Efficacy

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

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

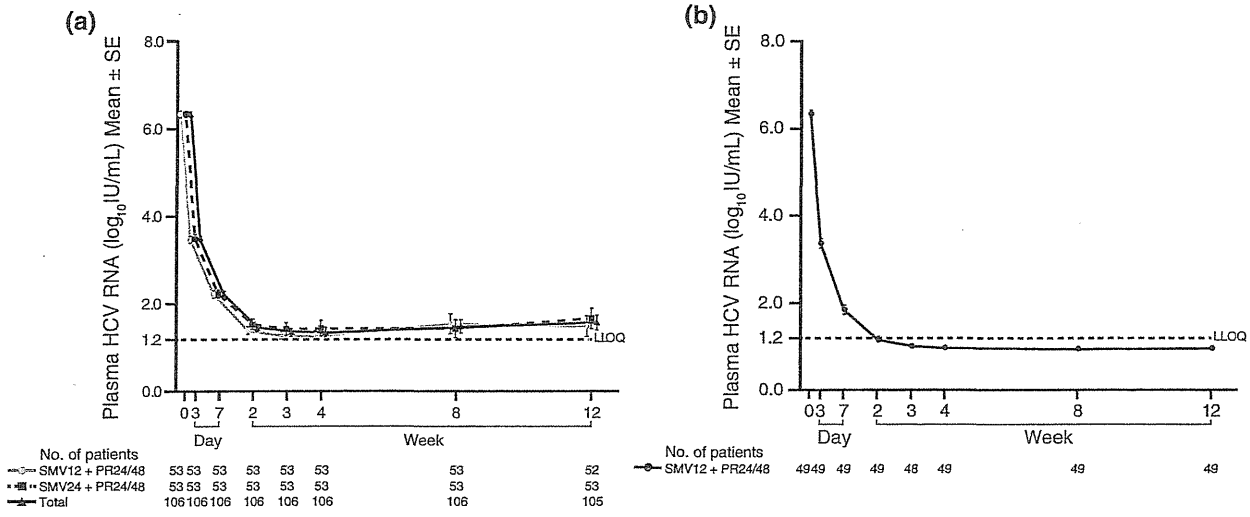

Fig. 1 Mean (±SE) plasma HCV RNA from baseline through week 12 **a** CONCERTO-2 and **b** CONCERTO-3 (SE values are too small to be viewed on **b**). *HCV* hepatitis C virus, *LLOQ* lower limit of quantification, *PR* peginterferon-α-2a/ribavirin, *SE* standard error, *SMV* simeprevir

Table 2 Virologic response rates

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[a] <65 years

[b] ≥65 years

No apparent trend was noted in relation to SVR12 rates for the selected demographic and baseline characteristics. Analysis of SVR12 rates according to *IL28B* genotype showed no consistent trend (Table 3).

A total of 57 patients (SMV12/PR24/48, $n = 26$; SMV24/PR24/48, $n = 31$) were described as 'failures' (defined as having viral breakthrough or relapse, meeting virologic stopping criteria, and/or having detectable HCV RNA at end of treatment), and 56 of these patients had available NS3 sequence information (unavailable for 1 patient, SMV12/PR24/48 group). Of these patients, 46/56 (82.1 %) had at least one emerging NS3 mutation (positions 36, 43, 54, 80, 122, 138, 155, 156, 168, or 170) at the time of failure despite the absence of baseline polymorphisms. No apparent difference in the rate of emerging NS3 mutations was observed among patients with failure in the SMV12/PR24/48 versus the SMV24/PR24/48 treatment groups (80.0 % and 83.9 %, respectively).

Alanine aminotransferase The proportions of patients whose ALT levels were abnormal at baseline and within normal range (≤40 IU/mL) at the end of treatment were 58.8 % in the SMV12/PR group and 80.0 % in the SMV24/PR group.

CONCERTO-3 (prior relapsers following IFN-based therapy)

Virologic response HCV RNA levels declined rapidly during the first 2 weeks of treatment with simeprevir and were below the LLOQ in all patients for the remainder of the 12-week simeprevir treatment period (Fig. 1). The RVR and cEVR rates were 81.6 % (40/49) and 100 % (48/48), respectively. The rate of SVR12 (primary endpoint) was 95.9 % (47/49), which was higher ($p < 0.0001$) than the 50 % proportion specified in the null hypotheses (Table 2).

The vast majority (95.9 %; 47/49) of patients met the RGT criteria and completed treatment with peginterferon α-2a and RBV at week 24. Of these patients, 95.7 % (45) achieved SVR12.

The rate of SVR24 (95 % CI) was 89.8 % (77.77–96.60) (Table 2).

No apparent trend in SVR12 was noted for selected demographic and baseline characteristics; regardless of gender, age, HCV genotype, prior HCV treatment, or *IL28B* genotype, the SVR12 rate was >85 % for all patient subgroups (Table 3).

Viral breakthrough, viral relapse, or treatment failure There were no viral breakthroughs. Viral relapse was observed in 8.2 % (4/49) of patients: two patients at week 4 and two patients at week 24 of follow-up. No patient met the virologic stopping rule.

Two patients (4.1 %) who did not achieve SVR12 had detectable HCV RNA after 12 weeks of treatment with simeprevir. None of the patients had detectable HCV RNA at the end of treatment or missing data at the SVR12 timepoint.

Alanine aminotransferase The proportion of patients whose ALT level was abnormal at baseline and within normal limits (≤40 IU/mL) at the end of treatment was 73.3 % (11 of 15).

Viral population sequencing Most patients enrolled in Japanese studies were infected with HCV genotype 1b, and only four were infected with genotype 1a (three patients in CONCERTO-2, and one patient in CONCERTO-3).

In CONCERTO-2, there were no notable differences in the position and proportion of baseline polymorphisms between the two treatment groups. The highest prevalence of baseline HCV polymorphisms at NS3 positions was observed at position 170 (39.6 %), followed by 122 (34.9 %), and 80 (11.3 %). Of the 59 simeprevir-treated patients in CONCERTO-2 with treatment failure for any reason and with NS3 sequence information available, 54 (91.5 %) had emerging mutations at positions 80, 122, 155, and/or 168. These mutations were associated with reduced simeprevir activity in vitro at the time of treatment failure. Among these, an emerging D168 V mutation (alone or in combination with other mutations) was the most commonly observed mutation (Supplementary Figure 3). In CONCERTO-3, a higher prevalence of baseline HCV polymorphisms at NS3 positions was observed for polymorphisms at 170 (40.8 %), 122 (36.7 %), and 80 (14.3 %). Three of four patients with viral relapse and without baseline polymorphisms had an emerging D168V mutation at the time of relapse.

