(discontinuation rate of all drugs, 17% *vs* 7–10%; discontinuation of only TVR, 19% *vs* 7–12%) in a phase-3 study of triple therapy with TVR, Peg-IFN and RBV [5–9]. In particular, severe adverse events such as rash and anaemia were more frequent in Japan compared with Europe and the United States (rash, 12% *vs* <1%; anaemia, 11% *vs* 2%). Higher adverse events with triple therapy in Japanese patients may result from an excessive dose of TVR due to reduced body weight compared with Westerners. An initial dose reduction of TVR was therefore recommended in Japanese patients, especially for older patients, and we have reported similar SVR rates among two groups with the introduction of TVR at 1500 and 2250 mg [14]. However, the real impact of low-dose TVR on antiviral efficacy and adverse effects remains unknown. The optimum dosage of TVR should be examined for older patients in Japan because Japanese patients infected with HCV tend to be 10–20 years older than those in the United States and European countries.

In this study, we examined the antiviral efficacy and adverse effects with a focus on TVR dosage in Japanese patients with HCV genotype 1 treated with TVR, Peg-IFN and RBV.

PATIENTS AND METHODS

Patients

The current study was a retrospective, multicentre study conducted by Osaka University Hospital and other institutions participating in the Osaka Liver Forum. A total of 202 patients with chronic hepatitis C (CH-C) treated with TVR, Peg-IFN and RBV combination therapy between December 2011 and December 2012 were enrolled in this study.

Eligible patients were those who were 20 years of age and older, had chronic HCV genotype 1b infection with a viral load of more than 10^5 IU/mL and did not have co-infection with hepatitis B virus (HBV) or anti-human immunodeficiency virus (HIV). The patients were excluded if they had decompensated cirrhosis, HCC or other forms of liver disease (alcohol liver disease, autoimmune hepatitis), a history of splenectomy or partial spleen embolization (PSE), chronic renal failure, depression or immunodeficiency. Patients using erythropoietin were also excluded. After enrolment, 42 patients (co-infection with HBV, $n = 3$; co-infection with HIV, $n = 2$; splenectomy, $n = 5$; PSE, $n = 2$) were excluded, and a total of 166 CH-C patients were assessed. This study was conducted according to the ethics guidelines of the 1975 Declaration of Helsinki amended in 2002 and approved by the ethics commission of Osaka University Hospital and independent or institutional review boards of all study centres. All patients provided written informed consent before participating in the study.

Study design

All patients received TVR (TELAVIC; Mitsubishi Tanabe Pharma, Osaka, Japan) with Peg-IFN alfa-2b (PEGINTRON; MSD, Tokyo, Japan) and RBV (REBETOL; MSD). TVR was administered orally at a dose of 500 or 750 mg every 8 h after food. Peg-IFN alfa-2b was administered subcutaneously once a week at a dose of 60–150 μg/kg based on body weight (body weight 35–45 kg, 60 μg; 46–60 kg, 80 μg; 61–75 kg, 100 μg; 76–90 kg, 120 μg; 91–120 kg, 150 μg). RBV was administered orally twice a day at a total dose of 600–1000 mg/day based on body weight (body weight <60 kg, 600 mg; 60–80 kg, 800 mg; >80 kg, 1000 mg), according to a standard treatment protocol for Japanese patients. In principle, the patients were treated with TVR, Peg-IFN and RBV for 12 weeks, followed by Peg-IFN and RBV for 12 weeks. If a patient had detectable HCV RNA at 12 weeks or any time during weeks 13 through 20, that patient was not permitted to complete the remainder of the assigned duration of therapy.

