Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C

Michael Manns[1,*], Stefan Zeuzem[2], Ajit Sood[3], Yoav Lurie[4], Markus Cornberg[1], Hartwig Klinker[5], Peter Buggisch[6], Martin Rössle[7], Holger Hinrichsen[8], Ismail Merican[9], Yaron Ilan[10], Stefan Mauss[11], Saif Abu-Mouch[12], Andryes Horban[13], Thomas H. Müller[14], Christoph Welsch[2], Rongdean Chen[15], Rab Faruqi[15], Lisa D. Pedicone[15], Heiner Wedemeyer[1]

[1]*Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany;* [2]*Department of Medicine I, J.W. Goethe University Hospital, Frankfurt, Germany;* [3]*Dayanand Medical College and Hospital, Ludhiana, Punjab, India;* [4]*Gastroenterology and Hepatology, Sourasky Medical Center, Tel Aviv, Israel;* [5]*Division of Infectious Diseases, Department of Internal Medicine II, University of Wurzburg Medical Center, Wurzburg, Germany;* [6]*Liver Center Hamburg, IFI-Institute, Hamburg, Germany;* [7]*Center for Ambulatory Gastroenterology and Endocrinology, Freiburg, Germany;* [8]*Practice for Gastroenterology and Hepatology, Kiel, Germany;* [9]*Selayang Hospital, Selangor, Malaysia;* [10]*Department of Medicine, Hebrew University-Hadassah Medical Center, Jerusalem, Israel;* [11]*Center for HIV and Hepatogastroenterology, Dusseldorf, Germany;* [12]*Hillel-yaffe Medical Center, Hadera, Israel;* [13]*Warsaw Medical University & Hospital of Infectious Diseases, Warsaw, Poland;* [14]*Institute for Medical Informatics, Biometry and Epidemiology, University of Munich, Munich, Germany;* [15]*Schering–Plough Corporation, Now Merck & Co., Inc., Whitehouse Station, NJ, USA*

Background: There is increasing interest in identifying patients with chronic hepatitis C genotype 2 or 3 infection in whom it is possible to lower the burden of therapy while retaining high levels of efficacy.

Methods: Treatment-naive patients with chronic hepatitis C genotype 2/3 infection were randomized to receive peginterferon alfa-2b (1.5 μg/kg/wk) for 24 weeks (group A); peginterferon alfa-2b (1.0 μg/kg/wk) for 24 weeks (group B); or peginterferon alfa-2b (1.5 μg/kg/wk) for 16 weeks (group C), each in combination with weight-based ribavirin (800–1200 mg/d). The study population comprised two cohorts: the Hep-Net cohort enrolled in Germany and an International cohort enrolled at study sites throughout Europe and Asia. The primary end point was sustained virological response (SVR).

Results: The study included 682 patients; 80.2% had genotype 3 infection. In the intent-to-treat population, SVR rates were 66.5%, 64.3%, and 56.6% in groups A, B, and C, and were similar in Asian and white patients. Treatment differences (A vs. B and A vs. C) failed to reach the predefined margin for noninferiority of -10%; and thus groups B and C failed to show noninferiority relative to group A. Among patients with undetectable HCV RNA at week 4, SVR rates were 75.3%, 75.9%, and 72.4%, respectively. Relapse rates were 17.8%, 16.3%, and 29.3%, respectively. Treatment-emergent serious adverse events were highest in group A and lowest in group C, and adverse events leading to discontinuation were similar across treatment arms.

Conclusions: For patients with chronic hepatitis C genotype 2/3 infection, 24 weeks of peginterferon alfa-2b (1.5 μg/kg/wk) plus weight-based ribavirin remains a standard-of-care therapy; however, treatment for 16 weeks may be considered for patients with undetectable HCV RNA at week 4 of the treatment.

Keywords: Hepatitis C; Randomized controlled trial; Noninferiority; Drug therapy; Whites; Asians.

* Corresponding author. Address: Department of Gastroenterology, Hepatology and Endocrinology, Medical School of Hannover, Carl-Neuberg Str. 1, 30625 Hannover, Germany. Tel.: +49 511 532 3305; fax: +49 511 532 4896.
E-mail address: manns.michael@mh-hannover.de (M. Manns).

Abbreviations: CHC, chronic hepatitis C; G, genotype; IFN, interferon; PEG-IFN, pegylated interferon; SVR, sustained virological response; RVR, rapid virological response; HCV, hepatitis C virus; HIV, human immunodeficiency virus; EVR, early virological response; ETVR, end of treatment virological response; AE, adverse event; ITT, intention-to-treat; CI, confidence interval; SAE, serious adverse event.

Introduction

Chronic hepatitis C (CHC) genotype (G) 2 or 3 infection responds readily to interferon-based antiviral therapy. Peginterferon (PEG-IFN) alfa-2b (1.5 μg/kg/wk) plus ribavirin (800–1400 mg/d) or PEG-IFN alfa-2a (180 μg/wk) plus ribavirin (800 mg/d) for 24 weeks are established as the current standard of care for patients with CHC G2/3 [1,2].

With these standard-of-care regimens now achieving sustained virological response (SVR) rates of up to 80% in G2/3 patients [1,2], it is becoming increasingly unlikely that further substantial efficacy gains can be made through regimen refinements. Therefore, interest has focused on identifying patient subgroups in which it is possible to lower the therapeutic burden without compromising levels of efficacy. A number of studies have examined the efficacy of lower PEG-IFN alfa doses [1,3,4] while others have evaluated a shortened treatment duration of 12–16 weeks [3,5–8]. Although this area of research has yielded

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024

Research Article

some interesting findings, current data suggest that treatment duration can only be reduced in patients who attain a rapid virological response (RVR, undetectable hepatitis C virus [HCV] RNA at week 4). An increased risk of relapse also appears to be a common consequence of reduced treatment durations [8].

Herein, we report the final analysis of the International reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in European and Asian genotype 2 and 3 CHC patients (REDD 2/3).

Methods

This was an open-label, multicentre, randomized, parallel-group study conducted at 51 centers in Europe and Asia. This study started in 2003 as an investigator-initiated open-label, multicentre, randomized study conducted in Germany by Hep-Net (the "Hep-Net" cohort), the German network of competence on viral hepatitis [9]. In January 2005, Schering–Plough Corporation assumed sponsorship of the study and expanded it to include additional centers in Europe and Asia (the "International" cohort).

