in SVR12 rates for the selected demographic and baseline disease characteristics. For non-responders, the number of patients in each subgroup was too small to draw firm conclusions. One prior non-responder who was infected with HCV genotype 1a did not achieve SVR12.

Normalization of ALT

At the end of treatment, the proportion of patients for whom ALT levels were abnormal at baseline and changed to be within the normal limits (based on WHO toxicity grades) was 13/15 (86.7%) for treatment-naïve patients, 8/13 (61.5%) for prior relapsers and 8/13 (61.5%) for prior non-responders.

Safety

Adverse events and laboratory investigations reported as AE during the entire treatment period are summarized in Table 4. All patients experienced at least one AE. No deaths occurred. Two serious AE occurred during treatment – peripheral T-cell lymphoma (unspecified) and hyperbilirubinemia – of which hyperbilirubinemia was considered by the investigator likely to be related to simeprevir. The majority of AE were grade 1 or 2. Grade 3 AE mainly occurred by week 4 and were reported for 17 patients; the most frequent grade 3 AE were neutropenia (6.3%), decreased white blood cell count (5.1%), leukopenia (3.8%) and decreased neutrophil count (3.8%). One patient experienced grade 4 decreased neutrophil count at week 1, which was considered unrelated to simeprevir. No neutropenia-related AE were serious or led to permanent discontinuation of study treatment.

Three patients discontinued treatment due to AE. One patient discontinued all three study medications at week 8 owing to grade 1 anemia, which was considered very likely related to RBV. Two patients discontinued PEG IFN-α-2b/RBV after the simeprevir treatment period owing to grade 3 allergic dermatitis and grade 2 depression, considered probably related to RBV and PEG IFN-α-2b, respectively. Rates of PEG IFN-α-2b and RBV dose interruptions due to AE were 12.7% and 17.7%, respectively, with anemia being the most frequently reported AE leading to dose interruption (5.1% for PEG IFN-α-2b and 7.6% for RBV).

The most common AE reported in more than 30% of patients overall during the entire treatment period were pyrexia (84.8%), anemia (50.6%), decreased white blood cell count (58.2%), malaise (48.1%) and headache (45.6%). During the simeprevir treatment period, the most common AE were pyrexia (83.5%), decreased white blood cell count (58.2%) and malaise (48.1%). There were no differences between patient groups in the incidence of each AE (Table 4).

Rash (any type) was reported in 34 patients (43.0%) during the entire treatment period (25 patients [31.6%] during the simeprevir treatment period), which included rash ($n = 30$; 38.0%), erythema ($n = 6$; 7.6%), skin exfoliation ($n = 2$; 2.5%), erythema multiforme ($n = 1$; 1.3%) and photosensitivity reaction ($n = 1$; 1.3%). All rash AE were of grade 1 or 2 severity. None of these AE were serious or led to permanent discontinuation of the study treatment.

Median values over time for selected laboratory parameters are presented in Fig. 4. Median bilirubin values increased transiently during the first two weeks of simeprevir treatment in all patient groups, but returned to baseline levels by week 16 (i.e. within 4 weeks of the end of the simeprevir treatment period). Median levels between weeks 2 and 16 were slightly higher in prior relapsers. Elevation of bilirubin levels was not associated with increases in ALT or AST. Seven patients experienced grade 3 elevations (>2.5 mg/dL) in blood bilirubin and one patient experienced a grade 4 elevation (>5.0 mg/dL). None of the increased bilirubin-related AE led to permanent discontinuation of study treatment. No changes were noted for uric acid or creatinine.

The incidences of grade 3 or 4 treatment-emergent or worsened laboratory abnormalities were low (occurring in <5% of patients), with the exceptions of decreases in absolute neutrophil count (grade 3, 21.5%; grade 4, 2.5%) and increases in bilirubin (grade 3, 8.9%; grade 4, 1.3%).

DISCUSSION

THIS STUDY INVESTIGATED the efficacy and safety of simeprevir in combination with PEG IFN-α-2b/RBV in a mixed population of both treatment-naïve and treatment-experienced patients chronically infected with HCV genotype 1. The dose of simeprevir (100 mg Q.D. as part of triple therapy) and treatment duration (12 weeks) was chosen based on the results of a phase II, dose and duration ranging study in Japanese treatment-naïve patients infected with genotype 1 HCV (DRAGON study).[29]

In this study, simeprevir 100 mg Q.D. for 12 weeks in combination with PEG IFN-α-2b/RBV (administered for a total of 24 or 48 weeks) demonstrated high rates of SVR12 (91.7–100%) and SVR24 (91.7–96.6%) in treatment-naïve patients and prior relapsers. Although

Table 4 Summary of AE during the entire treatment period and during treatment with simeprevir plus PEG IFN-α-2b/RBV (safety population†)

No. of patients (%)	Entire treatment period				Simeprevir + PEG IFN-α-2b/RBV treatment period			
	Treatment-naïve ($n = 24$)	Prior relapsers ($n = 29$)	Prior non-responders ($n = 26$)	Total ($n = 79$)	Treatment-naïve ($n = 24$)	Prior relapsers ($n = 29$)	Prior non-responders ($n = 26$)	Total ($n = 79$)
Discontinuation of any study medication due to AE‡	1 (4.2)	1 (3.4)	1 (3.8)	3 (3.8)	0	1 (3.4)	0	1 (1.3)
Discontinuation of simeprevir alone due to AE	0	0	0	0	0	0	0	0
Temporary interruption of PEG IFN-α-2b due to AE	3 (12.5)	4 (13.8)	3 (11.5)	10 (12.7)	N/A	N/A	N/A	N/A
Dose reduction of PEG IFN-α-2b due to AE	11 (45.8)	4 (13.8)	9 (34.6)	24 (30.4)	N/A	N/A	N/A	N/A
Temporary interruption of RBV due to AE	4 (16.7)	6 (20.7)	4 (15.4)	14 (17.7)	N/A	N/A	N/A	N/A
Dose reduction of RBV due to AE	10 (41.7)	11 (37.9)	9 (34.6)	30 (38.0)	N/A	N/A	N/A	N/A
Any serious AE	1 (4.2)	0	1 (3.8)	2 (2.5)	1 (4.2)	0	0	1 (1.3)
Grade 3/4 AE	6 (25.0)	5 (17.2)	7 (26.9)	18 (22.8)	5 (20.8)	4 (13.8)	5 (19.2)	14 (17.7)
Death	0	0	0	0	0	0	0	0
Common AE§								
Pyrexia	18 (75.0)	27 (93.1)	22 (84.6)	67 (84.8)	17 (70.8)	27 (93.1)	22 (84.6)	66 (83.5)
Decreased white blood cell count	17 (70.8)	16 (55.2)	13 (50.0)	46 (58.2)	17 (70.8)	16 (55.2)	13 (50.0)	46 (58.2)
Anemia	11 (45.8)	21 (72.4)	8 (30.8)	40 (50.6)	11 (45.8)	16 (55.2)	6 (23.1)	33 (41.8)
Malaise	12 (50.0)	12 (41.4)	14 (53.8)	38 (48.1)	12 (50.0)	12 (41.4)	14 (53.8)	38 (48.1)
Headache	11 (45.8)	12 (41.4)	13 (50.0)	36 (45.6)	13 (41.7)	10 (34.5)	12 (46.2)	32 (40.5)
Decreased appetite	12 (50.0)	12 (41.4)	7 (26.9)	31 (39.2)	12 (50.0)	12 (41.4)	7 (26.9)	31 (39.2)
Injection-site reactions	11 (45.8)	8 (27.6)	12 (46.2)	31 (39.2)	10 (41.7)	7 (24.1)	11 (42.3)	28 (35.4)
Rash	12 (50.0)	8 (27.6)	10 (38.5)	30 (38.0)	10 (41.7)	7 (24.1)	8 (30.8)	25 (31.6)
Alopecia	14 (58.3)	9 (31.0)	5 (19.2)	28 (35.4)	Overall incidence <30%			
Arthralgia	11 (45.8)	10 (34.5)	6 (23.1)	27 (34.2)	10 (41.7)	10 (34.5)	6 (23.1)	26 (32.9)
Decreased neutrophil count	11 (45.8)	8 (27.6)	7 (26.9)	26 (32.9)	11 (45.8)	8 (27.6)	7 (26.9)	26 (32.9)
Decreased platelet count	11 (45.8)	6 (20.7)	8 (30.8)	25 (31.6)	11 (45.8)	6 (20.7)	7 (26.9)	24 (30.4)

†All patients who received study drugs. ‡Permanent discontinuation of all study medication (i.e. discontinuation of simeprevir and PEG IFN-α-2b/RBV at the same time, or discontinuation of PEG IFN-α-2b/RBV after completion or discontinuation of simeprevir). §Occurring in >30% patients overall.
AE, adverse events; N/A, not available; PEG IFN, peginterferon; RBV, ribavirin.

