Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Marcellin P. et al. (2012) Safety profile of standard- vs. high-dose peginterferon alfa-2a plus standard-dose ribavirin in HCV genotype 1/4 patients: pooled analysis from 5 randomized studies. *Expert Opinion on Drug Safety*, 11(6):901-909.
Date of Review:	March 1, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **HCV genotype 1 or 4 patients** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **France** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; compare the safety of the standard dose (180 μg/week) of Peg-IFN α-2a with that of high-dose (360 μg/week), administered in combination with ribavirin, in 5 randomized trials consisted of patients with chronic hepatitis C genotype 1 or 4
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☐	☒	☐	Study aimed to provide information on the comparative tolerability of the two dosage regiments of Peg-IFN α-2a

Effectiveness	☐	☒	☐	
The best practice/intervention has been evaluated in more than one patient setting to assess:				
Efficacy	☐	☒	☐	
Effectiveness	☐	☒	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☐	☐	☒	Data for analysis are from five large, randomized, multicenter trials
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☒	☐	
There is evidence of outreach models and case studies to improve access and availability	☐	☒	☐	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	Methodology clearly stated
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Expert Opinion on Drug Safety*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☐	☒	☐	Available with journal subscription from http://informahealthcare.com/
Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	

How is the best practice/intervention funded? ***Please got to Comments section***	☐	☐	☒	Support for third-party writing assistance for this manuscript was provided by F. Hoffmann-La Roche Ltd.
Other relevant information: _____	☐	☐	☐	- Overall frequency of adverse events are similar in patients who received a 12 week standard dose and in patients who received high-dose regimen

EXPERT OPINION

Safety profile of standard- vs. high-dose peginterferon alfa-2a plus standard-dose ribavirin in HCV genotype 1/4 patients: pooled analysis from 5 randomized studies

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Objective: This analysis examines the safety profile of standard- versus high-dose peginterferon alfa-2a.
Methods: Data were pooled from five trials including HCV genotype 1- or 4-infected naive and treatment-experienced patients (n = 2,940). Patients were randomized to receive peginterferon alfa-2a at 180 μg/week (standard-dose; n = 1,672) or 360 μg/week (high-dose; n = 1,268) plus ribavirin 1,000/1,200 mg/day for 12 weeks; after 12 weeks, all received standard dose. This safety analysis was restricted to the first 12 weeks.
Results: In standard and high-dose groups, similar frequencies of serious adverse events (SAEs, 3.2 and 4.2%, respectively) and treatment discontinuations for safety reasons (2.8 and 2.9%) were reported. More patients reported weight decrease as an adverse event (AE) in the 360 μg/week group (7.7 vs. 3.3%). Significant ($p < 0.05$) independent predictors for discontinuation due to safety were older age, male gender, lower albumin and low neutrophil count, but not the starting dose of peginterferon alfa-2a. Although more laboratory abnormalities were reported in patients receiving high-dose peginterferon alfa-2a, this was not reflected in AEs or discontinuations, suggesting these are adequately managed by dose modification.
Conclusions: High-dose peginterferon alfa-2a for 12 weeks does not significantly increase the incidence of SAEs or discontinuations for safety reasons, beyond that of a standard dose regimen.

Keywords: hepatitis C, high dose induction, peginterferon alfa-2a, safety

*Expert Opin. Drug Saf. (2012) **11**(6):901-909*

1. Introduction

Peginterferon (Peg-IFN) plus ribavirin has a well-established role in the therapy of chronic hepatitis C. Approximately 50% of treatment-naive patients achieve a sustained virological response (SVR) after treatment with the dual combination of Peg-IFN and ribavirin [1]. In an effort to improve SVR rates, a number of studies have explored higher doses and/or longer treatment durations of Peg-IFN [2-7]. Collectively, these studies show that induction therapy increases the rate of early virological response (EVR), but that this effect is transient and does not translate into higher overall rates of SVR. However, higher doses of Peg-IFN may provide additional benefit in some patient subgroups [8,9].

