Table 1 Baseline characteristics of patients

Factor	TVR-2250	TVR-1500	*p* value
Number	41	40	
Age (years old)	60.1 ± 8.7	61.0 ± 8.8	0.50
Gender (male/female)	23/18	23/17	1.00
Body weight (kg)	*60.6 ± 11.3*	*60.4 ± 11.2*	*0.98*
BMI (kg/m^2)	*23.0 ± 3.4*	*22.9 ± 3.2*	*0.81*
Past history of IFN: naïve/relapse/non-response	15/20/5	15/17/8	0.63
HCV RNA (median, $\log_{10}$ IU/ml)	6.9	6.8	0.87
Liver histology[a]: activity: A0/1/2/3	0/22/6/0	0/21/4/0	0.73
Liver histology[a]: fibrosis: F0/1/2/3/4	1/12/8/5/2	2/9/9/4/1	0.89
White blood cell (/μl)	4943 ± 1266	4980 ± 1499	0.79
Neutrophils (/μl)	2578 ± 919	2559 ± 1131	0.85
Red blood cell (×10^4/μl)	451 ± 53	447 ± 65	0.65
Hemoglobin (g/dl)	14.5 ± 1.4	14.3 ± 1.2	0.46
Platelets (×10^4/μl)	16.5 ± 4.4	17.3 ± 5.7	0.84
AST (IU/l)	55 ± 68	42 ± 26	0.16
ALT (IU/l)	63 ± 87	50 ± 39	0.15
Serum creatinine (mg/dl)	0.74 ± 0.19	0.72 ± 0.17	0.36
Uric acid (mg/dl)	5.5 ± 1.4	5.5 ± 1.4	0.70
Estimated glomerular filtration rate (ml/min)	75.4 ± 15.8	77.9 ± 14.6	0.36
IL28B SNP (rs8099917): TT/TG/GG	19/4/1	18/6/0	0.49
TVR dose (mg/kg/day)	38.4 ± 7.3	25.7 ± 5.0	<0.001
Peg-IFN dose (μg/kg/week)	1.49 ± 0.12	1.47 ± 0.13	0.44
RBV dose (mg/kg/day)	11.3 ± 1.5	11.5 ± 1.7	0.63

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *IL28B SNP* interleukin 28 B single nucleotide polymorphism, *TVR* telaprevir, *Peg-IFN* pegylated interferon, *RBV* ribavirin

[a] METAVIR

2250 group and 3 partial-responders and all of the 4 null-responders were included in the TVR-1500 group; the SVR rates were 100 % (7/7) among all partial-responders and 50 % (2/4) among the null-responders in the TVR-1500 group. Thus, the administration of TVR at 1500 mg/day is considered appropriate for naïve patients and relapsers, although further analysis is needed for the patients with non-response. This is supported by the report that the antiviral effect was almost the same in both groups of TVR at 750 mg every 8 or 12 h with Peg-IFN alfa-2b and RBV Japanese patients with IL28B rs8099917 TT or relapse to previous IFN therapy [15].

Regarding safety, the rates of discontinuation of all drugs and the rates of discontinuation of TVR were almost the same in both groups. These discontinuations resulted from adjustment such as drug reduction or interruption of TVR, Peg-IFN and RBV during treatment by a physician in patients in the TVR-2250 group. Indeed, the two-thirds of patients decreased or discontinued TVR and the three-fourths of patients reduced or discontinued Peg-IFN in the TVR-2250 group. However, when adverse effects occurred early in treatment, missing the opportunity to reduce the drug dose might lead to serious adverse effects. Regarding serious adverse effects, the cumulative occurrence of rash more than grade 2 and severe anemia more than grade 3 was significantly lower in the TVR-1500 group. Rash more than grade 2 occurred in 30 % at week 1 and 35 % at week 2 in the TVR-2250 group compared with 8 and 8 % in the TVR-1500 group. Although the differences in occurrence of severe anemia were marked after 6 weeks of treatment, the decreases of Hb from baseline were significantly greater in the TVR-2250 group than in the TVR-1500 group at 4 weeks of treatment. Moreover, two patients developed rash more than grade 3 and discontinued treatment (day 10, day 30), and both of them were in the TVR-

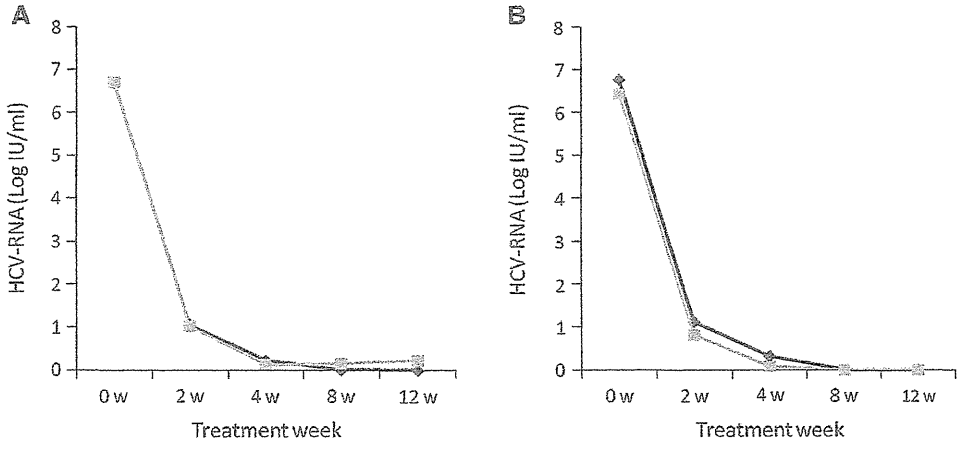

Fig. 2 The mean HCV RNA level. **a** The mean HCV RNA level among all patients. **b** The mean HCV RNA level among naïve patients. *Black line* TVR-2250 group. *Gray line* TVR-1500 group

