

Individualized Treatment Duration for Hepatitis C Genotype 1 Patients: A Randomized Controlled Trial

Alessandra Mangia,¹ Nicola Minerva,² Donato Bacca,³ Raffaele Cozzolongo,⁴ Giovanni L. Ricci,⁵ Vito Carretta,⁶ Francesco Vinelli,⁷ Gaetano Scotto,⁸ Giuseppe Montalto,⁹ Mario Romano,¹⁰ Giuseppe Cristofaro,¹¹ Leonardo Mottola,¹ Fulvio Spirito,¹ and Angelo Andriulli¹

It was hypothesized that in hepatitis C virus (HCV) genotype 1 patients, variable treatment duration individualized by first undetectable HCV RNA is as effective as standard 48-week treatment. Patients ($n = 696$) received peginterferon alfa-2a, 180 mg/week, or peginterferon alfa-2b, 1.5 mg/kg/week, plus ribavirin, 1000-1200 mg/day, for 48 weeks (standard, $n = 237$) or for 24, 48, or 72 weeks if HCV-RNA–negative at weeks 4, 8, or 12, respectively (variable, $n = 459$). Sustained virologic response (SVR) was achieved in 45.1% [95% confidence interval (CI) 38.8-51.4] of the patients in the standard group and in 48.8% (CI 44.2-53.3) of the patients in the variable group ($P = 0.37$). The percentages of patients who first achieved undetectable HCV RNA at weeks 4, 8, or 12 were 26.7%, 27.8%, and 11.3%, respectively. In the standard treatment group, 87.1%, 70.3%, and 38.1% of patients who first achieved undetectable HCV RNA at 4, 8, or 12 weeks attained SVRs, respectively. In the variable group, corresponding SVR rates were 77.2%, 71.9%, and 63.5%. Low viremia levels and young age were independent predictors of response at week 4 [rapid virologic response (RVR)]. RVR patients with baseline viremia $\geq 400,000$ IU/mL achieved higher SVR rates when treated for 48 weeks rather than 24 weeks (86.8% versus 73.1%, $P = 0.14$). The only predictive factor of SVR in RVR patients was advanced fibrosis. **Conclusion:** Variable treatment duration ensures SVR rates similar to those of standard treatment duration, sparing unnecessary side effects and costs. (HEPATOLOGY 2008;47:43-50.)

For the management of chronic hepatitis C virus (HCV) genotype 1 infection, 48 weeks of therapy with peginterferon (Peg-IFN) plus ribavirin (RBV) is recommended.¹ With this regimen, up to 45% of pa-

tients will attain a sustained virologic response (SVR).¹⁻⁴ Current therapeutic strategies to improve this SVR rate rely on treatment individualization. For example, there is accumulating evidence that patients with a < 2 -log decrease in HCV-RNA levels by week 12 of treatment will not attain SVR,^{5,6} and discontinuation of treatment in nonresponders at this time is recommended to avoid unnecessary therapy.^{1,7}

As a further step toward individualized treatment, shortening the length of therapy to 12-16 weeks in patients with a rapid virologic response (RVR) at week 4 has been demonstrated to be as effective as the standard 24-week regimen in HCV genotype 2 and 3 infection in all but one trial.⁸⁻¹² For patients with HCV genotype 1 and viremia levels $\leq 600,000$ IU/mL at baseline, Zeuzem et al.¹³ reported SVR rates of up to 89% after an abbreviated course of 24 weeks of therapy in the subset of patients who became HCV-RNA–negative at week 4. In contrast, in patients without RVR, the shortened treatment duration resulted in a high rate of relapse after cessation of therapy.¹³ As patients with low viremia represent approximately one-third of the overall HCV genotype 1 population, the suggested 24-week treatment duration would benefit only a minority of patients.

Abbreviations: ALT, alanine transferase; BMI, body mass index; CI, confidence interval; EOT, end of treatment; HCV, hepatitis C virus; OR, odds ratio; PCR, polymerase chain reaction; Peg-IFN, peginterferon; RBV, ribavirin; RVR, rapid virologic response; SD, standard deviation; SVR, sustained virologic response; unl, upper normal limit.

