

ORIGINAL ARTICLE

Peginterferon Alfa-2b and Ribavirin for 12 vs. 24 Weeks in HCV Genotype 2 or 3

Alessandra Mangia, M.D., Rosanna Santoro, Bs.D., Nicola Minerva, M.D.,
Giovanni L. Ricci, M.D., Vito Carretta, M.D., Marcello Persico, M.D.,
Francesco Vinelli, M.D., Gaetano Scotto, M.D., Donato Bacca, M.D.,
Mauro Annese, M.D., Mario Romano, M.D., Franco Zechini, M.D.,
Fernando Sogari, M.D., Fulvio Spirito, M.D., and Angelo Andriulli, M.D.

ABSTRACT

BACKGROUND

We hypothesized that in patients with hepatitis C virus (HCV) genotype 2 or 3 in whom HCV RNA is not detectable after 4 weeks of therapy, 12 weeks of treatment is as effective as 24 weeks.

METHODS

A total of 283 patients were randomly assigned to a standard 24-week regimen of peginterferon alfa-2b at a dose of 1.0 μ g per kilogram weekly plus ribavirin at a dose of 1000 mg or 1200 mg daily, on the basis of body weight. Of these, 70 patients were assigned to the 24-week regimen (standard-duration group) and 213 patients to a variable regimen (variable-duration group) of 12 or 24 weeks, depending on whether tests for HCV RNA were negative or positive at week 4. The primary end point was HCV that was not detectable by polymerase-chain-reaction (PCR) assay 24 weeks after the completion of therapy.

RESULTS

In the standard-duration group, 45 (64 percent) patients had HCV that was not detectable by PCR assay at week 4, as compared with 133 (62 percent) in the variable-duration group (difference [the rate in the standard-duration group minus that in the variable-duration group], 2 percent; 95 percent confidence interval, -11 to 15 percent). Fifty-three patients (76 percent) in the standard-duration group and 164 patients (77 percent) in the variable-duration group had a sustained virologic response (difference, -1 percent; 95 percent confidence interval, -13 to 10 percent). Fewer patients in the variable-duration group receiving the 12-week regimen had adverse events and withdrew than in the group receiving the 24-week regimen ($P=0.045$). The rate of relapse (defined as HCV not detectable at the end of treatment but detectable at the end of follow-up) was 3.6 percent in the standard-duration group and 8.9 percent in the variable-duration group ($P=0.16$). Overall, the rate of sustained virologic response was 80 percent among patients with HCV genotype 2 and 66 percent among those with genotype 3 ($P<0.001$).

CONCLUSIONS

A shorter course of therapy over 12 weeks with peginterferon alfa-2b and ribavirin is as effective as a 24-week course for patients with HCV genotype 2 or 3 who have a response to treatment at 4 weeks.

From the Gastroenterology Unit, IRCCS Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo (A.M., R.S., F. Spirito, A.A.); the Department of Internal Medicine, Hospital Canosa, Canosa (N.M.); the Department of Internal Medicine, University La Sapienza, Rome (G.L.R.); the Department of Internal Medicine, Hospital Venosa, Venosa (V.C.); the Department of Internal Medicine, Federico II University, Naples (M.P.); the Department of Gastroenterology, Ospedali Riuniti, Foggia (F.V.); the Department of Infectious Disease, University of Foggia, Foggia (G.S.); the Department of Internal Medicine, Hospital Casarano, Casarano (D.B.); the Department of Internal Medicine, Hospital Policoro, Policoro (M.A.); the Department of Internal Medicine, Sant'Andrea Hospital, Rome (M.R.); the Liver Unit, Sovrano Ordine di Malta, Rome (F.Z.); and the Department of Internal Medicine, Santissima Annunziata Hospital, Taranto (F. Sogari) — all in Italy. Address reprint requests to Dr. Mangia at the Gastroenterology Unit, Casa Sollievo della Sofferenza Hospital IRCCS, 71013 San Giovanni Rotondo, Italy, or at a.mangia@tin.it.

N Engl J Med 2005;352:2609-17.

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IN MOST PATIENTS WITH CHRONIC HEPATITIS C virus (HCV) genotype 2 or 3 infection, therapy with pegylated interferon and ribavirin administered for a period of 24 or 48 weeks ensures a sustained virologic response.¹⁻³ Although these schedules are effective, side effects increase with the length of treatment.⁴ Furthermore, there have been isolated reports of patients who, with therapy withdrawn after only 8 to 12 weeks, have a response.⁵ Therefore, current recommendations may lead to overtreatment of some patients with chronic HCV infection.

