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Abatacept: A New Treatment Option for Refractory Adult Autoimmune Enteropathy

Nitin K Gupta, M.D.^a, Omer Yilmaz, M.D., P.h.D.^b, Mark Fisher, M.D.^c, and Vijay Yajnik, M.D., P.h.D.^a

^aGastrointestinal Unit, Massachusetts General Hospital, Boston, MA

^bDepartment of Pathology and Laboratory Medicine, Massachusetts General Hospital, Boston, MA

^cRheumatology, Allergy and Immunology Division, Massachusetts General Hospital, Boston, MA

Abstract

Autoimmune enteropathy is a rare disease that has been observed in both children and adults. It typically manifests with symptoms of diarrhea, requiring long-term immunosuppression. Endoscopically, the duodenum typically exhibits villous blunting with histology showing partial or complete villous blunting, deep crypt lymphocytosis, increased apoptotic bodies, and minimal intra-epithelial lymphocytosis. The pathophysiology of autoimmune enteropathy likely involves a hyperactive immune state in the setting of a T-cell regulatory defect, resulting in destruction of the enterocyte. We report a case of a 49-year-old female who presented with refractory diarrhea, diagnosed as autoimmune enteropathy. After failing multiple conventional therapies, she demonstrated clinical and histological response to abatacept, a selective modulator of T-cell activation. We aim to increase awareness of this rare inflammatory disorder and new treatment options for this debilitating condition.

Keywords

Autoimmune enteropathy; enteritis; abatacept; diarrhea

Introduction

Autoimmune enteropathy (AIE) was first described in 1982 in a child with clinical features of celiac disease and villous blunting that did not respond to a gluten free diet¹. The disease has an incidence of 1 in 100,000 and is seen primarily in infants and young children, who often have other concurrent autoimmune diseases; though over the years, it has also been

Address correspondence to Vijay Yajnik, M.D. Ph. D., Gastrointestinal Unit, Massachusetts General Hospital, 55 Fruit Street, Blake 4, Boston MA 02114. Fax: 617-726-3080, Telephone: 617-724-6005. vyajnik@partners.org.

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recognized in adults². The incidence in the adult population has yet to be determined and is mainly described either as a case report or as a case series³. Diarrhea associated with AIE can be quite debilitating, resulting in electrolyte disturbances, weight loss, and malabsorption, and often requiring the initiation of parenteral nutrition. AIE can also be associated with other systemic diseases, including thyroid disease, common variable immune deficiency (CVID), selective IgA deficiency, IPEX (immune dysregulation polyendocrinopathy enteropathy X-linked syndrome), APECED (autoimmune phenomena, polyendocrinopathy, candidiasis, and ectodermal dystrophy), and APS (autoimmune polyglandular syndrome)^{3,4}.

The diagnostic criteria for AIE has been updated since 1982, and now requires all of the following (A to D): (A) chronic diarrhea (> 6 weeks duration), (B) malabsorption, (C) small bowel histology showing partial or complete villous blunting, deep crypt lymphocytosis, increased apoptotic bodies, minimal intra-epithelial lymphocytosis, and (D) exclusion of other causes of villous atrophy including celiac disease, refractory sprue, and intestinal lymphoma; (E) presence of an anti-enterocyte and/or anti-goblet cell antibody supports the diagnosis and sometimes correlates with disease improvement, but is not required to make the diagnosis⁵. Though the diagnostic criteria require the exclusion of refractory sprue, in some aspects, refractory sprue may represent a clinical spectrum of AIE. The diagnosis of refractory sprue requires a prior diagnosis of celiac disease, persistent gastrointestinal symptoms, villous atrophy despite gluten free diet for over 12 months, and normal tissue transglutaminase antibody titers. These patients, similar to those with AIE, often require use of steroids and immune suppression in order to maintain disease remission.⁶ The pathophysiology of AIE continues to be elucidated, but likely involves a hyperactive immune state in the setting of a T-cell regulatory defect in which the destruction of epithelial cells is mediated via activation of CD4 T lymphocytes upon exposure of the epithelial cell surface of enterocytes^{2,3,7}.

Immunosuppressive drugs are the mainstay of treatment for AIE. Most patients require corticosteroids to induce remission, which in some cases can be maintained with budesonide. Similar to inflammatory bowel disease, patients who are steroid dependent must be considered for immunosuppressive therapies and biologics. Treatment options that have been reported include steroids, IV immunoglobulins (IVIG), azathioprine, budesonide, 6-mercaptopurine (6-MP), methotrexate, cyclosporine A, tacrolimus, sirolimus, mycophenolate mofetil, rituximab, cyclophosphamide, and anti-TNF inhibitors such as infliximab^{2-5,7,8}.

