SVR rate was 33% in the PSE group, whereas no patient in the non-PSE group achieved SVR (15). Thus, the SVR rate of 66.7% in our study was higher than those reported previously. The pretreatment with PSE may be more beneficial prior to triple combination therapy for patients with advanced fibrosis. The SVR rate in patients who received triple combination therapy, but did not undergo PSE because of a sufficiently high platelet count, was previously reported to be 70-80% (16-18), which suggests that the SVR rate in those who underwent PSE because of a low platelet count may have been slightly lower. However, if patients with a low platelet count received triple combination therapy without the pretreatment with PSE, they may not have been adequately medicated or may have had to discontinue the therapy. Therefore, the SVR rate may have been even lower.

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

Zeuzem et al. noted no significant adverse reactions in patients with advanced fibrosis (17). However, Hezode et al. concluded that triple combination therapy has a poor safety profile in patients with compensated hepatic cirrhosis and should not be used when the patient's platelet count is $\leq 100\times10^3/mm^3$ and serum albumin level is ≤3.5 g/dL (28). Ogawa et al. reported that advanced fibrosis patients with serum albumin levels ≤3.5 g/dL were subject to many infections while receiving telaprevir-based triple therapy (29). Three of the patients in the present study had a platelet count $\leq100\times10^3/mm^3$ and serum albumin level ≤3.5 g/dL before PSE. Although one patient ceased the treatment due to the occurrence of hepatocellular carcinoma, no patient discontinued therapy due to adverse events. However, the safety of telaprevir-based triple therapy has not yet been established in patients with a decreased hepatic functional reserve or decompensated hepatic cirrhosis. Therefore, careful monitoring and prompt action for adverse effects are needed for triple combination therapy in these patients.

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

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

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

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

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

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Original Article

Factors associated with sustained virological response in 24-week telaprevir-based triple therapy for chronic hepatitis C genotype 1b patients with the *IL28B* minor genotype

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Aim: Single nucleotide polymorphisms (SNP) near the interleukin-28B (*IL28B*) gene affect the outcome of 24-week telaprevir-based triple therapy with telaprevir, pegylated interferon-α and ribavirin for chronic hepatitis C virus (HCV) genotype 1b patients. We aimed to identify factors associated with treatment outcomes in patients with the unfavorable minor *IL28B* SNP genotype, who have poor response to combination therapy.

Methods: Pretreatment and on-treatment factors associated with sustained virological response (SVR) for 24-week telaprevir-based triple therapy were analyzed using multiple logistic regression analysis in 106 HCV genotype 1b patients with the minor *IL28B* SNP rs8099917 genotype (non-TT).

Results: Of the 106 non-TT patients, 62 (58.5%) achieved SVR. Of the 44 remaining patients, 22 experienced relapse, 13 experienced viral breakthrough and nine were non-responders. Pretreatment factors such as treatment-naïve/prior treatment response ($P = 0.0041$), high fasting serum low-density lipoprotein cholesterol (LDL-C) concentration ($P = 0.0068$) and low serum HCV RNA levels ($P = 0.0088$) were significantly and independently associated with SVR. On-treatment factors such as achievement of rapid virological response (RVR) were significantly and independently associated with SVR ($P = 0.0001$). For both pre- and on-treatment factors, treatment-naïve/prior treatment response ($P = 0.0018$), low pretreatment serum fasting LDL-C ($P = 0.0062$) and achieving RVR ($P = 0.0021$) were significantly and independently associated with SVR.

Conclusion: In HCV genotype 1b patients with the minor *IL28B* SNP rs8099917 genotype, evaluating prior treatment response and achieving RVR and pretreatment serum fasting LDL-C concentrations were useful for predicting SVR achievement after 24-week telaprevir-based triple therapy.

Key words: fasting low-density lipoprotein cholesterol, hepatitis C virus, *IL28B* minor genotype, peginterferon, ribavirin, telaprevir

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INTRODUCTION

APPROXIMATELY 150 MILLION people are chronically infected with the hepatitis C virus (HCV) worldwide,[1] and chronic HCV infection is one of the most common causes of liver cirrhosis, portal hypertension, hepatic failure and hepatocellular carcinoma.[2,3] In Japan, approximately 70% of HCV patients carry HCV genotype 1.[4] Pegylated interferon-α (PEG IFN-α) plus ribavirin (RBV) combination therapy is frequently used to treat chronic HCV-infected patients and yields a sustained virological response (SVR) rate of 40–50% among patients with HCV genotype 1.[5–8] Addition of telaprevir, a first-generation non-structural (NS)3/4A HCV protease inhibitor, to the combination of PEG IFN-α plus RBV (PEG IFN-α/RBV) has been shown to significantly improve the SVR rate in both naïve and previously treated patients.[9–12] In previous studies, single nucleotide polymorphisms (SNP) near the interleukin-28B (*IL28B*) gene was one of the most important predictors of SVR in PEG IFN-α/RBV dual combination therapy.[8,13,14] Although it was reported that the value of the IL28B SNP is attenuated with 48-week PEG IFN-α/RBV/telaprevir triple therapy in a predominantly Caucasian cohort,[15] the SNP remained informative as a predictor of SVR to 24-week PEG IFN-α/RBV/telaprevir triple therapy for East Asian genotype 1b (G1b) patients.[16,17] In a previous East Asian cohort treated with the 24-week telaprevir-based triple therapy, the SVR rate was very high (94–97%) in patients with the rs8099917 genotype TT (*IL28B* major genotype), whereas it was relatively low (50–56%) in those with the genotype TG/GG (*IL28B* minor genotype).[16,17] Therefore, patients with the *IL28B* minor genotype remain difficult to treat and further information is required to determine what patients should be treated or wait for the next-generation treatment.

In this study, we clarified which factors could contribute to SVR in the case of 24-week telaprevir-based triple therapy in patients with the unfavorable *IL28B* minor genotype and evaluated what patients could be predicted to be optimal candidates for the treatment.

METHODS

Study population

BETWEEN JANUARY 2012 and August 2013, 436 consecutive patients who were chronically infected with HCV G1b received triple combination therapy with telaprevir (Telavic; Tanabe Mitsubishi Pharma, Osaka, Japan), PEG IFN-α-2b (PegIntron; MSD, Tokyo, Japan) and ribavirin (Rebetol, MSD) at multiple participating institutions. Of the 436 patients, 146 (33.5%) had the *IL28B* minor genotype. Of the 146 patients, 137 completed or discontinued treatment, and nine were undergoing treatment. Of the 137 patients, 116 were followed up for at least 24 weeks after treatment, and 21 were followed up for less than 24 weeks. One hundred and six of the 116 patients were treated with 24-week telaprevir with telaprevir-based triple therapy and were included in this analysis, and 10 patients were excluded because they had undergone 48-week telaprevir-based triple therapy. This study complied with the standards of the 2008 Declaration of Helsinki and current ethical guidelines, as reflected by the approval of the human ethics review committee of each institution. Written informed consent was obtained from each patient before entry into the study.

All of the patients satisfied the following criteria: (i) persistently seropositive for HCV RNA for more than 6 months, with the amount of serum HCV RNA determined by a quantitative real-time polymerase chain reaction (RT-PCR) method (COBAS TaqMan HCV test; Roche Diagnostics, Tokyo, Japan); (ii) each patient had a white blood cell count of 2000/μL or more, neutrophil count of 1500/μL or more, hemoglobin level of 11 g/dL or more and platelet count of 70 000/μL or more; and (iii) age range of 18–79 years and bodyweight of more than 35 kg at the time of study entry. The presence or absence of cirrhosis was determined by liver biopsy, using METAVIR scores[18] within 12 months of enrollment, or by an aspartate aminotransferase (AST) to platelet ratio index of more than 2, as proposed by Wai *et al.*[19] at the time of enrollment. The serum fasting low-density lipoprotein cholesterol (LDL-C) concentrations were calculated using the Friedewald formula[20] because there were no patients whose serum fasting triglyceride levels were 400 mg/dL or more. The exclusion criteria were as follows: (i) positive results for the hepatitis B surface antigen; (ii) positive results for the anti-HIV antibody; (iii) hepatocellular carcinoma; (iv) other liver diseases; (v) psychiatric conditions; and (vi) consumption of more than 20 g alcohol/day.