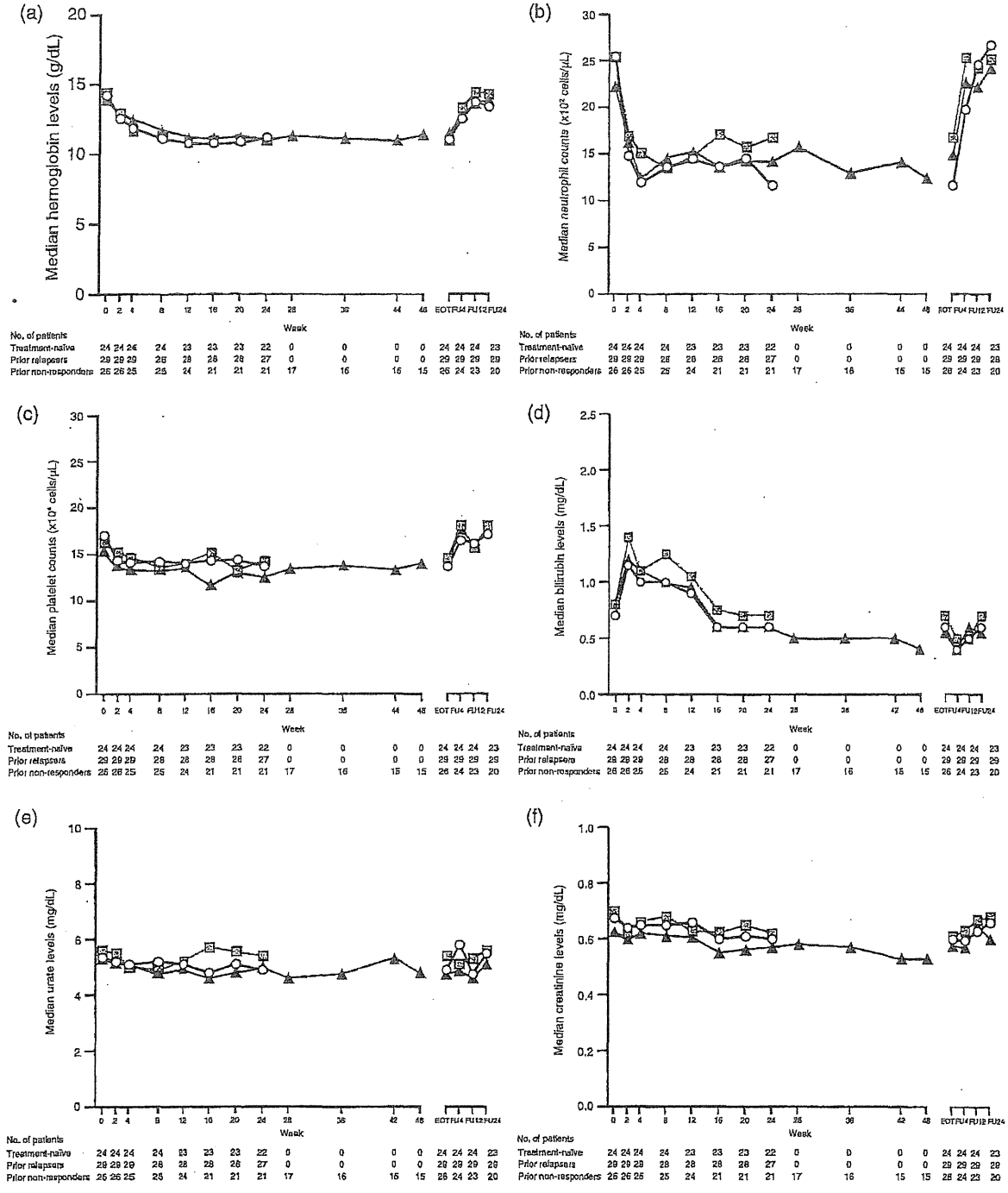

Figure 4 Changes in laboratory parameters over time. (a) Hemoglobin; (b) neutrophil count; (c) platelet count; (d) bilirubin; (e) urate; and (f) creatinine. EOT, end of treatment; FU, follow-up. —○—, treatment-naïve ($n = 24$); —□--, prior relapsers ($n = 29$); —△—, prior non-responders ($n = 26$).

our study is somewhat limited by the small patient numbers and non-comparative design, the results in this study population are consistent with the high rates of virologic response that have been reported previously for simeprevir in combination with PEG IFN-α-2a/RBV in other phase III studies in Japan[25,26] and in international studies.[22–24] In QUEST-2, a phase III study conducted outside Japan, simeprevir combined with PEG IFN-α-2a/RBV or PEG IFN-α-2b/RBV was found superior to each PEG IFN-α/RBV regimen alone in treatment-naïve HCV genotype 1 patients.[30] The response rates also compare favorably with those demonstrated in trials of telaprevir in combination with PEG IFN-α-2b/RBV in treatment-naïve patients and prior relapsers.[11,13]

The rates of SVR among prior non-responders who received 48 weeks of treatment with PEG IFN-α-2b/RBV were lower than those for treatment-naïve patients and prior relapsers, consistent with other studies of prior non-responders.[11,16,22] Most patients had received prior treatment with PEG IFN/RBV. A high proportion of the patients in this group had heterozygous TG genotypes for a polymorphism (rs8099917) in the *IL28B* locus that has been associated with poor response to therapy.[31]

All patient groups showed a rapid reduction in HCV RNA levels within the first two weeks of treatment with simeprevir, and most patients achieved RVR at week 4 (60.0–86.2%) and cEVR at week 12 (79.2–100%). All treatment-naïve patients and prior relapsers had undetectable HCV RNA at the end of treatment, with no viral breakthrough and a very low incidence of viral relapse during follow-up in these two groups. Six (23%) of 26 prior non-responders had viral breakthrough, which was documented during simeprevir treatment for three of these patients. Emerging mutations in the NS3 protease domain were identified for isolates from all six patients at the time of breakthrough and for 16 of the 17 patients classified as treatment failures in the study. All patients except for one prior non-responder were infected with HCV genotype 1b. Some of the mutations identified (D168E/T/V, Q80R/K, R155K) have been previously described in HCV genotype 1b isolates following exposure to simeprevir *in vitro* and in clinical studies[23,25,27] and are thought to confer reduced susceptibility. Data from studies of other PI suggest that poor response to IFN-based therapy increases the likelihood of the emergence of resistant isolates.[6] However, further studies are needed to evaluate emerging mutations in HCV genotype 1 and their clinical impact.

In this study, an RGT approach (based on levels of HCV RNA) was used to determine whether treatment-naïve patients or prior relapsers could reduce the duration of PEG IFN-α-2b/RBV therapy to 24 weeks. More than 90% of these patients were able to stop PEG IFN-α-2b/RBV at 24 weeks rather than continuing to 48 weeks. Those patients who stopped therapy at 24 weeks had high rates of SVR12 and SVR24 (90.9–100%), despite the shorter treatment duration. The reduction in exposure to PEG IFN-α-2b/RBV therapy following initial triple combination therapy with simeprevir could potentially limit the extent and duration of PEG IFN-α-2b/RBV-related AE.