Participants

All patients provided written informed consent. Patients were eligible for enrollment if they had CHC G2 or G3 infection and were treatment naive. All patients had detectable hepatitis C virus (HCV) RNA, abnormal alanine aminotransferase, and compensated liver disease, and were eligible for treatment according to current consensus guidelines [10,11]. Patients were required to have hemoglobin levels $\geqslant$11 g/dl (women) or $\geqslant$12 g/dl (men), platelet count $\geqslant$100,000 cells/mm^3, neutrophil count $\geqslant$1500 cells/mm^3, and thyroid stimulating hormone levels within normal limits. Patients were excluded if they had human immunodeficiency virus (HIV) or hepatitis B coinfection, creatinine clearance <50 ml/min, cause of liver disease other than CHC, evidence of advanced liver disease, pre-existing psychiatric conditions or history of severe psychiatric disorder. Patients with a history of substance abuse were required to have remained abstinent for 6 months prior to study entry and patients receiving buprenorphine were required to have been stable for 6 months.

Study design

The trial was conducted in accordance with the Declaration of Helsinki, current guidelines on Good Clinical Practices and local ethical and legal requirements. Eligible patients were randomized in a 1:1:1 ratio to three treatment arms: standard treatment (group A), consisting of PEG-IFN alfa-2b (1.5 μg/kg/wk; PegIntron, Schering–Plough Corporation, Now Merck & Co., Inc., Whitehouse Station, NJ) plus ribavirin (800–1200 mg/d: 800 mg/d for patients with body weight <65 kg; 1000 mg/d for those weighing 65–85 kg; and 1200 mg/d for those weighing >85 kg) for 24 weeks; reduced-dose treatment (group B), consisting of PEG-IFN alfa-2b (1.0 μg/kg/wk) plus ribavirin (800–1200 mg/d) for 24 weeks; and reduced-duration treatment (group C), consisting of PEG-IFN alfa-2b (1.5 μg/kg/wk) plus ribavirin (800–1200 mg/d) for 16 weeks (Fig. 1A).

Randomization was achieved using an interactive voice response system. Patients attended clinic visits every 4 weeks until week 24 (groups A and B) or week 16 (group C), then an additional follow-up visit 24 weeks after completing the treatment. HCV RNA was measured at baseline, week 4 (International cohort only), week 12, end of treatment, and 24 weeks after treatment completion. Standard criteria were employed for dose reduction and treatment discontinuation in patients experiencing hematological toxicity: use of erythropoietin or colony-stimulating factors was prohibited. Compliance was assessed by comparing the amount of study drug administered to the patient with the amount of study drug returned by the patient at all visits.

End points

The primary end point was SVR, defined as undetectable HCV RNA 24 weeks after the last dose of therapy. Serum HCV RNA was measured quantitatively by polymerase chain reaction with a detection limit of $\geqslant$600 IU/ml at local laboratories. All values that were below the limit of detection were considered negative. Qualitative assays had varying degrees of sensitivity for the lower limit of detection (10–640 IU/ml).

Other virological end points included early virological response (EVR; $\geqslant 2\ \log_{10}$ decline in HCV RNA at week 12), end-of-treatment virological response (ETVR; undetectable HCV RNA at week 24 in groups A and B and week 16 in group C), and relapse rate (ETVR and detectable HCV RNA at 24-week follow-up). RVR was assessed only in the International cohort, because the importance of week-4 HCV RNA levels was not widely recognized when the Hep-Net protocol was designed in 2002.

The incidence of adverse events (AEs) was also assessed. Patients who developed grade 3 AEs (except flu-like symptoms) had doses of both drugs reduced. If dose reduction was required to maintain a patient with a grade 2 AE or grade 3 flu-like symptoms in the study, the doses of both study drugs were reduced. Treatment with the full dose was resumed if the AE remitted (mild severity); however, if the AE persisted despite the use of the reduced dose, both drugs were interrupted for a maximum period of 2 weeks. After resolution of the AE, treatment was restarted at reduced doses and if these doses were tolerated for at least 2 weeks, therapy was increased to the full dose. If the AE recurred, the patient was maintained at the reduced doses of both study drugs or was discontinued. Patients who developed life-threatening grade 4 AEs were discontinued permanently.

Statistical analysis

Efficacy analyzes were undertaken on the intent-to-treat (ITT) population, which included all randomized patients who received at least one dose of the study drug, and repeated in a completers analysis, which included patients with end-of-treatment and 24-week follow-up results with imputation (if week-24 follow-up was missing and either end-of-treatment or week-4 follow-up was detectable, then it was assumed that week-24 follow-up was detectable). The safety population included all patients who received at least one dose of the study medication and had a safety assessment.

For the primary analyses, the effect of PEG-IFN alfa-2b dose was assessed by comparing the difference in SVR rates of groups A and B. The null hypothesis was that the difference in SVR between groups A and B (B–A) was less than or equal to the prespecified noninferiority margin of −10%. Noninferiority of group B with respect to group A was to be concluded if the lower bound of the 1-sided 95% confidence interval (CI) of the treatment difference was greater than the noninferiority margin. Similarly, noninferiority of group C with respect to group A was assessed using a similar comparison (C–A). The Hochberg procedure was used to adjust for the multiple comparisons. If the lower limits of the 1-sided 95% CIs were greater than −10% for both comparisons (B–A) and (C–A), then the null hypothesis was to be rejected for both comparisons.

When the original Hep-Net study was initiated, target enrollment was set at 900 patients (300 per arm); however, this target was revised later when Schering–Plough assumed sponsorship of the study. It was then estimated that 600 evaluable patients (200 per group) would be required, assuming an SVR of around 80%. Under these estimates, there was an 80% probability that the lower bound of the 1-sided CI would exceed a −10% noninferiority margin. Assuming a drop-out rate of 10%, 667 patients were the target sample size for enrollment.

Analysis of the primary end point was also evaluated by cohort. Similar comparisons between treatment groups were undertaken for RVR, ETVR, and relapse rates, but with 2-sided 95% CIs and no hypothesis testing.

Results

Patient demographics

Between July 2003 and March 2006, 361 patients with CHC G2/3 were enrolled and randomized in the Hep-Net cohort, and 347 received study drug. Subsequently, between January 2005 and March 2007, an additional 335 patients were enrolled and randomized in the International cohort (Fig. 1b). The study population comprised 547 (80.2%) G3 patients and 135 (19.8%) G2 patients. Demographics were well balanced across treatment groups (Table 1); however, the Hep-Net population was composed almost completely of white patients whereas the International cohort included 47.2% white patients and 52.8% Asian patients (Supplementary data Table 1).