All patients were scheduled to receive telaprevir (1500–2250 mg/day) combined with weekly s.c. injections of PEG IFN-α-2b (1.5 μg/kg) and ribavirin (600–1000 mg/day, according to bodyweight: <60 kg, 600 mg/day; 60–80 kg, 800 mg/day; >80 kg, 1000 mg/day). If the patient's hemoglobin level was less than 13 g/dL at the start of therapy, the ribavirin dose was reduced by 200 mg for 12 weeks. This was followed by 12 weeks of PEG IFN-α-2b/RBV combination therapy.

When the baseline hemoglobin concentration was less than 13 g/dL, the dose of RBV was reduced by 200 mg. Telaprevir was administrated every 8 h after meals at a dose of 500 mg or 750 mg, or every 12 h after meals at a dose of 750 mg or 1125 mg. Ribavirin was administrated p.o. every 12 h after meals. Telaprevir adherence was calculated based on a dose of 2250 mg/day. On-treatment dose reduction, modification and discontinuation of PEG IFN, RBV or telaprevir followed the criteria and procedures according to the proper usage guidelines for telaprevir[21] or patient condition to reduce or avoid adverse effects and treatment discontinuation. In patients who had HCV RNA levels of more than 3 $\log_{10}$ IU/mL at week 4, detectable HCV RNA levels at week 12 or a 2-$\log_{10}$ IU/mL increase in HCV RNA from the lowest level during therapy, the therapy was discontinued due to the extremely low likelihood of achieving SVR and the high risk of developing antiviral resistance. In patients who had HCV RNA levels of 3 $\log_{10}$ IU/mL or less at week 4, the therapy was continued as the 24-week telaprevir-based triple therapy, though the therapy was discontinued on viral breakthrough.

Virological response was analyzed on an intention-to-treat basis. The primary end-point was SVR, defined as an undetectable serum HCV RNA level at 24 weeks post-treatment. Relapse was defined as undetectable HCV RNA levels by the end of treatment and detectable levels during the follow-up period. Viral breakthrough was defined as undetectable HCV RNA levels during treatment but detectable levels prior to the end of treatment. Non-response (NR) was diagnosed when HCV RNA levels did not drop below the detection level during therapy. NR was further divided into partial response and null response. Partial response was defined as viral load decline from the baseline level of 2.0 $\log_{10}$ IU/mL or more at 12 weeks of treatment but with persistently detectable viremia during treatment. Null response was defined as a viral load decline of less than 2.0 $\log_{10}$ IU/mL at 12 weeks of treatment and persistent viremia during treatment. We also defined rapid virological response (RVR) as the absence of detectable HCV RNA levels at 4 weeks after starting treatment.

All patients were treated at Jikei University Katsushika Medical Center, Jikei University Kashiwa Hospital, Shinmatsudo Central General Hospital, Nippon Medical School Chiba Hokusoh Hospital, Nippon Medical School Hospital, Kagawa Prefectural Central Hospital, Kurume University School of Medicine, Tokyo Metropolitan Bokutoh Hospital or Ogaki Municipal Hospital.

HCV-related markers

The HCV G1b genotype was determined by direct sequencing followed by phylogenetic analysis of the NS5B region.[22] The serum HCV RNA concentration was measured at the initiation of therapy and every 4 weeks thereafter until 24 weeks after the end of therapy. This was performed using the previously described RT–PCR method. The linear dynamic range of the assay was 1.2–7.8 $\log_{10}$ IU/mL. Samples below the level of detection were considered HCV negative. Amino acid (a.a.) substitutions at a.a. 70 of the viral core and in the IFN sensitivity-determining region between sites 2209 and 2248 of NS5A were determined using a direct sequencing method.[23,24] The "wild-type" a.a. 70 in the core region is arginine and a "mutant-type" causes a change to glutamine or histidine.

Genetic variation near the *IL28B* gene

Genomic DNA was extracted from whole blood using the MagNA Pure LC and the DNA Isolation Kit (Roche Diagnostics). The rs8099917 SNP near the *IL28B* gene[14] was genotyped by RT–PCR using the TaqMan SNP Genotyping Assay and the 7500 Fast RT-PCR System (Applied Biosystems, Foster City, CA, USA). The rs8099917 genotype was classified into two categories: TT (major genotype) and non-TT genotype (minor genotype, TG or GG).

Statistical analyses

The Mann–Whitney *U*-test was used to analyze differences between continuous variables. Fisher's exact tests were used to analyze differences in categorical data. To determine the baseline factors associated with SVR, univariate and multivariate logistic regression analyses were performed. Statistical significance was determined by applying a two-tailed test and resulted in a *P*-value of less than 0.05. $P < 0.1$ was considered marginal. To identify independent predictive factors of SVR, variables that were significant or marginal in the univariate analysis were used as candidates for multivariate logistic regression analysis by the forward and backward stepwise selection method. All statistical analyses were carried out using STATISTICA for Windows version 6 (StatSoft, Tulsa, OK, USA).

RESULTS

Treatment outcome

THE BASELINE CHARACTERISTICS of the 106 non-TT patients are summarized in Table 1. Of the 106 patients, 62 (58.5%) achieved SVR. The remaining

Table 1 Patient profile at start of 24-week telaprevir-based PEG IFN plus RBV combination therapy in HCV genotype 1b infected patients with the minor genotype at the rs8099917 single nucleotide polymorphism near the interleukin-28B gene

Demographic data	
No. of patients	106
Sex (male/female)	55/51
Age (years)	61 (18–79)
Bodyweight (kg)	60.3 (40.8–92.8)
Body mass index (kg/m^2)	23.3 (17.2–31.9)
Absence or presence of cirrhosis (non-cirrhosis/cirrhosis)	80/26
Amino acid substitutions in the HCV genotype 1b	
Core amino acid substitution 70 (wild-type/mutant-type/ND)†	52/53/1
No. of amino acid substitution in ISDR (0–1/≥2/ND)	87/17/2
Laboratory data	
HCV RNA ($\log_{10}$ IU/mL)	6.3 (5.0–7.6)
White blood cells (/μL)	4 660 (2 000–11 100)
Hemoglobin (g/dL)	14.1 (11.4–17.7)
Platelets (×10^4/μL)	17.35 (6.4–40.7)
Aspartate aminotransferase (IU/L)	42 (16–149)
Alanine aminotransferase (IU/L)	41.5 (14–261)
γ-Glutamyltransferase (IU/L)	48 (12–427)
Albumin (g/dL)	4.2 (2.8–4.8)
Fasting total cholesterol (mg/dL)	163 (111–253)
Fasting low-density lipoprotein cholesterol (mg/dL)	88 (39–204)
Fasting plasma glucose (mg/dL)	99 (74–210)
Homeostasis Model of Assessment – Insulin Resistance	2.17 (0.33–24.92)
α-Fetoprotein (ng/mL)	6.2 (1.0–192.0)
Treatment	
Initial dose of PEG IFN (μg/kg)	1.51 (1.04–1.94)
Initial dose of RBV (mg/kg)	11.3 (3.5–13.5)
Initial dose of TVR (1500/2250 mg)	55/51
Prior treatment response	
Naïve/relapse/partial response/null response	35/34/22/15

†"Wild-type" (arginine) or "mutant-type" (glutamine or histidine).
Data expressed as number of patients or median (range).
HCV, hepatitis C virus; ISDR, interferon-sensitivity determining region; ND, not determined; PEG IFN, peginterferon; RBV, ribavirin; RVR, rapid virological response; TVR, telaprevir.

44 (41.5%) patients were classified as non-SVR. Of the 44 non-SVR patients, 22 experienced relapse, 13 had viral breakthrough and nine were NR. Of the 106 patients, 11 (10.4%) did not complete the triple therapy; this was because of the stopping rule (serum HCV RNA detectable at 12 weeks of therapy) for seven patients (6.6%) and adverse events (severe skin lesion in one patient, severe digestive syndrome in two patients and severe anemia with renal dysfunction in one patient) for four patients (3.8%).

Pretreatment factors contributing to SVR

Low serum HCV RNA level (per 1.0 $\log_{10}$ IU/mL, $P = 0.0193$), high white blood cell count (per 1000/μL, $P = 0.0431$), high platelet count (per 10 000/μL, $P = 0.0285$), low serum AST level (per 10 IU/L, $P = 0.0327$), high fasting serum LDL-C concentration (per 10 mg/dL, $P = 0.0136$) and treatment naïve/prior relapsers/prior partial responders (vs prior null responders, $P = 0.0021$) were significantly associated with SVR as determined by univariate analysis. Hemoglobin level ($P = 0.0586$) and HCV core a.a. substitution 70 ($P = 0.0929$) were found to be marginally significant. Multiple logistic regression analysis identified significantly independent pretreatment factors associated with SVR: low serum HCV RNA level (odds ratio [OR], 0.263; 95% confidence interval [CI], 0.097–0.708; $P = 0.0088$), high fasting serum LDL-C concentration (OR, 1.394; 95% CI, 1.098–1.768; $P = 0.0068$) and response to prior PEG IFN-α-2b/RBV treatment (OR, 0.023; 95% CI, 0.001–0.292; $P = 0.0041$) (Table 2). There was no significant correlation between fasting serum LDL-C concentration and the presence of cirrhosis ($P = 0.1691$, data not shown).

