

# Meta-analysis: mortality and serious adverse events of peginterferon plus ribavirin therapy for chronic hepatitis C

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## Abstract

**Background** Pegylated interferon (PEG-IFN) plus ribavirin (RBV) therapy is the current standard of care for patients with chronic hepatitis C. Determining precisely the risk of serious adverse events (SAEs) and mortality from a single study is rather difficult because of the infrequency of such events. The aim of this systematic review was to assess the rates of SAEs and the mortality of PEG-IFN/RBV therapy in a pooled large sample, and to assess the relationship between SAEs and mortality rates and therapeutic characteristics.

**Methods** A literature search was conducted using MEDLINE, EMBASE, and the Cochrane Library to identify randomized controlled trials evaluating the efficacy and safety of PEG-IFN/RBV therapy. We calculated the crude mortality and SAE rates with 95 % confidence intervals (CIs).

**Results** Eighty studies with 153 treatment arms that included 27569 patients were enrolled (14401 patients treated with Peg-IFN alpha-2a/RBV and 13168 with Peg-IFN alpha-2b/RBV). All-cause and treatment-related deaths were observed in 50 (0.18 %; 95 % confidence interval [CI] 0.13–0.24 %) and sixteen (0.058 %; 95 % CI 0.033–0.094 %) patients, respectively. The crude SAE rate was 7.08 % (95 % CI 6.75–7.41 %). Subgroup analysis

revealed higher SAE rates in patients receiving PEG-IFN alpha-2a than in those with PEG-IFN alpha-2b (7.45 vs. 6.74 %), and higher SAE rates with higher doses than with the lower doses in PEG-IFN-2a and 2b (11.94 vs. 6.99 %, 7.10 vs. 5.05 %, respectively), and with extended duration (>48 weeks) than with standard duration (48 weeks) (15.5 vs. 6.67 %) in PEG-IFN alpha-2a.

**Conclusion** The mortality rate during PEG-IFN/RBV therapy was acceptably low, but the rate of SAEs was not negligible in a treatment for a benign disease, and the rate was affected by treatment regimens.

**Keywords** Peginterferon · Ribavirin · Hepatitis C · Mortality · Adverse event · Systematic review

## Abbreviations

CI	Confidence interval
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
PEG-IFN	Pegylated interferon
RCT	Randomized controlled trial
RBV	Ribavirin
SAE	Serious adverse event
SVR	Sustained virological response
WHO	World Health Organization

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## Introduction

Chronic hepatitis C virus (HCV) infection affects more than 170 million people worldwide and is a major cause of cirrhosis and hepatocellular carcinoma (HCC) [1, 2]. Currently the standard of care for patients with chronic hepatitis C is peginterferon (PEG-IFN) plus ribavirin (RBV) therapy,

which can induce a sustained virological response (SVR) in 40–50 % of treatment-naïve patients with genotype 1 and an SVR of approximately 80 % in treatment-naïve patients with genotypes 2 or 3 [3–8]. After an SVR is achieved, the risk of developing liver failure and HCC is greatly reduced [9]. However, this treatment is associated with various types of complications, some of which lead to fatal outcomes. Because death during treatment is a rare event, a large sample size is needed to accurately assess the mortality rate and risk factors. The aim of this systematic review was to assess the rates of serious adverse events (SAEs) and mortality during PEG-IFN/RBV therapy in a pooled large-sized sample and to assess the relationship between mortality and SAE rates and therapeutic characteristics.

## Methods

### Study search protocol

We searched MEDLINE, EMBASE, and the Cochrane Library to identify randomized controlled trials (RCTs) evaluating the efficacy and safety of PEG-IFN/RBV therapy published between December 1999 and October 2010. We used the following search terms: *chronic hepatitis C*, *interferon*, and *pegylated* or *peg* or *peginterferon* or *pegasys* or *pegintron*. The search was limited to the English language.