Experimental data substantiate these observations. On the initiation of interferon therapy, there is a rapid decline in viral load, reflecting the efficiency of interferon-dependent inhibition of the production of the virus, its release, or both. This rapid decline is followed by a slower one that is dependent on the rate of death of infected cells and that is estimated to vary from 1.7 days to more than 70 days.⁶ Both the effectiveness of interferon in blocking production of the virus in the first phase of decline and the rate of decline in the second phase differ in patients with HCV genotype 1 and in those with genotype 2 or 3, with a decline eight times faster in patients with genotypes other than 1.^{7,8} This difference suggests that patients with HCV genotype 2 or 3 infection need shorter courses of therapy than the regimens currently recommended.^{9,10} Changes in viremia levels over the first weeks of therapy correlate with the likelihood of the eradication of HCV, and undetectable viral levels at week 12 are predictive of a response after 48 weeks of therapy.^{6,8,11} Moreover, the early viral response can vary in patients with HCV genotype 1 and those with genotypes other than 1, and this variation is an independent predictor of sustained virologic response.¹²⁻¹⁵

Data on viral kinetics have led to the hypothesis that in patients with HCV genotype 2 or 3 in whom HCV RNA is not detectable after 4 weeks of therapy, 12 weeks of treatment may be as effective as the recommended course of 24 weeks.

METHODS

STUDY DESIGN

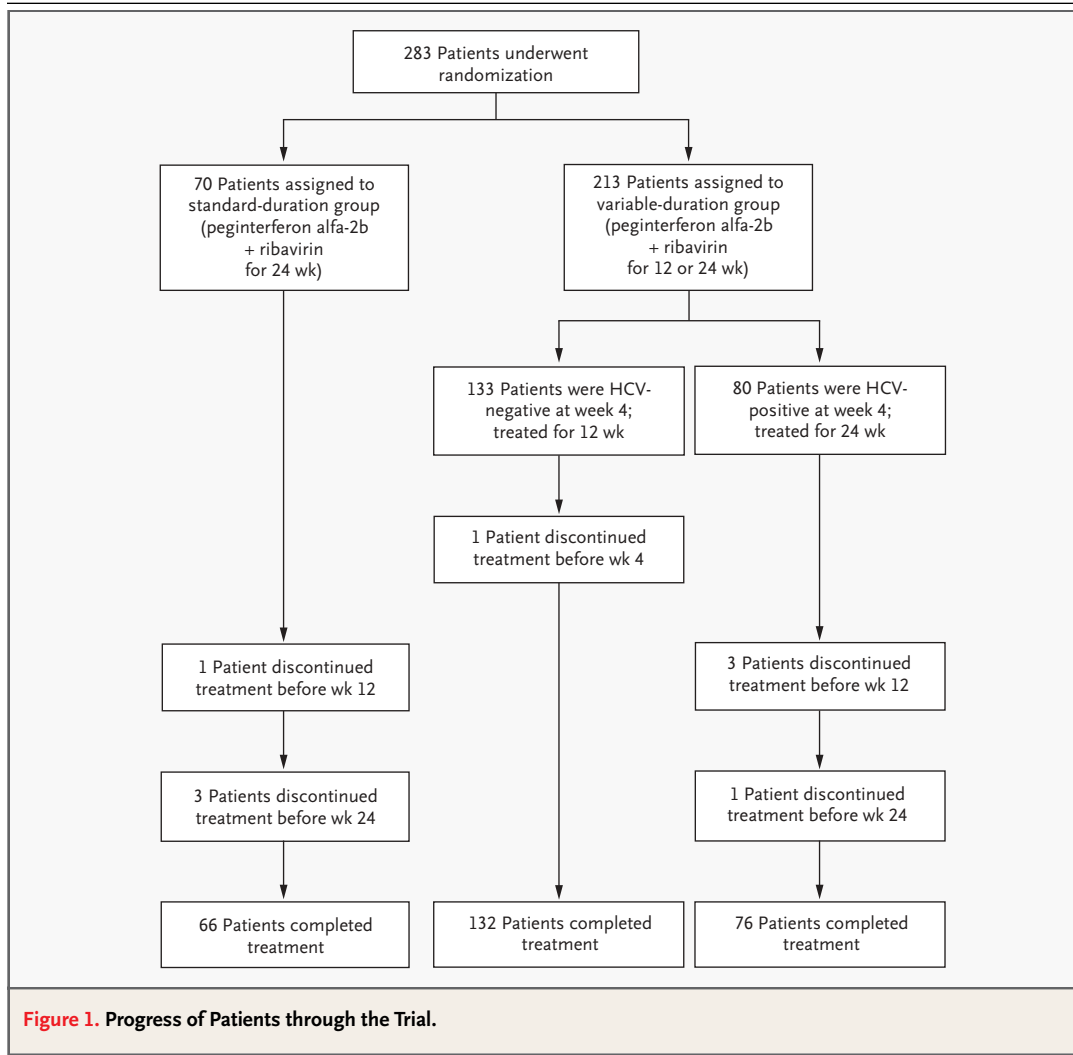
We conducted a randomized trial in patients with HCV genotype 2 or 3 comparing the standard 24-week regimen with a variable-duration regimen. Patients with a virologic response at 4 weeks received treatment for 12 weeks and those without a virologic response at 4 weeks received treatment for 24

