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Relevance of the Core 70 and IL-28B polymorphism and response-guided therapy of peginterferon alfa-2a ± ribavirin for chronic hepatitis C of Genotype 1b: a multicenter randomized trial, ReGIT-J study

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Abstract

Background We conducted a multicenter randomized clinical trial to determine the optimal treatment strategy against chronic hepatitis C virus (HCV) with genotype 1b and a high viral load (G1b/high).

Methods The study subjects included 153 patients with G1b/high. Patients were initially treated with PEG-IFNα-2a alone and then randomly assigned to receive different treatment regimens. Ribavirin (RBV) was administered to all patients with HCV RNA at week 4. Patients negative for HCV RNA at week 4 were randomly assigned to receive PEG-IFNα-2a (group A) or PEG-IFNα-2a/RBV (group B). Patients who showed HCV RNA at week 4 but were negative at week 12 were randomly assigned to receive weekly PEG-IFNα-2a (group C) or biweekly therapy (group D). Patients who showed HCV RNA at week 12 but were negative at week 24 were randomly assigned to receive PEG-IFNα-2a/RBV (group E) or PEG-IFNα-2a/RBV/ fluvastatin (group F).

Results Overall, the rate of sustained virological response (SVR) was 46 % (70/153). The total SVR rate in the group (A, D, and F) of response-guided therapy was significantly higher than that in the group (B, C, and E) of conventional therapy [70 % (38/54) versus 52 % (32/61), $p = 0.049$]. Although IL28-B polymorphism and Core 70 mutation were significantly associated with efficacy, patients with rapid virological response (RVR) and complete early virological response (cEVR) achieved high SVR rates regardless of their status of IL-28B polymorphism and Core 70 mutation.

Conclusion In addition to knowing the IL-28B polymorphism and Core 70 mutation status, understanding the likelihood of virological response during treatment is critical in determining the appropriate treatment strategy.

Keywords Chronic hepatitis C · IL-28B · Peginterferon alfa-2a · Ribavirin · Response-guided therapy

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Introduction

The introduction of combined treatment with peginterferon (PEG-IFN) and ribavirin (RBV) has dramatically increased the rate of sustained virological response (SVR) in patients with genotype 1 high virus titer chronic hepatitis C (HCV RNA titer $\geq$ 5 Log IU/mL), a disease generally considered intractable, to approximately 50 % [1–4]. Currently, a protease inhibitor, telaprevir, can be used for the treatment of chronic hepatitis C, further increasing the SVR rate to approximately 70 % after initial treatment; however, adverse events such as severe anemia, dermatopathy, and renal dysfunction due to increased creatinine level have been reported [5, 6].

RBV is also associated with adverse events, such as anemia, dermatopathy and taste disturbance, and these events can be accentuated in elderly patients or patients with renal dysfunction or anemia. In Japan, there are many elderly patients with chronic hepatitis C and they often cannot tolerate a treatment combination involving RBV [7]. For such patients, PEG-IFN monotherapy could be a treatment option. It has been reported that patients with genotype 1 high virus titer chronic hepatitis C are more likely to achieve SVR if their HCV RNA becomes negative within 4 weeks after initiation of PEG-IFN monotherapy (Rapid Virological Response: RVR) [8].

Patients receiving the PEG-IFNα-2a/RBV combination therapy can also achieve an excellent SVR rate if their HCV RNA becomes negative within 12 weeks after initiation of treatment, whereas the rate is known to decrease with a delay in the timing of HCV RNA-negative conversion [3]. Based on these findings, we propose the use of "response-guided therapy", in which a treatment regimen is modified according to viral kinetics. For the treatment of genotype 1 chronic hepatitis C, proposed treatment strategies include shortening of treatment period in patients with RVR and extension of treatment period in patients with a delayed response to the initial treatment as judged at week 12 [9–17]. For the treatment of genotype 1 high virus titer chronic hepatitis C, shortening of the treatment period may not be recommended even if RVR is achieved because of a possible reduction in the SVR rate, whereas extension of the treatment period to 72 weeks has been reported to increase the SVR rate in patients showing a delayed response to the initial treatment [12, 14–18]. In addition, combined use of HMG-CoA reductase inhibitors and IFN has been shown to enhance the antiviral effects in a synergistic manner [19]. Addition of fluvastatin (FLV), an HMG-CoA reductase inhibitor reported to exhibit the highest antiproliferative activity against hepatitis C virus, to PEG-IFNα-2a/RBV combination therapy has improved the SVR rate [20–22].

