JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2012, **19,** e120–e125 doi:10.1111/j.1365-2893.2011.01515.x

Peginterferon alfa-2b plus weight-based ribavirin for 24 weeks in patients with chronic hepatitis C virus genotype 1 with low viral load who achieve rapid viral response

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Received April 2011; accepted for publication June 2011

SUMMARY. In chronic hepatitis C (CHC), treatment duration may be individualized according to time to first undetectable hepatitis C virus (HCV) RNA, with patients who attain undetectable HCV RNA early in treatment being candidates for shorter regimens. The aim of this study was to determine the relapse rate in patients with CHC genotype (G) 1 infection and low baseline viral load who achieved undetectable HCV RNA by week 4 [rapid virologic response (RVR)] when treated for 24 weeks. This was an open-label, multicentre, noninterventional study. Adult patients with G1 CHC infection and baseline viral load <600,000 IU/mL who attained RVR were treated with peginterferon alfa-2b (1.5 μg/kg/week) plus ribavirin (800–1200 mg/day) for 24 weeks, then followed for a further 24 weeks. The primary endpoint was relapse rate, defined as the proportion of patients with undetectable HCV RNA at treatment week 24 and detectable HCV RNA at week 24 follow-up. The secondary efficacy endpoint was sustained virologic response (SVR). Overall, 170 patients were included in the efficacy-evaluable population. The relapse rate was 9.7% (16/165, 95% confidence interval: 0.06–0.15), and SVR was attained by 149 of 170 patients (87.6%). Virologic outcomes were consistent regardless of age, gender, body weight and genotype. Seven patients reported treatment-emergent serious adverse events (AEs), and four patients discontinued treatment because of an AE. This study further demonstrates that peginterferon alfa-2b plus weight-based ribavirin for 24 weeks is an effective treatment strategy for treatment-naive patients with G1 CHC and low viral load who attain RVR.

Keywords: hepatitis C virus genotype, peginterferon, relapse, ribavirin, viral load.

INTRODUCTION

An increase in relapse rate is the principal concern when reducing treatment duration in patients infected with G1 CHC. Shortening duration of treatment reduces the on-treatment period during which hepatitis C virus (HCV) RNA is undetectable and increases the risk of post-treatment relapse [1]. The relationship between on-treatment duration of undetectable HCV RNA and treatment outcome has thus become an important factor in defining treatment regimens in the era of response-guided therapy [2]. Low viral load prior to commencing treatment can also mitigate the risk of relapse associated with a shortened treatment duration strategy and is considered a favourable prognostic factor in the treatment of patients with G1 CHC [3–5].

In patients with chronic hepatitis C G1 infection, shortened treatment strategies have been extensively evaluated [4,6–9]. An earlier study to test this hypothesis was reported by Zeuzem *et al.* in 2006. This study showed that in G 1 treatment-naive patients with a pretreatment baseline viral

Abbreviations: HCV, hepatitis C virus; SVR, sustained viral response; RVR, rapid virologic response; PEG-IFN, peginterferon; SAE, serious adverse event; AE, adverse event; CI, confidence interval; LLD, lower limit of detection; OR, odds ratio.

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load ≤600 000 IU/mL who achieved undetectable HCV RNA after 4 weeks [rapid virologic response (RVR)], treatment duration could be shortened from the standard 48 weeks to 24 weeks without any significant decline in sustained virologic response (SVR) or increase in relapse (SVR, 85% *vs* 89%; relapse, 8% *vs* 8%) [10].

The study by Zeuzem *et al.* formed the basis for the approval of peginterferon (PEG-IFN) alfa-2b plus weight-based ribavirin therapy for a period of 24 weeks in treatment-naive patients with G1 infection and low baseline viral load who attain RVR by the European Medicines Evaluation Agency [11], a strategy that has also been subsequently adopted for PEG-IFN alfa-2a plus ribavirin [12]. However, because the study by Zeuzem *et al.* was a noncomparative, historical control study using a highly selected patient cohort [treatment-naive patients from the study by Manns *et al.* [13] who were selected on the basis of tolerability, compliance and adherence], further supporting evidence was also deemed necessary. The aim of the current study was therefore to determine the relapse rate in patients with chronic hepatitis C G1 infection and favourable predictors of responsiveness (low baseline viral load and undetectable HCV RNA by week 4) when receiving PEG-IFN alfa-2b plus ribavirin therapy for a total of 24 weeks in a situation akin to real-life practice at experienced referral centres.

