

Rapid Virological Response and Treatment Duration for Chronic Hepatitis C Genotype 1 Patients: A Randomized Trial

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Recommended treatment for hepatitis C virus genotype 1 (HCV-1) patients is peginterferon plus ribavirin for 48 weeks. We assessed whether treatment duration of 24 weeks is as effective as standard treatment in HCV-1 patients with a rapid virological response (RVR; seronegative for hepatitis C virus [HCV] RNA at 4 weeks). Two hundred HCV-1 patients were randomized (1:1) to either 24 or 48 weeks of peginterferon-alpha-2a (180 µg/week) and ribavirin (1000-1200 mg/day) with a 24-week follow-up. The primary endpoint was a sustained virological response (SVR; seronegative for HCV RNA at 24-week follow-up). Overall, the 48-week arm had a significantly higher SVR rate (79%) than the 24-week arm (59%, $P = 0.002$). For 87 (43.5%) patients with an RVR, the 24-week arm had a lower SVR rate [88.9%; 95% confidence interval (CI): 80%-98%] than the 48-week arm (100%, $P = 0.056$). For 52 patients with low baseline viremia (<400,000 IU/mL) and an RVR, the 24-week arm had rates (CI) of relapse and SVR of 3.6% (-3%-11%) and 96.4% (89%-103%), respectively, which were comparable to those of the 48-week arm (0% and 100%) with difference (CI) of 3.6% (-7.2%-6.6%) and -3.6% (-14.3% to -0.6%), respectively. Multivariate analysis in all patients showed that RVR was the strongest independent factor associated with an SVR, followed by treatment duration, mean weight-based exposure of ribavirin, and baseline viral load. **Conclusion: HCV-1 patients derive a significantly better SVR from 48 weeks versus 24 weeks of peginterferon/ribavirin even if they attain an RVR. Both 24 and 48 weeks of therapy can achieve high SVR rates (>96%) in HCV-1 patients with low viral loads and an RVR. (HEPATOLOGY 2008;47:1884-1893.)**

Abbreviations: CI, 95% confidence interval; EVR, early virological response; HCV, hepatitis C virus; HCV-1, hepatitis C virus genotype 1; HVL, higher viral load; LVL, lower viral load; PCR, polymerase chain reaction; RVR, rapid virological response; SVR, sustained virological response.

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Hepatitis C virus (HCV) genotype plays an important role in the response to antiviral treatment.^{1,2} HCV genotype 1 (HCV-1) is more resistant to interferon-based treatment compared with HCV-2/3.³ Peginterferon/ribavirin combination treatment has been recommended for all HCV-infected patients; however, the treatment duration varies depending on the HCV genotype. For HCV-1 patients, the recommended treatment duration is 48 weeks, whereas for HCV-2/3 patients the recommended treatment duration is 24 weeks.^{4,5} Nevertheless, up to 49% of HCV-1 patients could achieve a sustained virological response (SVR) with 24 weeks of peginterferon/ribavirin.^{6,7} Because side effects of anti-HCV treatment are common and sometimes serious, an increase in treatment duration may lead to premature termination of treatment in a significant number of patients.^{8,9} Thus, to reduce the treatment cost and the incidence of adverse events, it is desirable to tailor the treatment regimen to a shorter duration while not compromising efficacy.

A rapid virological response (RVR) at 4 weeks has been the single best predictor of an SVR for anti-HCV treatment.¹⁰⁻¹⁴ Although three previous studies demonstrated that a shorter duration of peginterferon/ribavirin over 12 weeks to 16 weeks is as effective as a 24-week regimen for HCV-2/3 patients with an RVR,¹³⁻¹⁶ a recent large trial showed that 24 weeks was superior to 16 weeks in all HCV-2/3 patients, including those with an RVR.¹⁷ These findings call into question whether shorter treatment duration can yield high SVR rates for HCV-1 patients with an RVR. A retrospective analysis observed that, among RVR HCV-1 patients, the SVR rates were comparable between 24-week and 48-week peginterferon/ribavirin.¹¹ Another single-arm, historical control trial for HCV-1 demonstrated that 24-week and 48-week treatments had similar SVR rates for RVR patients with low viremia.¹⁸ Recently, an Italian group showed that individualized treatment according to on-treatment virological response ensures SVR rates similar to standard 48-week treatment duration for HCV-1 patients.¹⁹ Nevertheless, racial factors have been independently associated with treatment outcome for chronic hepatitis C.²⁰ The current randomized, controlled study is the first study in Asia to report the role of an RVR as a guide for determining treatment duration for HCV-1 patients.

In this study, we conducted a prospective, randomized, active-controlled study to determine the role of RVR on the response to 24 weeks or 48 weeks of peginterferon/ribavirin for HCV-1 patients. The primary aim of the current study was to evaluate whether 24 weeks of peginterferon/ribavirin is sufficient to achieve an SVR rate comparable to that of the standard 48-week regimen in HCV-1 patients achieving an RVR. The secondary aim was to investigate the factors associated with RVR and SVR among patients receiving 24-week or 48-week treatment.

