Outcome of Combination Therapy with Sofosbuvir and Ledipasvir for Chronic Type C Liver Disease

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Key Words

Sofosbuvir · Ledipasvir · Chronic type C liver disease

Abstract

Introduction: Recently, the treatment of chronic hepatitis C has markedly advanced. A phase III clinical study of combination therapy with sofosbuvir (SOF) and ledipasvir (LDV) was conducted in Japan, and the additive therapeutic effects were reported. In this study, we report the results of treatment in our hospital. **Methods:** Of 147 patients with chronic type C liver disease who had consulted our hospital since September 2015 and received SOF/LDV therapy, in 91 subjects a sustained virological response of 12 weeks (SVR12) could be evaluated. **Results:** In all 91 patients, end treatment response was achieved. Subsequently, recrudescence was noted in 1 before the completion of treatment (week 12); an SVR12 was achieved in 90 patients (99%). The following adverse reactions were observed in 3 patients (3.3%): bradycardia, paroxysmal atrial fibrillation, and heart failure with QT prolongation, which were associ-

ated with heart disease. **Conclusion:** A favorable SVR was achieved by SOF/LDV therapy even in elderly patients, those with liver cirrhosis, or those having undergone radical treatment of liver cancer. Furthermore, a high tolerance was demonstrated, but adverse reactions associated with the heart may appear in patients with heart disease as an underlying disease; strict management during treatment is necessary.

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Introduction

Chronic hepatitis C is one of the major etiologies of hepatocellular carcinoma [1–3], which is the third leading cause of cancer death. Therefore, treatment of hepatitis C is an important issue to prevent hepatocarcinogenesis [4]. Recently, the treatment of chronic hepatitis C has markedly advanced. In 2011, telaprevir [5–7] was approved as a directly acting antiviral agent. In 2013, simeprevir was approved [8–12]; the efficacy has

Table 1. Patient background (n = 91)

Age, years	
Median (range)	71 (36–88)
≥65 years, n (%)	65 (71)
≥75 years, n (%)	41 (45)
Male sex, n (%)	38 (42)
Cirrhosis, n (%)	34 (37)
History of hepatocellular carcinoma, n (%)	23 (25)
Prior therapy	
Naïve, n (%)	31 (34)
No response, n (%)	12 (13)
Relapse, n (%)	4 (4)
Intolerant, n (%)	8 (9)
Ineligible, n (%)	36 (40)

Table 2. NS5A resistance mutations at baseline (n = 91)

Negative, n (%)	8 (9)
Y93H, n (%)	11 (12)
Y93H+L31M, n (%)	2 (2)
No measurement, n (%)	70 (77)

improved. However, it is necessary to combine these agents with peginterferon and ribavirin (RBV), raising the issue of tolerance. In other words, hepatitis C virus eradication has been successfully achieved in young patients and, as a result, the proportions of elderly patients in whom treatment was unsuccessful or discontinued and of those with deterioration of fibrosis have increased.

On this background, the necessity of developing a more tolerable, effective treatment method has been emphasized. In Japan, the first interferon (IFN)-free regimen, a combination therapy with asunaprevir and daclatasvir, became commercially available in September 2014 [13–16]. This therapy has been increasingly indicated for elderly patients and those with underlying diseases in comparison with treatments with IFN, decreasing the incidence of adverse reactions. On the other hand, the therapeutic effects were markedly reduced in patients with resistance mutations at baseline, and adverse reactions, such as liver dysfunction, made it difficult to continue treatment in some patients, raising issues. Based on such a background, a phase III clinical study of combination therapy with sofosbuvir (SOF) and ledipasvir (LDV) was conducted in Japan, and the additive therapeutic effects were reported [17]. In this study, we report the results of treatment in our hospital.

Fig. 1. Virological reactivity. In all 91 patients, end treatment response (ETR) was achieved. Subsequently, recrudescence was noted in 1 before the completion of treatment (week 12); an SVR12 was achieved in 90 patients (99%).

