Prediction of Sustained Virological Response to Telaprevir/Simeprevir-Based Triple Therapy in Patients with Genotype 1 Hepatitis C Virus Using Super-Early Viral Response within 2 Weeks

Yoshinori Ozono[1], Yuka Takaishi[1], Mai Tsuchimochi[2], Kenichi Nakamura[1], Hiroo Abe[1], Tadashi Miike[1], Kazunori Kusumoto[3], Hisayoshi Iwakiri[1], Mitsue Sueta[5], Yoshihiro Tahara[1], Shojiro Yamamoto[1], Satoru Hasuike[1], Kenji Nagata[2*] and Kazuya Shimoda[1,2,4]

[1]Department of Gastoroenterology and Hematology, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan

[2]Department of Liver disease, University of Miyazaki Hospital, Miyazaki, Japan

[3]Department of Internal Medicine, Koga General Hospital, Miyazaki, Japan

[4]Oncology Unit, University of Miyazaki Hospital, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan

Corresponding author: Kenji Nagata, Department of Liver disease, University of Miyazaki Hospital, 5200 Kihara, Kiyotake, Miyazaki 889-1601, Japan, Tel: +81 985 85 9121; E-mail: nagatakj@med.miyazaki-u.ac.jp

Abstract

Objective: Rapid virological response (RVR), defined as undetectable serum hepatitis C virus (HCV) RNA at week 4, is a useful predictor of sustained virological response (SVR) to peginterferon (PEG-IFN) plus ribavirin (RBV) therapy and protease inhibitor (telaprevir (TVR)/simeprevir (SMV)) based triple therapy for patients infected with genotype 1 HCV. The aim of this study was to predict SVR using viral response within 2 weeks of therapy initiation.

Methods: Fifty-two HCV genotype 1b patients with high viral loads treated with protease inhibitor (TVR/SMV)-based triple therapy were analysed. Thirty-seven patients were treated with TVR-based triple therapy and 15 with SMV-based triple therapy. HCV RNA levels were measured at the following points: the day of therapy initiation, at days 1 and 3, and at weeks 1 and 2.

Results: SVR was achieved in 87% (45/52) of patients. There was no difference in SVR rate between the TVR-based triple therapy group (92%) and the SMV-based triple therapy group (73%) (P=0.1726). Univariate analysis of contributors to SVR showed a significant effect of liver fibrosis, platelet count, aspartate transaminase, α-fetoprotein in terms of pre-treatment factors, and HCV RNA load at week 2, reduction of HCV RNA at day 1 and week 2, RVR, and PEG-IFN adherence in terms of on-treatment factors. By multivariate analysis, platelet count and HCV RNA load at week 2 were independently associated with high SVR rate.

Conclusion: HCV RNA level at week 2 was the most useful predictor of SVR after TVR/SMV-based triple therapy in patients with genotype 1 HCV.

Keywords Chronic hepatitis C; Telaprevir; Simeprevir; Sustained virological response; Prediction

Introduction

Hepatitis C virus (HCV) infection is a major worldwide cause of liver-related diseases such as chronic hepatitis (CH), liver cirrhosis (LC), liver failure and hepatocellular carcinoma (HCC) [1,2]. Since 2004, peginterferon (PEG-IFN) plus ribavirin (RBV) therapy (PEG-IFN/RBV therapy) has been standard for HCV genotype 1 patients in Japan. Sustained virological response (SVR), defined by undetectable HCV RNA at 24 weeks after the completion of therapy, was observed in approximately 50% of CH-C patients [3,4]. Large prospective clinical trials compared the NS3/4A protease inhibitors telaprevir (TVR) or simeprevir (SMV) in combination with PEG-IFN plus RBV (TVR/SMV-based triple therapy) with conventional dual therapy in patients with CH-C [5-15]. Both in treatment-naïve patients and those previously treated with IFN, the SVR rate following TVR/SMV-based triple therapy was higher than that after dual therapy.

