LETTER TO THE EDITOR

The use of partial splenic artery embolization made it possible to administer interferon and ribavirin therapy in a liver transplant patient with fibrosing cholestatic hepatitis C complicated with thrombocytopenia

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Hepatitis C virus (HCV) cirrhosis is a leading indication for orthotopic and living related liver transplantation (LT) [1]. However, the recurrence of HCV viremia is nearly universal after LT [2], and more than half of all patients develop clinical liver disease within a few years [3,4]. Although recurrent liver disease is clinically mild but progressive in most of these patients, a small number of these patients exhibit a fulminant course with progression to death, which is called fibrosing cholestatic hepatitis (FCH) [5,6]. Recently, interferon (IFN) and ribavirin have been shown to be effective in ameliorating hepatocellular injury in recurrent HCV after LT [7–9]. However, the adverse effects associated with this therapy, such as anemia, leukopenia, thrombocytopenia, make it necessary to discontinue this treatment interruption in a significant proportion of cases and the resulting poor adherence also reduces the efficacy of antiviral therapy in LT recipients in which a sustained virological response occurs in <20% of the treated patients [7–9]. It thus remains a big problem regarding how to manage these side effects in order to allow such patients to complete the IFN and ribavirin therapeutic regimen.

In this letter, we report a patient with FCH because of hepatitis C after LT, who successfully overcame thrombocytopenia as the result of IFN therapy after pretreatment with transcatheter partial splenic embolization (PSE). As a result, she was able to complete the IFN and ribavirin therapeutic regimen without any complications.

A 54-year-old woman with liver cirrhosis secondary to an HCV infection underwent a living related liver LT in August 2002. She was discharged from the hospital without any notable postoperative complications with immunosuppression consisting of FK506 (2 mg/day) and prednisolone (PSL) (5 mg/day). However, elevated liver function tests had been noted throughout the 1-year follow-up period after LT. In March 2003, at 7 months after LT, the first liver biopsy was performed. The liver specimen showed chronic active hepatitis caused by an HCV infection, mild activity and slight fibrosis with piecemeal necrosis. Then, IFN monotherapy with natural IFNα, three mega unit (MU) three times/week, was started. Two weeks later, however, her platelet count decreased to 30,000/mm^3, which thus made it necessary to discontinue the IFN therapy. Thereafter, the liver function tests remained abnormal. In August 2003, at 12 months after LT, her laboratory data showed markedly elevated levels of serum alkaline phosphatase (ALP) 1153 IU/l, r-glutanyl transpeptidase (rGTP) 2110 IU/l, and total bilirubin (T-Bil) 7.9 mg/dl, whereas the serum asparate aminotransferase (AST) 131 IU/l and the alanine aminotransferase (ALT) 75 IU/l level both moderately increased. On admission her laboratory data showed 2010 KIU/ml of HCV-RNA, genotype 2A, negative HBs-Ag and positive HBs-Ab. A liver biopsy performed on the following day revealed no evidence of rejection but progressive fibrosis with lobular regeneration, moderate inflammatory cell infiltration, and neo-ductular proliferation with hypercellularity. She was diagnosed to have FCH. Antiviral treatment, especially IFN and ribavirin combination should be administrated to such cases, as FCH is reported to be associated with a high viral load in the tissue and in the serum [6]. As a result, we decided to perform PSE prior to the therapy, as previous IFN treatment had been discontinued because of thrombocytopenia. A gel foam spongel with antibiotics (1 g of Cefazolin sodium) and contrast material was infused from the branch of splenic artery to embolize 50% of her spleen. No notable adverse effects were observed. As expected, her platelet count increased from 45 000 to 120 000/mm^3 2 weeks after PSE. We then started IFN and ribavirin combination therapy, IFN α2b, 3 MU three times/week and ribavirin 400 mg/day, in October 2003. As her platelet count did not deteriorate to <90 000/mm^3, we therefore completed the 8 month, combination therapy regimen in May 2004. The T-Bil, AST and ALT levels all normalized and the serum HCV-RNA also became negative 3 weeks after the initiation of the therapy. In May 2004, HCV RNA in the serum and liver tissue was still negative, and, as a result,

the treatment regimen was successfully completed. In May 2005, 12 months after the end of therapy, the patient's liver function tests were still normal and the serum HCV RNA level was continuously negative.

We herein showed our successful clinical observations in a patient with FCH because of hepatitis C after LT, who successfully overcame thrombocytopenia induced by IFN and ribavirin therapy by pretreatment with PSE, and thereafter was able to complete the IFN and ribavirin therapy for 8 months. This observation showed two important findings. Firstly, that IFN and ribavirin therapy was effective for FCH caused by hepatitis C. Secondly, PSE could be a promising optional treatment when thrombocytopenia causes IFN therapy to be discontinued.

Recently, IFN and ribavirin, when used as a therapy for post-LT hepatitis C, have been shown to reduce the serum ALT and HCV-RNA levels [10]. Especially, when a severe type of recurrent hepatitis C, such as FCH, occurred, these patients should be treated anti-viral therapy or a drastic reduction in immunosuppression, as the etiology is thought to be associated with high HCV viremia levels [4]. In our case, at 7 months after LT, we initially treated the patients with IFN monotherapy for her recurrent hepatitis C. However, the IFN therapy had to be discontinued within 2 weeks because of thrombocytopenia, despite the fact that both the transaminase levels and HCV viremia had been improving. Five months later, her next liver biopsy showed severe progressive fibrosis, a precirrhosis state, and FCH was thus diagnosed. Although several case reports have described that FCH improved after IFN and Ribavirin therapy, the effectiveness of this therapy for FCH remains unclear. However, since we did not have any other therapeutic option, we decided to treat her with IFN and ribavirin combination therapy. Fortunately, owing to the IFN and ribavirin therapy, her liver function test recovered to almost normal levels and HCV-RNA in the serum disappeared. The liver function data were observed to be continuously normal after the therapy for 12 months. In order to successfully complete the combination therapy, the thrombocytopenia had to improve. As, thrombopoietin preparation is not available at the present time, a splenectomy and PSE were thus considered as options to increase her platelet count. However, very few reports have demonstrated the effectiveness, safety and adverse effects of these therapies in post-LT patients. As splenectomy was reported to have such complications as a serious infection and sepsis with a high frequency, ranging from 0% to 60% of post-LT patients in previous reports [11–13]. On the other hand, PSE has been reported to be relatively safe in comparison to a splenectomy; only two serious adverse effects, one with abdominal pain due to PSE and one with hepatic artery thrombosis, out of 21 patients from five reports had been observed, and these complications were not fatal [14–18]. The usefulness of PSE before peg-interferon plus ribavirin has recently been reported in three LT patients [18]. In the other disease patients, PSE was usually safely performed, although some non fatal complications, such as fever, abdominal pain etc, were observed [19,20]. In addition, as the effect of PSE for thrombocytopenia was usually maintained for >6 months [21], we thus decided to perform PSE for the pretreatment of IFN and ribavirin therapy. As expected, the platelet count increased, and we could complete the 8-month regimen for IFN and ribavirin therapy. In conclusion, IFN and ribavirin therapy was effective for FCH because of hepatitis C, and PSE is therefore considered to be a promising and effective adjuvant modality, in LT patients with hepatitis C recurrence, which allows them to overcome thrombocytopenia before undergoing IFN and ribavirin therapy.

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