Efficacy and Safety of Telaprevir-Based Antiviral Treatment for Elderly Patients with Hepatitis C Virus

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Key Words
Chronic hepatitis C · Telaprevir · Triple therapy

Abstract
Background: Telaprevir-based antiviral therapy has been the primary treatment for chronic hepatitis C genotype 1 at a high viral load since November 2011. On the other hand, a number of patients have been reported to require withdrawal from or reduced doses of drugs due to side effects, such as eruptions, anemia, and renal dysfunction. In addition, as hepatitis C patients are growing older, it is imperative to investigate the tolerability of triple combination therapy for elderly patients.

Subjects and Methods: The study subjects comprised 35 patients who received telaprevir combination therapy after November 2011. They were divided into group A (age: <65 years; n = 21) and group B (age: ≥65 years; n = 14) in order to compare the treatment completion rate, sustained virological response at week 24 (SVR24), and adverse events between the groups.

Results: The treatment completion rate was 82.8% (29/35) in all subjects, 90.4% (19/21) in group A, and 78.5% (11/14) in group B. The rate was lower in group B but without a significant difference between the groups (p = 0.804). The SVR24 rate was 88.5% (31/35) in all subjects, 90.4% (19/21) in group A, and 85.7% (12/14) in group B, without a significant difference between the groups (p = 0.161).

Conclusion: Although the incidence of anemia was higher in group B, there was no significant difference in the treatment completion or SVR24 rate between the groups. Telaprevir combination therapy is suggested to be tolerable for elderly hepatitis C patients.

Introduction

Hepatocellular carcinoma causes the death of approximately 600,000–700,000 individuals annually worldwide and it is commonly due to chronic viral hepatitis [1]. In Japan, hepatocellular carcinoma is often caused by hepatitis C virus (HCV) [2–4], and patients with chronic hepatitis C (CHC) are growing older [5]. As elderly patients with CHC have been reported to show a higher incidence rate of carcinogenesis in noncirrhotic liver than younger adults, the treatment of elderly hepatitis C patients is important [6].

In 2004, the concomitant use of pegylated interferon (PEG-IFN) α-2b and ribavirin (RBV) for 48 weeks became available for patients with hepatitis C genotype 1 at a high viral load, and, as a result, it has become possible to achieve a sustained virological response (SVR) in approximately 50% of cases [7,8]. However, the treatment of CHC patients, particularly elderly adults, has been challenging due to se-
vere side effects of PEG-IFN α-2b (e.g., anorexia, systemic lassitude, and cytopenia) and RBV (e.g., anemia) [9–11].

In 2011, the concomitant use of telaprevir, PEG-IFN, and RBV became available. Telaprevir strongly prevents viral multiplication by directly inhibiting HCV NS3/4A protease, which is a nonstructural protein [12]. It has been reported that this therapy achieves a higher SVR rate within a short period than when using the existing combination therapy with PEG-IFN and RBV [13–16]. However, the safety and beneficial effects of such a triple combination therapy for elderly patients have yet to be elucidated.

In the present study, we investigated older and younger adults who received telaprevir-based antiviral therapy at our hospital, in order to compare its safety and beneficial effects between the two groups.

**Subjects and Methods**

We conducted a retrospective study at Kinki University Hospital. The study subjects comprised 35 patients who received telaprevir-based antiviral therapy between November 2011 and March 2012. HCV-RNA levels were measured by the COBAS TaqMan HCV Test (Roche Diagnostics, Tokyo, Japan), and treatment-naive individuals were eligible when their HCV-RNA level was 5 log10 IU/ml or higher. Subcutaneous injections of PEG-IFN (Peg-Intron; Schering-Plough, Kenilworth, N.J., USA) were administered at a dose of 1.5 μg/kg once a week. RBV (Rebetol; Schering-Plough) was orally administered after a meal twice daily as follows: when the hemoglobin (Hb) level was ≥ 13 g/dl, 600, 800, and 1,000 mg for those weighing <60, 60–80, and >80 kg; and when the Hb level was <13 g/dl, 400, 600, and 800 mg for those weighing <60, 60–80, and >80 kg, respectively. Telaprevir (Telavic; Mitsubishi Tanabe Pharma, Osaka, Japan) was administered at a dose of 2,250 mg/day after a meal 3 times a day, but the dose was reduced to 1,500 mg/day when the subject was female, aged ≥ 70 years, or weighed ≤ 50 kg.