From ¹Gastroenterology, Istituto di Ricovero e Cura a Carattere Scientifico, "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Italy; ²Internal Medicine, Hospital Canosa, Italy; ³Internal Medicine, Hospital Casarano, Italy; ⁴Gastroenterology, Istituto di Ricovero e Cura a Carattere Scientifico, "De Bellis" Hospital, Castellana Grotte, Italy; ⁵Internal Medicine, University "La Sapienza," Rome, Italy; ⁶Internal Medicine, Hospital Venosa, Italy; ⁷Gastroenterology, Ospedali Riuniti, Foggia, Italy; ⁸Infectious Disease, University of Foggia, Italy; ⁹Internal Medicine, University of Palermo, Italy; ¹⁰Hepatology Unit "S. Pertrin" Hospital, Rome, Italy; and ¹¹Internal Medicine, Brindisi, Italy.

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Address reprint requests to: Alessandra Mangia, Gastroenterology Unit, Istituto di Ricovero e Cura a Carattere Scientifico "Casa Sollievo della Sofferenza" Hospital, 71013 San Giovanni Rotondo, Italy. E-mail: a.mangia@tin.it; fax: +39 0882 455161.

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In a post hoc analysis of data of a registrative trial, Drusano and Preston¹⁴ hypothesized that the longer HCV RNA remained undetectable after initial clearance, the higher the chance was of attaining SVR. This claim requires an experimental evaluation but at the moment would indicate that individualized treatment might also include extended treatment duration in patients with slow virologic responses, who are defined as HCV-RNA-positive at weeks 4 and 12 but negative at week 24.¹⁵⁻¹⁷ The subset of genotype 1 patients that needs to be treated longer than currently recommended remains to be further elucidated. Reserving a 72-week regimen to patients still viremic at week 12 but who cleared the infection by week 24 of treatment has resulted in only a marginal, although significant, increase in the SVR rate.^{16,17} In patients without RVR at week 4, Sanchez-Tapias et al.¹⁸ reported significantly higher SVR rates in the 72-week-treated patients in comparison with those in the standard, 48-week treatment duration (54% versus 32%). No information is available on the benefit of extended treatment duration in patients who become HCV-RNA-negative between weeks 4 and 12.

As the on-treatment virologic response appears crucial for both tailoring the length of therapy and influencing treatment outcome, we prospectively evaluated the efficacy of Peg-IFN alfa-2a or Peg-IFN alfa-2b in combination with RBV in treatment-naïve HCV genotype 1 patients randomized to the standard duration of 48 weeks or to a duration individualized according to the HCV-RNA clearance during the initial 12 weeks from the start of therapy.

Patients and Methods

Patient Selection

Treatment-naïve patients with compensated chronic HCV genotype 1 infection, 18 to 70 years old, were eligible for enrolment if they were anti-HCV-positive by third-generation enzyme immunoassay, were HCV-RNA-positive by qualitative reverse-transcription polymerase chain reaction (PCR), had neutrophil and platelet counts of $\geq 1500 \mu\text{L}$ and $\geq 90,000 \mu\text{L}$, had hemoglobin levels of $\geq 12 \text{ g/dL}$ for women and $\geq 13 \text{ g/dL}$ for men, and had creatinine levels of $< 1.5 \text{ mg/dL}$. Liver biopsy was not mandatory for the patients to be enrolled. Patients were excluded if they had other causes of liver disease, hepatitis B virus infection, human immunodeficiency virus infection, autoimmune disorders, clinically significant cardiac or cardiovascular abnormalities, systemic infection, an organ graft, clinically significant bleeding disorders, evidence of malignant diseases, concomitant immunosuppressive medication, excessive alcohol intake,

or concomitant drug abuse or if they were pregnant or lactating or were male partners of pregnant women.

Study Design

Eleven centers in the south of Italy took part in this prospective, randomized, controlled study. The study was investigator-designed and investigator-driven and received no support from pharmaceutical companies.

Patients received Peg-IFN alfa-2a (Pegasys, Roche Laboratories, Nutley, NJ), 180 $\mu\text{g/week}$, or Peg-IFN alfa-2b (PEG-Intron, Schering Plough, Kenilworth, NJ), 1.5 $\mu\text{g/kg/week}$, combined with RBV (Copegus, Roche Laboratories or Rebetol, Schering Plough), 1000 mg/day if body weight $\leq 75 \text{ kg}$ or 1200 mg/day if body weight $> 75 \text{ kg}$. Peg-IFN and RBV dose modifications followed standard criteria and procedures.

