizumab. As the number of patients with moderate to severe Crohn's disease being treated with vedolizumab has increased, better and faster overall outcomes are being seen, particularly in bio-naive patients.

> … nearly 80% of patients entering into the long-term extension were still in clinical remission after more than 5 years.

### G&H What long-term data are available regarding the use of vedolizumab for moderate to severe Crohn's disease?

**SH** Vedolizumab has been studied not only in the original GEMINI studies but also in long-term extensions. The vast majority of patients who respond continue to do so out to 5 years, which has been the limit of the exploration thus far. A recent article by Loftus and colleagues noted that nearly 80% of patients entering into the long-term extension were still in clinical remission after more than 5 years.

In addition, both the original GEMINI studies and long-term extensions (including the aforementioned article), as well as several real-world experiences, have demonstrated that the risk of serious infections or malignancies is no greater with vedolizumab than with placebo (ie, standard therapy). Thus, one of the advantages of vedolizumab's gut selectivity has been a reduction in the risk of pneumonias and other systemic infections. Because vedolizumab affects the intestine, it is still possible for patients to develop intestinal infections such as *Clostridioides difficile*. However, these have not been seen to occur more commonly with vedolizumab, and they appear to respond the same to treatment, regardless of whether a patient is taking vedolizumab.

### G&H How does the immunogenicity of vedolizumab compare with other biologics?

**SH** In contrast to TNF inhibitors, vedolizumab is minimally immunogenic. The drug has been engineered to be less immunogenic, and its longer half-life reduces the risk of low trough levels that contribute to the development of antidrug antibodies. Hence, immune-modifying agents are not needed to reduce immunogenicity with vedolizumab because it is so uncommon, as are infusion reactions, which are exceedingly rare.

### G&H How should patients with Crohn's disease be monitored while taking vedolizumab?

**SH** Patients taking vedolizumab should be monitored as with any other agent in the setting of Crohn's disease. This includes monitoring symptoms and tapering corticosteroids as appropriate. Indeed, another important outcome for vedolizumab in Crohn's disease has been an increase in corticosteroid-free remission as well as clinical remission. Clinicians should continue to monitor biomarkers, including fecal calprotectin, after several months. I do not perform endoscopic monitoring in patients with Crohn's disease usually for at least 6 months, and most often for a year, because Crohn's disease takes longer to heal endoscopically than ulcerative colitis.

### G&H Should therapeutic drug monitoring be performed with vedolizumab?

**SH** In clinical trial extensions published by Sands and colleagues, at least 30% of patients who initially responded to every-8-week dosing in Crohn's disease and then lost response were able to recapture response by moving to every-4-week dosing. Although my colleagues and I do not routinely use proactive therapeutic drug monitoring, we measure vedolizumab and antivedolizumab drug levels in patients who are having inadequate response or loss of response. We do this to determine whether we need to dose escalate or switch to a drug with a different mechanism if we find antidrug antibodies, which are usually rare.

### G&H Is it possible to predict which patients with Crohn's disease will respond to treatment, particularly vedolizumab?

**SH** A number of drugs with different mechanisms of action are currently available for the treatment of moderate to severe Crohn's disease. At this point, there is no gold standard biomarker that predicts which patients will respond to which mechanism of action. Nevertheless, clinicians can look at a variety of clinical and laboratory attributes of patients to help determine who will respond to which class of agents, and these attributes may differ across classes. Dr Parambir Dulai, one of my colleagues at Northwestern, has developed a series of clinical decision

support tools that have been reproduced in clinical practice. Vedolizumab appears to be most effective in patients with less-severe ulcerations in moderate to severe disease, and patients who have deeper ulcerations or transmural disease are less likely to respond to vedolizumab than patients who have less-severe endoscopic evidence of disease. I have also found vedolizumab to be particularly effective for preventing postoperative recurrence of Crohn's disease.

**G&H** What should doctors tell patients who are hesitant to take vedolizumab or biologics in general?

**SH** Because of vedolizumab's gut selectivity, it has been relatively easy to convince doctors as well as patients of the drug's safety. Many patients who were worried about infections or the risk of lymphoma, in particular with TNF blockers, do not have the same concerns with vedolizumab.

**G&H** What further research is needed?

**SH** Despite the purported mechanism of action inhibiting lymphocyte trafficking from blood vessels into tissue, vedolizumab dosing has been based on receptor saturation of the α4β7 integrin. Of interest, while all patients have near-complete saturation, there is still an association between trough drug levels of vedolizumab and endoscopic healing that is independent of receptor saturation. Thus, there may be another mechanism of action that is yet to be determined for vedolizumab in its efficacy in inflammatory bowel disease.

***Disclosures***

*Dr Hanauer is a consultant and clinical investigator for Takeda.*

## Suggested Reading


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