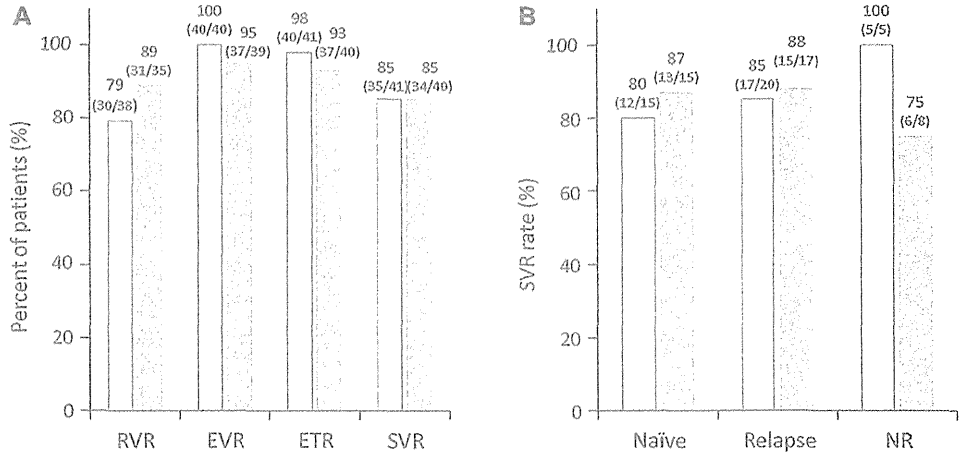

Fig. 3 The longitudinal HCV RNA negative rate and SVR rate. a The RVR, cEVR, ETR and SVR rates among all patients. b The SVR rates according to IFN history. *White bar* TVR-2250 group. *Gray bar* TVR-1500 group

Table 2 Dose reduction and discontinuation of TVR, Peg-IFN and RBV

	TVR		Peg-IFN		RBV	
	TVR 2250	TVR 1500	TVR 2250	TVR 1500	TVR 2250	TVR 1500
Completed treatment without dose reduction (%)	13 (32)	27* (68)	10 (24)	19** (48)	3 (7)	5 (13)
Completed treatment with dose reduction or temporally discontinuation (%)	18 (44)	4 (9)	25 (61)	17 (42)	32 (78)	31 (78)
Discontinuation (%)	10 (24)	9 (23)	6 (15)	4 (10)	6 (15)	4 (10)
Total dose (median)	162.8 g	125.3 g†	1840 μg	1850 μg	64 g	73 g

TVR telaprevir, *Peg-IFN* pegylated interferon, *RBV* ribavirin

* $p = 0.001$, TVR, Completed treatment without dose reduction, TVR-2250 group vs. TVR-1500 group

** $p = 0.03$, Peg-IFN, Completed treatment without dose reduction, TVR-2250 group vs. TVR-1500 group

† $p \leq 0.001$, TVR-2250 group vs. TVR-1500 group

2250 group. As for renal dysfunction, the serum creatinine levels were significantly lower and the eGFRs were significantly higher in the TVR-1500 group than the TVR-2250 group at the early treatment phase (weeks 1–4) (at week 4: serum creatinine, 0.80 ± 0.16 vs. 0.97 ± 0.26 mg/dl; eGFR, 69.3 ± 13.1 vs. 55.8 ± 13.2 ml/min). The tendencies were apparent among the older patients with inherently poor renal function. It was reported that C_{trough} tended to be higher in the 750-mg dose group than in the 500-mg dose group after treatment week 1 from phase 1 study in Japan comparing the two groups of TVR at 500 or 750 mg every 8 h with Peg-IFN alfa-2b and RBV (day 14, 2.64 ± 0.56 vs. 1.91 ± 0.72 μg/ml, day 85, 2.68 ± 0.36 vs. 2.11 ± 0.82 μg/ml) [13]. When TVR was given at 2250 mg/day, the high concentration of TVR at early treatment phase was thought to cause the adverse effects at early treatment phase. Thus, avoidance of such serious adverse effects at the early treatment phase by the reduced administration of TVR at 1500 mg/day can lead to an improved SVR rate among older patients with high risk of HCC and low tolerance for antiviral treatment.

We examined the efficacy and safety according to median of total dose of each drugs in both the TVR-2250 mg group and the TVR-1500 mg group (Supplemental table). Roughly, the SVR rates were higher in the higher total-dose group of each drug than in the lower total-dose group of each drug. On the other hand, the discontinuation rates of all drugs and the discontinuation rates of TVR were higher in the lower total-dose group of each drug than in the higher total-dose group of each drug. These results were thought to reflect that the lower total-dose group included many patients who could not attain SVR because of incompletion of the entire schedule of treatment.

At present, triple therapy is available as simeprevir (SMV) (a second-generation PI), Peg-IFN and RBV [16–18]. The SVR rate among the naïve patients and relapsers was almost 90 %, and the adverse effects profile was generally similar across the SMV and placebo control groups of Peg-IFN and RBV with the exception of mild reversible hyperbilirubinemia, without serum aminotransferase abnormalities. Therefore, triple therapy with SMV,

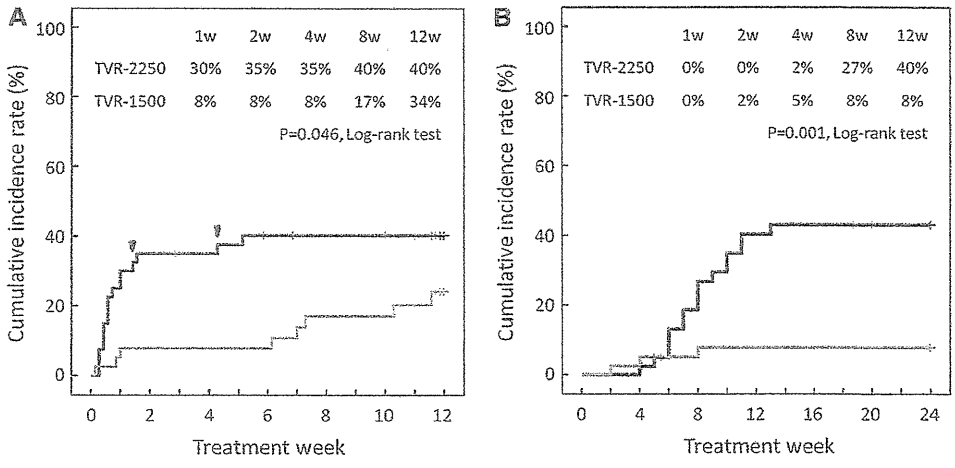

Fig. 4 Cumulative occurrence of rash more than moderate and severe anemia. a Rash more than moderate (Grade 2). b Severe anemia (Grade 3, hemoglobin <8.5 g/dl). *Black line* TVR-2250 group. *Gray line* TVR-1500 group. *Closed down triangle* patients with rash more than grade 3

Peg-IFN and RBV is recommended as first-line therapy for the naïve patients and relapsers. However, the SVR rate was insufficient at 34 % among the patients with non-response in Japan [9] and at 38–59 % among the patients with null-response in Europe [18]. Triple therapy with 1500 mg/day of TVR, Peg-IFN and RBV for the patents with non-response may allow for more treatment options, although the patients with non-response were too small to conclude the relationship between TVR dose and SVR rate in this study. Indeed, the treatment guideline from the Japanese Society of Hepatology recommends triple therapy with 1500 mg/day of TVR as well as triple therapy with SMV as a therapeutic option for the patients with non-response. Further analysis using a larger-cohort is needed to clarify the effect of 1500 mg/day of TVR in the patients with non-response.

