Pharmacokinetics and response of obese patients with chronic hepatitis C treated with different doses of PEG-IFN α -2a (40KD) (PEGASYS®)

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Obesity is a negative predictor of successful treatment in patients with chronic hepatitis C treated with peginterferon (PEG-IFN) and ribavirin.
- Obese patients may have suboptimal exposure of PEG-IFN contributing to the poor responses seen in this patient population.
- In non-obese patients doses of PEG-IFN α -2a (40KD) up to 360 μ g week⁻¹ have shown dose proportional pharmacokinetics.

WHAT THIS STUDY ADDS

- Here we show that among obese patients treated with the standard dose of PEG-IFN α -2a (40KD) (180 μ g week⁻¹) drug exposure was lower than that found in a large set of unpublished data among non-obese patients, but was generally similar to exposures found in a large set of unpublished data among similarly obese patients receiving the same dose of PEG-IFN α -2a (40KD).
- By increasing the dose of PEG-IFN α -2a (40KD) from 180 μ g week⁻¹ to 270 μ g week⁻¹ one can increase PEG-IFN α -2a (40KD) exposure, thereby potentially compensating for the apparent reduction in drug exposure in obese patients.

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AIMS

To evaluate whether higher doses of peginterferon α -2a (40KD) [PEG-IFN α -2a (40KD)] can compensate for lower exposure observed among obese patients with chronic hepatitis C (CHC) treated with the standard dose of PEG-IFN α -2a (40KD).

METHODS

Noncirrhotic, obese (body mass index ≥ 30 kg m⁻²) patients with CHC participated in a single-centre, open-label study. Patients were randomized to 180 or 270 μ g week⁻¹ PEG-IFN α -2a (40KD) + ribavirin (1000/1200 mg day⁻¹) for 48 weeks. Blood samples were collected predose and up to 168 h after the first dose and at week 12 for pharmacokinetic analysis. Trough serum concentrations (C_{trough}) were determined up to week 24.

RESULTS

In the 180 μ g week⁻¹ group mean $\pm$ SD steady-state (week 12) estimates of AUC_{0-168} (ng h⁻¹ ml⁻¹), C_{max} (ng ml⁻¹) and CL/F (l h⁻¹) were 2154 ± 919 , 13.8 ± 6.7 and 0.102 ± 0.051 , respectively. In the 270 μ g week⁻¹ group, estimates were 3374 ± 1844 , 23.4 ± 10.7 and 0.090 ± 0.042 , respectively. The mean (range) C_{trough} (ng ml⁻¹) was 11.2 (4.4–18.5) in the 180 μ g week⁻¹ group and 16.1 (0.4–44.2) in the 270 μ g week⁻¹ group. Overall, 14 of 20 (70%) and 16 of 20 (80%) patients in the 180 μ g week⁻¹ and 270 μ g week⁻¹ groups were infected with hepatitis C virus genotype 1 or 4. In the 180 μ g week⁻¹ and 270 μ g week⁻¹ groups 14 of 20 (70%) and 15 of 19 (79%) patients, respectively, achieved a sustained viral response. Safety was similar between groups.

CONCLUSIONS

Mean PEG-IFN α -2a (40KD) exposure was dose proportional from 180 to 270 μ g week⁻¹. Increasing PEG-IFN α -2a (40KD) from 180 to 270 μ g week⁻¹ achieves higher serum drug exposure in obese patients.

Introduction

The current standard of care for the treatment of chronic hepatitis C (CHC) is pegylated (PEG) interferon (IFN) α -2a (40KD) or α -2b (12KD) and ribavirin [1–3]. In the setting of a controlled clinical trial, the overall sustained virological response (SVR) using this regime is 54–63% [1–3]. Several factors, both viral and host mediated, have been shown to be partially responsible for this failure rate of approximately 40%. They include viral genotype 1 [1–3], high viral load [4, 5], African-American racial origin [6, 7], cirrhosis [8] and steatosis [9]. Results from large clinical trials using PEG-IFN α -2a (40KD) and PEG-IFN α -2b (12KD) have demonstrated obesity is also a risk factor for poor response to therapy [1, 4]. A retrospective cohort study has reported obesity, defined as a body mass index (BMI) $\geq 30 \text{ kg m}^{-2}$, to be an independent (of genotype and cirrhosis) negative predictor of response to CHC treatment [10].