Dose modification

Dose modification followed, as a rule, the manufacturer's drug information in Japan. The initial dose of RBV was reduced by 200 mg per day in case of the Hb level <13 g/dL at baseline. The dose of Peg-IFN alfa-2b was reduced to 50% of the assigned dose if the white blood cell (WBC) count declined to $<1500/mm^3$, the neutrophil count to $<750/mm^3$ or the platelet count to $<8 \times 10^4/mm^3$. RBV was also reduced from 1000 to 600 mg or 800 to 600 mg or 600 to 400 mg if the Hb level decreased to <12 g/dL and was reduced by an additional 200 mg per day when the Hb level was <10 g/dL. The dose of RBV was also reduced by 200 mg per day if the Hb level dropped by more than 1 g/dL within a week, and this level was <13 g/dL. TVR, Peg-IFN alfa-2b and RBV were withdrawn or interrupted if the WBC count declined to $<1000/mm^3$, the neutrophil count to $<500/mm^3$ or the platelet count to $<5 \times 10^4/mm^3$ or the Hb level decreased to <8.5 g/dL. TVR was reduced according to adverse events related to TVR by the physician's decision. The use of erythropoietin was not allowed for increasing the Hb level. In case of drug interruption of TVR or Peg-IFN and RBV, resumption of treatment was allowed if the peripheral blood findings or adverse events were reversed.

Histological evaluation

Pretreatment liver biopsies were conducted within 6 months of the start of combination therapy. Histopathological interpretation of the specimens was performed by experienced liver pathologists who had no clinical, biochemical or virologic information of the patients. The

histological appearance, activity and fibrosis were evaluated according to the METAVIR histological score [15].

Virologic assessment and definition of viral response

The serum HCV RNA level was quantified with the COBAS Taqman HCV test, version 2.0 (detection range 1.2–7.8 log IU/mL; Roche Diagnostics, Branchburg, NJ, USA) and was assessed before treatment, every 4 weeks during treatment and 24 weeks after therapy. A rapid virologic response (RVR) was defined as undetectable serum HCV RNA at week 4, a complete early virologic response (c-EVR) as undetectable serum HCV RNA at week 12 and an EOT response (ETR) as undetectable serum HCV RNA at the end of treatment (EOT). SVR was defined as an undetectable serum HCV RNA level at 24 weeks after EOT. Relapse was defined as an undetectable serum HCV RNA level at EOT but a detectable amount after EOT. Nonresponse was defined as a detectable HCV RNA level during therapy. Breakthrough was defined as quantifiable HCV RNA after undetectable HCV RNA during therapy.

Safety assessment

Chemical and haematologic assessments and safety assessment were performed every week during the start to first 12 weeks of treatment and every 4 weeks from week 12–24 of treatment. At each visit, data on adverse events were collected, and physical examinations were performed if clinically indicated.

Assessment of drug exposure

The amounts of TVR, Peg-IFN alfa-2b and RBV actually taken by each patient during treatment were evaluated by reviewing the medical records. The mean doses of each drug were calculated individually as averages based on body weight at baseline: TVR was expressed as mg/kg/day, Peg-IFN alfa-2b was expressed as μg/kg/week, and RBV was expressed as mg/kg/day.

Statistical analysis

Baseline continuous variables were expressed as the means ± standard deviation or median and categorical variables as frequencies. The virologic response was evaluated in an intention-to-treat (ITT) set. Differences between the two groups were assessed by a chi-square test or a Mann–Whitney *U*-test in univariate analyses. The factors selected as significant by the univariate analysis were evaluated by multivariate logistic regression analyses. The cumulative discontinuation of the drug was assessed by the Kaplan–Meier method and the log-rank test. A *P*-value <0.05 was considered significant. The statistical analysis was conducted using SPSS, version 19.0J (IBM, Armonk, NY, USA).

RESULTS

Progress of patients treated with TVR, Peg-IFN a-2b and RBV

The baseline characteristics of the patients are summarized in Table 1. There were 59 treatment-naïve patients and 73 and 29 relapsers and nonresponders to previous Peg-IFN with RBV treatment. Of the 166 patients, 119 completed the 12 weeks of TVR and 24 weeks of Peg-IFN and RBV, 42 discontinued TVR, and 22 discontinued Peg-IFN and RBV. Among the patients who discontinued TVR or Peg-IFN and RBV, 17 discontinued all drugs before treatment week 12.

