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Extended Treatment Duration for Hepatitis C Virus Type 1: Comparing 48 Versus 72 Weeks of Peginterferon-Alfa-2a Plus Ribavirin

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See editorial on page 1357.

Background & Aims: The treatment of patients infected with hepatitis C virus (HCV) type 1 remains a challenge necessitating innovative strategies to improve treatment outcome. The extension of treatment duration beyond 48 weeks is one possible strategy to address this problem. *Methods:* The efficacy and safety of 48 weeks (group A, N = 230) vs 72 weeks (group B, N = 225) of treatment with pegylated–interferon-alfa-2a (180 μg/wk) plus ribavirin (800 mg/day) were studied in treatment-naive patients with HCV type 1 infection. On-treatment and sustained virologic response (SVR) 24 weeks after stopping treatment was assessed by qualitative reverse-transcription polymerase chain reaction (sensitivity 50 IU/mL). *Results:* Overall, no significant differences could be observed in the treatment outcome between both groups. End-of-treatment and SVR rates in groups A and B were 71% vs 63% and 53% vs 54%, respectively. Patients with undetectable HCV-RNA levels already at weeks 4 and 12 had excellent SVR rates ranging from 76% to 84% regardless of treatment group, whereas patients shown to be still HCV-RNA positive at week 12 achieved significantly higher SVR rates when treated for 72 instead of 48 weeks (29% vs 17%, P = .040). A particular benefit from extended treatment duration was seen in patients with low-level viremia (<6000 IU/mL) at week 12. The frequency and intensity of adverse events was similar between the 2 groups. *Conclusions:* Extended treatment duration generally is not recommended in HCV type 1 infection and should be reserved only for patients with slow virologic response defined as HCV-RNA positive at week 12 but negative at week 24.

An estimated 3% of the world population is infected chronically with hepatitis C virus (HCV). Chronic hepatitis C is a major cause of cirrhosis and hepatocellular carcinoma and has become the most common indication for liver transplantation in many centers.[1,2]

The primary aim of antiviral therapy in patients with chronic HCV infection is a sustained virologic response (SVR) defined as undetectable serum HCV-RNA levels 24 weeks after the end of therapy by a sensitive molecular assay. The introduction of pegylated interferons (PEG–IFN-alfa) in combination with ribavirin in recent years greatly improved the treatment outcome of HCV infection.[3–6] Although the majority of HCV type 2– and type 3–infected patients can achieve virologic clearance, the treatment outcome of HCV type 1–infected patients

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; EVR, early virologic response; GGT, γ-glutamyl transpeptidase; OR, odds ratio; PEG-IFN, pegylated interferon; PCR, polymerase chain reaction; SVR, sustained virologic response.

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remains unsatisfactory and sustained responses can be obtained in only approximately 50%.[3,6–8]

The turnover of hepatocytes infected with HCV type 1 is slower than that of hepatocytes infected with other HCV genotypes. It has been argued that this contributes to the observed differences in virologic treatment response.[9] These viral kinetic studies certainly offer some arguments for a more refined antiviral strategy in HCV type 1 infection. It already has been shown that extension of the PEG–IFN-alfa-2a plus ribavirin treatment duration from 24 to 48 weeks in type 1–infected patients results in a significant increase in SVR rates from 42% to 52% and in those with high-level viremia at baseline from 26% to 47%. Thus, it appears that the observed reduction in virologic relapse rates is a consequence of the prolonged treatment time and that periods even longer than 48 weeks may effect relapse rates positively in these difficult-to-treat patients. Following this concept we randomized HCV type 1–infected patients into 2 groups receiving PEG–IFN-alfa-2a and ribavirin either for 48 or 72 weeks and evaluated the outcome according to their virologic response and relapse rates.

Materials and Methods

Patients

Patients of both sexes aged 18 to 70 years with compensated chronic HCV genotype 1 infection who had not been treated previously with IFN-alfa and/or ribavirin were eligible for enrollment and had to fulfill the following inclusion criteria: a positive test for anti-HCV (third-generation enzyme immunoassay); HCV-RNA level greater than 1000 IU/mL by quantitative reverse-transcription polymerase chain reaction (PCR) (Amplicor Monitor HCV v. 2.0; Roche Molecular Systems, Mannheim, Germany; lower limit of detection 600 IU/mL); increased serum alanine transaminase (ALT) levels at screening; a liver biopsy specimen taken in the preceding 18 months of study entry showing chronic hepatitis; neutrophil and platelet counts of at least 1500 μL and 90,000 μL; hemoglobin values of at least 12 g/dL for women and 13 g/dL for men; and creatinine levels less than 1.5 mg/dL.

Patients were excluded if they had HCV genotype other than type 1 infection (ie, HCV types 2–6), decompensated liver disease, other causes of liver disease, hepatitis B virus infection, human immunodeficiency virus infection, autoimmune disorders, clinically significant cardiac or cardiovascular abnormalities, organ grafts, systemic infections, clinically significant bleeding disorders, evidence of malignant neoplastic diseases, concomitant immunosuppressive medication, excessive daily intake of alcohol, or drug abuse within the past year. Further exclusion criteria were as follows: unwillingness to use contraception, pregnancy, lactation, and male partners of pregnant women.