Safety

No deaths were reported in either study. AEs are summarized in Table 4. Overall, the incidence of the most common AEs (i.e. occurring in >10 % of patients) was similar between the two studies. In CONCERTO-2, nasopharyngitis and injection-site reaction were considerably more common (>10 %) in the SMV24/PR group compared with the SMV12/PR group (30.2 % vs 18.9 % and 11.3 % vs 22.6 %, respectively). The majority of AEs were grade 1 or 2 in severity. Grade 3/4 AEs were reported for 26.4 % of patients in CONCERTO-2 and 34.7 % of patients in CONCERTO-3. Grade 4 AEs occurred in 6.6 % (7) of patients in CONCERTO-2 and 2.0 % (1) of patients in CONCERTO-3. These AEs were decreased neutrophil count (7 patients) and neutropenia (1 patient); none were classed as serious or led to discontinuation of any study

Table 4 Adverse events occurring in ≥25 % of patients in either study

n (%)	Entire treatment period			Simeprevir/placebo + PR period		
	CONCERTO-2 ($N = 106$)		CONCERTO-3 ($N = 49$)	CONCERTO-2 ($N = 106$)		CONCERTO-3 ($N = 49$)
	SMV12 + PR24/48 ($n = 53$)	SMV24 + PR24/48 ($n = 53$)	SMV12 + PR24/48	SMV12 + PR24/48 ($n = 53$)	SMV24 + PR24/48 ($n = 53$)	SMV12 + PR24/48
Any AE	53 (100.0)	52 (98.1)	49 (100)	53 (100.0)	52 (98.1)	49 (100)
Grade 3/4 AE	11 (20.8)	17 (32.1)	17 (34.7)	10 (18.9)	17 (32.1)	11 (22.4)
SAE	2 (3.8)	3 (5.7)	6 (12.2)	0 (0.0)	3 (5.7)	1 (2.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment discontinuation due to AE						
Simeprevir only	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (2.0)
All treatment[a]	2 (3.8)	2 (3.8)	2 (4.1)	1 (1.9)	2 (3.8)	1 (2.0)
Common AEs[b]						
Pyrexia	33 (62.3)	31 (58.5)	36 (73.5)	32 (60.4)	31 (58.5)	36 (73.5)
White blood cell decreased	33 (62.3)	31 (58.5)	30 (61.2)	30 (56.6)	31 (58.5)	30 (61.2)
Anemia	28 (52.8)	31 (58.5)	22 (44.9)	26 (49.1)	31 (58.5)	20 (40.8)
Neutrophil count decreased	28 (52.8)	28 (52.8)	30 (61.2)	26 (49.1)	28 (52.8)	29 (59.2)
Malaise	30 (56.6)	24 (45.3)	23 (46.9)	30 (56.6)	23 (43.4)	22 (44.9)
Platelet count decreased	27 (50.9)	21 (39.6)	22 (44.9)	26 (49.1)	21 (39.6)	20 (40.8)
Headache	23 (43.4)	23 (43.4)	25 (51.0)	20 (37.7)	23 (43.4)	25 (51.0)
Rash	20 (37.7)	23 (43.4)	16 (32.7)	17 (32.1)	23 (43.4)	14 (28.6)
Alopecia	21 (39.6)	15 (28.3)	17 (34.7)	4 (7.5)	15 (28.3)	5 (10.2)
Pruritus	16 (30.2)	12 (22.6)	19 (38.8)	15 (28.3)	12 (22.6)	16 (32.7)
Decreased appetite	12 (22.6)	15 (28.3)	14 (28.6)	11 (20.8)	15 (28.3)	13 (26.5)
Arthralgia	13 (24.5)	13 (24.5)	20 (40.8)	13 (24.5)	13 (24.5)	19 (38.8)
Hemoglobin decreased	13 (24.5)	12 (22.6)	20 (40.8)	9 (17.0)	11 (20.8)	15 (30.6)
Myalgia	7 (13.2)	6 (11.3)	13 (26.5)	7 (13.2)	6 (11.3)	13 (26.5)
Hematocrit decreased	8 (15.1)	8 (15.1)	13 (26.5)	5 (9.4)	7 (13.2)	10 (20.4)
Nasopharyngitis	10 (18.9)	16 (30.2)	5 (10.2)	8 (15.1)	12 (22.6)	3 (6.1)

AE adverse event, *PR* pegylated interferon α-2a and ribavirin, *SAE* serious adverse event, *SMV* simeprevir

[a] Patients discontinued PR treatment regardless of completion or discontinuation of simeprevir

[b] Common AEs were classified as those occurring in >25 % of patients in the simeprevir group in either study

medications. Six serious AEs (SAEs) were reported in five patients in CONCERTO-2 (erythema multiforme, hypoesthesia, anemia, laceration, pyelonephritis acute, and calculus ureteric). Seven SAEs were reported in six patients in CONCERTO-3 (malaise and nausea, pneumonia, cerebral hemorrhage, appendicitis, herpes zoster, and breast cancer female). No individual SAE was reported in more than one patient.

In CONCERTO-2, no AEs resulted in permanent discontinuation of simeprevir. In CONCERTO-3, one patient experienced an AE of abnormal hepatic function, which led to discontinuation of simeprevir. This patient continued to receive treatment with PR and subsequently experienced two SAEs (nausea and malaise), resulting in discontinuation of PR. In CONCERTO-2, three patients permanently discontinued all treatment because of AEs. These included anemia, interstitial lung disease, and erythema multiforme. One patient permanently discontinued PR during the PR-only period due to erythema multiforme. One further patient in CONCERTO-3 discontinued PR during the PR-only period due to a breast cancer-related SAE.

Rash (of any type) was reported in 43.4 % (SMV12/PR) and 49.1 % (SMV24/PR) of patients in CONCERTO-2 and 49.0 % of patients in CONCERTO-3. Erythema was reported in 3.8 %–6.1 % of patients across the two studies. The majority of rashes were of grade 1/2 severity. Only one grade 3 rash was reported for two patients in CONCERTO-2. Grade 3 rash was not reported in any patient in CONCERTO-3, and no grade 4 rash was reported in either study.

