

Induction and Maintenance Therapy with Vedolizumab, a Novel Biologic Therapy for Ulcerative Colitis

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.

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by inflammation of the mucosal layer of the colon. The resulting disease includes episodes of recurrent rectal bleeding, increased stool frequency and urgency, abdominal cramps and pain, and systemic symptoms (such as fever, anemia, and weight loss).¹ Historical studies have estimated that approximately half of the IBD cases in the United States were attributed to UC; a recent study estimated that UC affected approximately 593,000 persons, with an incidence rate of 8 to 12 per 100,000 persons per year.^{2,3}

The introduction of tumor necrosis factor (TNF) antagonist agents dramatically changed the treatment landscape for UC. As of late 2013, 3 anti-TNF agents have been approved in this setting—infliximab (Remicade, Janssen), adalimumab (Humira, AbbVie), and golimumab (Simponi, Janssen)—with slightly different indications specific for each. Each of these agents has demonstrated benefit for the induction and maintenance of remission in moderate or severe UC. In addition, these biologic agents are noted for their ability to change the natural course of the disease by inducing mucosal healing, reducing glucocorticoid dependence, and decreasing the need for colectomy.

Despite their clear impact on the course of therapy, anti-TNF therapy remains inadequate in a significant portion of patients with UC. Approximately 40% of patients with UC fail to respond to infliximab, and another 30% or 40% of patients with UC begin to lose response to infliximab over time.⁴⁻⁶ Thus, alternative therapies have been investigated for UC. One class of agents targets the integrins, cell surface adhesion molecules involved in lymphocyte migration.^{5,7} Because leukocyte invasion of the intestinal mucosa has been shown to have a role in the pathogenesis of IBD,⁸ integrin antagonists have been explored for their efficacy in UC. One of the first agents in this class to be evaluated was natalizumab (Tysabri, Biogen Idec) in Crohn's disease. However, due to its association with progressive multifocal leukoencephalopathy

(PML), use of natalizumab has been severely limited in this population. The link between natalizumab and PML has been attributed to its inhibition of both the gut-specific $\alpha_4\beta_7$ integrin and the central nervous system-specific $\alpha_4\beta_1$ integrin.⁵

Vedolizumab is a novel integrin antagonist that, due to its mechanism of action, only targets the gut-specific $\alpha_4\beta_7$ integrin for inhibition.^{9,10} Here, Feagan and colleagues report on a phase 3 study that investigated the efficacy and safety of vedolizumab in patients with previously treated moderate to severe active UC.¹¹

Study Description

The GEMINI 1 study was a double-blind, placebo-controlled, randomized, international, multicenter, phase 3 trial that included separate induction and maintenance portions. Patients between age 18 and 80 years were enrolled between 2008 and 2012. All patients had active UC, which was defined by a Mayo Clinic score of 6 to 12 and a minimum sigmoidoscopy subscore of 2. Patients also were required to have a disease extent of at least 15 cm from the anal verge.

To be eligible for the study, patients had to have failed previous treatment with 1 or more glucocorticoids, immunosuppressive agents (including azathioprine and 6-mercaptopurine), or anti-TNF agents (>60 days prior to enrollment). Prior treatment with vedolizumab, natalizumab, efalizumab, or rituximab (Rituxan, Genentech) was not permitted. Other exclusion criteria included toxic megacolon, abdominal abscess, symptomatic colonic stricture, stoma, history of colectomy, increased risk of infectious complications, clinically meaningful laboratory abnormalities, and pregnancy or lactation, among others. Immediately prior to randomization, a sigmoidoscopy was performed, which provided a baseline Mayo Clinic score.

For the induction portion of the GEMINI 1 study, patients were randomized 3:2 to receive either 300 mg intravenous vedolizumab (n=225) or placebo (n=149)

on Days 1 and 15. Prior to randomization, patients were stratified according to use or nonuse of concurrent glucocorticoids and concomitant or prior use or nonuse of anti-TNF agents. (Prior anti-TNF agent exposure was limited to only half of the study population.) An additional 521 patients were enrolled into the maintenance portion of the trial as part of an open-label group to meet the requirements for sample size. These patients received the same active induction regimen that was given to patients in the blinded induction arm of the study. Patients were allowed to continue to receive aminosalicylates (continued through the induction and maintenance portions), prednisone (up to 30 mg daily through induction and then tapered after clinical response at Week 6), or immunosuppressive agents during the study (stopped after the induction portion in the United States or continued through the maintenance portion elsewhere).

