

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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## Safety and Positioning of Vedolizumab in Patients With Inflammatory Bowel Disease



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### **G&H** How safe is vedolizumab? What is its side-effect profile?

**BF** Most drugs used to treat inflammatory bowel disease (IBD) are systemically immunosuppressive, which means that they affect the immune system throughout the entire body. The key advantage of vedolizumab (Entyvio, Takeda) over other IBD drugs is that its mechanism of action targets only the gut (ie, its mucosal vascular addressin cell adhesion molecule [MAdCAM] expression is selective for the gut). Thus, its safety profile does not include the side effects associated with systemic immunosuppressives such as tumor necrosis factor (TNF) antagonists and corticosteroids or conventional immunosuppressives such as azathioprine or methotrexate. The most common side effect with those drugs is an increased risk of serious infection, in particular pneumonia. That signal is not seen with vedolizumab. Thus, the side-effect profile is superior to that of other agents, with the possible exception of the newest drug for Crohn's disease, ustekinumab (Stelara, Janssen), which appears to be very safe.

### **G&H** Could you further discuss vedolizumab's mechanism of action and its relationship to safety?

**BF** The safety of vedolizumab, the first gut-selective agent for IBD, is directly related to its mechanism of action.

Vedolizumab is a monoclonal antibody that targets  $\alpha 4\beta 7$ , a protein that is expressed on approximately 3% of circulating T cells that are specifically homing to the gut. The ligand, or the molecule that interacts with  $\alpha 4\beta 7$ , is MAdCAM, which is expressed on the endothelial cells of the blood vessels of the gut. In a healthy gut, when there is no inflammation in the tissue, the T cells remain in laminar flow in the blood and do not interact with the cells lining the vessel walls, continuing to circulate around the body. However, in the setting of inflammation, chemical messages (ie, small proteins) are released from the site of inflammation in the bowel wall or the submucosa and travel to the cells that line the blood vessels, causing them to upregulate the expression of MAdCAM on the endothelial cell surface. When MAdCAM is expressed in high concentrations on the surface cells, it interacts with  $\alpha 4\beta 7$ , and the cells that normally flow along in the blood without interacting with the tissue become stuck to the endothelial cell surface. Eventually, they become firmly attached to the lining of the blood vessels and then migrate between the cells into the tissue, where they participate in the pathologic inflammatory process that is IBD. The antibody vedolizumab sticks to  $\alpha 4\beta 7$  so that the molecule cannot interact with MAdCAM, effectively trapping the cells in the blood vessels and preventing them from entering the tissue. This process downregulates inflammation in both ulcerative colitis and Crohn's disease (and theoretically any inflammatory process that involves T cells in the gut).

### G&H Are there any other differences in safety between vedolizumab and other IBD treatments?

**BF** The primary difference is that vedolizumab is gut-selective, whereas other treatments have systemic effects. Another difference, also related to its mechanism of action, is that some IBD drugs, most notably azathioprine, have an increased risk of skin cancer and lymphoma. We do not think that vedolizumab's mechanism of action increases the risk of malignancies, although longer-term data are needed to fully assess this issue. Vedolizumab also has a low risk of infusion reactions and can be infused over a half hour, making it relatively easy to administer in clinical practice.

### G&H Are there any significant side effects, risks, or limitations with vedolizumab?

**BF** Vedolizumab is a foreign protein, so allergic reactions may occur, but they are very uncommon. This agent has a very clean safety profile.

### G&H How are real-world experiences with vedolizumab playing out? Have they been living up to clinical trial findings?

**BF** Real-world experiences with vedolizumab have been favorable for the most part. At this point, approximately 10 studies on real-world experiences of vedolizumab have been published by various groups around the world, including the VICTORY Consortium in the United States. Considerable long-term safety experience has been accumulated since the launch of the drug with over 100,000 patients treated. The results of this real-world experience have recapitulated findings of controlled studies with no evidence of serious safety concerns identified.

However, as someone who conducts clinical trials, it is important to point out that it is difficult to evaluate drugs in the real world because randomized, controlled trials solve 2 large problems associated with observational data, namely the lack of a control group and bias. Thus, real-world experiences can be problematic because physicians and patients want to get better, and if only symptoms are being measured, patients often report improvement due to expectation bias, and the results are more favorable than the results observed in randomized, controlled trials. In addition, real-world experiences do not adequately control for confounders, which is an important issue to acknowledge because confounders can influence results yet are not actually related to treatment. For example, IBD patients may have a confounder such as previous treatment. We know that patients who fail TNF antagonists generally have a poor prognosis. Thus,

in a controlled trial, researchers take steps to control for this confounder, but in the real world—observational studies—this does not happen. All of this should be taken into account when looking at data from recent non-controlled studies.

