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Original Article

Interleukin 28B polymorphism predicts interferon plus ribavirin treatment outcome in patients with hepatitis C virus-related liver cirrhosis: A multicenter retrospective study in Japan

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Aim: This study evaluated the efficacy of interferon plus ribavirin and examined whether interleukin 28B (IL28B) polymorphism influenced treatment outcome in Japanese patients with hepatitis C virus (HCV)-related liver cirrhosis (LC).

Methods: Fourteen collaborating centers provided details of 261 patients with HCV-related LC undergoing treatment with interferon plus ribavirin. Univariate and multivariate analyses were used to establish which factors predicted treatment outcome.

Results: Eighty-four patients (32.2%) achieved a sustained virological response (SVR). SVR rates were 21.6% (41/190) in patients with HCV genotype 1 with high viral load (G1H) and 60.6% (43/71) in patients with non-G1H. In patients with non-G1H, treatment outcome was effective irrespective of IL28B polymorphism. In those with G1H, SVR was achieved in 27.1% of patients with the IL28B rs8099917 TT allele compared with 8.8% of those with the TG/GG alleles ($P = 0.004$). In patients with G1H having TT allele, treatments longer than 48 weeks achieved significantly higher SVR rates than treatments less than 48 weeks (34.6% vs 16.4%, $P = 0.042$). In patients with G1H having TG/GG alleles, treatments longer than 72 weeks achieved significantly higher SVR rates than treatments less than 72 weeks (37.5% vs 4.1%, $P = 0.010$).

Conclusion: Interferon plus ribavirin treatment in Japanese patients with non-G1H HCV-related LC was more effective than those with G1H and not influenced by IL28B polymorphism. In those with G1H, IL28B polymorphism may predict SVR and guide treatment duration: SVR rates were higher in those with the TT allele treated for more than 48 weeks and those with the TG/GG alleles treated for more than 72 weeks.

Key words: cirrhosis, hepatitis C virus, interferon, interleukin 28B, ribavirin

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INTRODUCTION

CHRONIC HEPATITIS C virus (HCV) infection is a leading cause of liver cirrhosis worldwide.[1] Patients with HCV-related liver cirrhosis (LC) are at increased risk of hepatic decompensation and hepatocellular

carcinoma (HCC).[2–4] The therapeutic goal in these patients should be the prevention of liver-related mortality. A randomized trial conducted in Japan was the first to suggest that interferon (IFN) may reduce the risk of HCC in patients with HCV-related LC.[5] Recent studies have shown that patients with HCV-related LC who achieved a sustained virological response (SVR) with antiviral therapy had a significant reduction in liver-related mortality.[6,7] However, patients with HCV-related LC show a lower SVR rate than non-cirrhotic patients, as well as a reduced tolerance to the therapy.[8,9] A previous meta-analysis revealed that the overall SVR rate in patients with cirrhosis was 33.3%, and was significantly higher in patients with HCV genotypes 2 and 3 (55.4%) than in those with HCV genotypes 1 and 4 (21.7%).[10]

Genome-wide association studies have recently shown that single nucleotide polymorphisms (SNP) near the interleukin 28B (IL28B) region (rs8099917, rs12979860) are the most powerful predictors of SVR to pegylated (PEG) IFN plus ribavirin in patients with HCV genotype 1 infection.[11–13] However, it is not clear whether IL28B polymorphism can be used to predict the virological response to treatment of HCV-related LC. This study evaluated the efficacy of IFN plus ribavirin, and the association between IL28B polymorphism and the treatment efficacy in Japanese patients with HCV-related LC.

METHODS

THIS WAS A multicenter retrospective study of patients with HCV-related LC who had received treatment with IFN plus ribavirin in 14 hospitals in Japan.

Patient selection

Data were collected from 290 patients with HCV-related LC receiving treatment with IFN plus ribavirin in 14 academic and community hospitals. All patients had compensated HCV-related LC with clinical or histological data available. The diagnosis of cirrhosis met at least one of the following criteria: liver biopsy specimens with cirrhosis, diffuse formation of the nodules on the liver surface in peritoneoscopy, over 12.5 kPa in liver stiffness values on transient elastography, signs of portal hypertension on ultrasound scan (splenomegaly, portal vein enlargement, re-permeabilization of the umbilical vein, or presence of portal-systemic shunts), presence of esophageal varices on endoscopy or positive values using the following discriminant by Ikeda and colleagues: $z = 0.124 \times (\gamma\text{-globulin [\%]}) + 0.001 \times$ (hyaluronate) ($\mu g\ L^{-1}$) $- 0.075 \times$ (platelet count [$\times 10^4$ counts/mm^3]) $- 0.413 \times$ sex (male, 1; female, 2) $- 2.005$.[14–16] Principal investigators in 14 hospitals identified eligible patients and entered data in a predefined database.

Combination therapy

Of the 290 patients identified, 29 were not genotyped for IL28B SNP, thus the data of 261 patients were analyzed. A total of 190 patients were infected with HCV genotype 1 with high viral load (>100 KIU/mL) (G1H) (72.8%) and the remaining 71 (27.2%) were classified as non-G1H. Twenty-two patients were HCV genotype 1 with low viral load, 46 were genotype 2a or 2b, and three were of unknown genotype. Two hundred and twenty-four (85.8%) patients were treated with PEG IFN-α-2b (1.5–1.0 μg/kg bodyweight per week), 20 (7.7%) patients were treated with PEG IFN-α-2a (45–180 μg/week) and the remaining 17 (6.5%) patients were treated with IFN-α-2b or IFN-β. IFN-α-2b and IFN-β were administrated at a median dose of 6 million units each day (seven times per week for the initial 2 or 4 weeks, followed by three times per week thereafter). All patients also received oral ribavirin (600–1000 mg/day). Median treatment duration was 48 and 28 weeks in G1H and non-G1H, respectively. The individual attending physician determined the treatment regimes and their duration.

Virological response during therapy and definitions

The efficacy end-point was SVR, defined as undetectable serum HCV RNA 24 weeks after treatment. Relapse was defined as undetectable serum HCV RNA at the last treatment visit but detectable serum HCV RNA again at the last follow-up visit. Breakthrough was defined as reappearance of serum HCV RNA during treatment. A non-responder was defined as serum HCV RNA never undetectable during treatment. A rapid virological response (RVR) was defined as undetectable serum HCV RNA at treatment week 4, and a complete early virological response (cEVR) was defined as undetectable serum HCV RNA at treatment week 12. A late virological response (LVR) was defined as detectable serum HCV RNA at 12 weeks that became undetectable within 36 weeks of the start of treatment.

Determination of IL28B genotype

Interleukin 28B (rs8099917) was genotyped in each of the 14 hospitals by Invader assay, TaqMan assay or by direct sequencing, as previously described.[17,18]

Statistical analysis

Results were analyzed on the intention-to-treat principle. Mean differences were tested using Student's *t*-test. The difference in the frequency distribution was analyzed with Fisher's exact test. Univariate and multivariate logistic regression analyses were used to identify factors independently associated with SVR. The odds ratios (OR) and 95% confidence intervals (95% CI) were also calculated. The parameters that achieved statistical significance on univariate analysis were entered into multivariate logistic regression analysis to identify significant independent factors. Data were analyzed with JMP version 9.0 for Macintosh (SAS Institute, Cary, NC, USA). All statistical analyses were two sided, and $P < 0.05$ was considered significant.

RESULTS

OF THE 261 patients included in our analysis, 84 patients (32.2%) achieved SVR (Fig. 1). The rate of relapse and breakthrough was 24.9% and the non-responder rate was 33.3%. There were 25 patients (9.6%) who required early discontinuation of treatment because of adverse events. Baseline demographic and clinical features are summarized in Table 1. The age of the patients was 60.7 ± 8.9 years and 50.6% were male. Of the patients studied, 125 patients (47.9%) had been treated with IFN previously, and 75 (28.7%) had not responded to previous treatment. One hundred and six patients (40.6%) had been treated for HCC before. There were 85 patients with esophageal varices (32.6%). There were 190 patients with G1H and 133 (70%) of these had the TT allele at IL28B rs8099917. There were 71 patients in the non-G1H group, 51 (71.8%) of whom were found to have the TT allele at IL28B rs8099917.

Virological response rates in patients with G1H and non-G1H HCV-related LC

The SVR rates were 21.6% (41/190) in patients with G1H and 60.6% (43/71) in patients with non-G1H (Table 2). There were no statistically significant differences between the G1H and non-G1H groups with regard to dose reduction rates of IFN or ribavirin. Dose reduction of IFN was required in 51.3% of patients and dose reduction of ribavirin in 53.6% of patients. Treatment duration in patients in the G1H group was significantly longer than those in the non-G1H group ($P = 0.010$).