Methods

Patients and Treatment Schedule

Of 147 patients with chronic type C liver disease who had consulted our hospital since September 2015 and received SOF/LDV therapy, in 91 subjects a sustained virological response of 12 weeks (SVR12) could be evaluated. The administration period was 12 weeks, and follow-up was performed until 12 weeks after the completion of treatment. SOF at 400 mg and LDV at 90 mg were orally administered once a day.

Resistance Test

Hepatitis C virus NS5A and NS3/4A resistance was measured using the PCR-invader method. Strains with a mutant virus rate of <1% were regarded as negative, those with a mutant virus rate of 1–19% as weakly positive, and those with a mutant virus rate of ≥20% as positive.

Statistical Analysis

Changes in hepatic reserve, estimated glomerular filtration rate (eGFR), and corrected QT (QTc) were analyzed using Student's t test. A p value of 0.05 was regarded as significant.

Results

Patients

Of 147 patients with chronic type C liver disease who had consulted our hospital since September 2015 and received SOF/LDV therapy, in 91 subjects an SVR12 could

Fig. 2. Changes in QTc before and during treatment. In 17 patients who underwent electrocardiography before treatment and every 2 weeks during treatment, the QTc interval was measured. In 2 (11.7%) of the 17 patients, the QTc interval was markedly prolonged (from 369 to 482 ms and from 437 to 458 ms, respectively).

Table 3. Adverse reactions leading to the discontinuation of oral administration

Adverse reaction	Onset time	Outcome	SVR	Age	Sex	Cirrhosis	eGFR	Underlying disease
Bradycardia, QT prolongation	day 14	recovery through drug withdrawal alone	SVR12	75	F	absent	77	absent
Paroxysmal atrial fibrillation	day 34	recovery through administration and discontinuation	SVR12	79	F	absent	52	paroxysmal atrial fibrillation
QT prolongation, heart failure	day 77	recovery through administration and discontinuation	SVR12	78	F	present	84	heart failure

be evaluated. The median age was 71 years. Patients aged 65 years or older accounted for 71% (n = 65), and those aged 75 years or older accounted for 45% (n = 41). The subjects' age was more advanced than in the phase III clinical trial in Japan. Furthermore, they included 34 patients with liver cirrhosis (37%) and 23 patients having undergone radical treatment of liver cancer (25%). Concerning previous treatment, 31 patients (34%) had not received any biological preparation. There were 12 (13%) nonresponders to IFN, and recrudescence was noted in 4 (4%). IFN was inappropriate/intolerable in 44 (49%), showing the highest percentage (table 1).

NS5A Resistance Mutations at Baseline

Eight patients (9%) were negative for NS5A resistance mutations. Y93H was detected in 11 patients (12%), and Y93H+L31M in 2 (2%). Measurement was not performed in 70 (77%) (table 2).

Virological Reactiveness

In all 91 patients, end treatment response was achieved. Subsequently, recrudescence was noted in 1 before the completion of treatment (week 12); an SVR12 was achieved in 90 patients (99%) (fig. 1).

Virological Ineffectiveness

After completion of the 12-week treatment, recrudescence was noted in 1 patient. This patient had multiple resistant strains, Y93H and L31M, at baseline.

Adverse Reactions Leading to the Discontinuation of Oral Administration

Such adverse reactions were observed in 3 patients (3.3%): bradycardia, paroxysmal atrial fibrillation, and heart failure with QT prolongation, which were associated with heart disease. Furthermore, many patients had heart disease as an underlying disease (table 3).

Changes in QTc before/during Treatment

In 17 patients who underwent electrocardiography before treatment and every 2 weeks during treatment, the QTc interval was measured. In 2 (11.7%) of the 17 patients, the QTc interval was markedly prolonged (from 369 to 482 ms and from 437 to 458 ms, respectively) (fig. 2).

Changes in Hepatic Reserve before and after Treatment

The serum albumin levels at the time of treatment introduction and its completion were 4.0 ± 0.5 and 4.2 ± 0.4 (mean $\pm$ SD), respectively, showing a significant increase ($p = 0.017$) (fig. 3a). When reviewing the results with respect to diseases (chronic hepatitis and liver cirrhosis), there was no difference in patients with chronic hepatitis (fig. 3b), whereas there was a significant improvement (from 3.7 ± 0.5 to 4.0 ± 0.5) in those with liver cirrhosis (fig. 3c, $p = 0.013$). In the latter, there was a significant improvement in the platelet count (from 8.8 ± 2.7 to 10.3 ± 3.5) ($p = 0.049$).