It is also important to note that real-world studies that include endoscopy are less susceptible to bias than those that only report clinical symptoms, especially if video recordings are taken of the endoscopies and evaluated by an independent reader. Several of the observational studies of vedolizumab have evaluated endoscopic improvement and reported reasonably good results.

### G&H Have there been any real-world analyses on the use of this drug vs other treatments?

**BF** There are no controlled comparative effectiveness trials of biologic drugs. Several network meta-analyses have made indirect comparisons with differing conclusions. However, a critical limitation of this methodology is the lack of at least 1 high-quality trial comparing the effectiveness of any 2 of the agents. This deficiency is a serious threat to the validity of the conclusions of these studies.

### G&H Based on the safety and efficacy data currently available, where specifically should vedolizumab be positioned among IBD treatments?

**BF** Vedolizumab can be positioned as a first-line therapy for both ulcerative colitis and Crohn's disease. In ulcerative colitis, vedolizumab is a rapidly active drug that is very effective; in fact, no class of drugs is superior to this agent with respect to efficacy, and the safety profile is excellent. Thus, there is no question that vedolizumab is first-line therapy for ulcerative colitis. In Crohn's disease, there is a common misconception that vedolizumab does not have a very good induction effect. It actually does have a good effect; it just has a more gradual onset of action than TNF antagonists. The drug should be evaluated after 12 to 14 weeks, whereas some other agents control symptoms very quickly. The real advantage of vedolizumab is the long-term safety profile. This is a drug that physicians can use to get Crohn's disease patients through induction into maintenance, and then reap the benefits of durable efficacy and safety. Vedolizumab is an excellent maintenance agent for these reasons.

### G&H What should be the main decision drivers when choosing a biologic for the first time?

**BF** Efficacy and safety should always be the main decision drivers, and then to a lesser extent perhaps the route

of administration. Although oral agents are convenient and do not result in sensitization, they are not necessarily safer, and adherence may be an issue.

### **G&H** Is vedolizumab most appropriate in any particular IBD patient subgroups?

**BF** Serious infection is a significant issue with IBD patients depending upon the age of the patient. Most patients with IBD are young, and young people treated with, for example, TNF blockers are at a fairly low risk of serious infection. However, older IBD patients are at increased risk of serious infections, such as pneumonia and herpes zoster. Vedolizumab itself is not associated with an increased risk of serious infections, so it is advantageous in older patients.

It should be noted that hospitalized patients with severe colitis, those with severe fistulizing disease, and those with severe extraintestinal manifestations, including pyoderma gangrenosum and uveitis, are more appropriately treated with infliximab (Remicade, Janssen).

### **G&H** In clinical practice, do you think that vedolizumab is being used where it should be, or are there any concerns or misconceptions regarding its use?

**BF** Gastroenterologists tend to be slow adapters. It took approximately 15 years for the average clinician to become comfortable with TNF antagonists. I believe that vedolizumab is underutilized in clinical practice because doctors are not familiar with it. However, the situation is changing as clinical experience accumulates and the valuable attributes of the drug are recognized by physicians.

### **G&H** Do you have any guidance or tips regarding the use of this agent, particularly in terms of sequencing?

**BF** We have come to learn that if a patient fails a biologic drug, especially in Crohn's disease, that patient will have

a very poor prognosis. Therefore, one tip that I would give is that if a physician thinks that a particular agent is the best option for a patient, that agent should be used first. For example, if a physician prefers vedolizumab because of its safety profile, then this agent should be used for first-line treatment rather than saving it for rescue therapy.

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

**BF** There are a number of interesting research topics that are being explored. Based on recent studies in Crohn's disease, we are finding that all agents have difficulties treating patients who have failed conventional biologic therapies (eg, TNF antagonists). Thus, drug combinations may be the way forward, like they are in some other diseases, such as hepatitis C virus, HIV, or hypertension.

*Dr Feagan has received honoraria from Takeda Pharmaceuticals, Janssen, and AbbVie.*

### **Suggested Reading**

Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut*. 2017;66(5):839-851.

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