Association between IL28B rs8099917 genotype and treatment response

Sustained virological response was achieved in 37.0% of patients with the rs8099917 TT allele and 20.8% in those with the TG or GG allele. Virological responses, including SVR, relapse and breakthrough, in patients with the rs8099917 TT allele were significantly higher than in those with rs8099917 TG or GG allele ($P = 0.013$ and 0.012, respectively; Table 3). The proportion of non-responders among patients with the rs8099917 TG or GG allele was significantly higher than in those with the TT allele ($P = 0.002$). There was no

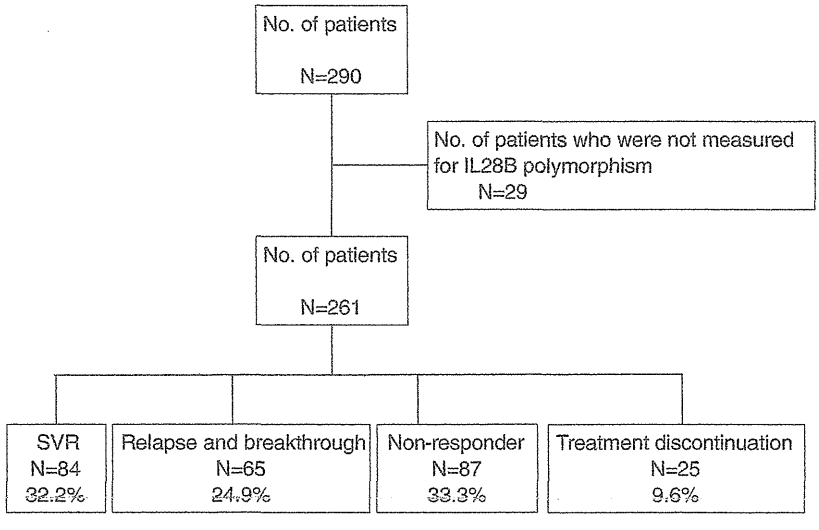

Figure 1 Flowchart showing the characteristics of the study cohort. IL28B, interleukin 28B; SVR, sustained virological response.

Table 1 Summary of demographic and baseline characteristics ($n = 261$)

	G1H, $n = 190$	Other than G1H, $n = 71$	All patients, $n = 261$
Sex (M : F)	95:95	37:34	132:129
Age (years)	60.5 ± 9.3	61.2 ± 7.8	60.7 ± 8.9
BMI (kg/m^2)	23.8 ± 3.5	23.4 ± 3.2	23.7 ± 3.4
IFN treatment history	91 (47.9%)	34 (47.9%)	125 (47.9%)
HCC treatment history	75 (39.5%)	31 (43.7%)	106 (40.6%)
Presence of EV	60 (31.6%)	25 (35.2%)	85 (32.6%)
Total bilirubin (mg/dl)	1.1 ± 0.9	1.1 ± 1.4	1.1 ± 1.2
AST (IU/L)	79.1 ± 44.2	75.8 ± 57.7	79.9 ± 52.7
ALT (IU/L)	82.4 ± 56.4	81.9 ± 75.4	83.3 ± 66.2
GGT (IU/L)	83.8 ± 107.8	87.0 ± 140.1	84.6 ± 115.8
Albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.4	3.7 ± 0.5
Prothrombin (%)	86.2 ± 14.4	83.7 ± 16.7	85.5 ± 15.1
WBC (/μL)	4407 ± 1592	4190 ± 1930	4348 ± 1667
Hemoglobin (g/dL)	13.2 ± 1.8	13.1 ± 1.8	13.1 ± 1.8
Platelets (10^4/mm^3)	11.8 ± 6.7	11.8 ± 6.3	11.8 ± 6.6
AFP (ng/mL)	48.9 ± 224.7	24.0 ± 29.3	45.4 ± 193.9
DCP (mAU/mL)	66.8 ± 372.3	155.3 ± 620.4	92.4 ± 450.8
IL28B (TT : TG + GG)	133:57	51:20	184:77

All values are expressed as mean ± standard deviation.
AFP, α-fetoprotein; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; DCP, des-γ-carboxy prothrombin; EV, esophageal varices; G1H, genotype 1 with high viral load; GGT, γ-glutamyltransferase; HCC, hepatocellular carcinoma; IFN, interferon; IL28B, interleukin 28B rs8099917 genotype; WBC, white blood cell.

significant association between the IL28B genotype and the incidence of adverse events.

Among patients in the G1H group, SVR was achieved in 27.1% (36/133) of those with the TT allele and 8.8% (5/57) of those with the TG or GG allele (Table 4). There was no statistically significant difference between IL28B genotype and viral response in patients with non-G1H.

Table 2 Summary of treatment and sustained virological response rates ($n = 261$)

	G1H, $n = 190$	Other than G1H, $n = 71$	All patients, $n = 261$
Dose reduction of IFN	$n = 98$ (51.6%)	$n = 36$ (50.7%)	$n = 134$ (51.3%)
Dose reduction of RBV	$n = 107$ (56.3%)	$n = 33$ (46.5%)	$n = 140$ (53.6%)
Treatment duration (weeks)			
Mean ± SD	45.3 ± 21.6	37.7 ± 19.6	43.2 ± 21.4
Median	48	28	48
SVR	$n = 41$ (21.6%)	$n = 43$ (60.6%)	$n = 84$ (32.2%)

G1H, genotype 1 with high viral load; IFN, interferon; RBV, ribavirin; SD, standard deviation; SVR, sustained virological response.

Table 3 Association between IL28B rs8099917 polymorphism and treatment response in 261 hepatitis C virus-related liver cirrhotic patients

IL28B	TT ($n = 184$)	TG + GG ($n = 77$)	*P*-value
SVR	68 (37.0%)	16 (20.8%)	0.013
Relapse and breakthrough	54 (29.3%)	11 (14.3%)	0.012
Non-responder	44 (23.9%)	43 (55.8%)	0.002
Discontinuation	18 (9.8%)	7 (9.1%)	1.000

IL28B, interleukin 28B rs8099917 genotype; SVR, sustained virological response.

Table 4 Sustained virological response associated between IL28B rs8099917 polymorphism and G1H in hepatitis C virus-related liver cirrhosis patients

IL28B	TT ($n = 184$)	TG + GG ($n = 77$)	*P*-value
G1H	36/133 (27.1%)	5/57 (8.8%)	0.004
Other than G1H	32/51 (62.7%)	11/20 (55.0%)	0.596

G1H, genotype 1 with high viral load; IL28B, interleukin 28B rs8099917 polymorphism.

Predictive factors associated with SVR

Differences in the characteristics of patients with SVR and those in whom SVR was not achieved are summarized in Table 5. Neither age, sex, alanine transaminase, aspartate aminotransferase, prothrombin activity, hemoglobin nor platelet counts appeared to significantly influence the chance of achieving SVR. The patients who achieved SVR had a lower body mass index, higher white blood cell count and higher serum albumin than those who did not, and were more likely to have non-G1H and the TT allele of IL28B rs8099917. Multivariate analysis identified that possession of the IL28B rs8099917 TT allele (OR = 2.85; 95% CI, 1.01–9.15; $P = 0.047$) and non-G1H (OR = 6.49; 95% CI, 1.77–26.43; $P = 0.005$) as significant determinants of SVR.

Treatment duration and efficacy in patients with G1H

Of the patients with G1H, 79 (41.6%) received less than 48 weeks of treatment. The number receiving 48–52 weeks, 53–72 weeks, over 72 weeks and unknown duration of treatment were 54 (28.4%), 41 (21.6%), 14 (7.4%) and two (1.1%), respectively. The median duration of treatment in patients who achieved RVR and cEVR was 48 weeks, but was significantly longer (66 weeks) in those with an LVR ($P < 0.001$). Table 6 shows the SVR rates of those with different IL28B genotypes and on-treatment viral response. The SVR rate in patients who achieved LVR was significantly lower than those who achieved RVR and cEVR ($P = 0.002$). Of the patients with G1H found to have the IL28B TG or GG genotype, none achieved RVR and only two achieved cEVR.

Predictors of SVR in patients with G1H and the TT allele

Patients with G1H and the TT allele who achieved SVR had higher platelet counts, higher serum albumin and had undergone over 48 weeks of treatment. Multivariate analysis identified platelet count (OR = 1.08; 95% CI, 1.01–1.18; $P = 0.047$), serum albumin (OR = 2.78; 95% CI, 1.14–7.42; $P = 0.031$) and over 48 weeks of treatment duration (OR = 2.53; 95% CI, 1.07–6.49; $P = 0.042$) as significant determinants of SVR (Table 7).

Predictors of SVR in patients with G1H and the TG or GG allele

Patients who had G1H and the TG or GG allele who achieved SVR had a higher total dose of ribavirin ($P = 0.011$) and more than 72 weeks of treatment duration ($P = 0.010$).

Treatment tolerability and adverse events

Table 8 illustrates details of the patients who experienced adverse events higher than grade 2. There were

Table 5 Factors associated with sustained virological response in hepatitis C virus-related liver cirrhosis patients

Factors	SVR (+), ($n = 84$)	SVR (−), ($n = 177$)	*P*-value	Multivariate analyses		
				Odds ratio	95% CI	*P*-value
BMI (kg/m^2)	22.9 ± 3.5	24.0 ± 3.3	0.019			
WBC (/μL)	4727 ± 2096	4168 ± 1376	0.013			
Albumin (g/dL)	3.83 ± 0.48	3.68 ± 0.46	0.018			
Other than G1H	$n = 43$ (51.2%)	$n = 28$ (15.8%)	<0.001	6.49	1.77–26.43	0.005
IL28B TT	$n = 68$ (81.0%)	$n = 116$ (65.5%)	0.012	2.85	1.01–9.15	0.047

P-values were obtained by logistic regression model.
BMI, body mass index; CI, confidence interval; G1H, genotype 1 with high viral load; IL28B, interleukin 28B rs8099917 polymorphism; SVR, sustained virological response; WBC, white blood cell.