MATERIALS AND METHODS

Patients

Adult patients with chronic hepatitis C G1 infection and with a baseline viral load <600 000 IU/mL prior to starting treatment were enrolled and followed according to the standard diagnostic and treatment policies of each site. However, patients who had received any previous treatment for chronic hepatitis C, women who were pregnant or planning to become pregnant and the sexual partners of women who intended to become pregnant were excluded.

Study design

This was an open-label, nonrandomized, multinational, multicentre, noninterventional study (NCT00709228). Merck's approach to the conduct of clinical trials is in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable regulatory requirements.

All patients received PEG-IFN alfa-2b (1.5 μg/kg/week) plus ribavirin (800–1200 mg/day) administered according to patient body weight. Patients weighing ≤64 kg received ribavirin 800 mg/day, patients weighing 65–85 kg received 1000 mg/day and those weighing >85 kg received 1200 mg/day. Treatment duration was 24 weeks and all patients were then followed for a further 24 weeks after completing therapy.

All patients were required to have undetectable HCV RNA at treatment week 4 to be enrolled in the study. Patients who maintained undetectable HCV RNA at treatment week 24 were given the option to stop therapy with the agreement of the investigator and were followed for 24 weeks post-treatment. These patients were included in the efficacy analysis. Patients who opted to continue therapy received treatment outside of the study protocol, were censored as treatment failures and were excluded from the efficacy-evaluable population. Patients with detectable HCV RNA at treatment week 4 also continued to receive treatment outside of the study protocol. Quantitative PCR testing of HCV RNA was performed at treatment weeks 4 and 24 and at week 24 of follow-up at local laboratories; results were reported in IU/mL.

Study endpoints

The primary endpoint was the relapse rate, defined as the proportion of patients with undetectable HCV RNA at treatment week 24 to detectable HCV RNA at week 24 follow-up. Patients who were identified as relapsers at the end of the follow-up phase were offered re-treatment with PEG-IFN alfa-2b plus ribavirin 800–1400 mg/day for an additional 48 weeks. The secondary efficacy endpoint was SVR, defined as the percentage of patients with undetectable HCV RNA at the end of the 24-week treatment period and at week 24 of follow-up.

Clinical assessment and review of laboratory data were used to monitor safety and tolerability of study drugs in accordance with routine clinical practice. Only data regarding serious adverse events (SAEs; as defined using the modified World Health Organization grading system) were collected.

The *all-enrolled population* included all patients who received at least one dose of study medication and who had undetectable HCV RNA at week 4 of treatment. Efficacy analyses were performed on the *efficacy-evaluable population*, which included all patients in the all-enrolled population who had undetectable HCV RNA at the end of 24 weeks of treatment and stopped treatment after 24 weeks. For analysis of relapse rates, patients also needed to have nonmissing HCV RNA assessment at 24 weeks of follow-up (an earlier detectable HCV RNA during the follow-up phase was carried forward to 24 weeks of follow-up visit). The primary safety analysis is presented for the all-enrolled population.

The *per-protocol population* consisted of all patients in the efficacy-evaluable population who did not have major protocol violations and who attended scheduled week-4, -12 and -24 visits and week-24 follow-up visit. For the purpose of assessing the effect of adherence on relapse and SVR in the per-protocol population, adherence was defined as patients who received at least 80% of the planned treatment for at least 80% of the scheduled treatment duration (80:80:80), as verified by review of patients charts. Treatment adherence was monitored by the investigator by tracking and recording

the prescribed treatment regimen, date of administration and dosing.

