Vedolizumab as a Treatment for Crohn's Disease and Ulcerative Colitis

Christina Ha, MD, and Asher Kornbluth, MD

Dr Ha is a health sciences assistant professor in the Division of Digestive Diseases at the David Geffen School of Medicine at UCLA in Los Angeles, California. Dr Kornbluth is a clinical professor in the Dr Henry D. Janowitz Division of Gastroenterology at the Icahn School of Medicine at Mount Sinai in New York, New York.

Address correspondence to:
Dr Asher Kornbluth
Dr Henry D. Janowitz Division of Gastroenterology
Icahn School of Medicine at Mount Sinai
1751 York Avenue
New York, NY 10128
Tel: 212-369-2490
E-mail: Asher.kornbluth@gmail.com

Keywords
Adhesion molecules, $\alpha_4\beta_7$ integrin, Crohn's disease, lymphocyte trafficking, ulcerative colitis, vedolizumab

Abstract: The management of Crohn's disease and ulcerative colitis has become increasingly complex. With the current utilization of immunosuppressive therapies earlier in the disease course for patients presenting with moderate to severe disease, there is a great need for additional biologic agents targeting inflammatory mediators other than anti–tumor necrosis factor-α (anti-TNF) agents. Although anti-TNF agents have positively impacted the treatment of inflammatory bowel disease, many patients can lose their response or develop intolerance to these agents over time through the formation of antidrug antibodies. Furthermore, a sizeable percentage of patients are primary nonresponders to anti-TNF drugs. Vedolizumab (Entyvio, Takeda Pharmaceuticals), a monoclonal antibody to the $\alpha_4\beta_7$ integrin, inhibits gut lymphocyte trafficking and has been demonstrated to be an effective and safe agent for the treatment of both Crohn's disease and ulcerative colitis. This article reviews the clinical trial evidence and rationale for the use of vedolizumab in moderate to severe Crohn's disease and ulcerative colitis.

The classic inflammatory bowel diseases (IBDs), Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract that affect more than 1 million persons in the United States, and their incidence and prevalence are increasing worldwide.[1,2] The mainstays of therapy include corticosteroids, which are used as inductive therapies for patients with moderate to severe CD or UC; immunomodulators, which are used primarily as maintenance therapies for patients with IBD who have responded to corticosteroid induction or as adjuncts to other therapies to augment response; and biologic agents, which include anti–tumor necrosis factor-α (anti–TNF-α) agents as well as antiadhesion therapies and are indicated for patients with moderate to severe disease or corticosteroid-refractory or -dependent disease.[3-5]

Most patients with UC have moderate to severe disease at the time of diagnosis, and in the majority of patients with CD, the disease will progress, exhibiting more aggressive stricture formation or

penetrating behavior over time.[6,7] Although corticosteroids, immunomodulators, and biologic agents are the mainstays for the treatment of moderate to severe disease, success in attaining sustained clinical remission with these agents has been variable.

Approximately 20% to 30% of patients with UC will require surgery during their disease course because of fulminant colitis, dysplasia, malignancy, or, most commonly, medically refractory disease.[7,8] With the introduction of biologic agents over the past decade, rates of colectomy appear to be decreasing, but approximately 7% to 15% of patients with UC will still require surgery within the first decade after diagnosis.[9-11]

Similarly, the probability that a patient with CD will require surgery is approximately 70% within the first 15 years following diagnosis, usually because of the development of more complicated disease behaviors or medically refractory disease.[12] The earlier use of biologics and immunomodulators may be contributing to the decreased surgical risks of patients with CD.[13] Recently published studies suggest that the earlier use of combination immunosuppression with biologics and immunomodulators yields longer periods of corticosteroid-free remission for patients with CD or UC.[14,15]

Anti-TNF drugs have been the most effective agents for both UC and CD. Currently, 4 anti-TNF agents approved by the US Food and Drug Administration (FDA) are commercially available for the treatment of IBD: infliximab (Remicade, Janssen Biotech; for CD and UC), adalimumab (Humira, AbbVie; for CD and UC), certolizumab pegol (Cimzia, UCB; for CD only), and golimumab (Simponi, Janssen Biotech; for UC only). Although these agents have all been demonstrated to be superior to placebo as induction and maintenance therapies, a sizeable proportion of patients in studies (approximately 40% of those with UC and 20% to 40% of those with CD) have been primary nonresponders to anti-TNF therapy.[16,17] Additionally, loss of response to therapy, due to accelerated drug clearance, the development of aberrant immune pathways, or the formation of antidrug antibodies, is common; approximately 30% to 40% of patients with UC and 40% of patients with CD who are treated with anti-TNF agents lose their response over time.[18] Among patients who either have never responded or have lost their response to anti-TNF therapies, there is a definite need for other therapies that target different mechanisms along the IBD inflammatory pathway so that the treatment of refractory IBD can be optimized. Most recently, focus has been increasing on the blockade of inflammatory cell migration and adhesion as a therapy for IBD.