Table 6 Sustained viral response rates between IL28B genotype and on-treatment viral response in the patients with G1H

	IL28B TT	IL28B TG/GG	All patients
RVR	7/7	0/0	7/7
	100%	0%	100%
cEVR	15/26	1/2	16/28
	57.7%	50%	57.1%
LVR	14/44	4/11	18/55
	31.8%	36.4%	32.7%

cEVR, complete early virological response (defined as serum HCV RNA negative at treatment week 12); G1H, genotype 1 with high viral load; HCV, hepatitis C virus; IL28B, interleukin 28B rs8099917; LVR, late virological response (defined as serum HCV RNA detectable at 12 weeks and undetectable at 36 weeks after the start of treatment); RVR, rapid virological response (defined as serum HCV RNA negative at treatment week 4).

two cases of liver decompensation, two cases of interstitial pneumonia, one case of cerebral hemorrhage and one case of cerebral infarction. The cause of death in two patients was decompensation of LC. In one patient, treatment was stopped after 4 weeks, and in another, treatment was stopped after 32 weeks because of hepatic failure. The IFN dose was reduced in 134 patients (51.3%), and the ribavirin dose was reduced in 140 patients (53.6%) and discontinued in 60 patients (23.0%). Among patients who had treatment discontinued, 27 patients (10.3%) had treatment withdrawn because of no virological response and 33 patients (12.6%) because of severe adverse events. In patients in whom treatment was discontinued, three patients had SVR and five had a relapse.

IL28B alleles predicting SVR in G1H group

The influence of IL28B rs8099917 genotype on SVR in G1H is shown in Figure 2. Overall, there were 84 patients (32.2%) who achieved SVR with IFN plus ribavirin in HCV-related LC. The SVR was 60.6% in those with non-G1H, and was not significantly influenced by IL28B rs8099917 genotype (the SVR in TT patients was 62.7% compared with 55.0% in TG or GG patients). In contrast, in patients with G1H, the SVR of patients with IL28B rs8099917 genotype TT was significantly higher than those with rs8099917 TG or GG (27.1% vs 8.8%, $P = 0.004$). In patients with G1H and IL28B TT, the SVR of those treated for over 48 weeks was significantly higher than those treated for less than 48 weeks (34.6% vs 16.4%, $P = 0.042$). In patients with G1H and IL28B TG/GG, the SVR of those treated for over 72 weeks was significantly higher than those treated for less than 72 weeks (37.5% vs 4.1%, $P = 0.010$).

Table 8 Adverse events higher than grade 2

	No. of patients (%)
Anemia	63 (24.1%)
Thrombocytopenia	31 (11.9%)
Leukopenia	19 (7.3%)
Rash and itching	17 (6.5%)
Fatigue and general malaise	15 (5.7%)
Gastrointestinal disorders	5 (1.9%)
Depression	5 (1.9%)
Development of hepatocellular carcinoma	3 (1.1%)
Respiratory disorders	3 (1.1%)
Liver decompensation	2 (0.8%)
Malignant neoplasm	2 (0.8%)
Interstitial pneumonia	2 (0.8%)
Cerebral hemorrhage	1 (0.4%)
Cerebral infarction	1 (0.4%)
Cholangitis	1 (0.4%)
Retinal hemorrhage	1 (0.4%)
Diabetes decompensation	1 (0.4%)
Palpitation	1 (0.4%)

DISCUSSION

WE FOUND THAT in Japanese patients with G1H HCV-related LC, the likelihood of achieving SVR with IFN plus ribavirin combination therapy was influ-

Table 7 Factors associated with sustained virological response in the patients with G1H and TT allele of IL28B rs8099917 ($n = 133$)

Factors	SVR (+) ($n = 36$)	SVR (−) ($n = 97$)	*P*-value	Multivariate analyses		
				Odds ratio	95% CI	*P*-value
Platelets (10^4/mm^3)	14.5 ± 11.5	10.6 ± 4.2	0.024	1.08	1.01–1.18	0.047
Albumin (g/dL)	3.92 ± 0.50	3.69 ± 0.46	0.018	2.78	1.14–7.42	0.031
Treatment duration, over 48 weeks	$n = 27$ (75%)	$n = 51$ (52.6%)	0.023	2.53	1.07–6.49	0.042

P-values were obtained by logistic regression model.
CI, confidence interval; G1H, genotype 1 with high viral load; IL28B, interleukin 28B; SVR, sustained virological response.

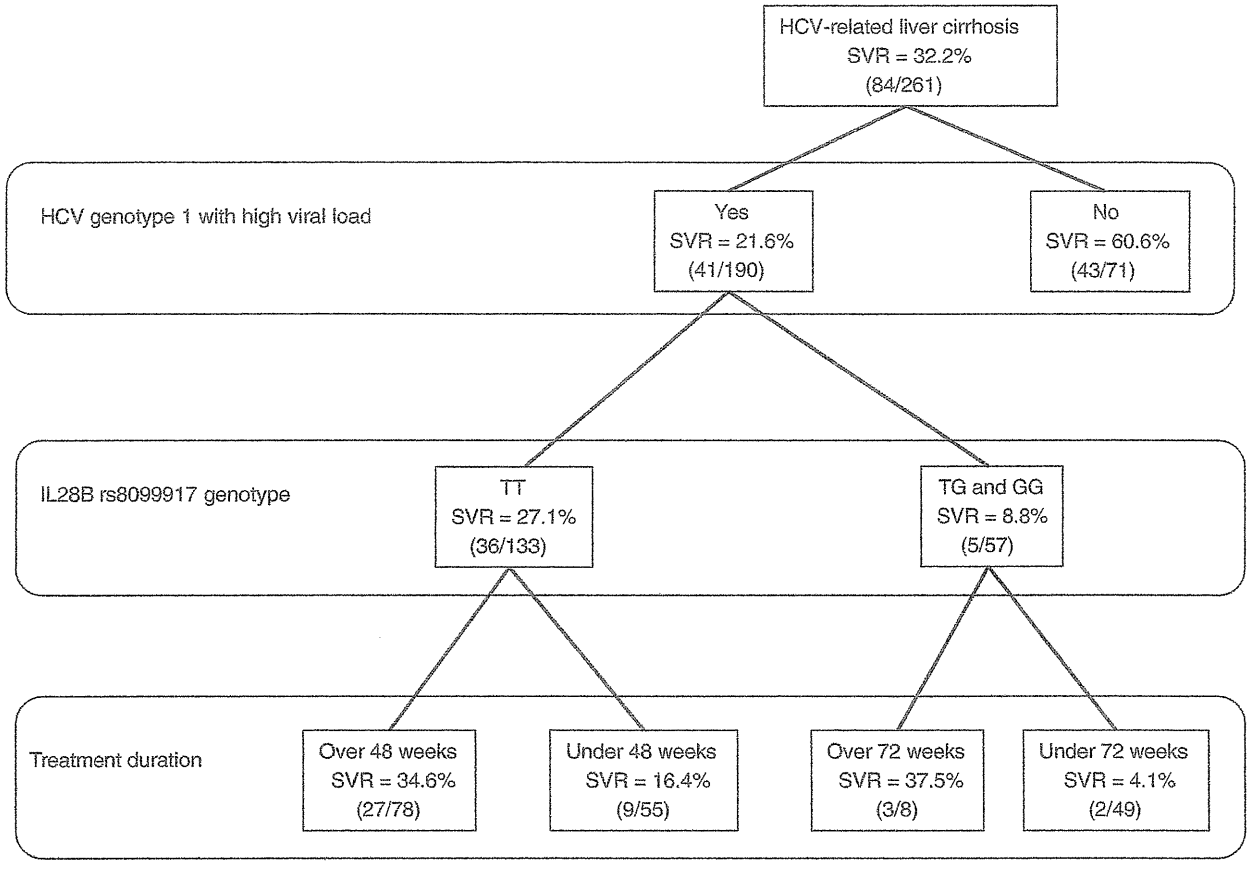

Figure 2 SVR in HCV-related liver cirrhosis patients treated with interferon plus ribavirin. In patients with G1H and the IL28B TT allele, the SVR rate of those who were treated for over 48 weeks was significantly higher than those treated for less than 48 weeks ($P = 0.042$). In patients with G1H and IL28B TG/GG, the SVR rate of patients treated for over 72 weeks was significantly higher than those treated for less than 72 weeks ($P = 0.010$). G1H, genotype 1 with high viral load; HCV, hepatitis C virus ; IL28B, interleukin 28B rs8099917; SVR, sustained virological response.

enced by a polymorphism at IL28B rs8099917. In contrast, SVR rates in non-G1H were higher than those in G1H, irrespective of IL28B genotype. This is the first report to demonstrate that an IL28B polymorphism can influence SVR rate in patients treated with IFN plus ribavirin combination therapy for G1H HCV-related LC. These results suggest that HCV genotypes, viral load and IL28B polymorphism should be taken into when determining antiviral therapy for HCV-related LC. In patients with HCV-related LC, IL28B genotyping may be a useful tool to determine the best antiviral therapy.