Patients and Methods

Selection of Patients. Eligible subjects were previously untreated Taiwanese patients with chronic hepatitis C, aged 18 to 65 years, who (1) were seropositive for HCV antibodies (third-generation, enzyme immunoassay; Abbott Laboratories, North Chicago, IL) and for HCV RNA by a qualitative polymerase chain reaction (PCR) assay (Cobas Amplicor Hepatitis C Virus Test, version 2.0; Roche Diagnostics, Branchburg, NJ; detection limit: 50 IU/mL); (2) had undergone a liver biopsy that was consistent with chronic hepatitis within 1 year before entry; (3) displayed an elevated serum alanine aminotransferase level for at least two measurements within 6 months preceding the trial entry; and (4) had a genotype

1 infection. Other eligibility criteria included neutrophil count greater than 1500 mm^{-3} , platelet count greater than $9 \times 10^4 \text{ mm}^{-3}$, hemoglobin level greater than 12 g/dL for men and greater than 11 g/dL for women, serum creatinine level less than 1.5 mg/dL, no pregnancy or lactation, and the use of a reliable method of contraception.

Patients with HCV genotype infections other than HCV-1, hepatitis B surface antigen, human immunodeficiency virus infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson disease, alpha₁-antitrypsin deficiency, decompensated cirrhosis, overt hepatic failure, a current or history of alcohol abuse (≥ 20 g daily), psychiatric condition, previous liver transplantation, or with evidence of hepatocellular carcinoma were excluded from the study.

Study Design. The current study was an investigator-initiated study. This randomized, open-label, active-controlled trial was carried out in one medical center and three regional core hospitals in Taiwan from April 2005 to May 2007. The study was approved by the ethics committees at the participating hospitals and carried out according to the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients gave written informed consent before enrollment.

A total of 200 protocol-eligible subjects were assigned randomly by computer coding with a 1:1 randomization ratio (Supplemental Fig. 1). The randomization sequence was centrally accessed through telephone or direct office visit. The details of the series were contained in a set of sealed envelopes and unknown to any of the investigators who enrolled study subjects. Subjects were treated with peginterferon- α -2a (PEGASYS, Roche, Basel, Switzerland; 180 $\mu\text{g}/\text{week}$ subcutaneously) plus oral ribavirin (1000 mg/day for body weight ≤ 75 kg and 1200 mg/day for body weight >75 kg) in two divided doses for either 24 weeks ($n = 100$) or 48 weeks ($n = 100$), with a 24-week follow-up period. Subjects had biweekly outpatient visits during the first month and monthly visits during the rest of the treatment period as well as during the 24-week follow-up. At each visit, subjects underwent a physical examination, and adverse events were recorded. Biochemical and hematological testing was done by commercial assays. HCV genotypes were determined by the method described by Okamoto et al.²¹ Serum HCV RNA at baseline, treatment weeks 4 and 12, the end of treatment, and 24 weeks after therapy were determined by qualitative PCR. Serum HCV RNA levels at baseline and week 12 of treatment were measured using the branched DNA assay (Versant HCV RNA 3.0, Bayer, Tarrytown, NJ; quantification limit: 615 IU/mL). Liver histology was graded and staged according to the scoring system described by

Table 1. Basic Demographic, Virological, and Clinical Features of the Patients

	24-Week Group	48-Week Group	P Value
Number	100	100	
Age, years	49.7 ± 11.6	49.1 ± 12	0.729
Male sex, n	57 (57%)	58 (58%)	0.886
Body weight, kg	65.5 ± 10.0	67.5 ± 15.8	0.299
Aspartate aminotransferase, IU/L	102 ± 52	90 ± 61	0.121
Alanine aminotransferase, IU/L	156 ± 84	137 ± 92	0.145
Liver histopathology			
Necroinflammatory activity	4.82 ± 2.55	4.41 ± 2.29	0.241
Fibrosis, n			0.306
F 0-2	75 (75%)	81 (81%)	
F 3-4	25 (25%)	19 (19%)	
Baseline HCV viral load, log IU/mL*	5.43 ± 1.00	5.66 ± 0.95	0.104
Baseline lower HCV viral load, <400,000 IU/mL, n	55 (55%)	56 (56%)	

NOTE. Values are means ± SD.

*HCV indicates, hepatitis C virus.

Knodell and Scheuer²² by a single pathologist who was blinded to the treatment of each patient.

Dose Modifications. Adverse events were graded as mild, moderate, severe, or potentially life-threatening. The dose modification of peginterferon and ribavirin was according to the strategy as described previously,¹⁴ except that dose reduction of ribavirin was a 200-mg stepwise decrease to enhance the adherence.

Assessment of Efficacy. The primary endpoint of this study was to assess SVR, which was defined as HCV RNA PCR-seronegative by the end-of-treatment and throughout the follow-up period. The others were classified as nonresponders. RVR was defined by PCR-negative serum HCV RNA at 4 weeks of therapy. Early virological response (EVR) was defined as PCR-negative or at least a 2-log₁₀ decline from baseline of serum HCV RNA at 12 weeks of treatment. End-of-treatment virological response was defined as PCR-negative serum HCV RNA at the end of treatment. Relapse was defined as HCV RNA reappearance during the follow-up period in patients who achieved an end-of-treatment virological response.

