

Early Identification of HCV Genotype 1 Patients Responding to 24 Weeks Peginterferon α -2a (40 kd)/Ribavirin Therapy

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Approximately one third of hepatitis C virus (HCV) genotype 1 patients achieved a sustained virological response (SVR) after 24 weeks of treatment with peginterferon α -2a (40 kd) plus ribavirin in a randomized, multinational trial. We aimed to identify factors associated with a rapid virological response (RVR) at week 4 (HCV RNA <50 IU/mL) and a SVR (HCV RNA <50 IU/mL at the end of follow-up) in these patients. Stepwise multiple logistic regression analysis was used to explore the prognostic factors for a RVR and SVR in genotype 1 patients treated for 24 weeks. Fifty-one of 216 (24%) genotype 1 patients in the 24-week treatment groups had a RVR. SVR rates were considerably higher in patients without a RVR (89% vs. 19%, respectively). Patients with a baseline HCV RNA of less than 200,000 IU/mL (OR 9.7, 95% CI 4.2-22.5; $P < .0001$) or 200,000-600,000 IU/mL (OR 3.6, 95% CI 1.5-9.1; $P = .0057$) were more likely to achieve a RVR than those with HCV RNA greater than 600,000 IU/mL. HCV subtype (1b vs. 1a) was also independently associated with RVR (OR 1.8, 95% CI 0.9-3.7; $P = .0954$). RVR (OR 23.7 vs. no RVR, 95% CI 9.1-61.7) and baseline HCV RNA less than 200,000 IU/mL (OR 2.7 vs. >600,000 IU/mL, 95% CI 1.1-6.3; $P < .026$) were significant and independent predictors of SVR in patients treated for 24 weeks. **In conclusion**, patients infected with HCV genotype 1 and treated with peginterferon α -2a/ribavirin sustained a RVR 24% of the time. This portends an 89% probability of a SVR after 24 weeks of treatment. (HEPATOLOGY 2006;43:954-960.)

Abbreviations: SVR, sustained virological response; HCV, hepatitis C virus; RVR, rapid virological response; LD, low dose; SD, standard dose.

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The treatment of choice for chronic hepatitis C is the combination of a pegylated interferon plus ribavirin. Overall sustained virological response (SVR) rates of up to 63% have been achieved with optimal regimens of peginterferon α -2a (40 kd) plus ribavirin in randomized phase III trials,^{1,2} although SVR rates are heterogeneous and vary significantly by hepatitis C virus (HCV) genotype. Current guidelines for the management of chronic hepatitis C recommend the combination of a pegylated interferon plus ribavirin 1,000 or 1,200 mg/d for 48 weeks as initial treatment for patients infected with HCV genotype 1.³ Treatment for a shorter duration (24 weeks), with a lower dose of ribavirin (800 mg/d), or both, is associated with markedly reduced SVR rates in this frequently encountered but difficult-to-treat subpopulation. These recommendations are based on the results of a large, multinational, phase III trial in which patients were randomized to 1 of 4 combination regimens of peginterferon α -2a (40 kd) plus ribavirin.²

The timing and magnitude of the virological response to antiviral therapy in patients infected with HCV genotype 1 are highly variable. Results of a retrospective trial in which patients were treated with pegylated interferon α -2b (12 kd) plus ribavirin suggested that the duration of therapy after HCV RNA is suppressed to a level below the limit of detection that is important in maximizing the probability of a SVR in genotype 1 patients.⁴ The authors concluded that treatment for 32 to 36 weeks after HCV RNA becomes undetectable would result in a SVR rate of 80% to 90%.⁴ An alternative hypothesis is that the probability of achieving a SVR increases with the rapidity of HCV RNA suppression.⁵ A retrospective analysis of data from patients treated with peginterferon α -2a (40 kd) plus ribavirin for 48 weeks in a randomized, multinational, phase III study demonstrated that 91% of genotype 1 patients who became HCV RNA–negative by week 4 had a SVR compared with 48% or fewer of those who did not become HCV RNA–negative until week 24.⁵ Moreover, recent data from an uncontrolled study suggest that HCV genotype 1 patients with low baseline HCV RNA levels may require just 24 weeks of treatment to achieve a SVR if they have undetectable HCV RNA at week 4 of therapy.⁶

Hadziyannis et al.² reported that more than one third of patients infected with HCV genotype 1 who were randomized to 24 weeks of treatment with peginterferon α -2a (40 kd) plus ribavirin achieved a SVR. Therefore, we performed a retrospective study to examine factors associated with a rapid virological response (RVR) at week 4 and a SVR in patients infected with HCV genotype 1 who were randomized to 24 weeks of treatment.