weeks. The primary measure of efficacy was a sustained virologic response, defined as HCV RNA that was not detectable in the serum 24 weeks after treatment was stopped. This open-label trial was conducted in 12 centers in Italy as an investigator-sponsored study without financial support from industry. The study was approved by a central ethics committee and was conducted according to the guidelines of the International Conference on Harmonization for Good Clinical Practice. Eligible patients were 18 to 70 years of age; had antibodies to HCV, infection with genotype 2 or 3, and abnormal alanine aminotransferase levels; and had not received therapy. All patients provided written, informed consent. Enrollment started in June 2002, and the trial ended in January 2004. Exclusion criteria included a leukocyte count lower than 3000 per cubic millimeter, a platelet count lower than 80,000 per cubic millimeter, a hemoglobin level lower than 12 g per deciliter for women and lower than 13 g per deciliter for men, infection with the human immunodeficiency virus, alcohol intake greater than 20 g daily, and the presence of drug abuse, chronic disease, psychiatric disease, autoimmune disease, or pregnancy and lactation.

Patients were randomly assigned in a 1:3 ratio to receive peginterferon alfa-2b (PEG-Intron, Schering) at a dose of 1.0 µg per kilogram of body weight weekly plus oral ribavirin (Rebetol, Schering) at a dose of 1000 mg (for those with a weight of <75 kg) or 1200 mg (for those with a weight of ≥75 kg) daily, administered either for the standard period of 24 weeks (in the control standard-duration group of 70 patients) or for a variable duration (in the variable-duration group of 213 patients), according to HCV RNA status at week 4 (Fig. 1). In the variable-duration group, 133 patients with an early response (those in whom HCV RNA was not detectable at week 4) stopped therapy at week 12, whereas 80 patients with detectable levels of virus at week 4 received therapy until week 24. The treatment of patients with detectable HCV RNA at week 4 was similar, whether they were in the standard-duration group or the variable-duration group. Participants were assessed on an outpatient basis at weeks 4, 8, 12, and 24 during treatment and at week 24 after treatment ended.

VIROLOGIC AND HISTOLOGIC EVALUATION

At each participating center, blood samples were collected at weeks 4, 12, and 24 during treatment and at week 24 of follow-up, and hematologic and virologic testing was performed within 10 days af-



ter collection on samples stored at -20°C (-4°F). Serum levels of HCV RNA were evaluated qualitatively at each time point by polymerase-chain-reaction (PCR) assay (Amplicor HCV test, version 2.0, Roche Diagnostics) and quantitatively at baseline (Cobas Monitor test, version 2.0, Roche Diagnostics). HCV genotyping was performed with the use of a hybridization technique (Innolipa HCV, Innogenetics). A total of 266 patients underwent liver biopsy before therapy, and histologic evaluation was carried out according to the Scheuer classification system.¹⁶ Steatosis was graded as mild (<30 percent), moderate (30 to 60 percent), or severe (>60 percent), according to the percentage of hepatocytes with macrovesicular steatosis. Treatment was started within one or two months after liver biopsy.

