Partial Splenic Embolization Facilitates the Adherence to Peginterferon in Chronic Hepatitis C with Thrombocytopenia

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Abstract

Objective Platelet counts before starting the treatment affect the discontinuation and dose reduction of peginterferon in chronic hepatitis C. Thrombocytopenia leads to failure to achieve sustained virological response. This study was undertaken to evaluate the efficacy of partial splenic embolization (PSE) prior to starting peginterferon therapy combined with ribavirin in chronic hepatitis C patients showing thrombocytopenia.

Patients and Methods We compared the clinical features of 11 patients receiving PSE (PSE group) prior to starting the combined therapy with those of 13 patients not receiving PSE (non-PSE group). All of the patients showed platelet counts ≤ 12x10⁴/mm³ and serum hepatitis C virus-RNA levels ≥ 100 KIU/mL at baseline. The end-point of PSE was a volume of splenic infarction over 75%. Peginterferon alpha-2b at a dose of 1.2 μg/kg was administered by subcutaneous injection once a week. The dose of ribavirin was weight adjusted.

Results PSE was successfully performed without serious adverse events. The period from PSE to starting the combined therapy was 14 (6-27) days. After PSE, platelet counts were significantly increased. In PSE group, platelet counts during the combined therapy were maintained above those at baseline. In non-PSE group, platelet counts at the 2nd week after the start of the combined therapy significantly decreased to less than those at baseline. Overall, 80% adherence to expected peginterferon dose was not achieved in 5 patients (45%) of PSE group and in 11 (85%) of non-PSE group (p=0.043).

Conclusion Increased platelet counts after PSE facilitates the adherence to peginterferon therapy in chronic hepatitis C patients with thrombocytopenia.

Key words: chronic hepatitis C, partial splenic embolization, peginterferon, thrombocytopenia


Introduction

Worldwide, approximately 170 million people are chronically infected with hepatitis C virus (HCV) (1). Chronic HCV infection results in the progression to liver cirrhosis and the development of hepatocellular carcinoma. The incidence of hepatocellular carcinoma in cirrhotic patients with chronic HCV infection is approximately 5% per year (2).

Interferon therapy reduces the incidence of hepatocellular carcinoma, especially in patients achieving sustained virological response (SVR) (3, 4). The current standard therapy in patients with chronic hepatitis C is the combination with peginterferon and ribavirin (5). SVR rate is approximately 50% in patients infected with HCV genotype 1 receiving the combined therapy for 48 weeks and approximately 80% in those infected with HCV genotype 2 receiving the combined therapy for 24 weeks (5).
On the other hand, the HALT-C trial (6) revealed that, in patients with platelet counts at baseline ≤12x10^9/mm^3, SVR rate was reported to be 11%, similar to the low SVR rate in cirrhotic patients, and that platelet counts at baseline affected the discontinuation and dose reduction of antiviral therapy. Platelet count at baseline is an important factor affecting the efficacy of antiviral therapy.

Thrombocytopenia, which is a common feature in advanced chronic hepatitis and liver cirrhosis, is considered because of the increasing platelet pool in the enlarged spleen, reduction of thrombopoietin production in the failing liver, and platelet destruction due to an immunological mechanism. Partial splenic embolization (PSE) is minimally invasive and effective for thrombocytopenia caused by hypersplenism and for improving liver function (7, 8). In this study, we evaluated the efficacy of PSE prior to starting the combined therapy with peginterferon and ribavirin in chronic hepatitis C patients with thrombocytopenia.

**Materials and Methods**

**Patients**

Twenty-four patients with chronic hepatitis C admitted to Mitoyo General Hospital between April 2005 and December 2008, who showed thrombocytopenia (platelet count at baseline ≤12x10^9/mm^3), serum HCV-RNA level of 100 KIU/mL or higher, and enlarged spleen (≥100 mm in diameter) evaluated by computed tomography, were included in this study. All of the patients received the combined therapy of peginterferon alpha-2b and ribavirin. Of the 24 patients, 11 patients received PSE prior to starting the combined therapy (PSE group). In contrast, the other 13 patients received the combined therapy without PSE (non-PSE group).

Patients with hepatocellular carcinoma or other chronic liver disease, such as hepatitis B, primary biliary cirrhosis, and autoimmune hepatitis, were excluded from this study.