Study Design

Eighteen centers in Germany took part in this study designed as a prospective, open, randomized, and actively controlled trial. Patients were randomized to 1 of the 2 treatment groups with active treatment for 48 weeks (group A) or 72 weeks (group B). PEG–IFN-alfa-2a (40 kilodaltons) (Pegasys; Roche, Basel, Switzerland) at a dose of 180 μg (.5-mL prefilled syringe) was injected subcutaneously once a week. Ribavirin (Copegus; Roche) was administered orally in a morning and evening dose of 400 mg each. After the end of treatment patients from both groups were followed-up for a further 24 weeks.

Reasons for 800-mg Ribavirin Dose

We chose this dose for our study because dose-finding studies that allowed an estimate of the optimal ribavirin dosage still were lacking when we initiated the study. Similar to other investigators we also were concerned whether a ribavirin dose of 1000–1200 mg/day would be justified, realizing also from previous studies that in up to 40% of patients who were treated with this dose of ribavirin a dose reduction was necessary. We also realized that the cumulative dose of ribavirin when given at 800 mg/day for 72 weeks is comparable with the cumulative ribavirin dose of 1200 mg/day for 48 weeks (ie, in total, ≈402 g). Finally, safety concerns also led us to choose this dose in view of the long period of drug exposure.

Dose modification followed standard procedures. Thus, according to the intensity of the adverse event the dose of PEG–IFN-alfa first was reduced to 135 μg, and then further to 90 or 45 μg/wk as appropriate. For ribavirin, 200-mg dose reduction steps were performed. Dose limits were not considered as criteria to remove patients from the study.

Patient Evaluation

All patients were evaluated as outpatients for safety, tolerance, and efficacy. HCV-RNA level as the primary efficacy variable was assessed at weeks 4, 12, 24, 48, and 72 (group B) and again during the follow-up period at weeks 12 and 24. The HCV-RNA level was quantified by PCR assay (Amplicor Monitor HCV v. 2.0; Roche Molecular Systems; lower limit of detection, 600 IU/mL). End-of-treatment and SVRs were assessed by qualitative PCR assay (Amplicor HCV; Roche Molecular Systems; lower limit of detection, 50 IU/mL). HCV genotyping was performed by reverse hybridization (Inno LiPA HCV; Innogenetics, Gent, Belgium). Histologic results were classified by local pathologists according to internationally standardized criteria.[10] For better comparison between the different local pathologists the individual fibrosis stage was documented as stage 3 or higher, or less than stage 3 (ie, presence of cirrhosis/transition to cirrhosis or no cirrhosis).

Patients with an HCV-RNA level decrease of less than 2 logarithmic steps after 24 weeks of treatment as compared with baseline were regarded as nonresponders and excluded from further study treatment.

The study received ethics committee approval at each center according to the Declaration of Helsinki and the International

Conference on Harmonization/Committee for Proprietary Medicinal Products guidelines "Good Clinical Practice." Eligible patients were assigned randomly to the 2 study treatments with a ratio of 1:1 without stratification. Randomization was performed centrally (Chiltern International GmbH, Frankfurt, Germany) by facsimile after availability of the laboratory analyses in fixed blocks of 4.

Primary End Point

The primary measure of efficacy was SVR, defined as undetectable HCV-RNA level in serum at the end of the follow-up evaluation analyzed by a qualitative reverse-transcription PCR test. Treatment failures were categorized as follows: breakthrough: a reappearance of hepatitis C viremia during the treatment phase; relapse: reappearance of hepatitis C viremia during the follow-up period after stopping therapy in patients with an end-of-treatment virologic response; nonresponders: patients who failed to test HCV-RNA negative at any point during the study; and unknown: patients for whom not enough data were available for categorization.

Secondary end points were as follows. First, sustained biochemical response, as defined by normalization of ALT levels at the end of the follow-up period. Second, on-treatment virologic response rates as determined by qualitative and quantitative HCV-RNA assays at weeks 4, 12, and 24, and at the end of treatment. Third, evaluation of predictive parameters associated with SVR. To find out which patients may especially benefit from longer treatment periods the following baseline parameters were analyzed: patient's age, ethnicity, sex, body weight, body mass index (BMI), γ-glutamyl transpeptidase (GGT), ALT, glucose, platelet count, HCV-RNA serum concentrations, HCV subtype (1a vs 1b), presence of cirrhosis, and the relevance of early virologic response (EVR) at weeks 4 and 12 as determined by qualitative and quantitative HCV-RNA tests. Finally, comparison of the safety and tolerability of the 2 treatment regimens.

Definition of Patient Populations for Analysis

The analysis of the study's primary and secondary efficacy parameters was performed primarily on the basis of the intention-to-treat sample population, which included all randomized patients who received at least 1 dose of the study medication.

Statistical Analysis

Determination of sample size. For the primary analysis, an SVR rate of approximately 30%–40% was estimated and the study aim was to detect a difference between the 48-week and the 72-week treatment schedule of at least 15% (corresponding to SVR rates of 35% and 50%, respectively) with statistical significance (α error, .05; 2-sided β error, .20). In this analysis, 366 evaluable patients were required (183 patients per treatment group). Assuming a drop-out rate of 20%, 458 patients were to be recruited, 229 in each treatment group.