For both the blinded and open-label cohorts, those patients who achieved a clinical response to vedolizumab by Week 6 were rerandomized in a 1:1:1 fashion to treatment for up to 52 weeks in 3 arms: vedolizumab every 4 weeks ($n=125$), vedolizumab every 8 weeks with placebo at every other visit to maintain blinding ($n=122$), or placebo ($n=126$). At rerandomization, patients were stratified by their induction cohort, the use or nonuse of concurrent glucocorticoids, and concomitant or prior use or nonuse of immunosuppressive agents or prior use or nonuse of anti-TNF agents.

For those patients who had not achieved a clinical response by Week 6, vedolizumab (300 mg) was continued every 4 weeks through Week 52. Patients in the original blinded induction cohort who had been randomized to the placebo arm continued to receive placebo through Week 52.

During the induction portion of the trial, patients were followed at Weeks 2, 4, and 6. All patients were then followed every 4 weeks thereafter until Week 52. Follow-up visits included the calculation of a partial Mayo Clinic score (without the sigmoidoscopy subscore). Serum laboratory analysis was conducted every 8 weeks, blood samples were analyzed for anti-vedolizumab antibodies every 12 weeks, and serum vedolizumab concentrations were assessed at Weeks 0, 2, 4, 6, and every 8 weeks thereafter. Additional sigmoidoscopies were conducted at Weeks 6 and 52.

The primary endpoint for the induction portion of the trial was a clinical response at Week 6. Clinical response was characterized by a reduction in the Mayo Clinic score of 3 or more points (including a decrease in the rectal bleeding subscale of at least 1 point or an absolute rectal bleeding score of 0 or 1), together with a decrease of 30% or more from the baseline score. The primary endpoint for the maintenance portion of the trial was clinical remission at Week 52.

Study Results

Patient demographic characteristics at baseline were comparable between the vedolizumab and placebo groups (overall median age, 40.3 ± 13.1 years; 58.7% male; 82.0% white). Patients had a median duration of disease of 6.9 ± 6.4 years and had various sites of disease involvement, including the left colon (37.9%), the entire colon (37.0%), the rectum and sigmoid colon only (13.0%), and proximal to the splenic flexure (12.2%). The median Mayo Clinic score at baseline was 8.6 ± 1.8 (partial subscore, 6.0 ± 1.6). Nearly half (48.2%) of patients had prior exposure to an anti-TNF agent, with 41.0% having had failed at least 1 of these agents. Similarly, the baseline characteristics among the 3 maintenance treatment arms were similar.

During the blinded induction portion of the GEMINI 1 trial, nearly twice as many patients in the vedolizumab arm than the placebo arm achieved a clinical response to induction therapy at Week 6 (47.1% vs 25.5%; $P<.001$). At Week 6, vedolizumab treatment was superior to placebo in relation to the proportion of patients achieving clinical remission (16.9% vs 5.4%; $P=.001$) or mucosal healing (40.9% vs 24.8%; $P=.001$). Among patients in the open-label cohort who received vedolizumab induction therapy, 44.3% achieved a clinical response, 19.2% had clinical remission, and 36.7% had mucosal healing by Week 6. Compared with placebo, vedolizumab-treated patients achieved a greater improvement at Week 6 in their mean partial Mayo Clinic score ($P<.001$), mean change from baseline in their IBD questionnaire (IBDQ) score ($P<.001$), and median fecal calprotectin value ($P<.001$).

