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Vedolizumab therapy in common variable immune deficiency associated enteropathy: A case series

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Abstract

A number of gastrointestinal complications occur in common variable immunodeficiency (CVID). Infections are one cause, but various forms of severe non-infectious enteropathy also lead to substantial morbidity. The presence of T cell lymphocytic infiltrates in the mucosa have suggested that vedolizumab, a humanized monoclonal antibody which binds to alpha4 beta7 integrin and inhibits the migration of effector T-lymphocytes into gastrointestinal tissues, would be an effective treatment. A previous report of 3 CVID cases suggested benefit in 2 subjects. In this study 7 CVID patients with severe enteropathy were treated with vedolizumab. Four of the 7 completed vedolizumab induction therapy but 3 subjects had acute decompensation during induction and treatment was stopped. While one subject showed improvement, 6 of the 7 patients were withdrawn from therapy. While vedolizumab may be of use in some CVID subjects, it was not ultimately found helpful in most of these patients.

Keywords

Common variable immune deficiency; CVID; Enteropathy; Vedolizumab

1. Introduction

Common variable immunodeficiency (CVID) is characterized by low serum immunoglobulin levels, impaired vaccine responses and increased susceptibility to infectious disease [1–3]. The prevalence of CVID is estimated between 1:10,000–100,000 [1]. Inflammatory or autoimmune conditions affect as many as 50% of CVID patients [4,5].

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Immune dysregulation leading to symptomatic gastrointestinal inflammation affects 9–34% of CVID patients; a subset of these develop CVID-associated chronic enteropathy (CVID-CE)—a complex disorder of severe gastrointestinal inflammation leading to weight loss, protein malnutrition, and in some, prolonged parenteral feeding [5–9]. Mucosal histopathology is often characterized by increased intraepithelial lymphocytes and absent plasma cells in the lamina propria [10]. Vedolizumab is a humanized monoclonal antibody to the $\alpha 4\beta 7$ integrin and blocks its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) thereby inhibiting lymphocyte egress into intestinal tissue. Vedolizumab was approved for the treatment of adults with moderate to severe inflammatory bowel disease in 2014. In 2017, Boland et al. published a study of three patients with CVID and gut inflammation, two of whom were successfully treated with vedolizumab [11]. A second report noted benefit in another case [12]. Here we describe our results with this therapy and show that for 6 of 7 cases of CVID-CE, vedolizumab was not found helpful.

2. Case Descriptions

Case 1:

A 42-year-old male with frequent respiratory infections was diagnosed with CVID at the age of 36. (Table 1) He later developed gastrointestinal symptoms of cramping abdominal pain, bloating and frequent diarrhea. He was initially treated with azathioprine without clinical response. Vedolizumab was started in January 2017 with subjective improvement in symptoms of bloating and diarrhea after eight weeks and return to pre-symptom weight after 9 months of therapy. He remains on this therapy and repeat endoscopy revealed normalization of mucosal biopsies. Genetic studies identified a mutation in *TACI*.

Case 2:

A 51-year-old female with CVID diagnosed with CVID at age 39, had the onset of severe gastrointestinal symptoms of frequent, large volume watery stools, progressing to protein-losing despite oral budesonide and rifaximin. She underwent a trial of infliximab from October 2013 to January 2014 without response and was started on parenteral nutrition. Vedolizumab was initiated in September 2014. She developed worsening enteropathy during induction culminating in hospitalization. Endoscopic biopsies were consistent with active CVID-CE. (Table 1) In February 2018 she was found to be PCR norovirus positive. In March of 2018, vedolizumab was again re-tried. She tolerated induction and remained on therapy for 12 months but was unable to discontinue TPN due to continued disease activity. Repeat endoscopic biopsies revealed continued marked small bowel intraepithelial lymphocytosis. Fig. 1 shows the chronic inflammation with villous blunting, and intra epithelial lymphocytes and neutrophils in the lamina propria. Vedolizumab was discontinued. She remains on TPN. Genetic studies identified a pathogenic mutation in *BACH2*.