### Inclusion criteria

Studies were included in the analysis if: (1) they were RCTs, (2) they included at least one PEG-IFN/RBV treatment group in patients with chronic hepatitis C, (3) they clearly specified adverse events, (4) patients were followed up until at least 24 weeks after the end of treatment, and (5) the studies had been published or accepted for publication as full-length articles. Studies were excluded if: (1) they dealt only with co-infection of HCV and HIV; (2) they dealt only with patients with a specific condition such as a comorbid disease (e.g., cryoglobulinemia), status after liver transplantation, or patients on dialysis; (3) they included patients under 18 years of age; or (4) they focused on specific adverse events or only on hemodynamic status. We restricted the included studies to RCTs on the premise that the quality of RCTs is superior to that of non-randomized or retrospective studies.

### Data extraction

Two authors (T. M. and T. K.) independently screened titles and abstracts for potential eligibility and the full texts for final eligibility. Disagreements were resolved by

consensus or by consulting a third author (R. T.). We extracted the data using a standardized data-collection form to record details of the study design, treatment doses and duration, number of patients in the arm, patient characteristics, and outcomes. A database using Microsoft Access 2010 (Microsoft, Redmond, WA, USA) was developed specifically for that purpose. Two authors independently entered data into the form, and the data were then compared. Any discrepancies were checked and resolved by consensus.

### Statistical analysis

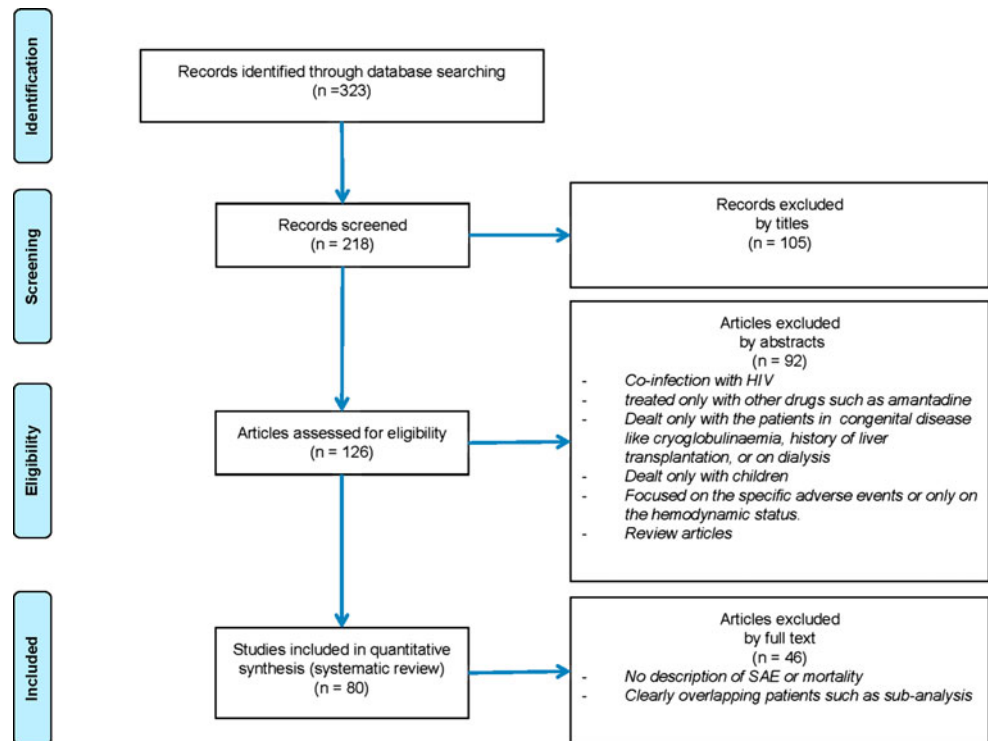
The primary and secondary outcome measures were mortality and SAE rates during PEG-IFN/RBV therapy, respectively. We recorded the number of SAEs and deaths observed in each arm of the included studies. We calculated crude mortality and SAE rates with 95 % confidence intervals (CI) by dividing the total number of deaths or SAEs observed by the total number of patients in the relevant group. Studies that did not discriminate serious adverse events from others were not included in the analyses of the corresponding outcome. We performed a subgroup analysis by comparing mortality and SAE rates between PEG-IFN alpha-2a and alpha-2b, high-dose and low-dose PEG-IFN, and shorter and longer treatment durations. We also performed a meta-regression analysis to investigate relationships between mortality and SAE rates and continuous variables (mean age; mean body weight; proportion of males; proportion of Caucasian, African, and Asian patients; and proportion of genotype 1 patients) using the random effects model. Heterogeneity was tested using the  $I^2$  test to calculate the percentage of variation caused by heterogeneity rather than by chance alone [10]. The analyses were performed with S-plus Ver. 7.0 (Insightful, Seattle, WA, USA) and StatsDirect version 2.7.7 (StatsDirect, Chesire, UK). The threshold of the reported  $P$  value accepted as indicating significance was  $<0.05$ .