The limitations of this study are described below. In order to prove non-inferiority of 1500 mg of TVR compared to 2250 mg of TVR for SVR, 123 patients in both group (total 246 patients) were required (expected SVR rate, 70 % in 2250 mg of TVR, 75 % in 1500 mg of TVR, $\alpha = 0.025$, $\Delta = 0.10$, power = 0.8). In the present study, we reported the preliminary results of the antiviral effect and the adverse effect among the TVR-2250 group and the TVR-1500 group. The non-inferiority of 1500 mg of TVR compared to 2250 mg of TVR for SVR could not be revealed because the number of cases enrolled in this study was too small. Second, in this randomized study, the naïve, relapse and non-response to previous treatment patients were divided into two groups without bias. However, among non-responders, the distribution of patients with null-response was to some extent idiosyncratic. Patients with null-response were too small in number to examine the antiviral efficacy of 1500 mg/day of TVR. A larger-cohort study should be conducted to clarify this. Third, a genetic polymorphism near the IL28B gene has been reported to be associated with SVR in triple therapy with TVR, Peg-IFN and RBV [19]. In this study, although the IL28B genotype was examined in approximately 60 % of patients, we could not obtain patients' consent for examination of IL28 SNP, which is information about the human genome in the remaining 40 % of patients. However, we tried to examine more closely the relationship between the IL28B genotype and the SVR rates in the cases in whom the IL28B genotype was obtained. According to IL28B single nucleotide polymorphism, the SVR rate was 95 % (18/19) in the TVR-2250 group and 83 % (15/18) in the TVR-1500 group among the patients with rs8099917 TT ($p = 0.34$). The patients with rs8099917 non-TT had small counts (5 cases with 80 % of SVR in the TVR-2250 group and 6 cases with 100 % of SVR in TVR-1500 group). As for the SVR rates according to the previous IFN treatment response and IL28B genotype, there were no significant difference between the TVR-2250 mg group and the TVR-1500 mg group among the same category of previous IFN treatment response and IL28B genotype (SVR rates of TVR-2250 mg group and TVR-1500 mg group, naïve patients with TT, 100 % (7/7) vs, 83 % (5/6), $p = 0.46$, naïve patients with non-TT, no patients vs. 100 % (2.2); relapser with TT, 89 % (8/9) vs, 88 % (8/9), $p = 1.00$, relapser with non-TT, 67 % (2/3) vs. 100 % (3/3), $p = 1.00$; NR patients with TT, 100 % (3/3) vs. 67 % (2/3), $p = 1.00$, NR patients with non-TT, 100 % (1/1) vs. 100 % (1/1), $p = 1.00$). Further analysis using a larger-cohort is needed to clarify the effect of IL28B status on the TVR-1500 group. Fourth, the concentration of TVR should be measured in order to examine the antiviral effect more closely. However, the concentrations of TVR measured, because the patients' serum, was not preserved in this study. This problem is also subject of future investigation.

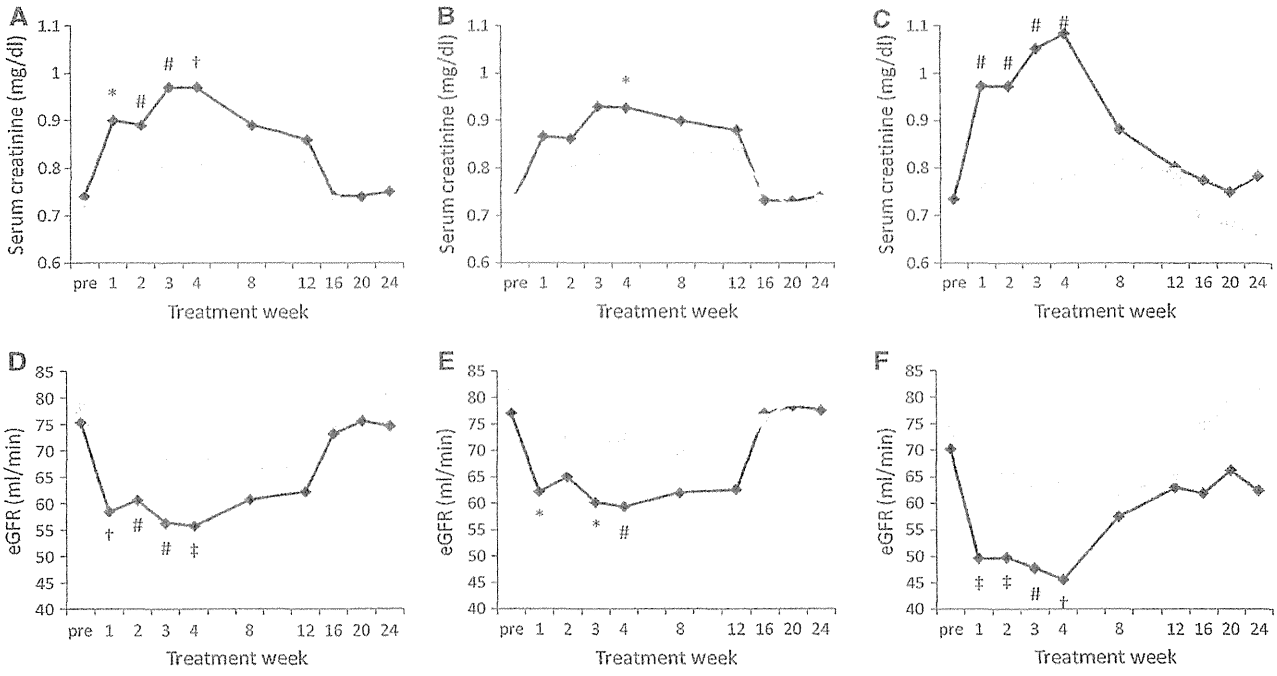

Fig. 5 The mean serum creatinine level and estimated glomerular filtration rates during the treatment. **a**–**c** The mean serum creatinine level during the treatment. **d**–**f** The mean estimated glomerular filtration rates during the treatment. **a**, **d** All patients. **b**, **e** Patients <60 years old **c**, **f** Patients ≥60 years old *Black line* TVR-2250 group. *Gray line* TVR-1500 group. $^{*}p < 0.05$, $^{\#}p < 0.01$, $^{\#}p = 0.001$, $^{\ddagger}p < 0.001$; TVR-2250 group vs. TVR-1500 group

In conclusion, the administration of a lower dose of TVR (1500 mg/day) can result in similar efficacy and fewer treatment-related adverse effects compared to the higher dose of TVR (2250 mg/day) in triple therapy with TVR, Peg-IFN and RBV.