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024

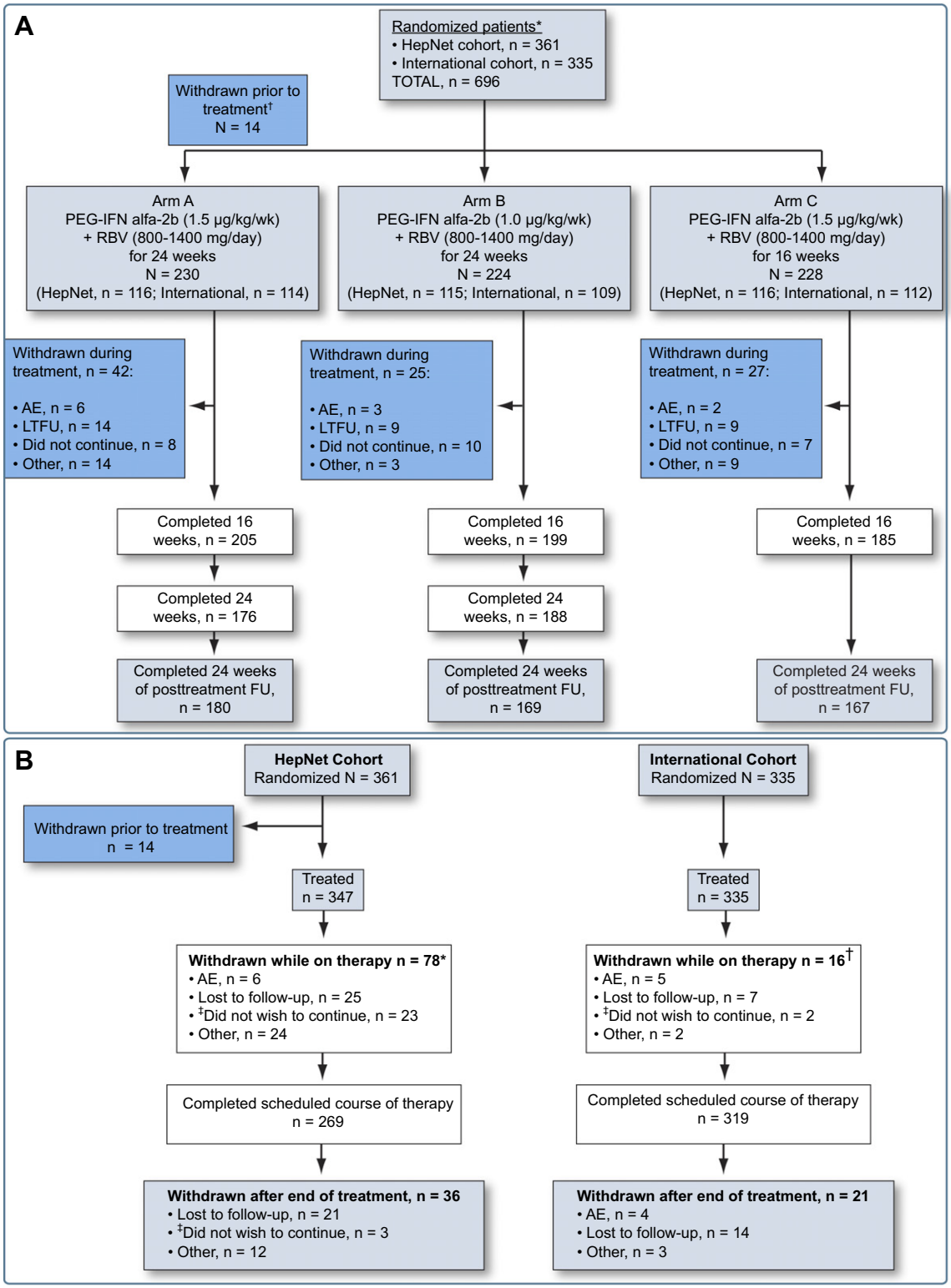

Fig. 1. (A) Patient flow diagram. *Due to incomplete reporting on the progress of some patients through the study, 12 patients in arm A, 11 patients in arm B, and 16 patients in arm C were not fully accounted for at all clinic visits. †14 patients from the HepNet cohort were randomized but did not receive study medication (Arm A, $n = 7$; Arm B, $n = 5$; Arm C, $n = 2$). (B) Patient flow diagram by enrollment cohort. *$n = 35$, $n = 20$, and $n = 23$ in arms A, B, and C, respectively. †$n = 7$, $n = 5$, and $n = 4$ in arms A, B, and C, respectively. ‡Decision to discontinue was unrelated to adverse event.

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024

Research Article

Table 1. Patient demographics.

	PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1400 mg/d (24 wk); n = 230	PEG-IFN alfa-2b 1.0 μg/kg/wk + RBV 800-1400 mg/d (24 wk); n = 224	PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1400 mg/d (16 wk); n = 228	Total N = 682
Age, mean (SD), y	38.8 (10.2)	39.9 (11.2)	39.7 (11.1)	39.5 (10.9)
Male, n (%)	139 (60.4)	146 (65.2)	148 (64.9)	433 (63.5)
Body weight, kg (SD)	73.7 (15.2)	72.8 (13.7)	72.5 (15.0)	73.0 (14.6)
Time since infection, y (SD)	7.3 (7.04)	7.6 (7.49)	7.3 (8.02)	7.4 (7.52)
Genotype, n (%)				
2	38 (16.5)	49 (21.9)	48 (21.1)	135 (19.8)
3	192 (83.5)	175 (78.1)	180 (78.9)	547 (80.2)
Baseline HCV RNA, n (%)				
≥600,000 IU/ml	119 (51.7)	120 (53.6)	123 (53.9)	362 (53.1)
<600,000 IU/ml	109 (47.4)	103 (46.0)	103 (45.2)	315 (46.2)

Virological outcomes

At treatment week 12, EVR was attained by 88.7%, 87.9%, and 86.8% of patients in groups A, B, and C, respectively. Additionally, 79.6%, 82.1%, and 82.9% of patients in groups A, B, and C attained ETVR. Overall, compliance was similar between treatment arms with 77.0%, 84.4%, and 83.3% of patients in arms A, B, and C, respectively, attending ⩾80% of scheduled visits and being ⩾80% compliant with both PEG-IFN alfa-2b and ribavirin.