Patients and Methods

Patients. HCV treatment–naïve adults with anti-HCV antibodies, quantifiable HCV RNA (>600 IU/mL via COBAS AMPLICOR HCV MONITOR Test, version 2.0; Roche Diagnostics, Branchburg, NJ) and elevated alanine aminotransferase activity in serum, liver biopsy findings consistent with the diagnosis of chronic hepatitis C, and compensated liver disease (Child-Turcotte-Pugh class A) were eligible for the study. Patients with neutropenia (neutrophil count $<1.5 \times 10^9$ cells/L), thrombocytopenia (platelet count $<90 \times 10^9$ cells/L), anemia (hemoglobin level <120 g/L in women and <130 g/L in men), or a serum creatinine level >1.5 times the upper limit of normal were excluded. Individuals coinfecting with hepatitis A or B virus or HIV, and those with severe psychiatric illness or clinically significant coexisting chronic medical conditions were also excluded. A more complete description of the inclusion and exclusion

criteria, study design, and primary results of the trial has been published elsewhere.²

Study Design. This study involved the *post hoc* analysis of data collected during a randomized, multinational, phase III study.²

Patients were randomized to treatment with subcutaneous peginterferon α -2a (40 kd) (PEGASYS; Roche, Basel, Switzerland) 180 μ g once weekly plus oral ribavirin (COPEGUS, Roche) in 1 of 4 groups that differed by treatment duration and ribavirin dose. The 4 treatment regimens by ribavirin dose and treatment duration were as follows: low dose (LD) (800 mg/d) for 24 weeks (24-LD); standard dose (SD) (1,000 mg/d for body weight <75 kg; 1,200 mg/d for body weight ≥ 75 kg) for 24 weeks (24-SD); 800 mg/d for 48 weeks (48-LD); or 1,000 or 1,200 mg/d for 48 weeks (48-SD).

The study used an unequal randomization procedure to limit the number of patients with more difficult-to-treat characteristics, such as HCV genotype 1 and high baseline HCV viral load, who would receive treatment for only 24 weeks. In the final amended protocol, patients with HCV genotype 1 infection and a baseline HCV RNA level of 2 million copies/mL or fewer were randomized to the 4 treatment groups (24-LD, 24-SD, 48-LD, 48-SD) in a 1:1:1:1 ratio, and patients with HCV genotype 1 infection and a baseline HCV RNA level greater than 2 million copies/mL were assigned to the 4 treatment groups (24-LD, 24-SD, 48-LD, 48-SD) in a 1:1:5:5 ratio.

The primary efficacy end point was SVR, defined as undetectable serum HCV RNA (<50 IU/mL) by qualitative polymerase chain reaction (COBAS AMPLICOR HCV MONITOR Test, version 2.0) at the end of a 24-week follow-up phase. Serum HCV RNA levels were also determined at weeks 4, 12, 24, and 48 (for the 48-LD and 48-SD groups) during therapy via qualitative polymerase chain reaction.

Although data from all 4 treatment groups were included in this analysis, our primary objective was to determine whether patients infected with HCV genotype 1 who achieved a SVR after 24 weeks of treatment could be identified on the basis of RVR at week 4, which was defined as undetectable serum HCV RNA (<50 IU/mL) via qualitative polymerase chain reaction.