Virologic response

Five patients (four patients discontinued TVR, one patient discontinued all drugs) were lost during follow-up and were excluded for the analysis of SVR. The RVR, cEVR, ETR and SVR rates were 82% (122/149), 96% (154/160), 93% (150/162) and 82% (132/161). The SVR rate was 85% (101/119) among the patients who completed the entire treatment schedule, 70% (26/37) among those who discontinued TVR, 57% (12/21) among those who discontinued Peg-IFN and RBV and 44% (7/16) among those who discontinued all drugs before treatment week 12.

Table 1 Baseline characteristics of patients

Factor	
Number	166
Age (y.o.)	60.3 ± 8.8
Gender: male/female	85/81
Past history of IFN*: naïve/relapse/nonresponse	59/73/29
HCV RNA (median, log IU/mL)	6.7
Liver histology†, ‡:	
Activity: A0/1/2/3	1/63/25/0
Fibrosis: F0/1/2/3/4	7/41/20/17/4
White blood cell (/μL)	4808 ± 1306
Haemoglobin (g/dL)	14.2 ± 1.4
Platelets ($\times 10^4$/μL)	16.4 ± 5.1
ALT (IU/L)	57 ± 55
IL28B SNP(rs8099917)§: TT/TG/GG	56/19/1
TVR dose at stat (mg/kg/day): 2250 mg/1500 mg	31.6 ± 7.9, 83/83
Peg-IFN dose at start (μg/kg/week)	1.48 ± 0.16
RBV dose at start (mg/kg/day)	11.3 ± 1.7

*Five patients missing.
†METAVIR.
‡77 patients missing.
§90 patients missing.

Discontinuation of treatment by adverse events

The discontinuance rate of all drugs was 11% (18/166), and the discontinuance rate of TVR was 26% (43/166). The discontinuance rates and the reasons for all drugs and TVR according to age are shown in Table 2. The discontinuance rate of TVR was significantly higher in patients ≥65 y.o. than that in those <65 y.o. ($P = 0.015$).

Factors associated with TVR discontinuance

The factors associated with TVR discontinuance were assessed among demographic, haematological, biochemical and virologic factors and drug adherence by a univariate analysis (Table 3A). Next, the factors selected as significant by the univariate analysis were evaluated by a multivariate analysis (Table 3B), and older age (≥65 y.o.) and higher TVR dose during treatment (≥35 mg/kg/day) were extracted as the factors associated with the discontinuance of TVR. Figure 1 shows the cumulative discontinuance of TVR according to age and TVR dose. The cumulative discontinuance rates were significantly higher in patients at ≥35 mg/kg/day of TVR than in those at <25 mg/kg/day of TVR among the patients <65 y.o. (Fig. 1a) and ≥65 y.o. (Fig. 1b). The cumulative discontinuance rate of TVR was highest in patients ≥65 y.o. at ≥35 mg/kg/day of TVR (58%). Among this group, 25% of the patients discontinued TVR during treatment week 1.

Factors associated with SVR

In a per protocol (PP) analysis including the patients who completed the entire treatment schedule, the SVR rate was very high in the patients at ≥25 mg/kg/day of TVR (25–35 mg/kg/day of TVR, 93%; ≥35 mg/kg/day of TVR, 95%) compared with 67% in those at <25 mg/kg/day (Fig. 2a). However, in an ITT analysis including the patients who discontinued any drugs as well as those who completed the entire treatment schedule, the SVR rate was higher at 91% in the patients at 25–35 mg/kg/day of TVR compared with 78% in those at ≥35 mg/kg/day and 71% in those at <25 mg/kg/day (Fig. 2b). According to previous IFN treatment response and TVR dose, the highest SVR rates (ITT analysis) were obtained at a dose of 25–35 mg/kg/day of TVR among naïve patients and prior relapsers; the SVR rate at ≥35 mg/kg/day of TVR was not less than that at 25–35 mg/kg/day among the nonresponders (80% *vs* 73%) (Fig. 2c).

