CASE REPORT

Long-term Combined Therapy with Very-low-dose Peginterferon and Ursodeoxycholic Acid Decreased the Spleen Size in a Patient with Hepatitis C Virus-related Cirrhosis

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Abstract

A 42-year-old woman with hepatitis C virus-related cirrhosis underwent peginterferon alpha-2b therapy combined with ribavirin but could not achieve a sustained viral response. Following discontinuation of this combined therapy, the patient’s serum transaminase levels suddenly became elevated. Therefore, the administration of very-low-dose peginterferon alpha-2a with ursodeoxycholic acid was introduced. Thereafter, the patient’s serum transaminase levels gradually improved. Four years later, enhanced computed tomography showed shrinkage of the spleen and enlargement of the liver. Long-term combined therapy with very-low-dose peginterferon and ursodeoxycholic acid may be effective not only in preventing disease progression, but also in improving portal hypertension in patients hepatitis C virus-related cirrhosis.

Key words: cirrhosis, hepatitis C, peginterferon, platelet, portal hypertension, ursodeoxycholic acid

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Introduction

It is estimated that 3-4 million people are newly infected with the hepatitis C virus (HCV) each year worldwide (1). Approximately 130-170 million people are chronically infected with HCV and at risk of developing liver cirrhosis and/or hepatocellular carcinoma. More than 350,000 people die from HCV-related liver diseases each year.

Recently, several new, potent anti-HCV agents have been developed (2-4). These new agents will enable approximately 80% of patients to achieve sustained viral responses (SVRs) thus leading to improvements in liver fibrosis and a reduced risk of mortality (5, 6). Unfortunately, the remaining patients will be unable to achieve a sustained viral response and may develop chronic liver failure and/or hepatocellular carcinoma.

The ability of low-dose maintenance therapy with peginterferon to improve the prognosis in patients who fail to achieve an SVR with interferon (IFN) treatment has been investigated in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial (7) and the Evaluation of PegIntron in Control of Hepatitis C Cirrhosis (EPIC3 program (8). Currently, the efficacy of low-dose maintenance therapy with peginterferon remains controversial.

In this report, we describe the case of an HCV-related cirrhotic woman who showed shrinkage of the spleen after undergoing four years of combined therapy with very-low-dose peginterferon and ursodeoxycholic acid.

Case Report

A 42-year-old woman consulted our hospital because abnormalities in her serum transaminase levels had been pointed out at a medical checkup. There was no history of alcohol abuse or blood transfusions. The laboratory data obtained at the first visit are shown in Table: platelet count: 12.2×10^4/mm^3, aspartate aminotransferase: 286 IU/L, alanine

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The patient was diagnosed with chronic hepatitis C based on positivity of serum anti-hepatitis C antibodies and HCV-RNA. The patient’s HCV genotype was 1b. There were no intra-hepatic masses on enhanced computed tomography (CT) despite elevation of the serum alpha-fetoprotein level. However, splenomegaly measuring 102 mm in diameter and 231 mL in volume was observed (Fig. 1A). The volume of the liver was 955 mL. Liver biopsy specimens obtained under ultrasonography guidance showed liver cirrhosis with inflammatory cell infiltration and interface hepatitis (Fig. 2).

Combined therapy with peginterferon alpha-2b at a dose of 60 μg weekly and ribavirin at a dose of 400 mg daily was introduced. Twenty weeks later, the serum HCV-RNA disappeared. However, 36 weeks after the introduction of the combined therapy, serum HCV-RNA reappeared. Therefore, the therapy was discontinued because the possibility of achieving an SVR was considered to be very low (Fig. 3).

Four weeks after the discontinuation of the combined therapy, the patient’s serum transaminase levels suddenly became elevated. The administration of ursodeoxycholic acid (UDCA) at a dose of 600 mg daily was introduced; however, the serum transaminase levels did not improve. Therefore, the administration of peginterferon alpha-2a at a dose of 180 μg weekly and ribavirin at a dose of 800 mg daily was introduced. Six weeks later, the serum HCV-RNA disappeared. Therefore, the therapy was continued because the possibility of achieving an SVR was considered to be very high (Fig. 3).
Introduction of combined therapy with peginterferon alpha-2a and UDCA, the aspartate aminotransferase to platelet ratio index the combined therapy with peginterferon alpha-2a and min levels increased by degree. During the administration of pertension and that the SVR rate achieved with antiviral therapy with peginterferon and ribavirin is as low as 14%. Gentilini et al. (10) reported that esophageal varices and ascites worsen the prognosis in cirrhotic patients. Therefore, in order to improve the prognoses of cirrhotic patients, treating portal hypertension is important. Generally, beta-blockers are administered in order to reduce portal venous pressure and prevent deterioration of esophageal varices (11, 12). The efficacy of simvastatin and losartan in treating portal hypertension has been reported (13, 14). On the other hand, is IFN therapy effective for portal hypertension? Portal venous pressure is reduced in HCV-related cirrhotic patients achieving an an study revealed that low-dose maintenance therapy with peginterferon reduces the frequency of adverse events related to portal hypertension such as ascites and variceal bleeding (8). In addition, in the present case, long-term combined therapy with very-low-dose peginterferon and UDCA decreased the spleen size and increased the peripheral platelet count. Portal venous pressure is correlated with spleen volume (16). Therefore, IFN may be effective for treating portal hypertension in some cirrhotic patients.

