What is the role of vedolizumab in the era of anti-TNF agents?

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Current treatment options for Crohn's disease (CD) include 5-aminosalicylates, steroids, immune suppressants, or biologics depending on the severity of a patient's symptoms. Biologics, initially limited to anti-TNF agents such as infliximab, adalimumab, and certolizumab pegol, have typically been reserved for patients with disease refractory to immune suppressants or with disease characteristics placing the patient at high risk for disability. Although highly effective, 20-40% of CD patients do not respond to induction therapy (1). Additionally, either due to neutralizing antibodies to the drug, accelerated drug clearance, or development of aberrant immune pathways, 30-40% of patients lose response to anti-TNF agents over time (2). Dose escalation can recapture a clinical response in 50-70% of patients. Also, approximately 40-80% of patients respond to switching to another anti-TNF in the short-term with one year response rates ranging from 19-68% (2).

Natalizumab is an anti-α4 integrin antibody that prevents or attenuates leukocyte extravasation into affected tissues; It has been utilized as an alternative treatment for patients with multiple sclerosis and for patients with CD who do not respond to or lose response to anti-TNF agents. Efficacy of *Natalizumab* in Crohn's Disease Response and Remission (ENCORE) demonstrated the efficacy of natalizumab for inducing clinical response and remission in patients with moderately to severely active CD. At week 12, 60% of patients receiving natalizumab achieved a clinical response versus 44% of those receiving placebo (P<0.001) (3). Evaluation of *Natalizumab* as Continuous Therapy (ENACT-2) demonstrated that at week 36, patients who responded to initial treatment with natalizumab were more likely to maintain clinical response (61% *vs.* 28%, P<0.001) and remission (44% *vs.* 26%, P=0.003) with continued treatment with natalizumab when compared to patients receiving placebo (4). Unfortunately, 3 patients receiving natalizumab developed progressive multifocal leukoencephalopathy (PML), a rare and often fatal neurological disease caused by the John Cunningham (JC) virus (5). As a result, the FDA withdrew natalizumab from the market. After a safety review was performed the FDA allowed natalizumab to be returned to the market in 2006 under a special prescribing program as monotherapy for MS (6). Natalizumab gained approval for CD in 2008, although patients receiving natalizumab as well as their providers are required to participate in a strict monitoring program [Biogen Idec Inc., *TYSABRI® (natalizumab) Injection Full Prescribing Information*, 2013, Biogen Idec Inc.: Cambridge, MA]. Since then, 395 cases of PML have been reported with an incidence of PML in natalizumab treated patients of 3.3 cases per 1,000 patient-years. The risk of developing PML is increased by ≥2 years of natalizumab therapy, JC virus seropositivity, and previous exposure to immune suppressants (6) [*TYSABRI® (natalizumab) Injection Full Prescribing Information*, 2013, Biogen Idec Inc.: Cambridge, MA].

Given that a significant proportion of patients with CD will not respond to or will lose response to TNF-α inhibitors and since natalizumab is associated with a rare but life threatening opportunistic infection, novel therapies are needed. Unlike natalizumab, vedolizumab is gut specific, only targeting $\alpha_4\beta_7$ binding with MAdCAM 1 (7). $\alpha_4\beta_7$-integrin expressing T cells are important in the pathogenesis of CD. Animal studies have shown that inhibition of binding of $\alpha_4\beta_7$ to MAdCAM-1 prevents the development of ileitis in mice (8,9). As a result of these observations, vedolizumab has been evaluated for the treatment of CD. A Phase II

trial conducted by Feagan *et al.* examined the efficacy of vedolizumab for the induction of clinical response and remission in 185 patients with active CD (10). Patients were treated with 0.5 mg/kg of vedolizumab, 2.0 mg/kg of vedolizumab, or placebo intravenously. Infusions were performed on days 1 and 29. At day 57, 37% and 30% of patients treated with 2.0 and 0.5 mg/kg, respectively, of vedolizumab achieved clinical remission compared with 21% of patients receiving placebo (P=0.04 for 2.0 mg/kg *vs.* placebo) (10). It has been hypothesized that preventing $\alpha_4\beta_1$ binding to VCAM-1 with natalizumab results in decreased immune surveillance within the central nervous system, in turn increasing the risk of developing PML. Since vedolizumab does not block this interaction, it is thought to be less likely to cause this infection.

In this issue of *The New England Journal of Medicine*, Sandborn and colleagues report the results of a prospective, 52-week double-blind, placebo-controlled randomized phase 3 trial to assess the effect of vedolizumab on the induction and maintenance of remission in patients with moderate to severe CD (11). Patients with active CD who had failed at least one conventional therapy were eligible to participate. Patients were required to have a C-reactive protein >2.87 mg per liter, colonoscopy findings of 3 or more large ulcers or 10 or more aphthous ulcers, or a fecal calprotectin >250 mcg per gram plus evidence of active disease on imaging or capsule endoscopy. Patients were required to be off of anti-TNF agents and to be on no more than 30 mg of prednisone at baseline. In addition, immune suppressants were discontinued at U.S. sites. For the induction study, patients received 300 mg of vedolizumab or placebo at weeks 0 and 2 and were followed through 6 weeks. A second cohort of patients received open label vedolizumab induction therapy. Patients from both cohorts with a clinical response at week 6, defined as a decrease in the Crohn's disease activity index (CDAI) by ≥70 points, were re-randomized in a 1:1:1 fashion to receive vedolizumab every 8 weeks, vedolizumab every 4 weeks, or placebo for up to 52 weeks. The two primary endpoints of the induction study were clinical remission, defined as a CDAI score of ≤150 points and a CDAI-100 response at 6 weeks. For the maintenance trial, the primary endpoint was clinical remission at week 52 (11).

