Autoimmune Hepatitis During Ledipasvir/Sofosbuvir Treatment of Hepatitis C: A Case Report

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We report the case of a woman with chronic hepatitis C and idiopathic thrombocytopenic purpura (ITP) who developed autoimmune hepatitis (AIH) during antiviral therapy with ledipasvir (LDV)/sofosbuvir (SOF). The onset of acute hepatitis rose two weeks after starting treatment with LDV/SOF when HCV-RNA tested negative, suggesting a link between rapid HCV clearance and de novo autoimmune diseases. Conclusion: This case report proposes new immunologic scenarios in patients with hepatitis C virus (HCV) with laboratory or clinical signs of autoimmunity during direct-acting antiviral (DAA) therapy. (Hepatology Communications 2018;2:1179-1183).

AIH is a rare disease that in the majority of patients occurs without any identifiable trigger. This is in contrast with patients who develop AIH as a consequence of exposure to medications, such as anti-inflammatory molecules, anti-tumor necrosis factor α monoclonal antibodies, and immune checkpoint inhibitors.1 In 2013, a coformulated oral regimen consisting of a nonstructural protein 5A (NS5A) inhibitor (LDV) and an NS5B nucleotide analog inhibitor (SOF) of the HCV became the standard of care to treat chronic infection with HCV genotypes 1 and 4 in adults and more recently in adolescents. Studies of antiviral therapy of HCV, while highlighting the safety and effectiveness of DAA regimens, have also reported sporadic episodes of adverse effects associated with immune dysregulation.2 We report the case of a woman with chronic hepatitis C and idiopathic thrombocytopenic purpura (ITP) who developed AIH during antiviral therapy with LDV/SOF.

The Case

A 72-year-old woman with chronic hepatitis C genotype 1b, arterial hypertension, type 2 diabetes mellitus, and ITP, who was diagnosed on the basis of anti-platelet glycoprotein Ia/IIa autoantibodies, was referred following the onset of acute hepatitis 2 weeks after starting treatment with LDV and SOF. Infection with HCV was diagnosed in 2002, but antiviral therapy was deferred to avoid worsening of severe ITP using interferon-based regimens. Since 2002, the patient had been under biannual surveillance with liver enzyme values repeatedly testing normal. In 2016, hepatitis flared with serum alanine aminotransferase (ALT) of 160 U/L and aspartate aminotransferase (AST) of 135 U/L; these were associated with 1.2 mg bilirubin, a low platelet (PLT) count (100,000/mm3), and a low virus load (HCV-RNA 520 IU/mL). Gamma-glutamyltransferase, alkaline phosphatase, and gamma

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; DAA, direct-acting antiviral; DILI, drug-induced liver injury; HCV, hepatitis C virus; IgM, immunoglobulin M; ITP, idiopathic thrombocytopenic purpura; LDV, ledipasvir; PLT, platelet; SOF, sofosbuvir.

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globulin levels were within the normal range (15%). A liver biopsy showed moderate portal-based active hepatitis (grade 2) without interface or lobular activity consistent with chronic HCV infection, with moderate fibrosis (stage 3) according to a FibroScan value of 11 kPa. At that time, no signs of AIH were present and serum autoantibodies were not tested. The patient had been receiving insulin and carvedilol 6.25 mg twice a day for more than 15 years. At this point, the caregivers decided to start LDV/SOF therapy for HCV.

After 2 weeks of antiviral therapy, ALT and AST flared to 923 U/L and 752 U/L, respectively, whereas serum markers of cholestasis were within the normal range and HCV-RNA was undetectable. At this point, the PLT count dropped to 11,000/mm³, causing ecchymoses at the sites of insulin injection. The finding of an anti-nuclear antibody (ANA) titer of 1:320 (immunofluorescence pattern not reported) led the caregivers to add on prednisone monotherapy 50 mg/day during the first month of antiviral therapy. Serum HCV-RNA remained undetectable, ALT progressively fell to normal values, and PLTs rose to 210,000/mm³. Prednisone monotherapy was tapered down during the remaining weeks of antiviral therapy. Two weeks after completion of antiviral therapy when prednisone was dosed at 2.5 mg/day, ALT broke through to 250 U/L whereas HCV-RNA remained undetectable and the PLT count fell to 65,000/mm³, a finding that caused prednisone monotherapy to be adjusted to 25 mg/day and led the patient to be referred to our center with a suspected diagnosis of AIH.

On physical examination, the patient showed no hepatosplenomegaly or skin ecchymoses. Serum markers of viral hepatitis, including hepatitis A virus immunoglobulin M (IgM), hepatitis B surface antigen, total hepatitis B core antibody, HCV-RNA, hepatitis E virus IgM, herpes simplex DNA, cytomegalovirus IgM, and Epstein-Barr virus DNA all tested negative; however, serum ANA was 1:80 speckled and the level of peripheral anti-neutrophil cytoplasmic antibodies (p-ANCA) was strongly positive (Fig. 1). Anti-mitochondrial antibodies, anti-smooth muscle antibodies, and anti-liver/kidney microsome antibodies were negative. Gamma globulin levels were normal (16%), the PLT count was 135,000 /mm³, and the ALT value was 65 U/L. Liver biopsy demonstrated the presence of plasma cells clustering in areas of piecemeal necrosis, which along with an AIH score of 22 was strongly suggestive of AIH (Fig. 2). One year after completion of LDV/SOF therapy, the patient was still on 7.5 mg prednisone monotherapy, serum HCV-RNA remained undetectable, and the ALT and PLT count were within the normal range (Fig. 3).