It was reported that HCV RNA dynamics were a useful predictor of SVR. In particular, rapid virological response (RVR), defined as undetectable serum HCV RNA at week 4, was associated with SVR after PEG-IFN/RBV therapy [16,17]. Similarly, RVR was associated with SVR after TVR/SMV-based triple therapy [10,13,18-20]. However, there are few reports on predicting the occurrence of SVR earlier than week 4 after the initiation of protease inhibitor-based triple therapy [21-23]. The aim of the present study was to evaluate whether SVR after TVR/SMV-based triple therapy in patients with a high viral load of HCV genotype 1 could be predicted on the basis of a super-early virological response i.e., within 2 weeks.

Methods

Patients and treatment regimens

We conducted a retrospective chart review of patients with HCV genotype 1b who were treated at University of Miyazaki between February 2012 and April 2014 with either TVR-based triple therapy

(37 patients) or SMV-based triple therapy (15 patients). This study was approved by the Research Ethics Committee of University of Miyazaki.

Patients were administered three agents (TVR or SMV/PEG-IFN/RBV) during the first 12 weeks of the treatment, followed by dual therapy (PEG-IFN/RBV) in the latter 12 weeks, for a total treatment period of 24 weeks. TVR was administered every 8 hours three times a day, while SMV was given once a day. The initiation dose of TVR was 2,250 mg daily in males with hemoglobin (Hb) ≥ 13 g/dL and in females with Hb ≥ 14 g/dL, and 1,500 mg daily in others. The daily dose of SMV was 100 mg. PEG-IFN α-2b was injected at a dose of 1.5 µg/kg, α-2a was at a dose of 180 µg once a week. RBV was administered twice a day with dose based on body weight: 600 mg for ≤ 60 kg; 800 mg for >60 ~ ≤ 80 kg; and 1000 mg for >80 kg. During treatment, TVR and SMV were withdrawn at the attendant physician's discretion. The dose of PEG-IFN was reduced by 50% when the leukocyte count decreased to $<1.5 \times 10^9$/L , neutrophil count to $<0.75 \times 10^9$/L or platelet count to $<80 \times 10^9$/L. When the Hb level decreased to <10 g/d, the dose of RBV was reduced from 600 mg to 400 mg, from 800 mg to 600 mg, or from 1000 mg to 600 mg, depending on the initial dose. All three drugs were discontinued when the leukocyte count decreased to $<1.0 \times 10^9$/L, neutrophil count to $<0.5 \times 10^9$/L, platelet count to $<50 \times 10^9$/L, or Hb level to <8.5 g/dl. Resumption of all 3 drugs was allowed if blood findings returned to within normal limits.

Laboratory tests and liver histology

Laboratory tests were performed in all patients before therapy. HCV RNA was measured using the COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). The dynamic range was 1.2-7.8 log IU/mL. A high viral load was defined as >5.0 logIU/mL using quantitative RT-PCR. HCV RNA levels were measured at the following points: the day of therapy initiation, at days 1 and 3, and at weeks 1 and 2. During therapy, quantitative HCV RNA and biochemical analyses (including blood counts and levels of serum aspartate aminotransferase (AST) and alanine transaminase (ALT)) were performed every 4 weeks up to 12-24 weeks after the end of therapy. Before treatment we evaluated the presence of the rs8099917 single nucleotide polymorphism (SNP) in the interleukin (IL)-28B host genotypes, as this was reported to be a pretreatment predictor of the efficacy of PEG-IFN/RBV therapy (24). Homozygosity for the major allele (T/T) was defined as the IL-28B major type, and heterozygosity (T/G) or homozygosity for the minor allele (G/G) was defined as the IL-28B minor type. Patients were examined for NS3/4A protease inhibitor-resistant variants by direct sequencing at baseline. NS3/4A protease inhibitor-resistant variants included V36A/M, T54A, V55A, Q80R/K/L, R155K/T/Q, A156V/T, D168A/V/T/H, and V170A [24-26]. TVR-resistant variants (at aa 36, aa 54, aa 155, aa 156, and aa 170) and SMV-resistant variants (at aa 80, aa 155, aa 156, and aa 168) were assessed [25,26]. In all patients except for one, core needle biopsy of the liver was performed under ultrasound guidance using a 14-G core biopsy needle within 3 months before the start of therapy. Histological findings were classified using the METAVIR scoring system [27].

