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Vedolizumab should be the next line agent for the treatment of refractory Crohn's disease

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ABSTRACT A critical appraisal and clinical application of Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. *Inflamm Bowel Dis*. 2015;21(12):2879-2885. doi:[10.1097/MIB.0000000000000561](https://doi.org/10.1097/MIB.0000000000000561)

Keywords: Crohn's disease, vedolizumab, steroid, refractory, anti-TNF alpha

Clinical Context

A 49 year old African American woman with a history Crohn's disease was admitted to the hospital over 12 times in the last year for Crohn's flares. The patient came to the hospital this time due to increasing episodes of watery, foul smelling stools, abdominal pain and nausea. The patient's medications included Azathioprine 150mg daily, Certolizumab 200mg twice monthly (a TNF-alpha inhibitor), and prednisone 40mg daily. The patient had been trying to taper off the prednisone without success. She had previously failed Adalimumab, another TNF alpha inhibitor. She could not take Mesalamine due to a sulfa allergy. She had been taking her current regimen for approximately four months. While the patient had noted some improvement, she still had two admissions during this time. A consulting gastroenterologist recommended Vedolizumab as maintenance therapy to help her reduce the frequency and severity of her exacerbations.

Clinical Question

Is vedolizumab an effective therapy for a patient with severe Crohn's disease resistant to anti-TNF alpha therapy and steroids?

Research Article

Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. *Inflamm Bowel Dis*. 2015;21(12):2879-2885. doi:[10.1097/MIB.0000000000000561](https://doi.org/10.1097/MIB.0000000000000561)

Literature Review

A literature review of vedolizumab (a monoclonal antibody which binds to an integrin receptor in the intestine) in the treatment of Crohn's disease yields 97 results in PubMed using search terms, "Vedolizumab" and "Crohn's disease." Previous studies, especially the GEMINI trial, have shown the efficacy of vedolizumab in the treatment of Crohn's disease.² The Hazlewood study compared the effectiveness of vedolizumab in induction and maintenance of disease remission as compared to other biological treatments

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currently in use.³ While this study showed that anti-TNF alpha agents are superior treatment, it did not address the issue of refractory disease.

A further PubMed search using the terms “Vedolizumab” “Steroid Refractory” and “Crohn’s Disease” yielded only two results, of which only the Shelton was a clinical trial which addressed the issue of using vedolizumab after other conventional treatments have failed.

We know that vedolizumab has efficacy compared to placebo in the treatment of severe Crohn’s disease from the GEMINI trial.² Patients with active disease (as measured by Crohn’s Disease Activity Index) were included. However, patients also had to meet at least one other criteria, which included elevated CRP, endoscopic findings and increased fecal calprotectin with imaging evidence of ulcers. The medication is approved for an induction period of up to 14 weeks; however, the study used an induction period of only 6 weeks. This was an inadequate trial of the medication. The studied population of the GEMINI trial was dissimilar to my patient, as only 20% of patients had failed 2 or more anti-TNF alpha treatments. Nearly 80% of patients in the Shelton et al study had failed 2 or more anti-TNF inhibitors, which more closely reflects the severity of disease demonstrated by my patient. While no single trial provides adequate evidence to treat the patient described, I chose to evaluate the Shelton et. al. paper, while also being cognizant of the results of the GEMINI trial, which had a larger patient sample and a stronger study design.

Critical Appraisal

The paper appraised is an ecological, observation study of patients beginning vedolizumab and falls under level 2c evidence according to the Oxford Centre for Evidence based Medicine.⁴ Additionally, vedolizumab is licensed by Takeda pharmaceuticals and the corresponding author has received funding from them while another author has acted as a consultant. The rationale for initiating vedolizumab was not described. Therefore, this paper used a convenience sample that may not be representative of IBD. There is no comparison group and therefore a number needed to treat could not be calculated.

This study involved 172 patients spread over 2 clinical centers. Eligible patients were all patients with Crohn’s Disease, Ulcerative Colitis or unspecified IBD who were started on vedolizumab. Patients without active disease were excluded. I have decided to focus on the subgroup of patients who had active Crohn’s Disease, since that is most consistent with my patient.