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The risk : benefit profile of Peg-IFN alfa-2a (PEGASYS®, Roche, Basel, Switzerland) at a dose of 180 µg/week has been comprehensively described. In order to fully understand the risk : benefit ratio of high-dose Peg-IFN it is necessary to analyze the safety of the high-dose regimen. The objective of this retrospective analysis is to compare the safety of the standard dose (180 µg/week) of Peg-IFN alfa-2a with that of the high-dose induction regimen (360 µg/week), administered in combination with ribavirin, and to explore the time course of safety events in patients with chronic hepatitis C, including those patients with difficult-to-cure characteristics.

2. Patients and methods

This was a retrospective analysis of pooled data from five large, randomized, multicenter trials, three of which investigated a 12-week high-dose induction regimen of Peg-IFN alfa-2a [4,5,7,10,11].

2.1 Patients

This analysis includes patients randomized to subcutaneous Peg-IFN alfa-2a 180 µg/week (standard-dose group) or 360 µg/week (high-dose group) plus oral ribavirin (Roche, Basel, Switzerland) at a dosage of 1,000 mg/day (body weight ≤ 75 kg) or 1,200 mg/day (body weight > 75 kg), and to have at least one post-baseline safety assessment.

The analysis was limited to the first 12 weeks of treatment as the 360 µg/week induction dose of Peg-IFN alfa-2a was fixed for this duration. After week 12, all patients received the standard dose of Peg-IFN alfa-2a (180 µg/week) in all studies.

The population comprised treatment-naive patients [5,7,10,11] and non-responders to a previous course of Peg-IFN alfa-2b plus ribavirin [4]. Chronic hepatitis C patients included in this analysis had hepatitis C virus (HCV) genotype 1 or 4 infection and quantifiable HCV RNA levels (> 600 IU/mL) as measured by the Cobas® Amplicor HCV Monitor Test, version 2.0 (Roche Diagnostics, Basel, Switzerland). Patients with cirrhosis were eligible if they had compensated liver disease (Child-Pugh class A). Patient exclusion criteria included infection with hepatitis B virus and/or HIV and any serious concomitant disease. Non-responders were ineligible if they had previously discontinued treatment with Peg-IFN plus ribavirin because of haematological AEs [4].

2.2 Safety outcomes

Safety data were collected in a consistent manner across all of these trials. Safety outcomes included AEs, severe/life-threatening AEs, serious AEs (SAEs), laboratory abnormalities, treatment discontinuations, dose modifications and AEs of interest. Step-wise dose adjustments of Peg-IFN alfa-2a and ribavirin for adverse events or laboratory abnormalities were done according to pre-specified criteria in each trial. Dose modifications reported as being due to laboratory abnormalities (neutropenia or thrombocytopenia) may not have been reported as AEs as well. The criteria and steps were generally similar across the trials, with the exception that the ribavirin dose was decreased to 600 mg in one step in three trials, [4,10,11], but was decreased in 200 mg decrements in the other two [5,7]. AEs of special interest included those events typically associated with interferon-based treatments and those considered potentially serious or indicative of other serious complications. In assessing the safety margin of the higher dose of Peg-IFN alfa-2a, the AEs of special interest included infections, weight loss, psychiatric disorders, neutropenia (defined as neutrophil counts < 0.5 cells $\times 10^9$/L) and thrombocytopenia (defined as platelet count < 50 cells $\times 10^9$/L). Cough, dyspnoea and pneumonia (both as separate terms and combined) were included as markers of pulmonary AEs to determine whether the incidence of respiratory events increased when patients were treated with the higher dose of Peg-IFN alfa-2a.

2.3 Statistical analyses

Multiple logistic regression analyses were performed to explore the effects of Peg-IFN alfa-2a dose and baseline factors on completion of 12 weeks of treatment and dose modifications of Peg-IFN alfa-2a. In addition to the dose of Peg-IFN alfa-2a (360 vs. 180 µg/week), baseline factors included as explanatory variables were age, gender, body mass index (BMI), HCV genotype, race, histological status, HCV RNA, alanine aminotransferase (ALT) ratio, platelet count, serum albumin level, creatinine clearance, risk factor for infection and neutrophil count. Kaplan–Meier curves and univariate Cox proportional hazard methods were used to investigate various time-to-first-event endpoints and to estimate the hazard ratios (HRs) (and 95% confidence intervals [CIs]) for occurrence of these events. Wald chi-square tests were performed to compare the time-to-event endpoints within the first 12 weeks.