In the ITT analysis, SVR rates were 66.5%, 64.3%, and 56.6% in groups A, B, and C, respectively (Fig. 2). The lower limit of the 1-sided 95% CI for the treatment comparison between groups B and A (B–A) for SVR was on the borderline value of the noninferiority margin at −10%, and this was reflected in the statistically significant p value ($p = 0.041$) at the 5% level. For the treatment comparison between groups C and A (C–A), the lower limit of the 1-sided 95% CI was below −10%; therefore, the Hochberg procedure was applied to adjust for the multiple treatment comparisons of (B–A) and (C–A), and 2-sided 95% CIs were produced. As the lower limits of the 2-sided 95% CIs for both of these treatment comparisons were less than −10%, noninferiority could not be concluded for either treatment comparison.

Overall, SVR was generally higher in the International cohort than in the Hep-Net cohort. In addition, the number of patients who completed therapy was higher in the International cohort (89.0% vs. 68.4%). In the completers analysis, the treatment difference between groups A and C was −0.14 ($p = 0.798$) with a 1-sided CI of −0.21, greater than the noninferiority margin of −10% (Fig. 2).

In the ITT analysis of the Hep-Net cohort, treatment differences were 0.01 for groups A and B, and −0.11 for groups A and C; respective 1-sided CIs were −0.09 and −0.22. For the ITT analysis of the International cohort, treatment differences were −0.06 for A versus B and −0.08 for A versus C with 1-sided CIs of −0.16

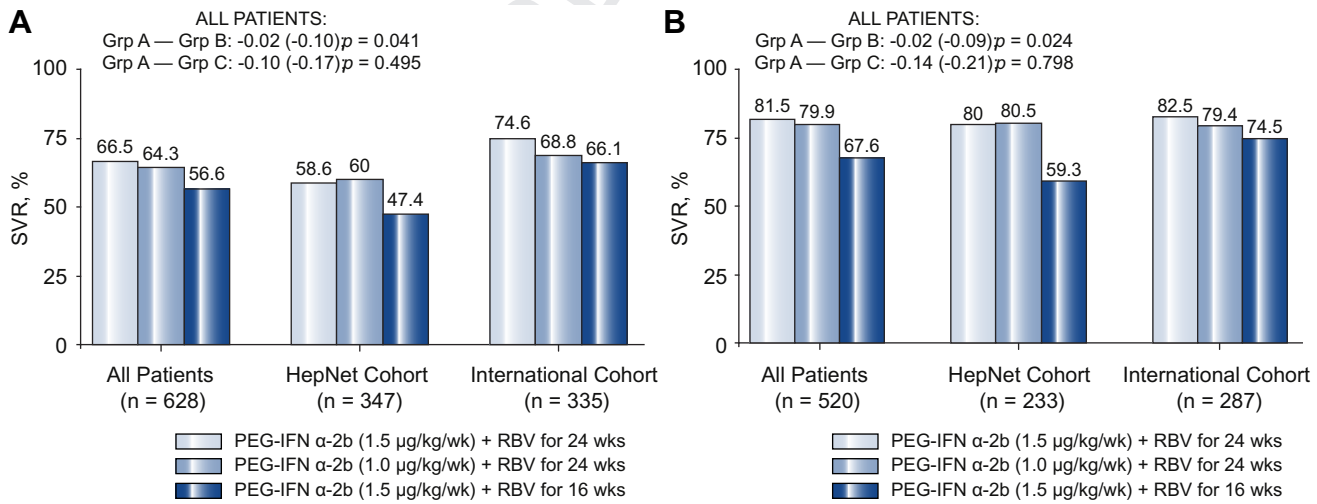

Fig. 2. Sustained virological response. (A) Intent-to-treat analysis and (B) completers analysis. *Completers analysis includes subjects who had both end-of-treatment and 24-week follow-up results with imputation (if 24-week follow-up was missing and either end-of-treatment or 4-week follow-up was detectable, then 24-week follow-up was assumed to be detectable).

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024

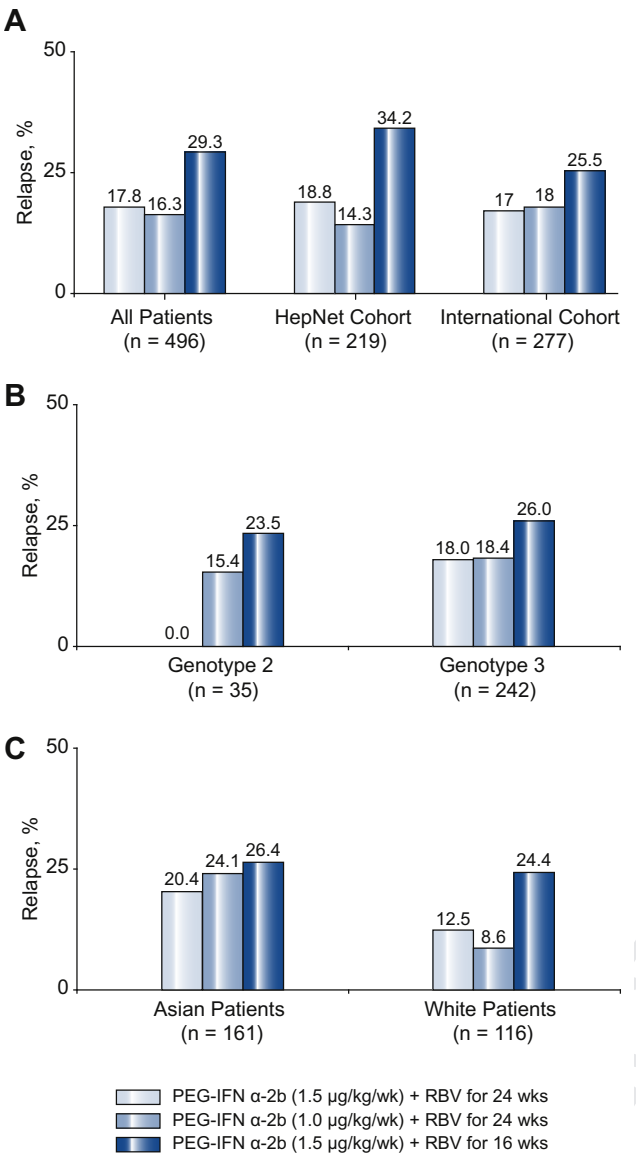

Fig. 3. Relapse rates according to (A) enrollment cohort, (B) within the International cohort, genotype, and (C) ethnic origin.

and −0.18, respectively. Thus, ITT analysis of each individual cohort also failed to demonstrate noninferiority. Similar outcomes were reported for each cohort in the completers analysis.