SAFETY ANALYSIS

Adverse events were graded as mild, moderate, or severe. When severe events other than anemia occurred, the dose of peginterferon alfa-2b was decreased by 50 percent and the dose of ribavirin was lowered to 800 mg daily; full doses were resumed when the event abated. If the event persisted, both drugs were discontinued. In the presence of anemia, the dose of ribavirin was lowered to 800 mg per day if hemoglobin levels were lower than 9.5 g per deciliter, and ribavirin was discontinued if the concentrations fell below 8.0 mg per deciliter.

STATISTICAL ANALYSIS

The study was designed as a noninferiority trial comparing the standard-duration and variable-duration strategies. It was recognized that data on

the standard-duration group would provide little new information and that experience gained with the new variable-treatment schedule would be advantageous. Therefore, for randomization a 3:1 ratio was considered, with approximately 210 subjects to be assigned to the variable-duration group and 70 to the standard-duration group. Randomization was performed centrally, without stratification according to genotype and with the use of a permuted-block method, in which each block included 28 patients, to ensure the 3:1 proportion of subjects in the two treatment groups. These sample sizes would provide the study with 80 percent power to rule out a difference of at least 12.5 percent, assuming an 80 percent rate of sustained virologic response in each group and with the use of a one-sided 95 percent confidence interval. If a rate of response of 80 percent was observed in the two treatment groups, a difference of at least 9.1 percent would be ruled out. Given the very high response rates attained by treatment of the standard duration and the considerable advantage of a shorter treatment as offered by the variable-duration regimen, a noninferiority margin of 12.5 percent was considered to be acceptable in this setting.

Patients who dropped out of the trial were classified as not having a virologic response. Patients with relapse were considered to be those with tests that were negative for HCV RNA at the end of therapy but positive at the end of follow-up. No interim analyses were performed, and the analyses included all randomized subjects for whom there were outcome data. Differences in baseline characteristics between the two groups were assessed with the use of the chi-square test with Yates's correction for discrete variables and the two-sided t-test with confidence intervals set at 95 percent. The primary comparison was between patients in the standard-duration group treated for 24 weeks and those in the variable-duration group treated for either 12 or 24 weeks. Patients assigned to the standard-duration group were subdivided at the end of week 4 into those in whom HCV RNA was not detectable (early response) and those with detectable levels of HCV RNA (no early response).

A prediction model for sustained virologic response based on undetectable HCV RNA levels at week 4 was developed that included HCV genotype, HCV RNA levels, body-mass index, alanine aminotransferase values, and the presence or absence of bridging fibrosis or cirrhosis. Stepwise logistic-regression analysis was performed to compare P val-

ues and odds ratios for the effect of prognostic factors and length of treatment on the response. At the start of the analysis, all considered variables were included in the model. A backward procedure was then applied, and a maximum-likelihood method was used for entering or removing terms (SPSS for Windows, version 11.0). All reported P values are two-sided and have not been adjusted for multiple testing.

RESULTS

Patients in the two treatment groups were well matched for baseline characteristics (Table 1). The ratio of those with HCV genotype 2 or 3 was approximately 3 to 1 in each group at the start of the trial.

RESPONSE RATES ACCORDING TO THERAPY AND GENOTYPE

In the standard-duration group, 45 of 70 patients (64 percent) had undetectable levels of HCV RNA at week 4, as compared with 133 of 213 patients (62 percent) in the variable-duration group (difference [the rate in the standard-duration group minus that in the variable-duration group], 2 percent; 95 percent confidence interval, -11 to 15 percent). Twenty-four weeks after completing treatment, 53 patients (76 percent) in the standard-duration group and 164 patients (77 percent) in the variable-duration group had a sustained virologic response (difference, -1 percent; 95 percent confidence interval, -13 to 10 percent). Since our prespecified margin was 12 percent and the upper limit of the confidence interval for the standard-duration group as compared with the variable-duration group was 10 percent, the criterion for noninferiority was satisfied.

In the standard-duration group (45 patients) and in the variable-duration group treated for 12 weeks (133 patients), 41 patients (91 percent) and 113 patients (85 percent), respectively, had a sustained virologic response, a difference of -6 percent (95 percent confidence interval, -16 to 4 percent). Twelve of 25 patients (48 percent) in the standard-duration group without an early response and 51 of 80 patients (64 percent) in the variable-duration group treated for 24 weeks were HCV RNA-negative 24 weeks after the completion of treatment, a difference of -16 percent (95 percent confidence interval, -6 to 38 percent).