3. Results

Of the 2,940 patients included in the analysis, 1,672 (56.9%) were treated with Peg-IFN alfa-2a 180 µg/week (standard-dose group) and 1,268 (43.1%) were treated with Peg-IFN alfa-2a 360 µg/week (high-dose group). Baseline characteristics are shown in **Table 1**. The demographics of the two dosage groups were similar: in the standard- (180 µg/week) and high-dose (360 µg/week) groups, respectively; the mean age was 45 and 46 years; mean BMI was 27.6 and 28.6 kg/m^2; the proportion of patients with bridging fibrosis or cirrhosis was 22 and 18%. Both groups included the same proportion of male patients (69%). At baseline, patients in both dosage groups were taking a mean of 1.7 concomitant medications and a total of 17.7 and 16.0% of patients in the high- and standard-dose groups were receiving at least 4 concomitant medications (**Table 1**).

During the first 12 weeks of treatment, patients in the standard-dose group received a mean cumulative dosage of

Table 1. Baseline characteristics.

	Standard-dose group Peg-IFN alfa-2a 180 μg/week (n = 1,672)	High-dose group Peg-IFN alfa-2a 360 μg/week (n = 1,268)
Male gender, n (%)	1,154 (69.0)	873 (68.8)
Race, n (%)		
Caucasian	1,438 (86.0)	1,091 (86.0)
Black	98 (5.9)	78 (6.2)
Oriental	94 (5.6)	73 (5.8)
Other	42 (2.5)	26 (2.1)
Mean age, years	45.2	45.9
Mean BMI, kg/m^2	27.6	28.6
Genotype, n (%)		
1	1,621 (96.9)	1,244 (98.1)
4	51 (3.1)	24 (1.9)
Mean serum HCV RNA, log_{10} IU/mL	6.19	6.36
*Histological diagnosis, n (%)**		
No bridging fibrosis/cirrhosis	1,200 (77.9)	940 (81.8)
Bridging fibrosis/cirrhosis	340 (22.1)	209 (18.2)
Mean albumin level, g/L	43.34	43.38
Mean haemoglobin, g/L	155.9	156.7
Mean platelet count, cells $\times 10^9$/L	214	221
Mean neutrophil count, cells $\times 10^9$/L	3.70	3.83
Mean number of concomitant medications used	1.7	1.7
Patients receiving antidepressants at baseline, n (%)	174 (10.4)	185 (14.6)
Number of concomitant medications, n (%)		
0	709 (42.4)	543 (42.8)
1	320 (19.1)	244 (19.2)
2	218 (13.0)	152 (12.0)
3	157 (9.4)	105 (8.3)
> 3	268 (16.0)	224 (17.7)

*Only patients with a pre-treatment biopsy result were included.

Peg-IFN alfa-2a of 2,073 μg (range 180 – 3,510 μg, mean 173 μg/week) compared with patients in the high-dose group who received a mean cumulative dosage of Peg-IFN alfa-2a of 4,022 μg (range 360 – 5,040 μg, mean 335 μg/week).

3.1 Treatment discontinuations and dose modifications

Among patients in the high- and standard-dose groups, 1,206 (95.1%) and 1,610 (96.3%) completed the initial 12 weeks of treatment. The proportion of patients who withdrew from the study due to safety reasons was 2.9% for the high-dose group compared with 2.8% for the standard-dose group (HR 1.05; p = 0.8368).

The incidence of Peg-IFN alfa-2a dose modifications for safety reasons (AEs and laboratory abnormalities) in the first 12 weeks of treatment was 18.0% in the high-dose group and thus significantly higher compared with 13.3% in the standard-dose group (HR 1.39; p = 0.0004). The proportion of patients who required modification of their ribavirin dose was 15.1% for the high-dose group and 14.2% for the standard-dose group (HR 1.07; p = 0.4656). Kaplan–Meier plots showing time to first Peg-IFN alfa-2a dose reduction and discontinuation for safety reasons are provided in **Figure 1A and 1B** respectively.