Relapse

Relapse was higher in patients treated for 16 weeks compared with 24 weeks (Fig. 3). Within the International cohort, relapse rates were numerically higher in Asian patients compared with white patients; and relapse rates were lower in patients with G2 compared with G3 infection within group A. In addition, among patients receiving PEG-IFN alfa-2b (1.5 μg/kg/wk) plus ribavirin for 24 weeks, relapse was higher in patients with G3 infection than in those with G2 infection (18% versus 0%); however, this difference was not evident in either of the other treatment arms.

Subgroup analyzes

Among G3 patients, SVR was generally higher in the International compared with the Hep-Net cohort (Table 2); however, this likely reflects the differences in study design (clinical trial vs. real-world setting), rather than any intrinsic differences in response to therapy. Among G3 patients in both cohorts, SVR was consistently lower in the 16-week compared with the 24-week treatment arms while results for the 24-week treatment arms in both cohorts were generally similar (Table 2). Within group A, SVR rates were highest in patients with G2 infection and low baseline viral load (82.3%) and lowest in those with G3 infection and high baseline viral load (61.2%; Table 2). Furthermore, even among patients with low baseline viral load, SVR rates were lower in group C compared with group A (G2: 57.9% vs. 82.3%; G3: 57.1% vs. 68.5%).

RVR was attained by 85.1%, 72.5%, and 77.7% of patients in groups A, B, and C, respectively ($p = 0.06$ for A vs. B and $p = 0.58$ for A vs. C). Among patients with RVR, SVR was consistently high across all treatment arms (Arm A = 75.3%, Arm B = 75.9%, Arm C = 72.4%; $p = 0.53$ for A vs. B; $p = 0.94$ for A vs. C; Table 2). However, among those patients who failed to attain RVR, SVR was lower in groups B and C, compared with group A (50.0% and 44.0% vs. 70.6%); however, for both comparisons the difference failed to reach statistical significance (group B–group A, −0.21 [−0.49, 0.08]; group C–group A, −0.27 [−0.56, 0.03]).

Within the International cohort, SVR was similar in Asian and white patients (Table 3). Likewise, SVR was similar in G3 Asian and white patients in the International cohort (75% vs. 74.5%). Interestingly, in the 24-week treatment arms relapse was appreciably higher in Asian patients than in white patients (PEG-IFN 1.5: 20.4% vs. 12.5% and PEG-IFN 1.0: 24.1% vs. 8.6%); however, in the 16-week arm relapse was high in both Asian and white patients (26.4% vs. 24.4%).

Safety and tolerability

Anemia was markedly lower in patients receiving PEG-IFN alfa-2b 1.0 μg/kg/wk than in those receiving 1.5 μg/kg/wk (4.9% vs. 10% and 11%) (Table 4). In addition, the incidence of anorexia and depression appeared higher in patients receiving PEG-IFN 1.5 μg/kg/wk for 24 weeks than in those receiving 1.0 μg/kg/wk. Fatigue and alopecia were more common in patients receiving PEG-IFN 1.5 μg/kg/wk for 24 weeks versus 16 weeks. Treatment-emergent serious adverse events (SAEs) were highest in patients receiving PEG-IFN alfa-2b (1.5 μg/kg/wk) for 24 weeks and lower in those receiving 16 weeks of therapy and PEG-IFN alfa-2b 1.0 μg/kg/wk. AEs leading to discontinuation of therapy were similar in all treatment arms. Dose reductions or interruptions due to anemia were reported in 14 (6.1%), 2 (0.9%), and 11 (4.8%) patients in arms A, B, and C, respectively.

Overall, tolerability was similar in Asian and white patients within the International cohort (Table 5). Of note, myalgia and arthralgia appeared to be more common among white compared with Asian patients, whereas pain and dyspepsia were more common among Asian patients. A total of 28 SAEs were reported in 15 patients in the International cohort. SAEs were reported by six patients receiving PEG-IFN alfa-2b for 24 weeks (four Asian and two white), three patients receiving low-dose PEG-IFN alfa-2b (one Asian and two white), and six patients in the 16-week arm (five Asian and one white).

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024

Research Article

Table 2. Subgroup analyzes.

	PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1200 mg/d	PEG-IFN alfa-2b 1.0 μg/kg/wk + RBV 800-1200 mg/d	PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1200 mg/d
SVR, n (%)	(24 wk)	(24 wk)	(16 wk)
Genotype 2			
Hep-Net (n = 84)	21/27 (77.8)	19/31 (61.3)	14/26 (53.8)
International (n = 51)	8/11 (72.7)	12/18 (66.7)	16/22 (72.7)
Genotype 3			
Hep-Net (n = 263)	47/89 (52.8)	50/84 (59.5)	41/90 (45.6)
International (n = 284)	77/103 (74.8)	63/91 (69.2)	58/90 (64.4)
Baseline viral load			
All patients <600,000 IU/ml	77/109 (70.6)	70/103 (68.0)	59/103 (57.3)
All patients ≥600,000 IU/ml	75/119 (63)	74/120 (61.7)	69/123 (56.1)
G2 <600,000 IU/ml	14/17 (82.3)	16/22 (72.7)	11/19 (57.9)
G2 ≥600,000 IU/nl	15/21 (71.4)	15/27 (55.6)	19/29 (65.5)
G3 <600,000 IU/ml	63/92 (68.5)	54/81 (66.7)	48/84 (57.1)
G3 ≥600,000 IU/ml	60/98 (61.2)	59/93 (63.4)	50/94 (53.2)
Body weight			
65 kg	46/70 (65.7)	46/75 (61.3)	45/78 (57.7)
>65 to <75 kg	36/59 (61.0)	38/58 (65.5)	26/54 (48.1)
≥75 to ≤85 kg	42/55 (76.4)	35/52 (67.3	32/57 (56.1)
>85 to ≤105 kg	24/39 (61.5)	24/36 (66.7)	22/34 (64.7)
>105 kg	5/7 (71.4)	1/3 (33.3)	4/5 (80.0)
Rapid virological response[a]			
Yes[b]	73/97 (75.3)	60/79 (75.9)	63/87 (72.4)
No	12/17 (70.6)	15/30 (50.0)	11/25 (44.0)

[a]Rapid virological response data are presented for the International cohort only.
[b]$p = 0.526$ for A vs. B, and $p = 0.938$ for A vs. C.