Treatment with simeprevir 100 mg Q.D. in combination with PEG IFN-α-2b/RBV was well tolerated, with mostly grade 1/2 AE. Notably, there was a very low incidence of treatment discontinuation due to AE, and those reported were considered to be related to PEG IFN-α-2b and/or RBV. This is in contrast to studies of first-generation PI, which have reported rates of treatment discontinuation due to AE of 10–20%.[11,12,14] In addition, serious toxicities that have been widely reported with first-generation PI (e.g. anemia, cutaneous reactions, neutropenia)[6,12,13,15,32] were mainly of grade 1 or 2 severity in this study of simeprevir. In phase II studies of simeprevir, mild transient hyperbilirubinemia has been reported.[21] Although patients in this study experienced a transient elevation of blood bilirubin, levels returned to baseline values after simeprevir treatment and the elevation was not associated with increases in ALT or AST levels. Also, there were no treatment discontinuations due to increased bilirubin-related AE. Telaprevir has been associated with increases in uric acid and creatinine.[14] No changes were noted in median uric acid and creatinine values in this study of simeprevir.

In conclusion, treatment with simeprevir 100 mg Q.D. for 12 weeks in combination with PEG IFN-α-2b/RBV (for 24 or 48 weeks) demonstrated potent antiviral activity and high rates of SVR in patients who were treatment-naïve or had previously relapsed after IFN-based therapy, with most patients having a shorter treatment duration. Antiviral activity was also demonstrated in patients who had failed to respond to prior IFN-based therapy. Simeprevir was well tolerated in all patients. The present phase III CONCERTO-4 study demonstrates the efficacy and safety of simeprevir in a relatively small sample of treatment-naïve and previously treated patients with chronic HCV genotype 1 infection, while CONCERTO-1, -2 and -3 provide further data on the efficacy and safety of this regimen in a larger population.

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REFERENCES

1 Chung H, Ueda T, Kudo M. Changing trends in hepatitis C infection over the past 50 years in Japan. *Intervirology* 2010; 53: 39–43.
2 Lavanchy D. The global burden of hepatitis C. *Liver Int* 2009; 29 (Suppl 1): 74–81.
3 Yuen MF, Hou JL, Chutaputti A. Hepatocellular carcinoma in the Asia pacific region. *J Gastroenterol Hepatol* 2009; 24: 346–53.
4 Editors of the Drafting Committee for Hepatitis Management Guidelines: The Japan Society of Hepatology. Guidelines for the Management of Hepatitis C Virus Infection: First edition, May 2012, The Japan Society of Hepatology. *Hepatol Res* 2013; 43: 1–34.
5 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011; 55: 245–64.
6 Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; 54: 1433–44.
7 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.
8 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975–82.
9 Manns MP, McHutchison JG, Gordon SC *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.
10 Bacon BR, Gordon SC, Lawitz E *et al.* Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364: 1207–17.
11 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.
12 Jacobson IM, McHutchison JG, Dusheiko G *et al.* Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; 364: 2405–16.
13 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.
14 McHutchison JG, Everson GT, Gordon SC *et al.* Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; 360: 1827–38.
15 Poordad F, McCone J, Jr, Bacon BR *et al.* Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364: 1195–206.
16 Zeuzem S, Andreone P, Pol S *et al.* Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; 364: 2417–28.
17 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.
18 Kuboki M, Iino S, Okuno T *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.
19 Sherman KE, Flamm SL, Afdhal NH *et al.* Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; 365: 1014–24.
20 Reesink HW, Fanning GC, Farha KA *et al.* Rapid HCV-RNA decline with once daily TMC435: a phase I study in healthy volunteers and hepatitis C patients. *Gastroenterology* 2010; 138: 913–21.
21 Moreno C, Berg T, Tanwandee T *et al.* Antiviral activity of TMC435 monotherapy in patients infected with HCV genotypes 2-6: TMC435-C202, a phase IIa, open-label study. *J Hepatol* 2012; 56: 1247–53.
22 Manns M, Reesink H, Berg T *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.

23 Fried MW, Buti M, Dore GJ *et al.* Once-daily simeprevir (TMC435) with peginterferon and ribavirin in treatment-naïve genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology* 2013; 58: 1918–29.
24 Zeuzem S, Berg T, Gane E *et al.* Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology* 2014; 146: 430–41.
25 Hayashi N, Izumi N, Kumada H *et al.* Once-daily simeprevir with peginterferon and ribavirin for treatment-naïve hepatitis C genotype 1 patients in Japan: CONCERTO-1. *J Hepatol* 2014; [Epub ahead of print].
26 Izumi N, Hayashi N, Kumada H *et al.* Once-daily simeprevir with peginterferon and ribavirin for treatment-experienced HCV genotype 1 patients in Japan: the CONCERTO-2 and -3 studies. *J Gastroenterol* 2014; 49: 941–53.
27 Lenz O, Verbinnen T, T L *et al. In vitro* resistance profile of the hepatitis C virus NS3/4A protease inhibitor TMC435. *Antimicrob Agents Chemother* 2010; 54: 1878–87.
28 Kieffer TL, Kwong AD, Picchio GR. Viral resistance to specifically targeted antiviral therapies for hepatitis C (STAT-Cs). *J Antimicrob Chemother* 2010; 65: 202–12.
29 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 (1): 138–47.
30 Manns M, Marcellin P, Poordad F *et al.* Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014; Jun 3. [Epub ahead of print].
31 Rauch A, Kutalik Z, Descombes P *et al.* Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology* 2010; 138: 1338–45.
32 Kong Y, Wang X, Shang Y *et al.* Efficacy and tolerability of telaprevir for chronic hepatitis virus C genotype 1 infection: a meta-analysis. *PLoS ONE* 2012; 7: e52158.

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Simeprevir with peginterferon/ribavirin for treatment-naïve hepatitis C genotype 1 patients in Japan: CONCERTO-1, a phase III trial

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Background & Aims: In a Japanese Phase II study, the hepatitis C virus NS3/4A protease inhibitor simeprevir demonstrated potent antiviral activity and significantly improved sustained virologic response rates when added to peginterferon α-2a/ribavirin in treatment-naïve patients infected with hepatitis C virus genotype 1.

Methods: CONCERTO-1 was a Phase III, randomized, double-blind, placebo-controlled trial. Treatment-naïve adults (⩽70 years) with chronic hepatitis C virus genotype 1 infection (hepatitis C virus RNA ⩾5 $\log_{10}$ IU/ml) were randomized (2:1) to simeprevir 100 mg once-daily with peginterferon α-2a/ribavirin for 12 weeks then response-guided therapy with peginterferon α-2a/ribavirin for 12 or 36 weeks, or to placebo with peginterferon α-2a/ribavirin for 12 weeks then peginterferon α-2a/ribavirin for 36 weeks.

Results: Overall, 183 patients were treated. Sustained virologic response 12 weeks after treatment end (primary efficacy endpoint) was achieved in 88.6% of simeprevir- and 61.7% of placebo-treated patients (p <0.0001 for stratum-adjusted between-group difference). Overall, 91.9% of simeprevir-treated patients met response-guided therapy criteria and completed treatment at week 24; sustained virologic response rate at 12 weeks in these patients was 92.0%. One simeprevir- (0.8%) and two placebo-treated patients (3.3%) experienced viral breakthrough; respective viral relapse rates were 7.6% and 30.6%. Overall adverse event profile in simeprevir-treated patients was comparable to that in patients who received peginterferon α-2a/ribavirin alone.

Conclusions: Simeprevir once daily with peginterferon α-2a/ribavirin significantly improved sustained virologic response rate 12 weeks after treatment end in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection, with a shorter 24-week treatment duration in most patients.

Keywords: Genotype 1; Hepatitis C virus; Once-daily; Peginterferon; Protease inhibitor; Ribavirin; Simeprevir; TMC435; Treatment-naïve.

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Abbreviations: HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; SVR, sustained virologic response; PI, protease inhibitor; AE, adverse event; QD, once-daily; CONCERTO, Clinical Optimization of New treatment strategy with TMC435 in Combination with peginterferon plus Ribavirin for Treatment-naïve and treatment-experienced patients infected with HCV genotype 1 (One); ALT, alanine aminotransferase; AST, aspartate aminotransferase; RGT, response-guided therapy; SVR12, sustained virologic response 12 weeks after the end of treatment; SVR24, sustained virologic response 24 weeks after the end of treatment.

Introduction

Japan has one of the highest rates of hepatitis C virus (HCV) infection worldwide, with around 2 million people estimated to be infected [1]. Of these, about 70% are infected with HCV genotype 1b, 20% with genotype 2a, and the remainder with genotype 2b or other genotypes. Hepatocellular carcinoma is a leading cause of cancer mortality in Japan, with approximately 70% of cases related to HCV infection [2].