On-treatment factors contributing to SVR

High adherence to PEG IFN-α-2b (per 10%, $P = 0.0092$), high adherence to RBV (per 10%, $P = 0.0361$) and achievement of RVR (vs non-RVR, $P = 7.35 \times 10^{-5}$) were significantly associated with SVR, as determined by univariate analysis. Multiple logistic regression analysis identified achievement of RVR (OR, 7.543; 95% CI, 2.783–20.440; $P = 0.0001$) as a significantly independent on-treatment factor associated with SVR (Table 2).

SVR rates according to each significantly independent factor

Pretreatment HCV RNA levels were 5.9 $\log_{10}$ IU/mL or less in 31 patients, 6.0–6.9 $\log_{10}$ IU/mL in 52 patients

Table 2 Patients that achieved an SVR

	SVR	Non-SVR	SVR vs non-SVR (1, non-SVR/2, SVR)			
			Univariate analysis	Multivariate analysis		
			P	OR	95% CI	*P*
Pretreatment factors						
Demographic data						
No. of patients	62	44				
Sex (1, male/2, female)	37/25	18/26	0.0611			
Age (years)	61.5 (18–75)	61 (40–79)	0.6697			
Bodyweight (kg)	60.3 (40.8–92.6)	60.3 (44.7–92.8)	0.5854			
Body mass index (kg/m^2)	23.0 (17.3–28.7)	23.4 (17.2–31.9)	0.3756			
Absence or presence of cirrhosis (1, non-cirrhosis/2, cirrhosis)	49/13	31/13	0.3161			
Prior treatment response						
Naïve/relapse/partial response/null response (1, naïve + relapse + partial response/2, null response)	20/28/13/1 (61/1)	15/6/9/14 (30/14)	0.0021	0.023	0.001–0.292	0.0041
Amino acid substitutions in the HCV genotype 1b						
Core amino acid substitution 70 (wild-type/mutant-type/ND)†	35/27/0	17/26/1	0.0929			
No. of amino acid substitutions in ISDR (0–1/≥2/ND)	50/12/0	37/5/2	0.3201			
Laboratory data						
HCV RNA ($\log_{10}$ IU/mL)	6.2 (5.0–7.2)	6.5 (5.5–7.6)	0.0193	0.263 (per 1.0 $\log_{10}$ IU/mL)	0.097–0.708	0.0088
White blood cells (/μL)	5 200 (2 000–11 100)	4 450 (2 200–7 900)	0.0431			
Hemoglobin (g/dL)	14.45 (11.7–16.8)	13.6 (11.4–17.5)	0.0586			
Platelets (×10^4/μL)	18.45 (7.4–40.7)	14.8 (6.4–25.9)	0.0285			
Aspartate aminotransferase (IU/L)	37.5 (16–149)	48.5 (22–139)	0.0327			
Alanine aminotransferase (IU/L)	36 (14–261)	45.5 (20–201)	0.1847			
γ-Glutamyltransferase (IU/L)	40 (12–328)	57 (14–427)	0.1603			
Albumin (g/dL)	4.25 (3.1–4.8)	4.1 (2.8–4.7)	0.2177			
Fasting total cholesterol (mg/dL)	164 (113–253)	155 (111–250)	0.3923			
Fasting low-density lipoprotein cholesterol (mg/dL)	96 (50–173)	82 (39–163)	0.0136	1.394 (per 10 mg/mL)	1.098–1.768	0.0068

Table 2 *Continued*

	SVR	Non-SVR	SVR vs non-SVR (1, non-SVR/2, SVR)			
			Univariate analysis	Multivariate analysis		
			P	OR	95% CI	*P*
Fasting plasma glucose (mg/dL)	100 (74–210)	97 (80–121)	0.1401			
Homeostasis Model of Assessment – Insulin Resistance	2.22 (0.33–20.7)	1.77 (0.49–24.9)	0.8409			
α-Fetoprotein (ng/mL)	5.0 (1.0–192)	9.0 (2.7–160)	0.2468			
Treatment						
Initial dose of PEG IFN (μg/kg)	1.51 (1.04–1.88)	1.56 (1.27–1.94)	0.1954			
Initial dose of RBV (mg/kg)	11.1 (3.0–13.3)	12.0 (7.6–13.6)	0.5974			
Initial dose of TVR (1500/2250 mg)	31/31	25/23	0.6455			
Initial dose of TVR (mg/kg)	30.0 (20.2–47.1)	30.9 (19.0–45.8)	0.9439			
On-treatment factors						
Treatment						
Adherence of PEG IFN (%)	100.0 (24.6–100.0)	100.0 (16.7–100.0)	0.0092			
Adherence of RBV (%)	76.9 (17.4–100.0)	67.2 (13.9–100.0)	0.0361			
Adherence of TVR (%)‡	66.7 (34.9–100.0)	66.7 (22.2–100.0)	0.1993			
Early virological response						
Achieving of RVR/non-RVR (1, non-RVR/2, RVR)	54/8 (87.1%)	21/23 (47.7%)	7.35×10^{-5}	7.543	2.783–20.440	0.0001

Background levels at starting of 24-week telaprevir-based PEG IFN plus ribavirin combination therapy in patients infected with the HCV genotype 1b and have the non-TT genotype of the rs8099917 SNP.
†"Wild-type" (arginine) or "mutant-type" (glutamine or histidine).
‡Calculated on the basis of 2250 mg/day.
Data expressed as number of patients or median (range).
CI, confidence interval; HCV, hepatitis C virus; ISDR, interferon-sensitivity determining region; OR, odds ratio; PEG IFN, pegylated interferon; RBV, ribavirin; RVR, rapid virological response; SNP, single nucleotide polymorphism; SVR, sustained virological response; TVR, telaprevir.