3.2 Factors associated with withdrawal from treatment and Peg-IFN alfa-2a dose modifications for safety reasons

In the multiple logistic regression analysis, significant baseline predictors for withdrawal from treatment for safety reasons within the first 12 weeks of treatment were identified as male gender (odds ratio [OR] = 2.3; 95% CI 1.3 – 4.2 [p = 0.0061]), older age (OR = 1.5 per 10-year increment; 95% CI 1.1 – 2.0 [p = 0.0104]), lower albumin (OR = 1.1 per 1 g/L decrement; 95% CI 1.0 – 1.2 [p = 0.0173] and neutrophil count < 2×10^9 cells/L (OR = 2.7; 95% CI 1.4 – 5.2 [p = 0.0029]). An initial starting dose of 360 μg/week for Peg-IFN alfa-2a was not a significant predictor for withdrawal from treatment for safety reasons within the first 12 weeks of treatment (OR = 0.9; 95% CI 0.5 – 1.4).

In the multiple logistic regression analysis for dose modification, higher starting dose of Peg-IFN alfa-2a was a significant independent predictor for Peg-IFN alfa-2a dose modification due to safety (OR = 1.5; 95% CI 1.2 – 1.9 [p = 0.0003]). Other predictors for dose modification were Caucasian versus Black race (OR = 1.7; 95% CI 1.0 – 2.7 [p = 0.0348]), a low platelet count, defined as 150– < 200 versus ≥ 250 $\times 10^9$ cells/L (OR = 1.5; 95% CI 1.1 – 2.1 [p = 0.0150]) and < 150 versus ≥ 250 $\times 10^9$ cells/L (OR = 2.5; 95% CI