In the maintenance portion, the patients who were randomized to receive vedolizumab (both the every-4-week and every-8-week groups) were more likely to be in clinical remission at Week 52 than those randomized to receive placebo (44.8% and 41.8% vs 15.9%; $P<.001$ for both comparisons). Also for patients in the maintenance portion, those in either the every-4-week or every-8-week vedolizumab arms achieved superior rates of durable clinical response compared with patients receiving placebo (52.0% and 56.6% vs 23.8%; $P<.001$ for both comparisons), durable clinical remission (24.0% and 20.5% vs 8.7%; $P=.001$ for the first comparison and $P=.008$ for the second comparison), mucosal healing (56.0% and 51.6% vs 19.8%; $P<.001$ for both comparisons), and glucocorticoid-free remission (45.2% and 31.4% vs 13.9%; $P<.001$ for the first comparison and $P=.01$ for the second comparison). The efficacy of vedolizumab was not significantly affected by concurrent treatment with either glucocorticoids or immunosuppressants or prior exposure to anti-TNF agents. Vedolizumab-treated patients achieved a greater

improvement at Week 52 in their mean partial Mayo Clinic score ($P<.001$ for both vedolizumab groups compared with placebo), mean change from baseline in their IBDQ score ($P<.001$ for both vedolizumab groups compared with placebo), median fecal calprotectin value ($P=.05$ and $P=.02$ for the every-4-week and every-8-week vedolizumab groups compared with placebo, respectively), and glucocorticoid dependence ($P<.001$ and $P=.009$ for the every-4-week and every-8-week vedolizumab groups compared with placebo, respectively). During both the induction and maintenance phases, the efficacy of vedolizumab was shared across all patient subgroups according to baseline demographic characteristics.

At Week 6, the mean trough vedolizumab concentration was 27.9 ± 15.5 mg/mL. During the maintenance portion, steady state mean vedolizumab concentrations were 38.3 ± 24.4 mg/mL in the every-4-week group and 11.2 ± 7.2 mg/mL in the every-8-week group. Throughout the study, 3.7% of vedolizumab-treated blood samples were positive for anti-vedolizumab antibodies at any one time; 1.0% was persistently positive over 2 or more consecutive samples. Blood samples from patients with concomitant immunosuppressive therapy showed lower rates of immunogenicity.

No clinically important differences were observed between vedolizumab and placebo among the frequently reported adverse events (including headache, UC, nasopharyngitis, upper respiratory tract infection, arthralgia, nausea, abdominal pain, anemia, fatigue, cough, blood chemistry profiles, and liver function tests). Serious infections occurred at the same rate in vedolizumab- and placebo-treated patients (1.9% vs 2.9%), and, importantly, no cases of PML were reported. The rate of serious adverse events was also similar (12.4% vs 13.5%). Additionally, there was not an increase in the peripheral blood total lymphocyte counts among vedolizumab-treated patients, which was a unique observation compared with that seen

with other anti-integrin therapies. Three cases of infusion reactions led to discontinuation of vedolizumab.

Study Conclusions

Overall, the GEMINI 1 trial established that the novel $\alpha_4\beta_7$ integrin antagonist vedolizumab was effective in the induction and maintenance of remission of patients with previously treated moderate to severe active UC. No cases of PML were reported, and the safety profile of vedolizumab was not significantly different from that of placebo. Future studies may investigate the optimal timing for induction therapy, as well as the optimal dose during maintenance treatment.

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Commentary

Vedolizumab: A New Mechanism of Action for the Treatment of Ulcerative Colitis

Stefan Schreiber, MD

Department of Internal Medicine I, University Hospital Schleswig-Holstein, Kiel, Germany

Significance

The study by Feagan and colleagues¹ is an important contribution to the field of ulcerative colitis treatment for 3 reasons. First, it examines a biologic agent with a novel mechanism of action for use in ulcerative colitis, vedolizumab, which is an integrin antagonist that targets the gut-specific $\alpha_4\beta_7$ integrin for inhibition.^{2,3} Currently, the biologics armamentarium for ulcerative colitis treatment consists of anti-tumor necrosis factor (anti-TNF) therapies—infliximab (Remicade, Janssen), adalimumab (Humira, AbbVie), and golimumab (Simponi, Janssen), which all deliver an anticytokine action. However, studies have shown that significant proportions of patients with ulcerative colitis do not respond or lose response to anti-TNF therapy.^{4,5} Thus, there is a need for alternative therapies in ulcerative colitis. The study by Feagan and colleagues¹ proves through a definitive, placebo-controlled, phase 3, clinical trial that the new therapeutic option of vedolizumab is effective for treating patients who are not responding to anti-TNF therapy as well as those who are naive to anti-TNF therapy.

