



## Vedolizumab Like Biological First Choice for Chronic Refractory Pouchitis in Patients with Ulcerative Colitis

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### Abstract

Chronic Antibiotic-Refractory Pouchitis (CARP) is a complication of Ileal Pouch-Anal Anastomosis (IPAA), which poses a therapeutic challenge. Vedolizumab, a gut-selective monoclonal antibody to the  $\alpha 4\beta 7$  of integrin, has been used in such patients, but data on its efficacy are limited. Our case suggests the efficacy and safety of vedolizumab as induction therapy in CARP patient without a previous experience with anti-TNF agents. Larger studies with a higher number of patients are required to confirm these findings.

**Keywords:** Vedolizumab; Chronic antibiotic-refractory pouchitis; Ulcerative Colitis

### Introduction

Ulcerative Colitis (UC) is a chronic disease of the colon and rectum. Primary treatment is medical therapy. Restorative total proctocolectomy with Ileal Pouch-Anal Anastomosis (IPAA) is one of the surgical modalities used to manage patients with refractory UC or develop severe complications such as colonic perforation, hemorrhage, or toxic megacolon. The ileal pouch serves as an internal reservoir of feces in the absence of rectum. Many patients develop long-term complication so-called pouchitis with an estimated incidence ranging from 46% to 82%, which includes a range of symptom severity such as abdominal cramping, pelvic pressure, and increased stool frequency with urgency, to more debilitating symptoms including abdominal pain, rectal bleeding, disorder defecation and incontinence [1]. Pouchitis is a nonspecific inflammation in the Ileoanal Pouch Anastomosis (IPAA). The pathophysiology of pouchitis remains poorly understood. Gut microbiota have an important role in fact increased bacterial levels and ileal reservoir dysbiosis appear to be major contributors [2]. Pouchitis may be difficult to treat as well as have a negative impact on the quality of life in these patients. Since dysbiosis is a key factor for pouchitis development, there is evidence for a therapeutic role of probiotics [3] (i.e., VSL#3 was able to prevent a relapse during a follow-up period of 9 months) [4] and antibiotics. Antibiotics therapy's, particularly ciprofloxacin and metronidazole, are the mainstay of treatment for acute pouchitis after having excluded other diagnoses (infections, Crohn's disease of the pouch, ischemia and irritable pouch) [5]. However, about 10% to 15% of patients with acute pouchitis do not respond to these treatments and develop chronic pouchitis, which is defined by symptoms persisting for more than 4 weeks. These patients often require prolonged courses of antibiotics combines with steroid therapy (budesonide) [6], immunomodulators (azathioprine) [7], and mesalamines with varying efficacy. CARP is diagnosis when patients do not respond to a 2-week course of ciprofloxacin, metronidazole, or rifaximin for pouchitis [8]. CARP is one of the most common causes of pouch failure.

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Received Date: 19 Jan 2023

Accepted Date: 01 Feb 2023

Published Date: 04 Feb 2023

#### Citation:

Vincenzo T, Annamaria D. Vedolizumab Like Biological First Choice for Chronic Refractory Pouchitis in Patients with Ulcerative Colitis. *Clin Case Rep Int.* 2023; 7: 1474.

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### Patient information

In our patient, a 52-year-old Caucasian male, restorative proctocolectomy had become necessary 28 years ago in severe refractory ulcerative colitis. Ileoanal Pouch Anastomosis (IPAA) was performed in 1999. Pouchitis was first diagnosed in 2020.

### Timeline

In August 2021, he developed a chronic diarrhea with up to 30 to 40 liquid (including 6 nightly) stools, accompanied with blood and mucus, associated with diffuse abdominal pain and bloating affecting his quality of life.

### Diagnostic assessment

Laboratory work-up revealed Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and stool calprotectin with no abnormalities. He denied sudden weight gain or weight loss. Endoscopy showed inflammation, ulcerations, edema and mucous exudates in the pouch and in the

afferent ileal limb. In particular, linear ulcerations were present in the pouch, circular ulcerations in the ileal mucosa. Histology confirmed the active phase of ileal ulcerative chronic inflammation combined with signs of regeneration (fibrosis).