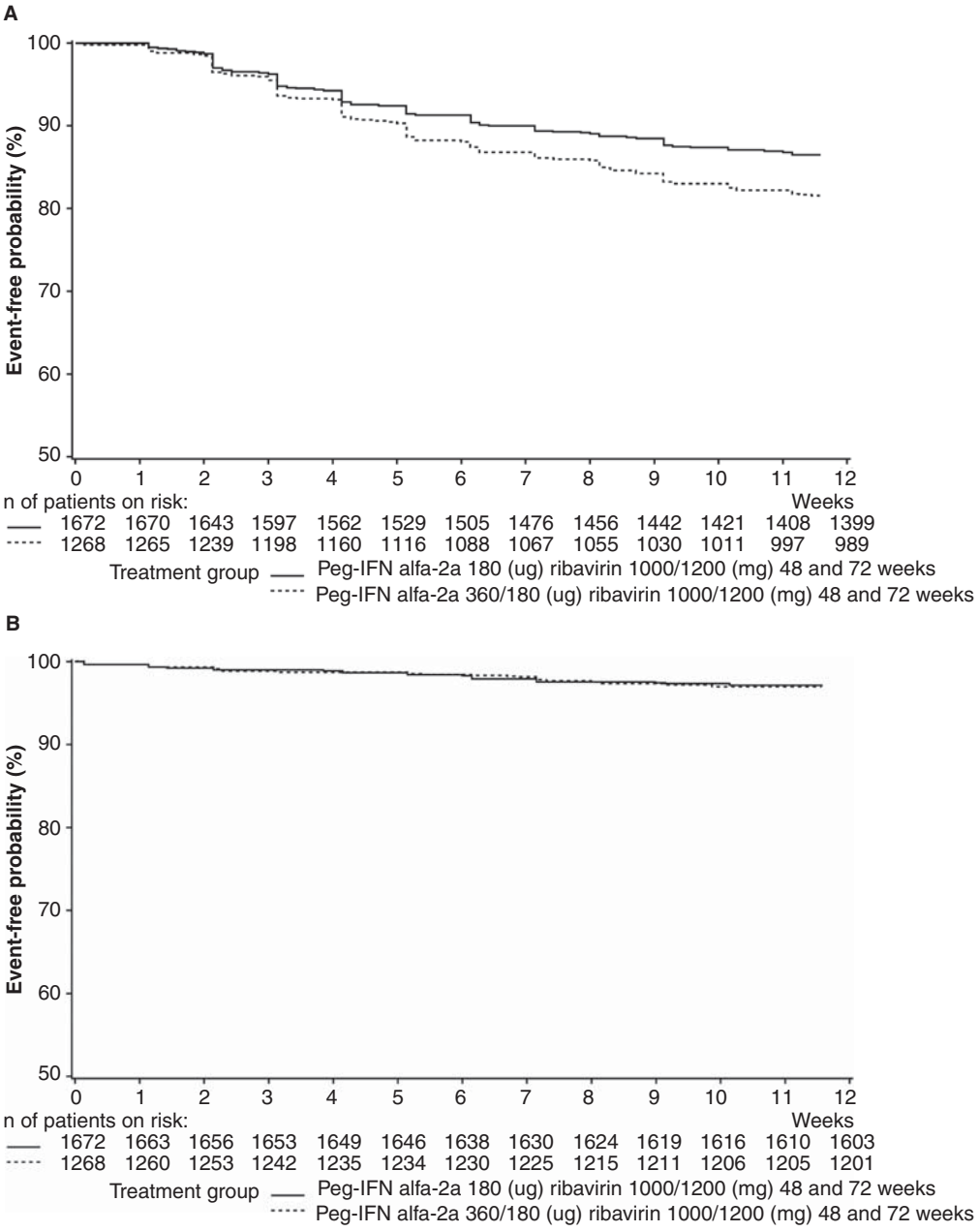

Figure 1. Kaplan–Meier plots for time to first peginterferon (Peg-IFN) alfa-2a (A) dose reduction and (B) treatment discontinuation for safety reasons.

1.7 – 3.7 [p < 0.0001]), and a neutrophil count, defined as 3 – < 3.5 versus ≥ 3.5 × 10^9 cells/L (OR = 1.4; 95% CI 1.0 – 2.1 [p = 0.0417]), 2 –< 3 versus ≥ 3.5 × 10^9 cells/L (OR = 3.2; 95% CI 2.4 – 4.2 [p < 0.0001]), < 2 versus ≥ 3.5 × 10^9 cells/L (OR = 6.4; 95% CI 4.4 – 9.4 [p < 0.0001]).

3.3 Adverse events

Almost all patients in both treatment groups (97.2% in the high-dose group and 96.2% in the standard-dose group) reported at least one AE within the first 12 weeks. The HR for time to first event was 1.09, indicating a statistically significant higher risk for occurrence of the first AE per time unit in the high-dose group compared with the standard-dose group (p = 0.0036). The mean number of AEs per patient was 7.0 for the high-dose group, only slightly higher compared with 6.6 for those in the standard-dose group. SAEs were reported in 53 patients in both treatment arms during the first 12 weeks (4.2% in the high-dose group vs. 3.2% in the standard-dose group). The HR for time to first SAE was 1.33, higher than the HR for any AE, but was not statistically significant

(p = 0.1357). This may be because the number of SAEs observed was low, thus limiting the power to detect a difference. The mean number of SAEs per patient was 0.050 and 0.038 for the high- and standard-dose groups, respectively.

The rate of severe or life-threatening AEs over the first 12 weeks of treatment was similar in the two dosage groups (0.298/patient in the standard-dose group and 0.284/patient in the high-dose group) (**Table 2**). Incidences of all AEs of interest (with HRs) are shown in **Table 2**. As shown in **Table 2**, the number of patients who reported a cough was similar in both dose groups (13.6 vs. 12.6% for the high- and standard-dose groups, respectively [p = 0.3173]), as was the number of patients reporting dyspnoea (12.6 vs. 12.4%, respectively [p = 0.7853]), while the proportion of patients who reported pneumonia as an AE was less than 1% in both groups (p = 0.9969). Because cough, dyspnoea and pneumonia may all be indicative of underlying drug-related pulmonary toxicity, all three terms were combined to explore whether these combined terms were related to the dose of Peg-IFN alfa-2a. This combined analysis showed no difference between the two dose groups (23.7 vs. 22.5% for the high- and standard-dose groups, respectively [p = 0.3596]).