The primary aim of our secondary analysis was to identify prognostic factors for SVR separately for both treatment groups. Depending on the prevalence or distribution of the potential predictors in our sample, the detectable effect sizes were comparable with those in the primary analysis.

The descriptive analysis included absolute and relative frequencies for grouped data, and means, SDs, and ranges for continuous scaled data. The assumption of normal distribution could be accepted (after logarithmic transformation of glucose, ALT, and GGT levels) for all continuously scaled data (criterion, skewness between −1 and +1). Statistical comparisons between patients with and without SVR used the χ^2 test (grouped data) and the t test (continuous data). To obtain a multivariate prognostic score, logistic regression analysis was used. Cross-classification was applied to obtain unbiased error rates for the multivariate prognostic score. The prognostic value of several predictors and the multivariate score was displayed using receiver operating characteristic curve analysis.

The level of significance was .05 (2-sided) for all statistical tests. Commercially available software (SPSS for Windows, SPSS Release 11.5, SPSS Inc, Chicago, IL) and, for cross-classification, a macro (button "makros"; available at: http://www.medizin.fu-berlin.de/statistik/) was used.

Results

Patient Profile

A total of 467 patients were screened between December 2000 and July 2001 against all inclusion and exclusion criteria for entry into the study. Eight patients were screening failures and 4 patients did not receive study medication, leading to a total of 455 randomized patients (230 and 225 in groups A and B, respectively). The trial profile is shown in Figure 1. Both groups showed similar demographic, biochemical, and virologic baseline characteristics (Table 1). More patients in group B than in group A discontinued treatment prematurely (41% vs 24%; odds ratio [OR], 2.2; 95% confidence interval [CI], 1.47–3.29; $P < .001$; see Figure 2).

Virologic and Biochemical Response

The primary end point, an SVR at the end of a 24-week follow-up period, was observed in 53% (95% CI, 46.2–59.1) of patients in group A and in 54% (95% CI, 47.3–60.3) of patients in group B ($P = .8$). In addition, the on-treatment virologic response rates at weeks 4, 12, 24, and at the end of treatment were not significantly different between both groups (Table 2). The sustained biochemical response rates at the end of the follow-up period, defined as the proportion of patients who normalized serum ALT levels, were almost identical in both treatment groups (53.9% and 53.8% in groups A and B, respectively).

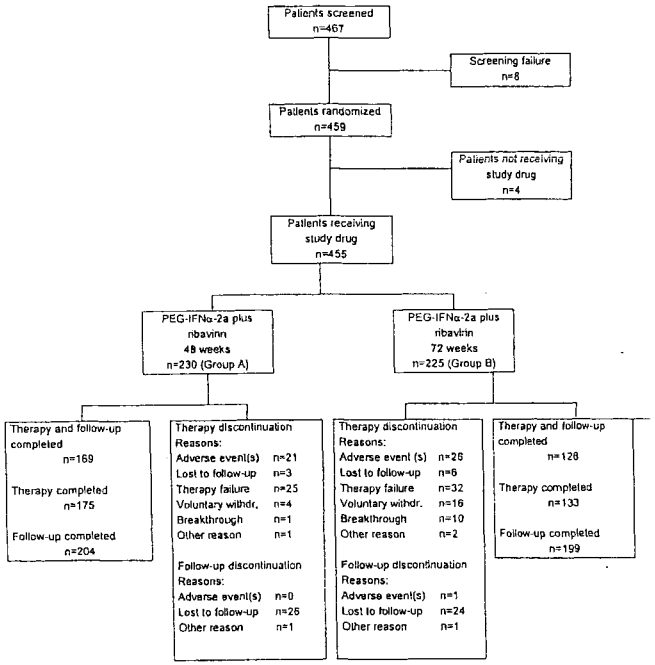

Figure 1. Trial profile.

SVR Rates in Patients With or Without EVR

Figure 3 shows the SVR rates in patients from groups A and B according to their EVR pattern as determined at treatment weeks 4 and 12 by qualitative HCV-RNA assay. Patients who were HCV-RNA positive at week 12 achieved significantly higher SVR rates when treated for 72 rather than 48 weeks (29% vs 17%; OR, 2.02; 95% CI, 1.034–3.94; $P = .040$), whereas patients with an EVR (HCV-RNA level, <50 IU/mL) at weeks 4 or 12 achieved SVR rates ranging from 76% to 84% independent of treatment duration.

Virologic Relapse Rates in Rapid and Slow Virologic Responders

The overall relapse rate in the intent-to-treat population was 29% (49 of 170) and 21% (33 of 154) in groups A and B, respectively ($P = .13$). However, when virologic relapse rates according to the on-treatment virologic response pattern were analyzed, significant differences could be observed between both groups as shown in Figure 4. In particular, patients with slow virologic response, defined as patients who were HCV-RNA positive at weeks 4 or 12 but HCV-RNA negative at week 24, showed benefit from extended treatment duration. Relapse rates were reduced in patients who first were HCV-RNA negative at week 12 (37% vs 23%; OR, 1.98; 95% CI, 1.13–3.46 in group A vs group B; $P = .016$) and in patients who first were HCV-RNA negative at week 24 (64% vs 40%; OR, 2.60; 95% CI, 1.16–5.88 in group A vs group B; $P = .021$). In patients with rapid virologic response, relapse rates were low and not influenced significantly by treatment duration (Figure 4).