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The real impact of telaprevir dosage on the antiviral and side effects of telaprevir, pegylated interferon and ribavirin therapy for chronic hepatitis C patients with HCV genotype 1

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SUMMARY. Triple therapy with telaprevir, pegylated interferon and ribavirin has been reported to improve antiviral efficacy but have potentially severe adverse effects in patients with chronic hepatitis C. To avoid the severe effects of telaprevir, lowering the dose has been suggested. However, impact of dosage changes on antiviral and adverse effects remains unclear. One hundred and sixty-six Japanese patients with HCV genotype 1 were treated with triple therapy. The drug exposure of each medication was calculated by averaging the dose actually taken. The overall SVR rate was 82%. The telaprevir discontinuation rate was 26%. The factors associated with discontinuation were an older age (≥65 y.o.) and a higher average dose during treatment. The telaprevir discontinuation rates were 42%, 25% and 14% in patients at ≥35, 25–35 and <25 mg/kg/day of telaprevir and 58% in older patients at ≥35 mg/kg/day of TVR. The factors associated with SVR were treatment-naïve, relapse to previous treatment, higher average telaprevir dose during treatment and completion of treatment. The SVR rate was higher, at 91%, in patients at 25–35 mg/kg/day of telaprevir than the 71% and 78% observed in those at <25 and ≥35 mg/kg/day of drug. In Japanese patients, a mean telaprevir dose of 25–35 mg/kg/day during treatment can augment its efficacy in triple therapy for patients with HCV genotype 1.

Keywords: chronic hepatitis C, discontinuation rate, drug adherence, older patients, telaprevir with pegylated interferon and ribavirin.

INTRODUCTION

Antiviral therapy for patients with chronic hepatitis C virus (HCV) genotype 1 infection has changed from interferon (IFN) monotherapy to dual therapy with pegylated interferon (Peg-IFN) and ribavirin (RBV) and even triple therapy with protease inhibitor (PI), Peg-IFN and RBV [1]. Although clinical trials of triple therapy with telaprevir (TVR), which is a first-generation PI, Peg-IFN and RBV have reported that the addition of TVR leads to a substantial improvement in sustained virologic response (SVR) [2–9], adverse effects caused by TVR, such as the rapid progression of anaemia, severe rash and renal dysfunction, have also been reported [2,3,8–11]. Patients with a high risk of hepatocellular carcinoma (HCC), such as older patients and patients with advanced liver fibrosis, should be treated with antiviral therapy as early as possible to eliminate HCV.

A 2250 mg/day fixed-dose regimen was selected for TVR worldwide [12,13], although the safety was inferior in Japan compared with Europe and the United States

Abbreviations: c-EVR, complete early virologic response; CH-C, chronic hepatitis C; EOT, end of treatment; ETR, end of treatment response; Hb, haemoglobin; HCV, hepatitis C virus; IFN, interferon; Peg-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RVR, rapid virologic response; SMV, simeprevir; SVR, sustained virologic response; TVR, telaprevir; WBC, white blood cell.

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(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 α-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

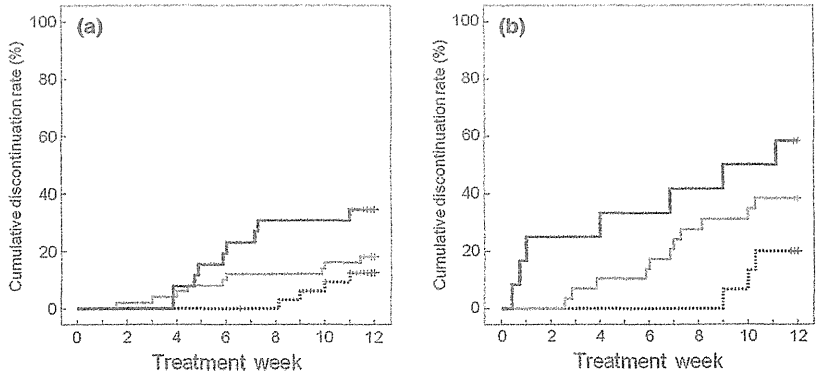

Fig. 1 The cumulative discontinuance rate of TVR according to the mean TVR dose. (**a**) age <65 y.o. (**b**) age ≥65 y.o. Dashed line, mean TVR dose <25 mg/kg/day. Grey line, mean TVR dose of 25–35 mg/kg/day. Black line, mean TVR dose ≥35 mg/kg/day. P = 0.025, mean TVR dose ≥35 mg/kg/day *vs* mean TVR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