Logistic Regression Analysis. Stepwise multiple logistic regression analysis was used to explore the prognostic factors for a RVR at week 4 and for a SVR. In the stepwise model-building process, a variable was added to the model if the adjusted chi-square statistic was significant at the 0.15 level and a variable was deleted from the model if the Wald chi-square statistic was not significant at the 0.1 level. The following baseline disease and demographic factors were considered for entry into the predic-

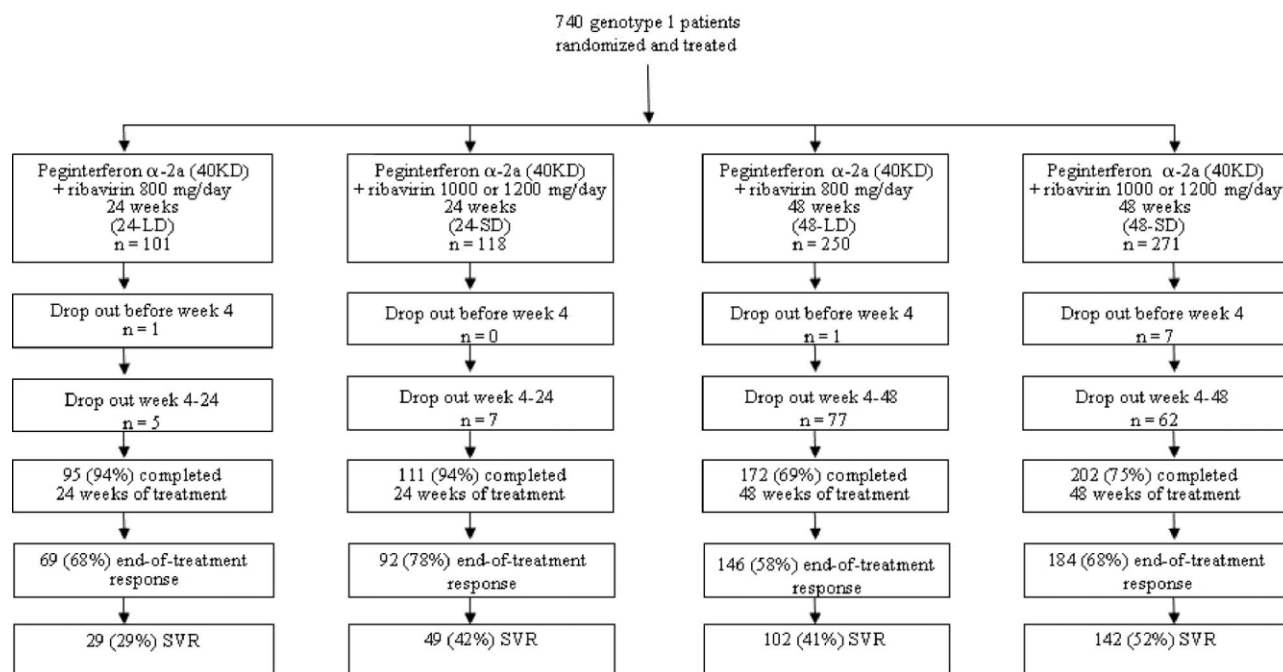


Fig. 1. Flow of patients and primary outcomes of the study. According to the protocol, patients without a virological or biochemical response after 24 weeks of treatment were classified as nonresponders and were discontinued from further treatment. LD, low dose; SD, standard dose; SVR, sustained virological response.

tive model for RVR: age, sex, weight, body mass index, body surface area, \log_{10} pretreatment serum HCV RNA level, histological diagnosis (bridging fibrosis/cirrhosis vs. no bridging fibrosis/cirrhosis), pretreatment alanine aminotransferase activity, qualifying alanine aminotransferase quotient, genotype 1 subtype (1b vs. 1a), and ribavirin dose at baseline. In constructing the multiple logistic regression model for SVR, RVR status (*i.e.*, yes or no) was considered in addition to the baseline disease and demographic factors. ORs and 95% CIs were estimated for the independent prognostic factors.