The factors associated with SVR were assessed among demographic, haematological, biochemical and virologic factors, drug adherence and treatment discontinuance by a univariate analysis (Table 4A). Next, the factors selected as significant by the univariate analysis were evaluated by a multivariate analysis (Table 4B). The favourable factors associated with SVR were treatment-naïve, relapse to previous treatment, TVR dose during treatment (25–35 mg/kg/day) and completion of treatment.

DISCUSSION

Baseline factors such as the virologic response to previous IFN therapy, the degree of liver fibrosis progression and genetic polymorphism near the IL28B gene have been reported to be associated with SVR in triple therapy with TVR, Peg-IFN and RBV [7,16,17]. The setting of an optimum dosage of TVR that can increase the antiviral effect and decrease adverse effects is necessary because such baseline factors do not change. Regarding the TVR dosage, a phase 1b, placebo-controlled, double-blinded study conducted in Europe indicated that HCV RNA reduction was greatest at 750 mg of TVR every 8 h than at 450 mg of TVR every 8 h or 1250 mg of TVR every 12 h; as a result,

Table 2 Adverse events leading to drug discontinuation

	All drug discontinuation		TVR discontinuation	
Factor	Age <65 y.o.	Age ≥65 y.o.	Age <65 y.o.	Age ≥65 y.o.
Rash	4	4	7	8
Anaemia	2	1	8	5
Gastrointestinal disorder	1	1	3	5
Fatigue	1	1	2	1
Hyperbilirubinaemia		1		2
Thrombopenia	1		1	
Renal dysfunction			1	
Unknown		1		
Discontinuance rate	8% (9/110)	16%* (9/56)	20% (22/110)	38%† (21/56)

*$P = 0.12$, Age <65 y.o. Age ≥65 y.o.
†$P = 0.015$, Age <65 y.o. Age ≥65 y.o.

Table 3 Factors associated with TVR discontinuation

A. Univariate analysis

Factor	No (n = 123)	Yes (n = 43)	P-value
Age (y.o)	59.1 ± 9.2	63.9 ± 5.9	0.002
Gender: male/female	67/56	18/25	0.15
Past history of IFN: naïve/relapse/nonresponse	44/52/24	15/21/5	0.48
HCV RNA (median, log IU/mL)	6.65	6.7	0.48
Liver histology: Activity: A0-1/2-3	45/21	19/4	0.28
Fibrosis: F0-2/3-4	49/17	19/4	0.57
White blood cell (/μL)	4928 ± 1357	4469 ± 1093	0.07
Haemoglobin (g/dL)	14.2 ± 1.4	14.0 ± 1.2	0.10
Platelets ($\times 10^4$/μL)	16.5 ± 5.3	16.2 ± 4.6	0.91
ALT (IU/L)	54 ± 38	64 ± 86	0.94
TVR dose (mg/kg/day): <25/25–35/35≤	42/59/22	7/20/16	0.013
Peg-IFN dose (μg/kg/week): <1.2/1.2–1.5/1.5≤	26/61/36	7/14/21	0.049
RBV dose (mg/kg/day): <6/6–10/10≤	35/59/29	12/21/9	0.96

B. Multivariate analysis

Factor	Category	Odds ratio	95% CI	P-value
Age	0: <65 y.o			
	1: ≥65 y.o.	2.266	1.062–4.835	0.034
TVR dose	0: <25 mg/kg/day			
	1: 25–35 mg/kg/day	2.062	0.778–5.469	0.146
	2: ≥35 mg/kg/day	3.877	1.323–11.362	0.014
Peg-IFN dose	0: <1.2 μg/kg/week			
	1: 1.2–1.5 μg/kg/week	0.792	0.275–2.279	0.666
	2: ≥1.5 μg/kg/week	1.701	0.598–4.839	0.319