On May 20, 2014, the FDA approved the use of vedolizumab (Entyvio, Takeda Pharmaceuticals) for inducing and maintaining response and remission in patients with UC, as well as achieving corticosteroid-free remission in patients with moderately to severely active UC. The FDA also granted an additional indication of improving endoscopic appearance. For patients with moderately to severely active CD, the approved indication is achieving response and remission, as well as corticosteroid-free remission. This article reviews data from randomized clinical trials of vedolizumab in patients with moderate to severe UC or CD. The article also reviews the practical clinical applications of vedolizumab as approved by the FDA based on available data.

Adhesion Molecules as Therapeutic Targets in the Treatment of Inflammatory Bowel Disease

During active IBD, one of the main components of the intestinal immune response is the migration of activated effector T cells through the vasculature into the intestinal tissue.[19] The process of specific T-cell migration into the lumen comprises a series of events that involve capture of the leukocyte from the circulating blood in the vasculature, tethering and rolling of the captured cell to the vascular wall with activation, and adhesion through interaction between adhesion molecules, which is then followed by migration into the tissue.[20,21] The integrins are a group of leukocyte adhesion molecules activated by T-cell–released chemokines that activate the tethered/rolling leukocytes and start the migratory process through the vasculature into the targeted site.[19] The integrins are classified based on their α and β subunits. Two α_4 integrins, $\alpha_4\beta_1$ and $\alpha_4\beta_7$, have been studied as targets of IBD therapy (eg, natalizumab [Tysabri, Biogen Idec] and vedolizumab). The $\alpha_4\beta_1$ integrin binds to vascular adhesion molecule 1 (VCAM-1), and $\alpha_4\beta_7$ binds to mucosal addressin-cell adhesion molecule 1 (MAdCAM-1), which is expressed on gut-associated lymphoid tissue in the small intestine and colon.[22,23] MAdCAM-1 expression is noted to be upregulated at sites of active IBD.[24]

The first commercially available antiadhesion molecule therapy for IBD was natalizumab, which is used for the treatment of moderate to severe CD and also for the treatment of multiple sclerosis. Natalizumab is a recombinant humanized monoclonal antibody against only the α_4 integrin subunit; therefore, it blocks both the $\alpha_4\beta_1$ (VCAM-1 target) and $\alpha_4\beta_7$ (MAdCAM-1 target) integrins. The $\alpha_4\beta_7$ subunit has been demonstrated to be gut lymphocyte–specific,[25] whereas the $\alpha_4\beta_1$ subunit interferes with leukocyte migration into the central nervous system (CNS), which explains its parallel efficacy in multiple sclerosis.[26,27]

Natalizumab was first reported to have clinical efficacy as a treatment for CD in a trial of 30 patients with active

disease (Crohn's Disease Activity Index score [CDAI] between 151 and 400) who were receiving a single 3-mg/kg infusion of natalizumab. The ENACT (Efficacy of Natalizumab as Active Crohn's Disease Therapy) trial enrolled 905 patients with CD, approximately 40% of whom had experienced prior anti-TNF exposure; 724 patients were randomized to receive induction therapy with natalizumab at a dose of 300 mg at weeks 0, 4, and 8. The rates of week 10 response and CDAI score decrease of at least 100 from baseline were higher among the patients treated with natalizumab than among those given placebo (56% vs 49%; *P*=.05), and higher week 10 remission rates were also noted (39% vs 30%; *P*=.12). During the maintenance phase of the study (ENACT-2), the week 36 sustained response rate was significantly higher among the patients treated with natalizumab than among those given placebo (61% vs 28%; *P*<.001), as was the week 36 remission rate, defined as a CDAI score below 150 (44% vs 26%; *P*=.003).[28] Similar findings were reported in the ENCORE (Efficacy of Natalizumab in Crohn's Disease Response and Remission) trial, in which week 12 response and remission rates among patients treated with 300 mg of intravenous natalizumab at weeks 0, 4, and 8 were superior to those of patients given placebo.[29] Two smaller case series of patients treated with natalizumab and followed up at major tertiary care IBD centers, the majority of whom had experienced prior anti-TNF exposure, showed a sustained response in almost half of the patients.[30-32]