Based on the Mayo Clinic study of 15 patients with AIE, 14 of the patients received immunosuppressive therapy⁵. 60% of the patients had a complete or partial response to steroids and 44% of these patients were able to see some response with use of azathioprine 2 mg/kg or 6-MP 1-1.5 mg/kg. Two of these patients were able to be maintained on budesonide 6-12 mg/day; azathioprine was added to one of these two cases. Infliximab (5 mg/kg) with induction at 0, 2, 6 weeks followed by maintenance every 8 weeks was able to induce remission in 2 out of the 15 patients. Two of the patients, who had CVID, received IVIG with no response. The other therapies mentioned above have been shown to be effective in various case reports of patients.

We present an interesting case of refractory autoimmune enteropathy that responded to abatacept, a selective modulator of T-cell activation.

Case Report

A 49-year-old Caucasian female with no prior past medical history first presented with symptoms of diarrhea in the fall of 2010 with diarrhea after a flu-like illness. The symptoms resolved completely with loperamide. However, one month later, her diarrhea recurred and no longer responded to loperamide. She was hospitalized at this time for dehydration. Stool studies were reportedly normal, with no evidence of an infectious etiology. An upper endoscopy and colonoscopy were performed and noted to be grossly normal. Biopsies from the upper endoscopy showed villous blunting and reported to be consistent with celiac disease, though serum IgA and tissue transglutaminase (TTG) levels were normal. Endomysial antibody titers were found to be negative. She was nevertheless started on a gluten free diet and discharged home. One month later, the patient presented to the same hospital with worsening diarrhea and dehydration. This time, she was noted to have lost over 50 pounds of weight. She had one non-bloody bowel movement every two to three hours while fasting and every one to two hours with any oral intake. She had no nausea, vomiting, or fevers. She had no prior travel history outside of Massachusetts and did not smoke, drink, or use recreational drugs. Due to her symptoms of weight loss, muscle atrophy, failure to thrive, diarrhea, and electrolyte abnormalities, she was initiated on parenteral nutrition. She was then transferred to our institution for further evaluation and management of her condition.

Her physical exam revealed that she was afebrile and had normal vital signs. She had noticeable temporal wasting and an overall emaciated appearance. Her cardiovascular, pulmonary, abdominal, skin, lymph node, joint and extremity examination were otherwise normal.

She was documented to have 9 liters of diarrhea over a 24-hour period of time while having no per oral intake. Stool electrolytes while fasting revealed a stool Na 52 mEq/L, stool K 12.5 mEq/L, and stool osmolality of 291 mOsm/kg. The calculated osmotic gap was 162 mOsm/kg. Though this calculation suggests an osmotic diarrhea, persistent diarrhea while fasting represents definitive evidence of a secretory diarrhea. Stool studies, including clostridium difficile, ova and parasite, gram stain, and culture for enteric pathogens were negative. Laboratory findings were as follows: Na 135 mmol/L (135-145), K 3.1 mmol/L (3.4-4.8), Cl 110 mmol/L (100-108), bicarbonate 15 mmol/L (23-31), magnesium 1.5 meq/L (1.4-2), albumin 2.5 g/dL (3.3-5), total protein 5.4 g/dL (6-8.3), amylase 46 U/L (3-100), lipase 78 U/L (13-60), and WBC 7.8 (4.5-11) with a normal differential. Quantitative stool fat over a 24 hour period, while having no per oral intake and on total parenteral nutrition was measured to be 149 g/24 hour (2-7). Additional testing for causes of an occult secretory diarrhea was also ruled out with the following: chromagranin A, plasma metanephrine and normetanephrine, vasoactive intestinal peptide, 5-hydroxyindoleacetic acid, somatostatin, gastrin, calcitonin, and cortisol stimulation test. Additional testing for HIV, antinuclear antibody, helicobacter pylori, celiac disease, complement levels, and serum protein electrophoresis were also normal. An anti-enterocyte antibody test was found to be positive.

Her outside hospital imaging, consisting of a neck, chest, and abdominal computed tomography were reviewed and found to be normal. A push enteroscopy was performed and showed grossly normal mucosa up to the mid-jejunum. A colonoscopy was performed and showed grossly normal mucosa up to the terminal ileum. A video capsule endoscopy was also found to be normal.

Biopsies from the duodenum showed complete villous atrophy and blunting, apoptosis, some neutrophilic cryptitis, and absence of intraepithelial lymphocytes with a confirmatory CD3 immunostain showing absence of T-cells (Figure 1). Similar findings were also seen in the jejunum and terminal ileum. Random biopsies throughout the entire colon were predominantly normal, though a few biopsies showed occasional inflammatory infiltrate within the lamina propria. The findings of inflammatory infiltrate within the colon were noted to be much milder when compared to the small intestines. Given her prolonged diarrhea, malabsorption, small bowel histology, exclusion of other diseases, and a positive anti-enterocyte antibody, a diagnosis of AIE was made. She was subsequently started on methylprednisolone 20 mg intravenously every 8 hours. Within 5 days, she was having solid bowel movements and was able to be transitioned off of parenteral nutrition and started on oral prednisone and azathioprine. She was subsequently discharged home.