In both CONCERTO-2 and CONCERTO-3, median total bilirubin levels increased from baseline during the

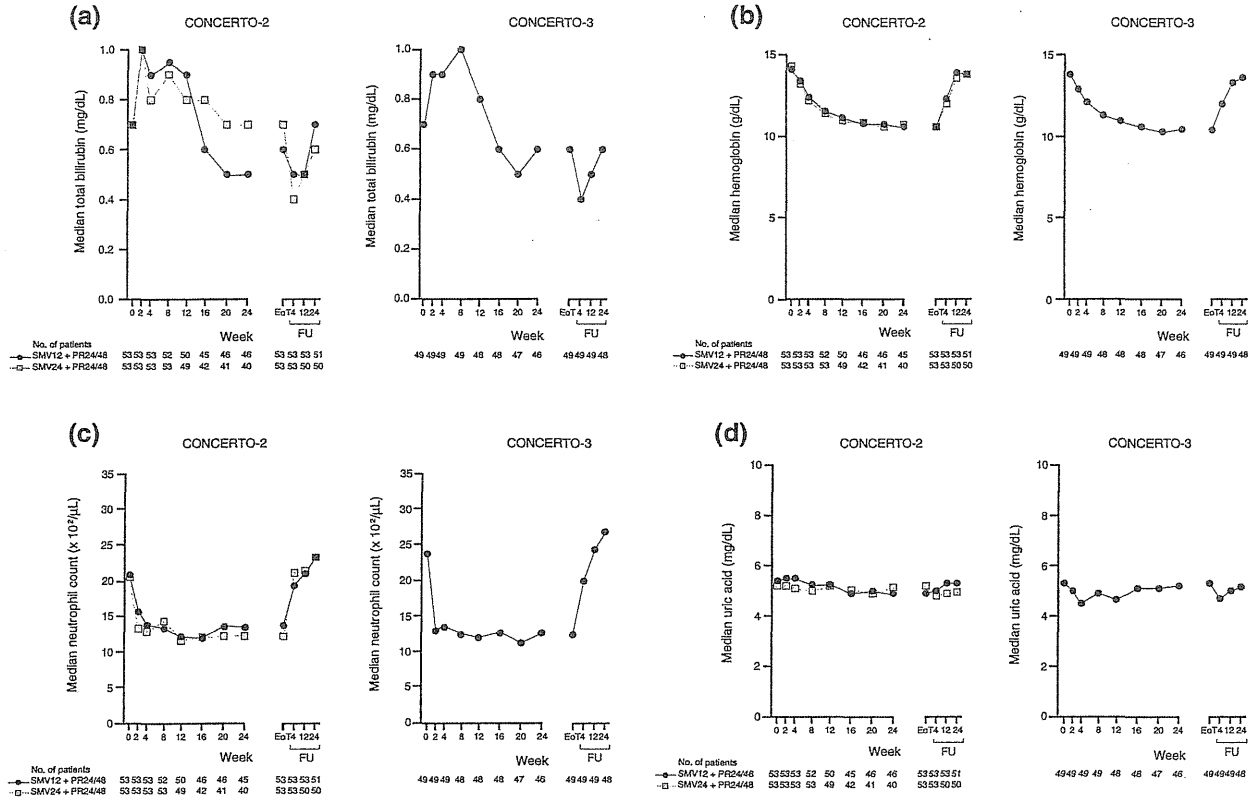

Fig. 2 Median plasma levels of **a** total bilirubin, **b** hemoglobin, **c** neutrophil counts, and **d** uric acid over the duration of follow-up. In CONCERTO-2 only one patient in each SMV treatment group continued treatment with PR from week 24 onwards, so these data are not shown. *EoT* end of treatment, *FU* follow-up, *PR* peginterferon-α-2a/ribavirin, *SMV* simeprevir

first 2 weeks and then gradually decreased to near baseline levels from week 4 to the end of treatment (Fig. 2). Bilirubin elevations were transient, rapidly returning to baseline or below after the end of simeprevir treatment, and were not associated with increases in ALT or AST.

Overall changes in platelets, neutrophils, and hemoglobin were similar between the two studies, with all of these parameters returning to baseline levels by the end of the post-treatment follow-up period (Fig. 2, Supplementary Figure 4). In CONCERTO-2, one patient discontinued simeprevir and PR due to grade 3 anemia (hemoglobin 7.5 g/dL).

No clinically relevant changes or consistent trends in the other laboratory parameters (including serum creatinine and uric acid) were reported (Fig. 2, Supplementary Figure 4).

Discussion

CONCERTO-2 and CONCERTO-3 evaluated the efficacy and safety of simeprevir as part of a treatment regimen including PR in treatment-experienced patients with genotype 1 and high HCV RNA levels in Japan. The vast majority of study participants were infected with HCV genotype 1b, reflecting the high prevalence of this subtype in Japan [2], and most had received previous treatment with PR. CONCERTO-2 and CONCERTO-3 enrolled two distinct cohorts: patients who had failed to respond to previous IFN-based therapy (CONCERTO-2) and patients who had relapsed after previous IFN-based therapy (CONCERTO-3). This allowed for an independent estimate of virologic response according to prior response to previous IFN-based therapy.

Our results are consistent with previous trials, conducted mainly in Europe and the U.S., showing high virologic response rates with simeprevir in treatment-experienced patients with HCV genotype 1 infection [23, 24]. We reported SVR12 rates of 52.8 % (SMV12/PR) and 35.8 % (SMV24/PR) in prior non-responders and 95.9 % (SMV12/PR) in prior relapsers. These results were statistically significant ($p \leq 0.0001$) for each study compared with the null hypothesis on the basis of the published clinical results after re-treatment with PR therapy (prior relapsers, 50 %; prior non-responders, 14 %).

CONCERTO-2 was not powered for statistical comparisons between the SMV12/PR and SMV24/PR

treatment groups. Consequently, the numerically less favorable SVR12 rates and viral relapse rates for patients in the SMV24/PR treatment group (compared to SMV12/PR) should be interpreted with caution. This study was not able to determine whether there is an additional efficacy benefit by prolonging simeprevir therapy beyond 12 weeks.

A limitation of CONCERTO-2 is that prior partial-response versus null-response status to previous IFN-based therapy was not clearly documented; therefore, randomization was not stratified based on these criteria (and may not have been balanced). Any such imbalance could have contributed to the numerical differences in SVR12 rates between the two groups, as it has previously been reported that SVR rates are lower among null responders versus partial responders [25]. In addition, it is possible that the differences in the proportion of patients who discontinued combination therapy with SMV/PR by week 24 contributed to the numerical difference in SVR12 rates between the treatment groups.

Given that patients enrolled in CONCERTO-3 had previously responded to IFN-based therapy before experiencing a relapse (compared to patients in CONCERTO-2, who had failed to respond to IFN-based therapy), the considerably higher SVR12 rate in CONCERTO-3 versus CONCERTO-2 was not unexpected.

SVR12 was the primary efficacy endpoint for both studies. SVR24 is a widely used virologic parameter for evaluating the efficacy of antiviral agents for the treatment of patients with HCV infection. For PR therapy it is well documented in the literature that the majority of viral relapses occur within the first 12 weeks of stopping therapy and that viral relapse rarely occurs between 12 and 24 weeks of follow-up [26]. Furthermore, a strong correlation between SVR12 and SVR24 rates has been demonstrated in completed Phase II/III Japanese [20] and European/U.S. studies of simeprevir [23, 27]. Therefore, the SVR12 rate was considered appropriate as a primary endpoint for both studies.

