Original Article

The Predictive Value of On-treatment Virological Response for Sustained Virological Response in Chronic Hepatitis C Patients Receiving a Personalized Treatment Program

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Objective To investigate the effects of individualised treatment with peginterferon alpha-2a (40 kD) plus ribavirin in Chinese patients with CHC.

Methods Total of 297 consecutive Chinese patients were enrolled, including 250 naïve cases and 47 cases who were previously treated. Treatment duration was determined according to viral genotypes, prior treatment history and viral responses at week 4, 12 and 24.

Results Totally, 235 patients (79.1%) completed treatment and 186 (87.3%) achieved SVR. And 219 out of 289 (75.8%) patients achieved HCV RNA negative at week 4 (RVR) and 259 of 276 (93.8%) at week 12. Among the 164 patients with RVR who completed follow-up, 158 (96.3%) achieved SVR. Patients with RVR had lower baseline viral loads than patients without RVR ($P = 0.034$). The positive predictive value (PPV) of RVR for SVR was 90.7% (OR 2.10 vs. non-RVR, 95% CI: 0.50 - 8.7). Similar outcomes were observed among patients with HCV undetectable at week 12.

Conclusions Complete viral suppression by week 4 is associated with a high rate of treatment success in treatment naïve and experienced patients receiving individualized CHC therapy.

Key words: Chronic hepatitis C; Early viral kinetics; Pegylated interferon; Ribavirin; Sustained virological response; Tailored regimen

Infection with hepatitis C virus (HCV) was commonly associated with post-transfusion hepatitis before the introduction of sensitive and specific assays to screen for the virus in donated blood. Most patients with HCV develop a chronic infection with progressive liver injury that can eventually result in liver cirrhosis and hepatocellular carcinoma. Considerable progress has been made in the treatment of chronic hepatitis C (CHC), most recently with the introduction of pegylated interferon and ribavirin therapy.^{1,2} This combination is widely recognized as

the standard care for chronic hepatitis C.³ However, not all patients are cured after treatment with pegylated interferon and ribavirin. Sustained virological response (SVR) rates have been reported to range from 42% to 52% in patients infected with HCV genotype 1, 76% to 80% in patients infected with genotype 2 or 3 and 66% to 72% in patients infected with HCV genotype 4.⁴

The efficacy of combination antiviral therapy for chronic hepatitis C is influenced by many factors.^{1,2,5-15} Important patient-specific factors include age, gender, race, body weight, serum ALT quotient, liver fibrosis and co-infection with other viruses such as hepatitis B virus or human immunodeficiency virus. Recently, host genetic factors have also been identified as critical determinates of treatment outcome.¹³ Important virus-specific factors include HCV genotype and serum HCV RNA level. Finally, important treatment-related factors include the type of interferon, dose of ribavirin and

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the duration and adherence to treatment.^{4-6,14} Patients with high body weight, high viral load and genotype 1 HCV infection are usually called “difficult-to-treat”.¹⁶⁻¹⁹ Duration extend of treatment has been shown to increase SVR rates in “difficult-to-treat” patients with a slow virological response and in those who have not responded to previous treatment with the standard care.²⁰⁻²⁴

Despite the importance of patient- and virus-specific factors, the most important indicator of treatment success is a rapid, profound and sustained decrease in serum HCV RNA levels after the start of treatment.²⁵⁻²⁹ Patients with a rapid virological response (RVR), defined as undetectable HCV RNA (< 50 IU/ml) by week 4 of treatment, have the highest SVR rates.^{25,30} Those patients without an RVR who become HCV RNA negative by week 12 still have a high probability of achieving an SVR, albeit lower than that of those with an RVR. At the other extreme, patients with a null response, defined as persistently detectable HCV RNA in serum and an absolute decrease of $< 1 \log_{10}$, are considered to be non-responders to interferon-based therapy.^{25, 30-32}

The on-treatment virological response can thus be taken to predict the probability that a given patient will achieve an SVR if they remain on therapy. It can also be used to individualize the duration of treatment.^{21, 22, 26, 33, 34} SVR rates of 90% or higher can be obtained in patients with an RVR after treatment for a standard duration (48 weeks for genotype 1 or 4, 24 weeks for genotypes 2 or 3).³³⁻³⁶ Abbreviated regimens may be suitable for some of these patients.^{33, 37} In contrast, patients without an RVR may benefit from extension of the treatment duration.^{22, 34}

In this study, we conducted exclusively in China, treatment for patients with chronic hepatitis C was individualized on the basis of clinical characteristics and the on-treatment virological response. The aim was to investigate the usefulness of undetectable HCV RNA levels at week 4 (RVR) and 12 (cEVR) in tailoring the duration of treatment and predicting SVR in a population of patients with an ongoing need for dual therapy with pegylated interferon plus ribavirin.