Factors affecting the efficacy of PEG-IFN/RBV combination therapy can be divided into viral and host factors. The viral factors include virus titer, genotype, amino acid substitution at position 70 of the core protein (Core 70) and mutations in the interferon sensitivity-determining region (ISDR) in the HCV NS5A region [23–27]. The host factors include age, sex, the degree of liver fibrosis, and a single nucleotide polymorphism (SNP) close to the IL-28B gene [28–33].

We therefore conducted a randomized trial to explore the optimal treatment strategy for patients with genotype 1 high virus titer chronic hepatitis C by comparing several treatment regimens modified according to the concept of "response-guided therapy" in consideration of tolerability (PEG-IFNα-2a monotherapy, PEG-IFNα-2a weekly or biweekly/RBV combination, and PEG-IFNα-2a/RBV/FLV combination therapy). We also evaluated the relations of IL-28B polymorphism and Core 70 mutation to the rate of HCV-RNA-negative conversion and SVR.

Patients and methods

Patients

The study subjects included 153 patients with genotype 1b high virus titer chronic hepatitis C (HCV RNA $\geq$ 5 Log IU/mL) who visited 17 institutions from April 2007 to December 2010 and met the following inclusion criteria: laboratory data before study treatment of white blood cell count $\geq$ 3,000/mm^3, neutrophil count $\geq$ 1,500/mm^3, platelet count $\geq$ 90,000/mm^3, and hemoglobin $\geq$ 12 g/dL. Before the study treatments were carried out, all patients gave written informed consent after receiving a sufficient explanation of the therapy. All patients had genotype 1b chronic hepatitis C with a mean HCV RNA titer of 6.4 Log IU/mL. There were 63 male and 90 female patients with a mean age of 56.5 years. Sixty patients had received prior treatment with IFN, though it was ineffective in 30 of these patients (Table 1).

Treatment protocol

The study design is shown in Fig. 1. After a lead-in therapy with PEG-IFNα-2a 180 μg/week alone (for 4 weeks), RBV was added to the treatment for patients without HCV RNA-negative conversion (according to their weight; $\leq$ 60 kg, 600 mg/day; 60–80 kg, 800 mg/day; and >80 kg, 1,000 mg/day). Patients with negative HCV RNA (TaqMan < 1.2 Log IU/mL) at week 4 (rapid virological response, RVR) were randomly assigned to receive PEG-IFNα-2a alone (group A) or PEG-IFNα-2a/RBV combination (group B). Patients with negative HCV RNA

Table 1 Baseline characteristics of patients ($n = 153$)

Age (years)	56.5 ± 11.1
Gender (male/female)	63/90
HCV RNA (Log IU/mL)	6.4 ± 0.7
BMI (kg/m^2)	22.8 ± 3.3
ALT (IU/L)	60.5 ± 41.3
AST (IU/L)	51.7 ± 31.5
Previous IFN (no/yes)	93/60 (non-responder for 30)
Fibrosis (F0-2/F3-4)	72/32 (unknown for 49)
Activity (A0-1/A2-3)	49/56 (unknown for 48)
Core 70 (wild/mutant)	54/38 (unknown for 61)
IL-28B, rs8099917 (TT/non-TT)	43/26 (unknown for 84)

Values are mean $\pm$ standard deviation (SD)

BMI body mass index, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase
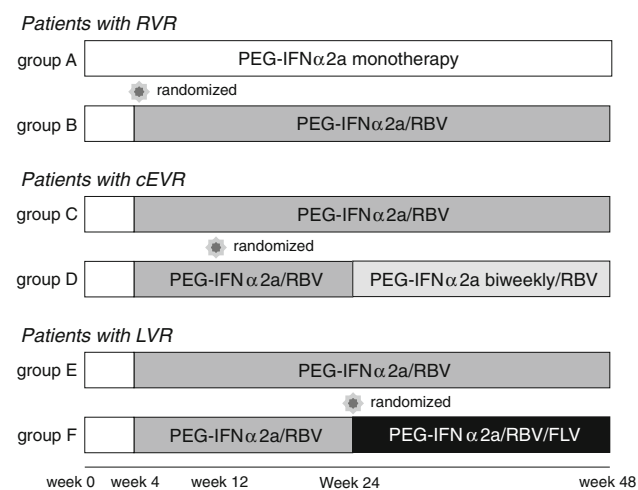
Fig. 1 Study design. After a lead-in therapy with PEG-IFNα-2a for 4 weeks, patients with negative HCV RNA at week 4 (RVR) were randomly assigned to receive PEG-IFNα-2a alone (group A) or PEG-IFNα-2a/RBV combination (group B). Patients with negative HCV RNA at week 12 (cEVR) were randomly assigned to receive weekly PEG-IFNα-2a/RBV combination (group C) or biweekly PEG-IFNα-2a/RBV combination (group D). Patients with negative HCV RNA at week 24 (LVR) were randomly assigned to receive PEG-IFNα-2a/RBV combination (group E) or PEG-IFNα-2a/RBV/fluvastatin (FLV) combination (group F)

at week 12 (complete early virological response, cEVR) were randomly assigned to receive weekly PEG-IFNα-2a/RBV combination (group C) or biweekly PEG-IFNα-2a/RBV combination (group D). Patients with negative HCV RNA at week 24 (late virological response, LVR) were randomly assigned to receive PEG-IFNα-2a/RBV combination (group E) or PEG-IFNα-2a/RBV/fluvastatin (FLV) combination (group F). For assignment, we used Microsoft Access to generate random numbers.

