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Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3^{☆,☆☆}

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Background/Aims: Treatment duration in patients with chronic hepatitis C in the era of standard interferon- α plus ribavirin was tailored according to hepatitis C virus (HCV) genotype: patients infected with HCV-1 were treated for 48 weeks, patients infected with HCV-2/3 for 24 weeks. The aim of the present study was to investigate this schedule for HCV-2/3 infected patients in the era of pegylated interferon- α plus ribavirin.

Methods: Patients chronically infected with HCV-2 ($n = 42$) or HCV-3 ($n = 182$) were treated with peginterferon alfa-2b 1.5 $\mu\text{g}/\text{kg}$ subcutaneously once weekly plus ribavirin 800–1400 mg/day based on body weight for 24 weeks.

Results: The end of treatment (EOT) and sustained virologic response (SVR) was higher in patients infected with HCV-2 (100 and 93%, respectively) than in patients infected with HCV-3 (93 and 79%, respectively). Baseline viremia ($P = 0.020$), treatment duration >16 weeks ($P < 0.001$) and steatosis ($<5\%$, $P = 0.015$) were significant independent predictors of SVR. Adverse events resulted in discontinuation in 5% and dose reduction in 22% of patients.

Conclusions: Treatment for 24 weeks with peginterferon alfa-2b and ribavirin is sufficient in HCV 2 or 3 infected patients. The lower SVR in patients infected with HCV-3 compared with HCV-2 infected patients may be related to higher levels of steatosis in this population.

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Keywords: Hepatitis C virus; Genotype 2 and 3; Treatment duration; Steatosis

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Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; ULN, upper limit of normal.

1. Introduction

Hepatitis C virus (HCV) infection may progress to chronic hepatitis, cirrhosis, and its sequelae [1–3]. Treatment of HCV-infected patients with interferon- α can achieve viral clearance and improve histology and prognosis [4,5]. In the era of standard interferon alfa plus ribavirin the duration of treatment in patients with chronic hepatitis C was tailored according to HCV genotype: patients infected with HCV-1 were treated for 48 weeks, patients infected with HCV-2 or HCV-3 for 24 weeks [6–9].

More recently, standard interferons have been chemically modified using polyethyleneglycol (PEG) to improve

antiviral efficacy. Higher sustained virologic response (SVR) rates in patients with chronic hepatitis C have been reported for the pegylated forms of interferons compared with standard interferons both in monotherapy as well as in combination therapy with ribavirin [10–13]. In these trials all patients were treated for 48 weeks. Prospective data defining whether the duration of treatment with pegylated interferon alfa in patients chronically infected with genotypes HCV-2 or HCV-3 can be reduced from 48 to 24 weeks without compromising antiviral efficacy are needed.

Therefore, the aim of the present study was to investigate efficacy and safety of peginterferon alfa-2b plus ribavirin administered for 24 weeks in patients chronically infected with HCV genotypes 2 or 3.

2. Patients and methods

2.1. Patients

Male and female patients aged 18–70 years with compensated chronic HCV infection not previously treated with interferon, ribavirin and/or amantadine were eligible for enrollment. Eligible patients tested positive for HCV-RNA by reverse transcription-polymerase chain reaction, had a liver biopsy taken within 12 months prior to the screening visit showing chronic hepatitis, and had at least one serum alanine aminotransferase (ALT) level elevated at screening or entry into the trial. Entry leucocyte and platelet counts had to be at least 3000 and 80,000/ μ l, respectively. Hemoglobin values at entry visit had to be at least 12 g/dl for females and at least 13 g/dl for males.

Patients with the following criteria were excluded: any other cause of liver disease or other relevant disorders including human immunodeficiency or hepatitis B virus coinfection, clinically significant hematologic, hepatic, metabolic, renal, rheumatologic, anaphylactic reactions, neurological or psychiatric disease, clinically significant cardiac or cardiovascular abnormalities, organ grafts, systemic infection, clinically significant bleeding disorders, evidence of malignant neoplastic disease, average daily intake of alcohol exceeding 80 g of ethanol, or drug abuse within the past two years. Further exclusion criteria were pregnancy and lactation.