The incidence of any infection that was reported as an AE was 20.7 and 18.9% among those treated with high-dose and standard-dose Peg-IFN alfa-2a, respectively (p = 0.1443).

The incidence of any psychiatric disorders between the high- and standard-dose groups was very similar (28 and 29%, respectively [p = 0.5396]). At baseline, 14.6 and 10.4% of patients in the high- and standard-dose groups were receiving antidepressant medications (**Table 1**). During the first 12 weeks of treatment an additional 11.0% (139/1268) and 7.2% (121/1672) patients in the two respective groups who were not on antidepressants at baseline started treatment with an antidepressant medication. When patients enrolled in the two older studies that did not include a high-dose induction group were excluded, the rate of antidepressant use was similar both at baseline (14.6% in both the high- and standard-dose groups) and after 12 weeks of treatment (25.6 and 24.6% in the high- and standard-dose groups, respectively).

Significantly more patients in the high-dose group (7.7%) reported a decrease in weight compared with those in the standard-dose group (3.3%; p < 0.0001).

Kaplan–Meier plots of time to first adverse event are shown in the Online Supplement **Figure 1A – D**.

3.4 Laboratory abnormalities

The incidence of neutropenia (defined as < 0.5 cells $\times$ 10^9/L) was significantly higher in the high-dose group (5.7%) compared with patients treated with the standard dose of Peg-IFN alfa-2a (2.2%; p < 0.0001) (**Table 2**). Similarly, thrombocytopenia (platelet count < 50 $\times$ 10^9/L) occurred in more patients in the high-dose group (4.7%) compared with the standard-dose group (2.5%; p = 0.0013). There was also a statistically significantly higher number of patients with a haemoglobin concentration < 100 g/L in the high-dose group (10.8%) compared with the standard-dose group (7.8%, p = 0.0043) (**Table 2**). Kaplan–Meier plots showing time to first event for low haemoglobin Online Supplement (**Figure 2C**) indicate that the difference increases over time.

Kaplan–Meier plots showing time to first event for neutropenia thrombocytopenia and a haemoglobin concentration < 100 g/L are shown in the Online Supplement **Figure 2A-C**.

4. Discussion

The results of this analysis extend the knowledge of the safety of Peg-IFN alfa-2a by demonstrating that the overall frequency of AEs was similar in patients who received a 12-week high-dose induction regimen of 360 µg/week and in patients who received the standard 180 µg/week dose.

Reductions in neutrophil and platelet counts and weight loss are well-characterized side effects of interferon-based therapy. Indeed, neutropenia is the most common reason for dose reduction of pegylated interferon [12]. In this analysis, laboratory abnormalities were more common among patients receiving the high dose (360 µg/week) than the standard dose (180 µg/week) of Peg-IFN alfa-2a. Significantly more patients in the high-dose group reported a decrease in weight compared with those in the standard-dose group. Weight loss is a common side effect of combination treatment with pegylated interferon and ribavirin, particularly at the start of therapy. The underlying mechanisms that lead to weight loss have yet to be identified, but may include a direct biological effect of interferon and a secondary effect of side effects such as fatigue, loss of appetite, nausea, vomiting and depression leading to decreased food uptake. Dietetic intervention may be required in some patients to mitigate the effects of interferon-associated weight loss [13]. In addition, in a recent study, SVR was associated with weight loss during therapy, suggesting that continuation of therapy despite adverse effects may be of benefit [14]. Significantly more patients in the high-dose group also became anaemic (haemoglobin concentration < 100 g/L) when compared with the standard-dose group. This may be due in part to an additive effect of interferon to that of ribavirin which is known to be associated with anaemia.