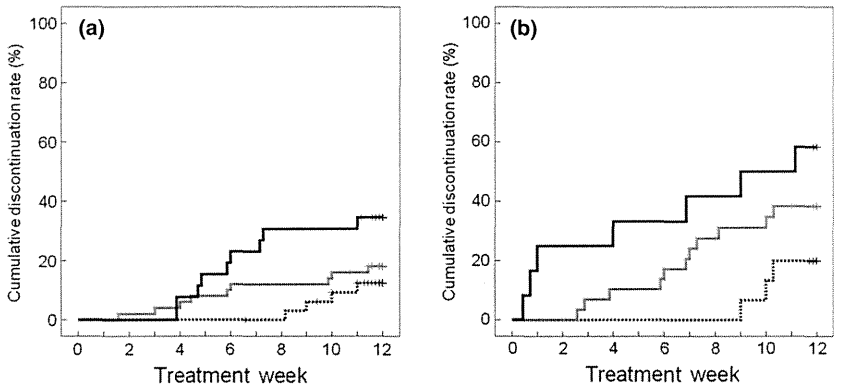

Fig. 1 The cumulative discontinuance rate of TVR according to the mean TVR dose. (**a**) age <65 y.o. (**b**) age ≥65 y.o. Dashed line, mean TVR dose <25 mg/kg/day. Grey line, mean TVR dose of 25–35 mg/kg/day. Black line, mean TVR dose ≥35 mg/kg/day. P = 0.025, mean TVR dose ≥35 mg/kg/day *vs* mean TVR dose <25 mg/kg/day among patients <65 y.o. P = 0.023, mean TVR dose ≥35 mg/kg/day *vs* mean TVR dose <25 mg/kg/day among patients ≥65 y.o.

the regimen of 750 mg of TVR every 8 h (total 2250 mg/day) was selected [12]. However, HCV RNA was reduced similarly with TVR at 500 or 750 mg every 8 h in a phase 1, open-label, two-arm study of TVR with Peg-IFN alfa-2b and RBV conducted in Japan using 20 patients with CH-C [13]. Recently, in Japanese CH-C patients limited with IL28B rs8099917 TT or relapse to previous IFN therapy, a similar antiviral effect was reported at 750 mg TVR every 8 or 12 h with Peg-IFN alfa-2b and RBV [18]. Furthermore, in a prospective study, we have reported that similar antiviral efficacies and fewer treatment-related adverse effects were obtained with initial TVR at 500 mg every