Recently, host genetic variation near the IL28B on chromosome 19, which encodes IFN-λ-3, have been shown to be associated with SVR to PEG IFN plus ribavirin in patients infected with HCV genotype 1.[11–13] Although some investigators have shown that IL28B polymorphisms are associated with a favorable response to treatment in patients with non-1 genotype infection, the association between the variants in IL28B and SVR in non-1 genotype-infected patients remains controversial.[19–25] IL28B polymorphisms are also a strong predictive factor for spontaneous HCV clearance.[26,27] However, the precise mechanism associated with the action of IL28B polymorphisms has not been fully elucidated.

Pegylated IFN plus ribavirin combination therapy has become the standard of care treatment for chronic HCV infection. The SVR rates range 42–46% in patients with HCV genotype 1 or 4 infection and 76–82% in patients with HCV genotype 2 or 3 infection, respectively.[9,28,29] However, in patients with HCV-related LC the SVR rate is even lower than in non-LC patients, reflecting reduced

tolerance to the therapy.[8–10] Although patients with HCV-related LC are difficult to treat, patients who achieved SVR showed a lower rate of liver-related adverse outcomes and improved survival.[8–10] Moreover, a randomized controlled trial showed that patients with HCV-related LC who received long-term PEG IFN treatment had a lower risk of HCC than controls.[30] Thus, IFN treatment for HCV-related LC is an effective means of preventing HCC, irrespective of whether SVR is achieved. In this study, the SVR was very low in patients with G1H and the TG or GG allele. Therefore, for these patients, long-term administration of maintenance IFN should be considered to reduce the risk of developing of HCC even if SVR is unlikely to be achieved.

Patients with advanced liver disease have a higher rate of adverse events when taking IFN and ribavirin combination therapy than patients with mild disease. Adverse events, such as neutropenia, thrombocytopenia and anemia, often require dose reduction of IFN or ribavirin. Previous studies have demonstrated that in patients with HCV-related LC, the rate of dose reductions in IFN and ribavirin range 6.9–20.6% and 16.7–27.1%, respectively.[31–33] In our study, IFN and ribavirin dose reductions were needed in 51.3% and 53.6% of patients, respectively. These are higher than those reported in other studies, but the discontinuation rate was slightly lower (12.6%).[33] Many patients required reductions in the doses of IFN and/or ribavirin early in the treatment period because of adverse events, but ultimately were able to tolerate long-term administration. It might be safer to start low-dose antiviral therapy with IFN plus ribavirin in HCV-related LC and titrating the dose upward as tolerated with the aim of long-term treatment, rather than beginning with the full dose and risking adverse events that would curtail antiviral therapy.

In patients infected with HCV genotype 1, previous studies have demonstrated that SVR rates of late virological responders (HCV RNA detectable at 12 weeks and undetectable at 24 weeks after the start of treatment) could be improved when treatment was extended to 72 weeks, compared with the standard treatment duration of 48 weeks, largely as a result of reducing post-treatment relapse rates.[34–37] In this study, the SVR rate in patients who had an LVR was significantly lower than those who achieved RVR or cEVR. However, the duration of treatment in the patients with a LVR was significantly longer than those who achieved cEVR or RVR. Individual physicians determined the duration of treatment based on the time at which serum HCV RNA became undetectable, accounting for the improved SVR rates in those receiving extended courses. Nevertheless, the safety and effectiveness of more than 48 weeks of antiviral therapy in patients with HCV-related LC has not been examined. We found that patients with the IL28B rs8099917 genotype TT, treatment of more than 48 weeks achieved a higher SVR rate than treatment of less than 48 weeks, and in those with the TG or GG alleles SVR rates were greater in those who received more than 72 weeks of treatment. The response to treatment is a very important guide of treatment duration in HCV-related LC. Further prospective studies using larger numbers of patients matched for race, HCV genotype, viral load and treatment durations would be required to explore the relationships between IL28B polymorphism and the treatment response to combination therapy in patients with HCV-related LC.

Recently, new trials of IFN-free combination therapy with direct-acting antivirals (DAA) such as protease-inhibitor, non-structural (NS)5A inhibitor or NS5B polymerase inhibitor nucleotide analog have shown a strong antiviral activity against HCV.[38–40] A previous study reported that the IL28B genotype can affect the response to an IFN-free regimen, but this result has been unclear in other regimens.[38–40] In a study of Japanese patients with HCV genotype 1b infection, dual oral DAA therapy (NS5A inhibitor and NS3 protease inhibitor) without IFN achieved an SVR rate of 90.5% of 21 patients with no response to previous therapy and in 63.6% of 22 patients who had been ineligible for treatment with PEG IFN.[41] However, lack of a virological response to DAA was also seen in patients with no response or partial response to previous therapy. In these patients with viral resistance to DAA, the combination therapy with IFN and DAA may be a means of eliminating HCV, and IL28B genotyping may be a useful tool in determining the best antiviral therapy and duration of treatment.

This study had certain limitations. Selection bias cannot be excluded, considering the retrospective nature of the work. However, all patients had well-established cirrhosis and had received IFN plus ribavirin in hepatitis centers throughout Japan. Our patients received a variety of IFN treatments (IFN-α, IFN-β and PEG IFN), several different doses of IFN and ribavirin, and several treatment durations. In the intention-to-treat analysis, the overall SVR rate was 32.2%; in patients with G1H it was 21.6% but was 60.6% in those with non-G1H. Interestingly, the overall SVR rate in this study was similar to that found in previous studies of patients with advanced fibrosis or cirrhosis treated with IFN or PEG IFN plus ribavirin.[8–10] Thus, although there were some

limitations, our findings contribute to providing valuable information to guide clinical decisions.

In conclusion, the combination therapy with IFN plus ribavirin in Japanese patients with non-G1H HCV-related LC was more effective than those with G1H and not influenced by IL28B polymorphism. However, in patients with G1H, IL28B polymorphism may be a strong predictive factor for SVR. Extending treatment may provide a better outcome in those with the IL28B TT allele treated for more than 48 weeks and in those with the TG/GG alleles treated for more than 72 weeks.

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Trial Registration: Evaluation of lenalidomide (Revlimid) to Treat Subjects with Cutaneous Lupus Erythematosus (CLE). Identified: #NCT00633945. http://www.clinicaltrial.gov/ct2/show/NCT00633945

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Biphasic skin reactions during telaprevir-based therapy of Japanese patients infected with hepatitis C virus

To the Editor: Telaprevir-based triple therapy, comprising 12 weeks' telaprevir administration with peginterferon and ribavirin, is highly effective for chronic hepatitis C.[1,2] However, telaprevir-related skin reactions are more severe than those related to peginterferon and ribavirin.[3] Telaprevir generally causes mild or moderate rash that occasionally progresses to serious skin reactions, including drug rash with eosinophilia and systemic symptoms and Stevens-Johnson syndrome.[2-4] To characterize the dermatologic adverse reactions associated with telaprevir, we enrolled 61 patients with chronic hepatitis C who were receiving telaprevir-based triple therapy at Toranomon Hospital as part of the phase 3 study in Japan.

Drug eruptions were noted in 83.6% (51/61) of patients and were classified according to severity as grade 1 in 37.7%, grade 2 in 44.3%, and grade 3 in 1.6% of patients.[2] The onset of the eruptions revealed a biphasic pattern (Fig 1). Early-phase reactions (EPRs) were noted in 62.3% (38/61) of subjects within 10 days of treatment initiation, while late-phase reactions (LPRs) were sporadically observed in 37.3% (23/61) of subjects between days 19 and 60. Both EPRs and newly occurring LPRs developed in 15 of the 23 patients with LPRs.

The clinical features of EPRs and LPRs were different (Fig 2). In a typical case of EPR, the skin reaction was millet-sized disseminated erythema, frequently accompanied by itching; the lesions generally occurred in a symmetrical manner and tended to develop in intertriginous regions (Fig 2, *A*). EPRs were relatively mild and tended to recover spontaneously. The EPRs disappeared without medication in 3 cases and were treated with topical and oral antihistamines in 7 cases. Others were generally managed with topical corticosteroids and oral antihistamines. EPRs resolved completely in all patients except 2, in whom a few papules persisted even after early erythema had resolved; both of these patients experienced new development and aggravation of erythema around day 40, which is indicative of LPRs.

