Safety and Efficacy of Partial Splenic Embolization in Telaprevir-based Triple Therapy for Chronic Hepatitis C

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Abstract

Objective Pegylated-interferon/ribavirin (peg-IFN/RBV) therapy with a protease inhibitor is the standard therapy for genotype 1b chronic hepatitis C. Despite improving treatment outcomes, patients with thrombocytopenia are often difficult to treat because interferon commonly exacerbates thrombocytopenia. In this study, partial splenic embolization (PSE) was performed in patients with hypersplenism-induced thrombocytopenia to determine the effectiveness of this method as a potential treatment.

Methods Patients were pretreated with PSE and then received triple combination therapy. The safety and efficacy of PSE was evaluated.

Results Eighteen patients were analyzed, including 12 patients with the interleukin 28B (IL28B) major genotype and 12 patients with the inosine triphosphatase (ITPA) major genotype. The median embolization rate with PSE was 70% (range: 40-85%). PSE increased the patients’ platelet counts from 71.5×10^3/μL (53-99×10^3/μL) to 121.5×10^3/μL (70-194×10^3/μL; p=0.0002). The patients’ platelet counts fluctuated above 50×10^3/μL during the treatment. Specifically, the increase in the platelet count was significantly associated with the ITPA major genotype compared with the minor genotype (p=0.0057 at 2 weeks, p=0.0031 at 3 weeks, and p=0.0148 at 4 weeks). Adherence to peg-IFN-α2b was sufficient (1.38 μg/kg/week). The rapid viral response rate was 72.2% (13/18), the end of treatment response rate was 88.9% (16/18), and the sustained virological response (SVR) rate was 66.7% (12/18). The SVR rate for patients with the IL28B major genotype was 83.3% (10/12). No adverse effect due to PSE pretreatment was found in any patients. Furthermore, no patient discontinued treatment due to thrombocytopenia.

Conclusion PSE, in conjunction with triple combination therapy, is a useful and safe method to treat genotype 1b chronic hepatitis C patients with hypersplenism-induced thrombocytopenia.

Key words: partial splenic embolization, telaprevir, pegylated-interferon, ribavirin, chronic hepatitis C, thrombocytopenia

(DOI: 10.2169/internalmedicine.54.3066)

Introduction

Up to 170 million people worldwide have chronic hepatitis C (1), which is known to progress to liver cirrhosis, a major risk factor for the development of hepatocellular carcinoma, over a time span of several decades (2, 3). Approximately 662,000 people around the world die of hepatocellu-
lar carcinoma annually (4). Patients with advanced fibrosis should be treated with antiviral therapy as soon as possible because of the increased risk of hepatocellular carcinoma (5-7). However, the efficacy of interferon (IFN)-based treatment is known to be reduced in patients with advanced fibrosis (8). Moreover, these patients often develop thrombocytopenia, which results in insufficient IFN-based antiviral therapy and poor treatment outcomes (9-13).

Therapeutic strategies have recently been reported for the induction of antiviral therapy following partial splenic embolization (PSE) or splenectomy in patients with advanced fibrosis. Foruny et al. reported a sustained virological response (SVR) rate of 38% with pegylated-IFN/ribavirin (peg-IFN/RBV) therapy following PSE for cirrhotic patients with severe hypersplenism (14). Miyake et al. assigned patients with thrombocytopenia to groups that either received or did not receive PSE and showed that favorable treatment outcomes were associated with PSE (15). However, the outcomes of IFN-based dual combination therapy for PSE-pretreated patients were unsatisfactory.

The SVR rate of peg-IFN/RBV therapy for chronic hepatitis C patients with genotype 1b was shown to be 40-50% (9, 10), while the protease inhibitor telaprevir, in combination with peg-IFN/RBV therapy, increased the SVR rate in these patients to approximately 70-80% (16-18). However, the total dosage of this triple combination therapy is often insufficient for chronic hepatitis C patients with thrombocytopenia caused by hypersplenism. PSE pretreatment prior to triple combination therapy may be useful in improving the outcomes of these patients. However, it has yet to be determined whether a pretreatment with PSE could increase the platelet counts in chronic hepatitis C patients with thrombocytopenia caused by hypersplenism prior to the administration of triple combination therapy. Furthermore, the safety of this pretreatment prior to and throughout triple combination therapy remains unknown.

To address these issues, we conducted a prospective pilot study to investigate the efficacy and safety of triple combination therapy following PSE in chronic hepatitis C genotype 1b patients with thrombocytopenia caused by hypersplenism.