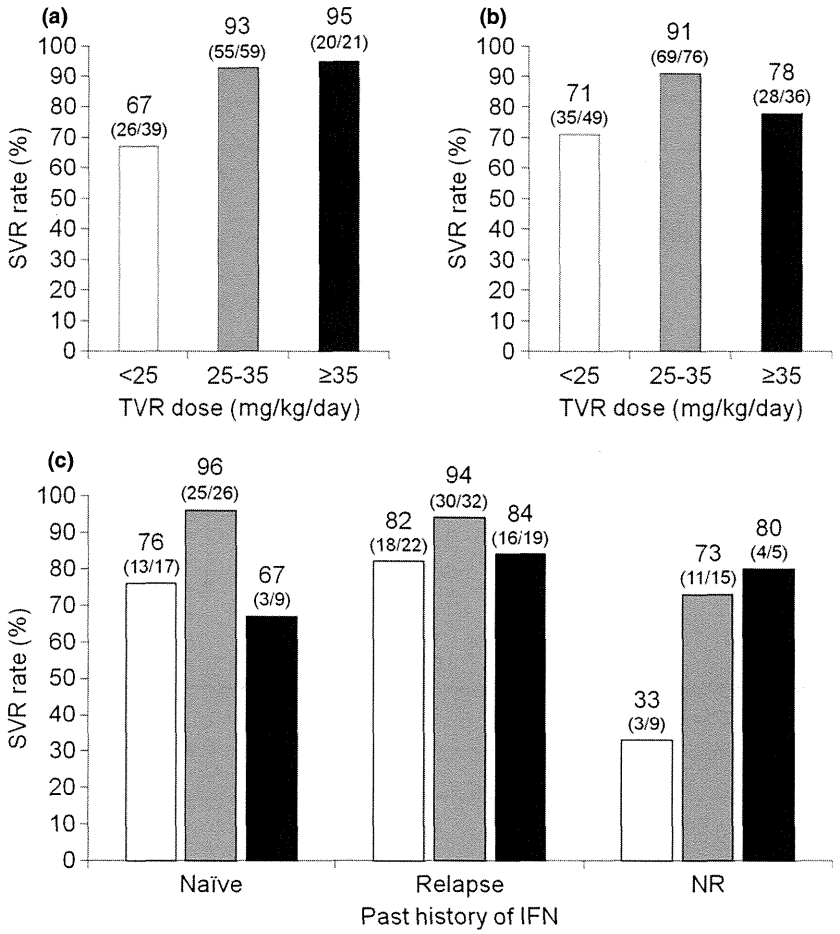

Fig. 2 The SVR rate according to the mean TVR dose. (**a**) Per protocol analysis. (**b**) Intention-to-treat analysis. (**c**) According to past history of IFN in intention-to-treat analysis. White bar, mean TVR dose <25 mg/kg/day. Grey bar, mean TVR dose of 25–35 mg/kg/day. Black bar, mean TVR dose ≥35 mg/kg/day.

8 h compared with initial 750 mg every 8 h with Peg-IFN alfa-2b and RBV. However, these reports have not shown how the dosage of TVR increases or decreases the antiviral effect and adverse effects in patients treated with TVR, Peg-IFN and RBV [14]. The usual dose for individuals originally differed on the basis of body weight, with an initial TVR dosage ranging from 22.5 to 45 mg/kg/day at 2250 mg/day and 15 to 30 mg/kg/day at 1500 mg/day among patients weighing 50–100 kg. In the present study, we examined the antiviral effect and prevalence of side effects with a focus on a weight-based TVR dosage.

The SVR rate was significantly higher, at 85%, in patients who completed the entire treatment schedule of all three drugs than the 70% found for those who discontinued TVR. Because the discontinuance rate of TVR was high at 25%, avoiding the discontinuance of TVR and completing treatment have the potential to increase the SVR rate. As a result of a multivariate analysis for TVR discontinuation, the factors of age and TVR dose were found to be significantly associated. Although it has been reported that there is no difference in the TVR discontinuance rate between patients <60 y.o. and those ≥60 y.o. [17], the TVR discontinuance rates in this study were significantly higher with advanced age (<60 y.o., 14%, 8/56; 60–64 y.o., 26%, 14/54; ≥65 y.o., 38%, 21/56, $P = 0.02$). Because the haematopoietic capacity and renal function are generally low in older patients, TVR tolerability can be poor. Moreover, the discontinuance of TVR occurred dose dependently, regardless of age. Remarkably, 58% of the patients ≥65 y.o. at ≥35 mg/kg/day of TVR discontinued TVR treatment. Therefore, older patients should be treated with caution to prevent the administration of a higher dose of TVR (≥35 mg/kg/day) to avoid its discontinuation. In contrast, even in the patients ≥65 y.o., none discontinued TVR before treatment week 8 if given <25 mg/kg/day.

The SVR reflects the result that increases according to the antiviral effect of the drug and is countered by the discontinuation of the drug. To examine the real impact of TVR dosage on antiviral effect, a PP analysis among the patients who completed the entire treatment schedule was