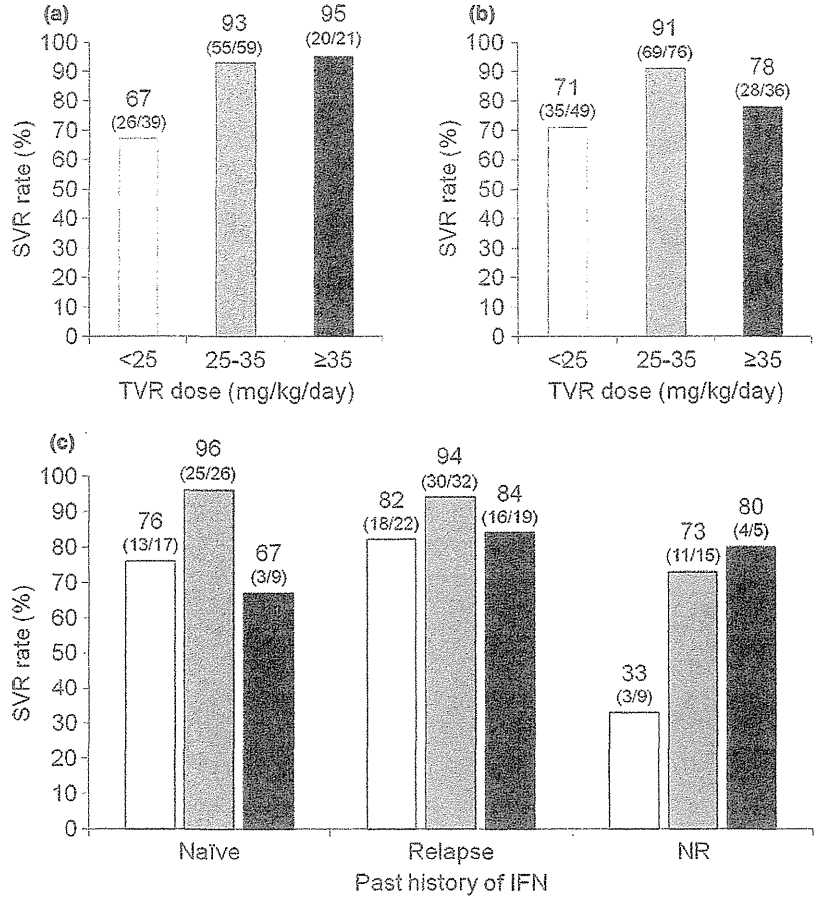

Fig. 2 The SVR rate according to the mean TVR dose. (a) Per protocol analysis. (b) Intention-to-treat analysis. (c) According to past history of IFN in intention-to-treat analysis. White bar, mean TVR dose <25 mg/kg/day. Grey bar, mean TVR dose of 25–35 mg/kg/day. Black bar, mean TVR dose ≥35 mg/kg/day.

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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Hepatology Research

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Review Article

Suppression of hepatocellular carcinoma development in hepatitis C patients given interferon-based antiviral therapy

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The advance of antiviral treatment for chronic hepatitis C has brought a high sustained virological response (SVR) rate. In this review article, the suppressive effect of interferon (IFN)-based therapy on the development of hepatocellular carcinoma (HCC), risk factors for developing HCC and the characteristics of HCC development after SVR among chronic hepatitis C patients given IFN-based therapy were studied. The HCC incidence has been revealed to decrease with IFN-based antiviral therapy, especially in SVR, and the risk factors for developing HCC were older age, advanced liver fibrosis and male sex. α-Fetoprotein levels at 24 weeks after the end of IFN-based treatment was associated strongly with HCC incidence irrespective of virological response. In patients with SVR, other risk factors were glucose metabolism disorders, lipid metabolism disorders and alcohol intake. Extra attention to the possibility of HCC incidence should be required for these SVR patients. Antiviral therapy with a combination of HCV-specific direct-acting antivirals (DAA) is expected to be utilized in the future. However, it is not known whether DAA-based treatment can suppress HCC to the level of IFN-based treatment. Further research is required to clarify this.

Key words: hepatocellular carcinoma, interferon therapy, sustained virological response

INTRODUCTION

IN ANTIVIRAL TREATMENT of chronic hepatitis C, a high sustained virological response (SVR) rate can be achieved by changing the treatment course from interferon (IFN) monotherapy to combination therapy with pegylated interferon (PEG IFN) and ribavirin (RBV), or combination therapy with protease inhibitor, PEG IFN and RBV. This has led to successful viral clearance even in elderly patients and patients with advanced liver fibrosis, for whom SVR was considered difficult. However, an increase in the proportion of elderly patients and patients with advanced liver fibrosis with SVR has given rise to concerns of a future increase in the rate of carcinogenesis following SVR.

This review describes the suppressive effect of IFN-based therapy on the development of hepatocellular carcinoma (HCC), risk factors for developing HCC and the characteristics of HCC development after SVR.

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SUPPRESSIVE EFFECT OF IFN TREATMENT ON HCC DEVELOPMENT

Chronic liver disease with hepatitis C virus (HCV) infection

A LARGE NUMBER of articles have been published, primarily in Japan, suggesting that IFN-based therapy is associated with the decrease of HCC development (Table 1). Regarding IFN monotherapy, Ikeda *et al.*[1] retrospectively analyzed 1643 patients with HCV-related chronic liver disease and reported that the 3-, 5- and 10-year cumulative carcinogenic rates were 2.8%, 4.8% and 12.4% for patients not treated with IFN and 1.1%, 2.1% and 7.6% for those treated with IFN, respectively. A study by Kasahara *et al.*[2] of 1022 patients treated with IFN reported 3-, 5- and 7-year cumulative carcinogenic rates of 1.6%, 4.3% and 4.3% for the sustained biochemical response (SBR) group (alanine aminotransferase [ALT] ≤40 IU/L at 24 weeks after the end of treatment) and 6.3%, 21.4% and 26.1% for the non-SBR group, respectively; the carcinogenic rate significantly decreased in the SBR group. Comparable results were obtained in other studies conducted by Yoshida *et al.*,[3] Imai *et al.*[4] and Okanoue *et al.*[5] According to these reports,[1–5] the risk factors for HCC development were indicated to be older age, male sex, advanced liver fibrosis, lack of IFN treatment and non-response (NR).

Table 1 Cumulative HCC incidence and risk factors for HCC in patients treated by interferon therapy