Results

The disposition of patients with HCV genotype 1 is shown in Fig. 1. A total of 740 patients infected with this genotype were randomized to treatment and received at least 1 dose of study drug during the trial. Week 4 virological test results were available for 729 patients. A total of 51 of 216 (24%) patients treated for 24 weeks had a RVR. The proportion of patients with a RVR at week 4 was numerically higher in patients infected with HCV genotype 1 who were randomized to a standard weight-based dose (88/389, 22.6%) versus a low dose of ribavirin (58/351, 16.5%).

Patients with a RVR in each of the 4 treatment groups in the study had consistently higher end-of-treatment virological response and SVR rates than patients without a

RVR (Fig. 2). End-of-treatment virological response rates in patients with a RVR ranged from 73% to 93%, compared with 56% to 70% in patients without a RVR. In patients with a RVR, SVR rates paralleled end-of-treatment virological response rates in each of the 4 treatment groups (range 73%-91%), indicating that virological relapse during follow-up was uncommon in these patients. In contrast, SVR rates were consistently lower than end-of-treatment virological response rates in patients without a RVR. Moreover, the SVR rates in individuals without a RVR increased with the intensity of treatment and ranged from 16% in the group that received the least intensive regimen (24-LD) to 44% in those who received the optimal regimen for genotype 1 (48-SD). Among patients treated for 24 weeks, overall SVR rates were considerably higher in patients who did versus those who did not achieve a RVR (89% vs. 19%, respectively).

Next, we examined the baseline disease and demographic characteristics of patients in both 24-week treatment groups according to RVR status (Table 1). In general, the data reveal 3 important characteristics among those who achieved a RVR: mean baseline HCV RNA levels were lower in patients with versus without a RVR; fewer patients with than without a RVR had bridging fibrosis or cirrhosis; and a lower proportion of patients had subtype 1a than subtype 1b infection among those with an RVR. There were no statistically significant dif-