The subjects received telaprevir-based antiviral therapy with telaprevir, PEG-IFN, and RBV for the first 12 weeks. After that, PEG-IFN and RBV were administered for 12 weeks if the subject showed an HCV-RNA level of <1.2 log10 IU/ml or was negative for HCV-RNA at week 4 and for the RNA at week 12. Individuals not meeting these criteria received response-guided therapy for 36 weeks from week 13.

Concerning skin disorders, localized lesions with areas accounting for ≤50% of the body surface were defined as grade 1; multifocal or diffuse lesions with areas accounting for ≤50% of the body surface along with a mucosal lesion not associated with ulcers or erosion were defined as grade 2, and systemic rashes with areas accounting for >50% of the body surface along with mucosal ulcers

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<table>
<thead>
<tr>
<th>Table 1. Baseline patient characteristics</th>
<th>Group A (aged &lt;65 years; n = 21)</th>
<th>Group B (aged ≥65 years; n = 14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>11/10</td>
<td>9/5</td>
<td>0.482</td>
</tr>
<tr>
<td>Age, years</td>
<td>57 (35–64)</td>
<td>69 (65–77)</td>
<td>0.166</td>
</tr>
<tr>
<td>BMI</td>
<td>23.4 (12.2–36.8)</td>
<td>23.4 (17.32–30)</td>
<td>0.57</td>
</tr>
<tr>
<td>rs8099917 (TT/non-TT)</td>
<td>15/6</td>
<td>12/1</td>
<td>0.143</td>
</tr>
<tr>
<td>WBC, x10^9/l</td>
<td>5.7 (3.1–13.8)</td>
<td>5.2 (2.5–6.7)</td>
<td>0.261</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>14.0 (11.7–17.3)</td>
<td>13.5 (11.9–15.3)</td>
<td>0.139</td>
</tr>
<tr>
<td>Platelets, x10^9/l</td>
<td>20.4 (7.9–35.7)</td>
<td>17.3 (9.2–23.9)</td>
<td>0.051</td>
</tr>
<tr>
<td>ALT, IU/l</td>
<td>35 (17–145)</td>
<td>34.55 (21–292)</td>
<td>0.44</td>
</tr>
<tr>
<td>γGTP, IU/l</td>
<td>31.5 (11–327)</td>
<td>30 (18–264)</td>
<td>0.733</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>4.3 (2.9–5.2)</td>
<td>4.4 (3.5–4.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>169 (75–237)</td>
<td>164 (125–224)</td>
<td>0.837</td>
</tr>
<tr>
<td>Viral load</td>
<td>6.5 (1.8–7.4)</td>
<td>6.65 (4.3–7.7)</td>
<td>0.653</td>
</tr>
<tr>
<td>PEG-IFN α-2b, μg</td>
<td>90 (40–150)</td>
<td>80 (80–100)</td>
<td>0.867</td>
</tr>
<tr>
<td>PEG-IFN α-2b/μg/kg/w</td>
<td>1.44 (0.80–1.81)</td>
<td>1.42 (0.71–1.73)</td>
<td>0.94</td>
</tr>
<tr>
<td>RBV, mg</td>
<td>600 (400–1,000)</td>
<td>600 (400–800)</td>
<td>0.34</td>
</tr>
<tr>
<td>RBV/μg/kg/day</td>
<td>8.09 (3.4–12.69)</td>
<td>7.33 (4.01–10.52)</td>
<td>0.248</td>
</tr>
<tr>
<td>TBV, mg</td>
<td>2,250 (1,500–2,250)</td>
<td>2,250 (1,500–2,250)</td>
<td>0.627</td>
</tr>
<tr>
<td>TBV/μg/kg/day</td>
<td>32.56 (18.75–45.91)</td>
<td>30.62 (15–40.17)</td>
<td>0.074</td>
</tr>
<tr>
<td>SVR24</td>
<td>19/2</td>
<td>12/2</td>
<td>0.161</td>
</tr>
</tbody>
</table>

For the categorical data, the number of patients in each category is shown. For the continuous data, the median and range are displayed. ALT = Alanine aminotransferase; BMI = body mass index; γGTP = γ-glutamyltranspeptidase; TBV = telaprevir; WBC = white blood cells.
or erosion, eye lesions, epidermolysis, blisters, or purpura associated with infiltration were defined as grade 3. Regarding anemia, Hb levels of ≥9.5 and <11 g/dl, ≥8 and <9.5 g/dl, and <8 g/dl were defined as grade 1, 2, and 3, respectively.