LPRs involved injection-site erythema accentuated by reddish papules, microvesicles, and concrescence of erythema with severe itching, lower limb purpura, and increase by approximately 10% in the eosinophil count (Fig 2, *B*). Among the 23 patients with LPRs, 8 required only topical corticosteroids, and 3 required both topical corticosteroids and oral antihistamines. Eleven patients with widespread erythema that was likely to progress to grade 3 without signs of severe drug eruption, such as systemic symptoms (e.g., pyrexia), mucous membrane lesions, and organ derangement, were treated with an oral corticosteroid along with topical corticosteroids and oral antihistamine, without discontinuing telaprevir-based triple therapy. In these cases,

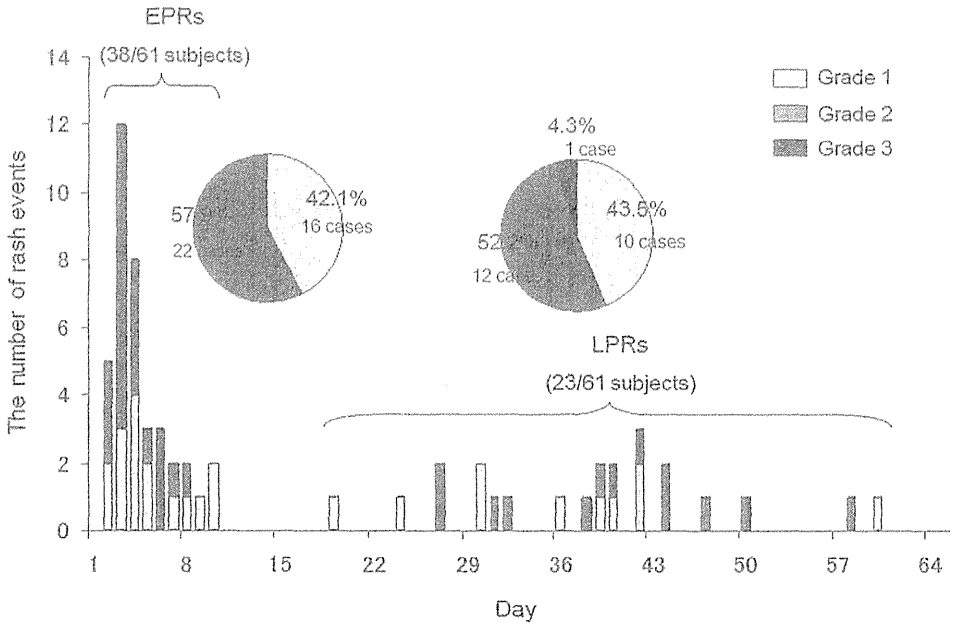

Fig 1. Time of onset of drug eruptions during administration of telaprevir-based triple therapy for hepatitis C. *EPRs*, Early-phase reactions; *LPRs*, late-phase reactions.

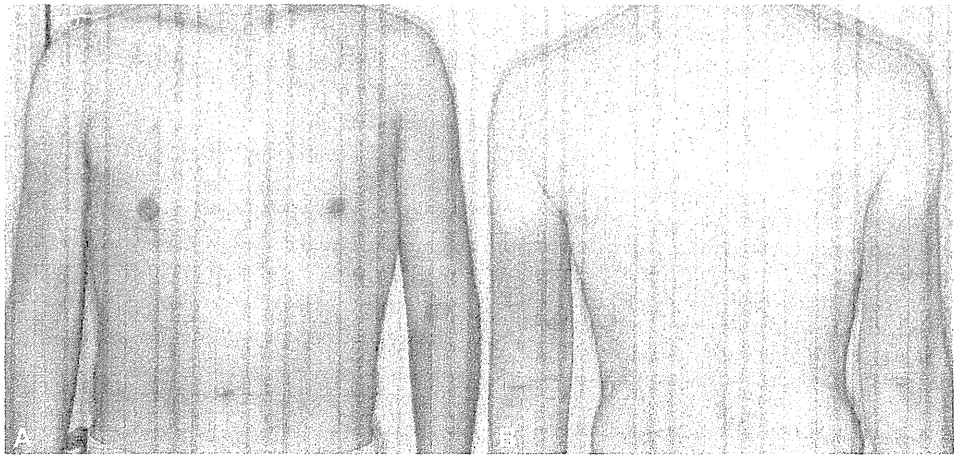

Fig 2. Comparison of early- and late-phase skin reactions in telaprevir-based triple therapy for hepatitis C. **A**, Skin reaction during the early phase (onset day: day 3, date of photo: day 4). **B**, Skin reaction during the late phase (onset day: day 31, date of photo: day 53).

prednisolone was orally administered at doses of 10 to 30 mg, which was gradually decreased without discontinuing telaprevir-based triple therapy; prednisolone was finally discontinued between 8 and 30 days, under careful observation. None of our patients had serious drug eruption. Telaprevir was continued in all patients except 1 who complained of strong itching sensation on day 64 without severe skin lesions.

Chronic hepatitis C is a fatal disease that can cause liver cancer. To continue the telaprevir-based triple therapy, good collaboration between hepatologists and dermatologists is important to appropriately evaluate skin symptoms and minimize the risk of serious drug eruptions.

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The diagnostic challenge of vulvar squamous cell carcinoma: Clinical manifestations and unusual human papillomavirus types

To the Editor: Treatment for early stage vulvar cancer lesions is readily available with limited morbidity; advanced stages of the disease, however, require interventions with serious morbidity. We sought to characterize clinical presentation of vulvar carcinoma to better understand reasons for delayed diagnosis and to determine which human papillomavirus (HPV) subtypes are causative.

Twenty-three cases of invasive vulvar squamous cell carcinoma (SCC) were identified using the pathology databases at the University of Pennsylvania. DNA was extracted from formalin-fixed paraffin embedded samples. HPV-PCR products were detected with PGMY-GP+-primer system. HPV-PCR products were then cloned and sequenced. NCBI-BLAST analysis revealed the presence of different HPV types.[1] Clinical data were extracted from the medical record (Table I).

Table I. Demographic and lesion characteristics

Age at diagnosis (median, IQR)	61	(43-76)
Smoking status (n, %)		
Never smoker	8	35%
Past smoker	6	26%
Current smoker	7	31%
Smoking status unknown	2	9%
Medical history (n, %)		
History of HIV infection	3	21%
History of genital warts	6	27%
History of diabetes	5	22%
History of inflammatory bowel disease	0	0%
History of organ transplant	2	9%
History of other cancer	4	17%
History of autoimmune disease	0	0%
History of eczema	1	4%
History of prior systemic treatments (n, %)		
Yes	3	14%
None/unknown	20	86%
History of topical treatments to vulvar area (n, %)		
Yes	8	35%
None/unknown	15	65%
History of abnormal Paps (n, %)		
Yes	8	35%
None/unknown	15	65%
History of concurrent or previous vulvar dermatoses diagnosed clinically (n, %)		
Yes	4	83%
None/unknown	19	17%
Previous vulvar symptoms (n, %)		
Yes	17	74%
None/unknown	6	26%
Lesion size in cm (median, IQR)*		
Type of provider who first evaluated patient (N)		
Ob/gyn	18	78%
Other	5	22%
Time from initial presentation in medical system to biopsy in months (Median, IQR)†	1	(0-2)

IQR, Interquartile range.
*Data available for 15 of 23 specimens.
†One day to 1 month rounded up to 1 month.

Studies have shown that vulvar cancer patients often have lengthy medical contact and treatment for vulvar symptoms prior to diagnosis.[2,3] Most patients in our study (74%) were aware of vulvar symptoms

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Once-daily simeprevir with peginterferon and ribavirin for treatment-experienced HCV genotype 1-infected patients in Japan: the CONCERTO-2 and CONCERTO-3 studies

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Abstract
Background Efficacy of available therapies for patients with HCV who have previously failed treatment is limited. Two Phase III, open-label trials in Japan investigated efficacy and safety of simeprevir and peginterferon-α-2a/ribavirin (PR) combination therapy in treatment-experienced patients with genotype 1 HCV infection.
Methods In CONCERTO-2, prior non-responders to IFN-based therapy ($N = 106$) received simeprevir (TMC435) 100 mg QD with PR for 12 (SMV12, $n = 53$) or 24 weeks (SMV24, $n = 53$) followed by response-guided therapy (RGT) with PR for 12/36 (SMV12) or 0/24 (SMV24) weeks. In CONCERTO-3, relapsers after IFN-based therapy ($N = 49$) received simeprevir 100 mg QD with PR for 12 weeks followed by RGT with PR for 12/36 weeks. Primary endpoints were the rates of sustained virologic response 12 weeks after treatment end (SVR12).
Results SVR12 rates were 52.8 % (SMV12) and 35.8 % (SMV24) for prior non-responders, and 95.9 % for prior relapsers (SMV12; $p \leq 0.0001$ vs null hypothesis, respectively). Most prior non-responders (SMV12: 81.1 %; SMV24: 73.6 %) and prior relapsers (95.9 %) met RGT criteria and completed PR to Week 24. Of these, 60.5 %, 48.7 %, and 95.7 %, respectively, achieved SVR12. Viral breakthrough occurred in 13.2 % (SMV12) and 11.3 % (SMV24) of prior non-responders; no viral breakthrough occurred in prior relapsers. Viral relapse occurred in 38.6 % (SMV12) and 51.1 % (SMV24) of prior non-responders and 8.2 % of prior relapsers. Simeprevir with PR was generally well tolerated in both studies.
Conclusion Re-treatment with 12 weeks of simeprevir QD with PR provided high SVR in treatment-experienced patients with chronic HCV genotype 1 infection, and allowed most patients to complete treatment in 24 weeks.

Keywords Chronic hepatitis C · Sustained virologic response · Simeprevir · TMC435 · Treatment-experienced

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Introduction

Infection with hepatitis C virus (HCV) is a global health problem and a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) [1]. Recent estimates suggest that approximately 2 million people are infected

with HCV in Japan [2]. Furthermore, HCC is one of the leading causes of cancer-related mortality in Japan, with approximately 70 % of HCC cases attributable to HCV infection [2, 3]. Among Japanese patients with HCV, genotype 1b is the most prevalent subtype, accounting for approximately 70 % of cases (versus 20 % for genotype 2a and 10 % for all other genotypes combined) [2].