HCV-RNA Log_{10} Decrease at Week 12 as a Measure of EVR

In contrast to absolute HCV-RNA levels, HCV-RNA $\log_{10}$ decrease at week 12 was less useful to identify patients who eventually may benefit from extended treatment duration. SVR rates in patients with EVR defined by a 2 $\log_{10}$ or more HCV-RNA decrease at week 12 were 68% (119 of 175 patients) in group A and 67% (115 of 171 patients) in group B ($P = .88$), and in those without a 2 $\log_{10}$ decrease were 4% (2 of 55 patients) and 11% (6 of 54 patients), respectively ($P = .15$). Only 26 of the 109 patients with a less than 2 $\log_{10}$ decrease at week 12 (24%) achieved an end-of-treatment virologic response. The relapse rates in these 26 end-of-treatment virologic responders was 87% (13 of 15 patients) when treated for 48 weeks (group A) and 46% (5 of 11 patients) when assigned to 72 weeks treatment (group B) (OR, 7.81; 95% CI, 1.16–52.63; $P = .034$).

Table 1. Summary of the Demographic, Biochemical, Serologic, Molecular, and Histologic Profiles of the Patients at Baseline

Characteristics	48 weeks (n = 230) (%)	72 weeks (n = 225) (%)	Total (n = 455) (%)
Sex			
Male	128 (55.7)	122 (54.2)	250 (54.9)
Female	102 (44.3)	103 (45.8)	206 (45.1)
Ethnic origin			
Caucasian	222 (96.5)	213 (94.7)	436 (95.6)
Asian	6 (2.6)	6 (2.7)	12 (2.6)
African American	2 (.9)	3 (1.3)	5 (1.1)
Other	0 (0)	3 (1.3)	3 (.7)
Age, *y*			
Mean ± SD	42.7 ± 11.22	42.7 ± 11.69	42.7 ± 11.44
Range	19–68	20–70	19–70
Height, *cm*			
Mean ± SD	172.6 ± 9.93	172.0 ± 9.62	172.3 ± 9.77
Range	146–196	143–197	143–197
Weight, *kg*			
Mean ± SD	76.3 ± 14.78	75.3 ± 14.30	75.8 ± 14.54
Range	42–161	39–128	39–161
BMI, kg/m^2			
Mean ± SD	25.6 ± 4.34	25.3 ± 4.00	25.5 ± 4.17
Range	17.0–47.0	15.6–37.4	15.6–47.0
Body surface, m^2			
Mean ± SD	1.9 ± .22	1.9 ± .21	1.9 ± .22
Range	1.3–2.9	1.3–2.6	1.3–2.9
Glucose, *mmol/L*			
Mean ± SD	5.24 ± 1.05	5.58 ± 2.11	5.41 ± 1.67
Range	3.1–10.0	3.4–22.4	3.1–22.4
ALT levels × upper limit of normal, *IU/L*			
Mean ± SD	2.58 ± 1.74	2.54 ± 1.51	2.52 ± 1.63
Range	.7–11.8	.4–8.0	.4–11.8
GGT levels × upper limit of normal, *IU/L*			
Mean ± SD	1.58 ± 1.51	1.83 ± 2.14	1.71 ± 1.85
Range	.2–11.3	.2–13.9	.2–13.9
HCV genotype			
Subtype 1b	155 (67.7)	132 (58.7)	287 (63.2)
Subtype 1a	60 (26.2)	67 (29.8)	127 (28.0)
Subtype 1a/1b	8 (3.5)	8 (3.6)	16 (3.5)
Type 1[a]	7 (3.0)	18 (8.0)	25 (5.5)
HCV RNA, *log IU/mL*			
Mean ± SD	5.79 ± .52	5.75 ± .52	5.77 ± .52
Range	3.24–7.24	3.60–7.39	3.24–7.39
Fibrosis stage			
Stages 0–2	214 (93.0)	205 (91.1)	419 (92.1)
Stages 3–4	16 (7.0)	20 (8.9)	36 (7.9)

[a]No subtype was determined.

Further Characterization of Slow Virologic Responders

The individual HCV-RNA levels at week 12 in slow virologic responders with or without virologic relapse are shown in Figure 4. Mainly patients with low-level viremia at week 12 achieved a benefit from extended treatment duration. In the group of patients with HCV-RNA concentrations less than 6000 IU/mL at week 12 the relapse rates were 57% (20 of 35 patients) vs 32% (12 of 37 patients) in groups A and B, respectively (OR, 2.78; 95% CI, 1.1–7.2; $P = .037$). In contrast, relapse rates were 91% (10 of 11 patients) and