Efficacy assessments

The definitions of virological response used in this study are as follows. Seronegativity for HCV RNA at 4 weeks after the initiation of therapy was considered a rapid virological response (RVR), while that occurring more than 12 weeks after the completion of therapy was defined as a sustained virological response (SVR). Relapse was considered to have occurred if HCV RNA was undetectable by the end of treatment but detectable during the follow-up period. Non-response was diagnosed if HCV RNA seronegativity did not occur during therapy. To assess the virological response within 2 weeks after therapy initiation, the HCV RNA load and its reduction from baseline was evaluated at day 1, day 3, week 1, and week 2.

Statistical Analysis

Therapeutic response was divided into two categories, SVR and non-SVR. Effectiveness of TVR/SMV-based triple therapy was evaluated using an intention-to-treat analysis. Statistical associations were calculated by univariate analysis comparing the two groups on each item, including pre- and on-treatment factors. Continuous variables between the SVR and non-SVR groups were compared by the Mann-Whitney test, and categorical variables were compared by the Chi-square test and Fisher's exact test. Variables significant at a p value <0.05 in the univariate analysis were included in a multivariate analysis based on a logistic regression model to identify which were independently related to the result of therapy. Statistical analyses were performed using the statistical software SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA), and p value <0.05 was considered significant.

Results

Patient characteristics

Fifty-two patients were analyzed in this study. Patient characteristics are presented in Table 1. The median age was 61, and 24 (46%) were male. All patients were diagnosed with CH or LC caused by HCV genotype 1b. Among the 51 patients who underwent liver biopsy before treatment, 40 (78%) had a histological grade of F1-2, and 11 (22%) had a grade of F3-4 (advanced fibrosis). Twenty-six patients (50%) were treatment-naïve, 14 (27%) experienced a previous treatment relapse, eight (15%) were previous non-responders, and the prior treatment status of four (8%) was unknown. Before treatment, the median HCV viral load was 6.5 log IU/mL (range 5.0-7.4). Genotyping of IL-28B at rs8099917 was performed in all of the patients; 38 patients (73%) had the IL28B T/T genotype, and 14 (27%) patients had the IL28B T/G or G/G genotype. All of the patients were NS3/4A protease-inhibitor naïve. Thirty-seven patients (71%) received TVR and 15 received SMV, and there was no apparent difference between the two groups (Table 1). NS3/4A protease inhibitor-resistant variants were observed in 3% (1/37) of TVR group and 7% (1/15) of SMV group.
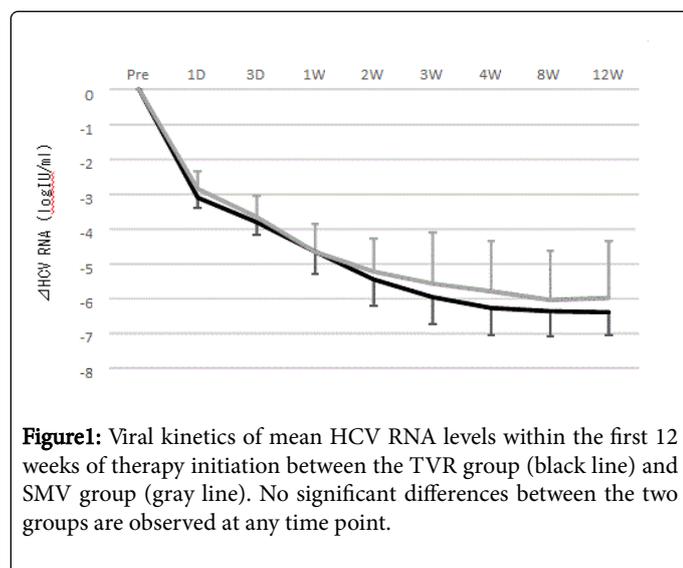
Characteristics	TVR (n=37)	SMV (n=15)	Total (n=52)	P-value
Sex (male/female)	18/19	6/9	24/28	0.795
Age (years)	62 (33-74)	58 (35-72)	61 (33-74)	0.2811