Patients received treatment for the standard duration of 48 weeks (standard group) or for an individualized duration based on the time when HCV RNA first became undetectable (variable group). In the variable group, patients who were first HCV-RNA-negative at week 4 were treated for a total of 24 weeks, whereas those who were first HCV-RNA-negative at weeks 8 and 12 were treated for a total of 48 and 72 weeks, respectively. Patients with a ≥ 2 -log drop in HCV-RNA levels at week 12 were treated for 48 and 72 weeks in the standard or variable group, respectively. Patients with a < 2 -log decline at week 12 had to stop treatment per protocol and were considered nonresponders. Similarly, all patients viremic at week 24 were considered nonresponders and excluded from further treatment. At the end of treatment (EOT), all patients were followed up for a further 24 weeks.

Dose reduction was performed stepwise on the basis of the neutrophil count to 135 and to 90 $\mu\text{g/week}$ for Peg-IFN alfa-2a and from 120 to 100 μg or from 100 to 80 μg for Peg alfa-2b according to neutrophil counts lower than 1000, 750, or 500. RBV was also reduced stepwise when it was lower than 10 mg/dL. The use of G-CSF was allowed only in patients with cirrhosis. Epoietin use was also admitted for a hemoglobin decrease of 2 mg/dL. RBV was stopped when haemoglobin values decreased below 8 mg/dL.

A computer-generated list of randomization was sent to each participating center, where, at the study entry, patients were allocated 1:2 to the standard or variable groups in blocks of five. Each participating investigator prescribed Peg-IFN alfa-2a or alfa-2b on a 1:1 basis. The study received ethics committee approval at each center and was conducted according to the Declaration of Helsinki.

Patient Evaluation

All patients were evaluated as outpatients for safety, tolerance, and efficacy. HCV-RNA levels were assessed at weeks 4, 8, 12, 24, 48, and 72 during treatment and at 24 weeks of follow-up after treatment. HCV-RNA levels were quantified at baseline (Amplicor Monitor HCV 2.0, Roche Diagnostics, Basel, Switzerland; lower limit of detection = 600 UI/mL) and qualitatively analyzed by PCR assay (Amplicor HCV, Roche Molecular Systems, Branchburg, NJ; lower limit of detection = 50 UI/mL) during and off therapy. HCV-RNA testing was carried out at the individual center, provided that all centers had in use the same assay. According to recent studies,¹⁹ a 400,000 IU/mL value of serum HCV RNA was chosen as the cutoff for low or high viral load.

HCV genotyping was performed by reverse hybridization (InnoLIPA HCV, Innogenetics, Gent, Belgium). Histologic results were classified by local pathologists following standard criteria.²⁰ For better comparison between the different pathologists, the individual fibrosis stage was documented as significant (cirrhosis/transition to cirrhosis) or not significant (no cirrhosis).

Endpoints

The primary endpoint was the comparison of SVR rates in the standard and variable groups. Secondary aims were to ascertain SVR rates according to on-treatment virologic response as determined by qualitative HCV-RNA assays at weeks 4, 8, and 12 and to compare these rates in the standard and variable groups. SVR was defined as undetectable serum HCV RNA at the end of the follow-up period, as determined by PCR test. Treatment failure was categorized as relapse (reappearance of HCV RNA during the follow-up period after an EOT response), nonresponse (HCV-RNA-positive at week 24), or discontinuation (treatment withdrawn for any reason).

The third endpoint was the evaluation of predictors of 12-week virologic response and SVR. Patient's age, gender, body weight, body mass index (BMI), serum alanine transferase (ALT) level, serum HCV-RNA level, HCV genotype, stage of fibrosis, and grade of inflammation were considered. Platelet counts below 140,000 per cubic millimeter were taken as evidence of advanced fibrosis in patients without biopsy, as this value was found in our previous investigations to possess a 77.4% positive and 93.1% negative prediction power for significant fibrosis.²¹

Sample Size Estimation

The study was designed as a noninferiority analysis, comparing standard and variable treatment duration. An SVR rate of 45% was expected on the basis of data from

previous international studies.²⁻⁴ To show that the variable treatment duration is no more than 5% different than the standard duration, with a 1-sided 95% confidence interval (CI), a sample size of 212 patients per treatment group was estimated to be required to obtain 80% power. With a dropout rate of 10% allowed, 237 patients per group were to be recruited. However, as our secondary aim was to investigate SVR rates according to on-treatment virologic response, double this number of patients were assumed to be recruited into the variable group for meaningful subgroup comparisons.