What kind of mechanism decreased the spleen size in the present case? The stage of liver fibrosis and the degree of inflammatory activity are significantly correlated with portal vein pressure (17). Furthermore, showing a response to IFN treatment is associated with reductions in portal vein pressure. In particular, sufficient improvements in hepatic inflammation result in great reductions in portal vein pressure (18). In the present case, the serum ALT levels fluctuated below 19 IU/L for the last two years despite the presence of continuous HCV viremia. The upper limit for a healthy serum ALT level in women has been reported to be 19 IU/L (19). Therefore, during the last two years, intrahepatic inflammation was considered to be completely suppressed. Sustained suppression of intrahepatic inflammation despite the presence of continuous HCV viremia improves liver fibrosis (20). In the present case, APRI, which has been reported to be correlated with the stage of liver fibrosis

Discussion

Portal hypertension, which leads to thrombocytopenia due to the development of splenomegaly, ascites and esophageal varices, is an important prognostic factor for HCV-related cirrhosis. Reiberger et al. (9) reported that thrombocytopenia is frequently observed in cirrhotic patients with portal hypotension and that the SVR rate achieved with antiviral therapy with peginterferon and ribavirin is as low as 14%. Gentilini et al. (10) reported that esophageal varices and ascites worsen the prognosis in cirrhotic patients. Therefore, in order to improve the prognoses of cirrhotic patients, treating portal hypertension is important. Generally, beta-blockers are administered in order to reduce portal venous pressure and prevent deterioration of esophageal varices (11, 12). The efficacy of simvastatin and losartan in treating portal hypertension has been reported (13, 14). On the other hand, is IFN therapy effective for portal hypertension? Portal venous pressure is reduced in HCV-related cirrhotic patients achieving an an study revealed that low-dose maintenance therapy with peginterferon reduces the frequency of adverse events related to portal hypertension such as ascites and variceal bleeding (8). In addition, in the present case, long-term combined therapy with very-low-dose peginterferon and UDCA decreased the spleen size and increased the peripheral platelet count. Portal venous pressure is correlated with spleen volume (16). Therefore, IFN may be effective for treating portal hypertension in some cirrhotic patients.

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in patients with chronic hepatitis C (21), was gradually decreased during the long-term combined therapy with very-low-dose peginterferon and UDCA. In particular, the APRI fluctuated below 1.0 during the last year. Therefore, we speculate that long-term combined therapy with very-low-dose peginterferon and UDCA improves liver fibrosis as a result of sustained suppression of intrahepatic inflammation, which leads to reduction of portal vein pressure and shrinkage of the spleen.

In addition, long-term combined therapy with very-low-dose peginterferon and UDCA led to enlargement of the liver volume in the present case. Liver volume is correlated with liver weight (22), and liver weight is correlated with the number of hepatocyte in the liver (23). Therefore, enlargement of liver volume is considered to be due to liver regeneration. Liver regeneration decreases portal venous pressure (24). Hence, in the present case, liver regeneration may have contributed to shrinkage of the spleen.

Peginterferon alpha-2a has been reported to exert more potent anti-viral effects in patients with chronic hepatitis C than peginterferon alpha-2b (25, 26). Did the change from peginterferon alpha-2b to peginterferon alpha-2a affect the patient’s clinical course in the present case? Peginterferon alpha-2a was administered at a dose of 90 μg every four weeks for the last three years. The doses of peginterferon alpha-2a administered in the present case were very low. Furthermore, the serum concentrations of peginterferon alpha-2a have been reported to return to near the initial values 336 hours after injection (27). Therefore, we speculate that the anti-viral effects of peginterferon alpha-2a are not maintained for four weeks after injection. On the other hand, in the present case, UDCA monotherapy was not effective in achieving normalization of the serum ALT levels. IFN therapy downmodulates the serum levels of Th1 and Th 17 pro-inflammatory cytokines (28, 29). In addition, UDCA has been shown to decrease the production of interleukin-2 in lymphocytes (30). Therefore, the sustained normalization of the serum ALT levels observed in the present case is considered to be due to the immunomodulatory effects of peginterferon alpha-2a and UDCA. However, it is necessary to investigate whether additional administration of UDCA and peginterferon is more effective than treatment with peginterferon alone.

In conclusion, long-term combined therapy with very-low-dose peginterferon and UDCA may be effective not only in preventing disease progression, but also in improving portal hypertension in patients with HCV-related cirrhosis. However, this is a case report, and a second liver biopsy was not performed in the present case. Therefore, prospective studies of large study populations undergoing paired liver biopsies are needed in order to confirm these findings.

The authors state that they have no Conflict of Interest (COI).

References