The goal of chronic HCV infection treatment is virus eradication, to prevent progression to cirrhosis and hepatocellular carcinoma. Until recently, standard of care was combination therapy with peginterferon (PegIFN) and ribavirin (RBV) for 24–48 weeks [3,4], resulting in sustained virologic response (SVR) in approximately 50% of patients [5,6]. However, HCV genotype 1 appears less responsive to PegIFN-based therapy than other genotypes [7].

The development of direct-acting antiviral agents represents a major breakthrough in the treatment of chronic HCV infection. These have been shown to improve SVR rates when combined with PegIFN/RBV in treatment-naïve and treatment-experienced patients [8,9]. Current Japanese guidelines recommend triple therapy with the HCV NS3/4A protease inhibitor (PI) telaprevir plus PegIFN/RBV for chronic genotype 1 HCV infection [10]. However, first-generation HCV PIs, such as telaprevir and boceprevir, are associated with two- or three-times daily dosing, the potential for adverse events (AEs) including anemia, rash, and renal dysfunction; and relatively rapid emergence of resistance in patients who do not achieve SVR [8,9,11–13].

Simeprevir (TMC435) is a potent, oral, once-daily (QD), HCV NS3/4A PI which has recently been approved in Japan [14]. In a Phase I study, simeprevir plasma exposure was found to be higher in healthy Japanese adult male volunteers than in healthy

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Caucasian volunteers [15]. Based on this finding, simeprevir doses of 50 and 100 mg QD were selected for use in further studies in Japan. A Phase II study in Japanese treatment-naïve patients with HCV genotype 1 infection and high viral load reported simeprevir (50 or 100 mg QD, for 12 or 24 weeks) in combination with PegIFNα-2a/RBV to be generally well tolerated and associated with improved SVR rates and shorter 24-week treatment duration in most patients [16]. The Clinical Optimization of New treatment strategy with TMC435 in Combination with peginterferon plus Ribavirin for Treatment-naïve and treatment-experienced patients infected with HCV genotype 1 (One; CONCERTO) studies were initiated to further explore efficacy and safety of simeprevir combined with PegIFN/RBV in patients with HCV genotype 1 infection in Japan. We present results of the CONCERTO-1 study (ClinicalTrials.gov: NCT01292239) in treatment-naïve patients.

Patients and methods

Patients

Treatment-naïve male and female patients aged 20–70 years with documented chronic genotype 1 HCV infection and plasma HCV RNA $\geqslant 5.0$ $\log_{10}$ IU/ml at screening were eligible. Key exclusion criteria included liver cirrhosis, hepatic failure, any other liver disease of non-HCV etiology and co-infection with HIV-1, HIV-2, hepatitis B, or non-genotype 1 HCV. Additional exclusion criteria are summarized in the Supplementary data. All patients provided written informed consent before study entry.

Study design

This Phase III, multicenter, randomized, double-blind, placebo-controlled trial assessed efficacy and safety of simeprevir combined with PegIFNα-2a/RBV in treatment-naïve patients with chronic genotype 1 HCV infection. The study was conducted at 37 sites in Japan from January 17, 2011 to October 22, 2012. The study protocol conformed to Good Clinical Practice Guidelines and to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutions' human research committee. (ClinicalTrials.gov: NCT01292239).

Eligible patients, stratified by age (<65 or $\geqslant$65 years old) and *IL28B* genotype (rs8099917; TT, TG, and GG), were randomized centrally 2:1 to simeprevir 100 mg QD plus PegIFNα-2a/RBV for 12 weeks followed by response-guided therapy (RGT) with PegIFNα-2a/RBV alone for 12 or 36 weeks, or placebo with PegIFNα-2a/RBV for 12 weeks followed by PegIFNα-2a/RBV for 36 weeks (see Supplementary data for details of treatment administration). Randomization was balanced by using randomly permuted blocks. Patients, study personnel, and the sponsor were blinded to treatment groups. According to RGT criteria, PegIFNα-2a/RBV therapy could be stopped at week 24 in simeprevir-treated patients who achieved HCV RNA <1.2 $\log_{10}$ IU/ml detectable or undetectable at week 4 and had undetectable HCV RNA at week 12. RGT was not permitted in the placebo group. All patients were followed for 72 weeks after treatment initiation.

Virologic stopping criteria were implemented to ensure that patients with a suboptimal response discontinued treatment in a timely manner in order to limit the risk of drug resistance and reduce unnecessary exposure to PegIFNα-2a/RBV. Patients with HCV RNA >3.0 $\log_{10}$ IU/ml at week 4 discontinued simeprevir or placebo but continued PegIFNα-2a/RBV. Patients with HCV RNA $\geqslant$1.2 $\log_{10}$ IU/ml at week 36 stopped PegIFNα-2a/RBV.

The primary efficacy endpoint was the proportion of patients with undetectable plasma HCV RNA at end of treatment and 12 weeks after end of treatment (SVR12). Other efficacy endpoints included: the proportion of patients with undetectable plasma HCV RNA at end of treatment and 24 weeks after end of treatment (SVR24); the proportion of patients with undetectable plasma HCV RNA at week 4 (rapid virologic response) or week 12 (complete early virologic response); incidence of viral breakthrough (>1 $\log_{10}$ IU/ml increase in plasma HCV RNA level from the lowest level reached, or plasma HCV RNA level >2.0 $\log_{10}$ IU/ml in patients whose plasma HCV RNA level had previously been <1.2 $\log_{10}$ IU/ml detectable or undetectable); viral relapse (detectable or quantifiable plasma HCV RNA at last available measurement during post-treatment follow-up in patients who had undetectable plasma HCV RNA at end of treatment), and the proportion of patients who had achieved normalization of ALT levels.

Study assessments

To assess virologic response, plasma HCV RNA was quantified at screening, baseline, day 3, weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 36, 48, 60, and 72 using the COBAS® TaqMan® HCV Auto Assay System (Roche, USA; lower limit of quantification, 1.2 $\log_{10}$ IU/ml). Plasma HCV RNA levels were also measured at weeks 42 and 52 in patients receiving PegIFNα-2a/RBV until week 48. ALT levels were measured at regular intervals throughout the study. Normal ALT levels, i.e., $\leqslant$40 IU/ml, were defined according to laboratory reference ranges.

Sequence analysis of the HCV NS3 protease domain was performed at baseline and in patients with simeprevir treatment failure (see Supplementary data for further details).

Safety was evaluated throughout the study. AEs were assessed during the treatment period and 28 days after the last dose of study medication. AE severity was graded by investigators using the World Health Organization grading scale. Certain AEs were identified as being of special or clinical interest (see Supplementary data for further details). Vital sign monitoring, electrocardiogram, and clinical laboratory tests were performed at regular intervals during treatment and the post-treatment follow-up period. Severity of laboratory abnormalities was classified according to the World Health Organization grading scale.

Statistical analysis

The sample size of the study (183 subjects) was calculated based on published data [16], and was considered to be sufficient to show superiority of simeprevir *vs.* placebo for the proportion of subjects achieving SVR12 with 90% power (see Supplementary data for further details). Efficacy analyses were performed on the full analysis set, which comprised all randomized patients who had received $\geqslant$1 dose of study medication for whom post-baseline efficacy assessment data were available. SVR rates between treatment groups were compared using the Cochran-Mantel-Haenszel test adjusted for the stratification factors (age and *IL28B* genotype). The 95% confidence interval of the stratum-adjusted difference in the proportions between the treatment groups was calculated.

The safety population comprised all patients who received $\geqslant$1 dose of study medication. Incidence of AEs and other safety endpoints was summarized for each treatment group.

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

Results

Study population

Overall, 223 patients were screened for study participation and 188 were randomized, and 183 received $\geqslant$1 dose of study medication (123 received simeprevir and 60 received placebo) (Fig. 1). Eleven patients (6.0%) discontinued the study during follow-up (3.3% and 11.7% in the simeprevir and placebo groups, respectively). The most common reason for study discontinuation was withdrawal of consent. In the simeprevir group, 92.7% completed the treatment period, as did 75.0% in the placebo group. Reasons for non-completion of all study medication are summarized in the Supplementary data.