Both the CONCERTO-2 and CONCERTO-3 studies evaluated an RGT strategy allowing for individualized treatment duration based on HCV RNA levels at week 4 and week 12. According to the RGT criteria, the vast majority of patients in both studies were eligible to shorten their PR treatment duration to just 24 weeks instead of the standard 48 weeks. Among these patients, SVR12 rates of 48.7 % and 60.5 % in prior non-responders and 95.7 % in prior relapsers were observed. These findings suggest that RGT is a valid approach for Japanese patients with HCV infection, providing the opportunity for shortened duration of PR therapy, which may ultimately translate into a shorter duration of AEs [28].

The results of the subgroup analysis by *IL28B* genotype demonstrated that there were no clinically relevant differences in efficacy according to genotype, although the number of patients in each subgroup was small. Consistent with our observation, however, another study has demonstrated that the *IL28B* genotype in IFN-based treatment-experienced patients (both prior relapsers and non-responders) receiving treatment with telaprevir/PR did not predict SVR rates [29].

The number of prior non-responders to IFN-based therapy who experienced viral breakthrough was low (12.3 %), and no prior relapsers experienced viral breakthrough. Rates of viral relapse were 44.9 % and 8.2 %, respectively. The majority of patients with viral breakthrough or relapse had emerging mutations in the HCV NS3 protease domain. These mutations were mostly D168V (alone, or in combination with other mutations) and consistent with earlier reports of mutations associated with reduced susceptibility to simeprevir in vitro [30]. Further investigation of the relevance of HCV NS3 protease domain polymorphisms is required in Japanese patients with HCV, most of whom are infected with HCV genotype 1b. Of note, mutations in the NS3 HCV protease domain at position 168 (mainly D168V) do not confer resistance to the first-generation protease inhibitor telaprevir, but are associated with resistance to second-generation agents such as vaniprevir and faldaprevir [31].

Simeprevir was generally well tolerated in both prior non-responders and prior relapsers. There was no noticeable difference in the incidence or profile of AEs, or discontinuations due to AEs between the two studies. Anemia and rash-related AEs have been documented as common, and sometimes severe, AEs associated with triple therapy regimens that include the first-generation PIs boceprevir and telaprevir [14–19]. Although rash and anemia AEs were relatively common in CONCERTO-2 and CONCERTO-3, the incidences of SAEs or grade 3/4 rash or anemia were low, as were the rates of treatment discontinuations due to these AEs. In both patient populations, mild hyperbilirubinemia was observed before week 4 during the SMV/PR treatment period, but bilirubin levels generally decreased after the first 2 weeks of treatment, returned to near baseline levels after completion of treatment, and were not associated with a concomitant increase in serum transaminases. In vitro data suggest that the observed increase in bilirubin levels during simeprevir therapy may be attributable to simeprevir-mediated inhibition of the transporters OATP1B1 and MRP2, which are involved in bilirubin clearance [32].

In conclusion, in treatment-experienced patients with HCV genotype 1 infection—including patients who failed to respond to, or had prior relapse on, previous IFN-based therapy—re-treatment with 12 weeks of oral simeprevir QD in combination with PR achieves high SVR rates, shortens the overall duration of treatment in

the majority of patients, and is well tolerated. These findings represent an important advance in the management of treatment-experienced patients with HCV genotype 1 infection.

Acknowledgments The authors would like to thank all patients, their families, principal investigators, and their staff at the following 28 study sites (in alphabetical order): Akio Ido (Kagoshima University Medical and Dental Hospital); Akito Sakai (Kanazawa University Hospital); Eiji Mita (National Hospital Organization Osaka National Hospital); Harumasa Yoshihara (Osaka Rosai Hospital); Hideki Hagiwara (Kansai Rosai Hospital); Hideyuki Nomura (Shin-Kokura Hospital); Hiromitsu Kumada (Toranomon Hospital); Hiroshi Yatsuhashi (National Hospital Organization Nagasaki Medical Center); Katsuaki Tanaka (Yokohama City University Medical Center); Kawakami Yoshiiku (Hiroshima University Hospital); Kiyomi Yasuda (Kiyokawa Hospital); Masashi Mizokami (Kohnodai Hospital, National Center for Global Health and Medicine); Masatoshi Kudo (Kinki University Hospital); Mina Nakagawa (Tokyo Medical And Dental University Hospital Faculty of Medicine); Kiyohide Kioka (Osaka City General Hospital); Namiki Izumi (Musashino Red Cross Hospital); Syuhei Nishiguchi (The Hospital of Hyogo College of Medicine); Takayoshi Ito (Showa University Hospital); Takeji Umemura (Shinshu University Hospital); Tatsuya Ide (Kurume University Hospital); Tetsuo Takehara (Osaka University Hospital); Toshifumi Ito (Osaka Koseinenkin Hospital); Toshihide Shima (Saiseikai Suita Hospital); Yoichi Hiasa (Ehime University Hospital); Yoshito Ito (University Hospital, Kyoto Prefectural University of Medicine); Yutaka Sasaki (Kumamoto University Hospital); Yoshiyasu Karino (Sapporo Kosei General Hospital). These studies were funded by Janssen Pharmaceutical K.K. Medical writing support was provided by Julie Adkins on behalf of Complete Medical Communications and was funded by Janssen Research & Development.

Conflict of interest Namiki Izumi received honoraria for lectures from MSD Co., Chugai Co., Daiichi-Sankyo Co., and Bayer Co.. Norio Hayashi, Hiromitsu Kumada, Takeshi Okanoue, and Hiroshi Yatsuhashi have no conflict of interest. Hirohito Tsubouchi has an advisory relationship with Janssen Paharmacutical K.K. Mai Kato, Ki Ritou, Yuji Komada, Chiharu Seto, and Shoichiro Goto are employees of Janssen Pharmaceutical K.K.