Several analyses have reported correlations between cytopenias and the magnitude of the virological response in patients treated with pegylated interferon plus ribavirin [15,16]. The somewhat greater reduction in neutrophil count, the greater weight loss and the higher EVR rate observed at the end of induction therapy may be a manifestation of this phenomenon.

The incidence of infection in our analysis was higher in patients in the high-dose group (20.7 vs. 18.7% in the standard-dose group) but the absolute difference was small. In light of the greater incidence of cytopenias in the high-dose group, this seems counterintuitive; however, a recent study showed that neutrophil function, as indicated by chemotaxis and oxidative burst, is enhanced during Peg-IFN alfa therapy [17]. This compensatory response may explain

Table 2. Adverse events (AEs) and treatment modifications and discontinuations during the first 12 weeks of treatment.

	Group A Standard-dose group Peg-IFN alfa-2a 180 μg/week (n = 1,672)	Group B High-dose group Peg-IFN alfa-2a 360 μg/week (n = 1,268)	Hazard ratio‡ Groups B/A (95% CI)
Patients with any AE, n (%)	1,609 (96.2)	1,233 (97.2)	1.09 (1.01 – 1.17)
Number of AEs per patient*	6.6	7.0	
Patients with a severe/life threatening AE, n (%)	294	198	0.89 (0.75 – 1.07)
Number of severe/life-threatening AEs per patient*	0.298	0.284	
Patients with serious adverse events (SAEs), n (%)	53 (3.2)	53 (4.2)	1.33 (0.91 – 1.95)
Number of SAEs per patient*	0.038	0.050	
AEs*, n (%)			
Cough, dyspnoea or pneumonia	376 (22.5)	300 (23.7)	1.07 (0.92 – 1.25)
Cough	210 (12.6)	173 (13.6)	1.11 (0.91 – 1.35)
Dyspnoea	207 (12.4)	160 (12.6)	1.03 (0.84 – 1.26)
Pneumonia	12 (0.7)	9 (0.7)	1.00 (0.42 – 2.37)
Psychiatric disorder§	487 (29.1)	357 (28.2)	0.96 (0.84 – 1.10)
Infection and infestation	313 (18.9)	262 (20.7)	1.13 (0.96 – 1.33)
Weight decrease	55 (3.3)	98 (7.7)	2.42 (1.74 – 3.36)
Severe/life-threatening adverse events*, n (%)			
Cough, dyspnoea or pneumonia	20 (1.2)	10 (0.8)	0.66 (0.31 – 1.41)
Psychiatric disorder	40 (2.4)	25 (2.0)	0.83 (0.50 – 1.36)
Infection	20 (1.2)	24 (1.9)	1.60 (0.88 – 2.90)
Weight decrease	1 (0.06)	1 (0.08)	1.33 (0.08 – 21.3)
Laboratory abnormalities¶, n (%)			
Neutrophil count < 0.5 cells × 10^9/L	36 (2.2)	72 (5.7)	2.71 (1.81 – 4.04)
Platelet count < 50 cells × 10^9/L	42 (2.5)	59 (4.7)	1.90 (1.28 – 2.82)
Haemoglobin < 100 g/L	131 (7.8)	137 (10.8)	1.41 (1.11 – 1.80)
Treatment discontinuation for safety, n (%)	47 (2.8)	37 (2.9)	1.05 (0.68 – 1.61)
Dose modification of Peg-IFN alfa-2a for safety, n (%)	223 (13.3)	228 (18.0)	1.39 (1.15 – 1.67)
Dose modification of ribavirin for safety, n (%)	238 (14.2)	191 (15.1)	1.07 (0.89 – 1.30)

*Patients with the AEs specified with onset between study day 1 and 84.

‡Hazard ratio based on unadjusted Cox proportional hazard model.

§Excluding insomnia.

¶Sample collection between study day 2 and 99.

why the rate of infectious complications during interferon-based therapy for hepatitis C is not correlated with the degree of neutropenia [18,19].