Cases with RVR: evaluation of necessity of RBV (PEG-IFNα-2a monotherapy versus PEG-IFNα-2a/RBV combination therapy)

Patients with negative HCV RNA at week 4 after the introduction of lead-in therapy with PEG-IFNα-2a alone (RVR) were randomly assigned to receive PEG-IFNα-2a alone (group A) or PEG-IFNα-2a/RBV combination (group B) to compare the efficacy and safety between the treatment groups and to evaluate the significance of addition of RBV in RVR cases.

Cases with cEVR: evaluation of dosage interval of PEG-IFNα-2a (weekly versus biweekly PEG-IFNα-2a in combination of RBV)

Patients positive for HCV RNA at week 4 but negative at week 12 (cEVR) were randomly assigned to receive weekly PEG-IFNα-2a/RBV combination (group C) or biweekly PEG-IFNα-2a/RBV combination (group D) after week 24, to compare the efficacy and safety between the treatment groups and to evaluate the dosage interval of PEG-IFNα-2a.

Cases with LVR: evaluation of clinical significance of addition of fluvastatin (PEG-IFNα-2a/RBV combination therapy versus PEG-IFNα-2a/RBV/FLV combination therapy)

Patients with positive HCV RNA at week 4 and 12 but negative HCV RNA at week 24 (LVR) were randomly assigned to a treatment group of PEG-IFNα-2a/RBV (group E) or PEG-IFNα-2a/RBV/FLV (group F) to compare the efficacy and safety between the treatment groups and to evaluate the significance of adding FLV. The dosage of FLV was set to 20 mg/day.

The primary efficacy endpoint was SVR. We also investigated correlations of IL-28B polymorphism (rs8099917) and Core 70 mutation with the rate of HCV RNA-negative conversion and SVR. The IL-28B polymorphism and Core 70 mutation were measured only in patients who wished to have this done. The genetic testing (IL-28B) was performed only in patients who gave written informed consent after obtaining the approval from the ethical committee. This study was a multicenter trial, and the numbers of patients with available HCV-RNA data were different for the week-4, -12, and -24 responses, because not all of the participating institutions completed all of these time points. Therefore, the numbers of patients with regard to IL28B and Core 70 mutation did not completely match at each time point.

If a decrease in the neutrophil count, platelet count, or Hb level reached a critical level or other adverse events

occurred, dose reduction or discontinuation of PEG-IFNα-2a or RBV was performed.

Statistical analysis

All statistical analyses were done using JMP version 9 (SAS). We used the *t* test, Chi-square test, and Fisher's exact test for univariate analysis. To identify factors affecting the SVR rate, we used the logistic regression test. A *p* value of less than 0.05 was considered statistically significant.
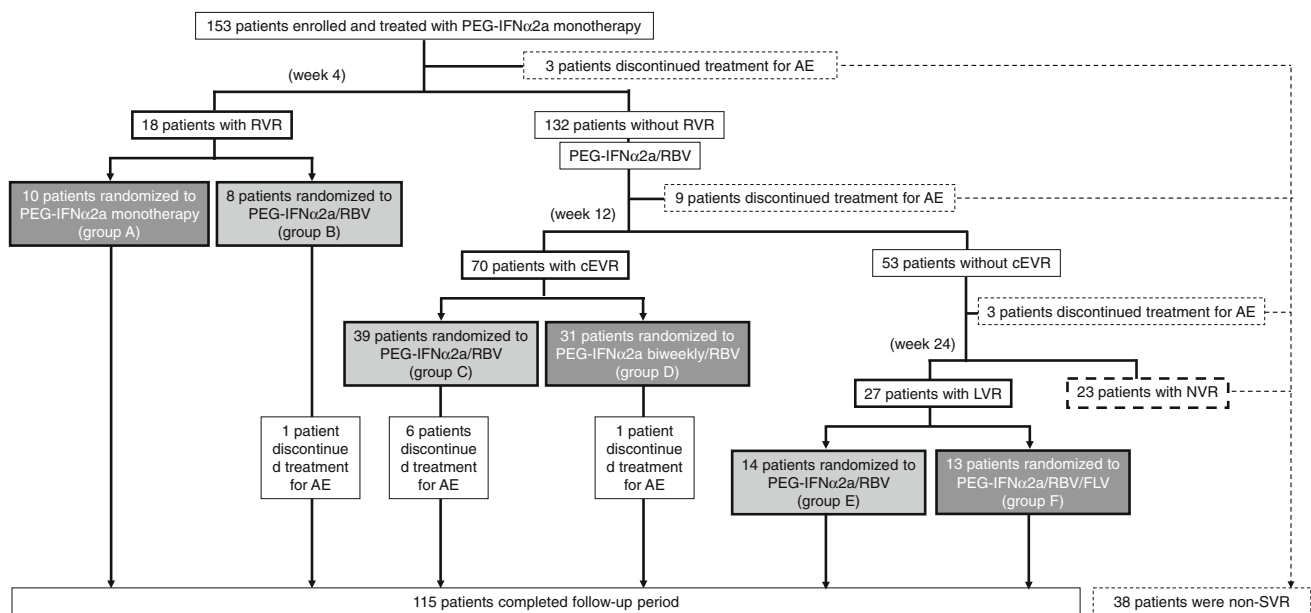
Results