Author (reference)	Patients (*n*)	Severity	HCV genotype (proportion)	Country	Observation period (mean, years)	IFN treatment	Risk factor for HCC	Cumulative incidence of HCC			
Ikeda *et al.* 1999[1]	ALL: 1643 IFN: 1191 control: 452	CH	Type 1: 72% Type 2: 28%	Japan	5.4	IFN	Age (≥50 years), fibrosis, male, γ-GT (≥50 IU/L), NR		IFN	Controls	
								3 years	1.1%	2.8%	
								5 years	2.1%	4.8%	
								10 years	7.6%	12.4%	
									SVR	SBR	NR
								3 years	0.7%	0.7%	1.5%
								5 years	1.4%	1.9%	2.9%
								7 years	1.4%	1.9%	7.6%
								10 years	1.4%	1.9%	17.5%
Kasahara *et al.* 1998[2]	1022	CH	Type 1: 77% Type 2: 23%	Japan	3	IFN	Age (≥55 years), male, NR		SBR	Relapse	NR
								3 years	1.6%	3.4%	6.3%
								5 years	4.3%	4.7%	21.4%
								7 years	4.3%	4.7%	26.1%
Yoshida *et al.* 1999[3]	ALL: 2890 IFN: 2400 control: 490	CH, LC	Type 1: 70% Type 2: 30%	Japan	4.3	IFN	Age, fibrosis, male, non-IFN				
Imai *et al.* 1998[4]	ALL: 563 IFN: 419 control: 144	CH, LC		Japan	IFN, 4; controls, 3.9	IFN	Age (≥60 years), fibrosis, non-IFN		IFN	Controls	
								4 years	6.6%	12.2%	
									SBR	Relapse	NR
								4 years	0.9%	6.1%	12.8%
Okanoue *et al.* 1999[5]	1148	CH, LC		Japan	F1, 3.5; F2, 3.3; F3, 3.4; F4, 3.8	IFN	Age, fibrosis, male, NR				
Serfaty *et al.* 1998[6]	ALL: 103 IFN: 59 control: 44	LC	Type 1: 71% Type 2: 7% Type 3: 22%	France	3.3	IFN	Non-IFN		IFN	Controls	
								2 years	1.8%	5%	
								4 years	4.4%	23%	
Shiratori *et al.* 2005[7]	ALL: 345 IFN: 271 control: 74	LC	Type 1: 73% Type 2: 27%	Japan	6.8	IFN	Age, non-IFN, Alb (≤40 g/L)				
Gramenzi *et al.* 2001[8]	ALL: 144 IFN: 72 control: 72	LC		Italy	IFN, 4.6; controls, 4.8	IFN	Non-IFN, AFP (≥20 ng/mL); size of varices, absent/F1/F2–3		IFN	Controls	
								2 years	1.5%	11%	
								5 years	11%	27%	
Bruno *et al.* 2007[9]; (Multicenter trial)	920	LC	Type 1: 72% Type 2: 23% Type 3: 3% Type 4: 2%	Italy	8	IFN	Age (>54 years), male, non-SVR, platelets ($\leq 109\times10^9$/L)				
Nishiguchi *et al.* 2001[10]	ALL: 90 IFN: 45 control: 45	CH, LC		Japan	IFN, 9.2; controls, 8.2	IFN	Non-IFN				
Bruno *et al.* 1997[11]	ALL: 163 IFN: 82 control: 81	LC	Type 1: 67% Type 2: 32% Type 3: 1%	Italy	5.7	IFN	Genotype 1b, male, age (>60 years)				
Hamada *et al.* 2002[12]	ALL: 469 IFN: 145 control: 324	CH		Japan	28	IFN	Age (≥56 years), fibrosis, alcohol, duration from HCV infection				
Kurokawa *et al.* 2009[13]	403	CH, LC	Type 1H: 73% Non-1H: 27%	Japan	3	IFN/RBV	Age (≥65 years), fibrosis, non-SVR		SVR	Relapse	NR
								3 years	2.0%	5.5%	9.5%
								5 years	7.5%	8.0%	12.0%

(Continues)

Table 1 (Continued)

Author (reference)	Patients (*n*)	Severity	HCV genotype (proportion)	Country	Observation period (mean, years)	IFN treatment	Risk factor for HCC	Cumulative incidence of HCC			
Ogawa *et al.* 2013[14]	1013	CH, LC	Type 1: 70% Type 2: 30%	Japan	3.6	PEG IFN/RBV	Age (≥60 years), male, platelet count (<150×10^9/L); AFP (≥10 ng/mL), LC, NR		SVR	Relapse	NR
								5 years (CH)	1.7%	3.2%	7.6%
								5 years (LC)	18.9%	20.8%	39.4%
Watanabe *et al.* 2011[15]	1865	CH, LC	Type 1: 80% Type 2: 20%	Japan	4.3	PEG IFN/RBV	Age (≥60 years), male, NR, platelet count (<10×10^4/mm^3), ALT at 24 weeks after end of treatment (>40 IU/L)		SVR	Relapse	NR
								2 years	0.6%	1.2%	2.8%
								3 years	0.9%	2.9%	4.3%
								4 years	0.9%	4.8%	6.1%
								5 years	1.1%	5.2%	8.5%
Cardoso *et al.* 2010[16]	307	CH, LC	Type 1: 60% Type 2: 8% Type 3: 16% Type 4: 13%	France	3.5	PEG IFN/RBV	Age (≥60 years), Bil (≥17 μmol/L), Alb (<40 g/L), non-SVR; platelet count (<150 Giga/L)				
Oze *et al.* 2014[17]	2600	CH, LC	Type 1: 78% Type 2: 22%	Japan	3.3	PEG IFN/RBV	Age (≥55 years), male, non-SVR, platelet (<15×10^4/mm^3), AFP24 (≥5 ng/mL)		SVR	Relapse	NR
								3 years	1.8%	2.9%	6.1%
								5 years	2.6%	7.3%	15.8%
Hung *et al.* 2011[18]	1470	CH, LC	Type 1: 49% Non-1: 51%	Taiwan	4.3	IFN/RBV, PEG IFN/RBV	Age, male, LC, non-SVR, platelet (<15×10^4/μL), pre-IFN AFP (≥20 ng/mL)		SVR	Non-SVR	
								2 years	1.0%	2.0%	
								4 years	2.8%	8.7%	
								6 years	4.5%	17.0%	
								8 years	6.1%	23.7%	
Tateyama *et al.* 2011[19]	ALL: 707 IFN: 373 control: 334	CH, LC	Type 1: 72% Type 2: 28%	Japan	8.2	IFN, IFN/RBV; PEG IFN, PEG IFN/RBV	Age (≥57 years), fibrosis, non-SVR, AFP (≥6 ng/mL)		SVR	non-SVR	controls
								5 years	0.8%	5.7%	11.8%
								10 years	3.1%	14.6%	29.5%
								15 years	3.1%	36.1%	48.0%
Arase Y *et al.* 2013[20]	4302	CH, LC	Type 1: 65% Type 2: 35%	Japan	8.1	IFN, IFN/RBV	Age, male, LC, non-SVR, DM, alcohol		SVR	non-SVR	
								10 years	2.8%	14.5%	
Kawamura *et al.* 2010[21]	2058	CH	Type 1: 64% Type 2: 36%	Japan	6.7	IFN, IFN/RBV	Age (≥60 years), male, AST (≥50 IU/L), AFP (≥20 mg/L), DM, non-SVR, platelet count (<17×10^4/mL)		SVR	non-SVR	
								4 years	0.7%	2.1%	
								8 years	1.0%	4.4%	
								12 years	1.6%	11.6%	
Asahina *et al.* 2010[22]	2166	CH, LC	Type 1: 71% Type 2: 29%	Japan	7.5	IFN, IFN/RBV; PEG IFN, PEG IFN/RBV	Age, male, fibrosis, liver steatosis, T-chol, FBS, non-SVR, pre-IFN AFP, post-IFN, AFP	Age <65 years			
									SVR	non-SVR	
								5 years	1.2%	3.6%	
								10 years	3.3%	10.9%	
								15 years	3.3%	15.5%	
								Age >65 years			
									SVR	non-SVR	
								5 years	6.0%	14.1%	
								10 years	11.0%	25.5%	
								15 years	11.0%	31.1%	

AFP, alpha-fetoprotein; Alb, albumin; CH, chronic hepatitis; DM, diabetes mellitus; FBS, fasting blood sugar; HCC, hepatocellular carcinoma; IFN, interferon; LC, liver cirrhosis; NR, non-response; PEG IFN, pegylated interferon; RBV, ribavirin; SBR, sustained biochemical response; SVR, sustained virological response; type 1H, genotype 1 with high viral load.