Statistical Analyses. Evaluation of efficacy of antiviral treatment was based on an intention-to-treat analysis. All patients receiving one treatment dose of peginterferon or ribavirin were analyzed. Anticipating a 10% dropout rate, the study was designed to detect a difference of 12% with 80% power or more. SVR and the associated 95% confidence interval (CI) for the differences were estimated. Frequency was compared between groups using the chi-square test, with the Yates correction, or Fisher's exact test. Group means (presented as mean ± standard deviation) were compared using analysis of variance and Student *t* test, or the nonparametric Mann-Whitney test when appropriate. Serum HCV RNA levels were expressed after logarithmic transformation of original values. The area under the curve was compared using

receiver operating characteristics analysis. An attempt was made to derive an optimal clinical cutoff of baseline HCV viral load that would best predict the RVR. The cutoff point was determined by choosing the point on the receiver operating characteristics curve with the closest distance to the point (0,1). Stepwise logistical regression was used to analyze which variables had a better predictive value for RVR and SVR. The procedures were performed using the SPSS 12.0 statistical package (SPSS, Chicago, IL). All statistical analyses were based on two-sided hypothesis tests with a significance level of *P* < 0.05.

Results

Patient Profile. Of the 200 patients randomized, 199 completed the study (Supplemental Fig. 1). Patients in the two groups were well matched for baseline characteristics (Table 1). All patients were infected with HCV-1b, except one with HCV-1a. Early discontinuation of treatment was significantly higher in the 48-week group than in the 24-week group (10% versus 3%, *P* = 0.045). One patient in the 48-week group was lost to follow-up 2 months after cessation of treatment and was classified as a nonresponder for final analysis.

Virological Responses. The rates (CIs) of RVR, EVR, and end-of-treatment virological response in the 24-week group were 45% (35%-55%), 95.9% (92%-100%), and 93% (88%-98%), respectively, which were comparable to the rates of 42% (32%-52%), 93% (88%-98%), and 90% (84%-96%) in the 48-week group. The relapse rate (CI) in the 24-week group was 36.6% (27%-47%), which was significantly higher than in the 48-week group (12.2%; CI: 5%-19%; *P* < 0.0001). The SVR rate (CI) was 59% (49%-69%) in the 24-week group, which was significantly lower than in the 48-week group (79%; CI: 71%-87%; *P* = 0.002).

Table 2. The Rates of End-of-Treatment Virological Response, Relapse, and Sustained Virological Response According to On-Treatment Virological Response and Regimen

	EOTVR				Relapsed				SVR			
	24-Week Group		48-Week Group		24-Week Group		48-Week Group		24-Week Group		48-Week Group	
	n/N	% (CI)	n/N	% (CI)	n/N	% (CI)	n/N	% (CI)	n/N	% (CI)	n/N	% (CI)
All patients	93/100	93 (0.88-0.98)	90/100	90 (0.84-0.96)	34/93	36.6 (0.27-0.47)*	11/90	12.2 (0.05-0.19)*	59/100	59 (0.49-0.69)†	79/100	79 (0.71-0.87)‡
RVR (+)	45/45	100	42/42	100	5/45	11.1 (0.02-0.2)†	0/42	0†	40/45	88.9 (0.8-0.98)†	42/42	100*
RVR (-)	48/55	87.3 (0.78-0.96)	48/58	82.8 (0.73-0.93)	29/48	60.4 (0.46-0.74)‡	11/48	22.9 (0.11-0.35)‡	19/55	34.5 (0.22-0.47)*	37/58	63.8 (0.51-0.76)*
EVR (+)	90/94	95.7 (0.92-1)	86/93	92.5 (0.87-0.98)	32/90	35.6 (0.26-0.46)§	7/86	8.1 (0.02-0.14)§	58/94	61.7 (0.52-0.72)**	79/93	84.9 (0.78-0.92)**
EVR (-)	2/4	50 (-0.07 to 1.07)	4/7	57.1 (0.18-0.97)	2/2	100	4/4	100	0/4	0	0/7	0

Statistical significance: *, ‡, §, and **, $P < 0.0001$; †, ¶, #, $P = 0.056$; ‡, #, $P = 0.002$.

CI, 95% confidence interval; EOTVR, end-of-treatment virological response; EVR, early virological response at week 12; RVR, rapid virological response at week 4; SVR, sustained virological response.

The relationship between on-treatment virological responses and SVR is shown in Table 2. Among patients with an RVR, the relapse rate in the 24-week group was higher than that in the 48-week group ($P = 0.056$; difference: 11.1%; CI: -0.4%-18%), whereas the SVR rate in the 24-week group was lower than that in the 48-week group with ($P = 0.056$; difference: 11.1%; CI: -22.6%-4.2%). Among patients without an RVR, the relapse rate in the 24-week group was significantly higher than that in the 48-week group ($P < 0.0001$; difference: 37.5%; CI: 17.2%-53.7%), whereas the SVR rate in the 24-week group was significantly lower than that in the 48-week group ($P = 0.002$; difference: 29.2%; CI: -48.7% to -13.4%).

Among patients without an EVR at week 12, the relapse rate was significantly higher and the SVR rate significantly lower in the 24-week group than in the 48-week group (both $P < 0.0001$). All patients without an EVR relapsed; none achieved an SVR.

Factors Associated with RVR, SVR, and Relapse.

Among all patients, factors associated with RVR were

analyzed. They included demographic features, liver enzyme and histopathology, baseline viral load, and received dose of ribavirin during the first 4 weeks (Table 3). Based on receiver operating characteristics analyses, 400,000 IU/mL was optimal for use as the cutoff point of baseline viral load to best discriminate those patients who might achieve an RVR. Lower baseline viral load (<400,000 IU/mL) was the only significant factor associated with RVR, with an odds ratio (CI) of 3.052 (1.706-5.458).