Body weight (kg)	58 (41-91)	61 (42-89)	59 (41-91)	0.5189
Prior treatment (naïve/relapse/non-response)	16/11/6	10/3/2	26/14/8	0.7434
Liver fibrosis (F1-2/F3-4)	28/8	12/3	40/11	0.8432
IL-28B genotype (TT/non-TT)	30/7	8/7	38/14	0.0809
HCV RNA (logIU/mL)	6.5 (5.0-7.4)	6.5 (5.2-7.0)	6.5 (5.0-7.4)	0.5453
Hemoglobin (g/dl)	13.8 (11.6-16.1)	13.5 (12.5-16.6)	13.8 (11.6-16.6)	0.5042
White blood cell count (× 109/L)	4.6 (3.0-7.1)	4.6 (3.5-7.4)	4.6 (3.0-7.4)	0.5247
Platelets (× 109/L)	155 (76-268)	155 (83-219)	155 (76-268)	0.2811
Total bilirubin (mg/dl)	0.8 (0.3-1.5)	0.9 (0.4-1.2)	0.8 (0.3-1.5)	0.5086
Aspartate transaminase (IU/L)	39 (21-123)	38 (27-165)	39 (21-165)	0.3676
Alanine transaminase (IU/L)	53 (15-186)	46 (30-170)	50 (15-186)	0.5277
γglutamyltransferase (IU/L)	37 (11-441)	41 (17-127)	39 (11-441)	0.45
Serum creatinine (mg/dl)	0.7 (0.4-1.3)	0.8 (0.6-1.1)	0.8 80.4-1.3)	0.5042
α-fetoprotein (ng/ml)	4.8 (1.6-76.9)	5.1 (1.9-22.7)	4.8 (1.6-76.9)	0.4207
Fatty liver (yes/no)	4/33	2/13	6/46	0.825
Diabetes mellitus (yes/no)	6/31	2/13	8/44	0.8704
NS3/4A resistant variants (yes/no)	1/36	1/14	2/50	0.4977
Data are expressed as number or median (range).				

Table 1: Baseline characteristics.

Kinetics of HCV RNA and virological response

Viral kinetics of mean HCV RNA levels during the first 12 weeks of treatment are shown in Figure 1. No significant difference was observed between the TVR and SMV groups. Forty-five patients eventually achieved SVR, and the overall SVR rate was 87%.

Figure1: Viral kinetics of mean HCV RNA levels within the first 12 weeks of therapy initiation between the TVR group (black line) and SMV group (gray line). No significant differences between the two groups are observed at any time point.

In patients receiving TVR-based triple therapy, the SVR rate (92%) was slightly higher than in those who underwent SMV-based triple therapy (73%), but the difference did not reach statistical significance (P=0.1726). The overall RVR rate was 81%. Similarly, no significant difference in RVR was observed between groups, with rates of 84% (31/37) and 67% (10/15) in the TVR and SMV patients, respectively (P=0.2062).

Factors associated with sustained virological response

SVR-associated factors were identified by univariate analysis. In terms of pre-treatment factors, significant differences between the SVR and non-SVR groups were noted in liver fibrosis, baseline platelet count, AST, and α-fetoprotein (AFP), while there were no differences in age, IL-28B genotype, previous treatment effect, or NS3/4A protease inhibitor-resistant variants (Table 2). As for on-treatment factors, significant differences between the two groups were noted in HCV RNA at week 2, reduction of HCV RNA at day 1 and week 2, RVR, and PEG-IFN adherence (Table 3). Subsequently, multivariate analysis of SVR was conducted for both the pre- and on-treatment factors. Platelet count before treatment and HCV RNA at week 2 were independently associated with higher SVR rates (Table 4). On the basis of receiver operating characteristic analyses, 1.2 logIU/mL was the optimal cut-off point for HCV RNA levels at week 2. Using this value, 32 of 45 patients with <1.2 logIU/mL HCV RNA at week 2 achieved SVR, and five of seven patients with ≥ 1.2 logIU/ml HCV RNA at week 2 did not achieve SVR. The sensitivity was 71.1%, specificity was 71.4%, positive predictive value was 94.1%, and negative predictive value was 27.8%.