References

1. Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect. 2011;17:107–15.
2. Chung H, Ueda T, Kudo M. Changing trends in hepatitis C infection over the past 50 years in Japan. Intervirology. 2010;53:39–43.
3. Umemura T, Ichijo T, Yoshizawa K, Tanaka E, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. J Gastroenterol. 2009;44(Suppl 19):102–7.
4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2011;55:245–64.
5. Izumi N. Diagnostic and treatment algorithm of the Japanese society of hepatology: a consensus-based practice guideline. Oncology. 2010;78(Suppl 1):78–86.
6. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002;347:975–82.
7. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358:958–65.
8. Iino S, Okita K, Omata M, Kumada H, Hayashi N, Tanigawa H. Clinical efficacy of PEG-interferon alpha-2b and ribavirin combination therapy for 48 weeks in chronic hepatitis C patients with genotype 1 and high viral load: retrospective comparison with interferon alpha-2b and ribavirin combination therapy for 24 weeks. Kantansui. 2004;49:1099–121.
9. Kuboki M, Iino S, Okuno T, Omata M, Kiyosawa K, Kumada H, et al. Peginterferon alpha-2a (40 KD) plus ribavirin for the treatment of chronic hepatitis C in Japanese patients. J Gastroenterol Hepatol. 2007;22:645–52.
10. Jacobson IM, Gonzalez SA, Ahmed F, Lebovics E, Min AD, Bodenheimer HC Jr, et al. A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. Am J Gastroenterol. 2005;100:2453–62.
11. Welsch C, Jesudian A, Zeuzem S, Jacobson I. New direct-acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. Gut. 2012;61(Suppl 1):i36–46.
12. Chayama K, Hayes CN, Ohishi W, Kawakami Y. Treatment of chronic hepatitis C virus infection in Japan: update on therapy and guidelines. J Gastroenterol. 2013;48:1–12.
13. 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:e134–42.
14. 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.
15. Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365:1014–24.
16. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364:2405–16.
17. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011;364:1207–17.
18. Hezode C. Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice. Liver Int. 2012;32(Suppl 1):32–8.
19. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364:1195–206.
20. Hayashi N, Seto C, Kato M, Komada Y, Goto S. Once-daily simeprevir (TMC435) with peginterferon/ribavirin for treatment-naïve hepatitis C genotype 1-infected patients in Japan: the DRAGON study. J Gastroenterol. 2014;49:138–47.
21. Kaiser S, Lutze B, Hass HG, Werner CR. High sustained virologic response rates in HCV genotype 1 relapser patients retreated with peginterferon alfa-2a (40KD) plus ribavirin for 72 weeks. Hepatology. 2008;48:1140A (abstract).
22. Jensen DM, Marcellin P, Freilich B, Andreone P, Di BA, Brandao-Mello CE, et al. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial. Ann Intern Med. 2009;150:528–40.
23. Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014;146:430–41.e6.

24. Manns M, Reesink H, Berg T, Dusheiko G, Flisiak R, Marcellin P, et al. Rapid viral response of once-daily TMC435 plus pegylated interferon/ribavirin in hepatitis C genotype-1 patients: a randomized trial. Antivir Ther. 2011;16:1021–33.
25. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364:2417–28.
26. Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclere L, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology. 2010;51:1122–6.
27. Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobsen I, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: the randomized PILLAR study. Hepatology. 2013;58:1918–29.
28. Reddy KR, Lin F, Zoulim F. Response-guided and -unguided treatment of chronic hepatitis C. Liver Int. 2012;32(Suppl 1):64–73.
29. Pol S, Aerssens J, Zeuzem S, et al. Limited impact of IL28B genotype on response rates in telaprevir-treated patients with prior treatment failure. J Hepatol. 2013;58:883–9.
30. Lenz O, Verbinnen T, Lin TI, et al. In vitro resistance profile of the hepatitis C virus NS3/4A protease inhibitor TMC435. Antimicrob Agents Chemother. 2010;54:1878–87.
31. Halfon P, Locarnini S. Hepatitis C virus resistance to protease inhibitors. J Hepatol. 2011;55:192–206.
32. Huisman MT, Snoeys J, Monbaliu J, Martens M, Sekar V, Raoof A. In vitro studies investigating the mechanism of interaction between TMC435 and hepatic transporters. Poster 278 presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, USA, 29 Oct-2 Nov, 2010.

Hepatology Research 2014; 44: 983–992 doi: 10.1111/hepr.12280

Original Article

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

Satoshi Shakado,[1,2] Shotaro Sakisaka,[1,2] Takeshi Okanoue,[3] Kazuaki Chayama,[4] Namiki Izumi,[5] Joji Toyoda,[6] Eiji Tanaka,[7] Akio Ido,[8] Tetsuo Takehara,[9] Kentaro Yoshioka,[10] Yoichi Hiasa,[11] Hideyuki Nomura,[12] Masataka Seike,[13] Yoshiyuki Ueno[14] and Hiromitsu Kumada[15]

[1]Department of Gastroenterology and Medicine, [2]Division of Advanced Clinical Research for Viral Hepatitis and Liver Cancer, Faculty of Medicine, Fukuoka University, Fukuoka, [3]Saiseikai Suita Hospital, [9]Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Suita, [4]Department of Gastroenterology and Metabolism, Applied Life Sciences, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, [5]Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Musashino, [6]Department of Gastroenterology and Hepatology, Sapporo Kousei Hospital, Sapporo, [7]Department of Medicine, Shinshu University School of Medicine, Matsumoto, [8]Department of Gastroenterology and Hepatology, Kagoshima University, Kagoshima, [10]Department of Liver, Biliary Tract and Pancreas Diseases, Fujita Health University, Toyoake, [11]Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Touon, [12]The Center for Liver Disease, Shin-Kokura Hospital, Kitakyushu, [13]Department of Gastroenterology, Faculty of Medicine, Oita University, Yufu, [14]Department of Gastroenterology, Yamagata University, Yamagata, and [15]Department of Hepatology, Toranomon Hospital, Kawasaki, Japan

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

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

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

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

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

INTRODUCTION

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

Correspondence: Dr Satoshi Shakado, Department of Gastroenterology and Medicine, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. Email: shakado @cis.fukuoka-u.ac.jp
Received 29 August 2013; revision 15 November 2013; accepted 17 November 2013.

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

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

METHODS

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

Patient selection

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

Combination therapy

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

Virological response during therapy and definitions

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

Determination of IL28B genotype

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

Statistical analysis

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

RESULTS

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

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

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

Association between IL28B rs8099917 genotype and treatment response

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

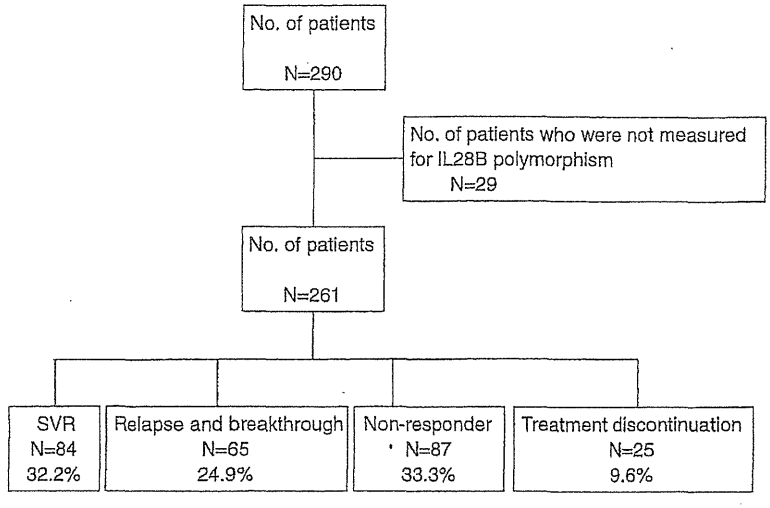

Figure 1 Flowchart showing the characteristics of the study cohort. IL28B, interleukin 28B; SVR, sustained virological response.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Predictive factors associated with SVR