2.2. Study design

This phase 4 study, single-arm, open-label, historical-control study assessed the safety and efficacy of 24 weeks of treatment with peginterferon alfa-2b plus ribavirin in previously untreated patients with chronic hepatitis C who were infected with genotype HCV-2 or -3. Eligible patients were treated with peginterferon alfa-2b (PegIntron[®], Schering Plough Corp., Kenilworth, NJ) 1.5 μ g/kg once per week subcutaneously plus ribavirin (Rebetol[®], Schering Plough Corp., Kenilworth, NJ) 800–1400 mg/day orally (<65 kg 800 mg; 65–85 kg 1000 mg; >85–105 kg 1200 mg; >105 kg 1400 mg). The dose of each study medication was based on the patient's weight at entry. Patients were treated for 24 weeks, then followed for an additional 24 weeks. The study was approved by the ethics committees at the participating centers and carried out according to the Declaration of Helsinki and the ICH/CPMP guidelines 'Good Clinical Practice'. All patients gave written informed consent before enrollment.

All patients were evaluated as outpatients for safety, tolerance, and efficacy at weeks 4, 8, 12, 18 and 24 during treatment and at weeks 4, 12 and 24 following the end of treatment (EOT). HCV-RNA was quantified by real-time polymerase chain reaction technology (lower limit of detection 29 IU/ml). HCV genotyping was performed by direct sequencing of the 5'-noncoding region. Liver biopsy specimens were assessed by an experienced pathologist who was unaware of clinical and biochemical data as well as of treatment regimen and response. Steatosis was graded according to the percentage of hepatocytes containing visible macrovesicular steatosis.

Histological results were classified according to internationally standardized criteria [14].

2.3. Study end points

The primary efficacy endpoint for this study was the proportion of patients with a SVR, defined as undetectable plasma HCV-RNA levels at 24 weeks following the EOT. The secondary endpoint was the proportion of patients with a SVR and normalization of ALT at the end of the follow-up period. The safety and efficacy of 24 weeks of treatment in this trial were compared with the historical control of 48 weeks of treatment in the same subgroups [12].

2.4. Statistical analysis

The primary analysis was based on all enrolled patients ($n = 224$). A prediction model for SVR was developed using data from Manns et al. [12]. This model included the following prognostic factors: genotype, baseline HCV-RNA level, presence or absence of bridging fibrosis (F3) or cirrhosis (F4), age and gender. The model was then used to predict SVR rates for the HCV-2 or -3 infected patients in the present study, had they received 48 weeks of treatment. If the estimated SVR rate for 48 weeks of treatment based on the model fell within the 95% confidence interval of the actually observed SVR rate of the present study, then it was concluded that 24 weeks of treatment is equivalent to 48 weeks of treatment.

Single-variable logistic regression was used to compute P -values and odds ratios for the effect of prognostic factors (those observed at baseline and also treatment duration) upon sustained response. Tree models (using SAS Enterprise Miner) suggested that splitting steatosis score at ≤ 5 vs. > 5 and duration of treatment at ≤ 16 vs. > 16 weeks would refine the multivariable logistic regression analysis. Stepwise regression analysis was performed to determine the significance of the results from the single-variable logistic regression analysis.

3. Results

This study was performed between October 2001 and June 2003 in 39 European centers. Three hundred and fourteen patients were screened, 224 patients were enrolled, however, one patient did not receive treatment (Fig. 1). The baseline characteristics of the patients are summarized in Table 1.