Materials and Methods

Study subjects

Patients with hypersplenism-induced thrombocytopenia were pretreated with PSE prior to receiving telaprevir-based triple therapy. The inclusion criteria for PSE were as follows: age between 20 and 70 years, high viral load (>5.0 LIU/mL) as quantified by real-time polymerase chain reaction (PCR) for hepatitis C virus (HCV) RNA, monoinfection with genotype 1b, white blood cell count >1,500/μL, platelet count ≤100x10^4/μL, to >50x10^4/μL, and hemoglobin level >10 g/dL. Hypersplenism was defined as the presence of a low platelet count (≤100x10^4/μL) and an enlarged spleen size (>10 cm) as evaluated by computed tomography. Platelet-associated IgG (PAIgG), platelet-binding IgG (PBlgG), and the anti-glycoprotein IIb/IIIa antibody concentrations were evaluated, and, as a consequence, idiopathic thrombocytopenic purpura was ruled out for all patients. The exclusion criteria were as follows: other liver diseases (including autoimmune hepatitis and alcoholic hepatitis), liver cirrhosis complicated with uncontrollable ascites or/and encephalopathy, severe renal disorders, abnormal thyroid function, poorly controlled diabetes, poorly controlled hypertension, medication with Chinese herbal medicine, medical history of interstitial pneumonia, severe depression, and allergies to interferon, ribavirin, and biological preparations (e.g., vaccines).

Eighteen patients who visited the Nippon Medical School Chiba Hokusoh Hospital, Shinmatsudo General Central Hospital, and Jikei University School of Medicine Katsusika Medical Center between January 2012 and December 2012 met the inclusion criteria and agreed to receive PSE followed by telaprevir with peg-IFN/RBV triple combination therapy.

The study protocol followed the ethical guidelines established in accordance with the 2008 Declaration of Helsinki and was approved by the Ethics Committee of each institution. Written informed consent was obtained from all subjects.

Partial splenic embolization (PSE)

PSE was performed at least one month prior to the initiation of triple therapy. A catheter was inserted through the femoral artery into the main splenic artery and 0.5 g cefazolin (CEZ) was then injected via the catheter. A microcatheter (Progreat Series, Terumo Clinical Supply, Tokyo, Japan) was selectively inserted into the inferior segmental branch of the splenic artery, and 70-80% of the spleen was embolized with gelatin sponge cubes (Gelfoam®, Pfizer, Tokyo, Japan) which were soaked in 0.5 g of CEZ.

An intravenous infusion of methylprednisolone (125 mg/day) was administered for three days after the embolization treatment to suppress excessive immune reactions. A dose of 2 g/day of CEZ was concurrently administered for the same three days to prevent splenic abscesses. The splenic infarction volume was estimated by computed tomography one week after PSE. Triple combination therapy was initiated after the patient’s platelet count increased to the plateau level.

Antiviral treatment protocol

All patients received combination therapy with peg-IFN-α2b (PegIntron®, MSD, Tokyo, Japan), ribavirin (Rebetol®, MSD, Tokyo, Japan), and telaprevir (Telavic®, Mitsubishi Tanabe Pharma, Osaka, Japan) for 12 weeks, followed by 12 weeks or 36 weeks of peg-IFN-α2b and ribavirin. Patients received a subcutaneous injection of peg-IFN-α2b (1.5 μg/kg/week) and orally administered ribavirin. The dose of ribavirin was adjusted by body weight (600 mg, 800 mg, and 1,000 mg per day for <60 kg, 60-80 kg, and >80 kg, re-
pectively). Telaprevir (750 mg) was administered every 8 hours after meals. The dosages of each drug were reduced appropriately when a critical adverse event occurred during the treatment course. Patients were followed for 24 weeks following completion of the treatment.

**Definition of a virological response**

A rapid virological response (RVR) was defined as undetectable serum HCV RNA at week 4 of the treatment. Patients who were negative for the virus at the time of treatment completion were defined as having an end of treatment response (ETR). Viral breakthrough was defined as undetectable serum HCV RNA after the treatment, but with the reappearance of serum HCV RNA during the treatment or an increase in the HCV RNA level of ≥1.2 log IU/mL from the lowest value during the treatment period. SVR was defined as a virus-negative status 24 weeks after treatment completion. Patients who exhibited an ETR but who were also positive for the virus 24 weeks after treatment completion were considered to have relapsed. Patients whose HCV RNA levels decreased by 2 log IU/mL, but never became undetectable, were considered to have had a partial response. Patients whose HCV RNA levels decreased by at least 2 log IU/mL during IFN-based therapy were considered to have had a null response.