Statistical Analysis

The intent-to-treat population, which included all randomized patients who received at least one dose of the study medication, was used for the analysis of the primary and secondary study endpoints.

The descriptive analysis included absolute and relative frequencies for grouped data and means \pm standard deviations for continuous scaled data. Statistical comparison between patients with and without SVR used the χ^2 test and the *t* test (continuous data). The level of significance was 0.05 (2-sided) for all statistical tests; all CIs provided are at 95%. A commercially available software program (SPSS for Windows, SPSS Release 11.5, SPSS, Inc., Chicago, IL) was used for the statistical analyses.

Results

Patient Population

Between June 2004 and December 2005, 997 patients with HCV genotype 1 were screened: 711 met all inclusion and exclusion criteria, and 15 did not receive a single dose of study medication. Of the remaining 696 patients, 237 were randomized to the standard group, and 459 were randomized to the variable group (Fig. 1). Baseline demographic, biochemical, and virologic characteristics of patients did not differ between the 2 groups (Table 1). The majority of patients were ≥ 45 years of age, had a BMI < 27 kg/m², had serum ALT levels < 3 times the upper normal limit, were infected with HCV genotype 1b, and had a high viral load and low activity. The fibrosis stage was ≥ 2 in more than 60% of patients. Baseline characteristics did not differ between patients treated with Peg-IFN alfa-2a and Peg-IFN alfa-2b (data not shown).

EOT Response and SVR According to the Treatment Group

In the standard group, 131 of 237 (55.3%) patients achieved an EOT response versus 278 of 459 patients (60.6%) in the variable group ($P = 0.22$). At the end of the 24-week follow-up, SVR was reported in 107 (45.1%, CI 38.8-51.4) patients in the standard group and in 224

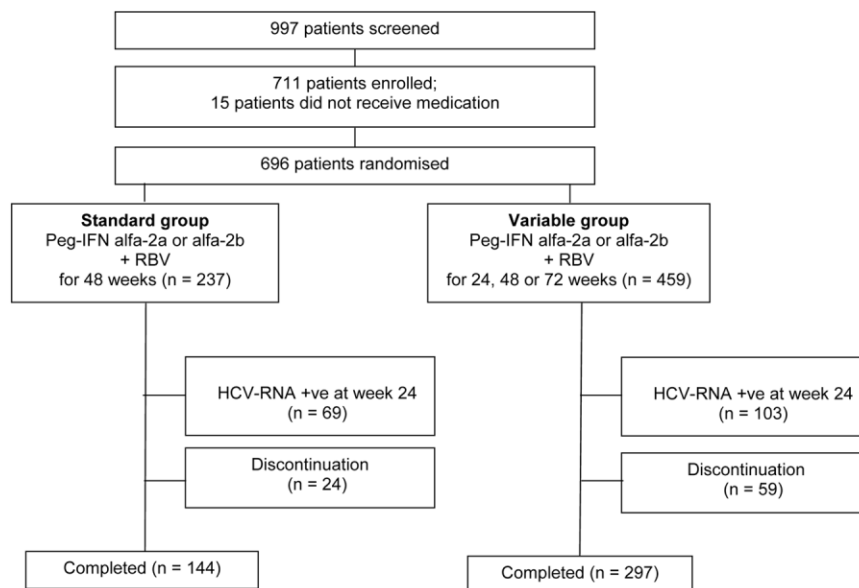


Fig. 1. Progress of patients through the study.

(48.8%, CI 44.2-53.3) patients in the variable group [$P = 0.37$; difference (the rate in the standard duration group minus that in the variable duration group) -3.7 , CI 3.3-4.0]. As this difference fell within our predefined criterion for a noninferiority study, the individualized regimen was considered equivalent to the standard regimen. The number of relapsers was similar between the 2 groups: 25 (19.1%) patients with EOT response in the standard group and 54 (19.4%) patients in the variable group ($P = 1.0$).

RVR, EOT, and SVR Responses According to the Type of Peg-IFN Administered

RVR was achieved in 105 of 362 (29%) patients treated with Peg-IFN alfa2b and in 80 of 334 (24%) patients treated with Peg-IFN alfa2a ($P = 0.14$). In the Peg-IFN alfa-2b group, 205 of 362 (56.6%) patients achieved EOT versus 204 of 334 (61.1%) in the Peg-IFN alfa-2a group ($P = 0.24$). At the end of the 24-week follow-up, SVR was reported in 165 (45.6%, CI 40.4-50.7) patients in the former group and in 164 (49.1%, CI 43.7-54.4) in the latter group ($P = 0.36$). Forty patients in each group relapsed off therapy.