Overall, 171 of 213 patients with HCV genotype 2 (80 percent) and 46 of 70 patients with HCV geno-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Standard-Duration Group (N=70)	Variable-Duration Group (N=213)	P Value
Age — yr	49.7±12.1	46.6±12.2	0.71
Male sex — no. (%)	39 (56)	119 (56)	0.50
Route of transmission — no. (%)			
Intravenous	13 (19)	41 (19)	0.92
Parenteral	15 (21)	49 (23)	0.77
Unknown	42 (60)	123 (58)	0.71
Body-mass index†			
Mean	26.0±3.2	25.7±3.7	0.06
≥27 — no. (%)	29 (41)	79 (37)	0.51
Body weight — kg			
Mean	69.5±10.3	69.4±9.7	0.31
≥75 kg — no. (%)	20 (29)	66 (31)	0.71
Alanine aminotransferase — U/liter‡			
Mean	109±10	110±5	0.82
>120 U/liter — no. (%)	17 (24)	72 (34)	0.11
HCV genotype — no. (%)			
2	53 (76)	160 (75)	0.53
3	17 (24)	53 (25)	0.50
HCV RNA — IU/ml			
Mean	809,000±960,000	1,019,000±1,430,000	0.20
>800,000 IU/ml — no. (%)	46 (66)	137 (64)	0.50
Moderate or severe steatosis — no. (%)	25 (36)	65 (31)	0.64
Liver fibrosis, stage ≥3 — no. (%)§	16 (23)	35 (16)	0.36

* Plus-minus values are means ±SD.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The upper limit of normal for alanine aminotransferase was 40 U per liter.

§ Liver histology was unavailable for 17 patients, 2 in the standard-duration group and 15 in the variable-duration group.

type 3 (66 percent) had a sustained virologic response, a difference of 14 percent (95 percent confidence interval, 2 to 27 percent; $P < 0.001$). There was no significant difference in the numbers of patients with genotype 2 or 3 in whom HCV RNA was undetectable by week 4: 137 patients with HCV genotype 2 (64 percent) and 41 with genotype 3 (59 percent) ($P = 0.47$). Among patients with HCV genotype 2, the rate of sustained virologic response was 76 percent in the standard-duration group and 82 percent in the variable-duration group (Table 2). Response rates among patients with HCV genotype 2 with undetectable HCV on PCR assay at the end of follow-up were 89 percent in the standard-duration group and 87 percent in the variable-duration group (difference, -1.3 percent; 95 percent confidence interval, -11 to 14 percent). When patients with HCV genotype 2 and an early response were considered in relation to length of treatment,

the response rates were 87 percent in the variable-duration group treated for 12 weeks and 89 percent in the standard-duration group ($P = 0.90$); continued treatment in patients with viremia at week 4 resulted in response rates of 50 percent among those in the standard-duration group without an early response and 72 percent in the variable-duration group treated for 24 weeks ($P = 0.13$). In patients with HCV genotype 3 and an early response, sustained virologic response rates were 77 percent among those in the variable-duration group treated for 12 weeks and 100 percent among those in the standard-duration group with an early response ($P = 0.24$), whereas among patients with viremia at week 4, the response rates were 43 percent among those in the standard-duration group without an early response and 41 percent among those in the variable-duration group treated for 24 weeks ($P = 0.68$).

Table 2. Patients Who Were HCV RNA–Negative at the End of Treatment and Follow-up, According to HCV Genotype and Regimen.*

Patients and Point in Study	Standard-Duration Regimen (24 Weeks)					Variable-Duration Regimen (12 or 24 Weeks)						
	All Patients	Negative at Week 4 (Early Response)		Positive at Week 4 (No Early Response)		All Patients	Negative at Week 4 (12-Week Treatment)		Positive at Week 4 (24-Week Treatment)			
		no.	%	no.	%		no.	%	no.	%		
All patients	70		45	64.3	25	35.7	213		133	62.4	80	37.6
End of treatment	55	79 (68–88)	42	93 (86–100)	13	52 (32–71)	180	85 (80–89)	126	95 (91–96)	54	68 (56–77)
End of follow-up	53	76 (66–86)	41	91 (83–99)	12	48 (28–67)	164	77 (71–83)	113	85 (79–91)	51	64 (53–74)
HCV genotype 2	53		35		18		160		102		58	
End of treatment	42	79 (68–90)	32	91 (82–100)	10	56 (32–78)	143	89 (65–94)	98	96 (92–99)	45	78 (67–88)
End of follow-up	40	76 (64–87)	31	89 (78–99)	9	50 (27–73)	131	82 (76–88)	89	87 (81–91)	42	72 (61–84)
HCV genotype 3	17		10		7		53		31		22	
End of treatment	13	76 (59–97)	10	100	3	43 (6–79)	37	70 (57–82)	28	90 (80–100)	9	41 (30–61)
End of follow-up	13	76 (56–97)	10	100	3	43 (6–79)	33	62 (49–75)	24	77 (63–92)	9	41 (30–61)