## Results

### Study characteristics

Figure 1 shows the results of the screening. Our initial database search retrieved 323 citations, of which 243 were excluded because they did not meet our inclusion criteria; therefore, a total of 80 RCTs with 153 arms that included 27569 patients were enrolled. Table 1 shows the characteristics of each enrolled study. All studies contained at least one treatment arm using PEG-IFN and RBV for chronic hepatitis C. There were 16797 male and 10254

**Fig. 1** The literature-search and study-selection process. SAE serious adverse events



females and the sex was not reported in the remaining 518 patients. The mean age was 45.9 years. A total of 14401 patients were treated with PEG-IFN alpha-2a/RBV, and 13168 with PEG-IFN alpha-2b/RBV. PEG-IFN alpha-2a was used at a fixed dose of 180–360 µg/body/week, and PEG-IFN alpha-2b at weight-based doses of 0.35–3.0 µg/kg/week. The RBV dose was fixed in 36 treatment arms and weight-based in 117 treatment arms. Treatment duration ranged from 12 to 72 weeks. The numbers of patients with HCV genotypes 1, 2, 3, and 4–6 were 18082, 3427, 3519, and 842, respectively. The genotype was not reported in the remaining 1699 patients. The treatment protocol is described in Supplementary Table 1.

#### Primary outcome

A total of 50 deaths from all causes were observed in the enrolled studies. Of these, sixteen were considered by the authors to be treatment-related. The crude overall and treatment-related mortality rates were 0.18 % (95 % CI 0.13–0.24 %) and 0.058 % (0.033–0.094 %), respectively. There was no evidence of heterogeneity among studies for mortality and treatment-related mortality ( $I^2 = 0$  in both). The causes of mortality were suicide ( $N = 6$ ), drug intoxication ( $N = 6$ ), myocardial infarction ( $N = 3$ ), sepsis ( $N = 3$ ), aortic dissection ( $N = 2$ ), traffic accident ( $N = 2$ ), HCC ( $N = 2$ ), rupture of a cerebral aneurysm ( $N = 1$ ), bronchitis ( $N = 1$ ), syncope ( $N = 1$ ), pulmonary tuberculosis ( $N = 1$ ), and unknown causes ( $N = 22$ ). The

six cases of suicide, the three of sepsis, two of drug intoxication, two of myocardial infarction, one of HCC, one of syncope, and one of pulmonary tuberculosis were considered by the investigators to be treatment-related mortality.

Subgroup analysis did not reveal any difference in mortality according to type and dose of PEG-IFN or in relation to duration of treatment (Fig. 2).

#### Secondary outcome

Seventy-two studies with 135 treatment arms including 23996 patients reported SAEs. They reported SAEs such as anemia requiring transfusion, neutropenia below 500/mm<sup>3</sup>, hypothyroidism, psychosis, pneumonia, and cellulitis. SAEs were not discriminated from other adverse events in the remaining eighteen studies. The crude SAE rate was 7.08 % (95 % CI 6.75–7.41 %). Significant heterogeneity among studies was found for this outcome ( $I^2 = 94.1$  %). SAE rates were higher in PEG-IFN alpha-2a than in PEG-IFN alpha-2b (7.45 vs. 6.74 %). In a subgroup analysis of the type and dose of PEG-IFN and duration of treatment, higher SAE rates were observed for intensive (270–360 µg) than for standard (180 µg) doses and for extended (>48 weeks) than for standard (48 weeks) treatment duration in patients treated with PEG-IFN alpha-2a, and for standard (1.5 µg/kg) than for lower ( $\leq 1.0$  µg/kg) doses in patients treated with PEG-IFN alpha-2b (Fig. 3). However, heterogeneity remained evident in all subgroups.