3.1. Biochemical and virological response

An overall intent-to-treat virologic response at the end of the therapy was achieved by 211 of 224 patients (94%) and a SVR by 182 of 224 patients (81%). The EOT and SVR was higher in patients infected with HCV-2 (100 and 93%, respectively) than in patients infected with HCV-3 (93 and 79%, respectively). The relapse rates by HCV genotype and baseline HCV-RNA are shown in Fig. 2. Relapsers were more likely to be male (16 vs. 7%), older than the age of 55 years (27 vs. 12%), to have a steatosis score above 32% (23 vs. 11%), to be infected with HCV-3 (14 vs. 7%), and to have a baseline HCV-RNA level $> 600,000$ IU/ml (20 vs. 7%).

Using the data of the study by Manns et al. [12], a SVR rate of 84.4% was predicted for 48 weeks treatment in the present study cohort. This estimated SVR rate fell within the 95% confidence interval (76.1–86.4%) of the observed virologic response rate after 24 weeks treatment in the study

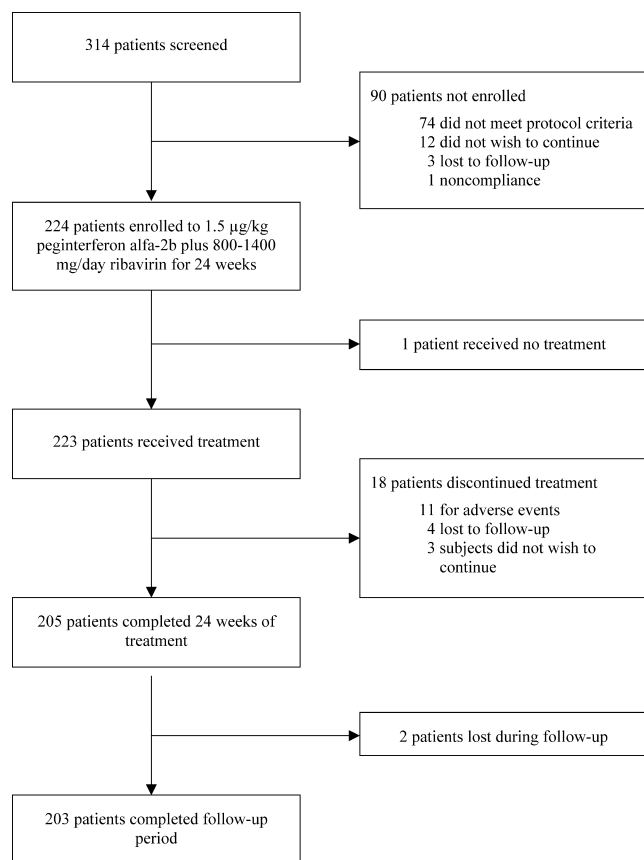


Fig. 1. Trial profile.

cohort and, therefore, satisfied the criterion for establishing effectiveness for the present study. Other models confirmed that the estimated sustained response rate for 48 weeks of treatment fell within the confidence interval observed for 24 weeks of treatment. These confirmatory models contained more informative covariates such as HCV genotype categorized as 1 vs. 2 vs. 3 instead of 1 vs. 2/3 and additional covariates such as ribavirin dose in mg/kg or in-treatment HCV-RNA levels.

At the end of follow-up 180 of 224 patients (80.4%) had ALT levels within the normal reference range and 175 of 224 patients (78.1%) had both normal ALT and undetectable HCV-RNA. The correlation between sustained biochemical and virologic response was 96.2% (175 of 182 patients). ALT levels in sustained virologic but not biochemical responders ($n = 7$) ranged from 1.05 to 1.28 times the upper limit of normal. Six of the seven subjects were infected with HCV-3. On the pretreatment liver biopsy two patients had grade 3 steatosis ($> 32 - \leq 67\%$ fat), four had grade 2 steatosis ($> 5 - \leq 32\%$ fat), and one had no detectable hepatic fat.