One possible explanation for obesity being an independent negative predictor for response could be that the pharmacokinetics (PK) of PEG-IFN α -2a (40KD) is altered in the obese patient, leading to low serum levels [11]. Standard IFN is absorbed through blood capillaries and the lymphatic circulation; but because of the size of PEG-IFN α -2a (40KD), the drug is predominately taken up by lymphatics. Obese people are known to have poor lymphatic circulation, and this could potentially lead to low serum levels of PEG-IFN α -2a (40KD) if uptake of the drug from the injection site is incomplete [12].

The pharmacokinetics of PEG-IFN α -2a (40KD) up to doses of $360 \mu\text{g week}^{-1}$ have previously been reported in non-obese patients and have been shown to be dose proportional [13]. Furthermore, other large studies exploring higher fixed-dose induction therapy with PEG-IFN α -2a (40KD) in a variety of populations are currently ongoing or recently completed [14–17].

Limited data are available on the pharmacokinetics of higher doses of PEG-IFN α -2a (40KD) in obese patients with CHC. The primary objective of this study was to determine if a higher dose ($270 \mu\text{g week}^{-1}$) of PEG-IFN α -2a (40KD) is associated with higher systemic exposure compared with the standard ($180 \mu\text{g week}^{-1}$) dose in obese patients with CHC. Secondary objectives included a comparison of PEG-IFN α -2a (40KD) exposure in the present study with historic data with the standard dose among non-obese and obese patients and the safety of higher doses of PEG-IFN α -2a (40KD) in obese patients.

Methods

Study design

This study was a Phase IIIb, open-label, randomized, stratified by hepatitis C virus (HCV) genotype, controlled, single-centre trial. Patients were recruited to be treated with one of two possible regimens: standard subcutaneous PEG-IFN

α -2a (40KD) $180 \mu\text{g}$ once weekly and ribavirin or subcutaneous PEG-IFN α -2a (40KD) $270 \mu\text{g}$ once weekly and ribavirin. Ribavirin was administered orally 1000 mg day^{-1} (if patient's body weight was $<75 \text{ kg}$) or 1200 mg day^{-1} (if patient's body weight was $\geq 75 \text{ kg}$). Randomization was centralized and stratified according to genotype: genotype 1 vs. genotype non-1.

This study had a screening phase that consisted of 56 days prior to the first dose of study drug. Eligibility for this study was established during this phase. The active treatment phase was 48 weeks. This was followed by a treatment-free follow-up period of 24 weeks. All patients provided informed consent and the research ethics board at the University Health Network, Toronto, Canada, approved the study protocol.

Patient selection

Patients with CHC and a BMI $\geq 30 \text{ kg m}^{-2}$ were eligible for this study if they met the following conditions: age ≥ 18 years, serological evidence of CHC infection by anti-HCV antibody test, detectable serum HCV RNA (COBAS AMPLICOR™ HCV MONITOR Test; Roche, Basel, Switzerland; lowest level of detection 50 IU ml^{-1}), elevated serum alanine aminotransferase value on at least two occasions, a minimum of 14 days apart within the 6 months prior to study entry, with at least one elevated value during the screening period preceding the initiation of study medication. All patients underwent a liver biopsy confirming a diagnosis of CHC without cirrhosis within the 6 months prior to the start of therapy. All women of childbearing potential needed a negative urine or blood pregnancy test documented within the 24-h period prior to the first dose of study drug. All fertile men and women had to be using two forms of effective contraception during treatment and the 6 months after stopping treatment. Protocol exclusion criteria were consistent with other PEG-IFN α -2a (40KD) and PEG-IFN α -2b (12KD) trials as described elsewhere [1–3].

Pharmacokinetic assessment and viral response end-point

Blood samples were drawn for PK analysis at predose; 24, 96 and 168 h postdose following the first dose; and at week 12. Trough concentrations (C_{trough}) of PEG-IFN α -2a (40KD) were also determined at weeks 2, 4, 8 and 24.

Serum concentrations of PEG-IFN α -2a (40KD) were measured by a quantitative sandwich enzyme-linked immunosorbent assay method at MDS Pharma Services (Basel, Switzerland). The quantifiable range of the assay was $0.25\text{--}4.0 \text{ ng ml}^{-1}$. Interassay precision (expressed as the percent coefficient of variation) of the quality control samples at 0.6, 1.6 and 2.5 ng ml^{-1} ranged from 10 to 34%, and the accuracy ranged from 98 to 104%. Serum concentrations of PEG-IFN α -2a (40KD) reported to three significant figures were used for analysis. Study samples with concentrations above the quantifiable range were diluted

and reanalysed, whereas samples with concentrations below the quantifiable limit were reported as below the limit of quantification.