Flowchart of the study

A flowchart of the study is shown in Fig. 2. PEG-IFNα-2a monotherapy was initiated in 153 patients, out of which 15 patients necessitated treatment discontinuation due to the patient's hope of recovery or adverse events. The timing of treatment discontinuation was within 4 weeks in three patients, between 5 and 12 weeks in nine patients, and between 13 and 24 weeks in three patients. RVR, cEVR, and LVR were achieved in 18, 70, and 27 patients, respectively, and these 115 patients were randomly assigned to treatment groups according to the response-guided therapy. However, 23 patients remained positive for HCV RNA (non-virological response, NVR) at week 24 and were finally judged as non-SVR.

Of 18 patients with RVR, 10 were assigned to group A (PEG-IFNα-2a monotherapy) and eight to group B (PEG-IFNα-2a/RBV combination); of 70 patients with cEVR, 39 were assigned to group C (weekly PEG-IFNα-2/RBV combination) and 31 to group D (biweekly PEG-IFNα-2/RBV combination); and of 27 patients with LVR, 14 were assigned to group E (PEG-IFNα-2a/RBV combination) and 13 to group F (PEG-IFNα-2a/RBV/FLV combination).

### PEG-IFNα-2a monotherapy versus PEG-IFNα-2a/RBV combination therapy in cases with RVR (group A versus group B)

The SVR rate in 18 patients with negative HCV RNA at week 4 after initiation of PEG-IFNα-2a monotherapy (RVR) was 100 % (10/10) in group A (PEG-IFNα-2a monotherapy) and 87.5 % (7/8) in group B (PEG-IFNα-2a/RBV combination), showing no significant difference between the two groups (*p* = 0.444). The rate of treatment discontinuation was 0 % (0/10) in group A. However, treatment discontinuation was required in one patient (12.5 %) in group B due to hemolytic anemia caused by RBV, resulting in non-SVR. Although the rate of RVR by PEG-IFNα-2a monotherapy was only 12 % (18/153), once

Fig. 2 Flowchart of the study. PEG-IFNα-2a monotherapy was initiated in 153 patients, of whom 15 patients necessitated treatment discontinuation. A total of 115 patients with RVR, cEVR, or LVR were randomly assigned to treatment groups, while 23 patients remained positive for HCV RNA (non-virological response, NVR) at week 24 and were finally judged as non-SVR. Of 18 patients with RVR, 10 were assigned to group A (PEG-IFNα-2a monotherapy) and eight to group B (PEG-IFNα-2a/RBV combination); of 70 patients with cEVR, 39 were assigned to group C (weekly PEG-IFNα-2/RBV combination) and 31 to group D (biweekly PEG-IFNα-2/RBV combination); and of 27 patients with LVR, 14 were assigned to group E (PEG-IFNα-2a/RBV combination) and 13 to group F (PEG-IFNα-2a/RBV/FLV combination)