3.2. Predictors of response

SVR by baseline demographic and disease characteristics is shown in Table 2. Gender, HCV genotype, baseline HCV-RNA level, source and time since exposure, steatosis,

Table 1
Demographic, biochemical, molecular, and histological profile of patients with chronic hepatitis C at baseline

Demography	
No (M/F)	224 (163/61) ^a
Caucasian	211 (94%)
Body weight (kg) ^b	75.7 (47–119)
Age (years) ^b	39.9 (18–65)
Risk factor for transmission	
Parenteral	132 (59%)
Transfusion	28 (13%)
Sporadic/other	64 (29%)
Time since exposure (years) ^{b,c}	15.5 (0.3–45.4)
Biochemistry	
ALT (\times ULN) ^b	3.17
Molecular parameters	
Genotype HCV-2	42 (19%)
Genotype HCV-3	182 (81%)
Log ₁₀ pretreatment HCV-RNA (IU/ml) ^b	5.55 (1.45–7.01)
Mean Knodell score	
I (periportal \pm bridging necrosis)	2.6
II (parenchymal injury)	1.7
III (portal inflammation)	2.5
I + II + III (total inflammation)	6.8
IV (fibrosis)	1.5
Steatosis according to genotype HCV-2/HCV-3	
0	16 (38%)/33 (18%)
> 0–5%	20 (48%)/63 (35%)
> 5–32%	6 (14%)/53 (29%)
> 32–66%	0 (0%)/17 (9%)
> 66%	0 (0%)/10 (6%)
Missing	0 (0%)/6 (3%)

ALT, alanine aminotransferase; ULN, upper limit of normal.

^a Two hundred and twenty-three patients were treated (the untreated patient was male, infected with HCV-3, baseline HCV-RNA $\leq 600,000$ IU/ml).

^b Mean (range).

^c Sporadic cases not considered.

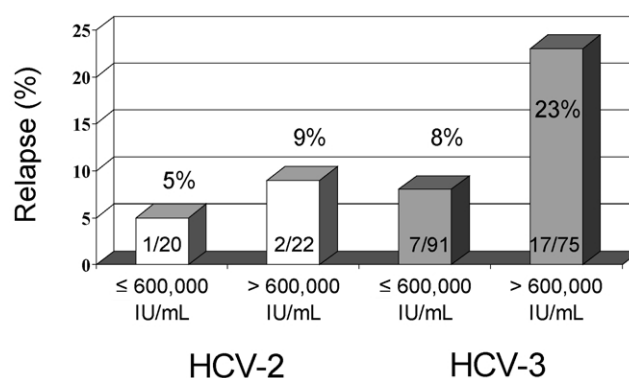


Fig. 2. Virologic relapse rates in patients treated with peginterferon alfa-2b and ribavirin for 24 weeks. Data are given according to HCV genotype and pretreatment HCV-RNA concentration. Patients with missing HCV-RNA values at the end of treatment ($n = 16$, all infected with HCV-3) were excluded from this analysis.

Table 2
Sustained virologic response rates by baseline demographic and disease characteristics