Baseline demographic and disease characteristics were generally similar between treatment groups (Table 1). All patients were Japanese, 34.4% were male, and median age was 55 years (range 23–69 years). Most patients had the major alleles TT for *IL28B* 8099917 and CC for *IL28B* 12979860 associated with higher likelihood of response to pegIFN/RBV (66.7% and 64.2% in the simeprevir group, respectively, and 70.0% for both in the placebo group). Almost all patients had HCV genotype 1b (98.4%), except for three patients with HCV genotype 1a (two in the simeprevir

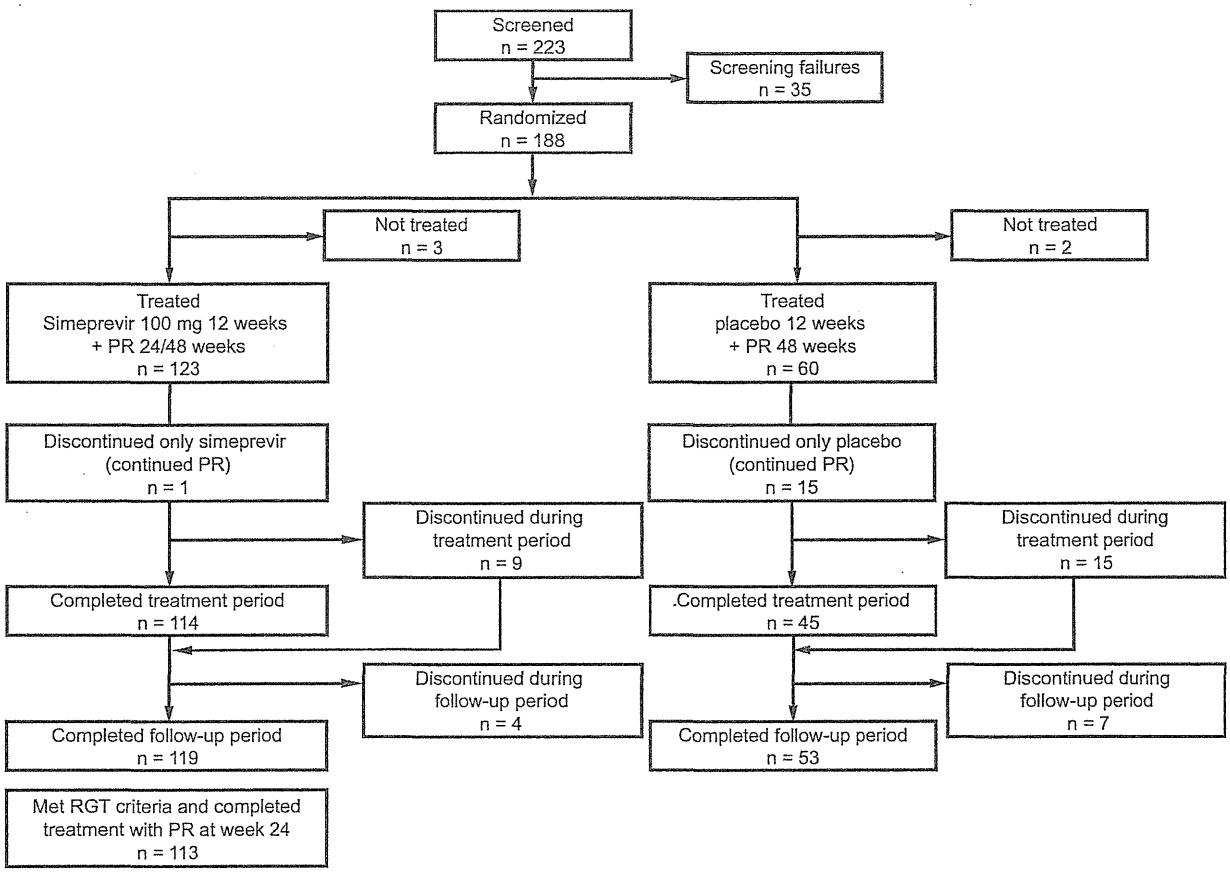

Fig. 1. Subject disposition. PR, peginterferon/ribavirin; RGT, response-guided therapy.

group and one in the placebo group). Median baseline HCV RNA was 6.3 $\log_{10}$ IU/ml (range 3.3–7.4 $\log_{10}$ IU/ml), with most patients in both groups having baseline HCV RNA levels $\geq$6 $\log_{10}$ IU/ml (74.0% for simeprevir and 76.7% for placebo).

Sustained virologic response

SVR12 was achieved in 88.6% of patients receiving simeprevir *vs.* 61.7% of patients receiving placebo (Table 2). The stratum-adjusted difference in SVR12 rate between the two groups was statistically significant (27.5% [95% confidence interval, 14.38–40.56%]; p <0.0001). Most (113/123; 91.9%) simeprevir-treated patients met RGT criteria and completed treatment at week 24. The SVR12 rate in these patients was 92.0%. Only one patient in the simeprevir group did not meet RGT criteria; this patient discontinued treatment with simeprevir only and completed treatment with PegIFNα-2a/RBV. The remaining nine patients discontinued the study before assessment of RGT criteria at week 24.

The proportion of patients achieving SVR24 was 88.6% in the simeprevir group and 56.7% in the placebo group (Table 2). Efficacy of simeprevir combined with PegIFNα-2a/RBV was statistically significantly superior to placebo combined with PegIFNα-2a/RBV (p <0.0001).

On-treatment virologic response

Onset of antiviral activity was more rapid with simeprevir than with placebo (Fig. 2). In the simeprevir group, 84.4% of patients had undetectable HCV RNA at week 4 *vs.* 13.3% in the placebo group (Table 2). The proportion of patients with undetectable HCV RNA at week 12 was also higher with simeprevir than with placebo (99.2% and 68.5%, respectively) (Table 2).

A notable difference in the proportion of patients achieving undetectable HCV RNA at weeks 4, 12, and 24 according to *IL28B* genotype at rs8099917 was seen between the simeprevir and the placebo groups (Fig. 3). With simeprevir, undetectable HCV RNA levels at week 4 were achieved by 87.8% of patients with the *IL28B* major allele (TT) and 75.6% of those with *IL28B* minor alleles (TG and GG). The proportion of simeprevir-treated patients with undetectable HCV RNA levels was increased at week 12 (96.3% with TT and 97.6% with TG and GG) and remained high at week 24 (92.7% with TT and 90.2% with TG and GG), irrespective of *IL28B* genotype. Undetectable HCV RNA levels at week 4 were achieved in 19.0% of placebo-treated patients with the *IL28B* major allele. No placebo-treated patients with *IL28B* minor alleles achieved undetectable HCV RNA at this time. Undetectable HCV RNA levels were achieved in 85.7% of placebo-treated patients with the *IL28B* major allele at weeks 12 and 24, and in

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Table 1. Baseline demographics and clinical characteristics.

Characteristic	Simeprevir group (n = 123)	Placebo group (n = 60)
Male, n (%)	39 (31.7)	24 (40.0)
Age (yr), median (range)	56.0 (23-69)	54.5 (30-69)
Age ≥65 years, n (%)	22 (17.9)	10 (16.7)
BMI (kg/m^2), median (range)	22.0 (16.9-32.9)	22.5 (17.3-33.2)
IL28B genotype (rs8099917), n (%)		
TT	82 (66.7)	42 (70.0)
TG/GG	41 (33.3)	18 (30.0)
IL28B genotype (rs12979860), n (%)		
CC	79 (64.2)	42 (70.0)
CT/TT	44 (35.8)	18 (30.0)
HCV genotype, n (%)		
1a	2 (1.6)	1 (1.7)
1b	121 (98.4)	59 (98.3)
Baseline HCV RNA (Log_{10} IU/ml), median (range)	6.3 (4.5-7.2)	6.4 (3.3-7.4)
Baseline HCV RNA category (Log_{10} IU/ml), n (%)		
<6.0	32 (26.0)	14 (23.3)
≥6.0 to <7.0	85 (69.1)	45 (75.0)
≥7.0	6 (4.9)	1 (1.7)
Metavir fibrosis stage,* n/N (%)		
0: No fibrosis	3/41 (7.3)	0
1: Periportal fibrosis expansion	28/41 (68.3)	18/24 (75.0)
2: P-P septae (>1 septum)	8/41 (19.5)	5/24 (20.8)
3: P-C septae	2/41 (4.9)	1/24 (4.2)
4: Cirrhosis	0	0
Platelets (×10^9/L), n (%)		
<150	30 (24.4)	10 (16.7)
≥150	93 (75.6)	50 (83.3)
ALT (IU/ml)		
<50	74 (60.2)	39 (65.0)
≥50	49 (39.8)	21 (35.0)
Total bilirubin (mg/dl), median (range)	0.7 (0.3-1.7)	0.7 (0.2-1.5)
Hemoglobin (g/dl), median (range)	13.9 (11.1-17.2)	14.1 (12.3-17.0)
Neutrophils (×10^2/μl), median (range)	24.2 (11.4-54.7)	22.5 (11.6-45.8)
Platelets (×10^4/μl), median (range)	18.3 (9.5-29.0)	20.2 (10.6-31.3)