PATIENTS AND METHODS

Patients

Consecutive patients with chronic hepatitis C who were admitted to hospital or treated as outpatients at Beijing Ditan Hospital, Capital Medical University

were eligible for the study. The present analysis is restricted to treatment of naïve patients infected with HCV genotype 1 or unknown genotype and assigned to a specified treatment duration and of all previously treated patients infected with any HCV genotypes.

The diagnosis of chronic hepatitis C was based on the detection of anti-HCV antibodies (anti-HCV) by a third generation microparticle chemiluminescence assay and HCV RNA by a reverse transcription polymerase chain reaction (RT-PCR) assay. In a subset of patients, HCV was genotyped by restriction fragment length polymorphism analysis of the 5'-noncoding region.⁴¹ Patients were required to have evidence of HCV infection for at least 6 months and were eligible regardless of whether they had normal or elevated serum ALT levels.

Patients were excluded if they had a haemoglobin level < 100 g/L; neutrophil count $< 1.5 \times 10^9$ /L; platelet count $< 50 \times 10^9$ /L; decompensated liver cirrhosis or liver disease other than that attributable to chronic hepatitis C; co-infected with hepatitis B virus or human immunodeficiency virus; or had an autoimmune disease, liver tumour, or severe cardiac diseases.

The study was approved by regional ethics committees according to the Declaration of Helsinki. All patients gave written informed consent before enrolment.

Treatment

All patients included in the analysis received peginterferon alpha-2a (40 kD) (Pegasys®; Roche, Basel, Switzerland) at a dose of 135 µg (if treatment-naïve and body weight < 60 kg) or 180 µg (if previously treated or body weight ≥ 60 kg) by subcutaneous injection once weekly. All patients received twice daily oral ribavirin at a target total daily dose of approximately $13 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$.

Among treatment-naïve patients (genotype 1 and unknown genotype), the duration of therapy was determined by the on-treatment virological response at week 4, 12 or 24. Patients with an RVR at week 4 (defined here as HCV RNA < 500 copies/ml) were assigned to complete a total of 48 weeks treatment. Patients without an RVR at week 4 (HCV RNA ≥ 500 copies/ml), but with undetectable HCV RNA at week 12 (cEVR) were assigned to continue treatment for a further 48 weeks (total duration of treatment as 60 weeks). Patients with detectable HCV RNA at week 4 and 12 (HCV RNA ≥ 500 copies/ml), but with undetectable HCV RNA at week 24, were assigned to complete a total of 72 weeks treatment. All previously

treated patients were assigned to complete 72 weeks treatment.

Dose adjustment

For patient who did not achieve an RVR at week 4, and provided they were not experiencing adverse events, the daily dosage of ribavirin was increased by approximately 200 mg, and for those who started treatment on a lower dosage, the dosage of peginterferon alpha-2a (40 kD) was increased from 135 µg/week to 180 µg/week. In the event of adverse events that could not be ameliorated with symptomatic treatment, the dose of peginterferon alpha-2a (40 kD) was reduced from 180 µg/week to 135 µg/week, and with ribavirin by approximately 200 mg/day decrease.

Outcomes

Quantitative HCV RNA detection was performed before treatment (week 0), at week 4, 12, 24 and at the end of treatment, and 24 weeks after completion of treatment through a commercially available real-time fluorescence quantitative PCR kit (with detection limit as 500 copies/ml, Piji Company, Shenzhen City, China) according to product instructions. The primary efficacy end-point was achievement of SVR defined as undetectable HCV RNA (< 500 copies/ml) at the end of a 24-week untreated follow-up period. The percentage of patients with undetectable HCV RNA (< 500 copies/ml) at week 4 (RVR), and 12 (cEVR) were secondary efficacy endpoints.

Haematological and biochemical tests were performed before treatment and every four weeks during treatment.