**Partial splenic embolization**

Splenic artery angiography was obtained using the intra-arterial administration of 61.24% iopamidol (Iopamiron 300; Bayer Schering Pharma, Osaka, Japan) at a rate of 2 mL/sec (for total of 10 mL) using a digital subtraction angiographic device (Phillips Electronics Japan, Tokyo, Japan). We used 4F catheters (MP-YT5.0F; MP-YT5.0F1-805-S, RM3; Cathex, Tokyo, Japan) and 2.3F micro catheters (SP cathe- ter; TERUMO, Tokyo, Japan). The transcatheter arterial embolization was performed by injecting gelatin sponge particles (SPONGEL; Yamanouchi, Tokyo, Japan) and placing platinum coils ranging from 3 to 6 mm in diameter (TruFill; Cordis Miami Lake, FL, USA) in the branches of the splenic artery. The end-point of PSE was a volume of splenic infarction over 75% to prevent relapse of hypersplenism. The infarction volume was estimated by a selective angiogram showing the reduction in the splenic vascularization and the residual spleen parenchyma.

**Therapy for hepatitis C virus**

The combination of peginterferon alpha-2b (Pegintron; Schering-Plough Pharmaceutical, Osaka, Japan) and ribavirin (Rebetol; Schering-Plough Pharmaceutical) was used. Patients infected with HCV genotype 1 were scheduled to receive the combined therapy for 48 weeks. Patients infected with HCV genotype 2 were scheduled to receive the combined therapy for 24 weeks. Peginterferon alpha-2b at a dose of 1.2 μg/kg was administered by subcutaneous injection once a week. The dose of ribavirin was weight adjusted: 400 mg for weight 50 kg or less, 600 mg for weight 50-60 kg, and 800 mg for weight 60 kg or above.

When the absolute counts of neutrophil or platelet were less than 750/mm^3 or 8x10^9/mm^3, respectively, the dose of peginterferon alpha-2b was decreased by 50%. If the absolute counts of neutrophil or platelet were less than 500/mm^3 or 5x10^9/mm^3, respectively, peginterferon alpha-2b was discontinued. When hemoglobin concentrations decreased to less than 10 g/dL, ribavirin of 200 mg/day was reduced. If hemoglobin concentrations were less than 8.5 g/dL, ribavirin was discontinued.

**Analytical assessment**

The end-point was the achievement of the adherence to the combined therapy with peginterferon alpha-2b and ribavirin, defined as the maintenance of ≥80% of expected peginterferon alpha-2b and ribavirin dosage during the combined therapy. Complete blood count and liver function tests were obtained before PSE (at baseline), before starting the combined therapy (after PSE), and at the 2nd, 4th, 8th, 12th, and 24th week after starting the combined therapy.

SVR was defined as serum HCV-RNA below the detection limit at 24th week after the completion of the combined therapy. Relapse was defined as reappearance of serum HCV-RNA after the completion of the combined therapy. Non-response was defined as failure to clear serum HCV RNA at the 24th week after starting the combined therapy (5).

**Statistical analysis**

Statistical analysis was performed using the SPSS statistical program (10.0.1 J; SPSS, Chicago, IL, UAS). Continuous variables were expressed as medians and ranges. Changes in hematological parameters and liver function tests during the clinical course were evaluated by the Wilcoxon test for two-related samples. The significance of differences in continuous variables between two groups was evaluated by the Mann-Whitney U test. Dichotomous variables were compared by χ²-test. P-values<0.05 were considered significant.

**Results**

Clinical characteristics and laboratory data at baseline are shown in Table 1, 2. Non-response to the previous interferon...
therapy was shown in 4 patients (36%) of PSE-group and none (0%) of non-PSE group (p=0.017). Seven patients (64%) of PSE group and 10 patients (77%) of non-PSE group were naive cases (p=0.48). HCV genotype 1 was found in 10 patients (91%) of PSE group and 8 (62%) of non-PSE group (p=0.098). Spleen size at baseline was 120 (100-144) mm in PSE group and 105 (100-144) mm in non-PSE group (p=0.098). Gender, man/female 5/6 6/7 0.97 HCV genotype, 1 / 2 10/1 8/5 0.098 HCV-RNA, KIU/mL 420 (100-550) 456 (100-510) 0.64