Case 3:

A 26-year-old male with CVID was diagnosed at the age of 18 due to diarrhea, fatigue, weakness, and leg swelling. He had treatment-resistant giardiasis which finally cleared 20 months after presentation. Infectious work up later revealed chronic norovirus which then

persisted after 10 months of ribavirin. Endoscopic biopsy in May 2016 was consistent with CVID-CE (Table 1). He has been on TPN for nutritional deficiencies and severe osteoporosis. He was started on vedolizumab in Jan 2017 and completed induction. Vedolizumab dosing frequency was increased to every 4 weeks in Feb 2018 without clinical response and therapy was discontinued in May 2018. Repeat endoscopic biopsies in April 2018 showed persistent inflammation with marked intraepithelial lymphocytosis. Genetic studies have not identified a genetic cause.

Case 4:

A 27-year-old female with CVID, first diagnosed at the age of 11. Gastrointestinal symptoms were reported as early as age 8, including an episode of hemorrhagic colitis. She had poor weight gain and required gastrostomy tube feedings for nutritional support as a child. She was treated with 6-MP for idiopathic colitis. She developed severe protein malnutrition and became TPN dependent. Endoscopic biopsies from February 2014 were consistent with CVID-CE (Table 1). A trial of azathioprine was discontinued after 4 months due to a failure to respond. Parenteral nutrition was complicated by multiple line infections. Vedolizumab therapy was initiated in July 2017. She was hospitalized during induction therapy for suspected drug induced liver injury prompting cessation of vedolizumab. She is currently on Remicade with weight gain and greatly reduced diarrhea. Genetic studies identified a damaging frameshift mutation in NFKB1.

Case 5:

A 64-year-old female was diagnosed with CVID at the age of 27. Chronic diarrhea was first reported in 1990. She has been TPN dependent. Her course was complicated by recurrent *Clostridium difficile* colitis requiring fecal transplantations, along with antimicrobial therapy. Endoscopic biopsies were consistent with CVID-CE (Table 1). Vedolizumab therapy was started in November 2017 and she completed 14 months of therapy after which it was discontinued due to lack of benefit. Treatment-resistant *Campylobacter* was identified in the gastric mucosa. Repeat colonoscopy in February 2019 showed continued active chronic lymphocytic inflammation of the small bowel and colon and she continues to require TPN on a chronic basis. Genetic studies have been negative.

Case 6:

This 37-year-old male started to have frequent watery diarrhea in 2011. He was started on mesalamine with partial remission of symptoms. However, on review of slides, plasma cells were absent, and with low immune globulins, the diagnosis of CVID was made and IVIG started. (Table 1) However, worsening of enteropathy led to 30 lb. weight loss and hospitalization for dehydration and malnutrition; he was treated with TPN and then 6-MP. A biopsy was positive for CMV and he was successfully treated with valganciclovir 900 mg twice daily. He continued on budesonide 9 mg and then tried on Vedolizumab in 2018. With no improvement in the following 6 months this was discontinued. Genetic studies have been negative.

Case 7:

This 77-year old woman was diagnosed with CVID about 21 years ago. About 8 years ago she began having diarrhea, bloating, and cramping. On colonoscopy, a biopsy was viewed as consistent with Crohn's disease and she was given prednisone, sulfasalazine, mesalamine, and pancreatic enzymes. About a year ago at age 76, with worsened symptoms, she was started on budesonide 9 mg daily, which controlled the diarrhea. However, she continued to lose weight, now a total loss of 25 lbs. Esophagogastroduodenoscopy and colonoscopy showed diffuse atrophic mucosa in the stomach, which was negative for *H. pylori*. Colonoscopy demonstrated scattered inflammation, moderate erosions and erythema in the terminal ileum with multiple ulcers and edema. She was started on vedolizumab, but within two days developed joint pain, nausea, headache, malaise with no fevers. Vedolizumab was continued for 3 more doses in the following 3 months, but this was then terminated due to excessive diarrhea and more weight loss. *Campylobacter* was found and treated. Genetic studies have been negative.