Factors predictive of SVR were analyzed in both groups. They included demographic features, liver enzyme and histopathology, viral load, 80/80/80 adherence, and RVR (Table 4). In the 24-week group, RVR, lower viremia (<400,000 IU/mL), younger age, and 80/80/80 adherence were associated with a higher SVR rate. Independent predictors of SVR in the 24-week group were RVR and lower viremia with odds ratios (CI) of 10.84 (3.189-36.82) and 3.087 (1.031-9.239), respectively. In the 48-week group, RVR was the only independent predictor of SVR, with an odds ratio of infinity.

Ribavirin Dose by Body Weight and SVR. The

Table 3. Factors Associated With Rapid Virological Response

	RVR (-)	RVR (+)	P Value
Number, n	113 (56.5%)	87 (43.5%)	
Age, years	50.7 ± 11.0	47.8 ± 12.6	0.086
Male sex, n	60 (53.1%)	55 (63.2%)	0.151
Body weight, kg	66.0 ± 10.1	67.1 ± 16.5	0.092
Alanine aminotransferase, IU/L	140 ± 90	154 ± 87	0.279
Liver histopathology			
Necroinflammatory activity	4.78 ± 2.41	4.41 ± 2.44	0.295
Fibrosis score, n			0.280
F 0-2	85 (75.2%)	71 (81.6%)	
F 3-4	28 (24.8%)	16 (18.4%)	
Baseline HCV RNA level, log IU/mL*	5.86 ± 0.72	5.13 ± 1.11	<0.0001†
Baseline HCV RNA level, <400,000 IU/mL, n	37 (32.7%)	52 (59.8%)	<0.0001†
Mean dose of ribavirin by body weight during 1 st 4 weeks of treatment, mg/kg/day	17.4 ± 2.66	17.3 ± 3.03	0.685

RVR indicates rapid virological response, which is defined as HCV RNA PCR-seronegative (<50 IU/mL) at week 4 of treatment. Values are means ± SD.

*HCV, hepatitis C virus.

†Statistically significant.

Table 4. Factors Associated With Sustained Virological Response

	24-Week Treatment Group			48-Week Treatment Group		
	Sustained Virological Response, n = 100		P Value	Sustained Virological Response, n = 100		P Value
	(-)	(+)		(-)	(+)	
No. of patients	41 (41%)	59 (59%)		21 (21%)	79 (79%)	
Age, years	52.4 ± 10.9	47.9 ± 11.8	0.055	51.4 ± 9.5	48.5 ± 12.5	0.337
Male sex, n	23 (56.1%)	34 (57.6%)	0.879	12 (57.1%)	46 (58.2%)	0.929
Body weight, kg	67.6 ± 11.0	64.1 ± 9.0	0.090	66.7 ± 10.3	67.7 ± 17.1	0.807
Alanine aminotransferase, IU/L	143 ± 71	164 ± 91	0.204	127 ± 74	140 ± 97	0.565
Liver histopathology						
Necroinflammatory activity	5.18 ± 2.65	4.58 ± 2.47	0.259	4.67 ± 2.50	4.34 ± 2.24	0.564
Fibrosis score, n			0.078			0.213
F 0-2	27 (65.9%)	48 (81.4%)		19 (90.5%)	62 (78.5%)	
F 3-4	14 (34.1%)	11 (18.6%)		2 (9.5%)	17 (21.5%)	
Baseline HCV RNA level, log IU/ mL†	5.92 ± 0.60	5.09 ± 1.08	<0.0001*	5.93 ± 0.86	5.58 ± 0.96	0.132
<400,000 IU/mL, n	11 (26.8%)	34 (57.6%)	0.002*	8 (38.1%)	36 (45.6%)	0.540
≥400,000 IU/mL, n	30 (73.2%)	25 (42.4%)		13 (61.9%)	43 (54.4%)	
80/80/80 adherence, n‡	32 (78%)	54 (91.5%)	0.056	16 (76.2%)	68 (86.1%)	0.317
RVR, n§			<0.0001*			<0.0001*
No	36 (87.8%)	19 (32.2%)		21 (100%)	37 (46.8%)	
Yes	5 (12.2%)	40 (67.8%)		0	42 (53.2%)	

Values are means ± SD.

*Statistically significant.

†HCV, hepatitis C virus.

‡Patients who had received ≥80% of expected peginterferon and ribavirin dose and completed at least 80% of expected duration.

§RVR, rapid virological response.

influence on SVR of mean ribavirin dose by body weight throughout the treatment period was analyzed. We stratified patients into three groups based on the received dose of ribavirin, lower (<13.3 mg/kg/day), moderate (13.3-15.2 mg/kg/day), and higher (>15.2 mg/kg/day), according to a previous study.²³ In the 24-week group, patients receiving a higher ribavirin dose had a significantly lower relapse rate ($P = 0.014$) and higher SVR rate ($P = 0.021$) than those receiving a lower or moderate ribavirin dose (Fig. 1). In the 48-week group, patients receiving a moderate or higher ribavirin dose had a significantly lower relapse rate ($P = 0.013$) and higher SVR rate ($P = 0.064$) than those receiving a lower ribavirin dose.

Factors Associated with SVR in All Patients. The independent predictive value of age, sex, body weight, liver enzyme and histopathology, baseline viral load, treatment adherence, received dose of ribavirin, and RVR for the achievement of an SVR was determined by using stepwise logistic regression analysis for all 200 patients. The most important independent predictors for SVR were RVR, followed by treatment duration, mean dose of ribavirin by body weight, and baseline viral load (Table 5).