* CI denotes confidence interval.

SAFETY

In the variable-duration group, adverse events (depression and thyroid dysfunction) occurred in 8 patients treated for 12 weeks (6 percent) and in 19 treated for 24 weeks (13 percent) ($P=0.056$). In the variable-duration group, fewer patients (one) treated for 12 weeks reported side effects that required withdrawal from the study therapy than those treated for 24 weeks (eight patients) ($P=0.045$) (Fig. 1). Hemoglobin levels were reduced to less than 9.5 g per deciliter in 6 patients (4 percent) in the variable-duration group treated for 12 weeks and in 14 patients (9 percent) treated for 24 weeks ($P=0.17$). Anemia (defined as a hemoglobin level of <12 g per deciliter in women or <13 g per deciliter in men) and neutrophil counts of less than 1000 per cubic millimeter required a reduction in the dose of the study drug in 7 patients treated for 12 weeks (5 percent) and 18 patients treated for 24 weeks (12 percent).

PREDICTORS OF RAPID RESPONSE

In the univariate analyses, low levels of viremia were significantly associated with an early response to treatment ($P=0.049$), and high alanine aminotransferase levels approached significance ($P=0.06$) (Table 3). In the multivariate analysis, no factors remained statistically significant (Table 3).

RELAPSE RATES

Among patients who were HCV-negative at the end of treatment, 2 of 55 (3.6 percent) in the standard-

duration group and 16 of 180 (8.9 percent) in the variable-duration group had detectable HCV RNA 24 weeks after the end of follow-up ($P=0.16$). Among patients with relapse in 24 weeks of follow-up who were HCV-negative at the end of treatment, 1 of 42 was in the standard-duration group with an early response (2 percent), 1 of 13 was in the standard-duration group without an early response (8 percent), 13 of 126 were in the variable-duration group treated for 12 weeks (10 percent), and 3 of 54 were in the variable-duration group treated for 24 weeks (6 percent). The rate of relapse among patients in the variable-duration group treated for 12 weeks was not different from that among patients in the standard-duration group with an early response ($P=0.19$). All patients with relapse in the variable-duration group who were treated for 12 weeks were offered retreatment with the same dose of peginterferon alfa-2b and ribavirin for an additional 24 weeks. Most of these patients (10 of 13) agreed to be retreated, and 9 had a sustained virologic response. No baseline characteristic was associated with relapse among the 133 patients in the variable-duration group treated for 12 weeks who had an initial response; however, there was a trend toward a higher rate of relapse among patients with alanine aminotransferase levels no more than three times the upper limit of normal than among those with levels more than three times the upper limit of normal (14 percent vs. 2 percent, $P=0.06$) (Table 4).

Table 3. Factors Associated with Early Virologic Response at 4 Weeks.*

Factor	Patients with Early Response (N=178)	Patients with Viremia (N=105)	P Value	Odds Ratio (95% CI)	P Value
			Univariate Analysis		Multivariate Analysis
	<i>number (percent)</i>				
Age <40 yr	52 (29)	37 (35)	0.42	0.87 (0.48–1.56)	0.64
Female sex	82 (46)	43 (41)	0.63	1.08 (0.63–1.85)	0.75
Body-mass index <27	108 (61)	69 (66)	0.61	0.92 (0.53–1.59)	0.76
Alanine aminotransferase >3× upper limit of normal	127 (71)	67 (64)	0.06	1.22 (0.69–2.15)	0.48
HCV RNA <800,000 UI/ml	121 (68)	62 (59)	0.049	1.56 (0.92–2.64)	0.09
HCV genotype					
2	137 (77)	75 (71)	0.37	0.84 (0.43–1.65)	0.62
3	41 (23)	30 (29)	0.37	0.84 (0.43–1.65)	0.62
Mild steatosis	114 (64)	64 (61)	0.89	1.01 (0.67–1.53)	0.94
Fibrosis, stage <3	135 (76)†	84 (80)‡	0.39	1.33 (0.68–2.16)	0.39

* Patients with early response were in the standard-duration group and those in the variable-duration group treated for 12 weeks. Patients with viremia were in the standard-duration group and those in the variable-duration group treated for 24 weeks. CI denotes confidence interval.

