Chronic Cholestatic Liver Injury Attributable to Vedolizumab

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Abstract

Drug-induced liver injury is a rare but clinically important diagnosis. Vedolizumab is an α4β7 integrin inhibitor recently approved for use in patients with moderate-to-severe inflammatory bowel disease. Cases of hepatotoxicity due to vedolizumab in the pre-marketing stage were rare, and all cases resolved upon drug withdrawal. We present here the first reported case of hepatotoxicity attributable to vedolizumab, which despite drug cessation persisted with chronic cholestatic liver injury.

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Keywords: Hepatotoxicity; Integrin inhibitor; Primary sclerosing cholangitis; Inflammatory bowel disease.

Abbreviations: DILI, drug-induced liver injury; VDZ, Vedolizumab; UC, ulcerative colitis; SAEs, serious adverse events; PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; AST, aminotransferase; ALT, alanine aminotransferase; TB, total bilirubin; INR, international normalized ratio; ULN, upper limit of normal.

Case Report

A 23-year-old Caucasian male with pancolonic UC diagnosed at age 19 and concurrent primary sclerosing cholangitis (PSC) diagnosed at age 22 was evaluated at our institution in the Digestive Health outpatient clinic. His prior inflammatory bowel disease (IBD) therapy included 5-aminosalicylate medications, corticosteroids, azathioprine and biologic agents (infliximab and adalimumab) prescribed by his gastroenterologist following the initial diagnosis, but achieved no clinical or endoscopic remission. Examination at the time of his initial adult consultation did not reveal any stigmata of advanced liver disease. Pre-treatment liver biochemistries were notable for aspartate aminotransferase (AST) at 31 U/L, alanine aminotransferase (ALT) at 33 U/L, alkaline phosphatase at 648 U/L (61% heat stable; normal range 25–40%), total bilirubin (TB) at 1.4 mg/dL and albumin at 2.9 g/dL. Gamma glutamyltransferase was 130 U/L (normal < 55 U/L). Other notable lab results included platelet count of 525 k/μL, international normalized ratio (INR) of 1.1, sedimentation rate of 24 mm/hr (normal 0–15 mm/hr) and C-reactive protein at 0.1 g/dL (normal < 0.5 g/dL).

After the patient’s initial consultation, he was initiated on VDZ and received three doses of 300 mg intravenous infusions at weeks 0, 2 and 6. After the third infusion, the patient developed insidious onset of jaundice and fatigue. Importantly, he had never experienced overt jaundice due to PSC previously. Laboratory tests at this time were remarkable for AST at 52 U/L, ALT at 27 U/L, alkaline phosphatase at 370 U/L, TB 13.3 mg/dL, and conjugated bilirubin 9.3 mg/dL. The R ratio was calculated [(ALT/upper limit of normal (ULN))/(alkaline phosphatase/ULN)] and found to be 1.1, indicating cholestatic liver injury (R ratio < 2 is diagnostic).

Magnetic resonance imaging of the abdomen, including magnetic resonance cholangiopancreatography scanning, did not reveal any dominant stricture and the findings were unchanged compared to the index images that were taken one year prior, at the time of the PSC diagnosis. A comprehensive hepatitis viral serology panel was unrevealing.
The patient denied any alcohol or toxin exposure. Testing for autoimmune hepatitis and hemochromatosis screening was negative. The Roussel Uclaf Causality Assessment Method (commonly known as RUCAM), which uses seven different criteria to quantify the strength of association between a liver injury and the medication, implicated VDZ as the offending agent with a score of 7 (probable liver injury) (Fig. 1).

VDZ was subsequently discontinued after the third infusion. Six weeks after the patient's last dose of VDZ, he experienced an increase in bowel frequency with associated bleeding and was started on prednisone. Lab results from several weeks after the corticosteroid administration showed marked improvement accompanying the continued corticosteroid use, with TB at 4.9 g/dL and alkaline phosphatase at 485 U/L. The patient's jaundice and fatigue also improved. Corticosteroid therapy was continued for the IBD, and anti-TNF therapy with adalimumab was resumed 4 months after the last dose of VDZ; the patient experienced intervals of improvement in his bowel symptoms but not complete clinical remission.
Importantly, the patient’s cholestatic liver injury persisted 5 months following the drug withdrawal, meeting criteria for chronic DILI with TB at 1.7 g/dL and alkaline phosphatase at 556 U/L. Pre-DILI diagnosis lab results were compared to post-DILI lab results within a 6-week window in each period by using a paired t-test. TB levels were significantly different (pre-DILI: 2.3 ± 0.6 g/dL vs. post-DILI: 10.4 ± 4.2 g/dL, \( p = 0.037 \)) while AST and ALT were not significantly different by the statistical testing (Table 1). Figure 2 shows the graphic trend in the patient’s liver-associated enzymes. Informed consent was obtained from the patient.