	Peginterferon alfa-2b 1.5 µg/kg qw plus weight-based ribavirin (RBV)				
	All patients ^a (n = 224)	< 65 kg (800 mg RBV) (n = 49)	65–85 kg (1000 mg RBV) (n = 125)	86–105 kg (1200 mg RBV) (n = 47)	106–125 kg (1400 mg RBV) (n = 3)
Genotype/HCV-RNA					
2/≤ 600,000 IU/ml	95.0% (19/20)	100% (4/4)	100% (12/12)	75.0% (3/4)	– ^b
2/> 600,000 IU/ml	90.9% (20/22)	100% (2/2)	83.3% (10/12)	100% (6/6)	100% (2/2)
3/≤ 600,000 IU/ml	85.9% (85/99)	86.4% (19/22)	84.6% (44/52)	91.7% (22/24)	0% (0/1)
3/> 600,000 U/ml	69.9% (58/83)	66.7% (14/21)	67.3% (33/49)	84.6% (11/13)	–
Age (years)					
≤ 35	86.8% (66/76)	85.7% (18/21)	84.6% (33/39)	93.8% (15/16)	–
> 35–55	78.9% (105/133)	73.9% (17/23)	77.6% (59/76)	87.1% (27/31)	66.7% (2/3)
> 55– < 65	76.9% (10/13)	80.0% (4/5)	75.0% (6/8)	–	–
≥ 65	50.0% (1/2)	–	50.0% (1/2)	–	–
Gender					
Female	93.4% (57/61)	90.3% (28/31)	95.5% (21/22)	100% (6/6)	100% (2/2)
Male	76.7% (125/163)	61.1% (11/18)	75.7% (78/103)	87.8% (36/41)	0 (0/1)
Body weight (kg)					
< 65	79.6% (39/49)	79.6% (39/49)	–	–	–
65–85	79.2% (99/125)	–	79.2% (99/125)	–	–
> 85–105	89.4% (42/47)	–	–	89.4% (42/47)	–
> 105	66.7% (2/3)	–	–	–	66.7% (2/3)
Exposure source					
Transfusion	67.9% (19/28)	100% (6/6)	52.6% (10/19)	100% (3/3)	–
Parenteral	81.1% (107/132)	72.7% (24/33)	84.9% (62/73)	84.0% (21/25)	0 (0/1)
Sporadic/other	87.5% (56/64)	90.0% (9/10)	81.8% (27/33)	94.7% (18/19)	100% (2/2)
Exposure (years)					
0–1	100% (6/6)	100% (2/2)	100% (3/3)	100% (1/1)	–
> 1–5	85.7% (12/14)	60.0% (3/5)	100% (7/7)	100% (2/2)	–
> 5–10	87.5% (21/24)	100% (4/4)	76.9% (10/13)	100% (7/7)	–
> 10	75.7% (87/115)	77.8% (21/27)	75.4% (52/69)	77.8% (14/18)	0 (0/1)
Sporadic/missing	86.2% (56/65)	81.8% (9/11)	81.8% (27/33)	94.7% (18/19)	100% (2/2)
Inflammatory score					
0–6	83.1% (59/71)	77.8% (14/18)	81.4% (35/43)	100% (10/10)	–
7–8	81.0% (68/84)	88.9% (16/18)	76.9% (30/39)	84.0% (21/25)	50.0% (1/2)
> 8	82.5% (52/63)	75.0% (9/12)	82.1% (32/39)	90.9% (10/11)	100% (1/1)
Missing	50.0% (3/6)	0 (0/1)	50.0% (2/4)	100% (1/1)	–
Fibrosis score					
0 (none)	80.0% (8/10)	100% (1/1)	71.4% (5/7)	100% (2/2)	–
1 (portal)	83.8% (129/154)	78.9% (30/38)	81.2% (69/85)	96.8% (30/31)	–
3 (bridging)	75.6% (31/41)	83.3% (5/6)	73.9% (17/23)	70.0% (7/10)	100% (2/2)
4 (cirrhosis)	84.6% (11/13)	100% (3/3)	100% (6/6)	66.7% (2/3)	0 (0/1)
Missing	50.0% (3/6)	0 (0/1)	50.0% (2/4)	100% (1/1)	–
Steatosis					
0	93.9% (46/49)	93.3% (14/15)	92.6% (25/27)	100% (7/7)	–
> 0–5%	85.5% (71/83)	76.2% (16/21)	87.8% (36/41)	94.7% (18/19)	50.0% (1/2)
> 5–32%	71.2% (42/59)	80.0% (8/10)	65.7% (23/35)	76.9% (10/13)	100% (1/1)
> 32–66%	64.7% (11/17)	50.0% (1/2)	60.0% (6/10)	80.0% (4/5)	–
> 66%	90.0% (9/10)	–	87.5% (7/8)	100% (2/2)	–
Missing	50.0% (3/6)	0 (0/1)	50.0% (2/4)	100% (1/1)	–

^a Two hundred and twenty-three patients were treated (the untreated patient was male, infected with HCV-3, baseline HCV-RNA ≤ 600,000 IU/ml).