Psychiatric AEs are frequently associated with interferon-based therapy. Interferon-induced depression is generally more common during the first month or two of treatment [20-22], and responds well to anti-depressant medication [23]. Importantly, there was no evidence of an increased rate of psychiatric disorders with higher doses of Peg-IFN alfa-2a in the present analysis. This may reflect in part the fact that patients with a history of severe psychiatric disorders were excluded from the studies and that interferon-induced depression is not necessarily a dose-related phenomenon. Differences in the rate of antidepressant use between the two dosage groups appear to have been driven by less frequent use of antidepressants in the two older studies, which suggests that clinicians have become more proactive in identifying and treating depression since these early studies were performed. Patients in these studies were enrolled at specialist centers and the investigators were knowledgeable about the management of interferon-related AEs.

Pulmonary events are rarely associated with interferon and it is unclear whether these effects are caused by interferon, and, if they are, whether the effects are dose-related [24]. Interstitial lung disease is a diagnostic challenge, can manifest as a sign of systemic chronic disease (e.g., rheumatoid arthritis or sarcoidosis), may occur after exposure to noxious materials such as cigarette smoke, and has been associated with HCV infection [25-27]. It must be acknowledged that cough, dyspnoea and pneumonia are very indirect indicators of pulmonary function; however, the comparable incidence of these phenomena in the two different dosing groups is reassuring and suggests that there is no dose-dependent pharmacodynamic (pulmonary) effect for Peg-IFN alfa-2a.

A multiple logistic regression analysis identified a number of baseline factors associated with withdrawal from treatment for safety reasons within the first 12 weeks, including older age, male gender and low neutrophil count, but interestingly not the starting dose of Peg-IFN alfa-2a. Therefore a higher dose of Peg-IFN alfa-2a was not associated with an increased likelihood of treatment discontinuation within the first 12 weeks of therapy. Although starting dose of Peg-IFN was

not identified as a factor associated with withdrawal from treatment it was shown to be a significant predictor of dose modifications. These two observations together suggest that for patients with treatment-related adverse events these events can be effectively managed by dose reductions rather than necessitating discontinuation from treatment. However, had patients been prevented from modifying their dose of Peg-IFN alfa-2a the comparison of overall adverse events and rates of treatment withdrawal might have been different with more patients on the high dose induction regimen reporting adverse events and discontinuing from treatment.

The finding that older patients are more likely to discontinue treatment prematurely is most likely one explanation for the observation that older patients have lower overall SVR rates [28]. The finding that Black patients are more likely to have the dose of Peg-IFN alfa-2a reduced because of laboratory abnormalities is consistent with the lower neutrophil counts and higher rates of neutropenia in this population [29].

Although this study provides valuable information on the comparative tolerability of two dosage regimens of Peg-IFN alfa-2a it has certain limitations. The study was retrospective and combined data from five studies. Thus, any differences in the definitions or collection of adverse events will affect the fidelity of this analysis.

Current treatment guidelines do not recommend high dose peginterferon for the treatment of patients with chronic hepatitis C [1] and with the approval of the first class of direct acting antiviral agents (HCV protease inhibitors), a new treatment paradigm is emerging [30]. However, interferon-free therapy is not yet a reality in the clinic: commercially available protease inhibitors must be administered in combination with Peg-IFN plus ribavirin. Thus Peg-IFN is likely to remain an essential component of treatment regimens for the forseeable future. This is especially true for patient subgroups that have high response rates and in settings in which the cost of protease inhibitors is prohibitive. For these reasons a more complete understanding of the safety of Peg-IFN is useful.

5. Conclusion

In conclusion, the results of this analysis add to the large body of data describing the safety and tolerability of Peg-IFN alfa-2a in combination with ribavirin, and indicate that Peg-IFN alfa-2a has a wide safety margin even when administered at twice the recommended dosage during the first 12 weeks of treatment. These data are important considering the recent observations that for certain types of patients and, in some subgroups of patients, higher doses of Peg-IFN may provide additional benefit [15,16]. Furthermore, in the era of direct acting antivirals which are associated with additional treatment-limiting adverse events it is important to fully characterize the safety profile of Peg-IFN including the time-dependence of adverse events.

Declaration of interest

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Supplementary material available online

Supplementary Figures 1, 2.

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