Her azathioprine was titrated to a dose of 2.5 mg/kg/day over the course of eight weeks. She was unable to wean her prednisone below 20 mg/day. Over the next two weeks, the patient was doing well until she developed severe pancreatitis with a serum lipase greater than 1000. She was also diagnosed with a deep vein thrombosis and pulmonary embolism. Imuran was thus stopped and started on anticoagulation. Upon discharge, she was started on infliximab at a dose of 5 mg/kg. The patient showed clinical response after the first dose and was able to wean to a maintenance dose of prednisone by week 6. However, during the week 6 infusion, the patient developed anaphylaxis. At that time, the infliximab was discontinued. Her dose of prednisone was increased to 30 mg/day and she was started on methotrexate 15 mg subcutaneous per week. Over the next 10 months, she needed to be maintained at the same dose of methotrexate and prednisone 20 mg/day. She had about three loose bowel movements per day. However, any attempts to reduce the dose of either medication resulted in development of profuse watery diarrhea.

Upper endoscopy was performed at this time to assess disease severity. There was no significant change between biopsies performed one-year prior. Due to concerns about ability to absorb per oral medications and patient concerns about side effects and drug level monitoring, a decision was made to continue subcutaneous methotrexate and start her on abatacept 125 mg subcutaneous every week. The day following treatment, the patient reported improvement in her diarrhea. By the second week, the patient was reporting constipation, requiring implementation of daily polyethylene glycol. Prednisone was weaned off over the next 6 weeks. Given her constipation, the dose of abatacept was extended to 125 mg subcutaneous every two weeks. Her methotrexate dose was reduced to 10 mg subcutaneous every week.

An upper endoscopy was performed 3 months into treatment, but showed no significant change in small bowel histology. However clinically, the patient continued to have one solid bowel movement every one to two days.

The patient continued to have clinical response and an upper endoscopy was performed 6 months into treatment to assess for histological response. The biopsies showed marked improvement in duodenal mucosa with development of normal villous architecture. There were regenerative changes and some lymphoid aggregates present. Overall, the degree of change was quite significant and much less involved compared to prior biopsy specimens (Figure 2).

Discussion

To our knowledge, this is the first reported case of AIE that has shown clinical response to abatacept. This case highlights the complex nature and management of AIE. This patient developed adverse reactions to standard medications typically used to treat AIE. She developed pancreatitis to azathioprine, anaphylaxis to infliximab, and a limited clinical response to a long duration of methotrexate. The patient also developed deep vein thrombosis and pulmonary embolus in the setting of systemic inflammation, since a hypercoagulable workup was found to be negative.

The patient wanted to use a medication that would have a limited side effect profile, have ease of administration, and not require level monitoring. We also wanted to use a medication that would have good absorption and be directed towards the pathogenesis AIE. To date of this report, the patient has been in clinical remission for about 9 months and histological remission for about 3 months.

Abatacept is a human fusion protein that modulates T cell activation. It has shown to be most effective in patients with rheumatoid arthritis who have had an inadequate response to conventional therapies such as methotrexate⁹. There has been limited success of abatacept in patients with established moderate to severe Crohn's disease and ulcerative colitis¹⁰, though it is not clear if individuals with small bowel disease alone would have a response. Use of abatacept is being investigated in other disease including lupus nephritis¹¹ and improvement of insulin resistance associated with diabetes¹². Due to low incidence of AIE, similar large-scale studies would be difficult to perform in order to determine effectiveness of abatacept. At this point, accumulation of anecdotal case reports will help guide new treatment options and gain insight towards disease mechanism.

Gastroenterologists should be aware about the diagnosis of AIE, its clinical course, and consider various treatment options, including abatacept, for refractory cases.

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Figure 1.

Autoimmune enteritis with duodenal biopsies prior to treatment:

- A). Biopsies reveal severe villous atrophy and blunting, apoptosis, and marked epithelial damage. (hematoxylin and eosin, 4X [A] and 20X [B]). The red arrow indicates a crypt, and the yellow arrow points to the villous-crypt junction, highlighting the lack of villi.
- C). Confirmatory staining of the duodenum shows lack of prominent intraepithelial lymphocytosis. (CD3 staining, 20X [C])

Figure 2.

Autoimmune enteritis with duodenal biopsies after 6 months of treatment with abatacept: A-B). Subsequent biopsies show marked improvement in duodenal mucosa with regenerative epithelial changes and slightly blunted villous architecture. Overall, there is significant improvement and the degree of immune cell mediated effects is much less when compared to prior. (hematoxylin and eosin, 4X [A] and 20X [B]).