3. Discussion

Both infectious and noninfectious gastrointestinal conditions occur in patients with CVID; not uncommonly, they may occur in the same patient. Chronic diarrhea, colitis, and gastritis are common and occur in 10 to 12% of patients [13]. The colon may be the most frequently affected site with microscopic colitis (more common) to severe colitis with ulcerations. In one cohort of 50 CVID patients, 40% had a chronic gastrointestinal complaint; half of which had evidence of malnutrition [10]. In another study of 30 patients who had endoscopy, 25 had abnormal endoscopic or histologic findings [14]. Of great concern, is that CVID patients with chronic enteropathy and significant malabsorption have a known increase in mortality, as shown in several studies. [15,16] The pathology in CVID enteropathy is characteristic for an increase in intraepithelial CD8⁺ T cell infiltrates in the intestinal lamina propria, increased IL-12 and IFN γ secretion [17], and a paucity or absence of plasma cells [10,18]. We have also found increased IFN γ secreting innate lymphoid cells (ILC) in blood, respiratory and gastrointestinal mucosa of CVID patients with inflammatory conditions [19]. Treatment of CVID enteropathy is challenging. Standard treatment with parenteral immune globulin has no apparent effect, and other methods, mostly borrowed from inflammatory bowel disease care, have been used, including mesalamine, budesonide, 6-MP, and non-absorbable antibiotics. Recently, two of three patients with CVID and enteropathy at one center, and in a separate report of another patient [12] were reported to have had benefit from treatment with Vedolizumab, [11] a monoclonal antibody to the $\alpha_4\beta_7$ integrin heterodimer, licensed for use in Crohn's disease and ulcerative colitis [20]. Vedolizumab blocks the interaction of $\alpha_4\beta_7$ integrin with MAdCAM-1, preventing leukocytes from adhesion with endothelial surfaces, thereby reducing T cell trafficking to the gut. Thus this therapy should provide a logical and targeted approach for treating CVID-CE. However, we report here that of the 7 subjects that we treated with Vedolizumab, only one showed proximate and sustained improvement. Three of the 7 cases also had acute decompensation after induction therapy, with one subsequently restarting therapy but then terminating this due to non-response.

While this therapy may be of use in some CVID subjects, it was not ultimately found helpful in most of the patients described here. To potentially dissect the use of this therapy in CVID, a previous work investigated the expression of $\alpha 4\beta 7^+$ T cells in the peripheral blood of 36 CVID patients as compared to 22 healthy donors. While there was an increased percentage of $\alpha 4\beta 7^+$ memory $CD4^+$ T cells and $CD25^+$ regulatory T cells (Tregs) in CVID subjects, this was not the case for $CD8^+$ T-cell populations [21]. There was also no difference in the expression of $\alpha 4\beta 7^+$ on T cells in CVID subjects with or without gastrointestinal complications [21]. In addition to the difficulty of dissecting the role of these cells in enteropathy in CVID, the subjects examined here have had at times, concomitant viral or bacterial infections which may have led to inflammatory changes that could not be addressed by vedolizumab therapy. We cannot exclude the possibility that this therapy may lead to improvement in subjects who do not have these concomitant infections. While a CVID-CE patient with a CTLA4 mutation was recently noted to have improvement with vedolizumab [22], two of the subjects presented here, with different pathogenic mutations (BACH2 and NFKB1) had adverse reactions to this therapy. Potentially, the underlying genetic factors in these subjects may have led to lack of response to this agent. Additional methods for selecting CVID-CE patients who may respond to this therapy, will be required.

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Fig. 1.

A.B.C. (40 $\times$, 100 $\times$, 200 $\times$): The small bowel of Case 2 shows active chronic inflammation with diffuse villous blunting, increased intraepithelial lymphocytes and neutrophils in the lamina propria. Plasma cells are absent. D.E.F. (40 $\times$, 100 $\times$, 200 $\times$): At low power the sigmoid colon shows crypt distortion and reactive changes. On higher power (200 $\times$), active inflammation characterized by neutrophils in the lamina propria and within the crypts (cryptitis) are seen. Plasma cells are absent.