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

Treatment duration and efficacy in patients with G1H

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

Predictors of SVR in patients with G1H and the TT allele

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

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

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

Treatment tolerability and adverse events

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

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

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

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

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

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

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

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

IL28B alleles predicting SVR in G1H group

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

Table 8 Adverse events higher than grade 2

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

DISCUSSION

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

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

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

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

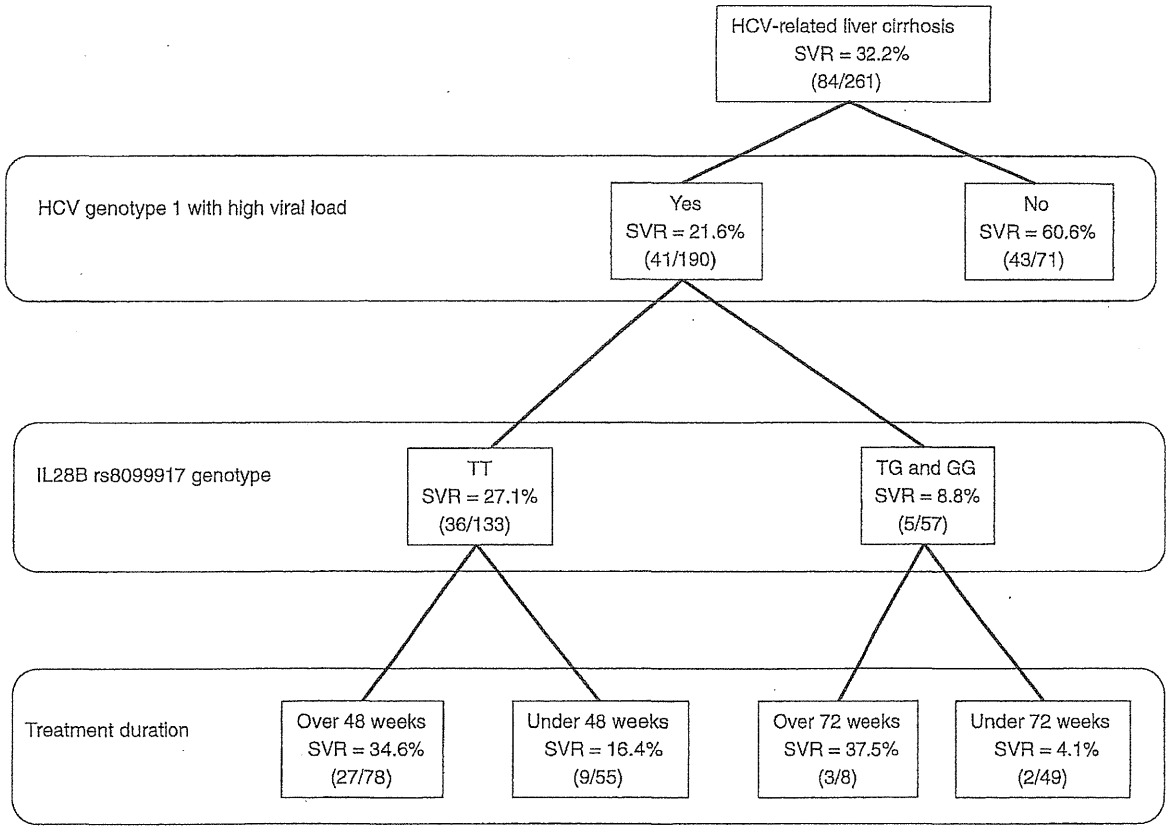

Figure 2 SVR in HCV-related liver cirrhosis patients treated with interferon plus ribavirin. In patients with G1H and the IL28B TT allele, the SVR rate of those who were treated for over 48 weeks was significantly higher than those treated for less than 48 weeks ($P = 0.042$). In patients with G1H and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

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

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

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

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

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

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

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

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

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

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

ACKNOWLEDGMENT

THIS STUDY WAS supported by a Grant-in-Aid from the Japanese Ministry of Health, Welfare, and Labor.

REFERENCES

1 Niederau C, Lange S, Heintges T *et al.* Progress of chronic hepatitis C: results of a large, prospective cohort study. *Hepatology* 1998; 28: 1687–95.
2 Fattovich G, Giustina G, Degos F *et al.* Morbidity and mortality in compensated cirrhosis type C; a retrospective follow up study of 384 paatients. *Gastroenterology* 1997; 112: 463–72.
3 Hu KQ, Tong MJ. The long-term outcomes of patients with compensated hepatitis C virus-related cirrhosis and history of parenteral exposure in the United States. *Hepatology* 1999; 29: 1311–16.
4 Sangionvanni A, Prati GM, Fasani P *et al.* The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. *Hepatology* 2006; 43: 1303–10.
5 Nishiguchi S, Kuroki T, Nakatani S *et al.* Randomized trail of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995; 346: 1051–5.
6 Shiratori Y, Ito Y, Yokosuka O *et al.* Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved. *Ann Int Med* 2005; 142: 105–14.
7 Bruno S, Stroffolini T, Colombo M *et al.* Sustained virological response to interferon-alpha is associated with improved outcome in HCV related cirrhosis: a retrospective study. *Hepatology* 2007; 45: 579–87.
8 Wright TL. Treatment of patients with hepatitis C and cirrhosis. *Hepatology* 2002; 36: S185–194.
9 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alpha-2b plus ribavirin compared with interferon aalpha-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001; 358: 958–65.
10 Bota S, Sporea I, Popescu A *et al.* Response to standard of care antiviral treatment in patients with HCV liver cirrhosis – a systematic review. *J Gastrointestin Liver Dis* 2011; 20: 293–8.
11 Ge D, Fellay J, Thompson AJ *et al.* Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; 461: 399–401.
12 Tanaka Y, Nishida N, Sugiyama M *et al.* Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; 41: 1105–9.
13 Suppiah V, Moldovan M, Ahlenstiel G *et al.* IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; 41: 1100–4.
14 Ziol M, Handra-Luca A, Kettaneh A *et al.* Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology* 2005; 41: 48–54.
15 Castera L, Vergniol J, Foucher J *et al.* Prospective comparison of transient elastography, fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; 128: 343–50.
16 Ikeda K, Saitoh S, Kobayashi M *et al.* Distinction between chronic hepatitis and liver cirrhosis in patients with hepatitis C virus infection. Practical discriminant function using common laboratory data. *Hepatol Res* 2000; 18: 252–66.
17 Ohnishi Y, Tanaka T, Ozaki K, Yamada R, Suzuki H, Nakamura Y. A high-throughput SNP typing system for genome-wide association studies. *J Hum Genet* 2001; 46: 471–7.
18 Suzuki A, Yamada R, Chang X *et al.* Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginie deminase 4, are associated with rheumatoid arthritis. *Nat Genet* 2003; 34: 395–402.
19 Kawaoka T, Hayes CN, Ohishi W *et al.* Predictive value of the IL28B polymorphism on the effect of interferon therapy in chronic hepatitis C patients with genotype 2a and 2b. *J Hepatol* 2010; 54: 408–14.
20 Sarrazin C, Susser S, Doehring A *et al.* Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. *J Hepatol* 2010; 54: 415–21.
21 Asselah T, De Muynck S, Broët P *et al.* IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. *J Hepatol* 2012; 56: 527–32.
22 De Nicola S, Aghemo A, Rumi MG *et al.* Interleukin 28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis C genotype 4. *Hepatology* 2012; 55: 336–42.
23 Akuta A, Suzuki F, Seko Y *et al.* Association of IL28B genotype and viral response of hepatitis C virus genotype 2 to interferon plus ribavirin combination therapy. *J Med Virol* 2012; 84: 1593–9.
24 Montes-Cano MA, Garcia-Lozano JR, Abad-Molina C *et al.* Interleukin-28B genetic variants and hepatitis virus