There have been some studies conducted on patients with cirrhosis. Of 103 patients with HCV-related cirrhosis who received IFN monotherapy in a study by Serfaty *et al.*,[6] the 2- and 4-year cumulative carcinogenic rates were 1.8% and 4.4% for the IFN treated group compared with 5% and 23% for the group without IFN treatment, respectively; fewer patients developed HCC in the IFN treatment group. Comparable results were obtained from other studies reported by Shiratori *et al.*[7] and Gramenzi *et al.*;[8] these studies reported that risk factors for HCC development were older age, albumin value, lack of IFN treatment, a high α-fetoprotein (AFP) level (≥20 ng/mL) and varix size. Bruno *et al.*[9] retrospectively examined the data of 883 patients with HCV-related cirrhosis according to IFN treatment efficacy in a multicenter trial and reported that the carcinogenic rate was 0.66/100 person-years in the SVR group compared with 2.10/100 person-years in the non-SVR group; the carcinogenic rate of the SVR group was significantly low. Nishiguchi *et al.*[10] conducted a randomized controlled trial (RCT) with 90 patients with chronic hepatitis and compensated cirrhosis and reported that HCC development was less frequent in the IFN treatment group. Only one report pointed to genotype 1b as the most important risk factor for HCC development in 163 patients with HCV-related cirrhosis.[11]

As for IFN or PEG IFN with RBV combination therapy, the cumulative carcinogenic rate was shown to decrease in the SVR group and in the SBR group. Independent risk factors for developing HCC were older age, advanced liver fibrosis and non-SVR.[13] A study conducted by Cardoso *et al.*[16] with 307 patients who received PEG IFN plus RBV combination therapy (~60% had cirrhosis) reported a carcinogenic rate of 1.24/100 person-years for the SVR group compared with 5.85/100 person-years for the non-SVR group; the carcinogenic rate of the SVR group was significantly low. Ogawa *et al.*[14] reported that, of 1013 patients with HCV-related chronic liver disease (863 patients with chronic hepatitis; 150 patients with cirrhosis) who received PEG IFN plus RBV combination therapy, the 5-year cumulative carcinogenic rates of patients with chronic hepatitis were 1.7% and 7.6% for the SVR group and non-SVR group, respectively, while that with cirrhosis was 18.9% and 39.4%; risk factors were older age, male sex, low platelet levels ($<150 \times 10^9$/L), high AFP levels (≥10 ng/mL), cirrhosis and NR.

In summary, with HCV-related chronic liver disease, the HCC incidence has been shown to decrease with IFN-based antiviral therapy, especially in SVR, and the risk factors for developing HCC were older age, advanced liver fibrosis and male sex.

Suppressive effect of IFN on recurrence after HCC cure

Regarding the suppressive effect of IFN on HCC development in patients who had been cured of HCC, Ikeda *et al.*[23] conducted an RCT that compared 10 patients who received IFN monotherapy with 10 untreated patients and reported that the recurrence rate was significantly lower in the treatment group than in the untreated group. Meta-analyses[24,25] also indicated that IFN significantly inhibits HCC recurrence. However, there have been few reports of the suppressive effect of PEG IFN plus RBV combination therapy on HCC recurrence. Tanimoto *et al.*[26] and Hagihara *et al.*[27] examined the prognosis of patients who received PEG IFN plus RBV combination therapy and reported that no significant difference was found between the IFN treatment group and the untreated group although the survival rate was higher in the IFN treatment group. Recently, Hsu *et al.*[28] conducted a study with a large sample of patients; among 2237 antiviral-naïve HCV-infected patients with curatively resected HCC, 213 patients receiving antiviral treatment with PEG IFN plus RBV were matched 1:4 with 852 untreated controls with HCV infection. As a result, the recurrence rate of HCC was reported to be significantly lower in the treated than the untreated cohort, at 52.1% and 63.9% after 5 years of follow up, respectively. Age, liver cirrhosis and diabetes mellitus were suggested to modify this association.

HCC DEVELOPMENT AFTER SVR TO IFN

HCC incidence after achieving SVR

TABLE 2 SHOWS the HCC incidence after SVR to IFN-based antiviral therapy. The rates of HCC development after SVR differed according to patient characteristics and types of antiviral therapy. Among patients who received IFN monotherapy, Hayashi *et al.* reported that the 3-, 5- and 10-year cumulative carcinogenic rates were 0.9%, 2.0% and 5.9%, respectively, for 2295 patients who achieved SVR (mean age, 50 years; F3–4, 14%; mean observation period, 6.1 years), based on nationwide data (Inuyama Symposium 2007). In a cohort study at a single institute, Ikeda *et al.*[29] reported that the 3-, 5- and 10-year cumulative carcinogenic rates were 0.5%, 3.3% and 11.1%, respectively, for 1056 patients who achieved SVR (median age, 50 years), and the carcinogenic rate was 0.56/100 person-years. Similarly, Arase *et al.*[20] reported that the 5-year cumulative carcinogenic rate was 2.8% for 1900 patients who achieved SVR, while the carcinogenic rate in patients