However, a major limitation to the routine prescribing of natalizumab for CD is the potentially increased risk for progressive multifocal leukoencephalopathy (PML), a serious and potentially fatal CNS infection caused by the John Cunningham (JC) virus.[33] Because natalizumab binds nonselectively to the α_4 integrin subunit, it antagonizes the interaction of the $\alpha_4\beta_1$ integrin with VCAM-1, resulting in the altered trafficking of T lymphocytes into the cerebrospinal fluid (CSF), a reduction in the number of helper CD4+ T cells in the CSF, and a relative CD4+ T-cell lymphopenia, which are risk factors for the development of PML.[34,35] Clinically relevant and demonstrable risk factors for PML include JC virus antibody positivity, concomitant or prior immunosuppressant use, and longer duration of natalizumab treatment.[36,37] As of March 6, 2014, the overall incidence of PML was 3.55 (95% CI, 3.23-3.89) per 1000 patients.[38] For patients with JC virus antibody positivity and prior immunosuppressive therapies, the estimated incidence after 25 to 48 months was calculated to be a prohibitive 13 per 1000 patients.[38] Because almost all patients with moderate to severe IBD activity will have had prior immunosuppressant exposure and because substantial percentages of patients are JC virus seropositive, the use of natalizumab as a therapeutic modality for IBD is currently limited.

Vedolizumab

Vedolizumab, a different selective adhesion molecule inhibitor recently approved by the FDA as a treatment for moderate to severe UC or CD, has a more specific molecular target than natalizumab. Vedolizumab is a humanized monoclonal antibody against only the $\alpha_4\beta_7$ integrin; therefore, it blocks the interaction between $\alpha_4\beta_7$ and MAdCAM-1, selectively impacting gut-specific lymphocyte trafficking.[39,40] Unlike natalizumab, vedolizumab does not interfere with $\alpha_4\beta_1$ integrin–VCAM-1 activity; therefore, it is not thought to have an effect on CNS lymphocyte trafficking or to increase the risk for PML. To examine the effect of vedolizumab on CNS lymphocyte homeostasis, Milch and colleagues examined the CSF of healthy subjects before and after a single 450-mg intravenous infusion of vedolizumab.[41] The authors found no differences before and 5 weeks following the infusion in terms of CD4-to-CD8 T-cell ratios in the CSF and of mean or median absolute cell counts, and they observed no peripheral lymphocytosis, which had developed with natalizumab.[41] Treatment with an $\alpha_4\beta_7$ monoclonal antibody led to the rapid resolution of chronic colitis among nonhuman primates, with a decrease in histologic inflammatory activity and the absence of lymphocyte homing inhibition outside the lumen of the gastrointestinal tract.[42]

Early Trials

In a phase 1 dose-ranging study of the safety and efficacy of selective antiadhesion molecule therapy, the original formulation of the $\alpha_4\beta_7$ monoclonal antibody (LDP02) demonstrated superiority to placebo in 29 patients with active UC in terms of clinical and endoscopic remission at 4 weeks.[43] Subsequently, a phase 2 trial of the $\alpha_4\beta_7$ monoclonal antibody therapy (referred to as MLN02) was performed in 181 patients with anti-TNF–naive active UC; the patients were randomized to receive placebo or MLN02 administered as an infusion of 0.5 or 2.0 mg/kg at days 0 and 29. The primary outcome measure was clinical remission at week 6, defined as a UC clinical score of 0 or 1 with no rectal bleeding based on a scoring system that included rectal bleeding, stool frequency, patient-based functional assessment, and physician global assessment. At week 6, 32% to 33% of the patients treated with vedolizumab were in clinical remission, compared with 14% of the placebo patients, and vedolizumab had additional notable outcomes of greater endoscopic improvement and remission compared with placebo at week 6. However, 44% of the patients tested positive for human–antihuman antibodies (HAHAs), and 24% had antibody titers greater than 1:125. As with anti-TNF–based antidrug antibodies, the HAHAs were associated with lower remission rates, similar to those for

placebo, whereas the patients with lower antibody titers or antibody-negative status had higher remission rates.[44]

A similarly designed randomized, multicenter, double-blind, phase 2 trial of $\alpha_4\beta_7$ monoclonal antibody therapy (referred to as MLN0002) investigated the potential efficacy and safety of MLN0002 infused at doses of 0.5 or 2.0 mg/kg on days 1 and 29 in 185 patients with anti-TNF–naive active CD, defined as a CDAI score between 220 and 400. The primary outcome was a clinical response, defined as a decrease in the baseline CDAI score by at least 70, by day 57. Although the clinical remission rates at day 57 were significantly higher among the patients treated with MLN0002 at a dose of 2.0 mg/kg than in those given placebo (37% vs 21%; *P*=.04), no significant differences were noted for either dosing group compared with the placebo group (43%-47% vs 31%; *P*=ns). In addition, no differences between the T- or B-cell counts of the vedolizumab-treated patients and those of the placebo-treated patients were reported, and there was no vedolizumab-associated lymphocytosis. As in the phase 2 study for UC, HAHA titers greater than 1:125 were detectable among 34% of the patients treated with vedolizumab at 2.0 mg/kg and 12% of the patients treated with vedolizumab at 0.5 mg/kg. Higher HAHA titers were associated with lower remission rates.[45]