^b –, indicates that no patient fell in the category.

and duration of treatment were identified by single-variable analysis as potential predictors of response. After stepwise multivariable logistic regression analysis, baseline HCV-RNA level ($P = 0.026$), treatment duration for at least 16

weeks ($P = 0.0003$), and steatosis of less than 5% ($P = 0.012$) remained significant independent predictors of SVR. A virologic relapse or non-response was observed in 3 of 42 patients infected with HCV-2 and in 39 of 182 patients

infected with HCV-3. None of these 3 HCV-2 infected patients, but 7 (all with a baseline HCV-RNA >600,000 IU/ml) of 36 HCV-3 infected patients had a steatosis score of more than 32% (in 3/39 HCV-3 infected patients no pretreatment biopsy steatosis score was available). Body weight was not a predictor of SVR by either single-variable or stepwise analysis.

The finding that steatosis score was a significant prognostic factor for sustained response in the multiple logistic regression resulted in further investigation. Stepwise logistic regression for steatosis as response variable, categorized as $\leq 5\%$ vs. $> 5\%$ steatosis (or missing score), was performed. Factors significantly associated with the steatosis score were found to be genotype HCV-3 ($P = 0.003$), baseline HCV-RNA above 600,000 IU/ml ($P = 0.001$), interaction between genotype and baseline viral load, and body weight ($P = 0.002$).

HCV-RNA was undetectable in serum after 4 weeks of therapy in 33 of 42 HCV-2 and 137 of 182 HCV-3 infected patients. This initial viral response was independent from baseline HCV-RNA levels in HCV-2 infected patients. The week 4 virologic response in HCV-3 infected patients, however, was higher for patients with a low baseline HCV-RNA level (90 vs. 79% for patients with baseline HCV-RNA $\leq 600,000$ and $> 600,000$ IU/ml, respectively).

The present study confirmed that an early virologic response predicts SVR [13,15]. The SVR rate in HCV-2 and HCV-3 infected patients who had undetectable serum HCV-RNA already after 4 weeks of combination therapy was 94% (31 of 33 patients) and 85% (117 of 137 patients), respectively. Thirty-five additional HCV-3 infected patients cleared HCV-RNA from serum by treatment week 12. The SVR rate in these 35 patients according to baseline HCV-RNA (\leq vs. $> 600,000$ IU/ml) was 85% (11/13) and 59% (13/22), respectively.

3.3. Adherence

Patients were considered adherent to the assigned dose regimen if they received at least 80% of both drugs for at least 80% of the treatment duration [16]. Patients who were able to adhere to assigned treatment regimen were compared with patients who received less than 80% of one or both drugs for at least 80% of the treatment duration; patients who discontinued therapy were excluded. The SVR rate in adherent patients was 86% (156 of 181 patients) compared with 75% (21 of 28 patients) in nonadherent patients.

3.4. Adverse events

Serious adverse events (SAE) were reported in 14 patients during the treatment period and in six patients during the follow-up period, representing a SAE rate of 6% during therapy and 3% during follow-up. In seven of the 14 patients with a SAE during therapy but in none during the

follow-up period, the event was considered by the investigator as probably related to study medication (hyperthyroidism, anorexia, diarrhea, anxiety, agitation, depression with suicidal ideation, vision abnormality).