Second, the study by Feagan and colleagues,¹ which is extensive and comprised of a large study population, reveals that, after undergoing a full year of treatment, vedolizumab has an efficacy that is very similar to that of anti-TNF therapy with an adverse-effect profile that appears to be very minimal. Having a minimal adverse-effect profile is an important feature of vedolizumab, as ulcerative colitis is a lifelong disease, and many patients with the condition are young. It appears that vedolizumab is not associated with any signs of systemic immunosuppression via its mechanism of action. Of course, the only way that we will know if this minimal adverse-effect profile will hold true in practice is through the treatment of tens of thousands of patients over time.

Address correspondence to:
Dr Stefan Schreiber, Department of Internal Medicine I, University Hospital Schleswig-Holstein, Schittenhelmstrasse 12, Kiel, Germany 24105;
Tel: 49-431-597-2350.

Third, the study by Feagan and colleagues¹ used an important secondary endpoint that measured the durability of response in addition to having the primary endpoint of corticosteroid-free remission. Durable response means that, once a patient enters remission, he or she is stable enough to remain in response at all the different time points throughout the rest of the trial. Although it is still important to report how many patients achieve remission at the end of the study and how many do not, this new definition of response and remission is more meaningful for everyday clinical practice, as it reflects the way that clinicians treat patients in real life. It is most important to know if a drug can keep a patient in remission than just bring the patient to remission temporarily. Many times, patients feel well at a certain point during treatment, but then their condition worsens. The concept of durable response and remission also was explored in the development of golimumab (although using a different definition).^{6,7} Sharpening endpoints is the natural evolution of clinical trials.

Limitations

A useful extension of the study by Feagan and colleagues¹ would be benchmarking vedolizumab against anti-TNF agents so that clinicians could see a comparative trial in which anti-TNF nonresponders are switched to vedolizumab and vice versa. The study by Feagan and colleagues¹ does not provide such a comparative assessment, which would allow better positioning of the new agent in the existing therapeutic landscape. Unfortunately, this is a shortcoming of many gastroenterology trials. Most are still conceptualized in the same way that they were when the first ulcerative colitis drugs were developed. At that time, it was fine to just conduct a placebo-controlled trial because there were no other treatment options; if a study showed that a new drug worked against placebo, that was enough for doctors and patients to try it. Now, however, there are several options for treating ulcerative colitis, so it is important to compare them carefully and against each

other to give each patient the best chance for achieving and staying in remission.

Future Directions

To date, there have not been any other large studies conducted on vedolizumab in ulcerative colitis to help shape its clinical use. I hope that this changes soon, but it is possible that further studies may be delayed until the drug is approved by the US Food and Drug Administration. There is still so much that we do not know about this drug that we know about anti-TNF agents. Ideally, there should be studies to explore whether early disease (ie, right after diagnosis) responds better than late disease to vedolizumab. Another area of research is the interaction between vedolizumab and coexisting therapies and whether the latter can be weaned or discontinued. We also need to determine how much the nonresponder populations overlap between vedolizumab and anti-TNF agents. For example, as with infliximab, approximately 60% of patients who take vedolizumab do not benefit from the drug in the long run. Is this 60% of vedolizumab failures the same as the 60% of infliximab failures, or are they different patient populations? Vedolizumab also needs to be examined in special populations, such as young patients and pregnant patients.

Going forward, the study by Feagan and colleagues¹ suggests that vedolizumab may be the forerunner of a new drug class resulting in advances in ulcerative colitis therapy.

This has been seen in drug development throughout history. The successful data from this trial may stimulate other companies to explore similar drugs in the same pathway.

Dr Schreiber has received on-spot consultancy fees from AbbVie, MSD, and Takeda/Millennium for participation in expert advisory activities.

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