Adverse events were defined as any untoward medical event which in the opinion of the investigator was considered either possibly or probably related to study medication.

Statistical analysis

The association between undetectable HCV RNA levels at week 4 (RVR) and week 12 (cEVR) and achievement of an SVR was analysed. Differences in HCV RNA levels between patients with and without an RVR were analysed using Student's *t*-test.

Positive predictive value (PPV) was defined as the proportion of patients who achieved an on-treatment response (undetectable HCV RNA at week 4 or 12) and an SVR. Negative predictive value (NPV) was defined as the proportion of patients who did not achieve an on-treatment response (RVR or cEVR) and who did not

achieve an SVR.

RESULTS

A total of 297 Chinese patients were enrolled in the study between February 2004 and May 2007. The baseline characteristics are presented in Table 1. The patient population included 250 treatment-naïve and 47 previously treated patients, 157 men (52.9%) and 140 women (47.1%) .

A total of 235 of 297 (79.1%) patients completed treatment. 31 (10.4%) patients are still undergoing treatment, five (1.7%) patients discontinued treatment because of an adverse event while 23 (7.7%) withdrew prematurely and 14 (4.7%) completed treatment but was lost during follow-up.

Among treatment-naïve patients with either genotype 1 infection or those with an undetermined genotype, 69, 14 and 7 individuals were assigned to complete 48, 60 or 72 weeks of treatment, respectively. Among treatment naïve-patients with non-genotype 1 infection 20 and 3 patients were assigned to complete 24 or 48 weeks of treatment respectively. All previously treated patients were assigned to complete 72 weeks of treatment.

Virological response

Among the 213 patients completed the study, 186 (87.3%) achieved an SVR, 14 (6.6%) relapsed during untreated follow-up, three (1.4%) experienced virological breakthrough during treatment, 12 (5.6%) did not have a virological response during treatment, five (1.7%) patients discontinued treatment because of an adverse event while 23 (7.7%) withdrew prematurely and 14 (4.7%) completed treatment but was lost during follow-up.

The percentage of patients with undetectable HCV RNA at week 4 and 12 and those with an SVR by allocated treatment and prior treatment status were summarized in Table 2.

HCV RNA assays were performed for 288 patients at week 4, of whom 220 individuals (76.4%) had an RVR. HCV RNA of 2 individuals (1.9%) were detectable at week 12. Among the 68 patients without an RVR, 51 had undetectable HCV RNA levels at week 12.

Among genotype 1 infected patients, the RVR rate was 80.7% (46/57) which was lower, but not significantly lower ($\chi^2 = 0.884$, $P = 0.347$), than that in non-genotype 1 patients (88.9%, 24/27).

Table 1. Baseline characteristics of patients

	Treated with conventional interferon alpha (n = 19)		Treated with peginterferon alfa-2a (40 kD) (n = 297)		All patients (n = 297)
	Treatment-naïve (n = 16)	Previously treated (n = 3)	Treatment-naïve (n = 252)	Previously treated (n = 45)	
Chinese race [n (%)]	16 (100)	3 (100)	252 (100)	45 (100)	297 (100)
Male/female [n, male %]	9/7 (56)	3/0 (100)	131/121 (131)	25/20 (25)	156/141 (156)
Age [mean (range), years]	38.7 (10–67)	29.0 (26–45)	40.9 (11–77)	40.6 (16–76)	40.9 (11–76)
Body weight [mean (range), kg]	60.1 (45–80)	67.3 (62–75)	61.8 (23–94)	71.6 (55–100)	62.4 (23–100)
Body weight < 60 kg [n (%)]	5 (8.7)	0 (0)	38 (38)	2 (10)	45 (32.4)
HCV RNA level <1 × 10 ⁶ copies/ml [n (%)]	5 (31.3)	1 (33.3)	100 (39.7)	13 (28.9)	113 (38.0)
HCV RNA level >1 × 10 ⁶ copies/ml [n (%)]	11 (68.8)	2 (66.7)	152 (60.3)	32 (71.1)	184 (62.0)
HCV genotype 1 [n (%)]	4 (25)	2 (66.7)	40 (40)	11 (55)	57 (41.0)
HCV non-genotype 1 [n (%)]	2 (12.5)	0	21 (21)	4 (20)	27 (19.4)
HCV genotype not determined [n (%)]	10 (62.5)	1 (33.3)	39 (39)	5 (25)	55 (39.6)
Ribavirin dose, mg/day [n (%)]					
≥900	12 (75)	3 (100)	216 (85.7)	41 (91.1)	247 (83.2)
600 – 800	0	0	27 (10.7)	2 (4.4)	29 (9.8)
< 600	2 (12.5)	0	6 (2.4)	2 (4.5)	8 (2.7)
Missing	2 (12.5)	0	3 (1.2)	0 (0)	3 (4.3)