Table 1 continued

Study	Peginterferon type and dose	Ribavirin	Duration, weeks <sup>a</sup>	Patients, N	Male, N	Age, years (mean)	BW, kg (mean)	Ethnic group, N				HCV genotype, N					
								Caucasian	African	Asian	Other	G1	G2	G3	G4–6		
Ferenci [43]	2a 180 µg	1000–1200 mg	48	95	65	44	NR	NR	NR	NR	NR	NR	NR	95	0	0	0
Ferenci [44]	2a 180 µg	400 mg, fixed	24	141	87	36.2	73.1	NR	NR	NR	NR	NR	NR	0	19	122	0
	2a 180 µg	800 mg, fixed	24	141	84	36.8	71.1	NR	NR	NR	NR	NR	NR	0	18	123	0
Ferenci [45]	2a 180 µg	1000–1200 mg	72 <sup>a</sup>	150	98	44.3	76.9	NR	NR	NR	NR	NR	NR	134	0	0	16
	2a 180 µg	1000–1200 mg	48	139	90	45.1	78.5	NR	NR	NR	NR	NR	NR	127	0	0	12
Fried [4]	2a 180 µg	1000–1200 mg	48	453	324	42.8	79.8	372	27	28	26	298	54	86	86	13	
Fried [46]	2a 180 µg	1200 mg, fixed	48	46	37	47.1	98.4	32	4	NR	10	46	0	0	0	0	
	2a 180 µg	1600 mg, fixed	48	47	41	49.6	100.3	29	6	NR	12	47	0	0	0	0	
	2a 270 µg	1200 mg, fixed	48	47	35	47.1	101	35	4	NR	8	47	0	0	0	0	
	2a 270 µg	1600 mg, fixed	48	47	37	48.5	97	32	5	NR	10	47	0	0	0	0	
Gish [47]	2a 180 µg	1000–1200 mg	24–48 <sup>a</sup>	45	32	49	80	38	NR	NR	NR	NR	NR	NR	NR	NR	NR
Glue [48]	2b 0.35 µg/kg	600–800 mg	24	12	NR	39.8	65.6	NR	NR	NR	NR	9	NR	NR	NR	NR	NR
	2b 0.7 µg/kg	600–1200 mg	24	18	NR	39.8	65.6	NR	NR	NR	NR	5	NR	NR	NR	NR	NR
	2b 1.4 µg/kg	600–1200 mg	24	18	NR	39.8	65.6	NR	NR	NR	NR	4	NR	NR	NR	NR	NR
Hadziyannis [6]	2a 180 µg	1000–1200 mg	24	280	185	42	77.1	254	9	16	1	118	53	91	NR	NR	NR
	2a 180 µg	1000–1200 mg	48	436	287	43	77.3	394	11	26	5	271	66	87	NR	NR	NR
	2a 180 µg	800 mg, fixed	48	361	226	42.6	77	315	11	31	4	250	46	53	NR	NR	NR
	2a 180 µg	800 mg, fixed	24	207	140	41.2	78.3	183	7	14	3	101	39	57	NR	NR	NR
Hasan [49]	2b 1.5 µg/kg	1000–1200 mg	48	21	16	NR	NR	0	19	2	0	4	0	0	0	17	
Helbling [50]	2a 180 µg	600–800 mg	48	60	36	47 <sup>b</sup>	73	NR	NR	NR	NR	25	7	24	3		
	2a 180 µg	1000–1200 mg	48	64	45	47 <sup>b</sup>	74	NR	NR	NR	NR	30	11	18	4		
Herrine [51]	2a 180 µg	800–1000 mg	48	32	24	48	NR	NR	NR	NR	NR	25	NR	NR	NR	NR	NR
Hezode [52]	2a 180 µg	1000–1200 mg	48	82	46	45 <sup>b</sup>	NR	76	2	4	0	82	0	0	0	0	0
Ide [53]	2b 1.5 µg/kg	600–1000 mg	48	56	26	55.3	NR	0	0	56	0	56	0	0	0	0	0
	2b 1.5 µg/kg	600–1000 mg	48–68 <sup>a</sup>	57	30	54.6	NR	0	0	57	0	57	0	0	0	0	0
Jacobson [54]	2b 1.0 µg/kg	1000–1200 mg	48	161	122	49.2	NR	118	23	NR	20	145	NR	NR	NR	NR	NR
	2b 1.5 µg/kg	800 mg, fixed	48	160	117	49.8	NR	106	27	NR	27	141	NR	NR	NR	NR	NR
Jacobson [55]	2b 1.5 µg/kg	800 mg, fixed	24–48 <sup>a</sup>	2444	1560	45.8	83.8	1926	237	59	222	1506	526	386	23		
	2b 1.5 µg/kg	800–1400 mg	24–48 <sup>a</sup>	2469	1539	45.8	84	1993	208	59	209	1512	499	421	33		
Jensen [56]	2a 180 µg	1000–1200 mg	48	313	212	48.5	80.9	282	25	NR	6	284	1	8	19		
	2a 180 µg	1000–1200 mg	72	156	107	49.4	81.2	137	17	NR	2	142	1	5	8		
	2a 360 µg	1000–1200 mg	48 <sup>a</sup>	156	94	48.8	81.1	141	10	NR	5	142	3	4	5		
	2a 360 µg	1000–1200 mg	72 <sup>a</sup>	317	203	48.1	81.5	279	29	NR	9	288	2	7	19		