### Therapeutic intervention

He started probiotic therapy, with VSL#3, but without successful clinical effects. Then he was prescribed metronidazole, from 250 mg to 500 mg orally two times daily. After many therapeutic interventions with metronidazole, the patient was unable to tolerate it. He was prescribed ciprofloxacin 500 mg orally two times daily, but without successful clinical effects. In the end he was prescribed ECN Nissle capsule and dipropionate Beclomethasone, from 5 mg to 10 mg orally one time daily, which developed corticosteroid resistant.

Therefore, this severe flare of pouchitis was refractory to metronidazole, Ciprofloxacin, VSL#3, ECN Nissle Capsule, dipropionate beclomethasone and mesalamine. Stool studies for clostridium difficile, viruses, and bacteria were negative. Endoscopy and Histology showed no improvement. For this reason, the patient was switched to anti-integrin therapy and showed sustained clinical and endoscopic response to Vedolizumab 300 mg i.v. at weeks 0, 2, 6, and every 8 weeks.

### Follow up and outcomes

After four doses, pouch and ileal ulcerations had healed completely and edema and mucous exudates were no longer present. C-Reactive Protein and stool calprotectin were also negative. Clinically, the patient is now in good condition, reports about 15 daily stools without any abdominal discomfort.

### Discussion

Biological therapy such as anti-Tumor Necrosis Factor (TNF) (infliximab, adalimumab) agents [9,10], vedolizumab or ustekinumab are some of the options used to treat chronic pouchitis. Vedolizumab is a monoclonal antibody that selectively blocks gut lymphocyte trafficking by interacting with  $\alpha 4\beta 7$  heterodimer [11]. The key to understanding the potential efficacy of vedolizumab is based on the fact that dysbiosis contributes to the attraction of leukocytes that will undergo adhesion by the integrin-MAcCAM interaction [12]. However, the effect of vedolizumab treatment on Chronic Antibiotic Refractory Pouchitis (CARP) is very limited. The largest study was a retrospective multicenter cohort study at five academic centers in the United States including 83 IPAA patients with endoscopically confirmed inflammation of the pouch. Some 87% of patients were previously treated with antibiotics for pouchitis, and 51% previously were treated with anti-TNFs for pouchitis. After at least 3 months follow-up, 71% of patients exhibited a clinical response, and 19.3% achieved clinical remission; 54% had endoscopic improvement while 17.6% achieved endoscopic healing. Patients who developed pouchitis symptoms within 1 year postoperatively were found to be less likely to respond to VDZ [18]. In a recent review Ribaldone DG reported that vedolizumab has significant efficacy in chronic refractory or antibiotic-dependent pouchitis, also in patients who failed to respond to other treatments including those with anti-TNF agents [13]. In literature, only twenty-one patients had a biological treatment with vedolizumab for CARP without a previous experience with anti-TNF agents [14-17]. Our case is important because it evaluates the efficacy of vedolizumab as a first-choice biological treatment in CARP and represents the first case report which evaluates a histological improvement thanks to the effectiveness of

vedolizumab in the treatment of chronic refractory pouchitis. In our single patient refractory to multiple therapies, we found good clinical and endoscopic response encouraging further investigations on clinical response, mucosal healing and histological improvement. In a recent meta-analysis Saurabh Chandan demonstrated that clinical improvement in symptoms was reported by 48.7% patients treated with VDZ, clinical remission was achieved by 45.4% patients treated with VDA and finally, endoscopic improvement and remission was seen in 61.2% patients treated with VDZ. Biologic therapy is safe and effective short-term as well as long-term in the treatment of CARP [19,20].

### Conclusion

Vedolizumab showed consistent treatment benefits across clinical, endoscopic and histological endpoint, together with safety consistent. Vedolizumab intravenous is effective in chronic refractory or antibiotic-dependent pouchitis so that can be value its use like first line in the biological therapy can be evaluated as confirmed by a recent study where demonstrates that T cell movementing mechanisms are important and vedolizumab antagonism in pouchitis has functional effects. A phase- 4 study aiming to evaluate the efficacy and safety of vedolizumab in the treatment of chronic pouchitis (EARNEST) has just been completed confirms these findings.

### Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection and were performed by Trapanese Vincenzo. The first draft of the manuscript was written by Trapanese Vincenzo and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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