Table 2. Virological response rates of patients [n (%)]

	Treatment-naïve (n = 250)	Previously treated (n = 47)	All patients (n=297)
HCV RNA undetectable at week 4 (RVR)	189/242 (78.1)	31/47 (66.0)	221/289 (76.5)
HCV RNA undetectable at week 12	218/230 (94.8)	41/46 (89.1)	259/276 (93.8)
SVR in patients with an RVR	136/139 (97.8)	22/25 (88.0)	158/164 (96.3)
SVR in patients with undetectable HCV RNA at week 12	150/155 (96.8)	27/33 (81.8)	177/188 (94.1)

Out of 166 patients with an RVR who completed follow-up, 156 (93.8%) achieved an SVR, which was higher, but not significantly higher, than the 61.4% (27 of 44) SVR rate among patients without an RVR who completed follow-up (Fisher's exact test, $P = 0.384$, Figure 1). The PPV of an RVR was 90.7% (OR: 2.10 versus those not achieving an RVR, 95% CI: 0.50 to 8.7) for an SVR.

A total of 276 patients had an HCV RNA determination at week 12 of treatment, of whom 259 (93.8%) achieved undetectable HCV RNA levels.

Among patients infected with HCV genotype 1 and non-1, the percentages of patients with undetectable HCV RNA at week 12 were similar at 91.2% (52/57) and 96.3% (26/27), respectively ($\chi^2 = 6.0$, $P = 0.112$).

The baseline HCV RNA level was significantly

lower in patients with an RVR than without an RVR at week 4 ($5.88 \pm 1.25 \log_{10}$ copies/ml vs. $6.50 \pm 0.69 \log_{10}$ copies/ml; $t = 2.15$, $P = 0.034$). In contrast, there was no statistically significant difference between the baseline HCV RNA level in patients with and without undetectable HCV RNA levels at week 12 ($5.97 \pm 1.32 \log_{10}$ copies/ml versus $6.22 \pm 0.854 \log_{10}$ copies/ml, $t = 0.582$, $P = 0.562$).

Among patients with a week 12 HCV RNA determination who completed treatment and follow-up, the SVR rate was significantly higher in those with undetectable HCV RNA levels than those with detectable HCV RNA [90.8% (108/119) versus 55.6% (5/9), Fisher's exact test, $P = 0.011$, Figure 1]. The PPV of undetectable HCV RNA at week 12 was 90.8% (OR: 7.855 versus those with detectable HCV RNA, 95% CI:

Table 3. HCV RNA and virological response assays

	Treated with conventional interferon alpha (n=19)		Treated with peginterferon alpha-2a (40 kD) (n=120)		All patients (n=139)
	Treatment-naïve (n=16)	Previously treated (n=3)	Treatment-naïve (n=100)	Previously treated (n=20)	
All patients					
HCV RNA undetectable at week 4 (RVR)*	10/11 (90.9%)	1/2 (50.0%)	79/90 (87.8%)	13/20 (65.0%)	103/123 (83.7%)
HCV RNA undetectable at week 12*	15/15 (100%)	2/3 (66.7%)	90/95 (94.7%)	17/20 (85.0%)	124/133 (93.2%)
SVR in patients with an RVR	8/9 (88.9%)	1/1 (100%)	71/78 (91.0%)	8/9 (88.9%)	88/97 (90.7%)
SVR in patients with undetectable HCV RNA at week 12	12/13 (92.3%)	2/2 (100%)	82/91 (90.1%)	12/13 (92.3%)	108/119 (90.8%)
Genotype 1					
HCV RNA undetectable at week 4 (RVR)*	3/4 (75.0%)	1/2 (50.0%)	35/40 (87.5%)	7/11 (63.6%)	46/57 (80.7%)
HCV RNA undetectable at week 12*	4/4 (100%)	1/2 (50.0%)	38/40 (95.0%)	9/11 (81.8%)	52/57 (91.2%)
SVR in patients with an RVR	3/3 (100%)	0/1 (0.0%)	26/26 (100%)	7/7 (100%)	36/37 (97.3%)
SVR in patients with undetectable HCV RNA at week 12	3/3 (100%)	1/1 (100%)	32/33 (97.0%)	6/7 (85.7%)	42/44 (95.5%)
non-genotype 1					
HCV RNA undetectable at week 4 (RVR)*	1/2 (50.0%)	0/0 (%)	19/21 (90.5%)	4/4 (100%)	24/27 (88.9%)
HCV RNA undetectable at week 12*	2/2 (100%)	0/0 (%)	20/21 (95.2%)	4/4 (100%)	26/27 (96.3%)
SVR in patients with an RVR	1/1 (100%)	0/0 (%)	16/16 (100%)	3/3 (100%)	20/20 (100%)
SVR in patients with undetectable HCV RNA at week 12	2/2 (100%)	0/0 (%)	18/18 (100%)	3/3 (100%)	23/23 (100%)