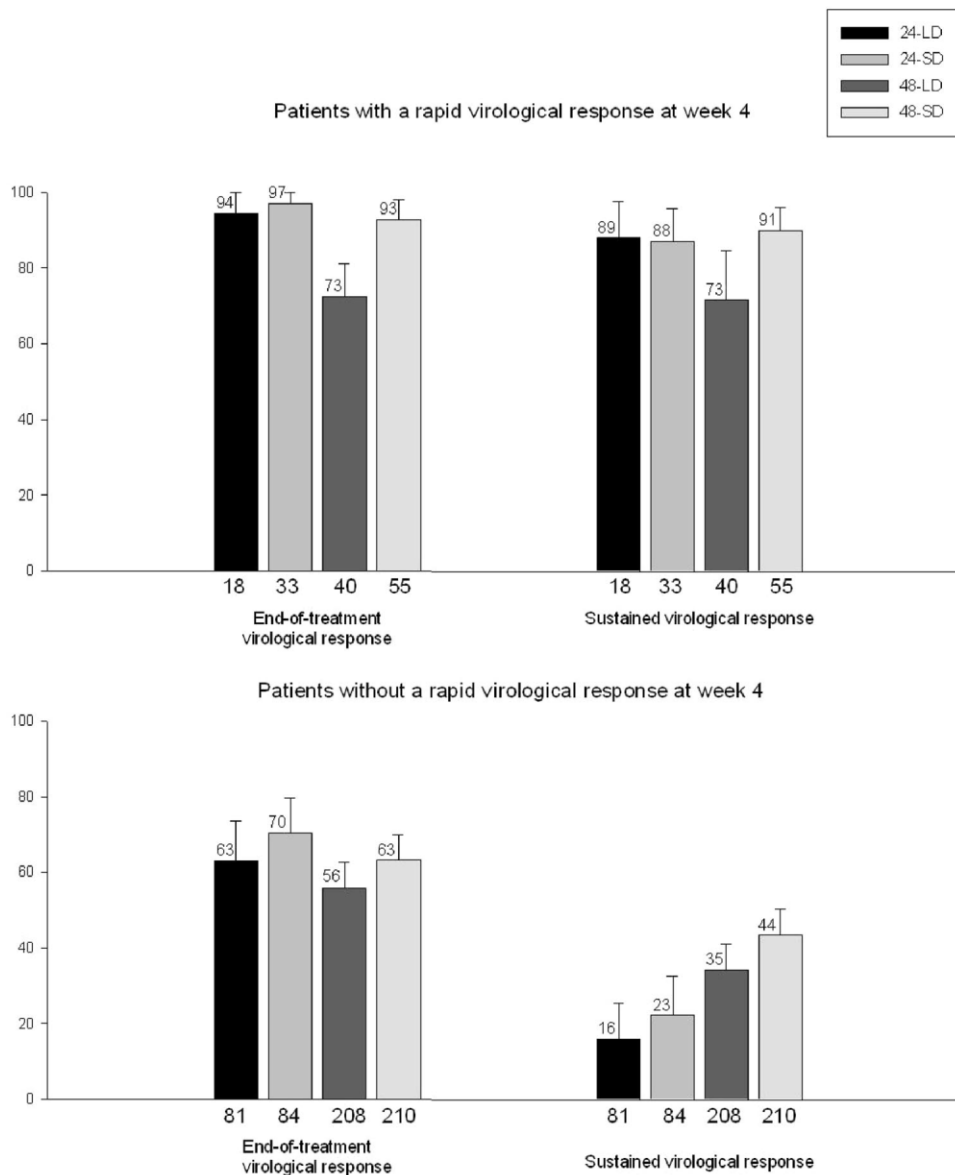


Fig. 2. End-of-treatment and sustained virological responses in patients with and without a rapid virological response (undetectable HCV RNA) at week 4. The number of patients in each group is presented at the base of each bar. LD, low dose; SD, standard dose.

ferences between patients infected with subtype 1a and 1b, although 13 patients with subtype 1b infection had an Asian ethnic origin compared with none of the patients with subtype 1a infection.

Multiple Logistic Regression Models. Independent factors associated with a RVR in the logistic regression analysis of baseline disease and demographic factors in patients treated for 24 weeks included baseline HCV RNA level and HCV subtype (Table 2). Patients with a baseline HCV RNA level <200,000 IU/mL (OR 9.7, 95% CI 4.2-22.5; $P < .0001$) or between 200,000 and 600,000 IU/mL (OR 3.6, 95% CI 1.5-9.1; $P = .0057$) were significantly more likely to achieve a RVR than those with a baseline HCV RNA level >600,000 IU/mL.

HCV subtype (1b vs. 1a) was also included in the final model (OR 1.8, 95% CI 0.9-3.7; $P = .0954$). For this reason, separate models were developed for patients infected with genotype 1a and 1b (Table 2). For patients infected with subtype 1a, a baseline HCV RNA level of 200,000 IU/mL or less (vs. >200,000 IU/mL) was an independent factor associated with a RVR (OR 5.9, 95% CI 2.0-17.6; $P = .0015$). For patients infected with genotype 1b, a higher HCV RNA threshold of 600,000 IU/mL or less (vs. >600,000 IU/mL) was significantly associated with a RVR (OR 10.3, 95% CI 3.6-29.4; $P < .0001$).

The relationship between baseline HCV RNA level, HCV genotype 1 subtype, and RVR in patients treated

Table 1. Baseline Disease and Demographic Characteristics of Genotype 1 Patients in the 24-Week Treatment Groups According to HCV RNA Status at Week 4