† Of 178 patients, 165 had a liver biopsy.

‡ Of 105 patients, 101 had a liver biopsy.

DISCUSSION

In patients with HCV genotype 2 or 3, a strategy of variable-duration treatment with peginterferon alfa-2b and ribavirin (so that patients with a response at week 4 were treated for 12 weeks rather than 24 weeks) achieved rates of sustained virologic response similar to those achieved with the standard treatment (24 weeks). Patients treated for 12 weeks were spared the expense and inconvenience of extended treatment and still had a high response rate. The shorter regimen was associated with fewer side effects and, consequently, less frequent withdrawals from therapy. Moreover, patients assigned to 12 weeks of treatment were less likely to require a reduction in the dose of peginterferon alfa-2b or of ribavirin. The proportion of patients with relapse was higher among those treated for 12 weeks than those treated for the standard 24 weeks. However, 90 percent of patients with a relapse after 12 weeks of treatment had a response after an additional 24-week course of therapy. Therefore, even taking into consideration the rate of relapse, treatment for 12 weeks rather than 24 weeks appears to be appropriate for patients with an early response.

These results are consistent with the results of

an uncontrolled Norwegian study in which 85 of 95 patients (89 percent) with HCV genotype 2 or 3 had a response 14 weeks after peginterferon alfa-2b and ribavirin therapy was initiated.¹⁷ That investigation and our study differed in the weekly dose of peginterferon alfa-2b: the Norwegian study administered 1.5 µg per kilogram of body weight, whereas the current trial used 1.0 µg per kilogram. In another study, by Manns et al., the benefit of a high-dose regimen was most apparent in patients with HCV genotype 1 infection, whereas those with genotype 2 or 3 achieved similar response rates with high- and low-dose peginterferon alfa-2b regimens.² However, because modification of the dose of ribavirin in patients with anemia was less stringent in our trial than in other trials,^{2,4,18} the overall dose of ribavirin received by our patients may have been higher than in previous trials. Furthermore, preliminary results have been presented from a randomized study comparing 16 weeks with 24 weeks of combination therapy with peginterferon alfa-2a plus ribavirin in patients infected with HCV genotype 2 or 3, in which combination therapy for 16 or 24 weeks achieved similar rates of sustained virologic response among patients with an early response at week 4.¹⁹

Table 4. Association between Baseline Characteristics and Rate of Relapse among 133 Patients in the Variable-Duration Group with Early Response Assigned to 12 Weeks of Treatment.

Characteristic	No. of Patients	No. with Relapse (%)	P Value
All patients	133	13 (10)	
Age			0.57
<40 yr	85	9 (11)	
≥40 yr	48	4 (8)	
Sex			0.42
Male	68	8 (12)	
Female	65	5 (8)	
Body-mass index			0.62
≥27	50	4 (8)	
<27	83	9 (11)	
Alanine aminotransferase			0.06
<3× upper limit of normal	87	12 (14)	
≥3× upper limit of normal	46	1 (2)	
HCV RNA			0.38
<800,000 IU/ml	45	3 (7)	
≥800,000 IU/ml	88	10 (11)	
HCV genotype			0.50
2	102	9 (9)	
3	31	4 (13)	
Steatosis			0.84
Moderate or severe	39	4 (10)	
Absent or mild	94	9 (10)	
Fibrosis, stage*			0.84
≥3	18	2 (11)	
<3	114	11 (10)	

* One patient declined to undergo the biopsy.