Subgroup Analysis for the "Easy-to-Treat" Population. Because RVR and low viral load were two major predictors for a shorter treatment duration of peginterferon/ribavirin for HCV-1 patients, we further stratified patients according to the presence of two favorable pre-

dictors: achievement of an RVR and low viral load (<400,000 IU/mL).^{7,24} For 52 patients with low viremia and an RVR, the rates (CI) of relapse and SVR in the 24-week group were 3.6% (-3%-11%) and 96.4% (89%-103%), respectively, which were comparable with 0% and 100% in the 48-week group (difference: 3.6%; CI: -7.2% to 6.6%; -3.6%; CI: -14.3% to -0.6%, respectively; Fig. 2). For 35 patients with high viremia and an RVR, the relapse rate was significantly higher (23.5%; 4 of 17; CI: 3%-44% versus 0%; 0 of 18; $P = 0.045$) and SVR rate was significantly lower (76.5%; 13 of 17; CI: 56%-97% versus 100%; 18 of 18; $P = 0.045$) in the 24-week group than in the 48-week group. For 148 patients with either high viremia or without an RVR, the relapse rate was significantly higher in the 24-week (50.8%; CI: 39%-63%) than in the 48-week group (16.7%; CI: 8%-26%; $P < 0.0001$); the SVR rate was significantly lower in the 24-week (44.4%; CI: 33%-56%) than in the 48-week group (71.4%; CI: 62%-82%; $P = 0.001$).

The mean daily doses of ribavirin were similar among patients with an RVR and low viremia, patients with an RVR and high viremia, patients without an RVR and low viremia, and patients without an RVR and high viremia in both 24-week and 48-week arms (Supplemental Table 1). For patients with low viremia and an RVR, the mean dose of ribavirin was comparable between sustained responders

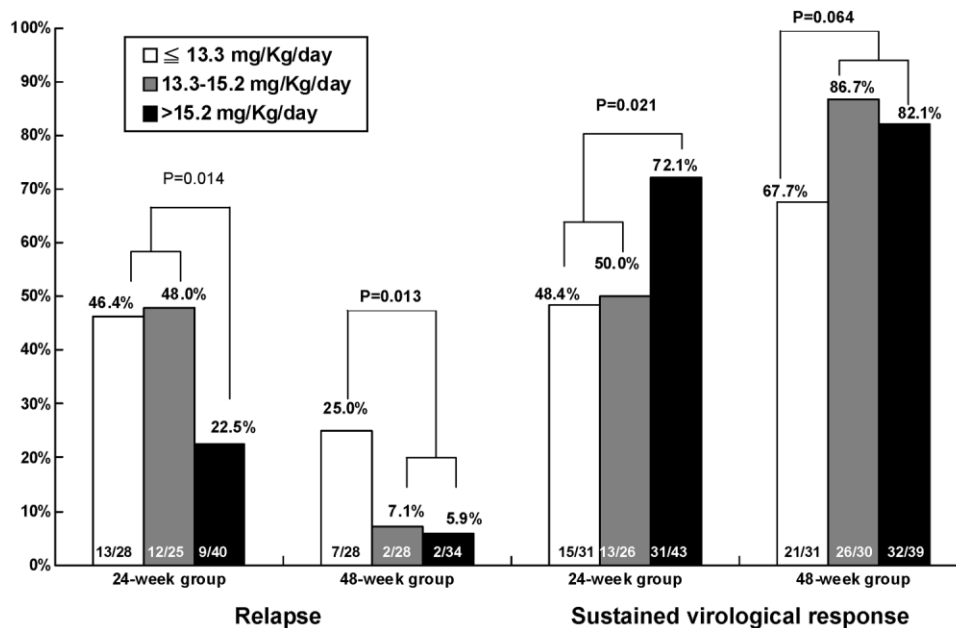


Fig. 1. Weight-based exposure of ribavirin and treatment response. Patients were stratified according to ribavirin exposure by body weight into three groups: lower (<13.3 mg/kg/day), moderate (13.3-15.2 mg/kg/day), and higher (>15.2 mg/kg/day). In the 24-week group, patients receiving a higher ribavirin dose had a significantly lower relapse rate and higher SVR rate than those receiving a lower or moderate ribavirin dose (relapse: 47.2% versus 22.5%, $P = 0.014$; SVR: 49.1% versus 72.1%, $P = 0.021$). In the 48-week group, patients receiving a moderate or higher ribavirin dose had a significantly lower relapse rate and higher SVR rate than those receiving a lower ribavirin dose (relapse: 25% versus 6.5%, $P = 0.013$; SVR: 67.7% versus 84.1%, $P = 0.064$).

and nonresponders of the 24-week group (14.4 ± 3.8 versus 15 mg/kg/day ; Fig. 3). For patients with either high viremia or without an RVR, a significantly lower daily dose of ribavirin in nonresponders than in sustained responders was observed in the 24-week group (13.7 ± 3.3 versus $16.1 \pm 3.3 \text{ mg/kg/day}$; $P = 0.004$, Mann-Whitney test), but not in the 48-week group (13.9 ± 3.5 versus $13.9 \pm 3.4 \text{ mg/kg/day}$).