Table 3. International cohort ethnicity analyzes.

	INTERNATIONAL COHORT (N = 335)					
	PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1400 mg/d (24 wk) [n = 114]		PEG-IFN alfa-2b 1.0 μg/kg/wk + RBV 800-1400 mg/d (24 wk) [n = 109]		PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1400 mg/d (16 wk) [n = 112]	
	White (n = 57)	Asian (n = 57)	White (n = 50)	Asian (n = 59)	White (n = 51)	Asian (n = 61)
SVR	42/57 (73.7)	43/57 (75.4)	34/50 (68.0)	41/59 (69.5)	34/51 (66.7)	40/61 (65.6)
Relapse*	5/40 (12.5)	11/54 (20.4)	3/35 (8.6)	13/54 (24.1)	10/41 (24.4)	14/53 (26.4)
Completers SVR	35/46 (76.1)	38/46 (82.6)	29/42 (69.1)	40/53 (75.5)	31/44 (70.5)	33/49 (67.4)
SVR by genotype						
2	70	100	58.3	83.3	70.6	80
3	74.5	75	71.1	67.9	64.7	64.3

*Relapse was defined as HCV-RNA negative at the end of treatment and HCV-RNA positive at week 24 follow-up. Relapse rates were calculated using patients who were HCV-RNA negative at the end of treatment and had HCV RNA tested at week 24 follow-up. Patients with positive or missing HCV RNA at the end of treatment and negative HCV RNA at 24 weeks follow-up were not included in the relapse calculation.

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024

Table 4. Safety and tolerability.

	PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1400 mg/d	PEG-IFN alfa-2b 1.0 μg/kg/wk + RBV 800-1400 mg/d	PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1400 mg/d
Events, %	(24 wk); n = 230	(24 wk); n = 224	(16 wk); n = 228
Pyrexia	37.8	37.1	44.3
Fatigue	22.6	22.3	15.8
Headache	22.6	25.4	25.4
Alopecia	20.9	16.1	13.6
Asthenia	19.1	27.7	19.7
Myalgia	15.2	12.1	14.9
Influenza-like illness	12.6	9.4	10.1
Pruritus	12.6	19.6	10.1
Weight decrease	12.6	10.7	13.6
Anorexia	12.2	4.9	9.6
Nausea	11.7	11.6	14.0
Injection-site erythema	11.3	13.8	7.5
Depressed mood	11.3	7.1	8.3
Arthralgia	10.9	7.6	10.5
Anaemia	10.0	4.9	11.0
Diarrhea	9.6	12.1	7.0
Dry skin	5.7	11.2	6.6
Treatment-emergent SAE	6.1	4.9	3.1
Treatment-emergent severe/life threatening AE	7.0	4.5	5.3
Deaths	<1	<1	0
AE leading to interruption, reduction, or increase	15.7	4.9	12.3
AE leading to discontinuation	1.3	1.3	2.2

Discussion

In this large randomized study, reducing treatment from 24 to 16 weeks for patients with CHC G2 or G3 was associated with a lower SVR rate, which occurred secondary to an increase in relapse. These observations support recent guideline updates which state that a 24-week treatment duration should be considered standard of care in this population [12]. The noninferiority design of this study does not permit direct comparison of any two individual arms; however, in concluding that noninferiority cannot be claimed for either treatment comparison (A vs. B or A vs. C), these data reinforce the use of a 24-week treatment duration in this population. Nevertheless, as a general observation, there was little difference between PEG-IFN alfa-2b 1.5 and 1.0 μg/kg/wk and while 1.0 μg/kg/wk does not appear much worse in terms of efficacy, 1.5 μg/kg/wk is not much worse in terms of tolerability. Similar observations were recently reported in the IDEAL study with SVR rates of 40% and 38% in US G1 patients receiving PEG-IFN alfa-2b 1.5 or 1.0 μg/kg/wk in combination with weight-based ribavirin for 48 weeks [13]. Thus, data from REDD 2/3 and IDEAL indicate that while PEG-IFN alfa-2b 1.5 μg/kg/wk should be regarded as the standard approved dosage, clinicians can feel confident that the dose can be reduced to 1.0 μg/kg/wk in patients with safety concerns without any marked decline in efficacy.

The relapse rates in this study are likely attributable to the unique characteristics of the enrolled patient population. The majority of patients were G3 and more than half of all patients had baseline viral load >600,000 IU/ml; both of these factors are indicative of a relatively difficult-to-treat patient population. Indeed, there is some evidence that patients with G3 infection and high baseline viral load may require longer treatment duration than the standard 24 weeks [14]. Furthermore, because patients were not randomized based on RVR, relapse rates in the 16-week treatment arm are higher than would otherwise be expected when treating patients who are selected for shortened treatment based on week-4 HCV RNA levels.

Overall, tolerability was similar between treatment arms and consistent with the known safety profile of these agents. However, the incidence of anorexia, depression, and anemia appeared higher in patients receiving PEG-IFN 1.5 μg/kg/wk for 24 weeks than in those receiving 1.0 μg/kg/wk. In addition, fatigue and alopecia were more common in patients receiving PEG-IFN 1.5 μg/kg/wk for 24 weeks versus 16 weeks. Thus, as would be expected, there appear to be some tolerability benefits associated with reducing

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024

Research Article

Table 5. Adverse events in the International cohort.

