

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Use of Vedolizumab for the Treatment of Crohn's Disease



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G&H How does vedolizumab work?

BB Vedolizumab (Entyvio, Takeda) works by interfering with lymphocyte trafficking in the gastrointestinal tract. Specifically, it binds to the $\alpha 4\beta 7$ integrin, which is a protein on the surface of lymphocytes targeted for the gastrointestinal tract. Thus, vedolizumab does not allow lymphocytes expressing $\alpha 4\beta 7$ to connect with mucosal vascular addressin cell adhesion molecules, which are expressed on the gastrointestinal epithelium. This disruption reduces inflammation in the gastrointestinal tract.

G&H Why has there been a perception that vedolizumab is slow to work in Crohn's disease?

BB Based on clinical trial data, real-world data, and my clinical experience, it is not my impression that vedolizumab is slow to work in Crohn's disease. This mistaken perception likely involves the first clinical trial that was conducted as part of the GEMINI program on the efficacy of vedolizumab for induction in Crohn's disease patients. Approximately 50% of patients in the first trial were anti-tumor necrosis factor (TNF) failures. At week 6 (which was after only 2 infusions and, thus, considered to reflect early onset of action), 15% met the primary endpoint of clinical remission (defined as a Crohn's Disease Activity Index [CDAI] score ≤ 150 points) compared to 7% of the placebo group, which was statistically significant. Also at week 6, clinical response (defined as a ≥ 100 -point decrease in CDAI score) was 31%, which is reasonable, but the placebo rate was high (26%), resulting in a difference that was not statistically significant. At the end of the maintenance phase of the

study, however, there was an approximately 40% clinical remission rate in the vedolizumab group, which was thought to be a reasonable and an expected outcome to demonstrate efficacy for a biologic agent in that Crohn's disease patient population at that timepoint. Thus, despite clinical remission rates that were in line with expectations, the lack of a statistically significant clinical response at week 6 may have led to a perception that vedolizumab might take a little longer to work.

However, the breadth of data argues against the perception of vedolizumab as slow-acting. Before the results of the first study were known, another induction study was conducted in Crohn's disease patients, with anti-TNF failures constituting 75% of the entire study population. In general, the expectation when evaluating a biologic agent in anti-TNF failures compared to anti-TNF-naïve patients is that the efficacy will be attenuated, meaning that it may take longer for any drug to work or the drug may not work as well. Thus, if vedolizumab was slow-acting in the first study, there would have been an even worse response in the second study, but that was not what we saw. In a sicker patient population after 2 infusions, at week 6, there was an approximately 39% response rate in the vedolizumab group compared to the placebo group, which had a rate of approximately 22%. This difference was statistically significant and argues against the perception that vedolizumab is slow according to clinical trial data.

In addition, multiple studies of real-world cohorts have examined the onset of action of vedolizumab. A meta-analysis performed by Dr Stefan Schreiber and colleagues approximately a year ago combined almost 90 publications, a majority of which (approximately 80%)

focused on anti-TNF–refractory patients. After 2 infusions, close to 60% of patients responded. Interestingly, this response rate was higher than that seen in ulcerative colitis patients at the same, early timepoint.

G&H Has any research examined even earlier response to vedolizumab in Crohn's disease patients?

BB Beyond evaluating week 6 response after 2 infusions, there has been analysis looking at even earlier timepoints, after the first infusion. A recent study conducted by Dr Brian Feagan and colleagues looked at the patient-reported outcomes of abdominal pain and stool frequency. After the first infusion in anti-TNF–naïve Crohn's disease patients, at week 2, there was already a statistically significant separation between patients who were on vedolizumab compared to those on placebo. This rapid response further emphasizes how quickly vedolizumab can work in some patients. Therefore, anti-TNF–naïve patients can be told that even after the first infusion, they may notice improvement in their symptoms. This is an important message and certainly highlights the fact that vedolizumab is not a slow-acting drug for Crohn's disease.

G&H What is the safety profile of vedolizumab, and how does it compare to that of other drugs?

BB Beyond providing rapid efficacy and long-term sustainable response in patients with Crohn's disease, the inherent advantage of vedolizumab is its safety. As mentioned in the discussion of its mechanism of action, this drug does not have systemic immune suppression; it is focused on interfering with lymphocyte trafficking of the gastrointestinal tract. Accordingly, it can be assumed that there are inherent advantages in its safety profile compared to other biologic agents, which have a more systemic immune suppression effect. Investigators of the long-term extension study of patients on vedolizumab for over 3 years compared the rates of adverse events with those associated with placebo. Reinforcing the advantageous safety profile of the drug, this analysis demonstrated a statistically significant reduction in the rate of all infections in patients on vedolizumab compared to those on placebo. In other words, if a patient was sick and there was a choice between not doing anything vs giving the patient vedolizumab, the latter would reduce his or her risk of infection. This is a novel and unique statement that we have not been able to make with other medications. In part, this result relates to the risk of infection in patients with inflammatory bowel disease being strongly dependent on disease

activity and corticosteroid exposure. Compared to placebo, giving a patient vedolizumab has a higher likelihood of controlling disease activity and reducing corticosteroid exposure. What may be unique for vedolizumab is that it does not bring its own risk of infection, which has been shown to happen with other biologic agents, in particular anti-TNF agents.