*HCV, hepatitis C virus; PSE, partial splenic embolization.*

### Table 2. Changes of Hematological and Biochemical Parameters before and after PSE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PSE group (n = 11) Before PSE</th>
<th>PSE group (n = 11) After PSE</th>
<th>Non-PSE group (n = 13) Before PSE</th>
<th>Non-PSE group (n = 13) After PSE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte counts, /mm³</td>
<td>4717 (2950-6330)</td>
<td>7199 (2840-11800)**</td>
<td>4447 (2600-6660)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil counts, /mm³</td>
<td>2584 (1752-3800)</td>
<td>4619 (1874-8000)**</td>
<td>2581 (1170-4416)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin concentrations, g/dL</td>
<td>12.7 (11.2-15.1)</td>
<td>12.2 (11.2-15.1)</td>
<td>13.8 (11.2-17.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet counts, ×10³/mm³</td>
<td>9.3 (6.1-11.7)</td>
<td>19.1 (11.3-30.2)**</td>
<td>11.1 (10.1-12.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>1.18 (0.50-2.10)</td>
<td>1.32 (0.6-2.3)</td>
<td>0.9 (0.5-1.5)</td>
<td></td>
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</tr>
<tr>
<td>Aspartae aminotransferase, IU/L</td>
<td>67 (19-127)</td>
<td>63 (15-123)</td>
<td>90 (34-210)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase, IU/L</td>
<td>72 (18-144)</td>
<td>48 (13-97)*</td>
<td>115 (33-376)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT-INR</td>
<td>1.27 (1.05-1.44)</td>
<td>1.34 (1.15-1.76)</td>
<td>1.18 (0.98-1.31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05; **, p < 0.01. Each parameters was compared with those before PSE in PSE group. PSE, partial splenic embolization; PT-INR, international normalized ratio of prothrombin time.

During the combined therapy, the decrease of neutrophil count to less than 750/mm³ was shown in one patient (9%) of PSE group and one patient (8%) of non-PSE group (p= 0.90). Anemia defined as the decrease of hemoglobin concentration to less than 10.0 g/dL was shown in 6 patients (55%) of PSE group and 4 patients (31%) of non-PSE group (p=0.24). In patients developing anemia, the period from the start of the combined therapy to the development of anemia was 9 (5-13) weeks in PSE group and 6 (4-9) weeks in non-PSE group (p=0.17). The decrease of platelet count to less than 8×10⁵/mm³ was shown in 4 patients (36%) of PSE group and 10 patients (77%) of PSE group (p = 0.045). In these patients, the period from the start of the combined therapy to the decrease of platelet count to less than 8×10⁵/mm³ was 2.5 (1-4) weeks in PSE group and 3.5 (1-23) weeks in non-PSE group (p=0.39).

Overall, 80% adherence to expected peginterferon alpha-2b dose was not achieved in 5 patients (45%) of PSE group and 11 patients (85%) of non-PSE group (p=0.043). On the other hand, 80% adherence to expected ribavirin dose was not achieved in 7 patients (64%) of PSE group and 5 patients (38%) of non-PSE group (p=0.22).

In PSE group, SVR was achieved in 2 of 10 patients (20%) infected with HCV genotype 1 and one patients (100%) infected with HCV genotype 2. In non-PSE group, 4 of 8 patients (50%) infected with HCV genotype 1 and 2 of 5 patients (40%) infected with HCV genotype 2 achieved SVR. Between PSE group and non-PSE group, there were no difference in SVR rate in patients infected with HCV.
genotype 1 and those infected with HCV genotype 2, respectively.

Discussion

In order to improve the SVR rate, 80% adherence to expected peginterferon and ribavirin dose for the duration of treatment is necessary (9). On the other hand, in chronic hepatitis C, platelet counts are correlated with the degree of liver fibrosis (10). Patients with advanced fibrosis or cirrhosis show lower platelet counts. Thrombocytopenia is frequently associated with dose reduction of peginterferon (11). Thus, in patients with the advanced disease, a countermeasure to thrombocytopenia is important to facilitate the adherence to the therapy and improve the SVR rate. This study showed that, in chronic hepatitis C patients with thrombocytopenia, PSE increased platelet counts. Furthermore, platelet counts during the combined therapy significantly decreased to less than those at baseline in non-PSE group; however those did not in PSE group. The maintenance of platelet counts during the combined therapy in PSE group led to the facilitation of the adherence to peginterferon and ribavirin may lead to the improvement of the SVR rate through the facilitation of the adherence to peginterferon in patients with thrombocytopenia.