**Table 1** continued

Study	Peginterferon type and dose	Ribavirin	Duration, weeks <sup>a</sup>	Patients, N	Male, N	Age, years (mean)	BW, kg (mean)	Ethnic group, N				HCV genotype, N					
								Caucasian	African	Asian	Other	G1	G2	G3	G4–6		
Kamal [57]	2b 1.5 µg/kg	1000–1200 mg	24	95	49	41.6	NR	NR	NR	NR	NR	NR	NR	0	0	0	95
	2b 1.5 µg/kg	1000–1200 mg	36	96	51	43.9	NR	NR	NR	NR	NR	NR	NR	0	0	0	96
Kamal [58]	2b 1.5 µg/kg	1000–1200 mg	48	96	50	41.2	NR	NR	NR	NR	NR	NR	NR	0	0	0	96
	2b 1.5 µg/kg	10.6 mg/kg	24 <sup>a</sup>	69	37	41 <sup>b</sup>	NR	NR	NR	NR	NR	NR	NR	69	0	0	0
Kawaoka [59]	2b 1.5 µg/kg	10.6 mg/kg	36 <sup>a</sup>	79	32	40.5 <sup>b</sup>	NR	NR	NR	NR	NR	NR	NR	79	0	0	0
	2b 1.5 µg/kg	10.6 mg/kg	48 <sup>a</sup>	160	100	42.2	NR	NR	NR	NR	NR	NR	NR	160	0	0	0
Khattab [60]	2b 1.5 µg/kg	10.6 mg/kg	48	50	26	43.2	NR	NR	NR	NR	NR	NR	NR	50	0	0	0
	2b 1.0 µg/kg	600–1000 mg	24	26	9	57 <sup>b</sup>	53	0	26	0	0	0	0	0	26	0	0
Kuboki [61]	2b 1.5 µg/kg	600–1000 mg	24	27	15	55 <sup>b</sup>	61	0	27	0	0	0	0	0	27	0	0
	2b 1.5 µg/kg	800–1400 mg	48	49	34	37	NR	0	0	0	0	0	0	0	0	0	49
Lagging [62]	2a 180 µg	600–1000 mg	48	100	74	52 <sup>b</sup>	66.7	0	100	0	0	0	0	85	15	0	0
	2a 180 µg	600–1000 mg	48	99	62	52	62.8	0	99	0	0	0	0	99	0	0	0
Langlet [63]	2a 180 µg	800 mg, fixed	12	194	123	41.5	79.8	NR	NR	NR	NR	NR	NR	0	55	137	0
	2a 180 µg	800 mg, fixed	24	188	105	42	76.5	NR	NR	NR	NR	NR	NR	0	49	139	0
Lee [64]	2a 180 µg	1000–1200 mg	24–48 <sup>a</sup>	314	173	45.4	73.1	278	7	5	166	NR	NR	38	38	0	0
	2b 1.5 µg/kg	1000–1200 mg	24	76	53	44.6	67.8	0	0	76	0	0	0	154	0	0	0
Liu [65]	2a 180 µg	1000–1200 mg	24	154	88	54	67.6	0	0	154	0	0	0	154	0	0	0
	2a 180 µg	1000–1200 mg	48	154	87	53	65.8	0	0	154	0	0	0	154	0	0	0
Lodato [66]	2b 1.0–1.5 µg/kg	10.6 mg/kg	24–48 <sup>a</sup>	43	23	49.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	2b 1.5 µg/kg	10.6 mg/kg	24–48 <sup>a</sup>	22	12	48.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mangia [7]	2b 1.0 µg/kg	1000–1200 mg	12	133	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	102	31	0
	2b 1.0 µg/kg	1000–1200 mg	24	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	58	22	0
Manns [3]	2b 1.0 µg/kg	1000–1200 mg	24	70	39	49.7	69.5	NR	NR	NR	NR	NR	NR	0	53	17	0
	2b 1.5 µg/kg	1000–1200 mg	48 <sup>a</sup>	514	346	44	83	NR	NR	NR	NR	NR	NR	349	NR	NR	12
Marcellin [67]	2b 1.5 µg/kg	800 mg, fixed	48	511	321	43	82	NR	NR	NR	NR	NR	NR	348	NR	NR	16
	2b 1.5 µg/kg	800–1200 mg	24 <sup>a</sup>	10	8	51.4	75.8	10	0	0	10	0	0	10	0	0	0
Marcellin [68]	2a 180 µg	1000–1200 mg	24–48 <sup>a</sup>	318	201	45.1	NR	256	17	11	34	212	47	47	47	NR	NR
	2a 180 µg [15]	1000–1200 mg	48	1035	613	47.6	82.8	733	200	20	82	1035	0	0	0	0	0
McHutchison [15]	2b 1.0 µg/kg	800–1400 mg	48	1016	607	47.5	83.4	724	187	21	84	1016	0	0	0	0	0
	2b 1.5 µg/kg	800–1400 mg	48	1019	613	47.5	84	732	183	10	94	1019	0	0	0	0	0
McHutchison [69]	2a 180 µg	1000–1200 mg	48	114	76	50 <sup>b</sup>	NR	100	10	2	2	114	0	0	0	0	0
	2a 180 µg	1000–1200 mg	12 <sup>a</sup>	72	NR	42 <sup>b</sup>	NR	NR	NR	NR	NR	NR	NR	0	NR	NR	0
Mecenate [70]	2a 180 µg	1000–1200 mg	24 <sup>a</sup>	67	54	45 <sup>b</sup>	NR	NR	NR	NR	NR	NR	NR	0	37	30	0
	2a 180 µg	1000–1200 mg	24 <sup>a</sup>	71	NR	42 <sup>b</sup>	NR	NR	NR	NR	NR	NR	NR	0	NR	NR	0