The study measured clinical remission and clinical response over a 14 week period. One clinical center collected outcome data prospectively, while the other collected data retrospectively. The prospective center used a standardized measure, HBI (Harvey-Bradshaw Index), to define response and remission. A decrease in HBI of at least 3 from baseline was considered response, while remission was defined as a HBI $\leq$ 4. The retrospective center used clinical response as assessed by the treating physician, introducing observation and measurement bias.

The study began with 107 patients with Crohn’s disease. At 14 weeks, 88 patients with Crohn’s disease had outcomes reported, yielding 26 (15%) patients without outcomes reported. Results showed response rates of 48.9%, remission rates of 23.9% and steroid free remission in 18.8% for Crohn’s Disease. Additionally, of the 46% of patients on steroids at baseline, 71.8% had decreased the dose of steroids by at least 50% at week 14. Of note, the retrospective and prospective arms of this trial demonstrated similar rates of response and remission. While the retrospective arm of the trial suffers from significant methodological flaws, this fact suggests that these flaws did not introduce excessive bias to the overall result.

One of the greatest strengths of this study was its inclusion criteria for participants. The study included all patients at the two centers with IBD who had received the loading doses of vedolizumab. The only exclusion criterion was patients without clinically active disease at baseline as measured by the Harvey-Bradshaw Index for Crohn’s. This choice to include all patients with active disease differentiates this paper from previous trials such as the GEMINI trial which had numerous inclusion criteria.² Allowing all patients into the study helps to ensure that the results are clinically relevant to all patients with IBD rather than a specific subset. This is especially important in a disease with diverse presentations like IBD which can affect many different areas of the digestive system.

While the criteria used by the authors were broadly inclusive there are several issues with this decision. One of these was the inclusion of several patients who had never received treatment with anti-TNF alpha agents. Such patients can skew the results of a

study that is focused on treating patients who are refractory to other treatments. Notably, 76.7% of participants with Crohn's disease had failed two or more anti-TNF alpha agents. As such, this likely affected the results of the study only minimally.

Another issue with the inclusion criteria that limits the application of this study is differing treatment regimens among patients. While everyone received the same dose of vedolizumab, patients were also on various other treatment regimens including steroids and immunosuppressants such as methotrexate and azathioprine. This calls into question which treatment or combination is responsible for the results of the study. However, this concern is mitigated by the strong clinical response rates and the high rate of patients who were able to reduce their steroid treatments.

Another strength of the study was the decision of the authors to look at outcomes over a 14 week period. Previous trials, such as the GEMINI trial, used 6 weeks as their outcome.² However, the authors recognized that achieving remission may take longer due to the mechanism of action of vedolizumab. Using this method, the authors found a higher remission rate than had previously been stated for the drug. The longer duration helps to give better accuracy to the actual remission and response rates that patients may have when using the drug for continued maintenance therapy.

The paper showed that vedolizumab had adverse events in 18 (10.5%) of patients, almost all of them were related to worsening of the underlying disease.

Clinical Application

While various treatment modalities such as anti-TNF alpha agents have changed the treatment of IBD in recent years, many patients have continued disease activity and hospitalizations despite numerous therapies. This patient was hospitalized for her Crohn's disease despite having tried multiple biologic treatments and Azathioprine. In the study, 78.1% of Crohn's disease patients on steroids were able to decrease them after 14 weeks. This data was shown in a population group similar to this patient. As such, this study suggests that vedolizumab for anti-TNF alpha refractory patients shows some promise and should be considered a reasonable next step in therapy for this patient.

Take Home Points:

- 1.) Many patients with IBD are refractory to anti-TNF alpha inhibitors which are the current mainstay of treatment.
- 2.) Based on my involvement in the care of this patient I would feel comfortable prescribing vedolizumab for patients with severely refractory Crohn's disease.
- 3.) For patients who suffer with multiple repeat hospitalizations, learning about the risks of benefit and risk of harm for newer therapies help initiate shared decision making conversations with patients.

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