Fig. 3 The SVR and treatment discontinuation rate in the group (A + D + F) of treatment regimens modified according to response-guided therapy and in the group (B + C + E) of PEG-IFNα-2a/RBV combination therapy
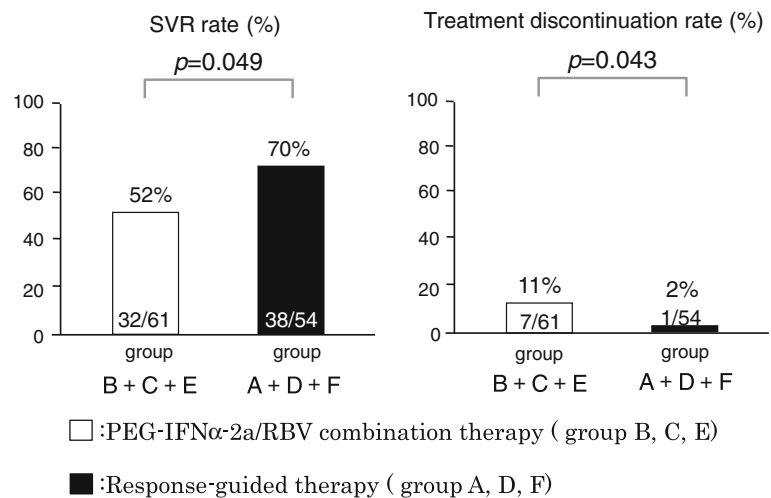
RVR is achieved, PEG-IFNα-2a monotherapy without addition of RBV can induce SVR at a high rate with a high tolerability.

Weekly PEG-IFNα-2/RBV combination versus biweekly PEG-IFNα-2/RBV combination therapy in patients with cEVR (group C versus group D)

The SVR rate in 70 patients with cEVR was 54 % (21/39) in group C (weekly PEG-IFNα-2/RBV combination) and 65 % (20/31) in group D (biweekly PEG-IFNα-2/RBV combination). Adverse events leading to treatment discontinuation occurred in six patients (15 %) in group C (a decrease in Hb level, chest pain, fatigue, dizziness, a sense of feeling bad, and a suspicion of HCC) but in only one patient (3 %) in group D (depression), suggesting that the rate of treatment discontinuation tended to be higher in group C than in group D ($p = 0.123$). The difference in the SVR rates between groups C and D may reflect the difference in the rate of treatment discontinuation between the groups.

PEG-IFNα-2a/RBV combination versus PEG-IFNα-2a/RBV/FLV combination therapy in patients with LVR (group E versus group F)

The SVR rate in 27 patients with LVR was 29 % (4/14) in group E (PEG-IFNα-2a/RBV combination therapy) and 62 % (7/13) in group F (PEG-IFNα-2a/RBV/FLV combination therapy), suggesting that the rate tended to be higher in group F than in group E ($p = 0.085$). Thus, addition of an HMG-CoA inhibitor, FLV, increased the SVR rate even in patients with LVR showing delayed negative conversion of HCV RNA. There were no adverse events leading to treatment discontinuation in both groups, and FLV did not augment the adverse events in group F.

Group with PEG-IFNα-2a/RBV combination therapy versus group with response-guided therapy (groups B + C + E versus groups A + D + F)

We then divided all of these groups into two groups according to treatment regimens, a group (A + D + F) in which treatment regimen was modified according to response-guided therapy and a group (B + C + E) of PEG-IFNα-2a/RBV combination therapy. The SVR rate in the response-guided therapy group was significantly higher than in the PEG-IFNα-2a/RBV combination therapy group [70 % (38/54) versus 52 % (32/61), $p = 0.049$].

The rate of treatment discontinuation due to adverse events was significantly lower in the response-guided therapy group than in the PEG-IFNα-2a/RBV combination therapy group [11 % (7/61) versus 2 % (1/54), $p = 0.043$] (Fig. 3).

Factors influencing negative conversion of HCV RNA at week 4, 12, and 24

Factors influencing negative conversion of HCV RNA at week 4 were analyzed in 18 patients with negative HCV RNA and 132 patients with positive HCV RNA. Factors identified as significantly different between the negative and positive groups were age and HCV RNA titer before study treatment, but IL-28B polymorphism and Core 70 mutation were not associated with negative conversion at this time point. Comparison between 88 negative and 53 positive HCV RNA patients at week 12 and that between 115 negative and 23 positive HCV RNA patients at week 24 identified IL-28B polymorphism and Core 70 mutation as factors, showing differences with a statistical significance (Table 2).

Table 2 Characteristics of HCV RNA-negative or positive patients at week 4, 12, and 24

At week 4	Negative ($n = 18$)	Positive ($n = 132$)	p value
Age (years)	49.5 ± 14.6	57.6 ± 10.3	0.003
HCV RNA (Log IU/mL)	6.0 ± 0.7	6.4 ± 0.7	0.009

At week 12	Negative ($n = 88$)	Positive ($n = 53$)	p value
Core 70 substitution (wild/mutant)	39/14	13/22	<0.001
IL-28B, rs8099917 (TT/non-TT)	31/8	10/18	<0.001