**Laboratory tests**

Peripheral blood examinations and liver function tests were performed weekly until 12 weeks after initiation of the treatment and then monthly until 24 weeks after the completion of treatment. In the biochemical tests performed before the initiation of treatment, data were obtained from patients in the fasting state. HCV RNA levels were measured using real-time PCR (COBAS AmpliPrep, Roche Diagnostics, Tokyo, Japan). Gene mutations in the core and NS5A regions of the HCV genome were determined by the direct sequencing method. Genomic DNA was extracted from whole blood using a DNA Isolation kit on a MagNA Pure LC instrument (Roche Diagnostics, Basel, Switzerland). Single nucleotide polymorphisms (SNPs) at rs8099917, which is located in the locus adjacent to the interleukin 28B (IL28B) gene on chromosome 19, were determined by real-time PCR using TaqMan SNP Genotyping Assays on a 7,500 Fast Real-Time PCR System (Applied Biosystems, Foster City, USA). The rs8099917 genotypes were classified into 2 categories: TT (major genotype) and non-TT (minor genotype: TG or GG). SNPs at rs1127354, which is located in the locus adjacent to the inosine triphosphatase (ITPA) gene, were similarly determined. The rs1127354 genotypes were classified into two categories: major genotype (CC) and minor genotype (non-CC; CA or AA).

**Statistical analysis**

We performed the Wilcoxon signed-rank test to analyze various factors, such as the platelet count and prothrombin time, between pre- and post-PSE states. We performed the Mann-Whitney U test to analyze the change in the platelet counts during the treatment. We performed Fisher’s exact test to analyze the SVR rates. All statistical analyses were performed using IBM SPSS version 17.0 (IBM Japan, Tokyo, Japan). The level of significance was set at p<0.05.

**Results**

**Background**

The patient population consisted of 10 men and 8 women with a median age of 62 years (range: 40-69 years), nine of whom were treatment naïve and nine who had previously undergone treatments (five relapers, two partial responders, and two null responders) (Table). Twelve patients had the IL28B major genotype TT and six patients had the IL28B minor genotype non-TT. Twelve patients had the ITPA major genotype CC and six had the ITPA minor genotype non-CC. Eleven patients received the treatment for 24 weeks and three patients received the treatment for 48 weeks. Four patients discontinued treatment before completing the 24-week treatment course.

**Efficacy of PSE**

The median PSE rate was 70% (range: 40-85%). The median platelet count was 71.5×10^3/μL (53-99×10^3/μL) before PSE and increased significantly to 121.5×10^3/μL (70-194×10^3/μL) after PSE (p=0.0002) (Fig. 1). Previous studies indicated that the hepatic functional reserve improved before and after PSE (14); therefore, changes in the prothrombin time activity (an indicator of hepatic reserve) before and after PSE were analyzed. The median prothrombin time was 78.7% (62.3-92.3%) before PSE and increased significantly to 83.3% (64-99.8%) with the administration of triple combination therapy (p=0.0166).

**Changes in the platelet count during the treatment according to the ITPA genotype**

Many patients maintained a platelet count of at least 50×10^3/μL during the treatment (Fig. 2). The treatment was not discontinued due to thrombocytopenia in any patients. Patients with the major ITPA genotype were more likely to develop RBV-induced anemia but less likely to develop thrombocytopenia (19). Therefore, changes in the platelet counts were evaluated according to the ITPA genotype. The platelet counts were significantly higher in patients with the ITPA major genotype than in those with the minor genotype (p=0.0057 at 2 weeks, p=0.0031 at 3 weeks, and p=0.0148 at 4 weeks) (Fig. 3).

**Virological responses associated with triple combination therapy**

The RVR rate was 72.2% (13/18 patients), ETR rate was 88.9% (16/18 patients), and SVR rate was 66.7% (12/18 patients). The SVR rate was 83.3% (10/12 patients) in patients with the IL28B genotype TT and 33.3% (2/6 patients) in
Table. Baseline Clinical Characteristics and On-Treatment Factors of the Total 18 Patients

