Attempted Salvage Therapy Through Initiation of Vedolizumab as an Inpatient in Two Patients with Refractory Active Ulcerative Colitis

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Attempted Salvage Therapy Through Initiation of Vedolizumab as an Inpatient in Two Patients with Refractory Active Ulcerative Colitis

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Background

- Ulcerative colitis (UC) is a chronic inflammatory bowel disease which can cause bloody diarrhea, abdominal cramps, and fatigue.[1]
- Disease severity in UC is measured using multiple scoring systems such as the Mayo Clinic score which takes into account stool frequency, rectal bleeding, endoscopic appearance, and a global assessment. A higher score correlates with more severe disease and the maximum score is 12.[2] The Inflammatory Bowel Disease Questionnaire (IBDQ) which considers social and emotional factors is used as well.[3]
- Severe acute UC is defined as ≥6 stools per day, tachycardia, anemia, and elevated erythrocyte sedimentation rate. Between 18-25% of UC patients will experience an episode of severe acute UC and 20-30% of these patients will require colectomy.[4]
- The management of UC has changed greatly due to the introduction of tumor necrosis factor-alpha (TNF-α) antagonists such as adalimumab and infliximab. However, there is a subset of patients with moderate to severe disease who are refractory or intolerant to these medications. It is also thought that 30-40% of patients will lose response to TNF antagonists over time.[5]
- Vedolizumab is a recombinant humanized IgG1 monoclonal antibody which binds α4β7 integrin resulting in a "gut selective" anti-inflammatory effect by inhibiting interaction with mucosal addressin-cell adhesion molecule 1 (MAdCAM-1) and therefore preventing migration of leukocytes.[1,6]
- Clinical trials, such as GEMINI I, have shown vedolizumab to be effective as both induction and maintenance therapy for UC.[1]
- Induction dosing is a 300mg infusion given over 30 minutes at weeks 0, 2, and 6 followed by maintenance infusions every 8 weeks thereafter. It is indicated for adults with moderate to severe active UC who have had an inadequate response with, lost response to, or were intolerant to a TNF-α blocker.[7]

A 40 Year-Old Male

…progressed from mild ulcerative proctitis to pancolitis over the course of a few months with worsening abdominal pain, bloody diarrhea, and intolerance to oral intake. He previously received the induction dose of infliximab without significant improvement to his symptoms and had already been referred to colorectal surgery to discuss surgical options. As his symptoms progressed he was admitted for generalized weakness and malnutrition and reported up to 18 stools per day. Colonoscopy revealed severe diffuse inflammation consistent with active UC (Image 1). Due to the severity of his disease it was decided to initiate the patient on vedolizumab during his inpatient stay. His Mayo Clinic score at that time was ≥11. Unfortunately, he did not respond and required total colectomy during this hospitalization.

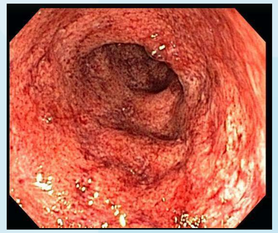

Image 1. Colonoscopy revealing continuous, diffuse inflammation consistent with severe ulcerative colitis.

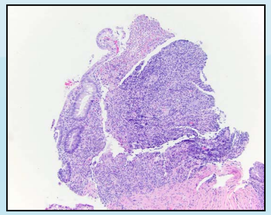

Image 3. Colon biopsy demonstrating crypt destruction and loss with expansion of the lamina propria by inflammatory cells and surface ulceration.

A 75 Year-Old Female

…with a three year history of UC was admitted with increased stool frequency and bloody bowel movements shortly after completing a steroid taper. She had been initiated on infliximab at the time of her diagnosis but this had been discontinued due to intolerance and was being treated with mesalamine at time of admission. Colonoscopy revealed severe pancolitis with mucosal edema, friability, and spontaneous oozing (Image 2). She was evaluated by colorectal surgery, but her preference was to avoid surgery and the decision was made to initiate vedolizumab. At this point her Mayo Clinic score was ≥9. She received her first dose as an inpatient and stabilized enough to allow discharge. However, she was soon readmitted with worsening symptoms and required total colectomy with end ileostomy.

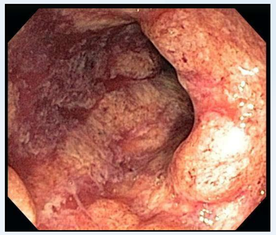

Image 2. Colonoscopy exhibiting severe mucosal changes of ulcerative colitis including friability, mucus, and circumferential edema with oozing.

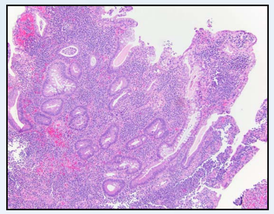

Image 4. Colon biopsy demonstrating crypt destruction with expansion of the lamina propria by inflammatory cells and surface ulceration.

Discussion:

- Clinical trials have established that vedolizumab is safe and effective in patients with moderate to severe UC, including those who have previously failed TNF antagonist therapy. This has lead to FDA approval in this cohort of patients.
- In an early trial of MLN02, the precursor of vedolizumab,[1] 181 adults with active UC demonstrated a clinical remission rate of 33% by six weeks following vedolizumab infusions at days 1 and 29. However, patients in this study were naïve to TNF antagonists and those with severe disease were excluded.[8]
- GEMINI I expanded on this study and validated effectiveness of vedolizumab over placebo for both induction and maintenance as measured by reduction in Mayo Clinic and IBDQ scores, mucosal healing, fecal calprotectin levels,[9] and decreased concomitant glucocorticoid requirements. This study enrolled patients with previous unsuccessful treatment with glucocorticoids, immunosuppressive medications, or TNF antagonists, and 71.5% of enrolled patients were continued on glucocorticoids and/or immunosuppressants during the trial.[1]
- GEMINI I also looked at vedolizumab concentrations during treatment and found that both every 4 week and every 8 week dosing regimens resulted in >95% saturation of α4β7 integrin on targeted T cells.[1]
- Our patients were initiated on vedolizumab as inpatients during severe acute colitis for attempted salvage therapy after failing TNF antagonists and neither was able to avoid surgery.
- One of the listed limitations of GEMINI I was that it "was not designed to identify the time of the maximal effect of vedolizumab as induction therapy." Also, the number of patients with previous TNF antagonist use was only 40% and those who received a TNF antagonist within 60 days were ineligible for enrollment.[1]
- Further studies of vedolizumab are required in the setting of severe acute colitis when glucocorticoids and/or TNF antagonists have failed; where it has great potential benefit to disease control and patient quality of life.

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