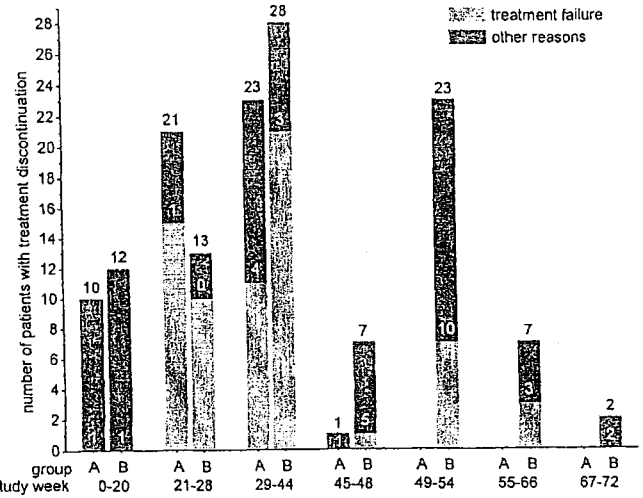

Figure 2. Comparison of the number of patients in groups A and B who discontinued treatment within a certain treatment period (weeks) either because of treatment failure or other reasons. *Treatment failure* includes patients who stopped treatment because of initial nonresponse or virologic breakthrough; *other reasons* includes those patients who prematurely discontinued treatment either because of adverse events and voluntary withdrawal or who were lost to follow-up evaluation. The figures on top of each column refer to the total number of patients with treatment discontinuation. The figures within the dark columns indicate the number of patients who achieved an SVR despite premature treatment discontinuation. □, Treatment failure; ■, other reasons.

87.5% (7 of 8 patients) in group A and group B slow responder patients with HCV-RNA levels of 6000 IU/mL or greater at week 12 (Figure 5).

Variables Associated With SVR

In the entire population, the presence of advanced fibrosis or cirrhosis (stages 3 or 4), age, BMI, triglyceride levels, GGT levels, baseline hepatitis C viremia ($P < .001$ each), body weight, glucose levels, ferritin levels ($P < .01$ each), body surface, cholesterol levels, alkaline phosphatase levels, aspartate transaminase levels, and platelets ($P < .05$) were significant predictors of SVR.

Multivariate analysis showed that only GGT level ($P < .001$), age, cholesterol, baseline hepatitis C viremia ($P < .01$), and BMI ($P < .05$) can be considered as significant predictors of SVR.

In group A, younger age, lower weight, BMI, body surface area, lower stage of fibrosis, lower glucose level, GGT level, and baseline HCV-RNA levels were associated with SVR by univariate analysis. In group B, only age, fibrosis stage, GGT level, and baseline HCV-RNA levels were associated with SVR (Table 3). By multivariate analysis, BMI, glucose level, GGT level, and baseline HCV-RNA levels in group A, and only GGT level in group B remained independent predictors for SVR.

The area under the receiver operating characteristic curve was .71 in group A (multivariate prognostic score of BMI, glucose level, GGT level, and baseline viral load cross-validated) and .70 in group B (GGT level only).

Table 2. Virologic Response Rates During Treatment and at the End of Follow-Up Evaluation

Virologic response (HCV-RNA concentration < 50 IU/mL)	Group A (48-wk treatment) (n = 230) (%)	Group B (72-wk treatment) (n = 225) (%)
On-treatment		
Week 4	51 (22%)	35 (16%)
Week 12[a]	130 (57%)	119 (53%)
Week 24	168 (73%)	145 (64%)
Week 48	163 (71%)	148 (66%)
Week 72	—	142 (63%)
End of follow-up period (SVR)	121 (53%)	121 (54%)

[a]A ≥ 2 $\log_{10}$ decrease in HCV-RNA concentrations at week 12 was achieved in 76% of patients (175 of 230) in group A and 76% of patients (171 of 225) in group B.

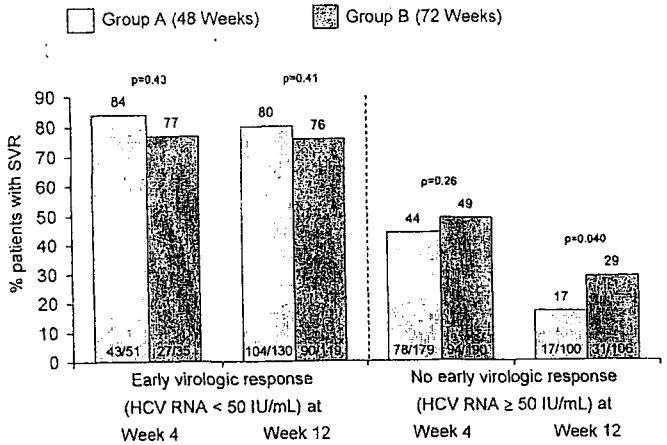

Figure 3. Treatment outcome according to EVR defined as being HCV-RNA negative by qualitative PCR test (detection limit, 50 IU/mL) at week 4 or week 12. SVR rates are shown as a percentage and the number of patients with an SVR in relation to the total number of patients examined is shown at the bottom of each column. □, Group A (48 weeks); ■, group B (72 weeks).