Eleven of 224 patients (5%) discontinued antiviral therapy because of adverse events. Four patients discontinued due to depression, two patients due to neutropenia, two patients due to thrombocytopenia, and one patient each for tooth abscess, musculo-skeletal pain, and hyperthyroidism, respectively. Forty-one of 224 patients (18%) required dose reduction or interruption due to adverse events (excluding patients who later discontinued due to an adverse event). Thrombocytopenia (4%), neutropenia (4%), and anemia (4%) were the most common adverse events leading to dose modification. These events appeared to be related to the weight-based ribavirin dose assigned, with 10% (5 of 49 patients) in the 800 mg/day dosing regimen group, 9% (11 of 125 patients) in the 1000 mg/day group, and 23% (11 of 47 patients) in 1200 mg/day group. Thrombocytopenia (0, 4 and 11% at doses of 800, 1000, and 1200 mg, respectively) accounted for most of the differences in adverse effects leading to dose modification. However, the effect of dose is difficult to assess since the majority of patients requiring dose modification started therapy with low normal platelet counts. Compared with the historical control of patients treated for 48 weeks and receiving > 10.6 mg/kg ribavirin, the rates of SAEs (6 vs. 12%), discontinuation due to adverse events (5 vs. 14%) and dose reduction due to adverse events (18 vs. 49%) were considerably lower in the present study.

4. Discussion

This study demonstrates that 24 weeks of therapy with peginterferon alfa-2b 1.5 $\mu\text{g}/\text{kg}$ per week plus weight-based ribavirin dosing is highly effective. Using the data of the study by Manns et al. [12], a SVR rate of 84.4% was predicted if the patients in the present study would have been treated for 48 weeks. This estimated SVR rate fell within the 95% confidence interval (76.1–86.4%) of the observed virologic response rate after 24 weeks treatment in the study cohort and, therefore, satisfied the criterion for establishing effectiveness for the present study.

In the present study, the SVR rate was higher in patients infected with HCV-2 than in those infected with HCV-3, suggesting that virologic response rates should be presented according to single genotypes rather than to any arbitrary combination of genotypes. Within the group of chronically HCV-3 infected patients, a higher virologic relapse rate was observed in patients with a baseline HCV-RNA concentration of more than 600,000 IU/ml. Noteworthy, that SVR rates in HCV-2 and -3 infected patients treated with peginterferon alfa-2a and ribavirin (79–84%) were not influenced by the baseline HCV-RNA concentration [17]. In this study by Hadziyannis et al., however, results were not

reported according to individual genotypes (i.e. HCV-2 vs. HCV-3). Additional prospective studies are required to address the question whether patients infected with HCV-3 and a high baseline viremia should be treated for longer than 24 weeks.

In particular genotype HCV-3 has been associated with hepatic steatosis [18,19]. In HCV-3 infected patients, steatosis is furthermore associated with a high pretreatment serum HCV-RNA concentration. In general, steatosis is also associated with lower SVR rates, even after taking into account other factors such as fasting glucose and triglyceride levels, viral load and fibrosis [19]. Stepwise logistic regression analysis identified pretreatment HCV-RNA levels and steatosis below 5% as independent predictors of SVR in the present study. Presence of steatosis was associated with HCV-3, high pretreatment HCV-RNA, and baseline weight. Thus, the lower SVR rate in patients infected with HCV-3 and high viral load compared with HCV-3 infected patients with low viral load and all HCV-2 infected patients may in part be related to higher levels of steatosis in this population.

A logistic regression model using the subset of patients infected with HCV-2 or -3 in the study by Manns et al. [12], and controlling for treatment group, genotype (HCV-2 or -3), baseline HCV-RNA, and age, provided an odds ratio of the weight effect which was 0.90 per increase of 10 kg, with a 95% confidence interval of 0.79–1.04. Although the effect of weight was not significant in this subgroup, this odds ratio was very similar to the one based on all genotypes (0.90; 95% CI 0.84, 0.96). In the present trial, the ribavirin dose was controlled by weight-based dosing. A similar logistic regression model based on the data of the present study, and controlling for HCV genotype, pretreatment HCV-RNA, and age, showed that weight was not statistically significant. The odds ratio per increase of 10 kg of weight was 1.06 (95% CI 0.81, 1.39). Thus, the results of this analysis suggest that using weight-based dosing of ribavirin in combination with peginterferon alfa-2b eliminates the residual effect of body weight upon the SVR rate.