Because of the relatively high prevalence of antidrug antibodies in patients treated with the initial formulation of the $\alpha_4\beta_7$ monoclonal antibody, the medication was reformulated to decrease its immunogenicity (MLN002 or vedolizumab) and tested in a phase 2 dose-ranging study for the safety, immunogenicity, and efficacy of 2 to 10 mg/kg, with 4 infusions administered over a period of 85 days. Although the study was not powered to determine efficacy, the rates of response, defined as a change in the partial Mayo score of at least 2, were greater than 50% across the dosing groups. Notably, no patient had detectable JC virus in the serum throughout the study, although 1 patient had detectable JC virus DNA before receiving treatment. Antihuman antibodies were present in 11% of the patients, the majority of whom had low antibody titers.[46]

The newly formulated vedolizumab was then tested in a long-term, open-label, dose-ranging, safety extension study of both patients with UC and patients with CD naive to anti-TNF therapy. They were randomized to receive vedolizumab at a dose of 2.0, 6.0, or 10.0 mg/kg on days 1, 15, and 43, with maintenance infusions every 8 weeks thereafter. Following the 3 induction doses of vedolizumab, the day 99 remission and response rates of the patients with UC and a pretreatment partial Mayo score of 4 or higher were 56% and 67%, respectively. Among the patients with CD, the day 99 remission and response rates were 13% and 56%, respectively; however, the remission rates did tend to increase over time, with a 38% remission rate at day 155 and a 45% remission rate by day 267. Importantly, HAHA positivity was present in only 4% (n=3) of the patients, and 2 of the 3 HAHA-positive patients had transient antibody positivity, with no antibodies present at later time points; this finding suggests that not only the new formulation of vedolizumab but also the higher induction dose may be associated with decreased immunogenicity.[47]

GEMINI I

More recently, results from the phase 3 studies of vedolizumab for moderate to severe UC (GEMINI I: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by MLN002 in Patients With Moderate to Severe Ulcerative Colitis) and CD (GEMINI II: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab [MLN002] in Patients With Moderate to Severe Crohn's Disease) have been published.

GEMINI I recruited patients with moderate to severe UC, including those with prior anti-TNF exposure, for a randomized, double-blind, placebo-controlled efficacy trial of vedolizumab as induction and maintenance therapies. The primary outcome was a clinical response at week 6, defined as a reduction in the Mayo score of at least 30% from baseline with a decrease in the rectal bleeding subscore of at least 1 point or an absolute subscore of 0 or 1. Remission was defined as a Mayo score of 2 or lower with no subscore above 1. The study involved 2 cohorts. The patients in cohort 1 were randomized into a blinded induction study of 300 mg of vedolizumab administered intravenously at weeks 0 and 2 vs placebo infusions, whereas the patients in cohort 2 received open-label induction treatment with vedolizumab at weeks 0 and 2. The week 6 vedolizumab responders were then randomized to receive 300 mg of vedolizumab every 4 or 8 weeks vs placebo for up to 52 weeks as part of the maintenance study. Corticosteroid doses of prednisone of up to 30 mg daily were allowed, continued through induction, and tapered starting at week 6 for responders. At week 6, the clinical response rates were 47% for vedolizumab vs 26% for placebo (*P*<.001), with 41% of the vedolizumab-treated patients who had UC achieving mucosal healing, defined as a Mayo endoscopic score of 0 or 1. Notably, among the patients with anti-TNF failure, the week 6 response rates were 39% for vedolizumab and 21% for placebo (*P*=.01). The rate of serious adverse events for the vedolizumab-treated patients was low, approximately 2%, and similar to that in the patients given placebo.[48]

For the maintenance phase, the primary endpoint was clinical remission at week 52; notable secondary endpoints included mucosal healing and corticosteroid-free remission at week 52. From cohorts 1 and 2, a total of 373 patients who were vedolizumab responders at week 6 were randomized to receive placebo, vedolizumab every 4 weeks, or vedolizumab every 8 weeks. At week 52, 42% of the patients treated every 8 weeks and 45% of those treated every 4 weeks were in clinical remission, compared with 16% of those given placebo (P<.001 for both vedolizumab groups). Mucosal healing rates ranged from 52% to 56% for vedolizumab, compared with 20% for placebo (P<.001). Notably, the corticosteroid-free remission rates at week 52 were 31% in the patients with UC treated with vedolizumab every 8 weeks and 45% in the patients with UC treated with vedolizumab every 4 weeks, compared with 14% of the patients given placebo. Additionally, among the patients with prior anti-TNF failure, the week 52 remission rates were 35% to 37% for those treated with vedolizumab vs 5% for those given placebo. The rates of serious adverse events (vedolizumab 13% vs placebo 12%) and infection (vedolizumab 2% vs placebo 3%) were similar throughout the maintenance phase.[48]