Table 1 continued

Study	Peginterferon type and dose	Ribavirin	Duration, weeks <sup>a</sup>	Patients, N	Male, N	Age, years (mean)	BW, kg (mean)	Ethnic group, N			HCV genotype, N					
								Caucasian	African	Asian	Other	G1	G2	G3	G4–6	
Mendez-Navarro [71]	2a 180 µg	1000–1200 mg	48	63	26	46.2	70.4	0	0	0	63	63	0	0	0	0
Meyer-Wyss [72]	2b 1.0 µg/kg	800 mg, fixed	24–48 <sup>a</sup>	113	64	39 <sup>b</sup>	72	NR	NR	NR	NR	49	14	41	9	0
Napoli [73]	2b 1.5 µg/kg	800 mg, fixed	24–48 <sup>a</sup>	106	76	42 <sup>b</sup>	73	NR	NR	NR	NR	64	10	26	6	0
Pearlman [74]	2b 1.5 µg/kg	800–1200 mg	48 <sup>a</sup>	14	10	46.9	NR	NR	NR	NR	NR	14	0	0	0	0
	2b 1.5 µg/kg	800–1200 mg	48	17	11	47.3	NR	NR	NR	NR	NR	17	0	0	0	0
	2b 1.5 µg/kg	800–1400 mg	48	49	23	56 <sup>b</sup>	NR	NR	NR	NR	NR	26	49	0	0	0
	2b 1.5 µg/kg	800–1400 mg	72	52	34	54 <sup>b</sup>	NR	NR	NR	NR	NR	27	52	0	0	0
Roberts [75]	2a 180 µg	1000–1200 mg	48	438	285	43.3	78.7	365	55	0	1	436	0	0	0	0
	2a 360 µg	1000–1200 mg	48 <sup>a</sup>	433	298	43.6	77.3	355	61	0	2	432	0	0	0	0
Roffi [76]	2b 1.0 µg/kg	1000–1200 mg	48	57	36	56 <sup>b</sup>	75	NR	NR	NR	NR	33	15	9	0	0
Rossignol [77]	2a 180 µg	1000–1200 mg	48	40	36	39	NR	NR	NR	NR	NR	0	0	0	40	0
Rumi [16]	2a 180 µg	1000–1200 mg	24–48 <sup>a</sup>	212	128	51.6	72.2	NR	NR	NR	NR	91	69	34	18	0
	2b 1.5 µg/kg	1000–1200 mg	24–48 <sup>a</sup>	219	120	52.8	68.9	NR	NR	NR	NR	87	74	32	26	0
Rustgi [78]	2a 180 µg	1000–1200 mg	24–48 <sup>a</sup>	117	81	50	89.7	79	26	0	12	117	0	0	0	0
Sanchez-Tapias [79]	2a 180 µg	800 mg, fixed	48	165	113	42.8	73.3	NR	NR	NR	NR	149	1	7	8	0