Changes in the Kidney Function (eGFR) before and after Treatment

Overall, the eGFRs at the time of treatment introduction and its completion were 73.0 ± 16.0 and 71.3 ± 15.0 (mean $\pm$ SD), respectively; there was no exacerbation. In patients with an eGFR of <60 at the time of treatment introduction, there was no further exacerbation either (fig. 4).

Fig. 3. a Changes in hepatic reserve before and after treatment. The serum albumin (ALB) levels at the time of treatment introduction and its completion were 4.0 ± 0.5 and 4.2 ± 0.4 (mean $\pm$ SD), respectively, showing a significant increase ($p = 0.017$). **b, c** When reviewing the results with respect to chronic hepatitis and liver cir-

rhosis, there was no difference in patients with chronic hepatitis (**b**), whereas there was a significant improvement (from 3.7 ± 0.5 to 4.0 ± 0.4) in those with liver cirrhosis (**c**, $p = 0.013$). In the latter, there was a significant improvement in the platelet count (PLT) (from 8.8 ± 2.7 to 10.3 ± 3.5) ($p = 0.049$).

(For rest of figure see next page.)

Fig. 4. Changes in kidney function (eGFR) before and after treatment. Overall, the eGFRs at the time of treatment introduction and its completion were 73.0 ± 16.0 and 71.3 ± 15.0 (mean $\pm$ SD), respectively; there was no exacerbation. In patients with an eGFR of <60 at the time of treatment introduction, there was no further exacerbation either. n.s. = Not significant.

Discussion

The phase III clinical study of SOF/LDV in Japan showed an SVR12 of 100%. On the other hand, an SVR was not achieved in 3 of 170 patients receiving combination therapy with SOF/LDV and RBV: administration was discontinued due to exanthema and cardiac arrest in 2, respectively, and recrudescence was noted after the completion of administration in 1 [17]. In our hospital, an SVR12 was achieved in 90 (99%) of the 91 patients. The remaining patient, in whom an SVR was not achieved, had multiple Y93H and L31M resistance at baseline, and recrudescence was noted 5 weeks after the completion of treatment. In the phase III clinical study, there was no difference in the therapeutic effects related to the presence or absence of resistance in the NS5A region at baseline. Furthermore, an SVR12 was achieved even in patients with multiple Y93H and L31M resistance [17]. No study has reported the effects of SOF/LDV on multiple resis-

tance in the NS5A region in a large number of patients. In the ELECTRON study, effects of SOF/RBV on G1 were obtained in 10–84% of the patients [18, 19], suggesting that the effects of SOF/LDV in patients with multiple NS5A resistance are limited.

Adverse reactions leading to the discontinuation of oral administration were observed in 3 patients (3.3%): bradycardia, paroxysmal atrial fibrillation, and heart failure with QT prolongation, which were associated with heart disease. Furthermore, many patients had heart disease as an underlying disease. In 2 of 17 patients in whom electrocardiograms could be serially measured, the QTc interval was markedly prolonged (from 369 to 482 ms and from 437 to 458 ms, respectively). There are patients with latent QTc prolongation in the absence of symptoms, although we cannot conclude this due to the small number of patients; therefore, strict electrocardiographic monitoring may be necessary during this therapy.

The hepatic reserve had improved at the completion of treatment. Concerning kidney function, we considered the influence of SOF, which is excreted in the kidneys, but there was no influence on kidney function in this study.

In conclusion, a favorable SVR was achieved by SOF/LDV therapy even in elderly patients, those with liver cirrhosis, or those after the radical treatment of hepatocellular carcinoma. Furthermore, a high tolerance was dem-

onstrated, but adverse reactions associated with the heart may appear in patients with heart disease as an underlying disease; strict management during treatment is necessary.

Disclosure Statement

The authors have no conflicts of interest to declare.

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