GEMINI II

GEMINI II, another randomized, multicenter, placebo-controlled trial, investigated the efficacy and safety of vedolizumab for patients with moderate to severe CD (CDAI score of 220 to 450 with recent objective data suggesting ongoing disease activity: C-reactive protein [CRP] level elevation, endoscopically visible active disease, or elevated fecal calprotectin with imaging-based evidence of disease activity); the study included patients with prior anti-TNF exposure. As in the UC trial, there were 2 cohorts; the patients in cohort 1 were randomized into a blinded induction study of vedolizumab at weeks 0 and 2 vs placebo, and those in cohort 2 received open-label vedolizumab at weeks 0 and 2. The week 6 responders, defined as those with a decrease from their baseline CDAI score of at least 70, were then enrolled into the maintenance study and followed for up to 52 weeks. The 2 primary endpoints for week 6 were clinical remission (CDAI score ≤150) and clinical response, defined as a difference of 100 from the baseline CDAI score. There was no significant difference between the week 6 response rate of the vedolizumab-treated patients (31%) and that of the patients given placebo (26%; P=.23). Although the clinical remission rates were low for both groups, more of the vedolizumab-treated patients (15%) than those given placebo (7%) had a CDAI score of 150 or lower (P=.02) at week 6. Similar rates of response (34%) and remission (18%) were noted among the patients receiving open-label induction vedolizumab as part of cohort 2. In addition, there was no significant difference between the CRP level change from baseline to week 6 of the vedolizumab group and that of the placebo group.[49]

For the maintenance phase, the primary endpoint was clinical remission at week 52, with notable secondary endpoints including corticosteroid-free remission and clinical response. From cohorts 1 and 2, a total of 461 vedolizumab responders at week 6 were randomized to receive placebo, vedolizumab every 4 weeks, or vedolizumab every 8 weeks. At week 52, the clinical remission rates of the vedolizumab-treated patients with CD were 36% to 39%, compared with 22% of the patients given placebo (P<.01 for both groups). Notably, at week 52, the clinical response rates (vedolizumab 44%-46% vs placebo 30%) and corticosteroid-free remission rates (vedolizumab 29%-32% vs placebo 16%) were significantly different. Patients with CD and known prior anti-TNF failure who were treated with vedolizumab had clinical remission rates of 27% to 28% at week 52, compared with 17% for the patients given placebo (P=.02). These maintenance data suggest a potentially longer time to response/remission during the induction phase for patients with CD, which may explain the lower remission and response rates at week 6. Serious adverse events were more common among the patients with CD treated with vedolizumab (24%) than among those given placebo (15%). Five deaths occurred during the study period, 4 among vedolizumab-treated patients due to 1 of the following reasons: prescription medication overdose, myocarditis, septic shock following colonoscopy-associated pneumoperitoneum, and sepsis in a patient with a known extensive venous thromboembolic burden.[49]

GEMINI III

A third randomized, controlled trial of vedolizumab, GEMINI III (A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab in Patients With Moderate to Severe Crohn's Disease), focused more specifically on patients with moderately to severely active CD, prior anti-TNF failure, and recent objective data suggestive of ongoing disease activity (CRP level elevations, endoscopically visible active disease, or elevated fecal calprotectin with imaging-based evidence of disease activity). Primary endpoints for induction and maintenance were the same as in GEMINI II. Among the 416 patients enrolled, 315 had experienced primary anti-TNF failure. At week 6, significantly more of the patients with anti-TNF failure receiving vedolizumab had a clinical response (39%), defined as a decrease from their baseline CDAI score of at least 100, than patients given placebo (22%; P=.001). Although the other primary endpoint, clinical remission, which was defined as a CDAI score of 150 or lower, did not differ significantly at week 6 between the vedolizumab-treated patients (15%) and

placebo-treated patients (12%) with anti-TNF failure, the difference between the groups became more apparent at week 10, with 27% of the vedolizumab-treated patients vs 12% of the placebo-treated patients achieving clinical remission (*P*=.001).[50] The rates of serious adverse events were similar in the vedolizumab-treated group (5%) and the placebo group (8%).

GEMINI LTS

To examine the safety and tolerability of vedolizumab, a long-term, open-label, 2-year extension study of subjects who had participated in a phase 2 or 3 vedolizumab trial, GEMINI LTS (A Phase 3, Open-Label Study to Determine the Long-Term Safety and Efficacy of Vedolizumab [MLN0002] in Patients With Ulcerative Colitis and Crohn's Disease) is currently under way. Based on the published studies, there appear to be similar adverse events across disease types (CD vs UC) among vedolizumab-treated patients. The most common adverse events reported in GEMINI I were colitis exacerbation (16%), headache (13%), and nasopharyngitis (13%).[48] Among the vedolizumab-treated patients with CD in GEMINI II, the most common adverse events were CD flares (20%), arthralgia (14%), pyrexia (13%), nasopharyngitis (12%), headache (12%), nausea (11%), and abdominal pain (10%).[49] Vedolizumab-treated patients with CD or UC enrolled in the maintenance studies had similar overall adverse event rates compared with placebo-treated patients, with upper respiratory tract infections occurring more frequently in the vedolizumab group. Serious adverse events were slightly more frequent among the vedolizumab-treated patients (19%) than in those given placebo (13%-15%), but no increased rates of gastrointestinal infections, including *Clostridium difficile* infection, or neoplasms were noted across study groups.[51] Notably, as of February 2013, there have been no reported cases of PML among vedolizumab-treated patients based on aggregate data from the estimated 3000 patients exposed to vedolizumab for a median of 19 months.[48,49] Pretreatment JC virus antibody status for the vedolizumab-exposed patients has not been reported because the commercial assay for testing was not available at the time of study recruitment, although at least 50% of patients with IBD have reported JC virus antibody positivity.[52,53]