Note: * Among patients with a week 4 or 12 HCV RNA test result.

Figure 1. SVR rates in patients with and without undetectable HCV RNA at week 4 (RVR) or week 12 who completed treatment and follow-up.

Notes: 90.7% achieved an SVR with an RVR, 82.4% achieved an SVR without an RVR, $P = 0.384$; 90.8% achieved an SVR with undetectable HCV RNA levels at week 12, 55.6% achieved an SVR without undetectable HCV RNA levels at week 12, $P = 0.011$.

1.84 to 33.6) for SVR.

The rate of patients with undetectable HCV RNA at week 4 (RVR) and 12 according to assigned treatment was shown in Figure 2.

HCV RNA data at week 4 and 12 were available for 44 of the 45 treatment-experienced patients. When retreated with peginterferon alpha-2a (40 kD), 30 of

these 44 individuals (71.4%) achieved an RVR, which was significantly lower than that in treatment-naïve patients (78.3%, 191/244, $\chi^2 = 4.651$, $P = 0.031$, Table 3). Total of 39 individuals (88.6%) had undetectable HCV RNA levels at week 12, which has no significantly difference with that in treatment-naïve patients (92.8%, 232/250, $\chi^2 = 1.99$, $P = 0.158$, Figure 3).

Figure 2. Patients with undetectable HCV RNA at week 4 (RVR) and week 12 according to assigned treatment.

There was no statistically significant difference in the rates of RVR between patients assigned to peginterferon alfa-2a at a dosage of 135 mg/week (84.2%) or 180 mg/week (83.3%), or conventional interferon (84.6%). Patients had undetectable HCV RNA at week 12 with no statistically significant difference between patients assigned to peginterferon alfa-2a at a dosage of 135 mg/week (95.0%) or 180 mg/week (92.0%), or conventional interferon (94.4%).

Figure 3. Patients with undetectable HCV RNA at week 4 (RVR) and week 12 according to prior treatment status.

The RVR rate in treatment-naïve patients was significantly higher than in previously treated patients (87.8% versus 65%, respectively, $P=0.031$). Patients with undetectable HCV RNA levels at week 12 in treatment-naïve patients was higher than in previously treated patients (94.7% versus 85%, respectively, $P=0.158$).

DISCUSSION

When used to treat chronic hepatitis C, the combination of interferon and ribavirin has direct antiviral effects and indirect immunomodulatory effects. The direct antiviral effects after interferon binds to its receptors on the surface of liver cells and induces expression of antiviral proteins within cells. These proteins degrade viral nucleic acid and inhibit virus replication.^{39,40} The indirect immunomodulatory effects result in establishment of virus-specific cellular immunity that leads to clearance of virus infected cells.⁴¹⁻⁴³

In clinical practice, effective antiviral activity

manifests as a rapid decline in HCV RNA levels after the start of interferon-based treatment and the absence of a relapse after the end of treatment. The currently accepted definition of a successful treatment outcome after interferon-based treatment for chronic hepatitis C is SVR, defined as undetectable HCV RNA 24 weeks after the completion of therapy.³ An SVR results from simultaneous achievement of the direct antiviral and indirect virus-specific cellular immune effects of interferon. Without direct antiviral activity, replication of the virus and infection of hepatocytes continues, the virus remains detectable in serum and injury to liver tissue persists. Without virus-specific immune effects,

infected hepatocytes cannot be cleared efficiently which eventually lead to persistence of virus or relapse after the end of treatment.