	INTERNATIONAL COHORT (N = 335)					
	PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1400 mg/d (24 wk) [n = 114]		PEG-IFN alfa-2b 1.0 μg/kg/wk + RBV 800-1400 mg/d (24 wk) [n = 109]		PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV 800-1400 mg/d (16 wk) [n = 112]	
	Asian (n = 57)	White (n = 57)	Asian (n = 59)	White (n = 50)	Asian (n = 61)	White (n = 51)
Any AE, n (%)[a]	54 (94.7)	51 (89.5)	57 (96.6)	45 (90.0)	59 (96.7)	46 (90.2)
Pyrexia	37 (64.9)	28 (49.1)	44 (74.6)	24 (48.0)	40 (65.6)	35 (68.6)
Asthenia	22 (38.6)	17 (29.8)	25 (42.4)	25 (50.0)	24 (39.3)	19 (37.3)
Pain	16 (28.1)	0 (0.0)	13 (22.0)	0 (0.0)	12 (19.7)	0 (0.0)
Alopecia	15 (26.3)	12 (21.1)	11 (18.6)	6 (12.0)	10 (16.4)	10 (19.6)
Headache	12 (21.1)	18 (31.6)	12 (20.3)	14 (28.0)	14 (23.0)	16 (31.4)
Cough	12 (21.1)	5 (8.8)	12 (20.3)	2 (4.0)	11 (18.0)	8 (15.7)
Diarrhea	10 (17.5)	4 (7.0)	12 (20.3)	1 (2.0)	5 (8.2)	7 (13.7)
Dyspepsia	8 (14.0)	1 (1.8)	20 (33.9)	0 (0.0)	11 (18.0)	2 (3.9)
Myalgia	8 (14.0)	18 (31.6)	7 (11.9)	16 (32.0)	5 (8.2)	21 (41.2)
Irritability	3 (5.3)	5 (8.8)	2 (3.4)	11 (22.0)	0 (0.0)	10 (19.6)
Arthralgia	3 (5.3)	12 (21.1)	3 (5.1)	8 (16.0)	1 (1.6)	7 (13.7)
Discontinuation due to an AE, n (%)	1 (1.7)	1 (1.7)	3 (5.1)	1 (2.0)	3 (4.9)	0 (0.0)
SAE, n (%)[b]	4 (7.0)	2 (3.5)	1 (1.7)	2 (4.0)	5 (8.2)	1 (2.0)

[a]Adverse events reported in ⩾20% of patients in any treatment arm.
[b]A total of 28 serious adverse events were reported in 15 patients.

the intensity of treatment either through dose reduction or decreasing treatment duration.

The present study is unique, with features of both an investigator-initiated study and an industry-sponsored study. Data collected from the Hep-Net cohort reflect the "real-world" treatment of CHC with many patients lost to follow-up. By contrast, within the International cohort >85% of patients completed therapy. The high rates of discontinuation in the Hep-Net cohort are also consistent with other real-world studies, such as the WIN-R trial [15], where patient retention is frequently subject to influences that do not necessarily affect the recruitment of patients in clinical trials. These data highlight the need for optimized patient management in a real-world setting.

Race and ethnicity are well-described predictors of treatment outcome for hepatitis C. The present study represents the largest evaluation of G3-infected Asian patients to date and showed no difference in treatment response for Asian versus white European patients. Demographic differences between Asian and white patients may render these populations differentially sensitive to therapy and affect treatment outcomes; however, further study is required to determine whether tailored treatment algorithms are needed for patients of differing ethnic origins.

Several smaller studies have suggested that shorter treatment durations are effective in patients who attain RVR [3,6,7]. In the present study, SVR rates were uniformly high among patients who attained RVR in all treatment arms, but declined with reduced PEG-IFN alfa-2b dose and treatment duration in patients who failed to attain RVR. These data, therefore, support using shortened treatment duration of 16 weeks in patients with G2/3 infection receiving PEG-IFN plus weight-based ribavirin who have undetectable HCV RNA at week 4 of therapy. Consistent with these data, there appears to be a consensus that reduced treatment duration should only be considered in patients who attain RVR [12]. In the present study, reduced treatment duration was associated with lower rates of SVR in unselected patients, even among those patients with low baseline viral load. It is also worth noting that body mass index >30 kg/m^2 and platelet count ⩽140,000 cells/mm^3 are significantly associated with relapse in G2/3 patients treated for 12 weeks [16]. Furthermore, shortened treatment duration has not been prospectively investigated in certain difficult-to-treat groups such as G3 patients with high baseline viral load, African-Americans, those with cirrhosis, and those with HCV-HIV coinfection, and thus caution should be exercised when considering truncated therapy for these patients [12]. Finally, ribavirin dosing also appears to be an important factor: Mangia and colleagues reported that in G2/3 patients with RVR receiving PEG-IFN plus ribavirin 1000–1200 mg/d, SVR rates were 85% and 91% when treated for 12 or 24 weeks, respectively [3]. Similarly in the NORTH-C study, SVR rates were 81% and 91% in G2/3 patients with RVR receiving PEG-IFN alfa-2b plus ribavirin (800–1400 mg/d) when treated for 14 or 24 weeks [7]. Although in the latter study, the difference between SVR rates failed to meet the predefined statistical criteria for noninferiority, the authors concluded that the SVR rate in the shortened treatment arm remained

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024

a favorable option. By contrast, G2/3 patients with RVR receiving a fixed 800-mg/d ribavirin dose showed a significant decline in efficacy when treatment was stopped at week 12 or 16 [5,8]. Thus, these studies, considered collectively and in concert with data regarding the inverse relationship between ribavirin dose and relapse rates taken from other settings [17], strongly suggest that weight-based ribavirin dosing is a key consideration in mitigating the risk of relapse. This is particularly relevant to physicians considering shortened treatment options where the risk of relapse is high: in this setting all appropriate measures to mitigate relapse should be implemented, and we would advocate that shortened therapy should not be considered in patients who are not candidates for weight-based ribavirin treatment.

In conclusion, these data show that PEG-IFN alfa-2b (1.5 μg/kg/wk) plus weight-based ribavirin for 24 weeks remains a standard of care for patients with CHC G2/3. In addition, a shortened treatment duration of 16 weeks may be considered for patients who have undetectable HCV RNA at week 4 of treatment: this strategy may be particularly suitable for patients who are not otherwise predisposed to relapse, such as those on weight-based ribavirin, those compliant with medication, those who do not have other characteristics associated with poor response (African American ethnicity, cirrhosis, or high baseline viral load) and for those in whom treatment shortening may be appropriate for other reasons like drug toxicity. PEG-IFN alfa-2b (1.5 μg/kg/wk) plus weight-based ribavirin offers favorable treatment outcomes for both Asian and white patients and is equally effective in G2 and G3 patients.

Clinical trial registration number

NCT00302081.