The Victory Consortium is starting to look at real-world experiences of patients taking vedolizumab and anti-TNF agents, including their adverse-event profiles. We are seeing signals in these data that there are fewer infections and statistically significantly fewer serious adverse events in patients taking vedolizumab vs those taking anti-TNF agents. This distinction is even more noticeable when looking at patients on monotherapy. Taking out the potentially confounding factor of exposure to azathioprine, which has its own adverse-event profile, and comparing the vedolizumab monotherapy group to the anti-TNF monotherapy group reveals a wider distinction demonstrating a better safety profile for vedolizumab compared to anti-TNF agents.

G&H Which Crohn's disease patients would benefit most from vedolizumab as the early option for therapy?

BB The patients who would benefit most are those who are naïve to biologic agents, at least anti-TNF agents. The likelihood of response to vedolizumab is probably highest in Crohn's disease patients with an inflammatory phenotype, as opposed to a stricturing or penetrating presentation.

G&H Where should the drug be positioned among the various treatment options currently available for Crohn's disease?

BB It depends somewhat on the phenotype of the disease. Based on vedolizumab's rapid onset of action and its ability to work better in an anti-TNF–naïve patient, a very strong case can be made for vedolizumab to be used as a first-line biologic agent for Crohn's disease, particularly in active, luminal Crohn's disease that has an inflammatory phenotype.

G&H Should the drug be avoided in any Crohn's disease patients?

BB It has not been as well studied in fistulizing Crohn's disease, which has a high morbidity. The drug with the best quality of evidence for this phenotype is infliximab (Remicade, Janssen), particularly in combination with azathioprine. Thus, the first-line treatment choice for

a patient with fistulizing Crohn's disease should remain infliximab.

G&H How should Crohn's disease patients be followed after starting vedolizumab therapy?

BB The follow-up of a Crohn's disease patient on vedolizumab should not be any different from that of a Crohn's disease patient on any other biologic agent. Crohn's disease treatment is usually started because of a patient's active inflammatory burden. The most accurate way to define this burden is with the endoscopic appearance of the disease. If endoscopic evaluation is not possible because of disease location, an inflammatory marker could be followed over time. An example is fecal calprotectin, which is both sensitive and specific in the right setting for active Crohn's disease. If the patient has symptoms, they constitute another target to assess and ideally control appropriately. Therefore, the overall goals of following patients on vedolizumab are to see symptomatic improvement as well as objective improvement in the inflammatory burden.

It should be noted that the timing for these goals differs. The previous discussion of the quick onset of vedolizumab for Crohn's disease referred to the early control of symptoms. Control of the inflammatory burden occurs later on, as with all biologic agents. The ideal time to perform a colonoscopy to reassess this burden is unknown, but is likely somewhere in the 6- to 9-month mark after starting any biologic agent for Crohn's disease.

G&H What are the next steps in research in this area?

BB An important next step in research is to understand sequencing of biologic agents. As discussed earlier, there is an advantage to starting vedolizumab before other anti-TNF agents with regard to its efficacy. However, for any biologic agent, it is likely that a patient will respond best when the agent is used as the first-line treatment option. Therefore, it would be helpful to have head-to-head trials featuring endpoints that physicians value, such as rapid

onset of action, long-term sustainable remission, and control of the inflammatory burden, to determine which biologic agent would be most likely to achieve these endpoints in comparison to other biologic agents.

Another potential area of research involves determining whether there is value in treating the immune dysfunction that defines Crohn's disease in multiple ways. We are gaining confidence in the safety profiles of biologic agents, but there is excitement regarding the reduced toxicity profiles of some of the newer agents. Research should be conducted to determine whether there would be enhanced value, defined by better efficacy, if biologic agents were combined to address patients' dysfunctional immune systems in multiple ways, as opposed to relying only on one mechanism of action each time patients are treated.

Dr Bressler has served as an advisor/speaker for Shire, Ferring, Janssen, AbbVie, Takeda, Actavis, Pfizer, and Novartis; has served as an advisor for Roberts Clinical Trials, Celgene, Microbiome Insights, Merck, Amgen, Pendopharm, Genentech, Celltrion, Allergan, and Protagonist; and has received research support from Janssen, AbbVie, GSK, BMS, Amgen, Genentech, Merck, RedHill Biopharma, BI, Qu Biologics, Celgene, and Alvine.

Suggested Reading

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