infection by different viral genotypes. *Hepatology* 2010; 52: 33–7.
25 Yu ML, Huang CF, Huang JF *et al.* Role of interleukin-28B polymorphism in the treatment of hepatitis C virus genotype 2 infection in Asian patients. *Hepatology* 2011; 53: 7–13.
26 Thomas DL, Thio CL, Martin MP *et al.* Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 2009; 461: 798–801.
27 Yang M, Rao HY, Feng B, Zhang W, Wei L. The impact of IL28B polymorphisms on spontaneous clearance of hepatitis C virus infection: a meta-analysis. *J Gastroenterol Hepatol* 2013; 28: 1114–21.
28 Hadziyannis SJ, Sette H Jr, Morgan TR *et al.* Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; 140: 346–55.
29 McHutchison JG, Lawitz EJ, Shiffman ML *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; 361: 580–93.
30 Lok AS, Everhart JE, Wright EC *et al.* Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. *Gastroenterology* 2011; 140: 840–9.
31 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975–82.
32 McHutchison JG, Lawitz EJ, Shiffman ML *et al.* Peginterferon alfa-2b with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; 361: 580–93.
33 Bota S, Sporea I, Sirli R *et al.* Severe adverse events during antiviral therapy in hepatitis C virus cirrhotic patients: a systematic review. *World J Hepatol* 2013; 27: 120–6.
34 Buti M, Valdés A, Sánchez-Avila F, Esteban R, Lurie Y. Extending combination therapy with peginterferon alfa-2b plus ribavirin for genotype 1 chronic hepatitis C late responders: a report of 9 cases. *Hepatology* 2003; 37: 1226–7.
35 Berg T, von Wagner M, Nasser S *et al.* Extended treatment duration for hepatitis C virus type 1: comparing 48 weeks versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006; 130: 1086–97.
36 Sanchez-Tapias JM, Diago M, Escartin P *et al.* Peginterferon-alfa-2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006; 131: 451–60.
37 Akuta N, Suzuki F, Hirakawa M *et al.* A matched case-controlled study of 48 and 72 weeks of peginterferon plus ribavirin combination therapy in patients infected with HCV genotype 1b in Japan: amino acid substitution in HCV core region as predictor of sustained virological response. *J Med Virol* 2009; 81: 452–8.
38 Poordad F, Lawitz E, Kowdley KV *et al.* Exploratory study of oral combination antiviral therapy for hepatitis C. *N Engl J Med* 2013; 368: 45–53.
39 Zeuzem S, Soriano V, Asselah T *et al.* Faldaprevir and deleobuvir for HCV genotype 1 infection. *N Engl J Med* 2013; 369: 630–9.
40 Gane EJ, Stedman CA, Hyland RH *et al.* Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; 368: 34–44.
41 Suzuki Y, Ikeda1 K, Suzuki F *et al.* Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infected and limited treatment options. *J Hepatol* 2013; 58: 655–62.

Journal of Viral Hepatitis, 2013 doi:10.1111/jvh.12162

Telaprevir impairs renal function and increases blood ribavirin concentration during telaprevir/pegylated interferon/ribavirin therapy for chronic hepatitis C

Y. Karino, I. Ozeki, S. Hige, M. Kimura, T. Arakawa, T. Nakajima, Y. Kuwata, T. Sato, T. Ohmura and J. Toyota *Department of Hepatology, Sapporo Kosei General Hospital, Sapporo, Japan*

Received May 2013; accepted for publication July 2013

SUMMARY. We aimed to examine the relationship between renal dysfunction and anaemia that may develop during combination therapy involving pegylated interferon, ribavirin and telaprevir (PEG-IFN/RBV/TVR) for the treatment of chronic hepatitis C. Sixty-eight patients with genotype 1b high viral loads were treated with PEG-IFN/RBV/TVR. Peg-IFN and RBV doses were administered according to body weight. TVR was prescribed at 2250 mg/day for 44 patients and at 1500 mg/day for 24 patients who had low haemoglobin level (<12 g/dL). When anaemia had developed, the RBV dose was decreased. The serum TVR concentration at day 8 was measured, and the serum RBV concentration was measured serially. The estimated glomerular filtration rate (eGFR) was estimated to assess renal function. At week 1, serum TVR concentration was not correlated with a decrease in eGFR; however, the TVR dose, on a weight basis (mg/kg), and eGFR were correlated ($r = 0.2691$; $P = 0.0265$). Moreover, there was a negative correlation between eGFR and RBV serum concentration ($r = -0.3694$; $P = 0.0025$), and the serum RBV concentration and decrease in the haemoglobin were significantly correlated from week 1 to week 8. In triple therapy, the TVR dose per weight is correlated with a decline in renal function. Thus, the serum concentration of RBV increases, with a concomitant decrease in haemoglobin. It is important to adjust the doses of TVR and RBV to avoid excessive serum RBV levels and the development of severe anaemia, to achieve a good clinical effect.

Keywords: anaemia, estimated glomerular filtration rate, hepatitis C virus, ribavirin, telaprevir.