SVR is clinically relevant because liver damage and fibrosis can improve in patients with an SVR, and the rate of relapse is only 2% to 4% when determined 5 to 10 years after completing treatment with conventional interferon,⁴⁴ and is less than 1% when determined up to 5 years after completing treatment with peginterferon.⁴⁵ The incidence of hepatocellular carcinoma is also reduced in patients who achieve an SVR, but not in patients who remain HCV RNA positive during treatment, even when treated for as long as 4 years.^{46, 47} Therefore, SVR should remain the goal of treatment for all patients with chronic hepatitis C.

Predicting which patients will achieve an SVR is an important focus of clinical research. During interferon-based treatment, the decline in HCV RNA is typically described as involving two phases. The first phase occurs during the first 24 to 48 hours after the initiation of treatment and reflects inhibition of viral replication and clearance of free virus particles from serum. The decline in HCV RNA levels during the second slower phase is log linear and is thought to be associated with the clearance of infected hepatocytes. Although the overall decline in virus over both phases is associated with a response, the decline during the second phase, in particular, is significantly correlated with achievement of SVR.⁴⁸⁻⁵¹

In practice, many studies have focused on the predictive value of an RVR and early virological response (EVR) for SVR and how long treatment should continue after viral clearance. Reau and colleagues retrospectively studied the predictive value of categorical virological responses at week 4 for SVR in 160 patients treated with peginterferon plus ribavirin.³² The authors classified week 4 response into mutually exclusive categories of virological decline including early null-response (eNR) which was defined as patients achieving $< 1 \log_{10}$ copies/ml at week 4. Among those who achieved an eNR, only 8% patients achieved SVR and the NPV for SVR was 93% (95% CI: 78% to 99%) (OR: 19.45, 95% CI: 7.85 - 48.21; $P < 0.0001$).⁵² In contrast, nearly 90% patients with RVR achieved an SVR after completing a standard course of treatment (24 weeks for genotypes 2/3 and 48 weeks for genotype 1).^{24,32,35} The accuracy of RVR for prediction of SVR was typically higher than that of EVR, including sensitivity, specificity and PPV.⁵³ Moreover, a high proportion of patients with an RVR achieve SVR, regardless of HCV genotype, baseline

viral load, histological diagnosis, race, and HIV infection status.^{25, 54-56}

Poordad and colleagues conducted a meta-analysis of data from 1 200 patients treated with peginterferon alpha-2b/ribavirin in six studies.⁵⁷ The results showed that, in patients with an RVR, the PPV for an SVR ranged from 75% to 90% and the NPV ranged from 41% to 79%.⁵⁷ In contrast, 24 weeks of treatment produced low SVR rates in genotype 2 and 3 patients without an RVR, even if they had a virological response at week 12.⁵⁸ These data demonstrated that achieving an RVR was the first and most important step in achieving an SVR and, for patients who failed to achieve an RVR, the duration of treatment may need to be extended to increase the probability of achieving an SVR.

In present study, 84% patients with HCV RNA assay results at week 4 achieved an RVR, which was generally higher than that reported in other studies.^{22,29,55,59-63} The reason for the high RVR rate in this study may be the individualization of the dose of peginterferon and ribavirin. For example, 78% patients received ribavirin dosages greater than 900 mg/day and up to 1 500 mg/day. The use of higher doses of ribavirin played an important role in achieving an RVR and higher weight-based doses of ribavirin have previously been reported to improve SVR rates.^{5,64,65} However, it should be noted that there was no statistically significant difference in the rates of RVR between patients assigned to peginterferon alpha-2a (40 kD) at a dosage of 135 μ g/week (84%) or 180 μ g/week (83%), or conventional interferon alpha (85%).