*Available for patients who had a liver biopsy within 2 years before informed consent or during the screening period.
BMI, body mass index; HCV, hepatitis C virus; P-P, portal-portal; P-C, portal-central; ALT, alanine aminotransferase.

11.1% and 44.4% of placebo-treated patients with *IL28B* minor alleles at week 12 and week 24, respectively.

Viral breakthrough, viral relapse, and treatment failure

Viral breakthrough was observed in one patient (0.8%) in the simeprevir group, occurring at week 17 during treatment with Peg-IFNα-2a/RBV alone. Viral breakthrough was reported in two patients in the placebo group (3.3%) at weeks 2 and 21.

Viral relapse rates were lower in the simeprevir group than in the placebo group (7.6% *vs.* 30.6%, respectively). Viral relapse mostly occurred at follow-up week 12 (9/9 patients in the simeprevir group; 12/15 patients in the placebo group).

The proportion of patients meeting virologic stopping criteria was lower in the simeprevir group compared with the placebo group (0.8% *vs.* 40.0%, respectively). All of these patients met virologic stopping criteria at week 4 (plasma HCV RNA levels >3.0 log_{10} IU/ml).

Sustained virologic response according to baseline characteristics

SVR12 rates were higher in the simeprevir group than in the placebo group for all baseline demographic and disease characteristic subgroups. SVR12 rate by baseline demographic and disease characteristics is summarized in Supplementary Table 1.

NS3 sequencing analysis

Most patients (87.4% in the simeprevir group; 84.5% in the placebo group) had no baseline polymorphisms at any NS3 positions associated with reduced antiviral activity to simeprevir *in vitro*. Further information is provided in the Supplementary data section.

Alanine aminotransferase

In most patients with abnormal ALT levels at baseline, ALT levels were normalized by end of treatment (73.5% in the simeprevir group; 76.2% in the placebo group).

Table 2. Virologic response rates.

Endpoint, n/N (%)*	Simeprevir group (n = 123)	Placebo group (n = 60)
SVR12		
All patients	109/123 (88.6)	37/60 (61.7)
Patients meeting RGT criteria	104/113 (92.0)	n.a.
SVR24	109/123 (88.6)	34/60 (56.7)
Undetectable HCV RNA at Wk 4 of treatment*	103/122 (84.4)	8/60 (13.3)
Undetectable HCV RNA at Wk 12 of treatment*	117/118 (99.2)	37/54 (68.5)
Viral breakthrough	1/123 (0.8)	2/60 (3.3)
Viral relapse**	9/118 (7.6)	15/49 (30.6)

SVR12, sustained virologic response 12 weeks after the end of treatment; RGT, response guided therapy; SVR24, sustained virologic response 24 weeks after the end of treatment; n.a., not available.

*Subjects who discontinued all study medication prior to assessment of undetectable HCV RNA at week 4 and week 12 of treatment were not included in the denominator for calculation of these on-treatment response rates.

**Viral relapse was only assessed in patients with undetectable HCV RNA at end of treatment and with at least one follow-up HCV RNA measurement.

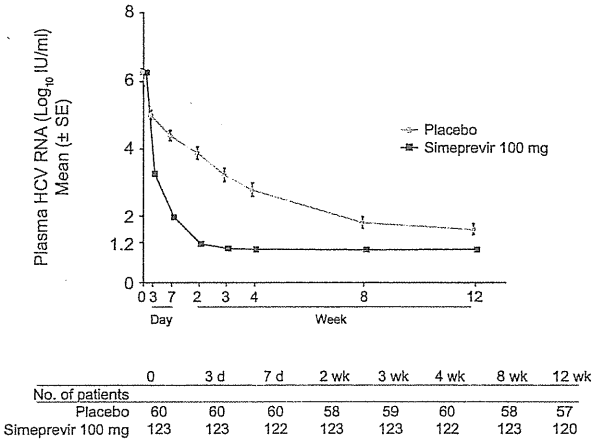

Fig. 2. Mean change from baseline in plasma HCV RNA levels up to week 12. HCV, hepatitis C virus; SE, standard error.

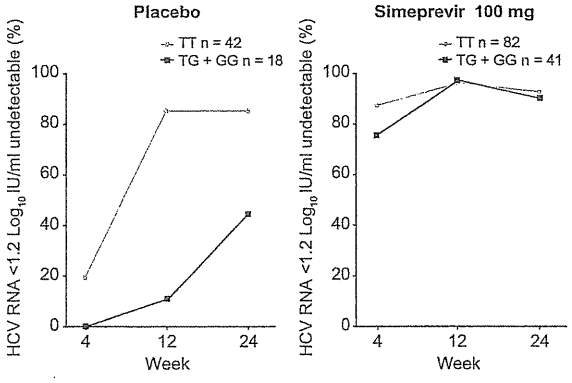

Fig. 3. Proportion of patients with plasma HCV RNA <1.2 log_{10} IU/ml undetectable according to *IL28B* genotype at rs8099917. HCV, hepatitis C virus.

Safety

For the entire treatment period, no clinically significant differences in the type and incidence of AEs were observed between groups (Table 3; Supplementary Table 2). Most AEs were grade 1/2 (72.4% in the simeprevir group; 66.7% in the placebo group). Rates of treatment discontinuation and PegIFNα-2a/RBV dose modification due to AEs were similar between groups, with no AEs leading to permanent discontinuation of simeprevir only. Serious AEs were observed in four patients (3.3%) in the simeprevir group and six patients (10.0%) in the placebo group. There were no deaths reported.

For AEs of special/clinical interest (Table 3), incidence was higher in the simeprevir group than in the placebo group for increased bilirubin-related AEs (22.8% *vs.* 10.0%) and photosensitivity conditions (1.6% *vs.* 0%). Incidence was lower in the simeprevir group than in the placebo group for rash (any type) and selected gastrointestinal events. For anemia, neutropenia, and pruritus-related AEs, incidence rates were similar in both groups. In the simeprevir group, all AEs of special/clinical interest were grade 1/2, except for grade 3 anemia-related AEs in one patient (0.8%) and grade 3/4 neutropenia-related AEs in 28 patients (22.8%). None of the neutropenia-related AEs were serious and none led to discontinuation of any study medications.

Fig. 4 shows changes in laboratory parameters over the entire duration of treatment and follow-up. Notably, only one patient in the simeprevir group continued treatment with PegIFNα-2a/RBV from week 24 onwards. Except for total bilirubin, no differences between groups were observed in median change from baseline for any of these laboratory parameters. Median total bilirubin levels increased in the simeprevir group from baseline to week 2 and then decreased to near baseline levels from week 4 to week 12. During this period, median levels remained within normal limits. From week 12, median values returned to baseline. Increases in total bilirubin levels were not associated with increased ALT or AST levels.

No consistent clinically significant differences in any other laboratory parameters, electrocardiogram parameters, or vital signs were observed between groups.

Discussion

This study was undertaken to assess efficacy and safety of simeprevir in combination with PegIFNα-2a/RBV in treatment-naïve

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Table 3. Summary of AEs reported in the entire study treatment period and during treatment with simeprevir plus PegIFNα-2a and ribavirin (safety population).