Clinical Use

On May 20, 2014, the FDA approved vedolizumab for moderately to severely active UC, with the following indications: inducing and maintaining a clinical response, inducing and maintaining a clinical remission, improving the endoscopic appearance of the mucosa, and achieving a corticosteroid-free remission. For CD, the approved indications were achieving a clinical response, achieving a clinical remission, and achieving a corticosteroid-free remission. For both diseases, the drug was approved at a fixed dose of 300 mg per infusion for adult patients with moderately to severely active UC or CD who had an inadequate response to, lost their response to, or were intolerant of a TNF blocker or immunomodulator, or who had an inadequate response to, were intolerant of, or demonstrated dependence on corticosteroids.[54]

Vedolizumab is administered as a 300-mg infusion over 30 minutes at weeks 0, 2, and 6 for induction therapy and then at 8-week intervals for maintenance. If there is no evidence of meaningful therapeutic benefit by week 14, it is recommended to discontinue vedolizumab therapy. The utility of continued maintenance dosing of vedolizumab for nonresponders is debatable because the maintenance data presented in the clinical trials represented the subset of patients with an initial response to induction dosing. However, patients with CD or UC who were deemed nonresponders at week 6 received 300 mg of vedolizumab every 4 weeks as part of the open-label treatment group to be included as part of the longer-term safety analysis. A variable subset of these initial nonresponders were able to achieve a response (39% of those with UC and 22% of those with CD) or remission (15% of those with UC and 11% of those with CD) at week 14. Among these week 14 responders, the response (54% of those with UC and 25% of those with CD) and remission rates (35% of those with UC and 19% of those with CD) at week 52 were noted to be higher than the rates in placebo-treated patients. However, the data on the initial study nonresponders should be interpreted with caution because the trials were not powered to investigate this patient group nor was this analysis an initial study endpoint, and vedolizumab maintenance every 4 weeks is not currently an FDA-approved dosing schedule for clinical practice.[55,56]

Because of the increased risk for infection, vedolizumab should not be used concomitantly with anti-TNF drugs. It is rated as a pregnancy category B drug; however, it is unknown at present whether vedolizumab is passed into breast milk. No cases of PML have been reported in patients treated with vedolizumab, and JC antibody testing was not recommended in the prescribing information approved by the FDA. However, the recommendation is to "monitor patients for any new or worsening neurologic signs or symptoms."[54]

Conclusion

In the clinical trial setting, vedolizumab has demonstrated superiority over placebo for the induction and maintenance of remission in patients with UC, including those with prior anti-TNF exposure. The response to induction in patients with CD does not appear to be as robust as that in patients with UC, although results for the efficacy of maintenance therapy demonstrate durable benefit. As

with any study design, the predetermined criteria and time points for assessing response or remission are fixed, and there are suggestions of data points with potentially increased efficacy if the assessment period for the primary endpoint is extended even by just a few weeks (eg, from week 6 to week 10) in the CD trials.

With the introduction of vedolizumab as another potentially effective therapy for patients with IBD, new questions emerge. Where in the therapeutic pyramid should vedolizumab be positioned? Should it be reserved for patients with disease that is refractory to anti-TNF treatment, or should it be considered on par with anti-TNF agents as a first-line biologic for corticosteroid-dependent patients with moderate to severe refractory disease? What about combination therapy with immunomodulators—can the effect of vedolizumab be potentiated by adding thiopurines, as has been demonstrated with anti-TNF agents? Are the remission rates sustainable for the longer term, or does immunogenicity or other loss-of-response mechanisms limit durability in initial responders? Can increasing the dose by shortening the interval be of benefit to patients with a secondary loss of response? Will assays for serum levels and antivedolizumab antibodies become commercially available? As the utilization of vedolizumab in real-world practice increases and as additional, longer-term efficacy and safety data emerge, patient- and disease-specific characteristics may be revealed to help guide the appropriate prescribing of antiadhesion molecule therapy relative to anti-TNF therapies. Regardless of the answers to these questions, the introduction of another non–TNF-based agent is timely as the management of IBD and affected patients becomes more complex. The introduction of vedolizumab as an additional option will offer the possibility of increasing disease-free remission for a greater proportion of patients with moderately to severely active UC and CD.