Statistics

The study was planned to enrol 150 patients with undetectable HCV RNA at treatment week 4, to ensure 126 patients who would stop treatment with undetectable HCV RNA at treatment week 24 and have virology results at week 24 of follow-up (the efficacy-evaluable population). Assuming a relapse rate of 9% [10], a sample population of 126 subjects would permit the estimation of relapse rate within ±5% by using 95% confidence intervals (CIs). The primary and secondary endpoints were summarized, and the corresponding 95% CIs were calculated using the Clopper–Pearson method.

RESULTS

Patient characteristics

In total, 187 patients met eligibility criteria and were enrolled in the study (the all-enrolled population), and of these 14 patients failed to complete the 24-week treatment duration (Fig. 1). The remaining 173 patients completed treatment, and 169 patients entered the post-treatment follow-up.

Because of the noninterventional nature of this study (treatment was administered in accordance with the product label, and treatment assignment was directed according to current clinical practice with no additional diagnostic or monitoring procedures), there was no protocol-mandated criterion for the sensitivity of the HCV RNA assays employed at the local laboratories. As a result, evaluation of the 187 enrolled patients was based on local laboratory assays with lower limits of detection (LLD) that ranged widely from 9.6 to 700 IU/mL, with most sites using assays with an LLD of <60 IU/mL. In total, HCV RNA levels for 84% of patients (157 of 187) were evaluated using assays with an LLD ≤60 IU/mL; the remaining 16% of patients (30 of 187) were evaluated with less sensitive assays ranging between 100 and 700 IU/mL.

Virologic outcomes

Overall, 170 patients from 14 European countries (Croatia, France, Germany, Greece, Israel, Italy, Norway, Portugal, Russia, Slovenia, Spain, Sweden, the Netherlands and United Kingdom) were included in the efficacy-evaluable population (Table 1). The relapse rate was 9.7% (16/165, 95% CI: 0.06–0.15), and SVR was attained by 149 of 170 patients (87.6%) (Fig. 2). Relapse and SVR rates in the per-protocol population and for patients in the per-protocol population who were 80:80:80 adherent are shown in Fig. 3.

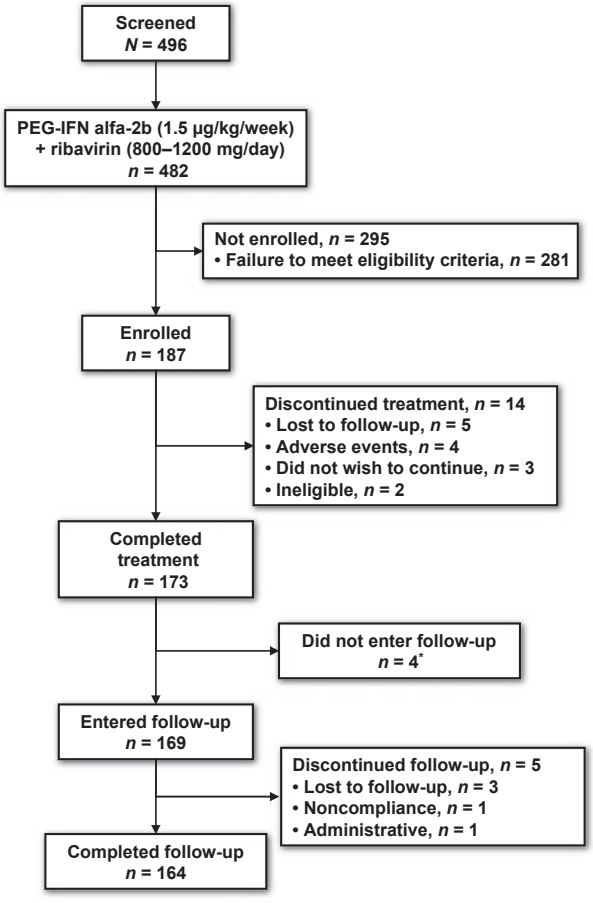

Fig. 1 Patient disposition. *Includes one patient with undetectable hepatitis C virus RNA at week 24 who was included in the efficacy-evaluable population. This patient had missing follow-up data, was classified as a nonresponder and was not included in the relapse analysis.