<table>
<thead>
<tr>
<th>Factors</th>
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<tbody>
<tr>
<td>Gender (Male/Female)</td>
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</tr>
<tr>
<td>Age (year)</td>
<td>62 (40-69)</td>
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<tr>
<td>Body weight (kg)</td>
<td>58.0 (40-74)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>21.8 (15.1-27.4)</td>
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<tr>
<td>Prior treatment response (Naïve/relapse/partial response/null response)</td>
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<tr>
<td>White blood cell count (µL)</td>
<td>3,100 (1,800-4,900)</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.4 (10.9-15.2)</td>
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<tr>
<td>Platelet count (+ 10^12/µL)</td>
<td>7.2 (5.3-9.9)</td>
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<tr>
<td>AST (IU/L)</td>
<td>68 (36-133)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>58 (31-142)</td>
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<tr>
<td>γ-GTP (U/L)</td>
<td>71 (23-267)</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>4.0 (3.3-4.5)</td>
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<tr>
<td>Total Bilirubin (mg/dL)</td>
<td>0.7 (0.4-1.1)</td>
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<tr>
<td>LDL-Cholesterol (mg/dL)</td>
<td>84 (49-136)</td>
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<tr>
<td>UA (mg/dL)</td>
<td>5.7 (2.8-7.7)</td>
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<tr>
<td>Alpha-fetoprotein (mg/mL)</td>
<td>8.9 (2.0-707.7)</td>
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<td>Creatinine (mg/dL)</td>
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<td>Glucose (mg/dL)</td>
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<tr>
<td>ITPA genotype (rs1127354) (CC/CA or AA)</td>
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<td>Initiation dose of Telaprevir (mg/day)</td>
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<tr>
<td>Total dose of Telaprevir (mg)</td>
<td>126,000 (73,500-189,000)</td>
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<tr>
<td>Pegylated interferon (µg/kg/week)</td>
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</tr>
<tr>
<td>Ribavirin (mg/kg/day)</td>
<td>7.43 (1.65-12.99)</td>
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<tr>
<td>Duration of treatment (24week/48week/drop out)</td>
<td>11/3/4</td>
</tr>
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</table>


those with the IL28B genotype non-TT. The SVR rate was numerically higher in the IL28B genotype TT patients; however, this difference was not statistically significant (p=0.1073) (Fig. 4). According to the prior treatment response, the SVR rates were 77.8% (7/9 patients) in treatment naïve patients, 80% (4/5 patients) in relapers, 50% (1/2 patients) in partial responders, and 0% (0/2 patients) in null responders. Four patients relapsed, one developed viral breakthrough, and one patient had a null response.

Adherence of each drug

Median drug doses were sufficient at 1.38 µg/kg/week (0.29-1.63 µg/kg/week) for peg-IFN-α2b, 7.43 mg/kg/day (1.65-12.99) for RBV, and 126,000 mg (73,500-189,000) for total telaprevir.

Safety

All patients developed mild pyrexia and abdominal pain following PSE but recovered with symptomatic treatment and did not develop serious complications.

Four patients discontinued triple combination therapy due to the occurrence of hepatocellular carcinoma in two patients, viral breakthrough in one patient, and acute pancreatitis in one patient. No patient discontinued the treatment due to cytopenia.

Discussion

Patients with advanced fibrosis often have thrombocytopenia due to hypersplenism (20, 21). These patients cannot achieve favorable outcomes with antiviral IFN-based therapy because a reduction in the dose administered or discontinuation of the treatment is frequently needed due to IFN-induced thrombocytopenia (9-11). This adverse effect reduces the effectiveness of the treatment even in telaprevir-based triple therapy, which has been shown to markedly improve the SVR rate, particularly in patients with advanced fibrosis complicated by thrombocytopenia. To overcome this
therapeutic difficulty, surgical splenectomy or PSE has been performed to artificially increase blood cell counts before IFN-based therapy (14, 15, 22, 23). However, the efficacy and safety of PSE before the initiation of triple combination therapy with the protease inhibitor telaprevir has not yet been investigated.

In a previous study on triple combination therapy for treatment-naïve chronic hepatitis C patients, 231 of 1,088 (21%) patients had bridging fibrosis or compensated cirrhosis (16). These patients achieved a significantly higher SVR rate when treated with triple combination therapy (62%, 45 of 73 patients) than with peg-IFN/RBV therapy (33%, 24 of 73 patients).