At week 24	Negative ($n = 115$)	Positive ($n = 23$)	p value
Core 70 substitution (wild/mutant)	48/23	4/11	0.003
IL-28B, rs8099917 (TT/non-TT)	38/14	3/10	0.003

Value are mean $\pm$ standard deviation (SD)
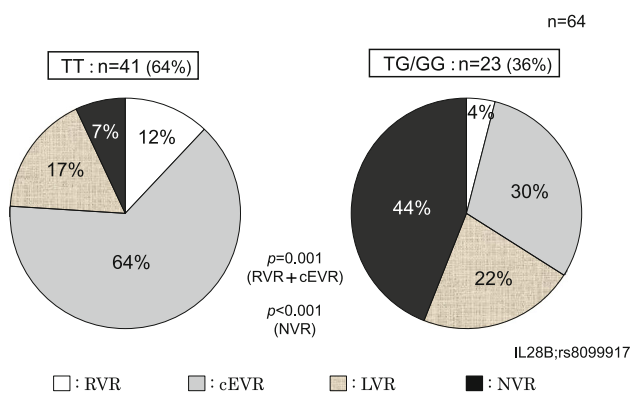
Fig. 4 Treatment response to PEG-IFNα-2a with or without RBV according to the IL-28B single nucleotide polymorphisms (TT versus TG/GG genotype)
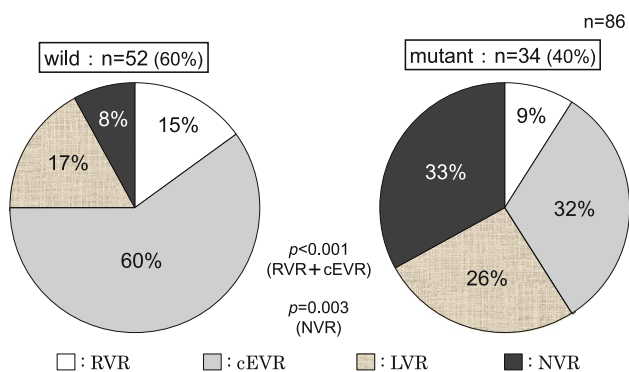
Fig. 5 Treatment response to PEG-IFNα-2a with or without RBV according to the Core 70 mutation (wild-type versus mutant Core 70)

We also investigated the correlation between IL-28B polymorphism and HCV RNA-negative conversion within 12 weeks (RVR + cEVR) in 64 patients in whom IL-28B polymorphism was examined. Negative HCV RNA was achieved within 12 weeks in 76 % of 41 patients with IL-28B TT genotype (major) and in 34 % of 23 patients with IL-28B TG or GG genotype (minor), showing a significant difference between them ($p = 0.001$). Especially in cases with NVR, negative HCV RNA was achieved in 7 % of patients with IL-28B major genotype and in 44 % of patients with IL-28B minor genotype ($p < 0.001$), suggesting that IL-28B polymorphism is strongly associated with treatment response (Fig. 4). Similarly, in 86 patients with determined Core 70 mutation status, negative HCV RNA was achieved within 12 weeks in 75 % of 52 patients with wild-type Core 70 and 41 % of 34 patients with mutant Core 70, showing a significant difference between them ($p < 0.001$). In patients with NVR, the rate of becoming HCV RNA-negative within 12 weeks was 8 % in patients with wild-type Core 70 and 33 % in those with mutant Core 70 ($p = 0.003$) (Fig. 5).

The SVR rates at different time points of HCV RNA-negative conversion by IL-28B polymorphism and Core 70 mutation

The SVR rates were investigated in patients with different time points of HCV RNA-negative conversion (RVR in six patients, cEVR in 33, LVR in 13, and NVR in 13) according to the IL-28B genotypes. The SVR rate was 100 % (5/5) in patients with RVR, 65 % (17/26) in patients with cEVR, 57 % (4/7) in patients with LVR, and 0 % (0/3) in patients with NVR with IL-28B major genotype; whereas the rate was 100 % (1/1) in patients with RVR, 43 % (3/7) in patients with cEVR, 83 % (5/6) in patients with LVR, and 0 % (0/10) in patients with NVR with IL-28B minor genotype. Similarly, the SVR rates were investigated in patients with different time points of HCV RNA-negative conversion (RVR in 11 patients, cEVR in 42, LVR in 18, and NVR in 15) according to the Core 70

Table 3 Characteristics of sustained virological response (SVR) and non-SVR patients