Safety and Treatment Modifications

The type and severity of adverse events occurring during treatment were not statistically different between both groups (data not shown). The frequency of serious adverse events varied between 11.1% (group B) and 15.6% (group A) (P = not significant). A dose reduction owing to adverse events was necessary in 76 group A patients (total of 85 reductions) and 82 group B patients

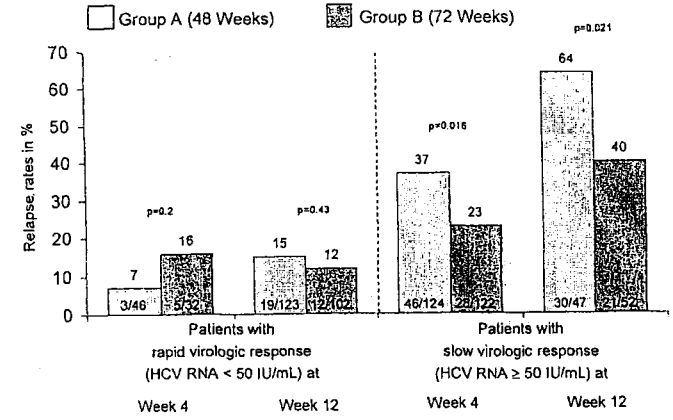

Figure 4. Frequency of virologic relapse rates in group A and B patients with rapid and slow virologic response analyzed at weeks 4 and 12. Relapse rates are shown as a percentage and the number of patients with relapse in relation to the total number of patients examined is shown at the bottom of each column. □, Group A (48 weeks); ■, group B (72 weeks).

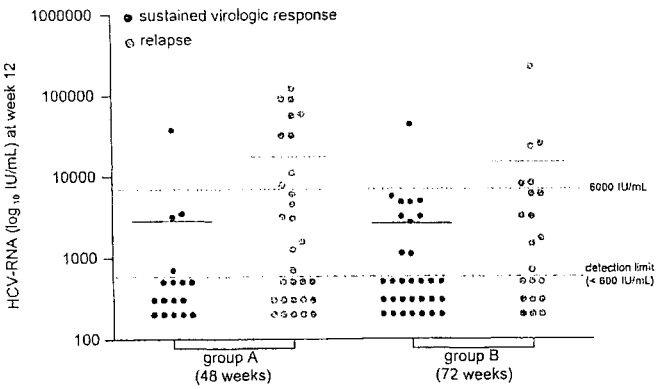

Figure 5. Week 12 individual HCV-RNA levels are presented for each of the 47 and 52 group A and B slow virologic responders (as defined in Figure 4) who achieved either an SVR (black dots) or an end-of-treatment virologic response but subsequently relapsed (grey dots). A reduction in the relapse frequency by extended treatment duration could be shown only for patients who had low-level viremia at week 12. Note that only 1 patient in each group with HCV-RNA levels greater than 6000 IU/mL (dotted line) achieved an SVR. The detection limit of the quantitative HCV-RNA test (ie, <600 IU/mL) also is shown. All dots below the detection limit of 600 IU/mL represent samples that were negative by quantitative PCR but positive by qualitative PCR. •, SVR; ○, relapse.

(total of 96 reductions) ($P > .05$). In group A, the dose of PEG–IFN-alfa, ribavirin, or both drugs was reduced in 37 (16%), 13 (6%), and 26 (11%) patients, and in group B in 26 (12%), 23 (10%), and 33 (15%) patients. Figure 6 shows at which time dose reduction was undertaken within each group. In most instances it occurred within the first 20 weeks of treatment (68 of 85 in group A and 68 of 96 in group B). The total frequency of treatment discontinuation was statistically higher in group B as compared with group A (41% vs 24%). A similar number of patients discontinued treatment within the first 44 weeks (54 in group A and 53 in group B), whereas after week 44 only 1 patient in group A but 39 patients in group B discontinued treatment prematurely. Reasons for treatment discontinuation and time to discontinuation are shown in Figure 2.

Discussion

The duration of antiviral therapy is one of the most important factors influencing treatment outcome, especially in HCV genotype 1–infected patients.[6,11–14] Forty-eight weeks of combination therapy with PEG–IFN-alfa plus 1000–1200 mg of ribavirin has become the accepted standard of care in type 1–infected patients.

In the current study we investigated whether extension of treatment duration from 48 to 72 weeks is a promising approach to increase SVR rates in the type 1–infected patient population by reducing the relapse rates. We therefore randomized patients to 48 vs 72 weeks of treatment and analyzed their SVR and relapse rates. Our data allow 2 conclusions. First, prolongation of the therapeutic regimen for up to 72 weeks does not lead to higher SVR rates in the intent-to-treat population, and therefore it is not advisable to extend treatment in the general type 1–infected patient population. Second, identifying patients with and without early virologic response by qualitative PCR test at weeks 4 and 12 facilitates the decision of how long patients should be treated. Patients with early virologic response in whom HCV-RNA levels were less than 50 IU/mL already at weeks 4 or 12 had excellent SVR rates, ranging between 76% and 84% at the end of the follow-up period independently from the treatment period. In contrast, patients who still were HCV-RNA positive at week 12 showed significantly higher SVR rates when treated for 72 weeks instead of 48 weeks (29% vs 17%).