Patient	1	2	3	4	5	6	7
Age/sex	47M	51F	26M	27F	54F	37M	77F
CVID Dx yr	2012	2007	4/2011	2003	1982		
Dx quant Ig	IgG 323; IgA 35; IgM 10	IgG 61; IgA 17; IgM < 1	IgG 146; IgA < 7; IgM < 5	IgG < 500; IgA < 7; IgM < 5	IgG < 500; IgA < 7; IgM < 5	IgG 105; IgA 6; IgM 14	IgG; IgA < 5; IgM < 6
Lymphocytes (per/mm ³)	CD3: 1077 CD4: 899 CD8: 209 CD19: 233 CD56/16: 207	CD3: 1051 CD4: 544 CD8: 493 CD19: 40 CD56/16: 41	CD3: 1017 CD4: 436 CD8: 559 CD19: 75 CD56/16: 139	CD3: 1684 CD4: 1129 CD8: 552 CD19: 0 CD56/16: 64	CD3: 994 CD4: 681 CD8: 367 CD19: 102 CD56/16: 111	CD3: 1544 CD4: 627 CD8: 850 CD19: 607 CD56/16: 284	CD3: 827 CD4: 648 CD8: 142 CD19: 149 CD56/16: 23
Genetic study	TAC7p.Leu69fs	BACH2p.Arg666Lys	No mutations found	NFKB1 p.Phe459fs	No mutations found	No mutations found	No mutations found
GI symptoms start	2013	2011	2015	2000	1990	2012	2011
Biopsy location	Duodenal: chronic, active duodenitis, villous blunting Jejunum: no disease Ileal: chronic active ileitis, focal cryptitis Colonic: normal	Duodenal: IEL, marked villous blunting, no PCs Jejunum: IEL, preserved villi, no PCs Ileal: IEL, preserved villi, no PCs Colonic: no PCs, normal	Duodenal: IEL, villous blunting, no PCs Jejunum: IEL, villous blunting, no PCs Ileal: IEL, no PCs Colonic: no PCs, normal	Duodenal: IEL, villous blunting, no PCs Jejunum: IEL, villous blunting, no PCs Colonic: crypt distortion, mild IEL, no PCs	Duodenal: IEL, villous blunting Jejunum: chronic enteritis Ileal: no data Colonic: nonspecific colitis w/occasional granulomatous changes	Duodenal: Villous blunting Jejunum: Diffusely atrophic small bowel mucosa worse in the colon Colonic: nonspecific colitis; No plasma cells	Stomach: atrophic mucosa; extensive intestinal metaplasia Duodenal: nonspecific duodenitis Jejunum: chronic inflammation; no plasma cells Colonic: inflammation, moderate erosions Absence of plasma cells
Previous treatment	Azathioprine	Budesonide, rifaximin, adalimumab	Budesonide, rifaximin, leflunomide, methotrexate	Budesonide, 6MP, azathioprine	Budesonide, rifaximin, Prednisone, anti-IL12, human breast milk, human fecal transplant	Mesalamine, 6MP, Budesonide; rifaximin, FODMAP and probiotics	Mesalamine, budesonide; steroids and probiotics
Parenteral nutrition	No	Yes	Yes	Yes	Yes	No	No
Treatment duration	> 12mo	Failed induction; > 12mo	> 12mo	Failed induction	> 12mo	> 12mo	> 6 mo
Response	Primary responder	Acute decompensation; insufficient response	Primary non-responder	Drug-induced liver injury	insufficient response	No response	Acute decompensation; insufficient response
Infections	None	None	Norovirus	None	Campylobacter, norovirus	Norovirus positive	Campylobacter

Patient	1	2	3	4	5	6	7
Post-vedolizumab Biopsy if done	clean	Continued intraepithelial lymphocytosis and absence of plasma cells	Mildly active chronic nonspecific duodenitis with villous blunting, gastric foveolar metaplasia, and markedly reduced/ absent plasma cells	Erosive gastritis; Mildly active chronic nonspecific ileitis with intraepithelial lymphocytosis Moderately active nonspecific colitis; markedly reduced or absent plasma cells	Moderately active chronic enteritis; Moderately active chronic duodenitis; Mildly active nonspecific colitis with occasional non-necrotizing granulomatous reaction. The lamina propria plasma cells are significantly decreased		