An *ad hoc* analysis was conducted to evaluate the effect of varying the sensitivity of assay used to evaluate week 4 HCV RNA levels on relapse and SVR rates. When the analysis was restricted to patients with treatment week 4 HCV RNA levels evaluated using an assay with an LLD of ≤60 IU/mL, the relapse rate was 6.4% (nine of 140) and the SVR rate was 91.6% (131/143). However, in patients evaluated at week 4 with a less sensitive assay (LLD >60 IU/mL), the relapse rate was 28% (seven of 25) and the SVR rate was 66.7% (18 of 27).

Virologic outcomes were generally similar among male and female patients and among younger and older patients (Table 2). Relapse was numerically lower in patients weighing >65–75 kg (ribavirin dose: 1000 mg/day) and >85–105 kg (ribavirin dose: 1200 mg/day) compared with patients weighing ≤65 kg and >75–85 kg; however, these differences did not reach statistical significance ($P = 0.19$ for both comparisons). Likewise, although SVR was numerically higher and relapse lower in patients with genotype 1a

Table 1 Patient characteristics

	All-enrolled patients (N = 187)
Male, *n* (%)	116 (62)
Race, *n* (%)	
White	182 (97)
Asian	3 (2)
Black	1 (1)
Other	1 (1)
Age	
Mean, years (SD)	37.8 (10.7)
18 to <40 years, *n* (%)	113 (60)
≥40 years, *n* (%)	74 (40)
Mean weight, kg (SD)	74.5 (14.2)
Genotype 1 subtype, *n* (%)	
1a	50 (27)
1b	116 (62)
Unspecified	21 (11)
Mean duration of exposure, years (SD)	13.2 (10.7)
Source of exposure	
Parenteral	103 (55)
Sporadic	48 (26)
Transfusion	24 (13)
Other	12 (6)

SD, standard deviation.

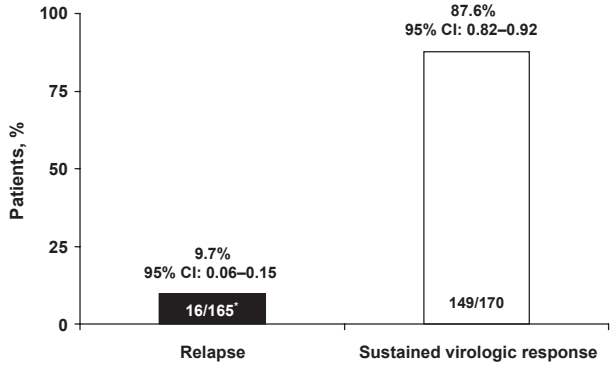

Fig. 2 Relapse and sustained virologic response rates in the efficacy-evaluable population.

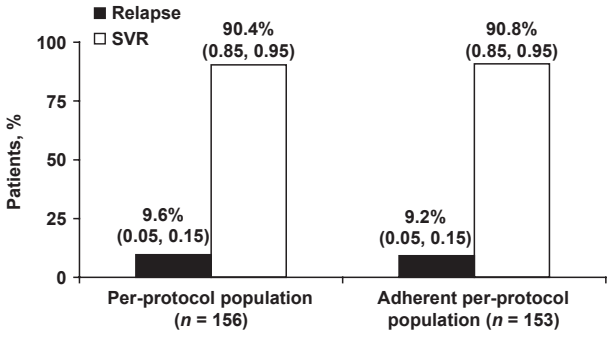

Fig. 3 Per-protocol analyses.