EOT Response and SVR According to Time of First Undetectable HCV RNA (Fig. 2)

In the entire population of 696 patients, 185 (26.6%) individuals had undetectable HCV RNA at treatment week 4: 62 (26.2%) patients from the standard group and 123 (26.8%) patients from the variable group ($P = 0.90$). In RVR patients, EOT and SVR responses, respectively, were reported in 60 (96.7%, CI 92.3-100) and 54

(87.1%, CI 78.7-95.4) patients treated for 48 weeks and in 117 (95.1%, CI 92.3-99.4) and 95 (77.2%, CI 69.8-84.6) patients treated for 24 weeks ($P = 0.42$ for EOT response, $P = 0.12$ for SVR; difference in SVR rates -9.9 , CI 10.5-9.2). Off therapy, virologic relapse occurred in 6 (10%) and 22 (18.8%) patients in the 2 groups, respectively ($P = 0.13$).

Of 511 viremic patients at week 4, HCV RNA was first undetectable by week 8 in 192 individuals: 64 (27.2%) and 128 (27.8%) patients in the standard and variable groups, respectively (Fig. 2). These 192 patients received therapy for a total of 48 weeks, and SVR rates of 70.3% and 71.9% were registered in the 2 groups, respectively ($P = 0.86$).

Of 319 patients with detectable HCV RNA at week 8, 73 tested negative at week 12: 21 (8.9%) and 52 (10.4%) patients in the standard and variable groups, respectively. SVR was reported in 8 patients (38.1%, CI 15.1-58.3) after 48 weeks of therapy and in 33 (63.5%, CI 50.3-76.5) patients after 72 weeks ($P = 0.068$; difference -25.4 , CI 22.3-28.4). Virologic relapse occurred in 6 of 14 (42.8%) patients with EOT response in the standard group and in 7 of 40 (15%) patients in the variable group ($P = 0.057$).

The remaining 246 patients, 90 from the standard group and 156 from the variable group ($P = 0.50$), were still viremic at week 12 (Fig. 2). Twenty-one and 53 of these patients had a ≥ 2 -log drop in HCV-RNA levels at this time of evaluation and were treated for 48 or 72 weeks, respectively: EOT response was reported in a single patient in the standard group (4.7%) and in 10

Table 1. Baseline Patient Characteristics (n = 694)

Characteristic	Standard Group (n = 237)	Variable Group (n = 459)	P Value
Age, mean years ± SD	52.6 ± 11.8	51.1 ± 12.1	0.12
Age, n (%)			
<45 years	52 (22)	105 (23)	0.84
≥45 years	185 (78)	354 (77)	
Gender, n (%)			
Female	105 (44)	201 (44)	0.93
Male	132 (56)	258 (56)	
Route of HCV transmission, n (%)			
Blood transfusion	50 (21)	93 (20)	0.81
Drug abuse	17 (7)	37 (8)	
Unknown	170 (72)	329 (72)	
BMI, mean kg/m ² ± SD	26.2 ± 3.5	25.7 ± 3.6	0.06
BMI, n (%)*			
<27 kg/m ²	152 (64)	301 (70)	0.09
≥27 kg/m ²	85 (35)	136 (30)	
Grade of activity, n (%)†			
0-2	167 (76)	306 (78)	0.42
3	54 (24)	89 (22)	
Fibrosis stage, n (%)‡			
0-2	140 (62)	258 (65)	0.33
3-4	87 (38)	134 (34)	
Steatosis§			
Yes	70 (31)	103 (26)	0.07
No	151 (68)	295 (74)	
Serum ALT, n (%)			
<3 unl	193 (81)	385 (84)	0.39
≥3 unl	44 (19)	74 (16)	
HCV genotype, n (%)			
1a	15 (6)	49 (11)	0.08
1b	222 (94)	410 (89)	
Serum HCV RNA, n (%)			
<400,000 IU/mL	62 (26)	103 (22)	0.30
≥400,000 IU/mL	175 (74)	356 (78)	
Treatment, n (%)			
Peg-IFN alfa-2b + RBV	127 (53)	235 (51)	0.52
Peg-IFN alfa-2a + RBV	110 (46)	224 (49)	

SD indicates standard deviation; and unl, upper normal limit.

*Twenty-two values were missing from the variable group.