Table 2 Cumulative HCC incidence in patients with sustained virological response

Author (reference)	SVR patients	Age (mean, years)	Liver fibrosis	HCV genotype 1	IFN treatment	Observation period (mean, years)	HCC development rate per 100 person-years	Cumulative incidence of HCC		
								3-year	5-year	10-year
Yoshida *et al.* 1999[3]	789				IFN	4.3	0.38			
Ikeda *et al.* 2005[29]	1056	50†		44%	IFN	4.7†	0.56	0.5%	3.3%	11.1%
Tokita *et al.* 2005[30]	126	53	F3–4, 25%	35%	IFN	5.5	–	0.9%	4.7%	7.5%
Bruno *et al.* 2007[9]	124	53	F4	37%	IFN	8	0.66			
Kurokawa *et al.* 2009[13]	139	53	F3–4, 25%	52%	IFN/RBV	3	–	1.0%	7.2%	
Cardoso *et al.* 2010[16]	103	55	F3, 42% F4, 58%	60%	IFN/RBV PEG IFN, PEG IFN/RBV	3.5†	1.24	2.0%	8.8%	8.8%
Hung *et al.* 2011[18]	1027				IFN IFN/RBV	4.3†	–	1% (2y)	2.8% (4y) 4.5% (6y)	6.1% (8y)
Tateyama *et al.* 2011[19]	139				IFN, IFN/RBV PEG IFN, PEG IFN/RBV	8.2	–			3.1%
Arase *et al.* 2013[20]	1900				IFN, IFN/RBV	8.1	CH, 0.16, LC, 1.82		2.8%	
Asahina *et al.* 2013[31]	913				IFN, IFN/RBV PEG IFN, PEG IFN/RBV	6.1	–		2.3%	5.5%
Ogawa *et al.* 2013[14]	CH, 503 LC, 53	CH, 54† LC, 61†	F4, 10%	CH, 57% LC, 45%	PEG IFN/RBV	3.6†	–		CH, 1.7% LC, 18.9%	
Aleman *et al.* 2013[32]	110	50	F4	24%	PEG IFN/RBV	5.3	1.00			
Oze *et al.* 2014[17]	1425	55	F3–4, 12%	68%	PEG IFN/RBV	3.3	–	1.8%	2.6%	

†Median.
CH, chronic hepatitis; HCC, hepatocellular carcinoma; IFN, interferon; LC, liver cirrhosis; PEG IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virological response.

with cirrhosis (1.82/100 person-years) was significantly higher than for those with chronic hepatitis (0.16/100 person-years).

Among patients who received PEG IFN plus RBV combination therapy, Cardoso *et al.*[16] reported that the 3- and 5-year cumulative carcinogenic rates were 2.0% and 8.8%, respectively, and the carcinogenic rate was 1.24/100 person-years for 103 patients with advanced liver fibrosis (METAVIR, F3/4; mean age, 55 years). Ogawa *et al.*[14] reported that the 5-year cumulative carcinogenic rate was 18.9% for 53 patients with cirrhosis who achieved SVR (mean age, 61 years). Oze *et al.*[17] analyzed the data for 1425 patients who achieved SVR by PEG IFN plus RBV combination therapy and reported that the 3- and 5-year cumulative carcinogenic rates were 1.8% and 2.6%, respectively (mean age, 55 years).

The retrospective analysis was performed for the outcome of sustained virological responders with histologically advanced chronic hepatitis C among patients who participated in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial.[33] However, that study was mainly studied for the outcome of the rate of death or liver transplantation, and of liver-related morbidity and mortality after antiviral therapy. Their results for HCC incidence of SVR patients may be an underestimate because 23% of SVR patients did not participate in the amended HALT-C trial.

In summary, the 3- and 5-year HCC incidences after SVR to IFN-based antiviral therapy for HCV-related chronic hepatitis C and cirrhosis with HCV infection were 0.5–2.0% and 2.3–8.8%, respectively.

Except for the studies among patients with cirrhosis, the 3- and 5-year cumulative carcinogenic rates were reported to be 0.5–0.9% and 2.3–4.7% among SVR patients treated with IFN monotherapy,[29,30] and 1.0–2.0% and 2.6–8.8% among those with IFN (PEG IFN) plus RBV combination therapy, respectively;[13,16,17] the higher carcinogenic rates were found among SVR patients treated with IFN plus RBV combination therapy. This can be due to an increase in the proportion of elderly patients and patients with advanced liver fibrosis among SVR patients treated with IFN plus RBV combination therapy. Further study is needed to clarify this.

Risk factors for HCC after achieving SVR

Table 3 shows the risk factors for developing cancer after SVR to IFN-based antiviral therapy. A number of studies have reported that elderly patients and patients with advanced liver fibrosis are at high risk of developing HCC.

Recent reports have analyzed pretreatment and post-treatment factors of antiviral treatment as predictors for HCC development.[3,9,13,14,16–20,29–32,34–36] Oze *et al.* performed a prospective study, collecting data from 2659 patients with chronic hepatitis C without a history of HCC who had been treated with PEG IFN plus RBV and examined potential associated factors using a Cox proportional hazards model for 1425 patients who had achieved SVR.[17] As a result, among patients with SVR, multivariate analysis showed that the significant factors were older age (≥65 years; hazard ratio [HR], 5.814) and higher levels of AFP at 24 weeks after the end of treatment (AFP24). The patients with post-treatment AFP24 levels of 5 ng/mL or more were at higher risk of developing cancer than the group with AFP24 levels of less than 5 ng/mL (HR, 8.096). In addition, the 5-year cumulative carcinogenic rate after treatment, based on AFP24, was 1.0% in the group with AFP24 levels of less than 5 ng/mL, which was significantly lower than that in the group with AFP24 levels of 5–10 mg/mL (5.8%) and the group with AFP24 levels of 10 ng/mL or more (10.3%). When comparing the ability of pre- and post-comparison AFP24 levels to predict HCC development using a likelihood ratio test, the post-treatment AFP24 level was a better predictor of cancer development. Asahina *et al.*[31] also reported that higher post-treatment AFP and ALT levels increased the risk of developing HCC and these were considered to be important markers for the prediction of HCC development.

Akuta *et al.*[36] reported a high risk of developing HCC after SVR with the following factors: older age (≥55 years; HR, 3.1), advanced liver fibrosis (≥F3; HR, 9.0), HCV genotype 1, and amino acid alterations in core region 70 (Arg to Gln or His; HR, 10.5). Other risk factors reported for the development of HCC are diabetes,[18,20] fatty liver[35] and alcohol intake.[20,30] Thus, counseling on daily lifestyle habits is considered important.

Characteristics of liver HCC development after achieving SVR

Next, the characteristics of patients who developed liver cancer after achieving SVR to antiviral therapy are summarized in Table 4. Reports[14,30,35,37–41] showed that the mean age of the patients was 60 years or more (range, 38–87 years), indicating that the majority of patients who developed cancer were elderly. More male patients developed HCC (220 men) than female patients (45 women).