Safety. Two serious adverse events were reported. One patient with cirrhosis in the 24-week group experienced variceal bleeding at the end of treatment. Another subject in the 48-week group suffered from severe myalgias over the lower back, resulting in disability of

gait during treatment. She was hospitalized for evaluation of neurological and musculoskeletal systems. No overt neurological finding was discovered; however, mild spondylolisthesis of the lumbar spine was found. Her symptoms/signs resolved after 5 days of inpatient care. Three patients in the 24-week group discontinued treatment because of adverse events. Ten patients in the 48-week group discontinued treatment: eight because of adverse events, one because of increased serum creatinine level, and one because of insufficient response. The rates of dose modification or transient interruption of peginterferon or ribavirin; gastrointestinal, psychiatric, dermatological, and hematological symptoms; and thy-

Table 5. Logistic Regression Analysis of Sustained Virological Response

Variables	Odds Ratio	95% Confidence Intervals	P Value
Rapid virological response at week 4			
No	1		<0.0001
Yes	17.74	6.106-51.55	
Treatment duration			
24 weeks	1		<0.0001
48 weeks	4.826	2.185-10.66	
Ribavirin dose by body weight			
<13.3 mg/kg/d	1		
13.3-15.2 mg/kg/day	2.969	1.088-8.103	0.034
>15.2 mg/kg/day	4.330	1.685-11.12	0.002
HCV viral load			
Per 1 - log increase	0.517	0.307-0.870	0.013

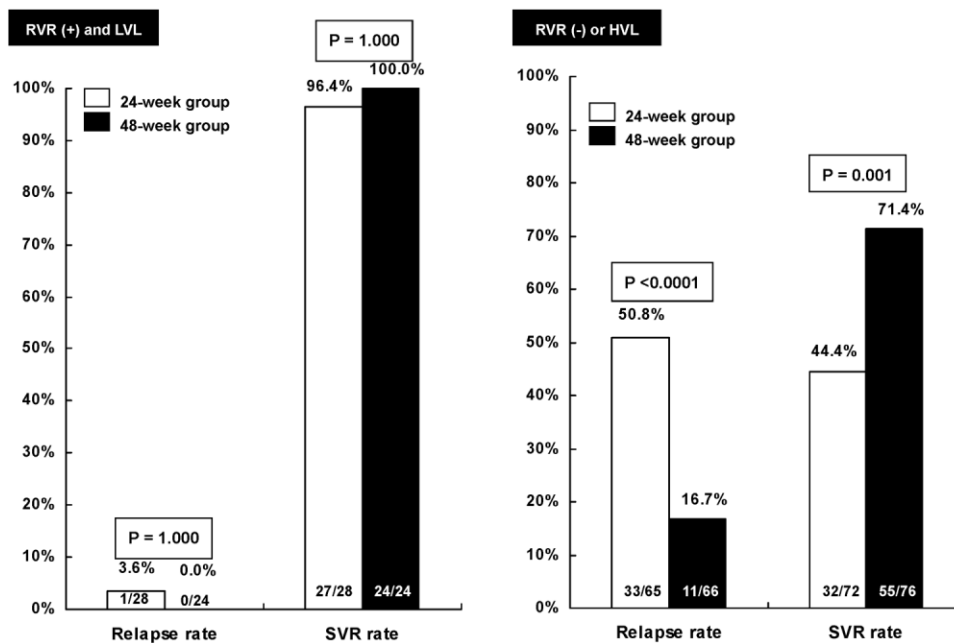


Fig. 2. Relapse and SVR rates in patients with an RVR and lower viral load. Rates of relapse and SVR, according to RVR and baseline viral load, among patients receiving 24 or 48 weeks of treatment. SVR, sustained virological response; RVR, rapid virological response at week 4; LVL, lower viral load, defined as baseline HCV viral load <400,000 IU/mL; HVL, higher viral load, defined as baseline viral load \geq 400,000 IU/mL.

roid dysfunction tended to be higher in the 48-week group than in the 24-week group (Supplemental Table 2). However, the differences did not reach statistical significance.

Discussion

In the current prospective, randomized, controlled trial to evaluate the use of an RVR as a guide to determine treatment duration for HCV-1 patients, we demonstrated that 24 weeks of peginterferon/ribavirin is inferior to 48 weeks of therapy even if an RVR is attained. Both 24 and 48 weeks of therapy can achieve high SVR rates (>96%) in HCV-1 patients with lower viremia and an RVR. RVR was the single best predictor of SVR in both the 24-week and 48-week groups. Patients with higher baseline viremia and suboptimal weight-based exposure of ribavirin had a higher likelihood of relapse with the shorter treatment duration, which may compromise the response to a 24-week treatment for HCV-1 patients.