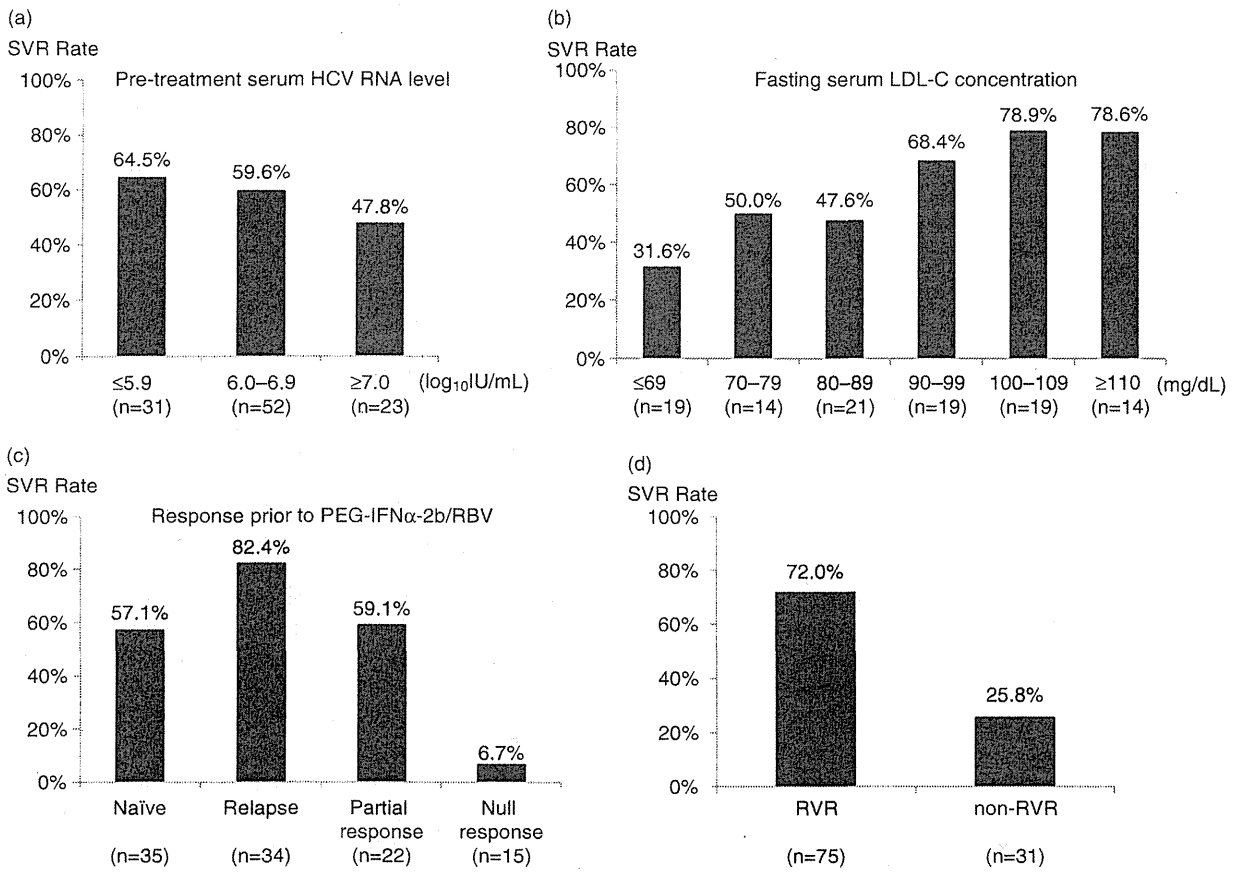

Figure 1 Sustained virological response (SVR) rates according to each independent, significant factor. (a) Pretreatment serum hepatitis C virus (HCV) RNA level ($P = 0.0088$). (b) Fasting serum low-density lipoprotein cholesterol (LDL-C) concentration ($P = 0.0068$). (c) Treatment-naïve/prior relapsers/prior partial responders versus prior null responders ($P = 0.0041$). (d) Achievement of rapid virological response (RVR) versus non-RVR ($P = 0.0001$). PEG IFN, pegylated interferon; RBV, ribavirin.

and 7.0 $\log_{10}$ IU/mL or more in 23 patients. SVR rates of patients with pretreatment HCV RNA levels of 5.9 $\log_{10}$ IU/mL or less, 6.0–6.9 $\log_{10}$ IU/mL and 7.0 $\log_{10}$ IU/mL or more were 64.5%, 59.6% and 47.8%, respectively. Fasting serum LDL-C concentrations were 69 mg/dL or less in 19 patients, 70–79 mg/dL in 14 patients, 80–89 mg/dL in 21 patients, 90–99 mg/dL in 19 patients, 100–109 mg/dL in 19 patients and 110 mg/dL or more in 14 patients. SVR rates of patients with fasting serum LDL-C concentrations of 69 mg/dL or less, 70–79 mg/dL, 80–89 mg/dL, 90–99 mg/dL, 100–109 mg/dL and 110 mg/dL or more were 31.6%, 50.0%, 47.6%, 68.4%, 78.9% and 78.6%, respectively. The SVR rates of treatment-naïve, relapsers, partial responders and null responders to prior PEG IFN-α-2b/RBV treatment were 57.1%, 82.4%, 59.1% and 6.7%, respectively. The SVR rates of patients with RVR achievement was 72.0%, while the rate of patients with RVR failure was 25.8% (Fig. 1).

Pre- and on-treatment factors contributing to SVR

Multiple logistic regression analysis identified three independent pre- and on-treatment factors that were significantly associated with SVR (Table 3): prior treatment response (naïve/relapse/partial vs null, $P = 0.0018$), serum fasting LDL-C (per 10 mg/dL, $P = 0.0062$) and early virological response (non-RVR vs RVR, $P = 0.0021$). Pretreatment serum HCV RNA level was not identified as a significant independent factor.

Table 3 Significantly independent pretreatment and on-treatment factors associated with SVR to 24-week telaprevir-based PEG IFN plus RBV combination therapy in patients infected with the HCV genotype 1b and have the non-TT genotype of the rs8099917 SNP (1, non-SVR/2, SVR)

Factor	OR	95% CI	*P*
Prior treatment response			
1: naïve/relapse/partial	1		
2: null	0.0186	0.0015–0.2274	0.0018
Serum fasting LDL-C (per 10 mg/dL)	1.3658	1.0928–1.7071	0.0062
Early virological response			
1: non-RVR	1		
2: RVR	7.0542	2.0310–24.5015	0.0021

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PEG IFN, pegylated interferon; RBV, ribavirin; RVR, rapid virological response; SNP, single nucleotide polymorphism; SVR, sustained virological response.

DISCUSSION

IL28B SNP ARE one of the strongest factors that contribute to SVR in PEG IFN-α/RBV dual combination therapy.[8,13,14] Addition of telaprevir to the PEG IFN-α/RBV combination remarkably improves the SVR rate in both treatment-naïve and previously treated patients,[9–12] which may decrease the value of *IL28B* SNP as a predictor of SVR.[15] However, in the 24-week telaprevir-based triple therapy for HCV G1b Japanese patients, *IL28B* SNP still remained informative as a strong predictor of SVR: the rate of 94–97% for those with the rs8099917 major genotype TT and 50–56% for those with the minor genotype TG/GG.[16,17] Therefore, this study focused on patients with the unfavorable *IL28B* minor genotype and analyzed factors associated with SVR in such a refractory patient subgroup.

In this study, high pretreatment serum fasting LDL-C and serum HCV RNA levels were elucidated as independent pretreatment predictors of SVR. Chronic HCV infection is known to strongly affect host lipid metabolism. In previous studies, low and high pretreatment serum LDL-C concentrations were found to be associated with poor response and SVR, respectively, to PEG IFN-α/RBV dual combination therapy,[25,26] especially in *IL28B* minor (but not major) genotype patients.[26,27] Interestingly, the *IL28B* genotype was reported to be linked to LDL-C levels, and low HCV RNA levels as well as high serum LDL-C concentrations were determined to be important predictors of SVR.[27] However, there was no report that supported these findings in telaprevir-based triple combination therapy. The pretreatment serum HCV RNA level is no longer believed to be a predictor of SVR in direct-acting antiviral therapies for patients including both *IL28B* minor and major genotypes. This study is the first report to identify the pretreatment fasting serum LDL-C concentration and serum HCV RNA level as significantly independent factors associated with SVR in the 24-week telaprevir-based triple therapy for the *IL28B* minor (but not major) genotype patients. However, the pretreatment serum HCV RNA level was excluded in this multivariate analysis including pretreatment and on-treatment factors, because it also significantly influenced RVR in this study (data not shown) but was consequently less significant than RVR. At the 24-week telaprevir-based triple therapy for the *IL28B* minor genotype patients start, pretreatment serum HCV RNA level may be useful to the estimation of SVR.

In this study, accomplishment of RVR was implicated as an important factor for achieving SVR in rs8099917 non-TT patients for the 24-week telaprevir-based triple therapy. In a previous Japanese study, the significance of RVR for achieving SVR was not seen for 24-week telaprevir-based triple therapy,[12] although the trial was performed for only naïve patients. On the other hand, in a study of non-responders to prior PEG IFN-α/RBV dual combination therapy, the SVR rate was significantly higher in patients who achieved RVR than in patients who did not achieve RVR.[28] Although *IL28B* was not evaluated, it seemed that rs8099917 non-TT patients occupied many of the non-responders to prior PEG IFN-α/RBV dual combination therapy. Therefore, our results do not contradict the previous study.[28]

The significance of the response to prior PEG IFN-α/RBV dual combination therapy with respect to the SVR rate for telaprevir-based triple therapy has been extensively studied. In the REALIZE trial,[29] the telaprevir-based treatment was continued for 48 weeks, and the

SVR rates of previous relapsers and partial responders were quite similar to those in our 24-week therapy: a previous relapse (83–88% in the REALIZE study and 82.4% in our study) and a partial response (54–59% and 59.1%, respectively). These findings suggested that prior response to combination therapy is critical for predicting SVR for telaprevir-based triple therapy without respect for genotype of *IL28B*. In addition, elongation of the phase of combination treatment from 12 to 24 weeks may not be effective for these patients.[11] However, as the SVR rate of prior null response patients in our study was extremely low (only 6.7%), target of the extension of therapy should be limited in prior null responders.

In this study, we found that high adherences of PEG IFN-α and RBV tended to be associated with achieving SVR as shown in the previous studies,[12,29] and the extension of treatment duration should be considered in the patients who were not given a sufficient dose of drugs in order to maintain the adherence.[30] In this study, however, adherence of telaprevir did not participate in SVR. In a Japanese previous report,[31] there was no difference in the SVR rate between telaprevir-based regimens of 2250 mg and 1500 mg. In our study, most patients were able to take 1500 mg as a minimum dose and the dose was rarely reduced. This may suggest that telaprevir dose does not participate in SVR in this study.