At baseline, 34%, 16%, and 17% of patients were on steroids alone, immune suppressants alone, or both steroids and immune suppressants. 62% of patients had received at least one anti-TNF and 36% had received two or more anti-TNF agents in the past. 42% of patients had undergone prior surgery for CD. 31% and 26% of patients treated with vedolizumab and placebo achieved a clinical response at week 6 (P=0.23). 34% of patients receiving open label vedolizumab achieved a clinical response at week 6. Clinical remission was noted in 15% of patients in the vedolizumab group compared with 7% in the placebo group (P=0.02). 18% of patients receiving open label vedolizumab achieved clinical remission at week 6 (11). Clinical remission was maintained at week 52 in 39% of patients receiving vedolizumab every 8 weeks and in 36% of patients receiving vedolizumab every 4 weeks compared with 22% in the placebo group (P<0.001 and P=0.004 for the comparison of the two vedolizumab groups, respectively, with placebo). Vedolizumab was also more effective in maintaining a clinical response and steroid-free remission at 52 weeks than placebo. Not surprisingly, patients with prior anti-TNF exposure had lower clinical response and remission rates at week 6 and week 52 than anti-TNF naïve patients. Only 23% and 10% of anti-TNF exposed patients were in clinical response and clinical remission at week 6. Similarly, clinical remission rates were 27-28% at week 52 in anti-TNF exposed vedolizumab treated patients.

Compared to placebo, vedolizumab treated patients had a higher incidence of serious adverse events (24% versus 15%), infections (44% versus 40%), and serious infections (6% versus 3%). One case of latent tuberculosis, one carcinoid tumor, and two cases of non-melanoma skin cancer developed in vedolizumab treated patients. Fourth deaths occurred in vedolizumab treated patients (two cases of sepsis, intentional overdose, and myocarditis). There were no reported cases of PML. Only one patient discontinued the study drug due to a serious infusion reaction. Immunogenicity was low in the study with only 4% of patients developing antibodies to vedolizumab; further less than 1% developed persistent antibodies (11).

How should these results be interpreted? The study did meet one of the two primary endpoints for the induction phase of the study (clinical remission) and the lone primary endpoint for the maintenance study (clinical remission). However, despite statistically significant differences between the vedolizumab and placebo groups, the actual response and remission rates were modest (31% and 15% respectively). This should not be surprising given the refractory nature of the patient population enrolled in the study. More than one half of patients overall had been treated with an anti-TNF agent in the past and more than a third had been treated with two or more anti-TNF agents. This patient population is difficult to manage in

clinical practice for a number of reasons including the possible presence of undetected strictures resulting in persistent symptoms and the development of aberrant immune pathways that are resistant to treatment. Another intriguing possibility for the low response rate seen in the induction phase of the study is that the mechanism of action for vedolizumab (inhibition of leukocyte migration) may require a longer induction period to achieve a clinical response. This is supported by the higher rates of clinical remission in the maintenance arm of the study and from prior studies with natalizumab where clinical response increased to week 12 (3,4,12).

In addition to the obvious strengths in trial design, the requirement for findings of active disease at enrollment in the study attempted to deal with the issue of imperfections in the CDAI score (13,14). This approach, although not perfect, was very effective at decreasing the placebo response and remission rates to 26% and 7% respectively (15). This is in stark contrast to the very high placebo response rate noted in other studies evaluating pharmacologic inhibition of leukocyte migration (3). Although not powered to detect differences in adverse events between vedolizumab and placebo treated patients, no significant difference in serious adverse events, infections, and serious infections were appreciated between the groups. The initial safety profile appears comparable to other biologic agents (16). Importantly, no cases of PML were observed in the study. This finding should be interpreted with caution since PML is rare, even in patients treated with agents inhibiting leukocyte migration and other immune suppressants. The authors point out that as of February 2013, approximately 3,000 patients have been treated with vedolizumab (1/3 for more than 2 years), most with a background of immune suppression treatment; no reported cases of PML have been seen thus far (11). Long-term observational studies will be required by regulatory agencies to evaluate the safety of vedolizumab compared to standard treatment for CD.

Additional studies will be needed to evaluate the effectiveness of vedolizumab in the treatment of complicated CD and in patients with perianal involvement. Furthermore, additional studies are needed to determine the optimal time to assess for response to vedolizumab. Would the results of induction therapy with vedolizumab be improved if re-assessment occurred at 8, 10 or 12 weeks instead of week 6? If it is confirmed that response in vedolizumab treated patients is delayed, it would be intriguing to determine if steroid induction therapy with vedolizumab as an "exit strategy" to successfully taper steroids is more effective than vedolizumab monotherapy. Lastly, observational studies are needed to determine response to vedolizumab beyond one year, including clinical factors associated with loss of response such as drug levels, immunogenicity, and concurrent immune suppression.

In summary, vedolizumab is a promising new medication that selectively targets $\alpha_4\beta_7$-integrin preventing leukocyte extravasation, achieving short term and long term clinical remission in CD. If approved by regulatory agencies, how will the drug be utilized in clinical practice? It is likely that vedolizumab will be an alternative to natalizumab in patients with moderate to severe CD who fail one or more anti-TNF agents. If no cases of PML are identified with long term use and the safety profile continues to be excellent, vedolizumab will likely supplant natalizumab in the treatment of patients with CD. Until long term safety data is available, it seems unlikely that vedolizumab would be used before anti-TNF agents except in circumstances where anti-TNF agents are contraindicated. It is likely that vedolizumab will be utilized more in the treatment of ulcerative colitis given the improved efficacy in this population (17) and the failure of a second anti-TNF agents to induce a clinical response in this disease (18).

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