Pre-treatment factors	SVR (n=45)	non-SVR (n=7)	P-value
Sex (male/female)	22/23	2/5	0.43
Age (years)	61 (33-74)	61 (53-64)	0.5416
Body weight (kg)	61 (41-91)	58 (42-73)	0.259
Prior treatment (naïve/relapse/non-response)	22/12/7	4/2/1	0.8788
Liver fibrosis (F1-2/F3-4)	38/6	2/5	0.0032
IL-28B genotype (TT/non-TT)	34/11	4/3	0.3696
HCV RNA (logIU/mL)	6.6 (5.0-7.4)	6.4 (6.3-6.7)	0.5689
Hemoglobin (g/dl)	13.9 (11.6-16.6)	13.4 (12.4-15.6)	0.3438
White blood cell count (× 109/L)	4.6 (3.0-7.4)	4.3 (3.9-6.7)	0.259
Platelets (× 109/L)	159 (82-268)	106 (76-158)	0.0036
Total bilirubin (mg/dl)	0.8 (0.3-1.5)	0.8 (0.5-1.1)	0.5385
Aspartate transaminase (IU/L)	37 (21-165)	72 (38-152)	0.0358
Alanine transaminase (IU/L)	43 (15-186)	109 (46-159)	0.0978
γglutamyltransferase (IU/L)	37 (11-441)	49 (31-139)	0.0928
αfetoprotein (ng/ml)	4.6 (1.6-76.9)	15.7 (5.3-55.1)	0.0221
Fatty liver (yes/no)	5/40	1/6	0.6955
Diabetes mellitus (yes/no)	6/39	2/5	0.2914
NS3/4A resistant variants (yes/no)	1/44	1/6	0.2533
Data are expressed as number or median (range).			

Table 2: Comparison of pre-treatment factors between patients with and without SVR.

On-treatment factors	SVR (n=45)	non-SVR (n=7)	P-value
HCV RNA at day1 (logIU/mL)	3.3 (1.9-4.5)	3.7 (2.5-4.4)	0.175
HCV RNA at day3	2.7 (1.2-3.8)	2.5 (1.7-3.5)	0.3987
HCV RNA at week 1	1.7 (0-2.9)	2.2 (1.2-2.8)	0.2483
HCV RNA at week 2	1.2 (0-2.1)	1.8 (1.2-2.9)	0.0147
Reduction of HCV RNA at day 1	3.2 (2.3-3.8)	2.7 (2.3-3.8)	0.0452
Reduction of HCV RNA at day 3	3.8 (2.5-4.6)	3.8 (3.1-4.6)	0.2698
Reduction of HCV RNA at week 1	4.6 (3.5-6.8)	4.3 (3.8-5.2)	0.2806
Reduction of HCV RNA at week 2	5.4 (4.3-7.1)	4.7 (3.4-5.2)	0.0251
Undetectable of HCV RNA at week 1 (yes/no)	4/41	0/7	0.9532
Undetectable of HCV RNA at week 2 (yes/no)	16/29	0/7	0.0852
Undetectable of HCV RNA at week 4 (yes/no)	39/6	3/4	0.0197
TVR/SMV adherence (%)	72 (17-100)	100 (45-100)	0.3264
RBV adherence (%)	81 (29-115)	63 (29-100)	0.4021

PEG-IFN adherence (%)	93 (30-117)	48 (39-95)	0.0113
Data are expressed as median (range).			

Table 3: Comparison of on-treatment factors between patients with and without SVR.

Factors	Univariate analysis	OR	Multivariate analysis	
	P-value		95%CI	P-value
Platelets (× 109/L)	0.0036	1.548	1.044-2.297	0.03
HCV RNA at week 2 (logIU/mL)	0.0147	0.15	0.030-0.746	0.02
OR-Odds Ratio; CI-Confidence Interval.				

Table 4: Multivariate analysis of factors associated with sustained virological response.

Discussion

This retrospective study was conducted to identify which virological factors earlier than RVR were associated with SVR. In multivariate analysis, baseline platelet count and HCV RNA at week 2 were independently associated with higher SVR rates after TVR/SMV-based triple therapy. Higher platelet count was reported to be associated with higher SVR rate after PEG-IFN plus RBV therapy [28] and after TVR-based triple therapy [29]. Reduction of HCV RNA at week 2 and HCV RNA level at week 2 were found to be correlated with a higher SVR rate after TVR-based triple therapy [21-23]. On the other hand, there have been no reports on whether HCV RNA dynamics occurring earlier than 4 weeks after the initiation of SMV-based triple therapy are associated with SVR. We showed here that as a substitute for RVR, the HCV RNA level (cut-off value, <1.2 logIU/mL) at week 2 is useful for SVR prediction after TVR/SMV-based triple therapy. Although platelet count has varied according to the degree of liver fibrosis, HCV RNA level has not varied. Therefore, HCV RNA level at week 2 might be more useful marker of prediction of SVR.