In conclusion, pretreatment serum fasting LDL-C concentration, prior treatment response and RVR achievement were useful for predicting SVR achievement for 24-week telaprevir-based triple therapy in patients with the non-TT genotype in rs8099917 near the *IL28B* gene. This was especially true for patients with a prior null response, as it was difficult to achieve SVR with the 24-week telaprevir-based triple therapy; therefore, it should be considered the extension of treatment or standing by the next-generation therapies.

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Relationship between HCV dynamics and sustained virological responses in chronic hepatitis C genotype 1b patients treated with telaprevir-based triple therapy

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Objectives **This study investigated the relationship between hepatitis C virus (HCV) dynamics and sustained virological response (SVR), as well as the efficacy of an extended treatment with telaprevir-based triple therapy among patients with chronic hepatitis C genotype 1b.**

Methods **Among 220 patients receiving triple therapy for 24 weeks, the SVR rate was analyzed at each time point at which HCV RNA became undetectable. The SVR rates in the patients who did not achieve a rapid virological response (RVR) were compared with those in 27 patients who received triple therapy for 48 weeks.**

Results **The SVR rates of interleukin 28B (*IL28B*) TT and non-TT patients were 100 versus 66.7% after 1 week, 97.6 versus 72.2% after 2 weeks, 95.2 versus 84.2% after 3 weeks, 93.1 versus 72.2% after 4 weeks, 76.9% versus 11.1% after 6 weeks, and 88.9 versus 14.3% after 8 weeks, respectively. All of the *IL28B* TT patients who showed undetectable HCV RNA levels until week 8 achieved an SVR. In contrast, the SVR rates in the *IL28B* non-TT patients who did not achieve RVR with 24 and 48 weeks of treatment were 11.8 and 62.5%, respectively ($P = 0.017$).**

Conclusion **These results suggest that an SVR can frequently be achieved by *IL28B* TT patients, even with 24 weeks of treatment, when HCV RNA remains undetectable until week 8, and also that *IL28B* non-TT patients should have RVR values to achieve an SVR with 24 weeks of treatment. The SVR rate was low in *IL28B* non-TT patients treated for 24 weeks who did not achieve an RVR; however, it could increase when the treatment duration was extended to 48 weeks. *Eur J Gastroenterol Hepatol* 26:1329–1334 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: chronic hepatitis C, hepatitis C virus dynamics, pegylated interferon, rapid virological response, sustained virological response, telaprevir

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Introduction

Pegylated interferon and ribavirin combined with protease inhibitors, such as telaprevir, boceprevir, and simeprevir, have become the standard treatment for genotype 1-infected chronic hepatitis C patients in many countries and regions [1–5]. The baseline factors contributing toward a sustained virological response (SVR) with telaprevir-based triple therapy were identified as the interleukin 28B (*IL28B*) single nucleotide polymorphism (SNP) genotype, virological response to prior treatments, rapid virological response (RVR), and the pre-existence of cirrhosis [6–8]. In pegylated interferon and ribavirin combination therapy, relevant on-treatment factors include drug adherence [9–11] and hepatitis C virus (HCV) dynamics [12–14]. Many studies have found that RVR and early virological response are relevant for predicting SVR [15,16] and that extended duration of treatment is effective for slow responders [17–19]. More recently, an undetectable serum HCV RNA level at 1 week of triple combination therapy with telaprevir, pegylated interferon, and ribavirin was reported to be an important predictor of SVR [20]. In addition, achievement of RVR appeared to be independent of the 1-week response [6]. However, the relationship between undetectable serum HCV RNA levels during the early treatment phase and the SVR rate remains unclear.

Here, we analyze the relationship between the time point at which HCV RNA becomes undetectable and SVR in telaprevir-based triple combination therapy, as well as the efficacy of extended treatment in those who do not achieve an RVR.

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Patients and methods

Study design

The participants in the present study were 247 consecutive patients who visited Nippon Medical School Chiba Hokusoh Hospital, Nippon Medical School, Shinmatsudo Central General Hospital, Jikei University School of Medicine Katsusika Medical Center, or Jikei University School of Medicine Kashiwa Hospital between December 2011 and November 2013 and met the inclusion criteria for the study, and agreed to receive triple therapy with telaprevir, pegylated interferon, and ribavirin. The study protocol was designed in accordance with the guidelines of the 2008 Declaration of Helsinki and was approved by the Ethics Committee of each institution.

Inclusion criteria were as follows: age between 18 and 75 years, chronic HCV genotype 1b infection, HCV RNA positive by real-time PCR, leukocytes greater than 2000/mm^3, platelets greater than 50 000/mm^3, and hemoglobin level greater than 10.0 g/dl. Exclusion criteria were as follows: other liver diseases, including autoimmune hepatitis, primary biliary cirrhosis, and alcohol-related diseases, positive results for hepatitis B surface antigens and antibodies to human immunodeficiency virus type-1, history of decompensated liver cirrhosis, severe renal disorder, abnormal thyroid function, poorly controlled diabetes, poorly controlled hypertension, severe depression or a psychiatric disorder, medication with Chinese herbal medicine, medical history of interstitial pneumonia, and allergy to interferon, ribavirin, or protease inhibitors.

Treatment protocol

All patients with chronic hepatitis C received combination therapy with telaprevir (Telavic; Mitsubishi Tanabe Pharma, Osaka, Japan), pegylated interferon α-2b (Peg-Intron; MSD, Tokyo, Japan), and ribavirin (Rebetol; MSD) for 12 weeks, followed by 12 weeks (T12PR24) or 36 weeks (T12PR48) of treatment with pegylated interferon α-2b and ribavirin. Patients received a subcutaneous injection of pegylated interferon α-2b at a dose of 1.5 μg/kg/week and were orally administered ribavirin. The dose of ribavirin was adjusted according to body weight (600, 800, and 1000 mg/day for < 60, 60–80, and > 80 kg, respectively) on the basis of the guidelines of the Ministry of Health, Labor, and Welfare of Japan. Telaprevir at a dose of 750 mg was administered every 8 h after meals. Doses were appropriately reduced when an adverse event such as anemia, skin rash, anorexia, or renal insufficiency occurred during the treatment course. The administration of pegylated interferon α-2b and ribavirin was completed with T12PR24 for patients with a favorable response to the treatment and sufficient dosages. When patients failed to achieve an RVR or received an insufficient dosage of agents, they were recommended an extension in the treatment duration to 48 weeks. T12PR48 was only administered if the patients agreed to the extended treatment regimen and gave their informed consent.

Definition of virological response

Patients were divided into categories according to the Japan Society of Hepatology guidelines [21]. When HCV RNA was undetectable after 4 weeks of treatment, patients were considered to have achieved RVR. When HCV RNA was undetectable at the completion of 24 weeks of treatment, patients were judged as having an end-of-treatment response. Patients who were negative for the virus at the completion of 24 weeks of treatment were judged as having an SVR. Patients who were persistently positive for HCV RNA throughout the treatment period were considered to be nonresponders. Of those considered to be nonresponders, patients whose plasma HCV RNA levels decreased by 2 log IU/ml from baseline after 12 weeks of treatment but never became undetectable were considered to be partial responders. Patients who failed to suppress serum HCV RNA levels by at least 2 log IU/ml from baseline after the treatment were considered to be null responders. Treatment was stopped for patients with HCV RNA levels greater than 3 $\log_{10}$ IU/ml after 4 weeks, with detectable HCV RNA levels after 12 weeks, or with a greater than 2 $\log_{10}$ IU/ml increase in HCV RNA levels from the lowest levels during therapy. Virological responses to pegylated interferon/ribavirin therapy were divided into three categories, that is, relapse, partial response, and null response. When patients did not receive pegylated interferon/ribavirin combination therapy, they were defined as naive.

Laboratory methods

Hematological and biochemical tests were performed weekly until 12 weeks after initiation of treatment, and then monthly until 24 weeks after completion of the treatment. HCV RNA levels were measured by real-time PCR (COBAS AmpliPrep; Roche Diagnostics, Tokyo, Japan). Gene mutations in the core regions of the HCV genome were determined using the direct sequencing method. Genomic DNA was extracted from whole blood using a DNA isolation kit on the MagNA Pure LC Instrument (Roche Diagnostics, Basel, Switzerland). The SNP rs8099917 of *IL28B* was determined by real-time PCR using the TaqMan SNP genotyping assay on a 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, California, USA). The rs8099917 genotype was classified into two categories: the TT genotype and the non-TT genotype (TG or GG).