	Entire treatment period		Simeprevir/Placebo + PegIFNα-2a/RBV	
No. of patients, n (%)	Simeprevir group (n = 123)	Placebo group (n = 60)	Simeprevir group (n = 123)	Placebo group (n = 60)
Treatment discontinuation due to AE				
Simeprevir/placebo only†	0	1 (1.7)	0	1 (1.7)
All study medication‡	6 (4.9)	5 (8.3)	4 (3.3)	3 (5.0)
Dose modification due to AE				
PegIFNα-2a	47 (38.2)	24 (40.0)	n.a.	n.a.
RBV	67 (54.5)	27 (45.0)	n.a.	n.a.
SAE	4 (3.3)	6 (10.0)	3 (2.4)	3 (5.0)
Death	0	0	0	0
AEs of special/clinical interest*				
Increased bilirubin-related AEs	28 (22.8)	6 (10.0)	28 (22.8)	6 (10.0)
Blood bilirubin increased	20 (16.3)	4 (6.7)	20 (16.3)	4 (6.7)
Hyperbilirubinemia	8 (6.5)	2 (3.3)	8 (6.5)	2 (3.3)
Rash (any type)	71 (57.7)	42 (70.0)	64 (52.0)	27 (45.0)
Rash	57 (46.3)	37 (61.7)	54 (43.9)	24 (40.0)
Erythema	17 (13.8)	4 (6.7)	13 (10.6)	2 (3.3)
Other events	6 (4.9)	3 (5.0)	4 (3.3)	2 (3.3)
Pruritus-related AEs	37 (30.1)	19 (31.7)	29 (23.6)	5 (8.3)
Pruritus	35 (28.5)	18 (30.0)	28 (22.8)	5 (8.3)
Pruritus generalized	2 (1.6)	1 (1.7)	1 (0.8)	0 (0)
Photosensitivity conditions	2 (1.6)	0	1 (0.8)	0 (0)
Photosensitivity reaction	2 (1.6)	0	1 (0.8)	0 (0)
Neutropenia-related AEs	97 (78.9)	49 (81.7)	90 (73.2)	42 (70.0)
White blood cell count decreased	78 (63.4)	41 (68.3)	74 (60.2)	35 (58.3)
Neutrophil count decreased	69 (56.1)	37 (61.7)	59 (48.0)	30 (50.0)
Neutropenia	8 (6.5)	1 (1.7)	8 (6.5)	1 (1.7)
Anemia-related AEs	97 (78.9)	45 (75.0)	74 (60.2)	30 (50.0)
Anemia	70 (56.9)	36 (60.0)	55 (44.7)	24 (40.0)
Hemoglobin decreased	27 (22.0)	9 (15.0)	19 (15.4)	6 (10.0)
Selected gastrointestinal events	53 (43.1)	38 (63.3)	46 (37.4)	28 (46.7)
Decreased appetite	28 (22.8)	20 (33.3)	28 (22.8)	14 (23.3)
Diarrhea	20 (16.3)	17 (28.3)	14 (11.4)	12 (20.0)
Nausea	16 (13.0)	12 (20.0)	15 (12.2)	9 (15.0)
Constipation	9 (7.3)	5 (8.3)	7 (5.7)	2 (3.3)
Vomiting	6 (4.9)	5 (8.3)	4 (3.3)	1 (1.7)

†Permanent discontinuation of simeprevir or placebo alone, PegIFNα-2a/RBV continued.
‡Discontinuation of simeprevir/placebo and PegIFNα-2a/RBV at the same time, or discontinuation of PegIFNα-2a/RBV after completion or discontinuation of simeprevir/placebo).
*See Supplementary data for further details.
AEs, adverse events; PegIFNα-2a, peginterferon α-2a; RBV, ribavirin; SAE, serious adverse event; n.a., not available.

patients with chronic HCV genotype 1 infection and high viral load in Japan. A simeprevir dose of 100 mg with a 12 week duration for triple therapy was selected for use in this study based on results of a previous Phase II trial [16]. Oral once-daily treatment with simeprevir 100 mg for 12 weeks was associated with a significant improvement in SVR12 rate in this patient population. An RGT strategy was employed to allow individualized shortening of PegIFNα-2a/RBV treatment duration to 24 weeks, based on early virologic response. Almost all simeprevir-treated patients (91.9%) met RGT criteria and were eligible to stop PegIFNα-2a/RBV at week 24. The SVR12 rate in these patients was 92.0%, supporting this approach. A shorter overall treatment duration is highly desirable in patients with chronic HCV infection as it reduces PegIFNα-2a/RBV exposure and the potential for treatment-related AEs [17].

Even in patients with unfavorable demographic and baseline disease characteristics for a response to PegIFNα-2a/RBV (e.g., older age, high baseline HCV RNA, and low baseline platelet counts), treatment with simeprevir was associated with significantly improved SVR rates (Supplementary Table 1). As expected, *IL28B* single nucleotide polymorphism was predictive of therapeutic effect for PegIFNα-2a/RBV. It is well documented that

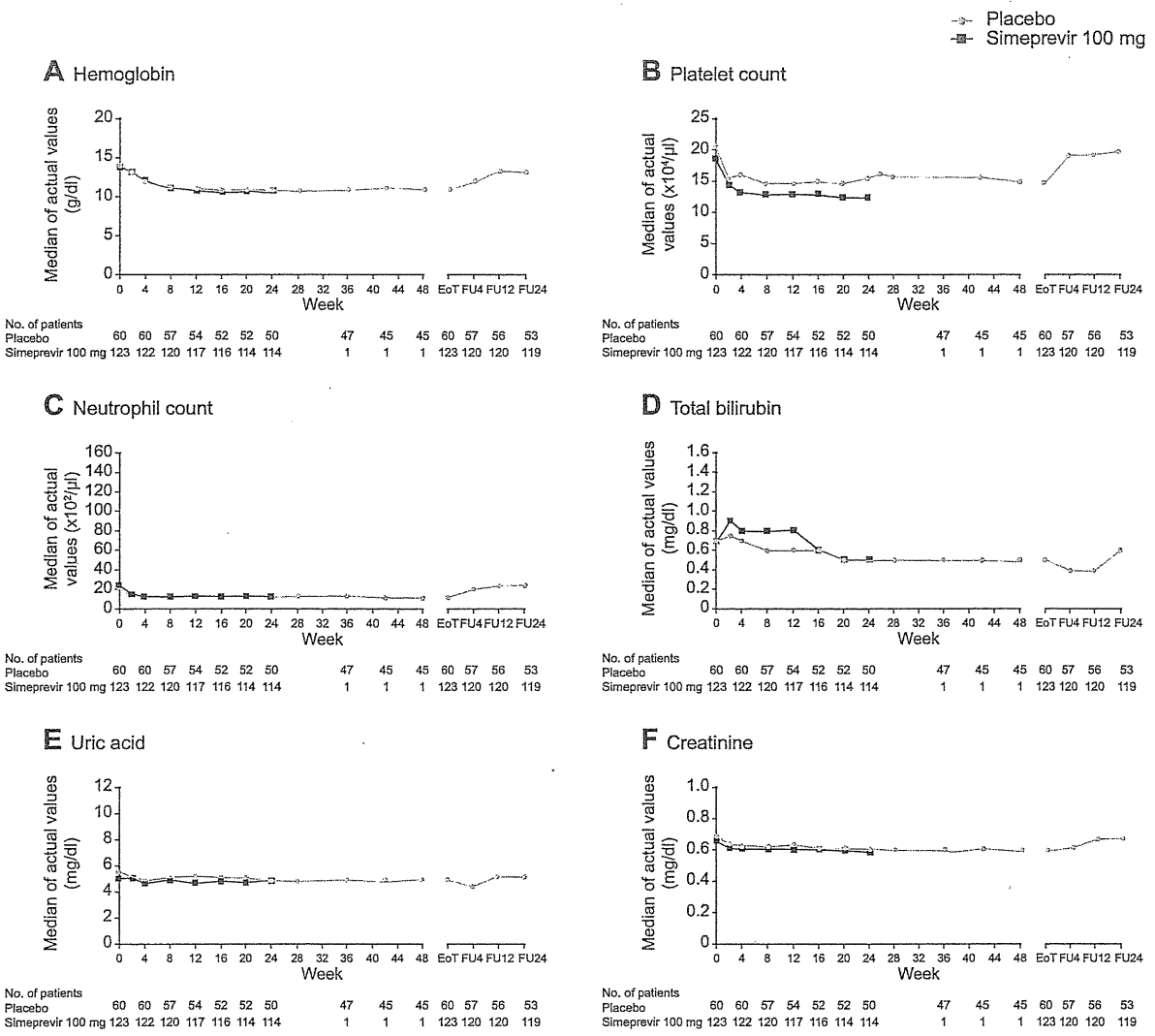

Fig. 4. Median changes in serum levels. (A) hemoglobin, (B) platelet count, (C) neutrophil count, (D) total bilirubin, (E) uric acid, and (F) creatinine over the entire duration of treatment and follow-up.*Only one patient in the simeprevir group continued treatment with peginterferon α-2a/ribavirin from week 24 onwards. EoT, end of treatment; FU, follow-up.