No quantitative estimation of HCV viremia was planned in the current study, because we defined an early virologic response as a negative test for HCV RNA after 4 weeks of treatment. So far, quantitative

evaluation of HCV RNA has been used as a criterion for stopping therapy in patients with HCV genotype 1 without early virologic response, but this criterion has not been used to tailor the length of therapy. It has recently been reported that antiviral therapy is more beneficial in patients with HCV genotype 2 than those with genotype 3,¹⁸ and data from our trial support these findings. Overall, response rates were 80 percent and 66 percent, respectively, in patients with these two genotypes ($P<0.001$). However, our findings suggest that stopping therapy after 12 weeks in patients with a response at 4 weeks is appropriate for patients with either genotype, because the rates of sustained virologic response were similar in patients with genotype 2 or 3 who had an early response and who were treated for 12 or 24 weeks. In keeping with a preliminary report from the DITTO study,¹³ after early viral clearance has been obtained, the role of genotype appears to be relatively small. From the current trial, it is evident that prolonging treatment in patients with detectable HCV RNA at week 4 of therapy achieved higher rates of response in those with genotype 2 than those with genotype 3; among patients who did not have an early response and were treated for 24 weeks, the rate of sustained virologic response was higher among those with HCV genotype 2 than among those with genotype 3.

In conclusion, our findings suggest that patients with HCV genotype 2 or 3 infection who have undetectable HCV RNA after 4 weeks of treatment with peginterferon alfa-2b and ribavirin achieve high response rates with 12 weeks of therapy and do not require 24 weeks of treatment. Tailoring treatment so that those with an early response are given a shorter course may make therapy more appealing to patients, without adversely affecting outcomes.

Dr. Andriulli reports having served as a speaker for and received institutional research grants from the Italian branch of Schering-Plough.

REFERENCES

- Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-82.
- Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958-65.
- Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346-55.
- McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002;123:1061-9.
- Nousbaum JB, Cadranel JF, Savary O, Legrand MC, Dumouchel P, Gouerou H. Sustained virological response after a short course of treatment with interferon and ribavirin in two chronic hepatitis C patients. *J Hepatol* 2003;39:655-6.
- Neumann AU, Lam NP, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. *Science* 1998;282:103-7.
- Zeuzem S, Herrmann E, Lee J-H, et al. Viral kinetics in patients with chronic hepatitis C treated with standard or peginterferon alpha2a. *Gastroenterology* 2001;120:1438-47.
- Neumann AU, Lam NP, Dahari H, et al. Differences in viral dynamics between genotypes 1 and 2 of hepatitis C virus. *J Infect Dis* 2000;182:28-35.
- National Institutes of Health Consensus Development Conference Statement: man-

- agement of hepatitis C 2002 — June 10–12, 2002. *Hepatology* 2002;36:Suppl 1:S3-S20.
10. Italian Association for the Study of the Liver. Guidelines: online final statement. (Accessed May 31, 2005, at <http://www.webaisf.org>.)
11. Zeuzem S, Lee JH, Franke A, et al. Quantification of the initial decline of serum hepatitis C virus RNA and response to interferon alfa. *Hepatology* 1998;27:1149-56.
12. Neumann AV, Zeuzem S, Brunda MJ, Hoffman JH. Rapid viral response to treatment with pegylated (40KD) interferon alfa-2a (Pegasys) is strongly predictive of a sustained virologic response in patients with chronic hepatitis C (CHC). *Hepatology* 2000;32:Suppl:318A. abstract.
13. Neumann AV, Zeuzem S, Ferrari C, et al. DITTO-HCV early viral kinetics report—novel decline patterns in gen 1 but not gen 2-3 patients treated with Peg-IFN-alfa-2a and ribavirin. *J Hepatol* 2002;36:Suppl 1:121.
14. Cheng DM, Lagakos SW. The one-sample problem from eradication studies of chronic viral infection. *Biometrics* 2000;56:626-33.
15. Zeuzem S, Pawlotsky JM, Hagi E, et al. International, multicenter, randomized, controlled study comparing standard versus dynamically individualized treatment in patients with chronic hepatitis C (DITTO-HCV project). *Hepatology* 2003;38:310A. abstract.
16. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol* 1991;13:372-4.
17. Dalgard O, Bjoro K, Hellum KB, et al. Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *Hepatology* 2004;40:1260-5.
18. Zeuzem S, Hultcrantz R, Bourliere M, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol* 2004;40:993-9. [Erratum, *J Hepatol* 2005;42:434.]
19. von Wagner M, Huber M, Berg T, et al. Randomized multicenter study comparing 16 vs 24 weeks of combination therapy with peginterferon alfa-2a plus ribavirin in patients chronically infected with HCV genotype 2 or 3. *Hepatology* 2004;40:Suppl 1:725A. abstract.

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