PK characteristics were evaluated on post-first-dose and week-12 samples using noncompartmental methods with WinNonlin Pro (version 4.1; Mountain View, CA, USA), model 200 with extravascular input. The actual sampling times and dose received by the patient were recorded.

PK parameters were calculated as follows: maximum serum concentration ($C_{\max}$); area under the curve of serum concentration vs. time from time zero to 168 h ($AUC_{0-168\text{ h}}$), determined by the linear trapezoidal method; serum trough concentrations (C_{trough}); apparent total body clearance (CL/F) = dose/ $AUC_{0-168\text{ h}}$ at week 12.

HCV RNA quantitative analysis (COBAS AMPLICOR™ HCV MONITOR) was performed at screening visit and at week 12 (limit of quantification 600 IU ml⁻¹). HCV RNA qualitative analysis was performed at weeks 24 and 48, and at the end of the untreated 24-week follow-up period. An SVR was defined as undetectable HCV RNA qualitative test (<50 IU ml⁻¹) at the end of the follow-up period.

Safety assessment

All patients who received at least one dose of either dose level of PEG-IFN α -2a (40KD) and had at least one safety assessment after receiving the drug were included. Patients who prematurely stopped taking their medication were followed for safety for at least 12 weeks following their last dose. The treating nurse recorded adverse events on a standard form and rated the severity as mild, moderate, severe, or life threatening. Patients were evaluated and laboratory tests were scheduled at weeks 2, 4, 8, 12 and 16, and then at 6-week intervals until week 24 of the untreated follow-up period. Dose modification of PEG-IFN α -2a (40KD) from 270 $\mu\text{g week}^{-1}$, to 180 $\mu\text{g week}^{-1}$, to 135 $\mu\text{g week}^{-1}$, to 90 $\mu\text{g week}^{-1}$ and to 45 $\mu\text{g week}^{-1}$ was permitted in patients who experienced either clinical or laboratory adverse events. Adverse events thought to be related to ribavirin were treated with a dose reduction initially by 200 mg day⁻¹, and then, if no improvement was seen, to 600 mg day⁻¹ provided the patient was without significant cardiovascular disease and had a fall in haemoglobin <10 g dl⁻¹ and >8.5 g dl⁻¹ or a patient had stable cardiovascular disease and a fall in haemoglobin >2 g dl⁻¹ any time during treatment. Ribavirin was discontinued if a patient without significant cardiovascular disease had a fall in haemoglobin <8.5 g dl⁻¹ or a patient with stable cardiovascular disease had a haemoglobin <12 g dl⁻¹ after 4 weeks on 600 mg of ribavirin.

Statistical analysis

All PK parameters were summarized using descriptive statistics. Virological response and safety data were summarized using descriptive statistics. These analyses were performed using Microsoft Excel (version 2000; Microsoft Inc., Redmond, WA, USA) and S-Plus version 7.0 student

edition (Insightful Corp., Seattle, WA, USA) software. The planned sample size of 20 patients per group was designed to detect an increase in exposure, with $\geq 80\%$ power, assuming the AUC in the PEG-IFN α -2a (40KD) 270 $\mu\text{g week}^{-1}$ was 1.4 times that of the PEG-IFN α -2a (40KD) 180 $\mu\text{g week}^{-1}$ group, an intersubject coefficient of variation of 45%, and statistical significance to be 0.05.

Results

Patient characteristics

Patients were recruited from August 2002 to March 2004. A total of 42 patients were recruited for this study. Two never started treatment and so were not included in any of the analyses. One patient in the 270 $\mu\text{g week}^{-1}$ PEG-IFN α -2a (40KD) group received only 6 weeks of treatment, so was not included in the PK or efficacy analyses. Baseline characteristics were generally similar between the two groups (Table 1).