Statistical analysis

The primary endpoint of the study was the relationship between when serum HCV RNA levels became undetectable and an SVR was achieved with telaprevir-based triple therapy. The secondary endpoint was whether

extending the treatment to 48 weeks for patients with a treatment-resistant factor conferred greater efficacy than 24 weeks of treatment. The Mann–Whitney *U*-test was used to compare SVR rates according to treatment duration (24 weeks or 48 weeks) in patients with the absence of an RVR or in null responders to prior treatment. All statistical analyses were carried out using IBM SPSS version 17.0 (IBM Japan, Tokyo, Japan). The level of significance was set at P less than 0.05.

Results

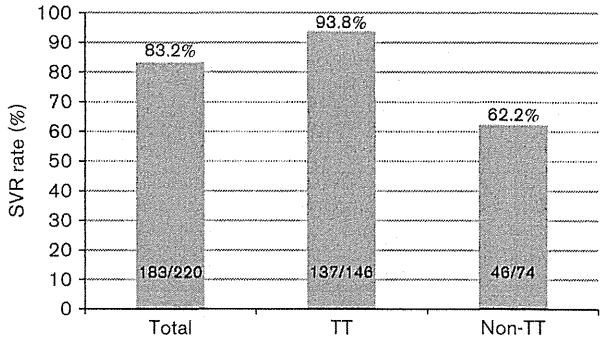
Background

A total of 220 patients received T12PR24. The median age was 59 years (range: 18–75 years); 99 patients (45.0%) were male, and 146 patients (66.4%) had the *IL28B* genotype TT. Of these patients, 119 were treatment-naive, 73 relapsed into viremia after prior pegylated interferon/ribavirin treatment, 18 showed a partial response, and 10 showed null response to prior combination therapy (Table 1). The remaining 27 patients received T12PR48. The median age was 58 years (range: 36–69 years); 17 patients were men (63%), and five patients had the *IL28B* genotype TT (18.5%). Of these patients, four were treatment-naive, six relapsed into viremia, three showed a partial response, and 14 showed null response (Table 1). In the frequency of patients with *IL28B* non-TT genotype and those with prior null response, there were significant differences between the 24-week and 48-week treatment group.

Treatment response

The overall SVR rate was 83.2% (183 of 220 patients) in the T12PR24 group. SVR rates were 93.8% (137 of 146 patients) among patients with the *IL28B* TT genotype and 62.2% (46 of 74 patients) among those with the *IL28B* non-TT genotype ($P = 1.04 \times 10^{-8}$; Fig. 1). We analyzed the relationship between undetectable serum HCV RNA levels at each time point during the early treatment phase and the SVR rate. In all of the *IL28B* genotype TT patients, serum HCV RNA levels became undetectable within the first 8 weeks of treatment: the SVR rates were 100% (11/11) at week 1, 97.6% (41/42) at week 2, 95.2% (40/42) at week 3, 93.1% (27/29) at week 4, 76.9% (10/13) at week 6, and 88.9% (8/9) at week 8 (Fig. 2). A significant decrease in SVR rates was not observed within the first 8 weeks of treatment. Among patients with the *IL28B* non-TT genotype, the SVR rates were 66.7% (2/3) at week 1, 72.2% (13/18) at week 2,

Fig. 1



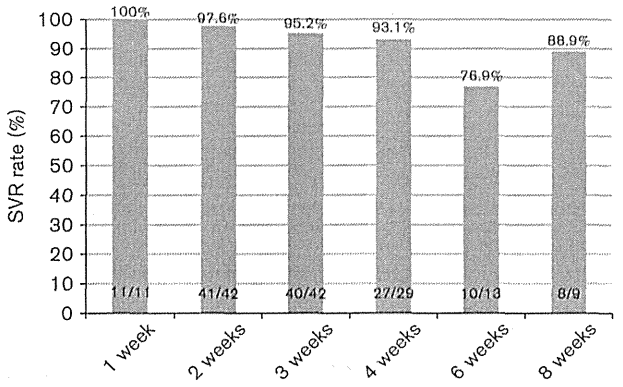
Overall sustained virological response rate for 24-week telaprevir-based triple therapy was 83.2% (183 of 220 patients). There was a significant difference in sustained virological response (SVR) rates between *IL28B* TT genotype patients and *IL28B* non-TT genotype patients ($P = 1.04 \times 10^{-8}$).

Table 1 Comparison of the clinical baseline characteristics between patients who received 24 weeks (T12PR24) and those who received 48 weeks (T12PR48) of telaprevir-based triple therapy

Factors	T12PR24 ($n = 220$)	T12PR48 ($n = 27$)	P-value
Age (years)	59 (18–75)	59 (36–69)	0.737
Sex (M/F)	99/121	17/10	0.102
Body weight (kg)	59.1 (40.0–115.8)	63.8 (44.7–91.6)	0.086
BMI (kg/m^2)	23.0 (15.1–37.8)	23.9 (19.3–32.5)	0.210
Prior treatment response (naive/relapse/partial responder/null responder)	119/73/18/10	4/6/3/14	0.002
Leukocytes (/mm^3)	4755 (2000–11100)	5000 (2700–9000)	0.558
Hemoglobin (g/dl)	14.1 (10.1–17.5)	14.2 (10.7–17.7)	0.504
Platelets (×10^3/mm^3)	166 (56–407)	192 (69–368)	0.519
AST (U/l)	41 (13–215)	42 (21–134)	0.739
ALT (U/l)	46 (11–305)	51 (16–148)	0.989
γ-GT (U/l)	40 (11–339)	50 (14–207)	0.022
α-Fetoprotein (ng/ml)	4.6 (1.0–625.7)	7.7 (2.3–90.1)	0.052
Total bilirubin (mg/dl)	0.8 (0.3–2.3)	0.7 (0.3–2.0)	0.939
Serum albumin (g/dl)	4.1 (2.8–5.0)	4.2 (3.1–5.1)	0.372
LDL cholesterol (mg/dl)	97 (38–194)	92 (51–204)	0.836
Tryglyceride (mg/dl)	94 (37–987)	100 (33–235)	0.419
Serum creatinine (mg/dl)	0.67 (2.1–7.8)	0.74 (0.49–1.18)	0.230
HCV RNA (log IU/ml)	6.6 (2.1–7.8)	6.6 (5.8–7.6)	0.877
Core amino acid 70 (wild/mutant)	142/73	14/13	0.200
Core amino acid 91 (wild/mutant)	142/73	15/12	0.292
IL28B genotype rs8099917 (TT/non-TT)	146/74	5/22	2.79×10^{-6}

Categorical values are represented as the number of patients. Continuous variables are represented as median (range).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyltransferase; HCV, hepatitis C virus; *IL28B*, interleukin 28B; LDL, low-density lipoprotein.

Fig. 2

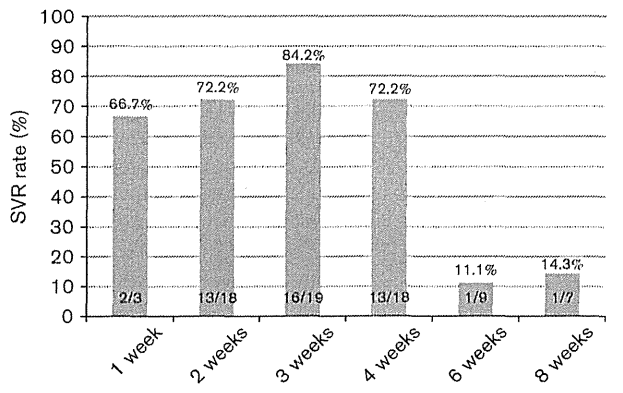


Among the *IL28B* TT genotype patients who received 24 weeks of treatment, the sustained virological response (SVR) rates were 100% (11/11) at week 1, 97.6% (41/42) at week 2, 95.2% (40/42) at week 3, 93.1% (27/29) at week 4, 76.9% (10/13) at week 6, and 88.9% (8/9) at week 8.

84.2% (16/19) at week 3, 72.2% (13/18) at week 4, 11.1% (1/9) at week 6, and 14.3% (1/7) at week 8 (Fig. 3). Thus, of the 58 patients who showed an RVR, 44 (75.9%) achieved an SVR. No significant changes were observed in the SVR rates within the first 4 weeks: weeks 1, 2, 3, and 4. In contrast, of the 16 patients who did not achieve an RVR, only two (12.5%) achieved an SVR ($P=6.43\times10^{-6}$). These results indicate that RVR was a more important milestone for predicting SVR with 24 weeks of treatment in the *IL28B* non-TT patients compared with the *IL28B* TT patients.