patients carrying *IL28B* minor alleles show greater resistance to PegIFN/RBV than those carrying major alleles [18–21]. Approximately two-thirds of patients in this study had favorable *IL28B* genotypes associated with higher likelihood of response to peg-IFN/RBV therapy. Nevertheless, our results suggest that addition of simeprevir to PegIFNα-2a/RBV reduces the impact of unfavorable *IL28B* minor alleles at rs8099917 and rs12979860. Consistent with the epidemiology of HCV infection in Japan [1], genotype 1b was dominant among patients enrolled in this study (98.4%). It has been suggested that HCV genotype 1a infection has a lower genetic barrier to resistance relative to genotype 1b infection [22].

The SVR rate in patients treated with PegIFNα-2a/RBV for 48 weeks is consistent with the original assumption for sample size estimation and is similar to that reported in a previous Phase III study of PegIFNα-2a/RBV in a comparable Japanese population [5]. The SVR rate observed in simeprevir-treated patients in this study is within the range reported in a previous dose-ranging Phase II study of simeprevir in treatment-naïve patients with chronic HCV genotype 1 infection in Japan [16].

Viral breakthrough was observed in one patient (0.8%) in the simeprevir group and two patients (3.3%) in the placebo group. Viral relapse occurred infrequently in simeprevir-treated patients compared with the placebo group, being observed in 7.6% of simeprevir-treated patients with undetectable plasma HCV RNA at end of treatment compared with 30.6% of patients who received placebo.

Sequence analysis of the HCV NS3 protease domain focused on detecting previously characterized HCV genotype 1 amino acid substitutions in the NS3 region that have been associated

with reduced susceptibility to simeprevir and other HCV NS3 PIs *in vitro* (43, 80, 155, 156, and 168) (see Supplementary data) [23,24]. Overall, 86.4% of patients did not have baseline polymorphisms at these positions. Emerging mutations were detected in most simeprevir-treated patients who experienced treatment failure, with D168V the most frequent emerging mutation. Emerging mutations identified at the time of treatment failure were generally not detectable at later time points, suggesting that these mutations do not persist and may resolve over time.

Simeprevir had a clinically favorable safety and tolerability profile in this patient population, with no notable differences in the type and incidence of AEs or discontinuations due to AEs observed between the simeprevir and placebo groups. In contrast to first-generation PIs, such as telaprevir [8,9,12,13], incidence of anemia- and rash-related AEs observed in simeprevir-treated patients was no higher than in placebo-treated patients, and no cases of severe anemia or severe rash were seen in simeprevir-treated patients in this study. Renal dysfunction has also been identified as a potential safety concern with currently marketed first-generation HCV PIs, including telaprevir; no clinically relevant changes in renal function parameters were reported in this study. Cases of sepsis and pneumonia have recently been reported in telaprevir-treated patients during post-marketing surveillance in Japan (Mitsubishi Tanabe, personal communication). However, no severe infectious diseases were reported in this study. Mild reversible transient increases in bilirubin levels were observed in simeprevir-treated patients, as reported previously [14,16]. *In vitro* data suggest that this results from inhibition of OATP1B1 and MRP2 transporters by simeprevir, as both play a role in bilirubin clearance [25].

In summary, results of the CONCERTO-1 study in treatment-naïve patients with HCV genotype 1 and high viral load show that oral once-daily simeprevir in combination with PegIFNα-2a/RBV significantly improves SVR rates and shortens treatment duration in most patients. Simeprevir has now been approved in Japan for the treatment of chronic HCV infection. Ongoing studies are investigating simeprevir in IFN-free combinations, including all oral regimens [26].

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Conflict of interest

Drs Okanoue, Tsubouchi, Kumada, and Hayashi consult and advise Janssen Pharmaceuticals. Drs Ki, Komada, Seto, and Goto are employed by Janssen Pharmaceuticals.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2014.04.004.

References

[1] Chung H, Ueda T, Kudo M. Changing trends in hepatitis C infection over the past 50 years in Japan. Intervirology 2010;53:39–43.
[2] Umemura T, Ichijo T, Yoshizawa K, Tanaka E, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. J Gastroenterol 2009;44:102–107.
[3] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011;55:245–264.
[4] Izumi N. Diagnostic and treatment algorithm of the Japanese society of hepatology: a consensus-based practice guideline. Oncology 2010;78:78–86.
[5] 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;22:645–652.
[6] 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;358:958–965.
[7] McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580–593.
[8] 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;364:1207–1217.
[9] 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;364:2405–2416.
[10] 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.
[11] Buti M, Agarwal K, Horsmans Y, Sievert W, Janczewska E, Zeuzem S, et al. Telaprevir twice daily is noninferior to telaprevir every 8 h for patients with chronic hepatitis C. Gastroenterology 2014;146:744–753.
[12] Hezode C. Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice. Liver Int 2012;32:32–38.
[13] Thompson AJ, Locarnini SA, Beard MR. Resistance to anti-HCV protease inhibitors. Curr Opin Virol 2011;1:599–606.
[14] Tanwar S, Trembling PM, Dusheiko GM. TMC435 for the treatment of chronic hepatitis C. Expert Opin Investig Drugs 2012;21:1193–1209.
[15] Verloes R, Shishido A. Phase I safety and PK of TMC435 in healthy volunteers and safety, PK and short-term efficacy in chronic hepatitis C infected individuals (abstract O-32). In: Japanese Hepatology Congress, Kobe, Japan, June 4–5, 2009.
[16] 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;49:138–147.
[17] Reddy KR, Lin F, Zoulim F. Response-guided and -unguided treatment of chronic hepatitis C. Liver Int 2012;32:64–73.
[18] Estrabaud E, Vidaud M, Marcellin P, Asselah T. Genomics and HCV infection: progression of fibrosis and treatment response. J Hepatol 2012;57:1110–1125.
[19] Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399–401.
[20] Hayes CN, Kobayashi M, Akuta N, Suzuki F, Kumada H, Abe H, et al. HCV substitutions and IL28B polymorphisms on outcome of peg-interferon plus ribavirin combination therapy. Gut 2011;60:261–267.
[21] Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009;41:1105–1109.
[22] Cento V, Mirabelli C, Salpini R, Dimonte S, Artese A, Costa G, et al. HCV genotypes are differently prone to the development of resistance to linear and macrocyclic protease inhibitors. PLoS One 2012;7:e39652.

[23] Kieffer TL, Kwong AD, Picchio GR. Viral resistance to specifically targeted antiviral therapies for hepatitis C (STAT-Cs). J Antimicrob Chemother 2010;65:202–212.
[24] Lenz O, Verbinnen T, Lin T-I, Vijgen L, Cummings MD, Lindberg J, et al. *In vitro* resistance profile of the hepatitis C virus NS3/4A protease inhibitor TMC435. Antimicrob Agents Chemother 2010;54:1878–1887.
[25] 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. In: Poster 278 presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, USA, 29 October–2 November, 2010.
[26] Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. Liver Int 2014;34:69–78.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

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

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

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

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Introduction

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

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

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

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

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

Methods

Patients

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

Study design

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

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

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

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

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

Treatment administration

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

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

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

Study assessments

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

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

Statistical analysis

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

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

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

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

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

Results

Patient disposition and baseline characteristics

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

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

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

Table 1 Baseline demographics and disease characteristics

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

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

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

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

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