Pharmacokinetic assessment

PK parameters of PEG-IFN α -2a (40KD) after the first dose (day 1) and at steady state (week 12) are summarized in Table 2. An approximate 1.5-fold increase in mean $AUC_{0-168\text{ h}}$ and $C_{\max}$ at steady state was observed in the 270- μg compared with the 180- μg arm. The apparent clearance was approximately 0.1 l h⁻¹ for both doses. These indicate a linear dose-exposure relationship in the study dose range. The accumulation rate from day 1 to week 12 was approximately 2.3-fold for both 180 and 270 $\mu\text{g week}^{-1}$ doses. A similar accumulation rate was also observed for $C_{\max}$. Individual patient $AUC_{0-168\text{ h}}$ after day 1 and at steady state are shown in Figure 1. Serum trough concentrations of PEG-IFN α -2a (40KD) appeared to reach

Table 1

Patient characteristics in the two treatment groups at baseline

Characteristic	180 $\mu\text{g week}^{-1}$ PEG-IFN α -2a (40KD) (n = 20)	270 $\mu\text{g week}^{-1}$ PEG-IFN α -2a (40KD) (n = 20)
Male/female (% male)	12/8 (60)	14/6 (70)
Age (mean $\pm$ SD), years	47.3 $\pm$ 9.2	44.3 $\pm$ 6.8
BMI (median, range), kg m ⁻²	34.0 (30.0–43.9)	31.4 (30.0–45.0)
Weight (median, range), kg	99.0 (77.0–118.0)	98.0 (70.7–140.0)
Abdominal circumference (mean $\pm$ SD), cm	114.4 $\pm$ 10.4	115.9 $\pm$ 15.2
Steatosis (median %, range)	7.5 (1.75, 10)	5.0 (0.5, 40)
HCV RNA $\times 10^6$ (median, range), IU ml ⁻¹	1.42 (0.16–6.24)	2.25 (0.06–10.24)
Genotype 1 or 4 (%)	14 (70)	16 (80)
ALT (median, range)	76 (36–287)	56 (13–285)

ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus.

Table 2

Summary of single-dose and steady-state pharmacokinetic parameters for PEG-IFN α -2a (40KD) 180 μ g or 270 μ g

	PEG-IFN α -2a (40KD) dose (μ g week ⁻¹)			
	180	% CV	270	% CV
AUC_{0-168 h} (ng ml⁻¹ h⁻¹)				
Day 1	980 $\pm$ 352	36	1403 $\pm$ 72	55
Week 12	2154 $\pm$ 919	47	3374 $\pm$ 1844	57
Accumulation ratio	2.20		2.40	
C_{max}, ng ml⁻¹				
Day 1	6.8 $\pm$ 3.2	47	9.9 $\pm$ 6.3	64
Week 12	13.8 $\pm$ 6.7	49	23.4 $\pm$ 10.7	46
CL/F, l h⁻¹ (week 12)	0.102 $\pm$ 0.051	50	0.090 $\pm$ 0.042	47

% CV, % coefficient of variation.

Figure 1

Individual patient AUC₀₋₁₆₈ after the first dose (week 1) and at steady state (week 12). Open circles represent the individual AUC₀₋₁₆₈ values. The mean values of each arm at week 1 and week 12 are plotted as solid horizontal lines and the median values as dashed lines

steady state by week 8 for both dose groups (Figure 2), and plasma concentration–time profiles following the first dose and at steady state are displayed in Figure 3.

The study results were compared with Roche data on file in non-obese patients (BMI < 30 kg m⁻²; range 18–29; n = 105 observations) and obese patients (BMI $\geq$ 30 kg m⁻²; range 30–51; n = 173 observations) with CHC. The mean steady-state serum C_{trough} of PEG-IFN α -2a (40KD) following 180 μ g dosing in the historical data sets for non-obese patients was 20.5 ng ml⁻¹ (range 0.1–59.2) and for obese patients 16.1 ng ml⁻¹ (range 0.2–52.4). In the present study in patients with BMI $\geq$ 30 kg m⁻² mean steady-state serum C_{trough} estimates for the 180 μ g week⁻¹ dose was 11.2 ng ml⁻¹ (range 4.4–18.5) and for the 270 μ g week⁻¹ dose was 16.1 ng ml⁻¹ (range 0.4–44.2).

Figure 2

Mean serum trough concentrations of PEG-IFN α -2a (40KD) from the two treatment groups (error bars = SD). 180 μ g/week (—◆—); 270 μ g/week (—■—)

Efficacy

An SVR was recorded in 14 of 20 (70%) and 15 of 19 (79%) patients completing treatment with PEG-IFN α -2a (40KD) 180 and 270 μ g week⁻¹ plus ribavirin, respectively (Table 3). All nine patients with genotypes 2 and 3 achieved an SVR. Of the six patients who failed to achieve an SVR following PEG-IFN α -2a (40KD) 180 μ g week⁻¹ plus ribavirin, three were nonresponders and three relapsers. Four patients did not achieve an SVR following PEG-IFN α -2a (40KD) 270 μ g week⁻¹ plus ribavirin: one was a nonresponder and three relapsers.