	2a 180 µg	800 mg, fixed	72	161	102	43.2	74.4	NR	NR	NR	NR	142	1	8	8	0
	2a 180 µg	800 mg, fixed	24	148	88	39.3	67.9	NR	NR	NR	NR	45	18	75	10	0
	2a 180 µg	800 mg, fixed	48	36	20	42.4	68.7	NR	NR	NR	NR	35	0	0	1	0
Scotto [17]	2a 180 µg	15 mg/kg	48	71	42	45.8	80.7	NR	NR	NR	NR	45	6	8	12	0
	2b 1.5 µg/kg	15 mg/kg	48	72	40	47.8	78.9	NR	NR	NR	NR	47	5	9	11	0
Shiffman [80]	2b 1.5 µg/kg	800–1400 mg	48	48	27	49 <sup>b</sup>	82	NR	NR	NR	NR	31	48	0	0	0
Shiffman [81]	2a 180 µg	800 mg, fixed	16	732	448	46	81.5	635	22	21	54	NR	372	358	NR	0
	2a 180 µg	800 mg, fixed	24	731	461	45.6	81.6	638	21	18	54	NR	356	369	NR	0
Shiffman [82]	2a 180 µg	1000–1200 mg	48	936	673	50	NR	693	157	NR	NR	936	0	0	0	0
Sjogren [83]	2b 1.5 µg/kg	1000–1200 mg	48	29	19	46 <sup>b</sup>	82	17	9	2	1	29	0	0	0	0
Sood [84]	2b 1.0 µg/kg	1000–1200 mg	24	76	67	43.1	NR	0	0	76	0	0	0	76	0	0
	2b 1.5 µg/kg	1000–1200 mg	24	27	21	37.3	NR	0	0	27	0	0	0	27	0	0
Tang [85]	2a 180 µg	1000–1200 mg	20 <sup>a</sup>	11	4	42 <sup>b</sup>	70	8	NR	NR	NR	3	11	0	0	0
	2a 180 µg	1000–1200 mg	32 <sup>a</sup>	10	5	38 <sup>b</sup>	69	10	0	0	0	10	0	0	0	0
	2a 180 µg	1000–1200 mg	44 <sup>a</sup>	11	8	41 <sup>b</sup>	79	10	NR	NR	NR	1	11	0	0	0
	2a 180 µg	1000–1200 mg	48 <sup>a</sup>	13	9	41 <sup>b</sup>	71	11	NR	NR	NR	2	13	0	0	0
Toyoda [86]	2b 1.5 µg/kg	600–1000 mg	8 <sup>a</sup>	15	5	53.6	NR	0	0	15	0	0	15	0	0	0
	2b 1.5 µg/kg	600–1000 mg	24 <sup>a</sup>	28	16	57.8	62.2	0	0	28	0	0	28	0	0	0
	2b 1.5 µg/kg	600–1000 mg	24 <sup>a</sup>	17	7	NR	NR	0	0	17	0	0	17	0	0	0