In a second step we analyzed relapse rates with respect to the early response pattern during therapy (ie, rapid or slow virologic response) to define those patients who may benefit most from extended treatment duration. A reduction of relapse rates in relation to the extended 72-week treatment period was observed in patients with slow virologic response, defined as patients who still were HCV-RNA positive at weeks 4 or 12, but negative at week 24. In patients with rapid virologic response, relapse rates were rather low (<16%) and therefore less

Table 3. Comparison of the Demographic, Biochemical, Serologic, Molecular, and Histologic Profiles of the Patients at Baseline With Respect to the Treatment Outcome, Separately for Each Study Arm

	Group A (48 weeks, n = 230)		Group B (72 weeks, n = 225)	
Characteristics	No SVR (n = 109)	SVR (n = 121)	No SVR (n = 104)	SVR (n = 121)
Sex	$P = .13$		$P = .92$	
Male	55 (50.5)	73 (60.3)	56 (53.8)	66 (54.5)
Female	54 (49.5)	48 (39.7)	48 (46.2)	55 (45.5)
Ethnic origin	$P = .31$		$P = .70$	
Caucasian	107 (98.2)	115 (95.0)	98 (94.2)	115 (95.0)
Asian	1 (.9)	5 (4.1)	2 (1.9)	4 (3.3)
African American	1 (.9)	1 (.8)	2 (1.9)	1 (.8)
Other			2 (1.9)	1 (.8)
Age, *y*	$P < .001$		$P = .008$	
Mean ± SD	45.4 ± 11.2	40.3 ± 10.8	44.9 ± 10.9	40.7 ± 12.1
Range	19–66	19–68	20–70	20–70
Height, *cm*	$P = .167$		$P = .732$	
Mean ± SD	171.7 ± 9.8	173.5 ± 10.1	172.3 ± 10.2	171.8 ± 9.2
Range	146–195	147–196	148–197	143–189
Weight, *kg*	$P = .003$		$P = .397$	
Mean ± SD	79.4 ± 16.1	73.5 ± 13.0	76.2 ± 14.1	74.6 ± 14.5
Range	51–161	42–109	48–128	39–113
BMI, kg/m^2	$P < .001$		$P = .339$	
Mean ± SD	26.9 ± 4.6	24.4 ± 3.7	25.6 ± 3.9	25.1 ± 4.1
Range	17–47	17–36	18–37	16–37
Body surface, m^2	$P = .032$		$P = .369$	
Mean ± SD	1.94 ± .23	1.88 ± .2	1.91 ± .22	1.88 ± .21
Range	1.5–2.9	1.3–2.4	1.5–2.6	1.3–2.4
Glucose, *mmol/L*	$P = .001$		$P = .382$	
Mean ± SD	5.47 ± 1.07	5.03 ± .99	5.72 ± 2.46	5.46 ± 1.77
Range	3.8–10.0	3.1–9.4	3.4–22.4	3.5–17.8
ALT levels × upper limit of normal, *IU/L*	$P = .194$		$P = .301$	
Mean ± SD	2.4 ± 1.59	2.75 ± 1.86	2.58 ± 1.63	2.34 ± 1.4
Range	.7–11.8	.8–11.6	.5–8.0	.4–7.7
GGT levels × upper limit of normal, *IU/L*	$P < .001$		$P < .001$	
Mean ± SD	1.85 ± 1.59	1.34 ± 1.39	2.42 ± 2.44	1.33 ± 1.7
Range	.3–11.3	.2–10.2	.2–13.9	.2–13.9
HCV genotype	$P = .166$		$P = .077$	
Subtype 1b	80 (73.4)	75 (62.5)	66 (63.5)	66 (54.5)
Subtype 1a	22 (20.2)	38 (31.7)	27 (26.0)	40 (33.1)
Subtype 1a/1b	5 (4.6)	3 (2.5)	6 (5.8)	2 (1.7)
Type 1[a]	2 (1.8)	4 (3.3)	5 (4.8)	13 (10.7)
HCV RNA, *log IU/mL*	$P = .009$		$P = .006$	
Mean ± SD	5.88 ± .46	5.7 ± .56	5.85 ± .46	5.66 ± .55
Range	3.24–7.24	4.12–7.1	4.14–7.29	3.6–7.39
Fibrosis stage	$P = .022$		$P = .007$	
Stages 0–2	97 (89.0)	117 (96.7)	89 (85.6)	116 (95.9)
Stages 3–4	12 (11.0)	4 (3.3)	15 (14.4)	5 (4.1)

[a]No subtype was determined.

influenced or not influenced by treatment prolongation. The analysis also revealed that measuring individual HCV-RNA levels at week 12 is a reliable parameter to decide how long patients should be treated. From our data, patients with low-level viremia (<6000 IU/mL) at week 12 had the largest benefit from extended treatment duration. Thus, the data from the present study support the concept that extending the HCV-RNA negative phase by consequent antiviral therapy can decrease relapse rates.[15,16]

Sanchez–Tapias et al[17] recently presented data from a study that also analyzed the effect of a prolonged treatment period using PEG–IFN-alfa-2a plus ribavirin in patients without early virologic response at week 4 (HCV-RNA positive by qualitative PCR). They showed that SVR rates were significantly higher in the 72-week group as compared with the 48-week group (45% vs 32%) and that the 72-week treated patients expressed significantly lower relapse rates (13% relapse vs 48% in the 48-week group). These data are basically in accor-