Safety assessment

All patients enrolled in the trial experienced at least one treatment-related adverse event, although most were mild in severity and no patients required premature withdrawal of medication due to an adverse event or laboratory abnormality. Adverse events were typical of those experienced during treatment with pegylated interferons and ribavirin and there was no clear dose response in adverse events. The most notable differences in the rates of adverse events between the two groups (defined as a rate of more than three patients in one group vs. the other) for PEG-IFN α -2a (40KD) 180 μ g week⁻¹ and PEG-IFN α -2a (40KD) 270 μ g week⁻¹ groups were dry skin (12 vs. four patients, respectively), vomiting (one vs. six patients, respectively) and infection (eight vs. one patients, respectively). Importantly, the rate of depression was similar in the two groups [four vs. five patients in the PEG-IFN α -2a (40KD) 180 μ g week⁻¹ and PEG-IFN α -2a (40KD) 270 μ g week⁻¹ groups, respectively], and the rate of neutropenia was low in both groups [three vs. no patients in the PEG-IFN α -2a (40KD) 180 μ g week⁻¹ and PEG-IFN α -2a (40KD) 270 μ g week⁻¹ groups, respectively].

Three patients in the PEG-IFN α -2a (40KD) 180 μ g week⁻¹ plus ribavirin and no patients in the PEG-IFN α -2a

Figure 3

Mean serum plasma concentration–time profiles of PEG-IFN α-2a (40KD) from the two treatment groups (error bars = SD) at week 1 (a) and at week 12 (b)

Table 3

Viral response from the two treatment groups

Treatment effects	180 µg week ⁻¹ PEG-IFN α-2a (40KD) (n = 20)	270 µg week ⁻¹ PEG-IFN α-2a (40KD) (n = 19)
Undetectable HCV RNA at week 12, n (%)	16 (80%)	16 (84%)
Undetectable HCV RNA at end of treatment, n (%)	16 (80%)	17 (89%)
Sustained viral response, n (%)	14 (70%)	15 (79%)
Genotype 1 sustained viral response, n/N (%)	8/14 (57%)	10/14 (71%)

HCV, hepatitis C virus.

(40KD) 270 µg week⁻¹ plus ribavirin group required reduction or omission of one or more dose of PEG-IFN α-2a (40KD) for a clinical or a laboratory abnormality.

Four serious adverse events were recorded, two in each treatment group. One patient in the PEG-IFN α-2a (40KD) 180 µg week⁻¹ plus ribavirin group had a myocardial inf-

arction, and another patient had pneumonia. The patient who had a myocardial infarction had a reduction in haemoglobin from a baseline of 14.2 g dl⁻¹ to 10.8 g dl⁻¹, which required dose reduction of ribavirin. The myocardial infarction occurred when haemoglobin was 10.8 g dl⁻¹. This occurred at week 20. Treatment was discontinued after this event. This patient was classified as a relapser because their HCV RNA was undetectable at week 12, but became detectable again on subsequent assessments. The patient with pneumonia had a low absolute neutrophil count (0.7×10^9 cells l⁻¹) at week 16 (dose was not reduced). By week 20 their absolute neutrophil count was within normal range. The patient was hospitalized for pneumonia at week 38, and by this time their neutrophil count had been $>1.0 \times 10^9$ cells l⁻¹ for the preceding 5 months prior to admission. Treatment continued in this patient. In the PEG-IFN α-2a (40KD) 270 µg week⁻¹ plus ribavirin treatment group, one patient was diagnosed with appendicitis and another patient had reported severe irritability. Treatment continued in the patient who had appendicitis. The patient with severe irritability was only 6 weeks into treatment, and was then lost to follow up; data from this patient were therefore not included in either the efficacy or PK analyses. No patient received erythropoietin during the trial. Overall, only one of the patients received <80% PEG-IFN α-2a (40KD), 80% ribavirin, 80% of the time.