	SVR ($n = 70$)	Non-SVR ($n = 83$)	p value
Age (years)	53.1 ± 12.7	59.4 ± 8.7	<0.001
Gender (male/female)	29/41	34/49	0.954
HCV RNA (Log IU/mL)	6.4 ± 0.7	6.4 ± 0.7	0.782
BMI (kg/m^2)	22.7 ± 3.9	22.9 ± 2.8	0.815
Previous IFN (no/yes)	49/21	44/39	0.032
Fibrosis (F0-2/F3-4)	41/9	31/23	0.007
Activity (A0-1/A2-3)	24/27	25/29	0.938
NS5A mutation, n (0-1/2-)	31/10	47/3	0.013
Core 70 substitution (wild/mutant)	30/11	24/27	0.012
IL-28B, rs8099917 (TT/non-TT)	26/9	17/18	0.027
HCV RNA-negative at week 12 (yes/no)	58/12	30/41	<0.001
Treatment group (B,C,E/A,D,F)	32/38	29/16	0.049

Values are mean ± standard deviation (SD)

BMI body mass index

Table 4 Associated factors with sustained virological response (SVR) by multivariate logistic regression analysis

Factor	Odds ratio	95 % CI	p value
Age (per 1 year)	0.94	0.89–0.98	0.005
Previous IFN (no/yes)	1.62	0.62–4.27	0.323
Fibrosis (F0-2/F3-4)	3.38	1.15–10.8	0.026
NS5A mutation, n (2-/0-1)	7.18	1.32–61.0	0.021
Core 70 substitution (wild/mutant)	2.49	1.51–8.28	0.044
IL-28B, rs8099917 (TT/non-TT)	1.85	0.85-8.61	0.563
HCV RNA-negative at week 12 (yes/no)	7.89	2.92–24.0	<0.001

mutation status. The SVR rate was 100 % (RVR), 58 % (cEVR), 44 % (LVR), and 0 % (NVR) in patients with wild-type Core 70; whereas the rate was 67 % (RVR), 55 % (cEVR), 33 % (LVR), and 0 % (NVR) in patients with mutant Core 70. Thus, when the SVR rates were investigated according to the different time points of HCV RNA-negative conversion, there was no association of IL-28B polymorphism or Core 70 mutation with the SVR rates.

Factors affecting the SVR rate

An univariate analysis in 70 SVR patients and 83 non-SVR patients identified age, previous IFN treatment, fibrosis, NS5A mutation, Core 70 mutation, EVR, IL-28B, and treatment group as factors affecting the SVR rate (Table 3). In this analysis, we examined 83 non-SVR patients: 45 non-SVR patients are presented in Fig. 3, and 38 non-SVR patients (23 patients with NVR and 15 patients who discontinued the Peg-IFN-RBV treatment prior to the enrollment of the randomized trial) are presented in Fig. 2. Multivariate analysis using a logistic regression analysis revealed age (younger), fibrosis (mild), NS5A mutation (two or more mutations), Core 70 status (wild-type), and

EVR (RVR + cEVR), to be independent factors affecting the SVR rate, and among them EVR was the most significant factor (odds ratio, 7.89; $p < 0.001$) (Table 4). Therefore, even in patients considered intractable based on the IL-28B genotype or Core 70 mutation status, SVR is expected to be achieved once RVR or cEVR is reached during treatment.

Discussion

The introduction of combined treatment with PEG-IFN and RBV has increased the SVR rate to approximately 40–50 % even in intractable cases with genotype 1b high virus titer chronic hepatitis C after a standard treatment course of 48 weeks [1–4]. In an attempt to further improve the SVR rate, we propose a concept of "response-guided therapy", in which the treatment regimen (such as an extension of a treatment period) is determined according to the viral response to the initial treatment [7–15]. In cases with positive HCV RNA at week 4 or 12, extension of the treatment period from 48 to 72 weeks has been reported to prevent the recurrence and improve the SVR rate [12–14]. Recently, Miyase et al. [34] showed that PEG-IFNα-2a/ribavirin combination therapy resulted in better SVR rates than PEG-IFNα-2b/ribavirin combination therapy in female, older or low-weight patients. In addition, Minami et al. [35] reported that the rate of severe adverse events was not negligible in PEG-IFN/ribavirin combination therapy, and the rate was affected by treatment regimens. Therefore, it is important to establish a treatment regimen of PEG-IFN/RBV combination therapy that has a high efficacy with minimal adverse events. We herein investigated the treatment regimens based on the concept of response-guided therapy to minimize the rate of treatment discontinuation, without changing the treatment period, in consideration of aged patients in Japan.