Discussion

While pre-marketing data suggests that hepatotoxicity in the setting of VDZ use for IBD is a rare and self-limiting event, with or without cholestasis,\(^6,7\) we present the first post-marketing case of chronic DILI attributable to VDZ use. Chronic liver injury from medications is becoming increasingly recognized,\(^6\) with prevalence rates approaching 20% based upon data from the Drug-Induced Liver Injury Network (DILIN).\(^3\) Patients with cholestatic injury, such as our patient, appear to be at increased risk for progressing to chronic injury.\(^3,10\) Adherence to appropriate prescription regimens remains one of the most important aspects for preventing DILI in patients with underlying chronic liver disease.\(^9\) The drug package insert for VDZ states that elevations of liver-associated enzymes have been reported in patients receiving VDZ and that in the absence of biliary obstruction VDZ should be discontinued in patients with jaundice or other evidence of significant liver injury.\(^6\)

Whether or not VDZ may worsen bile duct injury in the setting of PSC through an unknown mechanism remains to be determined. In general, PSC is not thought to place patients at increased risk for DILI.\(^2\) Rather, secondary sclerosing cholangitis typically occurs as a sequela of chronic drug-induced bile duct injury.\(^10\) A solitary case report of DILI in the setting of certirizine use in a patient with PSC has been reported.\(^11\) Based on the available evidence, in combination with our isolated case report, we cannot recommend avoiding...
VDZ in IBD patients with concomitant PSC; however, monitoring hepatic enzymes during VDZ therapy is warranted.

In general, treatment options for DILI are limited. Treatment is centered around prompt identification and removal of the offending drug. While corticosteroids were administered to several patients in the pre-marketing trials who experienced hepatotoxic events, the efficacy of the use of corticosteroids in treating DILI remains largely anecdotal. Immunosuppressive therapy may be considered on a case-by-case basis, where autoimmune-like DILI features, including the presence of auto-antibodies or liver histology supporting this diagnosis, are present and cessation of the drug does not lead to complete resolution of injury.

In this case, corticosteroids were administered to address worsening IBD activity and not as treatment for DILI, but they may have hastened clinical improvement following the hepatotoxic event. On the other hand, corticosteroids and adalimumab may have hastened clinical improvement following the hepatic enzymes during VDZ therapy is warranted.

While this case has several limitations, including an incomplete evaluation for other chronic liver diseases (namely, alpha-1 antitrypsin deficiency or Wilson’s disease) and a lack of liver biopsy as a confirmatory study, a high-index of suspicion for the development of hepatotoxicity in patients with IBD being treated with VDZ seems necessary based on our report, nonetheless.

Acknowledgement

The research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number T32DK007769. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest

None

Table 1. Liver-associated enzymes in the course of vedolizumab treatment

| Time after VDZ discontinuation | AST (U/L) | ALT (U/L) | Total bilirubin (mg/dL) | ALP (U/L) |
|------------------------------|-----------|-----------|------------------------|-----------|
| First VDZ infusion           | 31        | 33        | 1.8                    | 461       |
| 8 days after VDZ initiation  | 63        | 62        | 2.2                    | 513       |
| 15 days after VDZ initiation/second infusion of VDZ | * | * | 2.9 | 460 |
| 41 days after VDZ initiation/VDZ discontinued | 52 | 27 | 13.3 | 359 |
| 35 days after VDZ discontinuation | 48 | 25 | 13 | 370 |
| 49 days after VDZ discontinuation/prednisone (10 mg daily) initiated | 55 | 16 | 7.4 | 509 |
| 62 days after VDZ discontinuation | 78 | 52 | 4.9 | 485 |
| 92 days after VDZ discontinuation/Humira started | 50 | 33 | 5.3 | 513 |
| 156 days after VDZ discontinuation | 55 | 77 | 1.7 | 556 |

*The data of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at 15 days after VDZ initiation were not collected, and therefore not reported. ALP, alkaline phosphatase.

Author contributions

Manuscript design, manuscript writing, final approval (JGS), manuscript writing, final approval (JW), manuscript design, final approval (BWB).

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