†Data were unavailable from 78 patients, including 14 and 64 from the standard and variable groups, respectively.

‡Data were unavailable from 67 patients, including 10 and 57 from the standard and variable groups, respectively.

§Data were missing from 6 and 61 patients from the standard and variable groups, respectively.

(18.9%) patients in the variable group ($P = 0.22$). No patients in the standard group but 4 (7.5%) in the variable group achieved an SVR ($P = 0.30$). The remaining 172 patients with a <2-log decline at week 12 had to stop therapy per protocol.

Baseline Predictors of On-Treatment Virologic Response

Predictors of RVR. In univariate analysis, factors associated with RVR were young age ($P = 0.004$), low viremia levels ($P = 0.0001$), and fibrosis stage ≤ 2 ($P = 0.0001$). In multivariate analysis, the independent predictors of RVR were serum HCV-RNA levels <400,000

IU/mL [odds ratio (OR) 2.27, CI 1.49-3.41] and absence of advanced fibrosis (OR 1.40, 95% CI 1.15-1.64).

Predictors of First Response at Weeks 8 and 12.

Among patients with HCV RNA first undetectable at week 8, age <45 years ($P = 0.004$), BMI <27 kg/m² ($P = 0.02$), and HCV genotype 1a ($P = 0.03$) were predictors of response; in multivariate analysis, response was predicted by young age (OR 1.68, CI 1.06-2.65). Among patients with HCV RNA first undetectable at week 12, grade of activity ≥ 2 was the only predictor of response ($P = 0.039$).

Predictors of Nonresponse by Week 12. Failure to achieve viral clearance by week 12 was associated, in univariate analysis, with age ≥ 45 years ($P = 0.0001$), grade of activity ≤ 2 ($P = 0.0001$), fibrosis stage ≥ 3 ($P = 0.0001$), BMI ≥ 27 kg/m² ($P = 0.005$), and high viremia ($P = 0.013$). In multivariate analysis, all baseline characteristics except viral load and low activity grade were significant predictors of nonresponse: fibrosis stage >2 (OR 1.80, CI 1.21-2.52), age ≥ 45 years (OR 1.66, CI 1.06-2.57), and BMI ≥ 27 kg/m² (OR 1.43, CI 1.00-2.03).

Predictors of SVR

In RVR patients with baseline viremia $\geq 400,000$ IU/mL, SVR rates were observed in 33 of 38 patients (86.8%) after a treatment duration of 48 weeks and in 57 of 78 patients (73.1%) after 24 weeks of treatment ($P = 0.14$). In RVR patients with lower viremia, SVR was found in 20 of 24 patients (83.3%) and in 38 of 45 patients (84.4%), respectively ($P = 0.83$). The only independent predictor of SVR in RVR patients was a mild to moderate degree of fibrosis (OR 2.60, CI 1.09-6.17). Off therapy, 24.4% and 8.9% of patients with high or low viremia relapsed ($P = 0.05$).

Safety

The incidence of adverse events in the 2 treatment groups was similar (Table 2). A decrease in the hemoglobin level to <9.5 g/dL occurred in 20 (8.4%) patients in the standard group and in 33 (7.1%) patients in the variable group ($P = 0.66$). Neutrophil counts <1000/mm³ requiring Peg-IFN dose reduction occurred in 12 (5.1%) patients in the standard group and in 19 (4.1%) patients in the variable group ($P = 0.69$). Overall, 91 (73.4%) patients in the standard group and 190 (76.9%) patients in the variable group completed treatment on full doses of both drugs (Table 3); 32 (26.6%) and 47 (19.8%) patients, respectively, required dose reduction.

Side effects that led to treatment discontinuation occurred in 24 (10.1%) and 59 (12.9%) patients in the standard and variable groups, respectively ($P = 0.19$; Table 3). In the standard group, 21 patients discontinued