Factors influencing SVR have been evaluated in many studies that reported IL-28B (a host factor) and Core 70 mutation (a viral factor) as factors predicting the treatment outcome [23, 24, 36–38]. Our present study also demonstrate that the SVR rate was lower in patients with IL-28B minor genotype and those with mutant Core 70, suggesting that IL-28B polymorphism and Core 70 mutation represent factors largely influencing the negative conversion of HCV RNA. Regarding the correlation between treatment response and SVR, Thompson et al. [38] reported that RVR and cEVR rates were lower in patients with the IL-28B minor genotype than in those with the major genotype but the SVR rate was not affected by the IL-28B genotype in patients with RVR or cEVR. In recent studies published after recognition of IL-28B polymorphism, virological response at week 4 and 12 was highly associated with SVR [39, 40]. In our present results, if RVR or EVR is achieved, a high SVR rate can be obtained regardless of the IL-28B polymorphism or Core 70 mutation status.

If RVR is achieved, PEG-IFNα-2a monotherapy exhibits a treatment effect equivalent to that of PEG-IFNα-2a/RBV combination therapy. Conversely, one patient receiving PEG-IFNα-2a/RBV combination therapy developed anemia caused by RBV, resulting in treatment discontinuation and non-SVR. In a phase III clinical trial in Japanese patients, the SVR rate in patients with RVR was 100 % (14/14) in control patients receiving PEG-IFNα-2a monotherapy but was 78 % (18/23) in those receiving PEG-IFNα-2a/RBV combination therapy [41]. Therefore, in terms of preventing treatment discontinuation due to adverse events of RBV, PEG-IFNα-2a monotherapy is recommended in cases with RVR.

In cases with cEVR, the SVR rate in patients who received biweekly PEG-IFNα-2/RBV combination therapy was comparable or even higher as compared to those who received weekly PEG-IFNα-2/RBV combination therapy. This means that biweekly PEG-IFNα-2a in a later treatment period did not reduce the antiviral effects in a subset of cases achieving a good antiviral effect (cEVR). This is partly because the half-life of PEG-IFNα2a is longer than that of PEG-IFNα2b [42–44], thus enabling the maintenance of antiviral effects. Therefore, this biweekly regimen appears possible only with PEG-IFNα2a. Regarding treatment discontinuation, the rate of treatment discontinuation was 3 % (1/31) in patients receiving biweekly PEG-IFNα-2 and 15 % (6/39) in those receiving weekly PEG-IFNα-2, suggesting that the reduced rate of adverse events and subsequent treatment discontinuation by biweekly administration may lead to the increased SVR rate.

Ikeda et al. [19] reported that one of the HMG-CoA reductase inhibitors, FLV, exhibits inhibitory effects on HCV RNA replication in a system of HCV RNA replication clone. In the clinical setting, Sezaki et al. and Rao and Pandya [20–22] reported that combined use of FLV from the treatment initiation period improved the SVR rate [21]. The HCV RNA is replicated using the lipid droplet in hepatocytes [45, 46], and HMG-CoA reductase inhibitors are reported to inhibit the proliferation of HCV RNA by suppressing the synthesis of mevalonic acid through geranylgeranylation [47].

We investigated whether the SVR rate is improved by the addition of FLV only in cases with LVR, because a high SVR rate is expected in patients showing rapid negative conversion of HCV RNA (such as RVR and cEVR cases) without the combined use of FLV. Our results showed that combined use of FLV yielded a higher SVR rate (62 %) as compared to the rate (29 %) obtained without the use of FLV, suggesting that the difference in the recurrence rate may reflect the difference in the SVR rate in patients negative for HCV RNA. Thus, because we used FLV in patients with LVR at high risk of recurrence, but not in those with RVR or cEVR at low risk of recurrence, the difference in anti-HCV activities by FLV was more pronounced. It has been reported that treatment with HMG-CoA reductase inhibitors does not increase the risk of severe hepatotoxicity in patients with chronic hepatitis C [48], which is consistent with our present results showing no adverse events associated with the addition of FLV.

In summary, the SVR rate was 52 % (32/61) in the group receiving PEG-IFNα-2a/RBV combination therapy and 70 % (38/54) in the group receiving modified treatment regimens according to response-guided therapy, showing a significant increase in the latter group. This result may be attributed to the difference in the rate of treatment discontinuation, which was significantly lower in the response-guided therapy group [2 % (1/54)] than in the PEG-IFNα-2a/RBV combination group [11 % (7/61)]. In addition, anti-HCV effects of FLV in patients with LVR at high risk of recurrence may contribute to the improved SVR in the response-guided therapy group. Our results demonstrated the safety and efficacy of PEG-IFNα-2a monotherapy in patients with RVR, biweekly PEG-IFNα-2a/RBV combination therapy in those with cEVR, and PEG-IFNα-2a/RBV/FLV combination therapy in those with LVR.

In conclusion, for the treatment of genotype 1b high virus titer chronic hepatitis C, the selection of an optimal response-guided therapy option, taking into consideration the viral response to initial treatment, the IL-28B polymorphism and Core 70 mutation status, and the safety of individual patients, can improve the SVR rate.

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