Herman and colleagues identified a third phase of HCV RNA decline that became evident between day 7 and 28 of treatment with peginterferon alpha-2a (40 kD) plus ribavirin in a viral kinetic study.⁶⁶ The analysis of factors associated with an RVR showed that the baseline viral load in patients with an RVR was lower than that in patients without an RVR. This finding is consistent with the study by Jensen et al,⁵⁵ in which low viral load was associated with a higher probability of an RVR in treatment-naïve HCV genotype 1 patients treated with peginterferon alpha-2a (40 kD) plus ribavirin.

In the present study, the RVR rate in treatment-naïve patients was significantly higher than that in previously treated patients (88% versus 65%, respectively, $P = 0.031$). Based on this result we recommend that RVR be determined in patients being retreated and that the duration of treatment adjusted in those without an RVR.

The virological response at week 12 of treatment is also important. The PPV of an EVR for SVR has been reported to range from 65% to 86% and the NPV from 98% to 100%.^{31, 57} In our study, 93% of patients had undetectable HCV RNA at week 12 with no statistically significant difference between patients assigned to treatment with peginterferon alfa-2a (40 kD) at a dosage of 135 µg/week (95.0%) or 180 µg/week (92.0%), or conventional interferon alfa (94.4%). In treatment-naïve patients treated with peginterferon alpha-2a (40 kD), 95% of patients had undetectable HCV RNA at week 12, which was higher than in previously treated patients (85%).

Among 97 patients with an RVR who completed treatment and follow-up, 88 (90.7%) achieved an SVR, which was higher but not significantly higher than in patients without an RVR, who completed treatment and follow-up (82.4%). The reason for the lack of statistical significance between these two groups is likely attributable, in part, to the small number of patients and possibly to timely dosage adjustments in patients without an RVR.

However, there was a statistically significant difference between SVR rates in patients with undetectable HCV RNA levels at week 12 who finished treatment and follow-up (90.8%) and those with detectable HCV RNA at week 12 who completed treatment and follow-up (55.6%). The PPV of undetectable HCV RNA at week 4 (RVR) and week 12 was similar in this study.

Previous studies have reported high SVR rates in Chinese patients with chronic hepatitis C and genotype 1 infection (range 42% - 80%).^{4, 26} In addition, Missiha and colleagues reported a significantly higher SVR rate in Asian patients (65%) than in Caucasian patients (45%) in a retrospective analysis of data from a study in which patients were treated with peginterferon alpha-2a 180 µg/week plus ribavirin 800 mg/day.⁶⁷ Multiple logistic regression analysis identified Asian race as an independent predictor of SVR (OR 2.22, 95% CI: 1.11 - 4.46).⁶⁷

Up to 90% patients in this study obtained an SVR, in part, because of the ribavirin dosing regimen employed. Higher ribavirin doses are associated with lower rates of relapse. Additionally, genotype 1 patients with an RVR were treated for 48 weeks, those who did not become HCV RNA negative until week 12 continued treatment for an additional 48 weeks, and those that did not become HCV RNA negative until week 24 (and previously treated patients) received an extended 72-week regimen. Non-genotype 1 patients

with an RVR were treated for 24 weeks and those with detectable HCV RNA at week 4 (no RVR) but undetectable HCV RNA levels at week 12 were treated for 48 weeks. In the REPEAT study, which enrolled only patients who failed to respond to a previous course of peginterferon alpha-2b plus ribavirin, extension of re-treatment with peginterferon alpha-2a to 72 weeks was significantly more effective than a standard 48 week regimen, but the use of a 12-week fixed dose induction regimen of peginterferon alpha-2a (360 µg/week for 12 weeks) did not significantly increase SVR rates.²⁴

Based on an analysis by Drusano and Preston in genotype 1 patients treated with peginterferon alpha-2b plus ribavirin, it was concluded that in order to maximise the chances of achieving an SVR, HCV RNA replication must be suppressed for a particular length of time after achievement of an HCV RNA-negative state.⁶⁸ The design of the current study adopted this strategy and likely increased the overall rate of SVR compared to a fixed treatment duration.

CONCLUSIONS

The results of this study show that undetectable HCV RNA levels at week 4 (RVR) and week 12 are important and useful predictors of SVR in patients receiving interferon-based treatment for chronic hepatitis C.

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ABBREVIATIONS

cEVR = complete early virological response; EVR = early virological response; HCV = hepatitis C virus; NPV = negative predictive value; PPV = positive predictive value; RVR = rapid virological response; SVR = sustained virological response

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