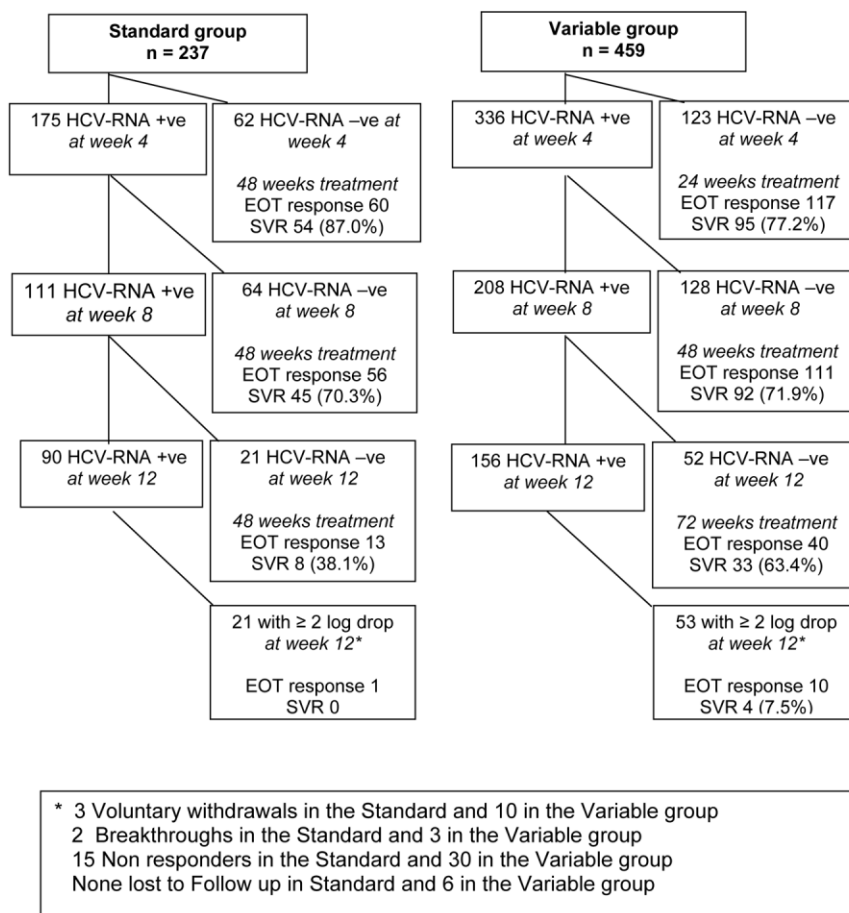


Fig. 2. Summary of study outcome.

treatment by week 12, and 3 patients discontinued treatment between weeks 24 and 48. In the variable group, 41 patients discontinued treatment by week 12, 16 discontinued treatment between weeks 24 and 48, and 2 discontinued treatment between weeks 24 and 72.

Lack of compliance was a further reason for treatment discontinuation in 8 (34.7%) patients in the standard group and in 29 (49.1%) patients in the variable group ($P = 0.49$; Table 3).

Discussion

The present prospective investigation in patients with HCV genotype 1 infection has shown equivalent rates of

lasting viral clearance after therapy with Peg-IFNs and RBV administered for the standard 48-week length or a variable duration tailored to the first undetectable HCV RNA during the initial 12 weeks of therapy. A relevant result of this finding is that current guidelines for treating these patients lead to overtreatment in some individuals and undertreatment in others.

Not all patients with HCV genotype 1 are alike in their responsiveness to antiviral therapy, and those most likely

Table 2. Treatment-Related Adverse Events

Adverse Event, n (%)	Standard Group (n = 237)	Variable Group (n = 459)
Asthenia	101 (42.6)	183 (39.8)
Influenza-like symptoms	34 (14.3)	87 (18.9)
Dermatologic symptoms	29 (12.2)	60 (13.0)
Psychiatric symptoms	4 (1.7)	7 (1.5)
Anemia	20 (8.4)	33 (7.1)
Leukopenia and thrombocytopenia	58 (24.4)	35 (7.6)
Thyroid diseases	7 (2.9)	11 (2.3)

Table 3. Summary of Treatment Outcome

Treatment Outcome, n (%)	Standard Group (n = 237)	Variable Group (n = 459)
Treatment completion	122 (51.4)	237 (51.6)
On full dose	90 (73.7)	190 (80.1)
With any dose reduction	32 (26.6)	47 (19.8)
No response at week 24	91 (38.4)	163 (35.6)
Treatment discontinuation	24 (10.1)	59 (12.9)
Before week 12	21 (87.5)	41 (69.4)
Between weeks 12 and 24	0	0
Between weeks 24 and 48	3 (12.5)	16 (32.7)
Later than week 48	0	2 (3.6)
Reason for discontinuation		
Adverse events	16 (66.6)	30 (51.0)
No compliance	8 (34.7)	29 (49.1)

to benefit from therapy are those capable of clearing the virus from the blood during the initial 12 weeks of therapy. About 36.4% of patients were not sensitive enough to the effect of Peg-IFN and RBV combination therapy to achieve on-treatment response by week 12. When patients who cleared HCV RNA by week 12 were compared with those still viremic at this time point, patients who were sensitive to antiviral therapy were characterized by BMI <27 kg/m², fibrosis stage ≤2, and age <45 years. A high viral load at baseline did not predict virologic response by week 12 as strongly as BMI, the severity of damage at histology, and patient's age.