Until recently, combination therapy comprising peg-interferon-α and ribavirin (PR) for 24–48 weeks was recognized as the standard treatment for patients with HCV infection [4, 5]. However, sustained virologic response (SVR) rates are typically just 40–50 % in patients with HCV genotype 1 infection treated with PR, and prolonged treatment is often required, resulting in increased rates of treatment discontinuations and dose reductions due to adverse events (AEs) [6–9]. Re-treatment for patients who do not achieve SVR is limited to re-exposure to PR with a modified dose and treatment duration. However, the SVR rates associated with PR re-treatment are low (16 % in one study) [10]. New regimens that increase SVR rates and shorten the treatment period below 48 weeks would benefit those patients who have previously failed therapy.

Efforts aimed at improving SVR rates in this patient group have focused on oral direct-acting antiviral agents (DAAs) that specifically inhibit the HCV NS3/4A viral protease essential for HCV replication. Two first–generation NS3/4A viral protease inhibitors (PIs), boceprevir and telaprevir, have already been approved in Europe and the U.S. for use in combination with PR for the management of treatment-naïve and -experienced patients with HCV infection [11]. One of these PIs, telaprevir, has also been approved in Japan and is recommended in Japanese treatment guidelines for use in combination with PR as triple therapy for chronic genotype 1 HCV infection [12–14]. Triple therapy regimens comprising PIs with PR have led to marked improvements in SVR rates compared with PR alone in both treatment-naïve and -experienced patients. Furthermore, a considerable number of patients may also qualify for shortened treatment duration while preserving high SVR rates by incorporating a response-guided therapy (RGT) regimen based on on-treatment virologic response milestones [15]. However, the requirement of multiple daily doses for both PIs currently licensed has increased the complexity of treatment [14–19], and the incidence and severity of AEs such as anemia, skin rash, and renal dysfunction are frequently increased compared with PR alone. Consequently, Japanese guidelines do not recommend the use of triple therapy regimens comprising telaprevir and PR in elderly (≥65 years) patients with chronic HCV genotype 1 with high virus levels [12].

Simeprevir is a one-pill, once-daily (QD), oral HCV NS3/4A protease inhibitor approved in Japan, Canada, and the United States; it is in registration in Europe. In a Phase II study conducted in Japan with treatment-naïve HCV genotype 1-infected patients, addition of simeprevir to PR was associated with greater plasma HCV RNA reductions, a higher SVR rate, and a generally good tolerability profile compared with PR alone [20]. CONCERTO-2 and CONCERTO-3 are two Phase III studies conducted in Japan to investigate the efficacy and safety of simeprevir (100 mg QD) with PR in patients with HCV genotype 1 infection who were non-responders (CONCERTO-2) or relapsers (CONCERTO-3) to previous interferon (IFN)-based therapy.

Methods

Patients

Male and female patients recruited into the CONCERTO-2 and CONCERTO-3 studies were aged between 20 and 70 years, had chronic HCV genotype 1 infection with plasma HCV RNA of ≥5.0 $\log_{10}$ IU/mL at screening, and were HCV treatment-experienced. CONCERTO-2 recruited non-responders, defined as patients who had failed IFN-based therapy administered for more than 24 weeks, or who had failed IFN-based therapy administered for <24 weeks because of <2 $\log_{10}$ IU/mL reduction from baseline in plasma HCV RNA level at week 12. CONCERTO-3 recruited prior relapsers, defined as patients who had received prior treatment with IFN-based therapy for at least 24 weeks with documented undetectable plasma HCV RNA at the last measurement on treatment, and subsequent detectable plasma HCV RNA level within 1 year after the last dose of medication. Patients with evidence of HCC, a history of liver cirrhosis or hepatic failure, or with any liver disease of non-HCV etiology, HIV or hepatitis B co-infection, or who had received previous treatment with any HCV therapy (including DAAs) other than IFN, peginterferon, or RBV were excluded from both studies. Patients were also excluded if they had any of the following laboratory abnormalities at screening: platelet counts <90,000/μL, absolute neutrophil counts <1,500/μL, white blood cell counts <3,000/μL, hemoglobin <12 g/dL, total serum bilirubin ≥1.5 mg/dL, or creatinine >1.5 mg/dL. All patients gave their informed consent to participate in the study.

Study design

CONCERTO-2 (TMC435-HPC3004; NCT01288209) was a Phase III, multicenter, open-label, two-arm, randomized study. Recruitment commenced on January 5, 2011, and the final patient's last observation was completed on

September 5, 2012. CONCERTO-3 (TMC435-HPC3008; NCT01290731) was a Phase III, multicenter, open-label, single-arm study. It was initiated on December 22, 2010, and was completed on August 14, 2012. Both studies were approved by the appropriate ethics committees and were performed in accordance with the ethical standards of the Declaration of Helsinki, as well as the Good Clinical Practice guidelines.

In CONCERTO-2, eligible patients were randomized (1:1 ratio) to one of two treatment groups, stratified by age (<65 or ≥65 years old) and *IL28B* genotype (rs8099917; TT or TG/GG): SMV12/PR or SMV24/PR (Supplementary Figure 1). In the SMV12/PR group patients received simeprevir 100 mg QD combined with PR for 12 weeks followed by PR alone for 12 weeks until week 24. In the SMV24/PR group, patients received simeprevir 100 mg QD combined with PR for 24 weeks. In CONCERTO-3 eligible patients received simeprevir 100 mg QD with PR for 12 weeks, followed by PR alone for 12 weeks until week 24 (SMV12/PR) (Supplementary Figure 1). In both studies at week 24, patients either stopped or continued treatment with PR according to RGT criteria. Patients were permitted to stop PR at week 24 if they achieved HCV RNA levels <1.2 $\log_{10}$ IU/mL detectable or undetectable HCV RNA at week 4 and undetectable HCV RNA levels at week 12. All other patients continued PR until week 48. Generally, all patients were followed up for up to 72 weeks after the start of treatment regardless of treatment duration.

In both studies, virologic stopping criteria were implemented to ensure that patients with a suboptimal response discontinued treatment in a timely manner in order to limit the risk of drug resistance and reduce unnecessary exposure to PR. The virologic stopping criteria were as follows: patients with HCV RNA levels >3.0 $\log_{10}$ IU/mL at week 4 stopped simeprevir and continued with PR therapy; patients with confirmed HCV RNA levels >2.0 $\log_{10}$ IU/mL at week 12 (CONCERTO–2) or <2 $\log_{10}$ IU/mL reduction from baseline at week 12 (CONCERTO-3), or confirmed HCV RNA (≥1.2 $\log_{10}$ IU/mL) at weeks 24 or 36 (both studies), stopped all study medications.

The primary efficacy endpoint for both studies was SVR12, defined as the proportion of patients with undetectable HCV RNA at the end of treatment and 12 weeks after the last dose of treatment. Key secondary efficacy endpoints included SVR24 (defined as the proportion of patients with undetectable HCV RNA at the end of treatment and 24 weeks after the last dose of treatment), and the proportion of patients with undetectable HCV RNA at week 4 (rapid virologic response; RVR), or week 12 (complete early virologic response; cEVR). The incidence of viral breakthrough (increase of >1.0 $\log_{10}$ IU/mL in HCV RNA level from the lowest level reached, or HCV RNA level of >2.0 $\log_{10}$ IU/mL in patients whose HCV RNA level had previously been <1.2 $\log_{10}$ IU/mL or undetectable), viral relapse (undetectable HCV RNA at end of treatment and detectable HCV RNA at the timepoints of SVR assessment), normalization of alanine aminotransferase (ALT) levels (at end of treatment and the timepoints of SVR assessment), and the viral NS3 sequence were also assessed.

Treatment administration

Simeprevir was administered orally as a single, 100 mg capsule QD. No simeprevir dose adjustments were permitted. Peginterferon α-2a (Pegasys®, Chugai Pharmaceutical Co., Ltd) was administered as a subcutaneous injection (180 μg once weekly) and RBV (Copegus®, Chugai, Japan) as oral tablets (600–1000 mg total daily dose, depending on body weight) in accordance with the prescribing information. Dose modifications, temporary interruptions, and discontinuations of Peginterferon α-2a or RBV were made in accordance with the manufacturer's prescribing information.

Patients stopped simeprevir if they experienced any of the following: grade 4 elevation of bilirubin, grade 4 elevation of aspartate transaminase (AST)/ALT >2 times baseline value, grade 3/4 skin events/allergic reactions, or worsening of hepatic disease. All study medications were stopped if patients experienced grade 4 AEs or laboratory abnormalities that were not considered to be related to simeprevir specifically, or were not expected toxicities of PR or HCV infection.

The use of erythropoietin for treatment of anemia was not permitted.

Study assessments

Plasma HCV RNA was determined at screening, baseline, on day 3, and at weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24 (all patients), and weeks 28, 36, 48, 60, and 72 (patients stopping PR at week 24), or weeks 28, 36, 42, 48, 52, 60, and 72 (patients receiving PR until week 48) using the Roche COBAS® TaqMan® HCV Auto assay system (lower limit of quantification [LLOQ], 1.2 $\log_{10}$ IU/mL). ALT levels were determined at screening and at intervals throughout the study. Normal ALT levels, i.e. ≤40 IU/mL, were defined according to laboratory reference ranges. To determine HCV variants at the time of failure (defined as the visit at which patients met virologic stopping criteria, had viral breakthrough, or viral relapse, or if they had detectable HCV RNA at the end of treatment), HCV NS3 sequencing was determined at baseline and scheduled visits.