Table 2 subgroup analyses

	Relapse (n = 165)*	SVR (n = 170)
Gender, *n* (%)		
Male	10/100 (10.0)	90/102 (88.2)
Female	6/65 (9.2)	59/68 (86.8)
Age, *n* (%)		
<40 years	8/97 (8.2)	89/101 (88.1)
≥40 years	8/68 (11.8)	60/69 (87.0)
Body weight, *n* (%)		
≤65 kg	6/47 (12.8)†	41/49 (83.7)
>65–75 kg	3/40 (7.5)	37/41 (90.2)
>75–85 kg	6/47 (12.8)‡	41/48 (85.4)
>85–105 kg	1/28 (3.6)	27/29 (93.1)
>105 kg	0/3 (0)	3/3 (100)
Subtype, *n* (%)		
1a	3/45 (6.7)§	42/45 (93.3)¶
1b	12/102 (11.8)	90/106 (84.9)
Unspecified	1/18 (5.6)	17/19 (89.5)

*Follow-up data were not available for five patients in the efficacy-evaluable population. †Comparison between ≤65 kg and >65–75 kg or >85–105 kg, Fisher's exact test P = 0.19. ‡Comparison between >75–85 kg and >65–75 kg or >85–105 kg, Fisher's exact test P = 0.19. §Comparison between genotype 1a and genotype 1b, Fisher's exact test P = 0.56. ¶Comparison between G1a and G1b, Fisher's exact test P = 0.19. SVR, sustained virologic response.

compared with those with genotype 1b infection, there were no significant differences between the G1 subtypes (SVR: 93.3% *vs* 84.9%, P = 0.19; relapse: 6.7% *vs* 11.8%, P = 0.56).

Safety and tolerability

Treatment-emergent SAEs were reported in seven patients (thrombosis, hypothyroidism, aggressive behaviour, pancreatitis, suicide attempt, neck abscess and personality disorder). In addition, one nontreatment-emergent SAE of acute psychosis occurred during the follow-up phase, ≥30 days after completing treatment.

Adverse events led to treatment discontinuations in four patients: pancreatitis, thrombosis and aggressive behaviour were considered SAEs, and one more patient discontinued treatment because of disturbance in attention, which was not considered an SAE (Table 3). Dose reductions or interruptions were required to manage 12 AEs in nine patients. The most common AEs leading to dose reduction or interruption were neutropenia (n = 3), anaemia (n = 2) and depression (n = 2); all other AEs were reported by one

Table 3 Adverse events (AEs)

	All-enrolled patients (N = 187)
Adverse events leading to study discontinuation, n (%)	4 (2)*
Adverse events leading to dose reduction/interruption, n (%)	9 (5)†
Serious AEs, n (%)	8 (4)‡

*Pancreatitis, thrombosis, aggressive behaviour and disturbance in attention. †12 events [neutropenia (n = 3), anaemia (n = 2), depression (n = 2), neck abscess, bronchitis, decreased haemoglobin, headache and dyspnoea (n = 1 each)] in nine patients. ‡Hypothyroidism, pancreatitis, neck abscess, acute psychosis, aggression, personality disorder, suicide attempt and thrombosis. Acute psychosis occurred ≥30 days after completion of treatment and was classified nontreatment-emergent.

patient each (bronchitis, decreased haemoglobin, headache and dyspnoea). Treatment was also interrupted in the patient with an SAE of neck abscess. There were no deaths during the study period.

DISCUSSION

This study confirms that 24 weeks of therapy with PEG-IFN alfa-2b plus weight-based ribavirin is sufficient to achieve high rates of SVR in treatment-naive patients with chronic hepatitis C G1 infection who have low viral load at baseline and attain a RVR.

Several previous studies have also examined a 24-week treatment strategy in G1 patients who attain RVR, and data from the present study are generally consistent with previous observations [4,7,10]. Zeuzem *et al.* reported an SVR rate of 89% and relapse rate of 8% in G1 patients with baseline viral load <600 000 IU/mL, which compared favourably with data derived from a historical control population treated for 48 weeks in which 85% of patients attained SVR and relapse rate was also 8% [10]. Similarly, Ferenci *et al.* and Mangia *et al.* have also reported favourable rates of SVR in G1 patients with RVR treated for 24 weeks, with both studies also indicating improved outcomes in the cohort of patients with low baseline viral load [4,7]. Recent data from the INDIV-2 study, where treatment was individualized according to the time to first undetectable HCV RNA, also confirm a favourable comparison of 24 weeks with 48 weeks of therapy in patients with G1 infection with baseline viral load <800 000 IU/mL who attained RVR. In patients who received 24 weeks of treatment, 88% attained SVR compared with 93% of patients who received 48 weeks of therapy [14].