Serum HCV RNA Level at Week 4 (n)	Peginterferon α -2a (40 kd) Plus Ribavirin 800 mg/d \times 24 Weeks (n = 101)		Peginterferon α -2a (40 kd) Plus Ribavirin 1,000/1,200 mg/day \times 24 Weeks (n = 118)	
	Negative (RVR) (n = 18)	Positive (No RVR) (n = 81)	Negative (RVR) (n = 33)	Positive (No RVR) (n = 84)
Sex, male/female (% male)	8/10 (44.4)	57/24 (70.4)	20/13 (60.6)	54/30 (64.3)
Mean age (yr) \pm SD	42.4 \pm 12.19	42.4 \pm 7.94	39.4 \pm 9.81	43.5 \pm 9.04
Mean BMI (kg/m ²) \pm SD	25.8 \pm 4.22	26.8 \pm 5.31	25.5 \pm 4.40	26.9 \pm 4.75
Race, n (%)				
Caucasian	17 (94.4)	71 (87.7)	28 (84.8)	75 (89.3)
Black	0	4 (4.9)	0	5 (6.0)
Asian	1 (5.6)	3 (3.7)	5 (15.2)	4 (4.8)
Other	0	3 (3.7)	0	0
ALT quotient,* n (%)				
\leq 3	14 (77.8)	56 (69.1)	20 (60.6)	61 (72.6)
$>$ 3	4 (22.2)	25 (30.9)	13 (39.4)	23 (27.4)
Mean ALT (U/L) \pm SD	70.7 \pm 37.68	81.2 \pm 54.15	85.1 \pm 45.48	83.1 \pm 59.38
Mean HCV RNA \times 10 ⁶ copies/mL \pm SD	2.01 \pm 3.02	4.21 \pm 4.28	1.89 \pm 4.18	4.83 \pm 5.44
HCV genotype 1 subtype, n (%)				
1a	5 (27.8)	40 (49.4)	13 (39.4)	40 (47.6)
1b	13 (72.2)	41 (50.6)	20 (60.6)	44 (52.4)
Histological diagnosis, n (%)				
No cirrhosis	13 (72.2)	63 (77.8)	28 (84.8)	62 (73.8)
Cirrhosis/bridging fibrosis	5 (27.8)	18 (22.2)	5 (15.2)	22 (26.2)

NOTE. Week 4 virological response data were missing for 2 patients in the 800 mg/d group and 1 patient in the 1,000/1,200 mg/d group.

Abbreviations: ALT, alanine aminotransferase; SD, standard deviation; RVR, rapid virological response.

*Divided by the upper limit of normal for the local laboratory.

for 24 weeks is shown in Fig. 3. Almost one half (49.1%) of the patients infected with HCV genotype 1 whose baseline HCV RNA level was 200,000 IU/mL or less achieved a RVR. In contrast, only 9.2% of those with a baseline HCV RNA level greater than 600,000 IU/mL had a RVR.

When HCV RNA status at week 4 was included in the logistic regression model for an SVR, only RVR status (OR 23.7, 95% CI 9.1-61.7) and baseline HCV RNA level were retained in the final model (Table 3). With respect to the baseline HCV RNA thresholds used in the model, patients with an HCV RNA level less than 200,000 IU/mL were significantly more likely to achieve a SVR than those with a level greater than 600,000 IU/mL (OR 2.7, 95% CI 1.1-6.3; $P < .026$).

Discussion

The results of this study demonstrate that rapid clearance of HCV RNA from the serum of patients infected with HCV genotype 1 significantly increased the probability of a SVR after 24 weeks of treatment with peginterferon α -2a (40 kd) plus ribavirin. Early clearance of HCV RNA not only increased the likelihood of an end-of-treatment response, but greatly reduced the likelihood of virological relapse during follow-up. The comparison of SVR rates in patients treated for 24 or 48 weeks demonstrates that there was no significant difference between SVR rates among patients who achieved a RVR at week 4.

Our findings are similar to those of a noncomparative prospective trial in which HCV genotype 1 patients with

Table 2. Independent Factors Predictive of a Rapid Virological Response (HCV RNA $<$ 50 IU/mL) at Week 4 in Patients Treated for 24 Weeks

Patients	Factor	OR	95% CI	P	
All	Baseline HCV RNA	$<$ 200,000 vs. $>$ 600,000 IU/mL	9.7	4.2-22.5	$<$.0001
All	Baseline HCV RNA	200,000-600,000 vs. $>$ 600 000 IU/mL	3.6	1.5-9.1	.0057
All	HCV subtype	1b vs. 1a	1.8	0.9-3.7	.095
Subtype 1a	Baseline HCV RNA	\leq 200,000 vs. $>$ 200,000 IU/mL	5.9	2.0-17.6	.0015
Subtype 1b	Baseline HCV RNA	\leq 600,000 vs. $>$ 600,000 IU/mL	10.3	3.6-29.4	$<$.0001

NOTE. Week 4 virological response data were missing for 3 patients.