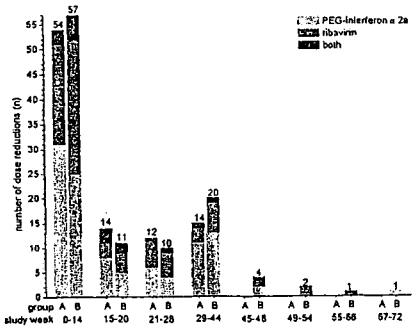

Figure 6. Number of dose reductions of either PEG–IFN-alfa, ribavirin, or both drugs according to treatment weeks in group A (48 weeks) and B (72 weeks) patients. A total of 85 and 96 dose reductions owing to adverse events had to be undertaken in 76 group A and 82 group B patients ($P > .05$). The figures on top of each column refer to the total number of dose reductions. □, PEG–IFN-alfa-2a; ▨, ribavirin; ■, both.

dance with the results of our present study and confirm the concept of extending treatment duration in slow virologic responders. However, from our data it can be deduced that the week-12 response might be a better time point from which to select patients for the evaluation of treatment duration because SVR rates were not significantly different in patients who already were HCV-RNA negative at week 4 and those becoming HCV-RNA negative at week 12.

Our study also raises the issue of whether the generally accepted stopping rule for patients with a less than 2 $\log_{10}$ decrease of HCV-RNA level within the initial 12 weeks of therapy should be reconsidered because the high negative predictive value of this stopping rule of 98%–100%[9,18,19] could be confirmed only for the 48-week treatment group but not for the 72-week group. Only 4% of patients with a less than 2 $\log_{10}$ HCV-RNA decrease treated for 48 weeks achieved an SVR whereas in patients treated for 72 weeks the SVR rates reached 11%. We further could confirm that the previously proposed stopping algorithm based on absolute HCV-RNA levels at week 12 (ie, <30,000 IU/mL)[20] was highly predictive for nonsustained response in both groups. However, because of the lower ribavirin doses in our study (ie, 800 mg/day) as compared with the previously cited studies (ie, 1000–1200 mg/day) these data must be interpreted with caution. Indeed it has been shown in recent trials of nonresponder patients that ribavirin dose reduction within the first 3 months especially may influence early response rates.[21]

Drusano and Preston[21] recently presented a mathematical model to predict whether patients may achieve SVR or suffer from relapse. It was concluded that type 1–infected patients require the continuous absence of detectable HCV RNA in serum for 36 weeks to attain 90% probabilities of an SVR (ie, relapse rate of 10%). We agree only to some extent with this predictive model, realizing that our week-12 rapid virologic responders who were HCV-RNA negative for at least 36 weeks also had low relapse rates (≤15%). However, group B late responders who first became HCV-RNA negative at week 24 (ie, who also had undetectable HCV-RNA levels during the last 36 weeks of the total 72-week treatment period) still had relapse rates of 40%, a finding that clearly contradicts the proposed Drusano and Preston[22] model. Obviously, the HCV-RNA negative phase required to prevent a relapse must be calculated in a more exponential way and seems to be dependent on how early a patient becomes HCV-RNA negative during treatment.

Multivariate analysis was used to identify prognostic baseline factors in both treatment groups. BMI, glucose, GGT, and baseline HCV-RNA levels proved to be independent predictors for SVR in group A, whereas in group B only the GGT level remained significant. These data confirm previous studies that showed the importance of GGT level in predicting nonresponse to treatment,[20,23] but also show that at least some negative predictors can be overcome by intensifying the treatment regimen.

We are aware that our study has some shortcomings. First, the ribavirin dose of 800 mg/day used in this trial was lower than the 1000/1200 mg/day dosage now recommended for HCV type 1–infected patients. In the Materials and Methods section we summarized the arguments for our decision. It is of interest that the SVR rates observed in both groups were quite similar to those observed in other studies in which patients received ribavirin at higher doses.[5,6] Second, the study was not blinded (ie, a placebo was administered to group A for weeks 49–72). Reflecting the different on-treatment discontinuation rate (for any reason) between both groups (24% in group A as compared with 41% in group B) one plausible explanation could be that more patients in group B than in group A failed to tolerate the long treatment period. From our experience, however, we believe that one can convince patients to accept the longer treatment period of 72 weeks by carefully explaining to them that extension of therapy ultimately will increase their chance to achieve an SVR.

From a per-protocol analysis, by including only the patients who received at least 80% of the PEG–IFN-alfa-2a and ribavirin dose and who completed the planned (± 4 weeks) treatment and follow-up period, a 10% difference in SVR rate in favor of group B became evident (68%; 95% CI, 60.6–76.2 [93 of 136] vs 78%; 95% CI, 69.2–86.1 [73 of 94] in group A vs group B; $P = .12$, data not shown).

In conclusion, the present study supports the concept that extension of treatment duration can reduce relapse rates only for a limited proportion of type 1–infected patients (about 20%, ie, slow virologic responder). Individual tailoring of treatment duration may be one option in the future to reduce relapse rates in HCV type 1–infected patients.

Appendix

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