Vedolizumab-Associated Hypereosinophilia and Hepatoxicity

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ABSTRACT

Vedolizumab, which is approved for the treatment of ulcerative colitis, has been associated with drug-induced liver injury because of an unclear mechanism. We describe the case of a 29-year-old man who presented with abnormal liver enzymes and peripheral hypereosinophilia after vedolizumab initiation. A complete workup for causes of hepatitis and hypereosinophilia was negative, and liver biopsy showed signs compatible with drug-induced liver injury. After the withdrawal of vedolizumab, the patient’s eosinophil count and liver enzymes normalized. As vedolizumab becomes more prominent, it is important to understand the potential side-effect profile of vedolizumab.

INTRODUCTION

Vedolizumab is currently approved for the induction and maintenance of remission in patients with moderate-to-severe ulcerative colitis (UC) and Crohn’s disease. It is a monoclonal antibody to α4β7 integrin, which is involved in lymphocyte trafficking. Vedolizumab is preferred over other integrin-blocking agents because it selectively inhibits gut lymphocyte tracking. As such, vedolizumab is generally a well-tolerated therapy. Premarketing phase 3 trials demonstrated a similar serious adverse event profile between the vedolizumab arm (7%–12%) and the placebo arm (4%–9%).1,2

Vedolizumab-associated drug-induced liver injury (DILI) is a rare occurrence. Premarketing data of 3,326 vedolizumab-exposed patients in phase III studies report that less than 2% of patients experience elevations higher than 3 times the upper limit of normal in aminotransferases.1,2 In the landmark GEMINI trial of vedolizumab as treatment in patients with UC, only 3 patients had vedolizumab discontinued in the context of hepatic events.1,3 Cases of DILI, with and without the presence of cholestasis, have been reported and have resulted in drug insert recommendations for cessation of the drug in the presence of hepatic injury.3 We present the first case of vedolizumab-associated hypereosinophilia and DILI.

CASE REPORT

A 29-year-old man, known to have UC previously treated with vedolizumab for 6 months without complications but discontinued because of loss to follow-up, presented to hospital with a UC flare. After endoscopic confirmation of active UC, the patient was reinduced with vedolizumab 2 years after receiving his last dose. Two months after the induction, the patient was noted to have an elevated alanine aminotransferase (ALT) of 348 U/L, an elevated alkaline phosphatase (ALP) of 238 U/L, an elevated gamma glutamyl transferase of 308 U/L, an elevated aspartate aminotransferase of 89 U/L, and a normal total bilirubin of 15 μmol/L. The patient’s complete blood count was unremarkable, except for an acute eosinophilia with an absolute eosinophil count of 3.22 × 109/L similar to his initial induction 3 years earlier but without any transaminitis at the time. A complete workup revealed positive hepatitis A total ab (IgM-negative) and negative hepatitis B and C. Ceruloplasmin, alpha-1 antitrypsin, immunoglobulins, and ferritin were within normal limits while, anti-mitochondrial antibodies and anti-smooth muscle antibodies were negative. Anti-nuclear antibodies were positive at a 1:160 titer. An infectious screen—including human immunodeficiency virus, cytomegalovirus, Epstein-Barr Virus, Toxoplasma,
Fasciola, Toxocara, and Trichinella—was negative. The patient’s eosinophilia was further assessed by tropical medicine and hematology. Although a previous exposure to schistosomiasis was identified, this was not believed to be causing this presentation. Parasitic infections and myeloproliferative neoplasia were excluded, although a bone marrow biopsy was not performed as per the patient’s wishes. Abdominal ultrasound revealed normal liver and biliary systems. The patient also underwent endoscopic ultrasound-guided fine-needle biopsy of the liver. Histopathologic examination showed multifocal, predominantly portal, chronic inflammation in keeping with early primary sclerosing cholangitis (PSC) and foci of inflammation with a small-to-moderate number of eosinophils (Figures 1 and 2). The patient’s vedolizumab was suspended for 1 month, and his ALT decreased to 88 U/L while his ALP and eosinophils remained stable. After this dose, vedolizumab was stopped, and his ALT reduced progressively to 149 U/L 3 months later. Six months after drug cessation, the patient’s ALT was 88 U/L; ALP was 174 U/L; and his eosinophil count had normalized. The patient was also offered prednisone for his UC but refused.

**DISCUSSION**

DILI is a rare yet important adverse effect in patients taking vedolizumab. Limited data suggest that vedolizumab-associated DILI presents as a mixed or cholestatic profile, with onset ranging anywhere from 14 to 275 days after exposure.4,5 Similar to other published cases in the literature, ALT and ALP gradually improve when the medication is stopped. The prolonged recovery of ALP is believed to be due to prolonged cholangiocyte regeneration in patients with mixed DILI.4 The Roussel Uclaf Causality Assessment Method calculated a score of 8, supportive of DILI.

The underlying mechanism for vedolizumab-associated DILI remains unclear. Vedolizumab acts by inhibiting the α4β7 integrin, which prevents interaction with the mucosal addressin cell adhesion molecule and inhibits T lymphocyte and eosinophil migration and adhesion to gastrointestinal tissues.3,7 After reintroduction of vedolizumab, our patient saw an increase in his peripheral eosinophilia, which could represent an increase in the context of the α4β7 inhibition. Moreover, the increased eosinophilia could also represent a possible allergy-like immune response to vedolizumab in this patient, although he did not have any clinical signs or symptoms of such.

Eosinophils express complement receptors and Fc receptors capable of antibody-dependent cellular cytotoxicity and, in the context of autoimmune disease, can affect host cells by binding autoantibodies. Eosinophils have also been demonstrated to promote fibroblast proliferation, proteoglycan accumulation, and matrix metalloproteinase formation, and these profibrotic properties can cause further tissue dysfunction. The increased recruitment of eosinophils results in the increase in granular proteins and other inflammatory mediators in the intestinal tract, resulting in tissue disease.7,8 The inhibition of gastrointestinal tissue migration and eosinophil response to vedolizumab administration in this patient could represent the underlying mechanism for DILI and explains the marked peripheral hypereosinophilia.

When evaluating a patient with UC and abnormal liver enzymes, it is important to consider coincidental PSC or autoimmune hepatitis.4,6 In this case, the finding of early PSC on liver biopsy did not fit with the clinical presentation. In addition, these histopathologic findings can be seen in secondary sclerosing cholangitis secondary to drug-induced injury to the biliary epithelium.5–9 Another important differential to consider in this case includes eosinophilic cholangitis (EC). Although EC associated with vedolizumab has been described in the literature, the absence of wall thickening or stenosis of the biliary system makes the diagnosis of EC less likely in our patient.10

As the use of vedolizumab becomes more prominent in inflammatory bowel diseases, it is important to understand the side-effect profiles of this monoclonal antibody. Although the
exact mechanism of vedolizumab-associated DILI is not known, clinicians should continue to monitor eosinophil patterns and liver function tests during therapy.

DISCLOSURES

Author contributions: Conception and design of the article by A. Benmassaoud. Analysis, interpretation of the data, and manuscript drafting by D. De Marco. Critical revision and approval of the article by all authors. A. Benmassaoud is the article guarantor.

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