Adverse event assessments were performed through to 28 days after the last dose of study medication (treatment-emergent AEs), and then until the end of the post-treatment follow-up period. AEs were graded by investigators according to the World Health Organization (WHO) grading scale. Clinical laboratory tests, electrocardiogram, vital signs (blood pressure, pulse, and temperature) and physical examinations were performed at screening and at regular intervals throughout the study. Laboratory abnormalities were graded according to WHO criteria.

Statistical analysis

Efficacy analyses for both studies were performed on the full analysis set (FAS; all patients who received at least one dose of study medication and had post-baseline efficacy assessment data). The safety analyses were performed on the safety population (all patients who received at least one dose of study medication).

The sample size calculation for both studies was based on published data for PR [10, 21, 22]. For both CONCERTO-2 and CONCERTO-3, assumptions were based on approximately 10 % of patients withdrawing early from either study. Therefore, for CONCERTO-2, it was calculated that 15 patients in each treatment group would be required to provide 90 % power to detect a significant difference in SVR24 versus the null hypothesis, and that $\leq$14 % of patients who previously failed to respond to 48 weeks of PR would achieve SVR24 after re-treatment with PR (5 % significance level, 2-sided). Similarly for CONCERTO-3, it was calculated that 47 patients would be required to provide more than 90 % power to detect a significant difference in SVR24 versus the null hypothesis, and that $\leq$50 % of patients who previously relapsed after 48 weeks of PR therapy would achieve SVR24 after re-treatment with PR (5 % significance level, 2-sided). On account of the strong correlation between SVR12 and SVR24 rates, the sample size determination based on the SVR24 rate was regarded as applicable for these studies in which the primary endpoints were the SVR12 rate.

All significance tests and confidence intervals were interpreted at the 5 %, 2-sided significance level.

Descriptive statistics were used to summarize demographic and other baseline characteristics including *IL28B* genotype. For efficacy endpoints, continuous variables were summarized using descriptive statistics, and dichotomous variables are presented as a percentage of the total. For the primary efficacy endpoint (SVR12) and SVR24 rate, a binomial test was performed versus the null hypothesis with a 95 % confidence interval (for both treatment groups in CONCERTO-2). Change from baseline in $\log_{10}$ IU/mL HCV RNA was summarized at each timepoint for each treatment group. Exploratory subgroup analyses were performed for SVR12, based on baseline HCV RNA levels, and other baseline characteristics including *IL28B* genotype and age. The proportions of patients with viral breakthrough and viral relapse were summarized. AEs were coded using Medical Dictionary for Regulatory Activities version 15.0. Clinical laboratory abnormalities were determined according to the WHO grading scale.

All statistical analyses were performed using SAS® version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

Patient disposition and baseline characteristics

Of 128 patients screened in CONCERTO-2, 108 were randomized, and 106 (SMV12/PR24/48, $n = 53$; SMV24/PR24/48, $n = 53$) subsequently received study treatment and were included in both the FAS and safety populations (Supplementary Figure 2a). Of the 63 patients screened for CONCERTO-3, 49 subsequently received treatment and were included in the FAS and safety populations (Supplementary Figure 2b). Only 4.7 % of patients in CONCERTO-2 and 2.0 % in CONCERTO-3 discontinued the studies. The most common reason for discontinuation in both studies was withdrawal of consent [CONCERTO-2, 4 (3.8 %) patients; CONCERTO-3, 1 (2.0 %) patient).

A total of 84 (77.8 %) patients in CONCERTO-2 completed all treatments. Of the 22 patients who did not, 3 discontinued PR after completion of simeprevir. 9 discontinued simeprevir only and then discontinued PR, and 10 discontinued all study treatments concurrently. In CONCERTO-3, 47 (95.9 %) patients completed all treatments. Of the remaining two patients, one completed simeprevir treatment and discontinued PR, and the other patient discontinued all study treatments. Ten (9.4 %) patients in CONCERTO-2 and none in CONCERTO-3 discontinued treatment because they met virologic stopping criteria during the study treatment period.

Patient demographics and baseline characteristics are summarized in Table 1. The median patient age in CONCERTO-2 and CONCERTO-3 was 60.0 years (range 24–70) and 61.0 years (range 22–70), respectively. Half of the patients (50.0 %) in CONCERTO-2 and 40.8 % of the patients in CONCERTO-3 were male. The median baseline HCV RNA level in CONCERTO-2 and CONCERTO-3 was 6.40 $\log_{10}$ IU/mL (range 4.6–7.3) and 6.50 $\log_{10}$ IU/mL (range 5.0–7.0), respectively. In CONCERTO-2 most patients (86.7 %; 92/106) had the *IL28B* minor allele (TG/GG) genotype, whereas 13.2 % (14/106) had the *IL28B* major homo (TT) genotype (SNP rs8099917). In

Table 1 Baseline demographics and disease characteristics

Characteristic	CONCERTO-2 ($N = 106$)[a]		CONCERTO-3 ($N = 49$)
	SMV12 + PR24/48 ($n = 53$)	SMV24 + PR24/48 ($n = 53$)	SMV12 + PR24/48
Male, *n* (%)	27 (50.9)	26 (49.1)	20 (40.8)
Age (years), median (range)	60.0 (30–70)	60.0 (24–70)	61.0 (22–70)
Age ≥65 years, *n* (%)	14 (26.4)	12 (22.6)	12 (24.5)
BMI (kg/m^2), median (range)	22.30 (16.8–29.5)	21.90 (19.2–33.4)	22.30 (17.9–32.2)
HCV genotype, *n* (%)			
1a	0 (0.0)	3 (5.7)	1 (2.0)
1b	53 (100.0)	50 (94.3)	48 (98.0)
IL28B genotype (rs8099917), *n* (%)			
TT	8 (15.1)	6 (11.3)	35 (71.4)
TG/GG	45 (84.9)	47 (88.7)	14 (28.6)
IL28B genotype (rs12979860), *n* (%)			
CC	8 (15.1)	6 (11.3)	35 (71.4)
CT/TT	45 (84.9)	47 (88.7)	14 (28.6)
HCV RNA ($\log_{10}$ IU/mL), median (range)	6.40 (4.6–7.3)	6.40 (5.1–7.0)	6.50 (5.0–7.0)
HCV RNA ($\log_{10}$ IU/mL), n (%)			
<6.0	10 (18.9)	11 (20.8)	9 (18.4)
≥6.0 to <7.0	36 (67.9)	39 (73.6)	39 (79.6)
≥7.0	7 (13.2)	3 (5.7)	1 (2.0)
Bilirubin (mg/dL), median (range)	0.7 (0.4–2.2)	0.7 (0.3–1.7)	0.7 (0.4–1.6)
Hemoglobin (g/dL), median (range)	14.1 (11.8–16.8)	14.3 (11.4–16.9)	13.8 (11.9–17.9)
Neutrophils ($\times 10^2$/μL), median (range)	20.8 (11.4–68.4)	20.5 (10.0–52.3)	23.7 (12.9–53.2)
Platelets ($\times 10^4$/μL), median (range)	16.8 (9.0–39.2)	16.2 (9.6–31.4)	18.2 (10.6–27.3)
Metavir fibrosis stage,[b] *n/N* (%)			
F0: *no fibrosis*	0 (0.0)	2/11 (18.2)	0 (0.0)
F1: periportal fibrosis expansion	11/20 (55.0)	2/11 (18.2)	9/16 (56.3)
F2: P–P septae (>1 septum)	3/20 (15.0)	4/11 (36.4)	4/16 (25.0)
F3: P–C septae	6/20 (30.0)	3/11 (27.3)	3/16 (18.8)
F4: cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)
Prior therapy, *n* (%)			
IFN only	4 (7.5)	2 (3.8)	2 (4.1)
Peg/IFN only	0 (0)	1 (1.9)	2 (4.1)
IFN/RBV	4 (7.5)	4 (7.5)	4 (8.2)
PR	45 (84.9)	46 (86.8)	41 (83.7)

BMI body mass index, *HCV* hepatitis C virus, *IFN* interferon, *PR* pegylated interferon α-2a and ribavirin, *SMV* simeprevir

[a] All patients were Asian Japanese except one patient, who was Brazilian

[b] Available for patients who had a liver biopsy within two years prior to informed consent or during the screening period

contrast, the majority of patients in CONCERTO-3, (71.4 %; 35/49) had genotype TT and 28.6 % (14/49) had the minor allele genotype (TG/GG). Patient baseline characteristics were generally well matched between the two treatment groups in CONCERTO-2. The majority of patients in both studies [85.8 % (91/106) in CONCERTO-2 and 83.7 % (41/49) in CONCERTO-3] had previously received treatment with PR.