Table 4 The factors associated with SVR

A. Univariate analysis

Factor	SVR (n = 132)	Non-SVR (n = 29)	P-value
Age (y.o)	60.0 ± 9.1	61.3 ± 7.0	0.90
Gender: male/female	72/60	10/19	0.05
Past history of IFN: naïve/relapse/nonresponse	46/64/18	9/9/11	0.01
HCV RNA (median, log IU/mL)	6.7	6.5	0.35
Liver histology: Activity: A0-1/2-3	53/17	9/7	0.12
Fibrosis: F0-2/3-4	55/15	10/6	0.18
White blood cell (/μL)	4869 ± 1409	4467 ± 725	0.15
Haemoglobin (g/dL)	14.2 ± 1.4	13.9 ± 1.3	0.30
Platelets ($\times 10^4$/μL)	16.8 ± 5.1	14.5 ± 4.9	0.01
ALT (IU/L)	54 ± 57	73 ± 44	0.002
IL28B SNP(rs8099917): TT/non-TT	45/14	10/6	0.27
TVR dose (mg/kg/day): <25/25–35/35≤	35/69/28	14/7/8	0.02
Peg-IFN dose (μg/kg/week): <1.2/1.2–1.5/1.5≤	25/63/44	7/9/12	0.32
RBV dose (mg/kg/day): <6/6–10/10≤	40/62/30	5/15/8	0.40
TVR discontinuation: no/yes	105/27	18/11	0.045
PEG/RBV discontinuation: no/yes	120/12	20/9	0.001
RVR: yes/no	105/15	16/12	<0.001

B. Multivariate analysis

Factor	Category	Odds ratio	95% CI	P-value
Past history of IFN	0: Naïve			
	1: Relapse	1.183	0.320–4.371	0.801
	2: NR	0.185	0.048–0.702	0.013
Platelets	By 1 × 10^4 /μL	1.087	0.962–1.228	0.180
ALT	By 1 IU/L	0.995	0.988–1.002	0.133
TVR dose	0: <25 mg/kg/day			
	1: 25–35 mg/kg/day	4.537	1.348–15.266	0.015
	2: ≥35 mg/kg/day	2.602	0.651–10.398	0.176
TVR discontinuation	0: no			
	1: yes	0.563	0.148–2.143	0.399
PEG/RBV discontinuation	0: no			
	1: yes	0.154	0.034–0.703	0.016
RVR	0: RVR			
	1: Non-RVR	0.442	0.129–1.514	0.194

performed. In the PP analysis, TVR was dose dependently correlated with SVR, and the SVR rate was higher in patients at ≥25 mg/kg/day of TVR than that in those at <25 mg/kg/day. In addition, TVR was also dose dependently correlated with the discontinuance of TVR, and the discontinuance rate of TVR was lower in patients at <25 mg/kg/day of TVR and higher in patients at ≥35 mg/kg/day. As a result, according to an ITT analysis, among the patients at <25 mg/kg/day of TVR, the discontinuance rate of TVR decreased, but the SVR rate also decreased due to a poor antiviral effect; among the patients at ≥35 mg/kg/day of TVR, the SVR rate decreased because the discontinuance rate of TVR increased. Finally, based on the ITT analysis, the highest SVR rate was obtained in the patients at 25–35 mg/kg/day of TVR. Therefore, a TVR dose of 25–35 mg/kg/day can be optimal. As for the results of the multivariate analysis for SVR in the ITT analysis for all patients including those who discontinued any drugs as well as those who completed the entire treatment schedule, the factors of treatment-naïve, relapse to previous treatment, TVR dose during treatment and completion of treatment were found to be the significant factors. Regarding the response to previous treatment and TVR dose during treatment, similar results that the highest SVR rate was obtained in patients at 25–35 mg/kg/day of TVR in the ITT analysis were obtained in the naïve patients and relapsers. However, because the patient group with nonresponse to previous Peg-IFN and RBV was too small to

examine the relationship between the SVR rate and TVR dose, there was no significant difference between the SVR rate and TVR dose. However, the SVR rate among patients with nonresponse to previous Peg-IFN and RBV was insufficient in triple therapy with simeprevir (SMV), a second-generation PI, Peg-IFN and RBV; the SVR rates were calculated to be 51.7% (46/89) from a phase-2 study of triple therapy with SMV, Peg-IFN and RBV [19]. Moreover, because SMV is one tablet (100 mg of 150 mg), dose adjustment is impossible. In contrast, TVR doses are adaptable, and higher doses of TVR might have the potential to increase SVR in nonresponse patients. Further analysis using a larger cohort is needed to clarify the optimal dose of TVR in patients with nonresponse.