**Discussion**

Liver injury following exposure to medications, herbs, or other toxic substances stands as one of the most common causes of acute liver damage, yet a differential diagnosis between a drug-induced liver injury (DILI) and an AIH is almost impossible to obtain in many patients. Differential diagnosis between those conditions is in fact often clouded by the appearance of immunologic markers, such as serum tissue autoantibodies and elevated immunoglobulin G levels, and overlapping histologic patterns of liver injury, particularly in patients with idiosyncratic DILI. Several lines of evidence indicate that AIH develops as a consequence of a loss of liver capacity for immune tolerance, an event that allows for an interaction between the liver, drugs, and antigens derived from the gut and ultimately leads to chronic inflammation of the liver. One teaching example of this is patients with tuberculosis exposed to isoniazid who suffer a transient increase of liver enzymes followed by spontaneous recovery despite continued dosing with the offending drug. While this condition is considered a clinical
adaptation reflecting the development of immune tolerance against isoniazid, some patients may mount a “defective adaptation” to the drug regimen, leading to development of a liver injury with continued exposure to the offending drug. (8) Although this is particularly true in patients with idiosyncratic DILI who develop unpredictable, non-dose-related liver injury, (9) it is worth mentioning that medications, such as oxyphenisatin, statin, nitrofurantoin, minocycline, chlomectin, and alpha-methyl-dopa, may trigger a liver injury that persists after drug discontinuation, suggesting that liver disease is caused by a true autoimmune reaction. (10,11)

Characteristically, infection with HCV may trigger a variety of immune reactions, including onset of non-organ-specific autoantibodies, cryoglobulins, autoimmune dysthyroidism, arthralgias, myalgias, and lichen planus. (12) Such a link between HCV and immune reactions has been a reason for deferring therapy with interferon of patients at risk of exacerbating a latent autoimmune disorder; this barrier has recently been lifted following the arrival of DAAs, which offered the opportunity to safely treat patients infected with HCV who present with various autoimmune phenomena. (13‒16) Recently, a multidisciplinary consensus and evidence-based recommendations on the management of HCV extrahepatic manifestations have been proposed that suggest considering DAA as first-line treatment for HCV-mixed cryoglobulinemia. (13) Furthermore, many reported cases suggest that HCV eradication is often associated with the improvement of lichen planus, (17) another HCV-associated immunologic condition. The impact of DAA on other rheumatologic manifestations, such as Sjögren’s syndrome and arthralgia/myalgia, is lacking. Few reports show a DAA treatment for patients with HCV and autoimmune liver diseases. Interestingly, Sugiura et al. (18)
achieved a sustained virologic response (SVR) in a patient affected by HCV-AIH overlap syndrome. In this scenario, DAA seems to be a safe and effective treatment in patients with HCV and immunologic disorders. However, some evidence suggests alterations of immune status are DAA induced. Kanda et al.\(^2\) treated 5 patients with HCV plus primary biliary cholangitis and 7 patients with HCV-AIH overlap syndrome and achieved a 100\% rate of SVR. Of the 7 patients with HCV-AIH overlap syndrome, 3 received prednisone at baseline and 3 did not receive prednisone during DAA therapy; in 1 female patient with HCV-AIH overlap syndrome plus cirrhosis who was treated with LDV/SOF, prednisone was not administered at baseline but was given after 8 weeks of liver chemistry abnormalities. Kanda et al. concluded that, in this category of patients, clinicians should pay special attention to acute exacerbation of liver diseases. Another example of immune imbalance induced by DAA therapy of HCV is the unexpected high rate of de novo or recurrent hepatocellular carcinoma (HCC) that has been reported in patients with HCV after DAA therapy\(^{19,20}\) despite the co-occurrence of such relevant confounding factors as heterogeneity of follow-up, starting point of analysis, time lag between DAA initiation and HCC onset, and modalities of cancer therapy. To reconcile the anti-HCV activity of DAAs with their potential to stimulate host immunity, it has been suggested that rapid elimination of HCV might favor a dysregulation of immune surveillance through a variety of mechanisms\(^{21-23}\) with some evidence that HCC might preferentially develop in patients whose immune backgrounds are already affected prior to DAA exposure.

Considering that before DAA administration, the patient in this case report had persistently normal values of serum aminotransferases during 15 years of surveillance at biannual intervals, the onset of acute hepatitis 2 weeks after starting treatment with LDV/SOF when HCV-RNA tested negative points to drug-induced AIH as a culprit. Furthermore, even if serum autoantibodies were not tested before LDV/SOF therapy for HCV, baseline liver biopsy and blood tests ruled against the coexistence of chronic hepatitis C with AIH. On the other hand, the fact that our patient developed a concurrent ITP is consistent with AIH being frequently associated with extrahepatic autoimmune disorders, such as rheumatoid arthritis, Sjögren’s syndrome, and chronic thyroiditis. The association of ITP with AIH has been reported at a prevalence of around 2\%\(^{24}\) whereas it is a well-documented complication of HCV infection, ranging from 3\% to 20\% depending on the geographic area.\(^{25}\) While the true origin of thrombocytopenia seen in our patient remains elusive, i.e., autoimmune-associated versus...
virus-associated ITP,\(^{25}\) we outline that its presence stands as a marker of autoimmunity that may herald development of autoimmune disease following a DAA-driven imbalance of the immune system.

Although firm experimental evidence supporting a link between rapid HCV clearance and \textit{de novo} autoimmune diseases is still lacking, the patient described here with chronic hepatitis C associated with ITP might well represent a candidate predisposed to develop AIH with rapid suppression of HCV with DAA therapy. This case report further emphasizes the need for patients with either laboratory or clinical signs of autoimmunity to be carefully monitored for the risk of developing AIH during DAA therapy of HCV.

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