RVR has been found to be associated with SVR not only in the context of PEG-IFN/RBV therapy [16,17] but also with TVR/SMV-based triple therapy [10,13,18-20]. The present study extracted both RVR and HCV RNA load at week 2 as predictive factors for SVR in univariate analysis, but only the latter was extracted in multivariate analysis. It was reported that HCV RNA decay during antiviral treatment followed a biphasic profile, and protease inhibitor-based triple therapy was associated with a faster first and second phase compared to regimens not including a direct-acting antiviral [30]. The SVR rate after TVR/SMV-based triple therapy was shown to be higher than that after PEF-IFN/RBV therapy [5-15], and this augmented antiviral effect was due to the addition of protease inhibitors. Taken together, the direct effect of protein inhibitors, which promoted faster HCV clearance, might be represented by the HCV RNA load at week 2, and as such this factor may be a powerful predictor for SVR.

Compared with PEG-IFN/RBV therapy, protease inhibitor-based triple therapy can cause several severe adverse effects, including serious skin disorders and anemia in TVR-based triple therapy [5-9] and hyperbilirubinemia and photosensitivity reaction in SMV-based triple therapy [12,14]. Furthermore, serious adverse effects occurred with greater frequency in elderly and advanced fibrosis patients receiving TVR-based triple therapy [20,31]; the safety of SMV-based triple therapy in these patients has not been established. However, since these patients are at high risk of developing HCC, antiviral therapy should be initiated as soon as possible [32]. If treatment efficacy can be predicted in the early stages of therapy, unnecessary treatments and side effects might be avoided. Therefore, the early prediction of SVR will be especially useful for elderly and advanced fibrosis patients.

One limitation of the present study is the small number of patients. In order to establish the present results, further large scale prospective studies are necessary.

In conclusion, our analysis of viral dynamics within 2 weeks of therapy initiation demonstrated that the HCV RNA level at week 2 is the most useful predictor of SVR after TVR/SMV-based triple therapy in patients with genotype 1 HCV. The virological response within 2 weeks is a possible substitute for RVR in predicting SVR.

References

1. Hoofnagle JH (2002) Course and outcome of hepatitis C. Hepatology 36: S21-29.
2. Seeff LB (2002) Natural history of chronic hepatitis C. Hepatology 36: S35-46.
3. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, et al. (2002) Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 347: 975-982.
4. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, et al. (2001) Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 358: 958-965.
5. Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, et al. (2012) Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol 56: 78-84.
6. Hayashi N, Okanoue T, Tsubouchi H, Toyota J, Chayama K, et al. (2012) Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C. J Viral Hepat 19: e134-142.
7. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, et al. (2011) Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 364: 2405-2416.
8. Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, et al. (2011) Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med 365: 1014-1024.

9. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, et al. (2011) Telaprevir for retreatment of HCV infection. N Engl J Med 364: 2417-2428.

10. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, et al. (2014) Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 384: 403-413.

11. Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, et al. (2014) 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 384: 414-426.

12. Hayashi N, Izumi N, Kumada H, Okanoue T, Tsubouchi H, et al. (2014) Simeprevir with peginterferon/ribavirin for treatment-naive hepatitis C genotype 1 patients in Japan: CONCERTO-1, a phase III trial. J Hepatol 61: 219-227.

13. Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, et al. (2014) Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. Gastroenterology 146: 1669-1679.

14. Izumi N, Hayashi N, Kumada H, Okanoue T, Tsubouchi H, et al. (2014) Once-daily simeprevir with peginterferon and ribavirin for treatment-experienced HCV genotype 1-infected patients in Japan: the CONCERTO-2 and CONCERTO-3 studies. J Gastroenterol 49: 941-953.

15. Kumada H, Hayashi N, Izumi N, Okanoue T, Tsubouchi H, et al. (2014) Simeprevir (TMC435) once daily with peginterferon-alpha-2b and ribavirin in patients with genotype 1 hepatitis C virus infection: The Concerto-4 study. Hepatol Res 45:501-513.