The outcomes in 24 patients with null response to prior treatments were analyzed. Twenty (83.3%) of the 24

Fig. 3



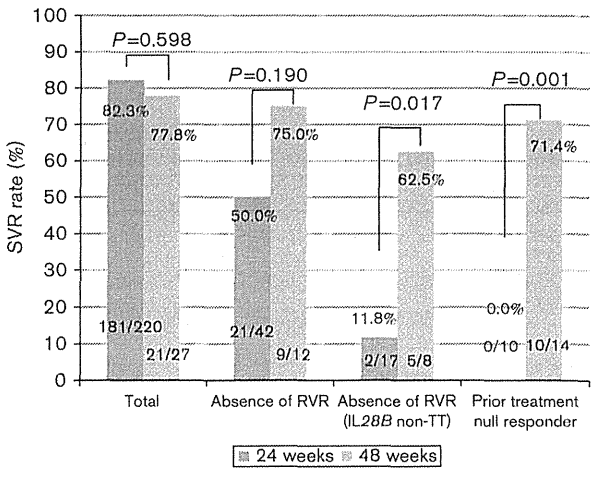
Among the *IL28B* non-TT patients who received 24 weeks of triple treatment, the sustained virological response (SVR) rates were 66.7% (2/3) at week 1, 72.2% (13/18) at week 2, 84.2% (16/19) at week 3, 72.2% (13/18) at week 4, 11.1% (1/9) at week 6, and 14.3% (1/7) at week 8.

patients had the *IL28B* non-TT genotype. Serum HCV RNA levels were undetectable in none (0%) of the 24 patients at 1 week, in one patient (4.2%) at 2 weeks, in four patients (16.7%) at 3 weeks, in eight patients (33.3%) at 4 weeks, in three patients (12.5%) at 6 weeks, and in three patients (12.5%) at 8 weeks. Serum HCV RNA levels were persistently detected in two of the 24 patients (8.3%). Of the 10 patients with a prior null response in the T12PR24 group, five patients (50.0%) had a viral breakthrough and three patients (33.3%) had a relapse after the completion of treatment. In contrast, of the 14 patients with a prior null response in the T12PR48 group, only one patient (7.1%) had a viral breakthrough. Most patients with viral breakthroughs were non-RVR cases. Viral breakthroughs occurred at 6–28 weeks.

Differences in sustained virological response rates between 24 and 48 weeks of treatment

No significant differences were observed in the SVR rates between the T12PR24 group (82.3%, 181 of 220 patients) and the T12PR48 group (77.8%, 21 of 27 patients; $P=0.598$; Fig. 4). Among the patients who did not show an RVR, the SVR rates were numerically higher in the T12PR48 group (75.0%, nine of 12 patients) compared with the T12PR48 group (50.0%, 21 of 42 patients; $P=0.190$; Fig. 4). As described above, the influence of RVR on SVR manifested differently between the *IL28B* SNP genotypes (Figs 2 and 3). Therefore, the analysis was focused on the *IL28B* non-

Fig. 4



Sustained virological response rates were not significantly different between patients who received 24 weeks of treatment and those who received 48 weeks of treatment. Among patients who did not show rapid virological response (RVR), the sustained virological response (SVR) rates were numerically higher in the 48-week treatment group compared with the 24-week treatment group, although not statistically significant. In *IL28B* non-TT patients without an RVR, the SVR rate was significantly higher in the 48-week treatment group compared with the 24-week treatment group.

TT patients without RVR, who showed extremely poor response to 24 weeks of treatment. The SVR rate was significantly higher in the T12PR48 group (62.5%, five of eight patients) compared with the T12PR24 group (11.8%, two of 17 patients; $P=0.017$; Fig. 4). In addition, extending the treatment to 48 weeks was more effective in patients with a prior null response, with SVR rates of 0.0% (0/10) in the T12PR24 group and 71.4% (10/14) in the T12PR48 group ($P=0.001$; Fig. 4). These results suggest that extending the treatment to 48 weeks could be more suitable for patients with the *IL28B* non-TT genotype who fail to achieve RVR or have a null response to prior treatment. Conversely, T12PR24 may suffice for patients with favorable factors, such as the *IL28B* TT genotype and virological responses during the early treatment phase.

Discussion

This is the first report to investigate the relationship between HCV RNA disappearance time and SVR rates with telaprevir-based triple therapy in chronic hepatitis C genotype 1b patients. Previous studies have reported the relationship between viral dynamics and outcomes such as SVR, virological relapse, and a null virological response with pegylated interferon/ribavirin dual combination therapy without telaprevir. High SVR rates were achieved by an early virological response – that is, at least a 2 log reduction in viremia levels from the baseline at 12 weeks [12]. Furthermore, an analysis of 432 patients with genotype 1 chronic hepatitis C demonstrated that reduction in viremia levels at 12 weeks, besides age and baseline viremia level, could influence relapse after the completion of treatment [13]. In 547 patients with genotype 1, reduced HCV RNA levels at 4 weeks, besides age, significantly contributed to SVR [14]. Thus, a reduction or loss in HCV RNA levels during the early phase of treatment is closely related to the outcome of pegylated interferon/ribavirin combination therapy.

Several studies have previously identified factors contributing to SVR with telaprevir-based triple combination treatment. Tsubota *et al.* [6] found that the *IL28B* SNP genotype, pre-existence of cirrhosis, prior treatment response, and achievement of RVR were important independent baseline and on-treatment factors contributing to SVR. Furusyo *et al.* [22] reported that serum HCV RNA levels on day 3 of treatment were related to RVR and SVR rates. Shimada *et al.* [20] found that patients with the *IL28B* TT genotype had a high SVR rate regardless of a reduction in viremia levels at 1 week of treatment, and also that the *IL28B* non-TT patients who showed a decrease of at least 4.7 $\log_{10}$ IU/ml at 1 week of treatment were more likely to achieve an SVR. These studies indicated that an early significant reduction in or the elimination of serum HCV RNA was a useful predictor of SVR. This study confirmed that SVR rates at time points at which serum HCV RNA levels became undetectable markedly differed between the *IL28B* SNP genotypes. Patients with the *IL28B* TT genotype showed high SVR rates regardless of the viremia disappearance time. In contrast, patients with the *IL28B* non-TT genotype who failed to achieve an RVR were the least likely to achieve an SVR.

The efficacy of extending treatment to 48 weeks in patients not achieving an RVR was analyzed because the SVR rate was low in T12PR24 for patients with the *IL28B* non-TT genotype who did not achieve an RVR. The SVR rate was markedly higher than at 24 weeks, which suggested that extending the treatment may be advantageous in improving the SVR rate among patients without RVR. Extending the treatment to 48 weeks in patients with a prior null response increased the SVR rate from 0% (T12PR24) to 71.4% (T12PR48). Therefore, patients with a prior null response should receive extended treatment to 48 weeks. Several studies have reported the effectiveness of 48 weeks of telaprevir-based triple therapy for null responders to prior treatment. Muir *et al.* [23] demonstrated that the SVR rates in the patients with the prior null response were 12.5% and 60% in T12PR24 and T12PR48, respectively. Shimada *et al.* [24] found that the extended treatment duration significantly improved the SVR rates from 22.6% (T12PR24) to 66.7% (T12PR48) on telaprevir-based combination therapy among prior null responders. Our results are consistent with those of the previous studies.

Caution should be exercised among patients with viral breakthroughs during telaprevir-based triple therapy. In the present study, viral breakthroughs occurred between 6 and 28 weeks. Therefore, the occurrence of viral breakthroughs should be considered when administering T12PR48 to the *IL28B* non-TT and non-RVR patients, as well as to those with a null response to prior treatments.

The present study has several limitations. We did not compare the 24-week and 48-week telaprevir-based triple therapies using a randomized controlled procedure. However, only the 24-week treatment duration had initially been approved in Japan, thus the treatment could not be continued for 48 weeks. Furthermore, we could not reach definitive conclusions because of the small sample size, especially for cases of T12PR48. As such, the results obtained in the present study on the relationship between the viremia disappearance time and SVR rates can contribute to next-generation antiviral therapy [25,26].