Sherman et al. administered triple combination therapy to 540 treatment-naïve patients and noted that the SVR rate in patients with bridging fibrosis or compensated cirrhosis was 63% when the treatment was completed, but was only 31% when the treatment was discontinued (18). Furthermore, triple combination therapy was very effective even in patients with fibrosis; therefore, the scheduled treatment could be successfully completed. The findings of these studies indicate that triple combination therapy may be more effective than conventional peg-IFN/RBV therapy in patients with advanced fibrosis who are able to complete the treatment.
Several studies have investigated various approaches to facilitate interferon-based treatment completion as well as treatment outcomes. Tahara et al. compared the outcomes of peg-IFN/RBV, IFN/RBV, or peg-IFN therapy in 25 patients who underwent PSE pretreatment and 23 patients who did not. Although the platelet counts during the treatment were significantly higher in the PSE group, no significant differences were observed in the SVR rate between the PSE (8%) and non-PSE groups (7%) (22). Foruny et al. reported that the SVR rate was 38% in eight patients with advanced fibrosis who underwent PSE before peg-IFN/RBV therapy (14). Miyake et al. compared the outcomes of ten patients who underwent PSE followed by peg-IFN/RBV therapy or recombinant IFN/RBV therapy with a ten-patient historical control group that underwent peg-IFN/RBV therapy without prior PSE. The
SVR rate was 33% in the PSE group, whereas no patient in the non-PSE group achieved SVR (15). Thus, the SVR rate of 66.7% in our study was higher than those reported previously. The pretreatment with PSE may be more beneficial prior to triple combination therapy for patients with advanced fibrosis. The SVR rate in patients who received triple combination therapy, but did not undergo PSE because of a sufficiently high platelet count, was previously reported to be 70-80% (16-18), which suggests that the SVR rate in those who underwent PSE because of a low platelet count may have been slightly lower. However, if patients with a low platelet count received triple combination therapy without the pretreatment with PSE, they may not have been adequately medicated or may have had to discontinue the therapy. Therefore, the SVR rate may have been even lower.

Previous studies identified the independent factors contributing to SVR in triple combination therapy as the IL28B genotype and a prior treatment response (24-27). In the present study, patients with the IL28B genotype TT achieved a high SVR rate of 83.3% (10 of 12 patients). This was not lower than previously reported SVR rates of triple combination therapy for patients without advanced fibrosis. Although the sample size of patients with the IL28B genotype non-TT was too small and may be inadequate for analysis, the SVR rate of triple combination therapy in those with the IL28B minor genotype was poor (33.3%). Zeuzem et al. found that the SVR rate was negatively impacted by hepatic fibrosis in patients with a null or partial response to a prior treatment but not in patients that relapsed following a prior treatment (17). The results of the present study suggest that PSE may be useful in the treatment of prior relapsers with triple combination therapy but may have little impact on the treatment outcomes of non-responders. Outcomes were poor in patients with non-virological responses to a prior treatment, whereas four of the five patients that relapsed following a prior treatment achieved SVR.

Zeuzem et al. noted no significant adverse reactions in patients with advanced fibrosis (17). However, Hezode et al. concluded that triple combination therapy has a poor safety profile in patients with compensated hepatic cirrhosis and should not be used when the patient’s platelet count is ≤ 100x10^3/mm^3 and serum albumin level is ≤3.5 g/dL (28). Ogawa et al. reported that advanced fibrosis patients with serum albumin levels ≤3.5 g/dL were subject to many infections while receiving telaprevir-based triple therapy (29). Three of the patients in the present study had a platelet count ≤100x10^3/mm^3 and serum albumin level ≤3.5 g/dL before PSE. Although one patient ceased the treatment due to the occurrence of hepatocellular carcinoma, no patient discontinued therapy due to adverse events. However, the safety of telaprevir-based triple therapy has not yet been established in patients with a decreased hepatic functional reserve or decompensated hepatic cirrhosis. Therefore, careful monitoring and prompt action for adverse effects are needed for triple combination therapy in these patients.

Functional variant rs1127354 in the ITPA gene is predictive of treatment-induced anemia during peg-IFN/RBV therapy (30, 31). This major genotype is associated with anemia but protects against reductions in the platelet count (19, 32). Of note, our results revealed that post-PSE patients with the major genotype generally maintained higher platelet counts during the treatment than those with the minor genotype. This result suggests that ITPA genotyping may be useful for monitoring post-PSE patients. However, the ITPA genotype did not appear to have an impact on the SVR rate of post-PSE patients.

There are several limitations associated with our study. First, we did not compare the efficacy of triple combination therapy with and without PSE in patients with thrombocytopenia. However, it is difficult to assign patients with thrombocytopenia as a control group because they may be excluded from the treatment according to the exclusion criteria or be at a greater risk of prematurely discontinuing the treatment or developing severe adverse effects, such as cerebral hemorrhage. Second, we could not reach any definitive conclusion due to the small sample size. A larger number of patients are needed to elucidate the clinical significance of PSE and identify optimal candidates for PSE.

In this study, administering PSE to patients with hypersplenic thrombocytopenia led to elevated PT levels and platelet counts. Conversely, this study suggests that patients with advanced hepatic fibrosis should be monitored carefully for the development of hepatocellular carcinoma, as was observed in two patients.

In summary, the results of the present study suggest that telaprevir-based triple therapy for genotype 1b chronic hepatitis C patients with low platelet counts due to hypersplenism may be safe when administered following PSE pretreatment. Outcomes were particularly favorable for patients with the IL28B genotype TT and patients who had relapsed following a prior treatment.

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

References


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