Disclosures

M.P. Manns consulted for Bristol-Myers Squibb, Valeant, Idenix, Vertex, GlaxoSmithKline, Merck, Astra/Arrows, Boehringer Ingelheim, Gilead, Schering–Plough Corp., Now Merck & Co., Inc., Roche, Novartis, and Tibotec, and receives grant/research support from Schering–Plough Corp., Now Merck & Co., Inc., Roche, Gilead, Novartis, Boehringer Ingelheim, Bristol-Myers Squibb. S. Zeuzem consults for Schering–Plough Corp., Now Merck & Co., Inc., Human Genome Sciences, Novartis, Roche and received speaker's honoraria from Schering–Plough Corp., Now Merck & Co., Inc., Novartis, and Roche. M. Cornberg reports receiving advisory fees, speakers honoraria, and grant/research support from Essex Pharma. H. Klinker consults for and received speaker's honoraria from Essex Pharma. P. Buggisch has received speaker's honoraria from Schering–Plough Corp., Now Merck & Co., Inc., and Roche. S. Mauss consults for and received speaker's honoraria from Schering–Plough Corp., Now Merck & Co., Inc., Novartis and Roche, and receives grant/research support from Roche. H. Wedemeyer reports receiving advisory fees, speakers honoraria, and grant/research support from Essex Pharma. R. Faruqi and R. Chen are employees of Schering Corp., Now Merck & Co., Inc. L.D. Pedicone is an employee of Schering Corp., Now Merck & Co., Inc., and is a stock holder in this entity.

A. Sood, Y. Lurie, M. Rössle, H. Hinrichsen, I. Merican, Y. Ilan, S. Abu-Mouch, A. Horban, T.H. Müller, and C. Welsch report having nothing to disclose.

Conflicts of interest

M.P. Manns consulted for Bristol-Myers Squibb, Valeant, Idenix, Vertex, GlaxoSmithKline, Merck, Astra/Arrows, Boehringer Ingelheim, Gilead, Schering–Plough Corp., Now Merck & Co., Inc., Roche, Novartis, and Tibotec, and receives grant/research support from Schering–Plough Corp., Now Merck & Co., Inc., Roche, Gilead, Novartis, Boehringer Ingelheim, Bristol-Myers Squibb. S. Zeuzem consults for Schering–Plough Corp., Now Merck & Co., Inc., Human Genome Sciences, Novartis, Roche and received speaker's honoraria from Schering–Plough Corp., Now Merck & Co., Inc., Novartis, and Roche. M. Cornberg reports receiving advisory fees, speakers honoraria, and grant/research support from Essex Pharma. H. Klinker consults for and received speaker's honoraria from Essex Pharma. P. Buggisch has received speaker's honoraria from Schering–Plough Corp., Now Merck & Co., Inc., and Roche. S. Mauss consults for and received speaker's honoraria from Schering–Plough Corp., Now Merck & Co., Inc., Novartis and Roche, and receives grant/research support from Roche. H. Wedemeyer reports receiving advisory fees, speakers honoraria, and grant/research support from Essex Pharma. R. Faruqi and R. Chen are employees of Schering Corp., Now Merck & Co., Inc. L.D. Pedicone is an employee of Schering Corp., Now Merck & Co., Inc., and is a stock holder in this entity.

A. Sood, Y. Lurie, M. Rössle, H. Hinrichsen, I. Merican, Y. Ilan, S. Abu-Mouch, A. Horban, T.H. Müller, and C. Welsch report having nothing to disclose.

Acknowledgments

Hep-Net cohort investigators: J. Arnold, P. Buggisch, H. Cordes, W. Fleig, W. Gickler, J. Gottberg, K. Gruengreiff, M. Heer, H. Hinrichsen, T. Kaser, H. Klinker, M. Manns, R. Markus, S. Mauss, U. Meyer, J. Ockenga, J. Pausch, T. Pohle, J. Riemann, M. Rössle, A. Schober, H. Steffens, A. Trein, K. Wiedmann, K. Wiegand, S. Zeuzem.
International cohort investigators: S. Abu-Mouch, D. Amarapurkar, Z. Ben-Ari, C. Choudhury, A. Chutaputti, M. Goenka, W. Halota, A. Horban, Y. Ilan, E. Janczewska-Kazek, A. Konar, L. Lesmana, S. Lim, Y. Lurie, V. Mahachai, I. Merican, T. Piratvisuth, D. Reddy, S. Sachithanandan, T. Safadi, S. Sarin, O. Segol, P.B. Setiawan, A. Sood, T. Tanwandee.
Writing assistance was provided by Tim Ibbotson, Ph.D., and Claudette Knight, Pharm.D. This assistance was funded by Schering–Plough Corporation, Now Merck & Co., Inc., Whitehouse Station, NJ, USA.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jhep.2010.12.024. Q1

References

[1] 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.
[2] 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.

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024

Research Article

[3] Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med 2005;352:2609–2617.
[4] Pockros PJ, Carithers R, Desmond P, Dhumeaux D, Fried MW, Marcellin P, et al. Efficacy and safety of two-dose regimens of peginterferon alpha-2a compared with interferon alpha-2a in chronic hepatitis C: a multicenter, randomized controlled trial. Am J Gastroenterol 2004;99:1298–1305.
[5] Lagging M, Langeland N, Pedersen C, Farkkila M, Buhl MR, Morch K, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology 2008;47:1837–1845.
[6] von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, et al. Peginterferon-alpha-2a (40 kDa) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology 2005;129:522–527.
[7] Dalgard O, Bjoro K, Ring-Larsen H, Bjornsson E, Holberg-Petersen M, Skovlund E, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology 2008;47:35–42.
[8] Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med 2007;357:124–134.
[9] Manns MP, Meyer S, Wedemeyer H. The German network of excellence for viral hepatitis (Hep-Net). Hepatology 2003;38:543–544.
[10] Dienstag JL, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. Gastroenterology 2006;130:231–264.
[11] Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39:1147–1171.
[12] Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–1374.
[13] McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavarin for treatment of hepatitis C infection. N Engl J Med 2009;361:580–593.
[14] Willems B, Hadziyannis SJ, Morgan TR, Diago M, Marcellin P, Bernstein D, et al. Should treatment with peginterferon plus ribavirin be intensified in patients with HCV genotype 2/3 without rapid virological response? J Hepatol 2007;46:S6.
[15] Jacobson IM, Brown Jr RS, Freilich B, Afdhal N, Kwo PY, Santoro J, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology 2007;46:971–981.
[16] Mangia A, Minerva N, Bacca D, Cozzolongo R, Agostinacchio E, Sogari F, et al. Determinants of relapse after a short (12 weeks) course of antiviral therapy and re-treatment efficacy of a prolonged course in patients with chronic hepatitis C virus genotype 2 or 3 infection. Hepatology 2009;49:358–363.
[17] Shiffman ML, Salvatore J, Hubbard S, Price A, Sterling RK, Stravitz RT, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. Hepatology 2007;46:371–379.

Please cite this article in press as: Manns M et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol (2011), doi:10.1016/j.jhep.2010.12.024