Conclusion

Patients with the *IL28B* TT genotype in whom HCV DNA levels became undetectable within the first 8 weeks of treatment were more likely to achieve an SVR with 24 weeks of treatment, even though an RVR was not attained. However, the SVR rate was extremely low in

patients with the *IL28B* non-TT genotype who did not achieve RVR. Patients with a null response to prior treatment also showed a very low SVR rate regardless of the *IL28B* genotype. Extending the treatment to 48 weeks may be useful in improving the SVR rate, specifically among patients with the *IL28B* non-TT genotype who did not achieve an RVR and who showed a null response to prior treatment.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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Clinical Study

Predictors of Response to 24-Week Telaprevir-Based Triple Therapy for Treatment-Naïve Genotype 1b Chronic Hepatitis C Patients

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We evaluated the genetic variation in rs8099917, substitutions in core amino acid (aa) 70, and the number of aa substitutions in the interferon sensitivity-determining region (ISDR) on the prediction of sustained virological response (SVR) in treatment-naïve hepatitis C virus (HCV) genotype 1b (G1b) patients. This multicenter study involved 150 Asian treatment-naïve patients infected with HCV G1b who received 12 weeks of telaprevir in combination with 24 weeks of peginterferon-α-2b and ribavirin. The baseline and treatment-related factors potentially associated with SVR were determined by multivariate logistic regression analysis. Virological response was analyzed on an intent-to-treat basis. Cessation of the therapy due to adverse effects occurred in only 2 patients, who discontinued the trial at 10 weeks and at 2 weeks due to cerebral infarction and renal impairment, respectively. Among the 150 patients in whom the final virological response was determined, only genotype TT in rs8099917 was identified as a pretreatment predictor ($P = 7.38 \times 10^{-4}$). Achievement of a rapid virological response (RVR), defined as undetectable HCV RNA at week 4 of treatment, was identified as an after-starting-treatment predictor ($P = 2.47 \times 10^{-5}$). However, neither a substitution in core aa 70 nor the number of substitutions in the ISDR affected treatment outcome.

1. Introduction

Chronic hepatitis C virus (HCV) infection was generally treated with pegylated interferon (PEG-IFN) and ribavirin combination therapy. This treatment provides rates of sustained virological response (SVR, undetectable serum levels of HCV RNA at least 6 months after completion of therapy) of 40–50% among patients with HCV genotype 1 (G1) who have not received previous treatment (treatment-naïve patients) [1–3].

Telaprevir, a first generation orally bioavailable inhibitor of the nonstructural 3/4A HCV protease, shows significantly higher rates of SVR than standard care of PEG-IFNα and ribavirin in patients with HCV G1 disease when given for 12 weeks in combination with regimens of PEG-IFNα plus ribavirin lasting 12, 24, or 48 weeks [4–6]. Although

the SVR rates in patients receiving telaprevir with PEG-IFNα and ribavirin (triple therapy) were higher than those in PEG-IFNα plus ribavirin (combination therapy) patients, drop-out rates due to increased side effects were also higher in the triple therapy patients [4–6]. Triple therapy is associated with increased risks of anemia, skin lesions, digestive symptoms, hyperuricemia, renal dysfunction, and other side effects compared to the combination therapy, especially among women and older patients [4, 7, 8]. The majority of patients in Japan who are infected with HCV genotype 1b (G1b) are older than the patients in the United States and/or Europe and the frequency of patients who discontinued due to adverse events was reported to be as high as 11.1–16.7% [7–9]. In most previous reports [4–10], the age inclusion criterion limited participants to those who were aged <65 years. Therefore, the safety and efficacy of the triple therapy for patients aged >65 has not been established.

The outcome of the triple therapy in patients who had previously received the combination therapy was largely dependent on the response to the previous therapy [10, 11]. In treatment-naïve patients, the genetic variation near the interleukin-28B (IL-28B) gene and amino acid (aa) substitution in the core 70 (core aa 70) of HCV may be the candidate predictors of the virological response to triple therapy. Although the significance of substitution in the core aa 70 on the outcome of the triple therapy has been reported [8, 9], a considerable number of the patients with a history of the combination therapy were included in these reports. Therefore, the factors predicting SVR in treatment-naïve patients have not been clearly determined.

In the present study, the SVR rate was examined in treatment-naïve patients with HCV G1b who were treated with a regimen consisting of 12 weeks of telaprevir, combined with PEG-IFNα and ribavirin, followed by 12 weeks of the PEG-IFN and ribavirin. The significance of genetic variation in rs8099917 near the IL28B gene (rs8099917 genotype), core aa 70, and the number of amino acid substitutions in the interferon sensitivity-determining region (ISDR) on the outcome of triple therapy were then evaluated. In addition, we evaluated the significance of rapid virological response (RVR, serum HCV RNA not detectable within 4 weeks of therapy) [12] in the prediction of SVR and tried to define the patients who were suitable for triple therapy.

2. Materials and Methods

2.1. Study Population and Study Design. A total of 359 patients, chronically infected with HCV G1b, were treated by triple therapy with telaprevir (Telavic, Tanabe Mitsubishi Pharma, Osaka, Japan), PEG-IFNα-2b (PegIntron, MSD, Tokyo, Japan), and ribavirin (Rebetol, MSD) between January 2012 and June 2013. The patients were treated at Jikei University Katsushika Medical Center, Jikei University Kashiwa Hospital, Shinmatsudo Central General Hospital, Nippon Medical School Chiba Hokusoh Hospital, Nippon Medical School Hospital, Kagawa Prefectural Central Hospital, Kurume University School of Medicine, Tokyo Metropolitan Bokutoh Hospital, or Ogaki Municipal Hospital. In these medical institutions, there were no patients who changed the treatment policy by the results of the genetic variation near the IL-28B gene, aa substitution in the core 70, and ISDR of HCV.

Of the 359 patients, 150 had not received previous combination therapy (i.e., they were treatment-naïve) and were included in this analysis (Table 1). The age range of the enrolled patients was 18–75 years. All of the patients satisfied the following criteria. The patients were persistently seropositive for HCV RNA for >6 months and the amount of serum HCV RNA, as determined by a qualitative real-time polymerase chain reaction (RT-PCR) method (COBAS TaqMan HCV test, Roche Diagnostics, Tokyo, Japan), was ≥5 $\log_{10}$ IU/mL, which has been defined as a "high viral load," according to the Japanese criteria [13]. In addition, they had white blood cell counts ≥2000 per cubic millimeter, neutrophil counts ≥1500 per cubic millimeter, hemoglobin levels ≥11 g/dL, and platelet counts ≥70,000 per cubic millimeter, were aged 18–75 years, and had body weights >35 kg at the time of study entry. The presence or absence of cirrhosis was determined by the liver biopsy METAVIR scores [14] within 12 months of enrollment or by an aspartate aminotransferase (AST) to platelet ratio index (APRI) > 2.0, as proposed by Wai et al. [15], at the time of the enrollment. Patients who were positive for the hepatitis B surface antigen or anti-human immunodeficiency virus antibody or who had hepatocellular carcinoma, other liver diseases, psychiatric conditions, or current alcohol consumption levels >20 g per day were excluded from this study.

All patients were scheduled to receive telaprevir (1500–2250 mg per day) combined with weekly subcutaneous injections of PEG-IFNα-2b (1.5 μg/kg) and ribavirin (600–1000 mg per day, according to body weight: <60 kg: 600 mg per day; 60–80 kg: 800 mg per day; >80 kg: 1000 mg per day; if the patient's hemoglobin was <13 g/dL at the start of therapy, ribavirin was reduced by 200 mg) for 12 weeks. This was followed by 12 weeks of PEG-IFNα-2b plus ribavirin combination therapy. Telaprevir was administered every 8 hours after meals at 500 mg or 750 mg, or every 12 hours after meals at 750 mg or 1125 mg. Ribavirin was orally administered every 12 hours after meals. The patient's attending physicians determined the initial dose of telaprevir (1500 mg per day or 2250 mg per day), based on patient age, gender, body weight, and hemoglobin level. Telaprevir adherence was calculated on the basis of 2250 mg per day. Each drug was appropriately reduced or withdrawn when a serious adverse event developed during the treatment course. In patients who had HCV RNA >3 $\log_{10}$ IU/mL at week 4, detectable HCV RNA at 12 week, or a 2 $\log_{10}$ IU/mL increase in HCV RNA from the lowest level during therapy, therapy was discontinued because of the extremely low likelihood of achieving SVR and the high risk of developing antiviral resistance.

Virological response was analyzed on an intent-to-treat basis. Virological "relapse" was defined as HCV RNA levels that became undetectable by the end of treatment but became positive again during the follow-up period; viral "breakthrough" was defined as HCV RNA levels that became undetectable during the treatment but became detectable again before the end of the treatment, and "nonvirological