INTRODUCTION

An estimated 170 million people are chronically infected with hepatitis C virus (HCV) worldwide [1]. Approximately 30% of the patients with chronic HCV develop life-threatening liver disease, such as decompensated cirrhosis and hepatocellular carcinoma [2,3]. Since Hoofnagle *et al.* [4] first reported the effectiveness of interferon (IFN) in the treatment of the so-called non-A non-B chronic hepatitis, IFN has played a central role in the antiviral therapy for chronic hepatitis C. Until recently, combined therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV), for 48 weeks, has been the standard-of-care for patients infected with HCV genotype 1 (HCV-1), which is the most prevalent genotype worldwide. However, sustained virological response (SVR) is achieved in only 42–52% of the patients treated with this regimen [5–7].

To achieve a better antiviral effect, investigators have developed several direct-acting antivirals, represented by NS3/4A protease inhibitors and NS5B polymerase or NS5A inhibitors [8]. Of these, telaprevir (TVR), an inhibitor of the NS3/4A serine protease, in combination with PEG-IFN and RBV (triple therapy), has been most promising and has been reported to achieve an SVR of up to 70% [9–13]. However, adverse events develop more frequently in patients treated with protease inhibitors than in those treated only with PEG-IFN and RBV. In TVR trials, rash, anaemia, pruritus, nausea and diarrhoea were found to develop more frequently in individuals who received PEG-IFN and RBV along with TVR than in those individuals who received PEG-IFN and RBV only [11]. In addition, a renal functional disorder associated with TVR therapy became evident in Japan after the Ministry of Health, Labour and Welfare approved the use of TVR [14]. RBV is excreted in the urine, and diminished renal function can interfere with its metabolism [15]. In this

Abbreviations: eGFR, estimated glomerular filtration rate; IL28B, interleukin 28B; ITPA, inosine triphosphatase; RBV, ribavirin; Scr, serum creatinine; SNP, single-nucleotide polymorphism; TVR, telaprevir.

Correspondence: Yoshiyasu Karino, Sapporo Kosei General Hospital, North-3 East-8, Chuou-Ku, Sapporo 060 0033, Japan. E-mail: ykarino-beagle@jcom.home.ne.jp

study, we aimed to examine the relationship between renal dysfunction and anaemia in patients undergoing triple therapy for HCV.

PATIENTS AND METHODS

Patients

We enrolled 68 patients with HCV-1 who were treated with PEG-IFN/RBV/TVR at the Sapporo Kosei General Hospital. All participants provided written informed consent according to the process approved by the hospital's ethical committee, and the study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Patients were excluded if they had evidence of autoimmune hepatitis; alcoholic liver disease; congestive liver failure; hepatitis B virus infection; markers for human immunodeficiency virus; hepatocellular carcinoma or other malignancies; or hepatic decompensation, associated with jaundice, ascites, encephalopathy, or gastrointestinal bleeding. The patient characteristics are shown in Table 1.

All patients were treated with PEG-IFN-a-2b, RBV and TVR triple therapy. PEG-IFN-a-2b (MSD, Tokyo, Japan) was injected subcutaneously at a median dose of 1.5 μg/kg per week. TVR and RBV doses were adjusted according to guidelines for the treatment of hepatitis B and C, established in 2012 by the Japanese Ministry of Health, Labour and Welfare [16]. Usually, 750 mg of TVR (Mitsubishi Tanabe Pharma, Tokyo, Japan) was administered orally every 8 h after meals. The dose of RBV (MSD) was adjusted according to the individual's body weight (600 mg for individuals weighing ≤60 kg; 800 mg for individuals weighing <60 to ≤80 kg; and 1000 mg for individuals weighing >80 kg) and was orally administered after breakfast and dinner. If the initial haemoglobin (Hb) level was <14 mg/dL in women, or <13 mg/dL in men, the RBV dose was reduced by 200 mg. Triple therapy with TVR was administered for 12 weeks, followed by an additional 12 weeks of PEG-IFN-a-2b and ribavirin therapy (combination therapy). If severe anaemia was present, the dosage of RBV, followed by that of TVR, was adjusted, as determined by the chief physician.

Hepatitis C virus genotype

Hepatitis C virus genotype was determined by analysis of the sequence in the NS5B region.

Hepatitis C virus RNA levels

Hepatitis C virus RNA levels were determined using the COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). The linear dynamic range of the assay was 1.2–7.8 $\log_{10}$ IU/mL.

Table 1 Characteristics of study patients in each telaprevir (TVR) dose

	Total	1500 mg/day	2250 mg/day	*P*
Number	68	24	44	
Sex (M/F)	34/34	4/20	30/14	<0.0001
Age (years old)	55.8 ± 10.5	59.6 ± 9.4	53.7 ± 10.6	0.0023
Height (cm)	161.4 ± 7.8	157.1 ± 6.8	163.8 ± 7.4	0.0023
Weight (kg)	62.1 ± 10.2	57.9 ± 9.0	64.5 ± 10.2	0.0090
rs12979860 (CC/TC/TT)	43/23/2	16/8/0	27/15/2	0.5186
rs1127354 (CC/CA/AA)	51/16/1	18/5/1	33/11/0	0.7695
WBC (/mm^3)	4663 ± 1271	4107 ± 1101	4934 ± 1288	0.0074
Haemoglobin (g/dL)	13.6 ± 1.2	12.9 ± 1.0	14.0 ± 1.1	0.0005
Platelet ($\times 10^4/mm^3$)	16.6 ± 4.6	15.8 ± 4.1	17.1 ± 4.8	0.3521
ALT (IU/L)	57.1 ± 47.4	51.3 ± 39.8	60.3 ± 51.3	0.2905
GGTP (IU/L)	52.1 ± 53.7	44.7 ± 44.9	56.1 ± 58.0	0.1902
estimated glomerular filtration rate (mL/min/1.73 $m^{2)}$	85.6 ± 15.2	81.5 ± 11.7	88.1 ± 16.4	0.1902
Viral genotype (1b/others)	68/0	24/0	44/0	
Virus titre (log IU/mL)	6.5 ± 0.6	6.2 ± 0.7	6.5 ± 0.7	0.2456
Pegylated interferon (μg/kg)	1.52 ± 0.11	1.54 ± 0.13	1.52 ± 0.10	0.5004
TVR (mg/kg)	32.5 ± 6.8	26.5 ± 3.9	35.8 ± 5.7	<0.0001
Ribavirin (RBV) (mg/day) (400/600/800/1000)	19/19/27/3	14/9/1/0	5/10/26/3	<0.0001
RBV (mg/kg)	10.2 ± 2.0	8.5 ± 1.2	11.2 ± 1.7	<0.0001

Data are presented as mean ± SD.