The study subjects were divided into 23 individuals aged <65 years (group A) and 12 individuals aged ≥65 years (group B), and we compared the treatment completion rate, SVR at week 24 (SVR24), and adverse events between the groups.

Statistical Analysis
Data are expressed as median (range) values. Differences between groups were examined for significance using the t test and Fisher exact test where appropriate. A p value <0.05 was regarded as statistically significant in all analyses.

Results

Patient characteristics are shown in table 1. The number of treatment-naive patients and previously treated individuals in whom hepatitis had relapsed or for whom the administered drugs had been ineffective was 20 and 15 overall, 11 and 10 in group A, and 9 and 5 in group B, respectively. As a result of investigating rs8099917, which is an IL28B genotype, the number of patients with genotypes of TT and non-TT was 27 and 7 overall, 15 and 6 in group A, and 12 and 1 in group B, respectively. There was no significant difference in the BMI, IL28B SNPs, Hb, albumin, viral load, initial dose, or adherence to the regimen between the groups.

The SVR24 rate was 88.5% (31/35) in all subjects, 90.4% (19/21) in group A, and 85.7% (12/14) in group B. The rate showed a tendency to be lower in group B but without a significant difference between the groups (p = 0.161). We also investigated the SVR24 rate according to the IL28B genotype, which revealed that the rate was 96.2% (26/27) and 57.1% (4/7) overall (p = 0.520), 100% (15/15) and 66.6% (4/6) in group A (p = 0.720), and 91.6% (11/12) and 0% (0/1) in group B (p = 1) in patients with genotypes of TT and non-TT, respectively (fig. 1). According to the IL28B genotype among the treatment-naive patients, the SVR24 rate was 93.7% (15/16) and 50% (2/4) overall (p = 0.666), 100% (8/8) and 66.6% (2/3) in group A (p = 1), and 83.3% (7/8) and 0% (0/1) in group B (p = 1) in patients with TT and non-TT, respectively (fig. 2). We also investigated the SVR24 rate according to the IL28B genotype among the previously treated individuals in whom hepatitis had relapsed, which clarified that the rate was 100% (9/9) and 66.6% (2/3) overall (p = 1), 100% (6/6) and 66.6% (2/3) in group A (p = 1), and 100% (3/3) and 0% (0/0) in group B in patients with TT and non-TT, respectively (fig. 3). Among the previously treated individuals in whom the administered drugs had been ineffective, SVR was achieved both in group A (1 patient with TT) and in group B (1 patient with TT). The SVR rate was compared to the initial dose of telaprevir, which revealed that among those receiving 1,500
mg of telaprevir, the SVR rate was 83.3% (5/6) and 80% (4/5) in group A and B, respectively (p = 1). Among those receiving 2,250 mg of telaprevir, the SVR rate was 93.3% (14/15) and 88.8% (8/9) in group A and B, respectively (p = 1; fig. 4).

The treatment completion rate was 82.8% (29/35) in all subjects, 90.4% (19/21) in group A, and 78.5% (11/14) in group B. The rate was lower in group B, but without a significant difference between the groups (p = 0.793). The reasons for treatment discontinuation were anemia.

Fig. 2. Age-specific SVR rates according to the IL28 genotype among treatment-naive individuals.

Fig. 3. Age-specific SVR rates according to the IL28 genotype among previously treated individuals in whom hepatitis C had relapsed.
(n = 1) and skin disorders (n = 1) in group A and brain infarction (n = 1), systemic lassitude (n = 1), and infective endocarditis (n = 1) in group B.

Drug-induced skin disorders were identified in 76.1% (16/21) and 64.2% (9/14) of cases in group A and B, respectively. Severe (grade 3) side effects occurred in 9.5% (2/21) and 0% (0/14) of cases in group A and B, respectively, but without a significant difference (p = 0.156; fig. 5).

The incidence of anemia was significantly higher in group B than in group A: 71.4% (10/14) versus 52.3% (11/21) (p = 0.002; fig. 6).

Discussion

In this study, high SVR24 rates were achieved by elderly patients with hepatitis C receiving telaprevir-based antiviral therapy, and its safety among these patients was verified.