Dr Ha serves on the advisory boards of and is a consultant for AbbVie and Takeda Pharmaceuticals. Dr Kornbluth serves on the advisory boards of and is a consultant for Prometheus Laboratories, Janssen Pharmaceuticals, AbbVie Pharmaceuticals, Takeda Pharmaceutical USA, and Pfizer. He is on the speakers bureaus of AbbVie Pharmaceuticals, Janssen Pharmaceuticals, Takeda Pharmaceutical USA, Salix Pharmaceuticals, and Prometheus Laboratories.

References

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* 2012;142(1):46-54.e42; quiz e30.
2. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol*. 2007;5(12):1424-1429.
3. Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol*. 2009;104(2):465-483.
4. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010;105(3):501-523.
5. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*. 2007;369(9573):1641-1657.
6. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis*. 2002;8(4):244-250.
7. Langholz E, Munkholm P, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of ulcerative colitis in Copenhagen county from 1962 to 1987. *Scand J Gastroenterol*. 1991;26(12):1247-1256.
8. Leijonmarck CE, Persson PG, Hellers G. Factors affecting colectomy rate in ulcerative colitis: an epidemiologic study. *Gut*. 1990;31(3):329-333.
9. Vester-Andersen MK, Prosberg MV, Jess T, et al. Disease course and surgery rates in inflammatory bowel disease: a population-based, 7-year follow-up study in the era of immunomodulating therapy. *Am J Gastroenterol*. 2014;109(5):705-714.
10. Rungoe C, Langholz E, Andersson M, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. *Gut*. 2014;63(10):1607-1616.
11. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology*. 2011;141(4):1194-1201.
12. Munkholm P, Langholz E, Davidsen M, Binder V. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology*. 1993;105(6):1716-1723.
13. Peyrin-Biroulet L, Oussalah A, Williet N, Pillot C, Bresler L, Bigard MA. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. *Gut*. 2011;60(7):930-936.
14. Colombel JF, Sandborn WJ, Reinisch W, et al; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362(15):1383-1395.
15. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology*. 2014;146(2):392-400.e3.
16. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106(4):644-659.
17. Leung Y, Panaccione R. Anti-adhesion molecule strategies for Crohn disease. *BioDrugs*. 2008;22(4):259-264.
18. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther*. 2011;33(9):987-995.
19. Thomas S, Baumgart DC. Targeting leukocyte migration and adhesion in Crohn's disease and ulcerative colitis. *Inflammopharmacology*. 2012;20(1):1-18.
20. von Andrian UH, Mackay CR. T-cell function and migration. Two sides of the same coin. *N Engl J Med*. 2000;343(14):1020-1034.
21. Goebel S, Huang M, Davis WC, et al. VEGF-A stimulation of leukocyte adhesion to colonic microvascular endothelium: implications for inflammatory bowel disease. *Am J Physiol Gastrointest Liver Physiol*. 2006;290(4):G648-G654.
22. Elices MJ, Osborn L, Takada Y, et al. VCAM-1 on activated endothelium interacts with the leukocyte integrin VLA-4 at a site distinct from the VLA-4/fibronectin binding site. *Cell*. 1990;60(4):577-584.
23. Tsuzuki Y, Miura S, Suematsu M, et al. alpha 4 integrin plays a critical role in early stages of T lymphocyte migration in Peyer's patches of rats. *Int Immunol*. 1996;8(3):287-295.
24. Briskin M, Winsor-Hines D, Shyjan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol*. 1997;151(1):97-110.
25. Picarella D, Hurlbut P, Rottman J, Shi X, Butcher E, Ringler DJ. Monoclonal antibodies specific for beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) reduce inflammation in the colon of scid mice reconstituted with CD45RBhigh CD4+ T cells. *J Immunol*. 1997;158(5):2099-2106.
26. Rudick RA, Stuart WH, Calabresi PA, et al; SENTINEL Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):911-923.
27. Lobatón T, Vermeire S, Van Assche G, Rutgeerts P. Review article: anti-adhesion therapies for inflammatory bowel disease. *Aliment Pharmacol Ther*. 2014;39(6):579-594.
28. Sandborn WJ, Colombel JF, Enns R, et al; International Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) Trial Group; Evaluation of Natalizumab as Continuous Therapy (ENACT-2) Trial Group. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2005;353(18):1912-1925.