This study shows that in HCV genotype 1 the treatment duration should be tailored to the 12-week on-treatment virologic response. Moreover, it confirms in a prospective fashion the concept emerging from a post hoc analysis of data that the longer the virus is rendered undetectable in serum, the better the probability of SVR is.¹⁴ About one-quarter of our patients first had undetectable HCV RNA at week 4 in serum and were randomized to short or standard duration of therapy: the SVR rate in patients treated for 24 weeks was substantial (77.2%) but lower than that in those treated for 48 weeks (87.1%). These differences did not attain the level of significance and may not have clinical relevance when we consider that about two-thirds of genotype 1 patients with response at week 4 may be safely treated for only 24 weeks. In order to further refine the subset of HCV genotype 1 patients who might benefit from short therapy, we have analyzed SVR rates according to baseline viremia. RVR patients with pretreatment HCV-RNA levels below 400,000 IU/mL achieved an excellent SVR rate of 84.4% after a short course of therapy, which was comparable to the 85.3% rate in the standard 48-week group. These data are in line with recent studies in which a truncated course of therapy in HCV-1-infected patients with low baseline viremia who became HCV-RNA-negative after 4 weeks of treatment did not impair the SVR rate.^{13,22} Conversely, in highly viremic patients at baseline who tested HCV-RNA-negative at treatment week 4, SVR rates declined from the 86.8% value after standard therapy to 73.1% after the short therapy because of a higher relapse rate off therapy. Despite the nonsignificant *P* value (*P* = 0.14) achieved in a comparison of 24 and 48 weeks in high viral load patients with RVR, a trend toward a lower rate of SVR after 24 weeks makes it difficult to reach a sound conclusion on this point. Although a favorable outcome for potential retreatment has been recently reported,²³ the clinical relevance of a relapse should be considered.

Beyond the virologic response at treatment week 4, a further original finding of the present study is the evaluation of SVR rates in patients clearing the virus at weeks 8

and 12 of treatment. The former subset of patients had to be treated per protocol for 48 weeks, independently of baseline viremia, and two-thirds of them experienced an SVR, which was predicted only by young age (OR 1.63, CI 1.06-2.65). This finding is confirmatory of other studies showing age as an independent predictor of SVR in HCV-1-infected patients treated with Peg-IFN alfa-2b and RBV.^{3,24}

Only a limited number of patients required 72 weeks of treatment after a first virologic response at week 12 in the variable group. However, the SVR rate for the 12-week responders was higher in the variable group than in the standard group (63.5% versus 38.1%), supporting the concept that prolongation of treatment beyond 48 weeks may be advantageous for these patients. Although it should be acknowledged that in noninferiority studies the statistical power declines in subanalyses because of shrinking numbers of patients, this difference is substantial and may warrant a prospective trial. Weight-based dosing of RBV, together with a strategy of excluding from longer treatment duration patients likely to achieve an SVR with the standard treatment duration,²⁵ might explain the SVR rate registered in this subset of patients, which was higher than the 32% value reported by Sanchez-Tapias et al.¹⁸ Disappointing rates of SVR were encountered in viremic patients with a ≥2-log decline of viremia at treatment week 12: no single patient cleared HCV after 48 weeks of therapy, whereas only 7.5% of such patients responded after the treatment was prolonged to 72 weeks. However, few patients assigned to the prolonged treatment duration were able to tolerate therapy, and the majority dropped out earlier because of the associated side effects. Intensifying follow-up visits might improve compliance and allow for implementation of individualized treatment regimens in this subset of patients.

In conclusion, variable treatment duration ensures an SVR rate similar to that of the standard treatment duration, with significant potential reductions in cost and side effects. We found that approximately a quarter of HCV genotype 1 patients may be cured by therapy in only 24 weeks and that an approximately comparable rate of patients may require extended treatment for 72 weeks. HCV RNA should be monitored qualitatively at week 4 to identify patients with the highest likelihood of response and at weeks 8 and 12 to determine if an extended treatment duration may be required.

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