When conducting PEG-IFN/RBV therapy for elderly patients, it is often necessary to reduce their doses or discontinue the therapy when side effects occur, such as systemic lassitude, depression, anemia, or thrombocytopenia. According to a Japanese study involving 1,251 subjects, the treatment completion rate was 57 and 75% in older (aged ≥65 years) and younger adults, respectively [5]. In the present study, the treatment completion rate was 75% in the older subjects (group B), which was a relatively favorable result. This was probably because our triple combination therapy was shorter (24 weeks) than the typical PEG-IFN/RBV therapy (48 weeks). In our study, the SVR24 rate in the older subjects was also favorable (83.3%), possibly due to the potent inhibitory effects of telaprevir against viral multiplication [12]. The SVR rate achieved by the older group was slightly lower than that shown by the younger group, but the difference was not significant, and this finding was similar to that reported by Furusyo et al. [17]. Such a favorable SVR rate achieved by the older group was probably due to the maintained adherence to telaprevir and IFN [17].

According to Akuta et al. [18] and Chayama et al. [19], similarly to when using PEG-IFN/RBV therapy, subjects with an IL28B genotype of TT showed a high cure rate with telaprevir-based antiviral therapy. In the present study, the SVR rate achieved by subjects with an IL28B genotype of TT was high (96.2%) but not significantly different from that shown by those with non-TT (57.1%). As a result of investigating the SVR rate according to age among subjects...
with TT, those aged <65 years and those aged ≥65 showed SVR rates of 100 and 91.6%, respectively, which were favorable results. On the other hand, among subjects with non-TT, the rates were 66 and 0% in the former and latter group, respectively. However, as there was only 1 non-TT subject aged ≥65 years, the IL28B genotype was not investigated among a sufficient number of older adults (fig. 1).

Telaprevir-based antiviral therapy has been reported to be highly beneficial for treatment-naive patients and previously treated individuals in whom hepatitis had re-
lapsed [13–15]. In the present study, we investigated treatment-naive patients and those who had previously been treated but had a relapse, which clarified that the therapy was highly effective. Among the treatment-naive subjects, the SVR rates were 71.4 and 92.3% in the older (group B) and younger patients (group A), respectively. Among the previously treated subjects, the rates were 100 and 88.8% in group B and A, respectively (fig. 2, 3). The 2 previously treated subjects, in whom the drugs used had been ineffective, both achieved SVR. This was possibly because the therapy was more likely to be effective for those with an IL28B genotype of TT.

In this study, both the older (group B) and the younger subjects (group A) showed favorable SVR rates (80 and 83.3%, respectively) when using telaprevir at a dose of 1,500 mg/day (fig. 4). Marcellian et al. [20] conducted a randomized controlled trial in which the subjects were assigned to receive either 2,250 or 1,500 mg of telaprevir, and found that the SVR rate was not significantly different between the groups, and the safety of the two regimens was similarly verified. Hara et al. [21] reported that a decrease in Hb levels was significantly inhibited among a group receiving 1,500 mg of telaprevir. In our study, the incidence of anemia was significantly higher in the older subjects (group B; fig. 6). We suggest that a dose of 1,500 mg may be sufficient for elderly individuals, as Japanese patients receiving telaprevir are growing older and their body weight is commonly lower than that of patients in the US and Europe.

Drug-induced skin disorders occurred at a high rate in both the older (group B; 58.3%) and the younger (group A; 78.2%) patients. The incidence showed a tendency to be higher in the latter group, but without a significant difference (fig. 5). A previous study also reported a similar incidence rate of skin disorders between older and younger subjects [17].

Many studies have reported that antiviral therapy is useful as a radical treatment for hepatitis C, and hepatocarcinogenesis can be inhibited by achieving SVR [6, 22–24]. However, therapies involving IFN are sometimes challenging due to adverse events. In recent years, combination therapies with direct-acting antivirals, which do not involve IFN, have been developed. A phase 3 trial of combination therapy with asunaprevir and daclatasvir achieved a high SVR rate (84.7%). In this trial, the therapy was discontinued due to adverse events in 5% of cases, with a low incidence of severe adverse events (5.9%) [25]. Combination therapy with direct-acting antivirals will probably become the primary treatment for hepatitis C. However, the inhibitory effects of such therapy against carcinogenesis are unknown due to researchers’ limited experience in this field.

The limitations of our study were that it was conducted in a retrospective manner and that it involved a small number of subjects. The treatment completion rate showed a tendency to be lower in the older group, but the SVR24 rate was equivalent between the two groups. Our findings suggest that telaprevir-based antiviral therapy may be tolerable for elderly hepatitis C patients.

**Disclosure Statement**

The authors declare that no financial or other conflicts of interest exist in relation to the content of this article.

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