Although inferior to the 48-week treatment, 24 weeks' use of peginterferon/ribavirin can achieve an SVR rate of more than one third for HCV-1 patients.^{6,7} Therefore, it is very important to identify simple, noninvasive markers for the easy-to-treat subgroup. A retrospective post hoc analysis of data collected during a randomized, multinational study observed that for HCV-1 patients with an RVR, the SVR rates were comparable among patients with 24 or 48 weeks of peginterferon/ribavirin (88% ver-

sus 83%, respectively).^{6,11} These findings have encouraged the use of RVR as the marker of shorter treatment duration for HCV-1 treatment. However, we observed that 24 weeks of peginterferon/ribavirin could not provide equal efficacy for HCV-1 patients with an RVR when compared with a 48-week regimen. Only for patients with an RVR and baseline viremia less than 400,000 IU/mL, which has been reported as the optimal cutoff point to best predict HCV-1 response to peginterferon/ribavirin,²⁴ is 24-week treatment as effective as the standard 48-week treatment. Our findings are consistent with a previous single-arm, historical-controlled study.¹⁸ In that study, HCV-1 patients with baseline viremia less than 600,000 IU/mL were treated with peginterferon/ribavirin for 24 weeks. The 24-week regimen provided equal efficacy for the subgroup with an RVR when compared with a 48-week regimen (89% versus 85%, respectively). A recent Italian study demonstrated that for HCV-1 patients with an RVR, the SVR rate in patients with 24-week treatment was substantial (77.2%) but lower than that in those with 48-week treatment (87.1%).¹⁹ RVR patients with baseline viremia less than 400,000 IU/mL achieved an SVR rate of 84.4% with 24-week treatment, which was comparable to the 83.3% rate in the 48-week group; however, RVR patients with baseline viremia greater than 400,000 IU/mL achieved lower SVR rates when treated for 24 weeks than for 48 weeks (73.1% versus 86.8%; $P = 0.14$).¹⁹ These findings

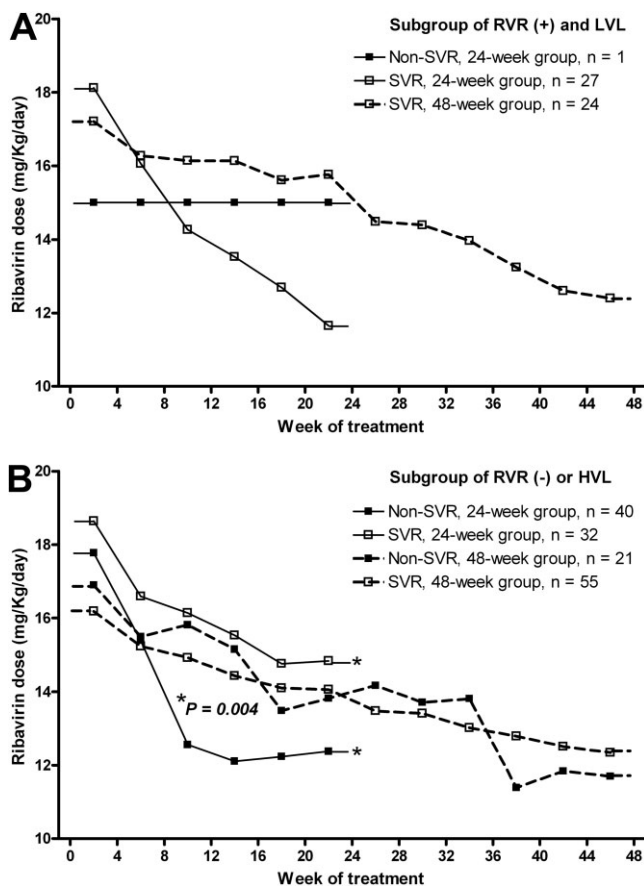


Fig. 3. Mean daily dose of ribavirin throughout the treatment period and treatment response, stratified by RVR, baseline viral load, and treatment duration. Mean daily dose of ribavirin was expressed per kilogram of body weight for (A) patients with lower viral load and an RVR and (B) patients with either high viral load or without an RVR. For patients with low viral load and an RVR, all patients achieved an SVR in 48-week group with a mean ribavirin dose of 14.9 ± 3.5 mg/kg/day; the mean dose of ribavirin was comparable between sustained responders and nonresponders of the 24-week group (14.4 ± 3.8 mg/kg/day versus 15 mg/kg/day, $P = 0.857$). For patients with either high viral load or without an RVR, a significantly lower daily dose of ribavirin in nonresponders than in sustained responders was observed in the 24-week group (13.7 ± 3.3 mg/kg/day versus 16.1 ± 3.3 mg/kg/day, $P = 0.004$, Mann-Whitney test*), but not in the 48-week group (13.9 ± 3.5 mg/kg/day versus 13.9 ± 3.4 mg/kg/day; $P = 0.676$). RVR, rapid virological response; LVL, lower viral load, defined as baseline HCV viral load $<400,000$ IU/mL; HVL, higher viral load, defined as baseline viral load $\geq 400,000$ IU/mL.

reinforce the RVR and baseline viral load as important signposts in the individualized treatment for HCV-1 patients.

Because RVR is the best predictor of SVR, characterization of the predictors of RVR is very important and may contribute to the efficacy of treatment response. Several factors were reported to predict an RVR. First, patients with viral loads less than 400,000 or less than 600,000 IU/mL are more likely to achieve an RVR.^{11,19,25} Second, HCV-1b had a higher chance of achieving an

RVR than HCV-1a.¹¹ Third, a standard weight-based dose of ribavirin has been associated with a higher RVR rate (1000-1200 mg/day; 22.6%) when compared with a low dose (800 mg/day; 16.5%).¹¹ A recent study demonstrated that the first 4 weeks of ribavirin exposure was the second-most important predictor of an RVR (17.5% versus 10% for ribavirin exposure greater than 13 versus less than 13 mg/kg/day; odds ratio: 2.15; CI: 1.41-3.27).²⁵ Only four of our patients received ribavirin exposure less than 13 mg/kg/day during the first 4 weeks, so we were unable to detect any potential difference. Nevertheless, for patients with ribavirin dose greater than 13 mg/kg/day during the first 4 weeks, a dose-related response of RVR was not observed in our study (data not shown). The optimal weight-based dose of ribavirin for maximizing the achievement of RVR remains to be studied.