29. Targan SR, Feagan BG, Fedorak RN, et al; International Efficacy of Natalizumab in Crohn's Disease Response and Remission (ENCORE) Trial Group. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. *Gastroenterology*. 2007;132(5):1672-1683.
30. Kane SV, Horst S, Sandborn WJ, et al. Natalizumab for moderate to severe Crohn's disease in clinical practice: the Mayo Clinic Rochester experience. *Inflamm Bowel Dis*. 2012;18(12):2203-2208.
31. Sakuraba A, Annunziata ML, Cohen RD, Hanauer SB, Rubin DT. Mucosal healing is associated with improved long-term outcome of maintenance therapy with natalizumab in Crohn's disease. *Inflamm Bowel Dis*. 2013;19(12):2577-2583.
32. Sakuraba A, Keyashian K, Correia C, et al. Natalizumab in Crohn's disease: results from a US tertiary inflammatory bowel disease center. *Inflamm Bowel Dis*. 2013;19(3):621-626.
33. Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med*. 2005;353(4):362-368.
34. Berger T, Deisenhammer F. Progressive multifocal leukoencephalopathy, natalizumab, and multiple sclerosis. *N Engl J Med.* 2005;353(16):1744-1746; author reply 1744-1746.
35. Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. *Lancet Oncol*. 2009;10(8):816-824.
36. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med*. 2012;366(20):1870-1880.
37. Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2006;354(9):924-933.
38. Tysabri [prescribing information, final update]. Cambridge, MA: Biogen Idec; 2014. http://www.tysabri.com/pdfs/I61061-13_PI.pdf. Accessed October 29, 2014.
39. Fedyk ER, Wyant T, Yang LL, et al. Exclusive antagonism of the $\alpha 4\ \beta 7$ integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. *Inflamm Bowel Dis*. 2012;18(11):2107-2119.
40. Soler D, Chapman T, Yang LL, Wyant T, Egan R, Fedyk ER. The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther*. 2009;330(3):864-875.
41. Milch C, Wyant T, Xu J, et al. Vedolizumab, a monoclonal antibody to the gut homing $\alpha 4\beta 7$ integrin, does not affect cerebrospinal fluid T-lymphocyte immunophenotype. *J Neuroimmunol*. 2013;264(1-2):123-126.
42. Hesterberg PE, Winsor-Hines D, Briskin MJ, et al. Rapid resolution of chronic colitis in the cotton-top tamarin with an antibody to a gut-homing integrin alpha 4 beta 7. *Gastroenterology*. 1996;111(5):1373-1380.
43. Feagan B, McDonald JW, Greenberg GR, et al. An ascending dose trial of a humanized A_4B_7 antibody in ulcerative colitis [abstract]. *Gastroenterology.* 2000;118(4):A874.
44. Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. *N Engl J Med.* 2005;352(24):2499-2507.
45. Feagan BG, Greenberg GR, Wild G, et al. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. *Clin Gastroenterol Hepatol*. 2008;6(12):1370-1377.
46. Parikh A, Leach T, Wyant T, et al. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. *Inflamm Bowel Dis*. 2012;18(8):1470-1479.
47. Parikh A, Fox I, Leach T, et al. Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2013;19(8):1691-1699.
48. Feagan BG, Rutgeerts P, Sands BE, et al; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2013;369(8):699-710.
49. Sandborn WJ, Feagan BG, Rutgeerts P, et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2013;369(8):711-721.
50. Sands BE, Feagan B, Rutgeerts P, et al. Vedolizumab induction therapy for patients with Crohn's disease and prior anti-tumour necrosis factor antagonist failure: a randomised, placebo-controlled, double-blind, multicentre trial. *J Crohns Colitis*. 2013;7:S5-S6.
51. Colombel JF, Sands BE, Feagan BG, et al. Integrated safety analysis of vedolizumab for the treatment of ulcerative colitis or Crohn's disease [abstract 643]. *Gastroenterology.* 2013;144(5 suppl 1):S-113.
52. Hwang C, Fisher ER, Terdiman JP, Mahadevan U, Velayos F. Clinical utility of anti-JC virus antibody testing in Crohn's disease: rate of seropositivity and impact on therapy with natalizumab [abstract 270]. *Gastroenterology.* 2012;142(5 suppl 1):S-64.
53. Verbeeck J, Van Assche G, Ryding J, et al. JC viral loads in patients with Crohn's disease treated with immunosuppression: can we screen for elevated risk of progressive multifocal leukoencephalopathy? *Gut*. 2008;57(10):1393-1397.
54. Vedolizumab [package insert]. Deerfield, IL: Takeda Pharmaceuticals USA; 2014.
55. Feagan BG, Sandborn WJ, Smyth MD, Sankoh S, Parikh A, Fox I. Effects of continued vedolizumab therapy for ulcerative colitis in week 6 induction therapy nonresponders [abstract Mo1222]. *Gastroenterology.* 2014;146(5 suppl 1):S-590.
56. Sandborn WJ, Feagan BG, Reinisch W, et al. Effects of continued vedolizumab therapy for Crohn's disease in week 6 induction therapy nonresponders [abstract Mo1217]. *Gastroenterology.* 2014;146(5 suppl 1):S-588.