A Case of Evan’s Syndrome Induced by Vedolizumab

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ABSTRACT

Vedolizumab is a monoclonal antibody against the α4β7 integrin receptor used for the treatment of ulcerative colitis and Crohn’s disease. Clinical trials have shown vedolizumab to be a safe and highly effective therapy in treating inflammatory bowel disease. Its unique gut-specific mechanism of action has made it an attractive agent in recent years. However, vedolizumab’s side effect profile and long-term effects are not fully understood. We report a patient with ulcerative colitis who presented with epistaxis 1 week after receiving the first induction dose of vedolizumab found to have a severe immune-mediated thrombocytopenia and hemolytic anemia, otherwise known as Evan’s syndrome.

INTRODUCTION

Vedolizumab is a humanized monoclonal antibody used for the treatment of ulcerative colitis (UC) and Crohn’s disease. It targets the α4β7 integrin receptor on T lymphocytes and blocks its interaction with mucosal addressin cell adhesion molecule 1 on intestinal vasculature.1 This prevents the migration of T lymphocytes into intestinal tissue. The GEMINI 1 and GEMINI 2 trials have shown vedolizumab to be a safe and highly effective therapy in treating moderate to severe inflammatory bowel disease (IBD).2 Its unique gut-specific mechanism of action has made it an ideal agent in recent years. However, as a novel agent, vedolizumab’s exact side effect profile and long-term effects are not yet fully understood. We present a case of a severe immune-mediated thrombocytopenia and autoimmune hemolytic anemia 1 week after the first vedolizumab infusion in a patient with UC.

CASE REPORT

A 26-year-old man with a medical history of ulcerative pancolitis presented initially with epistaxis and hematuria. He was diagnosed with UC 1 year before presentation. He was initially managed with mesalamine and subsequently adalimumab. After initial clinical improvement on adalimumab, he experienced a secondary loss of response with recurring symptoms. He was then started on a prednisone taper as a bridge to treatment with vedolizumab. Of note, his blood counts before his first vedolizumab infusion were completely normal. One week after his first infusion, he presented to the hospital with severe epistaxis and hematuria along with continued chronic bloody diarrhea. He had no other changes to his medications and denied use of over-the-counter supplements. His medications on admission were mesalamine 1.5 g orally daily, prednisone 40 mg orally daily, and vedolizumab. He had no reported allergies or surgical history. He denied any toxic habits including tobacco, alcohol, or recreational drug use. He reported a family history of celiac disease in his mother and sister but denied any family history of IBD, blood disorders, cancer, or other autoimmune disorders.

Physical examination was notable only for mild left lower quadrant tenderness. Digital rectal examination showed loose brown stool. Laboratory test results on admission revealed a severe thrombocytopenia with a nadir of 7 K/μL, decreased from a baseline before vedolizumab infusion of 271 K/μL. He had findings consistent with a hemolytic anemia with an indirect bilirubinemia, elevated lactate dehydrogenase level, and decreased haptoglobin level (Table 1). Direct Coomb’s testing was positive. His hemoglobin
and bleeding. It was fatigue, pallor, lightheadedness, jaundice related to hemolysis, levels were normal, making common variable immunodeficiency did not show any signs of lymphoma. Immunoglobulin vedolizumab discontinuation. In addition, computed tomography, and the subsequent recovery of his cell counts after likely, given the normal blood counts the week before vedolizumab infusion and the subsequent recovery of his cell counts is possible after treatment and discontinuation of the offending drug.

Patients with Evan’s syndrome show decreased percentages in T helper cells and increases in T suppressor cells. In addition, patients may have decreased apoptosis of activated lymphocytes leading to overaccumulation of subsets of T lymphocytes, which may contribute to autoantibody formation. Given the mechanism of action of vedolizumab in decreasing migration of T lymphocytes to intestinal cells, this could potentially increase circulating T lymphocytes and predispose to autoantibody formation. There have been a number of potential other known triggers of Evan’s syndrome along with several associated disorders reported in the literature, which were ruled out in our patient. These include certain other medications (ie, Orlistat), infections (ie, human immunodeficiency virus and hepatitis C virus), common immune variable deficiency, lymphoproliferative disorders, systemic lupus erythematosus, type 1 diabetes mellitus, and celiac disease. There has also been a case reported that was triggered after an autologous bone marrow transplant for recurrent Hodgkin’s disease.

Treatment is challenging because the disease is often characterized by a relapsing-remitting course unless the triggering medication is stopped. First-line therapy involves corticosteroids or intravenous immunoglobulin. Second-line therapies include other immunosuppressive agents such as cyclosporine, mycophenolate, danazol, and vincristine. Emerging evidence has shown rituximab to be an effective treatment as well. Splenectomy may be considered for patients not responding to medical therapy, but relapse is still possible after surgery. For more severe and refractory cases, stem cell transplantation offers a potential for long-term cure. In cases in which a medication trigger is identified and discontinued, full recovery of cell counts is possible after treatment and discontinuation of the offending drug.