The subgroup analyses reported in the present study are consistent with data derived from the large ''real-life'' cohort enrolled in the PROBE study, which also reported that SVR rates were lower among patients with G1b infection compared with G1a [15]. In the PROBE study, SVR rates were 44% in patients with G1a infection and 37% in those with G1b infection when treated with PEG-IFN alfa-2a or alfa-2b plus ribavirin. In logistic regression analysis, SVR was significantly more likely in G1a patients [odds ratio (OR): 1.36; 95% CI: 1.00–1.86; P = 0.05]. However, Jensen *et al.* reported that patients with G1b infection were more likely to attain RVR than those with G1a infection (OR: 1.8; 95% CI: 0.9–3.7; P = 0.095). In logistic regression analysis, a baseline viral load ≤200 000 IU/mL was an independent predictor of RVR among G1a patients (OR: 5.9; P = 0.0015), whereas a baseline viral load ≤600 000 IU/mL was significantly associated with RVR in G1b patients (OR: 10.3; P < 0.0001). Interestingly, within the group of patients with baseline viral load between 500 000 and 1 million copies/mL, RVR was attained by 12% of those with G1a and 40% of those with G1b [16].

Weight-based ribavirin is an established component of treatment for G1 chronic hepatitis C, with several studies showing a strong association between ribavirin dose per kilogram of body weight and SVR [13,17]. Shiffman *et al.* reported that increasing the ribavirin dose significantly increased the SVR rates from 19 to 29% in patients receiving ribavirin 13.3 mg/kg/day to 49% in those receiving 15.2 mg/kg/day, with the increase in SVR occurring secondary to a reduction in relapse (8% *vs* 36–40%; P < 0.05) [18]. In the present study, SVR rates were lower and relapse rates higher in the subgroups of patients weighing ≤65 kg and also those weighing >75–85 kg. Importantly, patients weighing >75–85 kg received a daily ribavirin dose of 1000 mg, which equates to dose per kilogram bodyweight of between 11.8 and 13.3 mg/kg/day, clearly falling in the dose range considered suboptimal according to Shiffman's data. This is in contrast to the patients with a lower bodyweight of >65–75 kg but who received the same ribavirin dose of 1000 mg/day and, consequently, in whom the dose per kilogram bodyweight was much higher (equivalent to 13.3–15.4 mg/kg/day). These data suggest that ribavirin dosing in the 75–85 kg patient group in this study was suboptimal and thus support the recent change in approval status of Rebetol® (Schering–Plough Corporation, now Merck & Co., Inc., Whitehouse Station, NJ, USA) at a dose of 1200 mg/day for patients with bodyweight 81–85 kg (increasing dose per unit bodyweight to 14.1–14.8 mg/kg in this population) [19].

In conclusion, this study is consistent with the report by Zeuzem *et al.*, indicating that PEG-IFN alfa-2b (1.5 μg/kg/week) plus weight-based ribavirin (800–1200 mg/day) for 24 weeks is an effective and sufficient treatment strategy for treatment-naive patients with G1 chronic hepatitis C with baseline viral load <600 000 IU/mL who attain RVR. Using a sensitive HCV RNA assay (<60 IU/mL) for the

evaluation of viremia at week 4 is an important element when considering a reduced treatment duration for patients with G1 HCV infection; use of a less sensitive assay should be avoided because of the elevated risk of post-treatment relapse.

ACKNOWLEDGEMENTS

Financial support was provided by Schering–Plough Corporation, now Merck & Co., Inc., Whitehouse Station, N.J., USA. The authors had complete access to the data supporting this publication. Medical writing and editorial assistance was provided by Tim Ibbotson, PhD, Claudette Knight, PharmD, and Santo D'Angelo, PhD, of ApotheCom, and funded by Merck Sharp & Dohme Corporation, a subsidiary of Merck & Co., Inc., Whitehouse Station, N.J., USA.