In contrast, in HCV-2 or -3 infected patients treated with peginterferon alfa-2a no statistically significant difference was observed in the SVR rates of patients treated with a flat ribavirin dose of 800 mg/day and those treated with 1000–1200 mg ribavirin/day according to body weight (< vs. \geq 75 kg) [17]. Thus, for patients infected with HCV-2 or -3 the recommendations for the dosing of ribavirin will differ between peginterferon alfa-2a and alfa-2b. Recent critical evaluations of current dosage recommendations on the basis of a population pharmacokinetic analysis showed that ribavirin should mainly be dosed according to renal function and not on body weight alone [20].

Overall, the safety profile of the 24-week treatment regimen was much improved compared with the 48-week profile in the study of Manns et al. [12]. When the 24-week results of the present study were compared with those patients in the study by Manns et al. [12] who received more

than 10.6 mg/kg ribavirin, treatment-emergent SAEs, as well as adverse events leading to treatment discontinuation of dose reduction, occurred at rates less than half of those observed with 48 weeks of treatment. In the present study, dose reduction for anemia was similar in patients treated with 800, 1000, or 1200 mg ribavirin. No patient discontinued treatment for anemia.

In conclusion, patients chronically infected with HCV-2 or HCV-3 should receive combination therapy for 24 weeks. To extend these observations to special populations further studies are necessary for immunocompromised patients (HIV/HCV co-infected, organ transplantation) and other groups (persistently normal ALT, African Americans).

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References

- [1] Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001;345:41–52.
- [2] Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002;36: S35–S46.
- [3] El-Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. *Hepatology* 2002;36:S74–S83.
- [4] Marcellin P, Boyer N, Gervais A, Martinot M, Pouteau M, Castelnau C, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. *Ann Intern Med* 1997; 127:875–881.
- [5] Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, et al. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. *Hepatology* 1998;28:1687–1695.
- [6] Poinard T, Marcellin P, Lee S, Niederau C, Minuk GS, Ideo G, et al. Randomised trial of interferon α 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon α 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998; 352:1426–1432.

- [7] McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *New Engl J Med* 1998;339:1485–1492.
- [8] EASL International Consensus Conference on Hepatitis C, Consensus statement. *J Hepatol* 1999;30:956–961.
- [9] National Institutes of Health Consensus Development Conference Statement, Management of hepatitis C. *Hepatology* 2002;36: S3–S20.
- [10] Lindsay KL, Trepco C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology* 2001;34:395–403.
- [11] Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;343:1666–1672.
- [12] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, 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;358:958–965.
- [13] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales Jr FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975–982.
- [14] Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981;1:431–435.
- [15] Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003;38:645–652.
- [16] McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepco C, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002;123:1061–1069.
- [17] Hadziyannis SJ, Sette Jr H, Morgan T, Balan V, Diago M, Marcellin P, et al. Peginterferon alfa-2a (40 kD) and ribavirin combination therapy in chronic hepatitis C: randomized study of the effect of treatment duration and ribavirin dose. *Ann Intern Med* 2004; in press.
- [18] Mihm S, Fayyazi A, Hartmann H, Ramadori G. Analysis of histopathological manifestations of chronic hepatitis C virus infection with respect to virus genotype. *Hepatology* 1997;25:735–739.
- [19] Poynard T, Ratziu V, McHutchison J, Manns M, Goodman Z, Zeuzem S, et al. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. *Hepatology* 2003;38:75–85.
- [20] Bruchfeld A, Lindahl K, Schvarcz R, Stahle L. Dosage of ribavirin in patients with hepatitis C should be based on renal function: a population pharmacokinetic analysis. *Ther Drug Monit* 2002;24: 701–708.