In the present report, we showed a comparative study of the efficacy of PSE prior to starting the combined therapy with peginterferon and ribavirin in chronic hepatitis C patients with thrombocytopenia. To date, several papers on the efficacy of PSE prior to starting interferon therapy have been already reported (12-16). First, Moreno et al (12, 13) reported the usefulness of PSE prior to starting the combined therapy with peginterferon and ribavirin in HCV cirrhotic patients with thrombocytopenia; however, their reports were one-arm studies and did not have a non-PSE group. Furthermore, although the currently recommended therapy of chronic HCV infection is the combination of peginterferon and ribavirin (5), the study population of other 2 reports mainly consisted of patients treated with conventional interferon or consensus interferon (14, 15). Thus, until recently, few comparative studies of the efficacy of PSE prior to starting the combined therapy with peginterferon and ribavirin in chronic hepatitis C patients with thrombocytopenia have been reported. Recently, Tahara et al (16) reported a comparative study of this point. Their report indicated that PSE maintained higher platelet counts during the combined therapy with peginterferon and ribavirin and it fa-

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**Figure 1.** Box plots indicate the median, interquartile range, and 90 percentile range of hematological parameters during the clinical course. Each parameter was compared with those at baseline. PSE: partial splenic embolization, TW: treatment week, *p<0.05, **p<0.01, □ PSE group, □ non-PSE group.
cilitated the adherence to peginterferon. These results are consistent with those of this study.

Generally, two procedures, PSE and splenectomy, are performed as a countermeasure to thrombocytopenia. A recent comparative study of PSE and splenectomy (17) showed that the increase in platelet counts was greater in patients receiving splenectomy than in those receiving PSE, and that splenectomy was superior in the facilitation of the adherence to interferon therapy to PSE. However, the increased risk of life-threatening bacterial infection has been reported to persist for decades after splenectomy (18). Furthermore, in another comparative study of PSE and splenectomy, PSE was reported to be a simple, rapid procedure, easily performed under local anesthesia, incurs less morbidity, and there was no need for blood transfusion (7). Increased platelet counts after PSE were reported to be maintained during one year after PSE (8). In this study, increased platelet counts after PSE could facilitate the adherence to peginterferon alpha-2b for 48 weeks. Thus, we consider that PSE prior to starting the combined therapy is a safe and useful procedure in patients with thrombocytopenia.

In the present study, PSE prior to starting the combined therapy with peginterferon alpha-2b and ribavirin did not increase the SVR rate despite of the improvement of the adherence to peginterferon alpha-2b. We consider that it was because patients showing non-response to the previous interferon therapy was more in PSE group. Recently, amino acid substitutions at position 70 in the HCV core region and interleukin-28B polymorphism were reported to be associated with the response to the interferon therapy (19-23). In this study, these factors were not checked. Hereafter, it should be investigated whether PSE prior to starting the combined therapy improved the SVR rate independent of these factors.

A previous report (24) showed that increased hemoglobin concentrations after PSE continued during several years. However, in this study, PSE prior to starting the combined therapy did not progress the adherence to ribavirin. Recently, erythropoietic agents are shown to be effective in treating anemia, preventing ribavirin dose reduction, and improving patients’ quality of life during the combined therapy (25). Hereafter, erythropoietic agents will be expected to improve and prevent anemia during the combined therapy.

Improved liver function after PSE or splenectomy was shown to be continued for several years in cirrhotic patients (24, 26). In this study, serum alanine aminotransferase levels were significantly decreased after PSE. However, in all patients receiving PSE, the combined therapy with peginterferon and ribavirin was performed. Interferon therapy influences liver function. Thus, in this study, the change of liver function for a long term after PSE was not fully evaluated.

In conclusion, PSE increased platelet counts in chronic hepatitis C patients with thrombocytopenia. Platelet counts which increased after PSE were maintained above those at baseline during the combined therapy with peginterferon alpha-2b and ribavirin and led to the progression of the adherence to peginterferon alpha-2b. However, in patients not receiving PSE, platelet counts during the combined therapy were significantly decreased to less than those at baseline, and most patients required the dose reduction of peginterferon alpha-2b. We consider that increased platelet counts after PSE will lead to allow the safe use of peginterferon and facilitate the adherence to peginterferon in chronic hepatitis C patients with thrombocytopenia. A further study with a larger number of patients is required to confirm these findings.

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

References