CONFLICT OF INTERESTS

A. Craxi is an advisor for and has received grants from Merck & Co., Inc.; Schering–Plough Corp., now Merck & Co., Inc.; Roche; Novartis International AG; and Tibotec BVBA. P. Ogurtsov has received lecture fees from Merck & Co., Inc. X. Yu is a former employee and R. Faruqi, E. Chaudhri and L.D. Pedicone are current employees of Merck, Inc. S. Koutsounas, L. Chemello, M. Maticic, J. Torras, M. Diago, M.T. Tartaglione, T. Witthoeft and E. Zuckerman have no commercial relationships to disclose.

REFERENCES

1 Drusano GL, Preston SL. A 48-week duration of therapy with pegylated interferon a2b plus ribavirin may be too short to maximize long-term response among patients infected with genotype-1 hepatitis C virus. *J Infect Dis* 2004; 189: 964–970.
2 Marcellin P, Heathcote EJ, Craxi A. Which patients with genotype 1 chronic hepatitis C can benefit from prolonged treatment with the 'accordion' regimen? *J Hepatol* 2007; 47: 580–587.
3 McHutchison JG, Lawitz EJ, Shiffman ML *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; 361: 580–593.
4 Mangia A, Minerva N, Bacca D *et al.* Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. *Hepatology* 2008; 47: 43–50.
5 Hadziyannis SJ, Sette Jr H, Morgan TR *et al.* Peginterferon-a2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; 140: 346–355.
6 Moreno C, Deltenre P, Pawlotsky JM, Henrion J, Adler M, Mathurin P. Shortened treatment duration in treatment-naive genotype 1 HCV patients with rapid virological response: a meta-analysis. *J Hepatol* 2010; 52: 25–31.
7 Ferenci P, Laferl H, Scherzer TM *et al.* Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. *Gastroenterology* 2008; 135: 451–458.
8 Berg T, Weich V, Teuber G *et al.* Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients. *Hepatology* 2009; 50: 369–377.
9 Neumann AU, Pianko S, Zeuzem S *et al.* Positive and negative prediction of sustained virologic response at weeks 2 and 4 of treatment with albinterferon alfa-2b or peginterferon alfa-2a in treatment-naive patients with genotype 1, chronic hepatitis C. *J Hepatol* 2009; 51: 21–28.
10 Zeuzem S, Buti M, Ferenci P *et al.* Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. *J Hepatol* 2006; 44: 97–103.
11 SP Europe. PegIntron (Summary of Product Characteristics). Bruxelles, Belgium: SP Europe, 2008.
12 Roche Registration Limited. Pegasys (Summary of Product Characteristics). Welwyn Garden City, UK: Roche Registration Limited, 2008.
13 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358: 958–965.
14 Sarrazin C, Schwendy S, Möller B *et al.* Completely individualized treatment durations (24, 30, 36, 42, 48, 60 or 72 weeks) with peginterferon alfa-2b and ribavirin in HCV genotype 1-infected patients (INDIV-2 study). *J Hepatol* 2009; 52(Suppl. 1): S25–S26.
15 Craxi A, Piccinino F, Alberti A, *et al.* Predictors of SVR in naive HCV G1 patients in real-life practice: results of the PROBE study 2008. Poster presented at: 43rd Annual Meeting of the European Association for the Study of the Liver; April 23–27, 2008; Milan, Italy.
16 Jensen DM, Morgan TR, Marcellin P *et al.* Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology* 2006; 43: 954–960.
17 Jacobson IM, Brown Jr RS, Freilich B *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.
18 Shiffman ML, Salvatore J, Hubbard S *et al.* Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. *Hepatology* 2007; 46: 371–379.
19 Schering–Plough. Rebetol® (Ribavirin UPS) Capsules, Oral Solution (Package Insert). Kenilworth, NJ: Schering–Plough, 2009.