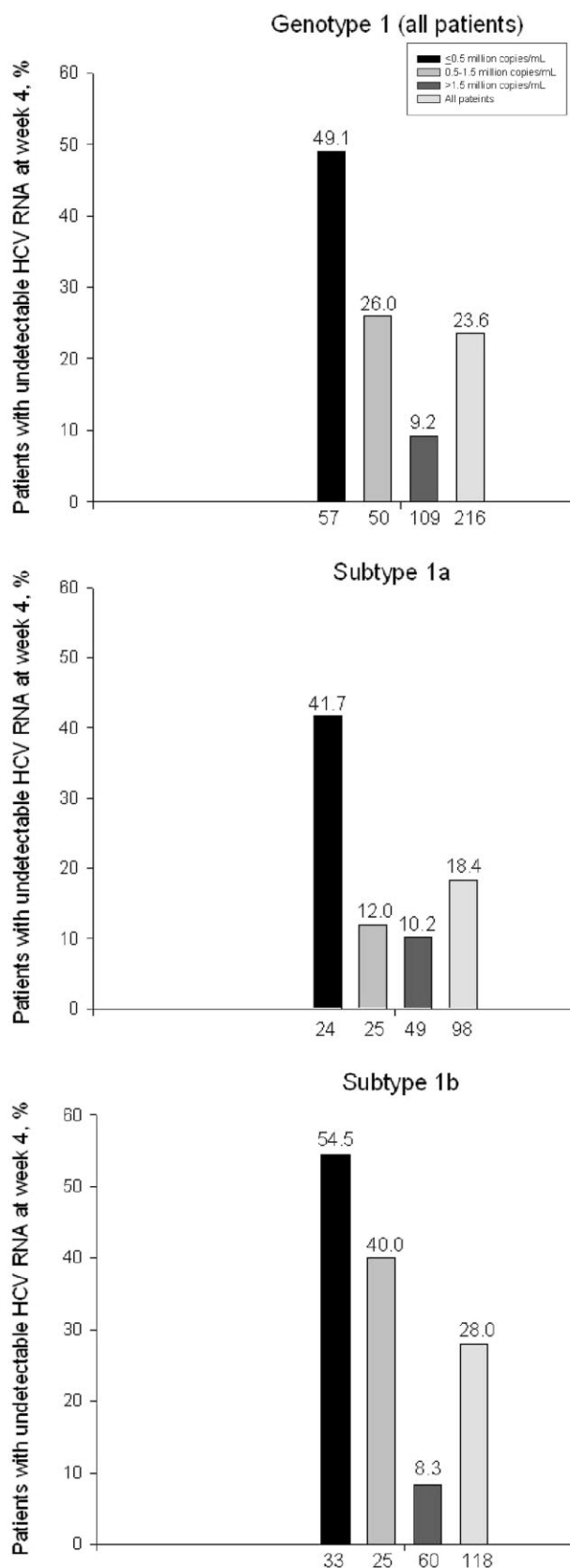


Fig. 3. Rapid virological response (undetectable HCV RNA) at week 4 according to HCV genotype 1 subtype and pretreatment HCV RNA level. The number of patients in each group is presented at the base of each bar. HCV, hepatitis C virus.

baseline HCV RNA levels 600,000 IU/mL or less received pegylated interferon α -2b (12 kd) plus ribavirin 800-1,400 mg/d for 24 weeks.⁶ Overall, this regimen was less effective than 48 weeks of combination treatment in historical control patients in the study by Manns et al.⁷; however, patients with undetectable HCV RNA at week 4 had the highest SVR rate (89%) and the lowest relapse rate (9%) during follow-up.

Our multiple logistic regression model demonstrates that HCV RNA level is the only independent and significant baseline predictor of RVR. Patients with higher baseline HCV RNA levels were less likely to achieve an RVR, although those with a RVR (9.2% of those with baseline HCV RNA >600,000 IU/mL) were as likely to achieve a SVR as patients with low baseline viral loads.