Efficacy

CONCERTO-2 (Prior non-responders to IFN-based therapy)

Virologic response During the first 2 weeks of simeprevir treatment there was an initial rapid reduction in plasma HCV RNA in both treatment groups (Fig. 1). From week 3 onwards, the majority of patients had HCV RNA levels below the LLOQ of the assay. RVR and cEVR rates in the SMV12/PR group were 58.5 % (31/53) and 88.0 % (44/50), respectively. Corresponding values in the SMV24/PR group were 50.9 % (27/53) and 83.7 % (41/49), respectively. SVR12 rates were 52.8 % (SMV12/PR) and

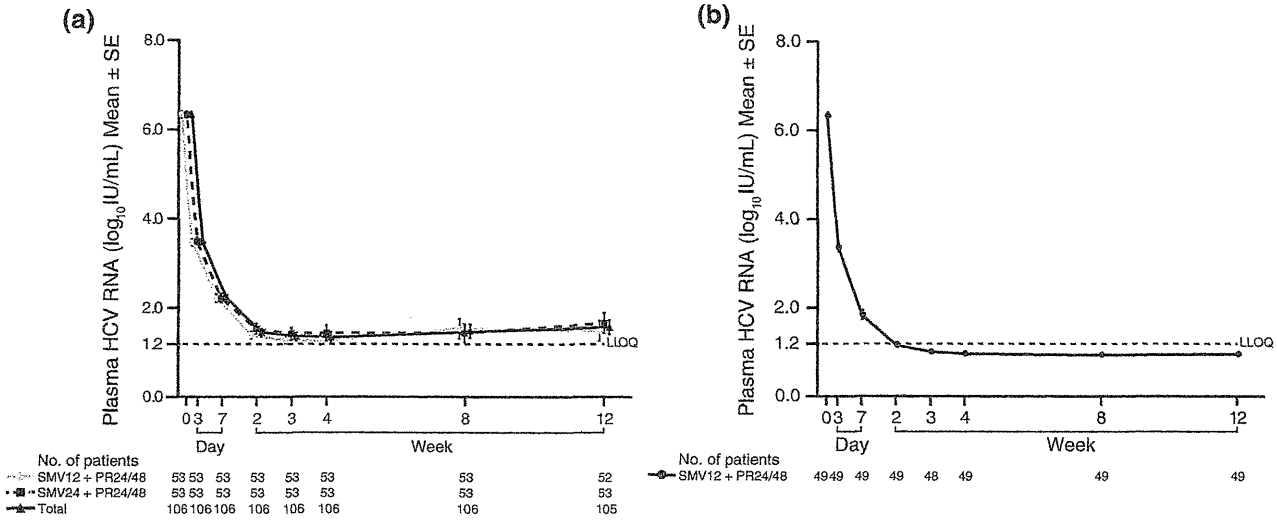

Fig. 1 Mean (±SE) plasma HCV RNA from baseline through week 12 **a** CONCERTO-2 and **b** CONCERTO-3 (SE values are too small to be viewed on **b**). *HCV* hepatitis C virus, *LLOQ* lower limit of quantification, *PR* peginterferon-α-2a/ribavirin, *SE* standard error, *SMV* simeprevir

Table 2 Virologic response rates

Endpoint, *n/N* (%)	CONCERTO-2 ($N = 106$)		CONCERTO-3 ($N = 49$)
	SMV12 + PR24/48 ($n = 53$)	SMV24 + PR24/48 ($n = 53$)	SMV12 + PR24/48
SVR12	28/53 (52.8)	19/53 (35.8)	47/49 (95.9)
95 % CI, *p* value	38.64–66.70, $p < 0.0001$[a]	23.14–50.20, $p = 0.0001$[a]	86.02–99.50, $p < 0.0001$[b]
SVR24	27/53[c] (50.9)	19/53 (35.8)	44/49[d] (89.8)
95 % CI, *p* value	36.84–64.94, $p < 0.0001$	23.14–50.20, $p = 0.0001$	77.77–96.60, $p < 0.0001$
RVR	31/53 (58.5)	27/53 (50.9)	40/49 (81.6)
cEVR	44/50 (88.0)	41/49 (83.7)	48/48[e] (100.0)
Viral breakthrough	7/53 (13.2)	6/53 (11.3)	0/49 (0.0)
Viral relapse	17/44 (38.6)	23/45 (51.1)	4/49 (8.2)

[a] One sample test for binomial distribution versus null hypothesis proportion ≤14 % for each treatment group

[b] One sample test for binomial distribution versus null hypothesis proportion ≤50 %

[c] One patient with SVR12 did not achieve SVR24 owing to viral relapse

[d] Three patients with SVR12 did not achieve SVR24; two had viral relapse, and one was missing at the SVR24 timepoint

[e] One patient permanently discontinued all study medication at week 7, therefore $N = 48$ for EVR and cEVR

cEVR complete early virologic response (undetectable HCV RNA at week 12 in treatment period), *HCV* hepatitis C virus, *PR* pegylated interferon α-2a and ribavirin, *RNA* ribonucleic acid, *RVR* rapid virologic response (undetectable HCV RNA at week 4 of treatment), *SMV* simeprevir, *SVR12* sustained virologic response 12 weeks after the end of treatment, *SVR24* sustained virologic response 24 weeks after the end of treatment; viral breakthrough, an increase of >1.0 $\log_{10}$ IU/mL in plasma HCV RNA from the lowest level reached or plasma HCV RNA >2.0 $\log_{10}$ IU/mL in patients whose HCV RNA had previously been <1.2 $\log_{10}$ IU/mL or undetectable; viral relapse, undetectable plasma HCV RNA at end of treatment and detectable or quantifiable HCV RNA at the last available measurement during the post-treatment follow-up period

35.8 % (SMV24/PR). The proportion of patients with SVR12 was higher than the proportion specified in the null hypotheses (14.0 %: SMV12/PR, $p < 0.0001$; SMV24/PR, $p = 0.0001$) (Table 2).

The majority of patients (77.4 %; 82/106) in the two treatment groups (SMV12/PR: 81.1 %; SMV24/PR: 73.6 %) met the RGT criteria and completed 24 weeks of treatment with PR. Of these, 82 patients, 60.5 % (26/43) and 48.7 % (19/39) in the SMV12/PR and SMV24/PR groups, respectively, achieved SVR12.

SVR24 rates (95 % CI) were 50.9 % (36.84–64.94) and 35.8 % (23.14–50.20) in the SMV12/PR and SMV24/PR groups, respectively (Table 2).

Viral breakthrough, viral relapse, and treatment failure Viral breakthrough occurred in 13 (12.3 %) of patients overall: 13.2 % (7/53) patients in the SMV12/PR group and 11.3 % (6/53) patients in the SMV24/PR group. Ten of these 13 patients experienced viral breakthrough during the simeprevir/PR treatment period and eight discontinued simeprevir owing to meeting the virologic stopping criteria at week 4 (Table 2).

Viral relapse rates were 38.6 % (17/44) in the SMV12/PR group and 51.1 % (23/45) in the SMV24/PR group. With the exception of one case that occurred at follow-up week 24 (SMV12/PR), all the cases of viral relapse occurred at follow-up week 4 or 12.

A total of 13 patients met a virologic stopping rule [SMV12/PR, $n = 8$ (15.1 %); SMV24/PR, $n = 5$ (9.4 %)].

The proportion of patients who failed to achieve SVR12 was 47.2 % (25/53; SMV12/PR) and 64.2 % (34/53; SMV24/PR). HCV RNA was detectable at the end of treatment for 17.0 % (9/53) and 15.1 % (8/53) of patients in the SMV12/PR and SMV24/PR groups, respectively, and at the time of the SVR12 assessment for 30.2 % (16/53) and 43.4 % (23/53), respectively. A further 5.7 % (3/53) of patients in the SMV24/PR group were missing at the SVR12 timepoint, as they had discontinued therapy for a reason other than an AE or meeting virologic stopping criteria.

Table 3 Rates of sustained virologic response at 12 weeks after end of treatment (SVR12) by selected demographic and baseline disease characteristics

Characteristic, *n/N* (%)	CONCERTO-2 ($N = 106$)		CONCERTO-3 ($N = 49$)
	SMV12 + PR24/48 ($n = 53$)	SMV24 + PR24/48 ($n = 53$)	SMV12 + PR24/48
Gender			
Male	16/27 (59.3)	10/26 (38.5)	19/20 (95.0)
Female	12/26 (46.2)	9/27 (33.3)	28/29 (96.6)
Age (years)			
≤45	2/5 (40.0)	3/7 (42.9)	
>45 to <65	19/34 (55.9)	16/34 (47.1)	35/37 (94.6)[a]
≥65	7/14 (50.0)	0/12 (0.0)	12/12 (100.0)[b]
HCV genotype			
1a	0/0 (0.0)	1/3 (33.3)	1/1 (100.0)
1b	28/53 (52.8)	18/50 (36.0)	46/48 (95.8)
IL28B genotype (rs8099917)			
TT	3/8 (37.5)	4/6 (66.7)	34/35 (97.1)
TG/GG	25/45 (55.6)	15/47 (31.9)	13/14 (92.9)
IL28B genotype (rs12979860)			
CC	3/8 (37.5)	4/6 (66.7)	34/35 (97.1)
CT/TT	25/45 (55.6)	15/47 (31.9)	13/14 (92.9)
Type of prior HCV therapy			
IFN only	3/4 (75.0)	2/2 (100.0)	–
IFN + RBV	3/4 (75.0)	2/4 (50.0)	–
PegIFN only	0/0 (0.0)	0/1 (0.0)	–
PR	22/45 (48.9)	15/46 (32.6)	–

HCV hepatitis C virus, *IFN* interferon, *PR* pegylated interferon α-2a and ribavirin, *RBV* ribavirin, *SMV* simeprevir

[a] <65 years

[b] ≥65 years