16. Yu JW, Wang GQ, Sun LJ, Li XG, Li SC (2007) Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. J Gastroenterol Hepatol 22: 832-836.

17. Martinot-Peignoux M, Maylin S, Moucari R, Ripault MP, Boyer N, et al. (2009) Virological response at 4 weeks to predict outcome of hepatitis C treatment with pegylated interferon and ribavirin. Antivir Ther 14: 501-511.

18. Chayama K, Hayes CN, Abe H, Miki D, Ochi H, et al. (2011) IL28B but not ITPA polymorphism is predictive of response to pegylated interferon, ribavirin, and telaprevir triple therapy in patients with genotype 1 hepatitis C. J Infect Dis 204: 84-93.

19. Abe H, Tsubota A, Shimada N, Atsukawa M, Kato K, et al. (2014) Factors associated with sustained virological response in 24-week telaprevir-based triple therapy for chronic hepatitis C genotype 1b patients with the IL28B minor genotype. Hepatol Res 45: 387-396.

20. Ogawa E, Furusyo N, Nakamuta M, Kajiwara E, Nomura H, et al. (2013) Telaprevir-based triple therapy for chronic hepatitis C patients with advanced fibrosis: a prospective clinical study. Aliment Pharmacol Ther 38: 1076-1085.

21. Tamai H, Shimizu R, Shingaki N, Mori Y, Maeshima S, et al. (2014) Prediction of Sustained Virological Response to Telaprevir-Based Triple Therapy Using Viral Response within 2 Weeks 2014: 748935.

22. Cento V, Di Paolo D, Di Carlo D, Micheli V, Tontodonati M, et al. (2015) Hepatitis C virus RNA levels at week-2 of telaprevir/boceprevir administration are predictive of virological outcome. Dig Liver Dis 47: 157-163.

23. Bailly F, Virlogeux V, Dufour C, Pradat P, Hezode C, et al. (2015) Early virological assessment during telaprevir- or boceprevir-based triple therapy in hepatitis C cirrhotic patients who failed a previous interferon based regimen - The ANRS CO20-CUPIC study. Clin Res Hepatol Gastroenterol 39: 443-450.

24. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, et al. (2009) Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 41: 1105-1109.

25. Romano KP, Ali A, Royer WE, Schiffer CA (2010) Drug resistance against HCV NS3/4A inhibitors is defined by the balance of substrate recognition versus inhibitor binding. Proc Natl Acad Sci USA 107: 20986-20991.

26. Barbotte L, Ahmed-Belkacem A, Chevaliez S, Soulier A, Hezode C, et al. (2010) Characterization of V36C, a novel amino acid substitution conferring hepatitis C virus (HCV) resistance to telaprevir, a potent peptidomimetic inhibitor of HCV protease. Antimicrob Agents Chemother 54: 2681-2683.

27. Bedossa P, Poynard T (1996) An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 24: 289-293.

28. Kurosaki M, Sakamoto N, Iwasaki M, Sakamoto M, Suzuki Y, et al. (2011) Pretreatment prediction of response to peginterferon plus ribavirin therapy in genotype 1 chronic hepatitis C using data mining analysis. J Gastroenterol 46: 401-409.

29. Akuta N, Suzuki F, Hirakawa M, Kawamura Y, Yatsuji H, et al. (2012) Amino acid substitution in HCV core region and genetic variation near the IL28B gene affect viral dynamics during telaprevir, peginterferon and ribavirin treatment. Intervirology 55: 417-425.

30. Guedj J, Perelson AS (2011) Second-phase hepatitis C virus RNA decline during telaprevir-based therapy increases with drug effectiveness: implications for treatment duration. Hepatology 53: 1801-1808.

31. Colombo M, Fernandez I, Abdurakhmanov D, Ferreira PA, Strasser SI, et al. (2014) Safety and on-treatment efficacy of telaprevir: the early access programme for patients with advanced hepatitis C. Gut 63: 1150-1158.

32. Guidelines for the Management of Hepatitis C Virus Infection: First edition, May 2012, The Japan Society of Hepatology. Hepatol Res 43:1-34.