The efficacy and safety of vedolizumab has been established in multiple clinical trials. Its gut-specific mechanism of action has made it ideal for patients with IBD who have failed or lost response to other therapies. Although we have excellent safety data so far, long-term follow-up is needed to identify rare adverse events.

| Table 1. Laboratory test result values during the hospital course |
|---------------------------------------------------------------|
| **Baseline** | **Admission** | **Hospital day 1** | **Hospital day 2** | **Hospital day 3** | **Hospital day 7 (discharge)** |
|----------------|---------------|-------------------|-------------------|-------------------|-------------------|
| WBC (K/μL)    | 10.5          | 14.08             | 17.27             | 10.46             | 14.56             | 20.52             |
| Hemoglobin (g/dL) | 13.9          | 13.3              | 11.8              | 8.9               | 7.0               | 7.7               |
| Hematocrit (%) | 42.8          | 40.0              | 35.0              | 26.2              | 20.5              | 23.3              |
| MCV (fL)      | 94.6          | 89.9              | 87.9              |                   |                   |                   |
| RDW (%)       | 16.3          | 14.8              | 15.0              |                   |                   |                   |
| Platelets (K/μL) | 271           | 17                | 9                 | 7                 | 17                | 28                |
| Reticulocyte count (%) | 2.46        |                   |                   |                   |                   |                   |
| LDH (IU/L)    | 1909          |                   |                   |                   |                   |                   |
| Haptoglobin (mg/dL) | <8.0         |                   |                   |                   |                   |                   |

LDH, lactate dehydrogenase; MCV, mean corpuscular volume; WBC, white blood cell.

The patient met the diagnostic criteria for Evan’s syndrome based on his Coombs-positive hemolytic anemia and thrombocytopenia. There was no identifiable trigger other than his recent first vedolizumab infusion. Other possible etiologies such as acute leukemia and lymphoma were considered but were unlikely, given the normal blood counts the week before vedolizumab infusion and the subsequent recovery of his cell counts after vedolizumab discontinuation. In addition, computed tomography did not show any signs of lymphoma. Immunoglobulin levels were normal, making common variable immunodeficiency unlikely as well. Although IBD has been associated with autoimmune disease in general, the temporal relationship and subsequent recovery made his Coombs-positive hemolytic anemia and thrombocytopenia. Signs and symptoms are related to deficiencies in these cell lines including fatigue, pallor, lightheadedness, jaundice related to hemolysis, and bleeding. It was first described by Evans et al. Its etiology and pathophysiology remains unclear, but some studies have shown the syndrome to be a disorder of T lymphocytes. Evan’s syndrome is a rare autoimmune disorder characterized by a simultaneous direct Coombs-positive autoimmune hemolytic anemia and immune thrombocytopenia. The peripheral smear showed only reactive lymphocytes, toxic granulation, and rare platelets. There was no evidence of schistocytes. Serum testing for viral etiologies such as parvovirus, hepatitis A/B/C, varicella-zoster virus, cytomegalovirus, human immunodeficiency virus, and Epstein-Barr virus was all negative. Quantiferon testing was negative. Stool testing for *Clostridium difficile* was negative.

DISCUSSION

Evan’s syndrome is a rare autoimmune disorder characterized by a simultaneous direct Coombs-positive autoimmune hemolytic anemia and immune thrombocytopenia. The syndrome is a relapsing-remitting course unless the triggering medication is stopped. First-line therapy involves corticosteroids or intravenous immunoglobulin. Second-line therapies include other immunosuppressive agents such as cyclosporine, mycophenolate, danazol, and vincristine. Emerging evidence has shown rituximab to be an effective treatment as well. Splenectomy may be considered for patients not responding to medical therapy, but relapse is still possible after surgery. For more severe and refractory cases, stem cell transplantation offers a potential for long-term cure. In cases in which a medication trigger is identified and discontinued, full recovery of cell counts is possible after treatment and discontinuation of the offending drug.

The efficacy and safety of vedolizumab has been established in multiple clinical trials. Its gut-specific mechanism of action has made it ideal for patients with IBD who have failed or lost response to other therapies. Although we have excellent safety data so far, long-term follow-up is needed to identify rare adverse events. The
effect of vedolizumab on T lymphocytes and the potential for autoantibody formation that can lead to Evan’s syndrome needs further study. In addition, research is needed to elucidate what predisposing factors, if any, may make a patient susceptible to such immune reactions to the drug. Although vedolizumab is efficacious in treating IBD, this case highlights a potential rare but serious paradoxical immunogenicity of the drug. Bloodwork should be monitored carefully after vedolizumab introduction, and ongoing postmarketing safety data are needed.

DISCLOSURES

Author contributions: H. Jen performed background research and wrote the manuscript. B. Morganstern and L. D’Souza drafted and edited the manuscript. L. D’Souza is guarantor of the article.

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REFERENCES

1. Amiot A, Grimaud JC, Biroulet LP, et al. Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease. Clin Gastro Hep. 2016;14:1593–601.
2. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn’s disease. Gut. 2017;66:839–51.
3. Evans RS, Takahashi K, Duane RT. Primary thrombocytopenic purpura and acquired hemolytic anemia. Arch Intern Med. 1951;87:48–65.
4. Wang W, Herrod H, Pui CH. Immunoregulatory abnormalities in Evans syndrome. Am J Hematol. 1983;15(4):381–90.
5. Teachey DT, Manno CS, Axsom KM, et al. Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome. Blood. 2005;105(6):2443–8.
6. Earnshaw I, Thachil J. Example of the drug interaction between ciclosporin and orlistat, resulting in relapse of Evans syndrome. BMJ Case Rep. 2016. (Available at doi: 10.1136/bcr-2016-217246).
7. Keung YK, Cobos E, Bolanos J, et al. Evans syndrome after autologous bone marrow transplant for recurrent Hodgkin’s disease. Bone Marrow Transpl. 1997;20(12):1099–101.
8. Norton A, Roberts I. Management of Evans syndrome. Br J Hematol. 2005;132:125–37.

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