Discussion

The reasons underlying the influence of obesity on a poor response rate to antiviral therapy in patients with CHC is unknown. It has been suggested that the poor response rate in obese patients may be a consequence of inadequate drug doses resulting in lower serum PEG-IFN-α levels [11]. This current open-labelled, randomized, single-centre study has suggested that PEG-IFN α-2a (40KD) 270 µg week⁻¹ increases PEG-IFN α-2a (40KD) levels in obese patients with CHC compared with the standard dose of 180 µg week⁻¹. The serum exposure and serum trough concentrations of this drug increased proportionally to the increased dose for the two different doses of PEG-IFN α-2a (40KD) used in this study. The PK parameters were characterized by a high degree of variability, as shown by the coefficient of variation in Table 2. This large variation in all the PK results has been previously appreciated [18, 19]. Studies by Silva and co-investigators [19] and DiBisceglie [18] have shown significant variability in exposure to PEG-IFN α-2a (40KD). The reason behind these variations is currently unknown. The possible clinical consequences of these findings require further research in an attempt to optimize treatment for all patients with CHC.

Recent data indicate there are other reasons why obese patients with CHC have a decreased response to antiviral therapy. Hepatic steatosis is estimated to be present in

70% of obese patients [20]. In patients with nongenotype 3 CHC, there is an association between BMI and hepatic steatosis [21]. Two mechanisms behind the presence of steatosis in patients with CHC have been suggested: host factors (visceral obesity) and viral factors (genotype 3a and levels of viraemia) [22]. It is possible that the aetiology of steatosis may influence its effect on antiviral response in patients with CHC. In patients infected with nongenotype 3 viruses, steatosis is a negative predictor of pegylated interferon or interferon α -2b and ribavirin [9]. However, steatosis appears not to influence antiviral responsiveness in patients infected with genotype 3 [22]. Adinolfi and colleagues have suggested that the steatosis has a negative influence in response to treatment only if steatosis is visceral in origin [22]. This hypothesis of steatosis negatively influencing antiviral response in nongenotype-3-infected patients has been supported in two other cohorts of patients being treated with interferon therapy [23, 24].

A more recent study supports our earlier conclusion that obesity and not steatosis is the negative predictor of a SVR in CHC [25]. Walsh and colleagues have taken this hypothesis one step further by demonstrating a possible reason for this relationship – the reduction of the biological response to IFN α /PEG-IFN α in obese patients. Both obesity and hepatic steatosis are known to be associated with elevated levels of serum tumour necrosis factor (TNF)- α [26, 27]. Patients with elevated circulating serum TNF- α have a poor response to IFN α therapy [28], possibly due to induction of suppressor of cytokine signalling (SOCS) proteins that interfere with the IFN α receptor and signalling proteins [29, 30]. In the study by Walsh *et al.* [25], various host factors in 145 patients were studied to determine those associated with nonresponse to antiviral therapy. Their multivariate analysis demonstrated that obesity and not steatosis was associated with nonresponse. Furthermore, among patients infected with genotype 1, obesity and not steatosis was associated with increased SOCS-3 mRNA levels in liver tissue. Hepatic expression of SOCS-3 was higher in obese patients, and in patients who were nonresponders to antiviral therapy. They also demonstrated a correlation between hepatic TNF- α and SOCS-3 mRNA levels, and a correlation between TNF- α and obesity. The authors of this study concluded that obesity's role in reducing a patient's response rate to antiviral therapy may be partially explained by inhibition of interferon signalling, thus reducing the biological response to IFN α .

The trial discussed in this paper showed an SVR of 70 and 79% in the standard and higher PEG-IFN α -2a (40KD) doses, respectively. These are higher rates of SVR than anticipated in light of the proportion of patients infected with genotype 1, and the fact that all the patients were obese. However, perhaps reflecting a more motivated cohort of patients in the present small single-centre study, all but one patient in either group received at least 80% of both drugs for >80% of the time, thus emphasiz-

ing how compliance is a major factor influencing SVR. This study was not powered to answer the question of whether higher doses of PEG-IFN α -2a (40KD) increase the SVR in this patient population, but was intended to help understand the impact obesity has on the PK of this medication in patients with CHC. It is uncertain what role a modest decrease in exposure, seen in this study, plays relative to other negative risk factors associated with this patient population. Increasing PEG-IFN α -2a (40KD) from 180 to 270 μ g in the present study achieved higher serum drug exposure in obese patients and led to exposure similar to the historical data in obese patients and only slightly lower than the historical data in non-obese patients. It is possible that an increased dose of PEG-IFN α -2a (40KD) may be required in obese patients because of the reduced biological action IFN α has in obese patients. Therefore, the clinical impact of this higher serum drug exposure in obese patients needs to be further studied.

Competing interests

E.J.H. has received research grants from F. Hoffman-La Roche. K.W. and J.F.G. are employees of F. Hoffmann-Roche. B.B. has no competing interests to declare.

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