Patients who achieve an RVR have a greater likelihood of achieving an SVR. In the current study, 43.5% (CI: 36.6%-50.4%) of patients achieved a RVR, which was similar to 47% in a previous European study for lower viremic HCV-1 patients.¹⁸ By contrast, the RVR rate was only 23.7% in Mangia et al.'s study,¹⁹ 19.7% in Jensen et al.'s study,¹¹ and 15.1% in Rodriguez-Torres et al.'s study,²⁵ which were enriched for a difficult-to-treat population. Compared with the current study, these three studies had a higher population of HCV-1a (44.5% in Jensen et al.'s study; 0.5% in our study), a higher proportion of patients with viral loads greater than 400,000 IU/mL (86.8% in Rodriguez-Torres et al.'s study; 76.3% in Mangia et al.'s study; 44.5% in our study), and a higher proportion of patients receiving ribavirin dose less than 13 mg/kg/day during the first 4 weeks (31.6% in Rodriguez-Torres et al.'s study; 2% in our study). Approximately half of the patients in Jensen et al.'s study were assigned a lower dose of ribavirin (800 mg/day). The mean body weight was 66.5 kg in our study, in contrast to 77 to 78 kg in Jensen et al.'s study and 82.4 kg in Rodriguez-Torres et al.'s study. The ribavirin exposure by 4 weeks was 17.4 mg/kg/day in the current study. In contrast, patients would have an exposure of no more than 14.5 mg/kg/day (starting dose of 1000-1200 mg/day) in Rodriguez-Torres et al.'s study²⁵ and 10.4 mg/kg/day (for patients with starting dose of 800 mg/day) in Jensen et al.'s study.¹¹ All of these factors might contribute to the lower chance of achieving an RVR.

Shorter treatment durations have been associated with higher relapse rates when compared with the standard recommended treatment,^{13,15} even in patients with an RVR.¹⁷ For RVR patients, we observed that the 24-week group was more likely to relapse with a subsequent lower SVR rate than was the 48-week group. The lower SVR rate with shorter treatment duration mainly exists in the

subgroup of patients with high viremia, which is consistent with previous findings that for HCV-1/4 patients with an RVR, the SVR rate was lower in patients with high viremia (74%) than in those with low viremia (92%) when treated with 24-week peginterferon/ribavirin.²⁶ We found that the association between lower weight-based exposure of ribavirin and treatment failure to 24-week peginterferon/ribavirin only existed among patients with high viremia or without an RVR but not among those with low viremia and an RVR. Peginterferon plus a higher starting dose of ribavirin (15.2 mg/kg/day) with erythropoietin to maintain the hemoglobin level at 12 to 15 g/dL had lower relapse and higher SVR rates when compared with standard weight-based ribavirin.²³ The ribavirin exposure of our sustained responders in the 24-week group was as high as 15.3 mg/kg/day, suggesting that ribavirin adherence and weight-based exposure of ribavirin may play a role in the response to a shorter treatment duration for subgroup of HCV-1 patients with high viremia or without an RVR, in terms of reducing the relapse rate.

Nearly one fourth of patients with high viremia and an RVR relapsed with the 24-week regimen, in contrast to none with the 48-week regimen. Whether treatment duration between 24 and 48 weeks could achieve a satisfactory response for the subgroup needs further study. More than one third of non-RVR patients remained refractory to the recommended 48-week regimen. Recently, the TeraViC-4 study randomly allocated non-RVR patients to either 48-week or 72-week peginterferon/ribavirin; the SVR rate was significantly higher in the 72-week group, primarily through the reduction of relapse.²⁷ The Italian group also demonstrated that the 72-week treatment attained a higher SVR rate (63.5%) than the 48-week treatment did (38.1%, $P = 0.068$) among patients who achieved their first undetectable HCV RNA at week 12.¹⁹

Consistent with previous studies,^{7,14} a better response to peginterferon/ribavirin was observed in Taiwanese patients than the reports for white patients. Lower viremia and body weight and relatively lower fibrosis scores might contribute to a higher SVR rate in Taiwanese patients. In addition, Asian race was shown to be an independent predictor of achieving an SVR, when compared with whites with chronic hepatitis C.²⁰ These findings suggested a genetic influence on the antiviral response.

One limitation of the current study is that patients were not randomized according to baseline viral load and RVR. Ideally, our results should be confirmed by prospective randomized trials on noninferiority of shorter treatment duration among patients with low viremia and RVR. Nevertheless, our findings should be sufficient to allow clinicians to formulate treatment strategies for HCV-1 patients with an aim toward reducing pharmaco-

logical costs.²⁸ The European Commission has approved revised dosing instructions for a 24-week course of peginterferon-alpha-2b/ribavirin for HCV-1 patients with low viremia and an RVR.²⁹

In conclusion, this study demonstrates that HCV-1 patients derive a significantly better SVR from 48 weeks versus 24 weeks of peginterferon/ribavirin even if they attain an RVR. HCV-1 patients require 48 weeks of therapy unless they have low baseline viral loads (<400,000 IU/mL) and achieve an RVR at week 4.

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