CASE REPORT

A case with acute-on-chronic liver failure receiving liver transplantation during daclatasvir and asunaprevir therapy in chronic hepatitis C patient

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Abstract

We report a case with hepatitis C virus genotype 1b liver cirrhosis who received liver transplantation because of acute-on-chronic liver failure during daclatasvir (DSV) and asunaprevir (ASV) combination therapy. To our knowledge, this is the first case received liver transplantation during DSV + ASV therapy. Therefore, clinicians should pay particular attention to the possibility of acute liver failure during DSV and ASV combination therapy.

Key words: Chronic hepatitis C; liver failure: daclatasvir; asunaprevir

Introduction

The combinations of direct-acting antivirals can achieve a high rate of sustained virologic response in patients with hepatitis C virus (HCV) [1–3]. Daclatasvir (Daklinza; Bristol-Myers Squibb) and asunaprevir (Sunvepra; Bristol-Myers Squibb) (DSV + ASV) combination therapy has been reported to be highly effective in HCV genotype 1b infection [3, 4]. However, elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most frequent adverse events [3, 4]. Herein, we report a first case with an HCV-related liver cirrhosis patient who received liver transplantation because of impending liver failure during DSV and ASV combination therapy.

Case presentation

A 68-year-old peginterferon-experienced man with genotype 1b HCV infection with compensated liver cirrhosis received daclatasvir (60 mg once daily) and asunaprevir (100 mg twice daily) combination therapy. He had no history of heavy alcohol drinking, drug allergies or fatty liver diseases. Initial laboratory data were as follows: AST 80 IU/L, ALT 20 IU/L, total bilirubin 1.0 mg/dL, albumin of 3.9 g/dL and international normalization ratio (INR) 1.1, white blood cell count (WBC) 2480/μL, eosinophil 3.2%, hemoglobin 15 g/dL, platelet count 71 000/μL and creatinine 0.9 mg/dL. The HBsAg and anti-HBs were negative and positive, respectively. Both IgG anti-HAV and anti-HCV were positive. The level of HCV RNA was 2.5 × 10^{6} IU/mL. Initial
abdominal computed tomography showed fissure widening and surface undulation of the liver with splenomegaly. There is no evidence of ascites, venous distension of esophagus and stomach. This patient's Child-Turcotte-Pugh score was 5.

After 4 weeks of DSV + ASV combination therapy, HCV RNA was not detected (<12 IU/mL). Serum AST and ALT levels were 72 IU/L and 80 IU/L, respectively. At 5 weeks of therapy, results were as follows: AST 111 IU/L, ALT 99 IU/L, albumin 3.7 g/dL and bilirubin 1.5 mg/dL. At 8 weeks of therapy, the patient was hospitalized for complained severe nausea. He denied heavy alcohol drinking, herbal-medicine use or any other hepatotoxic drug use. Body temperature was 36.6°C, sclera was icteric and abdomen was distended. The laboratory data were as follows: AST 1207 IU/L, ALT 1451 IU/L, albumin 2.6 g/dL, total bilirubin 21.7 mg/dL, INR 2.69, sodium 135 mmol/L, creatinine 0.88 mg/dL, WBC 4600/μL, eosinophil 3.1%, platelet counts 94 x 10^3/μL and bilirubin 15.6 mg/dL. The HCV RNA was detected in low levels (68 IU/mL) only once at 8 weeks of therapy. After then, HCV RNA was not detected anymore without antiviral therapy. DSV + ASV combination therapy stopped immediately. Further test results for other viral markers (hepatitis E virus, cytomegalovirus, Epstein-Barr virus and herpes simplex virus) and autoimmune markers (antinuclear antibody, anti-smooth muscle and anti-mitochondrial antibody) were negative. Abdominal computed tomography showed splenomegaly and ascites, without any evidence of biliary obstruction. The liver function tests did not improve even after supportive care. The results were as follows: AST 311 IU/L, ALT 446 IU/L, albumin 2.6 g/dL, total bilirubin 21.8 mg/dL (direct bilirubin 15.6 mg/dL), INR 3.14, ammonia 60 μmol/L, sodium 138 mmol/L, creatinine 1.06 mg/dL, platelet 81 x 10^3/μL and WBC 3300/μL (eosinophil 2.0%). The Child-Turcotte-Pugh score increased up to 14. Moreover, metal status changed into deep drowsy with rapid development of the hepatocellular dysfunction.

Three days after admission, the patient received a liver transplantation from a deceased donor. Macroscopic and microscopic findings of the explanted liver are shown in Figure 1. On the cut surface, the cirrhotic liver with fibrous scars and micronodularity was seen. Histologically, micronodules revealed severe lobular inflammation with lymphoplasmacytic infiltration and canalicular cholestasis. Four months after liver transplantation, laboratory test results were as follows: AST 18 IU/L, ALT 14 IU/L, albumin 0.7 mg/dL, total bilirubin 0.7 mg/dL, INR 1.1, WBC 2800/μL and platelets 131 x 10^3/μL. The clinical course of the patient is shown in Figure 2. HCV RNA was not detected without further antiviral therapy.

Discussion

In the clinical trials of DSV + ASV combination therapy, elevation of ALT occurred in 5–16% of patients and severe elevation
of ALT (≥5-fold the upper limit of the normal value) in 1–7% of patients [3, 4]. In most cases of ALT elevation during DSV + ASV combination therapy, ALT improved upon discontinuation of the therapy [3, 4]. Severe hepatotoxicity was reported in two patients who received DSV and ASV combination therapy [4, 5]. The liver injury in the previous two patients, who suffered from severe elevation of ALT, jaundice, high-fever eosinophilia and eosinophilic infiltration in the liver, suggests drug-induced immuno-allergic liver injury. However, the present case was not accompanied by fever, eosinophilia or eosinophilic infiltration in the liver. In this case, the exact mechanism of liver injury by ASV + DSV therapy is not known. But it is possible that this event is the result of idiosyncratic metabolic responses or unexpected reactions to medication, although the precise pathogenesis is poorly understood. Even though transient low levels of viremia were observed, the viremia did not persist for long. We speculated that HCV RNA might leak from a necrotic liver during severe liver damage. After discontinuation of DSV + ASV combination therapy, liver function tests did not improve. The patient received liver transplantation because of acute-on-chronic liver failure. Therefore, clinicians should pay particular attention to the possibility of severe liver injury during DSV + ASV combination therapy. If liver function abnormality persists or decompensated liver signs such as ascites appear, an adequate evaluation of the liver function and disease status should be evaluated by a specialist.

Conflicts of interest
None declared.

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