One other analysis has reported higher overall SVR rates in patients with subtype 1b than subtype 1a infection (53% vs. 45%, respectively, $P = .0039$) in patients treated for 48 weeks with peginterferon α -2a (40 kd) plus ribavirin.⁸ Our logistic regression model showed patients with subtype 1b infection responded particularly well to combination therapy if the HCV RNA level was below a threshold of 600,000 IU/mL. The corresponding threshold in patients infected with subtype 1a infection was lower ($\leq 200,000$ IU/mL). With the exception that all Asian patients had subtype 1b infection, there were no statistically significant differences between patients infected with subtypes 1a and 1b. This suggests that HCV genotype 1b is more sensitive to combination therapy. Further study is required to elucidate the mechanisms that underlie this phenomenon.

An earlier study⁵ reported higher SVR rates in patients with undetectable HCV RNA at week 4 than in those with detectable HCV RNA. Moreover, SVR rates were similar in genotype 1 patients who had a RVR and were treated with either peginterferon α -2a (40 kd) plus ribavirin (91%) or peginterferon α -2a (40 kd) plus placebo (93%). However, the overall numbers of obese patients (body mass index >30 kg/m²) and of patients with cirrhosis were not significant enough in these trials for conclusions regarding treatment duration to be extended to these subgroups.

The results of this study have practical significance. It is desirable to expose patients with chronic hepatitis C to the shortest duration of treatment possible to reduce the likelihood of adverse events and minimize costs. Patients with HCV genotype 1 are the most resistant to treatment and therefore are commonly selected for studies involving new antiviral agents. The ability to identify a group of patients that can be treated for 24 weeks would also reduce the cost of therapeutic

Table 3. Independent Factors Predictive of a Sustained Virological Response (HCV RNA >50 IU/mL) at End of Untreated Follow-up (Week 48) in Patients Treated for 24 Weeks

Patients	Factor		OR	95% CI	P Value
All	Baseline HCV RNA	<200,000 vs. >600,000 IU/mL	2.7	1.1-6.3	.026
All	Baseline HCV RNA	200,000-600,000 vs. >600,000 IU/mL	1.5	0.6-3.6	.366
All	RVR	Yes vs. no	23.7	9.1-61.7	<.0001

NOTE. Week 4 virological response data were missing for 3 patients.

trials of new agents and may even speed the development of new agents.

The treatment algorithm for patients with chronic hepatitis C continues to evolve. The results of this analysis and those from a recent randomized, multicenter trial⁸ demonstrate that week 4 HCV RNA testing is useful in the routine management of patients with genotype 1 infection. In the TeraViC-4 study, patients with detectable HCV RNA at week 4 were randomized to either 48 or 72 weeks of treatment with peginterferon α -2a (40 kd) plus ribavirin 800 mg/d. SVR rates in patients who did not achieve a RVR were significantly higher in the 72-week versus the 48-week treatment groups, primarily because of a reduced rate of virological relapse during follow-up.⁸ Conversely, the overall SVR rate in genotype 1 patients with a baseline HCV RNA level of 800,000 IU/mL or less who had a RVR at week 4 was 76% after 24 or 48 weeks of treatment.

The strength of our findings will be enough to persuade some clinicians to offer a shorter duration of treatment to patients with rapid viral clearance. Others may want to wait until the feasibility of this approach has been validated in a prospective randomized trial.

In conclusion, a RVR—defined as undetectable HCV RNA at week 4 of treatment with peginterferon α -2a (40 kd) plus ribavirin—was the single best predictor of end-of-treatment virological response and SVR, and was associated with a low rate of relapse during follow-up in HCV genotype 1 patients treated for either 24 or 48 weeks in a randomized, multinational trial. Low baseline HCV RNA levels and the presence of subtype 1b infection were independently associated with a RVR. Moreover, the development of a RVR was a significant and independent predictor of SVR in patients treated for 24 weeks. The use

of a qualitative serum HCV RNA assay at week 4 as a guide to determining treatment duration in patients with HCV genotype 1 infection should be considered, and, ideally, should be confirmed in prospective randomized trials.

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