In conclusion, in Japanese patients, the administration of 25–35 mg/kg/day of TVR can result in the highest SVR rate in TVR, Peg-IFN and RBV triple therapy. Although it is important to avoid adverse effects by reducing TVR dosage and to complete treatment, when TVR is reduced, special attention is needed not to reduce it to <25 mg/kg/day. These data have important implications for clinicians treating Japanese patients – whether similar dosing changes are appropriate for light weight elderly patients from other countries remains to be determined.

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CONFLICT OF INTEREST

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REFERENCES

1 Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; 54: 1433–1444.
2 McHutchison JG, Everson GT, Gordon SC *et al.* Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; 360: 1827–1838.
3 Hezode C, Forestier N, Dusheiko G *et al.* Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; 360: 1839–1850.
4 McHutchison JG, Manns MP, Muir AJ *et al.* Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010; 362: 1292–1303.
5 Jacobson IM, McHutchison JG, Dusheiko G *et al.* Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; 364: 2405–2416.
6 Sherman KE, Flamm SL, Afdhal NH *et al.* Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; 365: 1014–1024.
7 Zeuzem S, Andreone P, Pol S *et al.* Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; 364: 2417–2428.
8 Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. *J Hepatol* 2012; 56: 78–84.
9 Hayashi N, Okanoue T, Tsubouchi H, Toyota J, Chayama K, Kumada H. Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C. *J Viral Hepat* 2012; 19: 134–142.
10 Mauss S, Hueppe D, Alshuth U. Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir. *Hepatology* 2014; 59: 46–48.
11 Fukuda K, Imai Y, Hiramatsu N *et al.* Renal impairment during the treatment of telaprevir with peginterferon and ribavirin in patients with chronic hepatitis C. *Hepatol Res* In press; doi: 10.1111/hepr.12229
12 Reesink HW, Zeuzem S, Weegink CJ *et al.* Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase Ib, placebo-controlled, randomized study. *Gastroenterology* 2006; 131: 997–1002.
13 Suzuki F, Akuta N, Suzuki Y *et al.* Rapid loss of hepatitis C virus genotype 1b from serum in patients receiving a triple treatment with telaprevir (MP-424), pegylated interferon and ribavirin for 12 weeks.

Hepatol Res 2009; 39: 1056–1063.

14 Oze T, Hiramatsu N, Yakushijin T *et al.* The prospective randomised study on telaprevir at 1500 mg or 2250 mg with pegylated interferon plus ribavirin in Japanese patients with HCV genotype 1. *J Gastroenterol* 2014; In press; doi: 10.1007/s00535-014-0965-8

15 Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996; 24: 289–293.

16 Akuta N, Suzuki F, Hirakawa M *et al.* Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. *Hepatology* 2010; 52: 421–429.

17 Furusyo N, Ogawa E, Nakamuta M *et al.* Telaprevir can be successfully and safely used to treat older patients with genotype 1b chronic hepatitis C. *J Hepatol* 2013; 59: 205–212.

18 Kawakami Y, Suzuki F, Karino Y, Toyota J, Kumada H, Chayama K. Telaprevir is effective given every 12 hours at 750 mg with peginterferon-alfa-2b and ribavirin to Japanese patients with HCV-1b IL28B rs8099917 TT. *Antivir Ther* 2014; 19: 277–285.

19 Zeuzem S, Berg T, Gane E *et al.* Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology* 2014; 146: 430–441.

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基本から最前線まで

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肝疾患の基礎から診療の最前線まで 鋭く切り込むシリーズ
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◇C型肝炎研究の最前線を紹介

C型肝炎の現在(いま)と未来がわかる!

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