**Table 1** continued

Study	Peginterferon type and dose	Ribavirin	Duration, weeks <sup>a</sup>	Patients, N	Male, N	Age, years (mean)	BW, kg (mean)	Ethnic group, N				HCV genotype, N			
								Caucasian	African	Asian	Other	G1	G2	G3	G4-6
Wagner [87]	2a 180 µg	800–1200 mg	16	71	52	38	75.3	NR	NR	NR	NR	0	19	51	0
	2a 180 µg	800–1200 mg	24	71	41	39	74.6	NR	NR	NR	NR	0	19	52	0
	2a 180 µg	800–1200 mg	24	11	4	42	80.1	NR	NR	NR	NR	0	1	10	0
Wagner [88]	2a 180 µg	1000–1200 mg	48	352	183	45.4	74	344	0	8	352	0	0	0	0
Yenice [18]	2a 180 µg	800–1200 mg	48	37	13	49.9	NR	NR	NR	NR	NR	37	0	0	0
Yu [89]	2b 1.5 µg/kg	800–1200 mg	48	37	10	50.8	NR	NR	NR	NR	NR	37	0	0	0
	2b 80–100 µg	1000–1200 mg	24 <sup>a</sup>	45	28	45.4	68.3	0	0	45	0	45	0	0	0
Yu [90]	2b 80–100 µg	1000–1200 mg	48 <sup>a</sup>	15	11	45.1	68.6	0	0	15	0	15	0	0	0
	2a 180 µg	1000–1200 mg	16	50	32	50.8	67.7	0	0	50	0	0	50	0	0
Yu [91]	2a 180 µg	1000–1200 mg	24	100	58	49.9	65.8	0	0	100	0	0	100	0	0
	2a 180 µg	1000–1200 mg	24	100	57	49.7	65.5	0	0	100	0	100	0	0	0
Zeuzem [92]	2a 180 µg	1000–1200 mg	48	100	58	49.1	67.5	0	0	100	0	100	0	0	0
	2a 180 µg	800 mg, fixed	24	212	90	43.8	73.9	183	17	5	7	144	38	20	10
Zeuzem [93]	2a 180 µg	800 mg, fixed	48	210	82	43.9	73.7	180	20	4	6	141	41	18	10
	2a 180 µg	1000–1200 mg	24 <sup>a</sup>	43	33	39.1	74.7	NR	NR	NR	NR	23	NR	NR	1
Zeuzem [94]	2a 180 µg	1000–1200 mg	48	134	83	43.2	73.8	NR	NR	NR	NR	90	NR	NR	6
	2a 360 µg	1000–1200 mg	48	11	6	42.6	79	NR	NR	NR	NR	9	NR	NR	2
Zeuzem [95]	2b 1.5 µg/kg	800–1200 mg	24	237	127	42.2	71.3	225	NR	NR	NR	237	0	0	0
	2a 180 µg	1000–1200 mg	48	114	66	41.9	73.4	105	NR	NR	NR	9	114	0	0

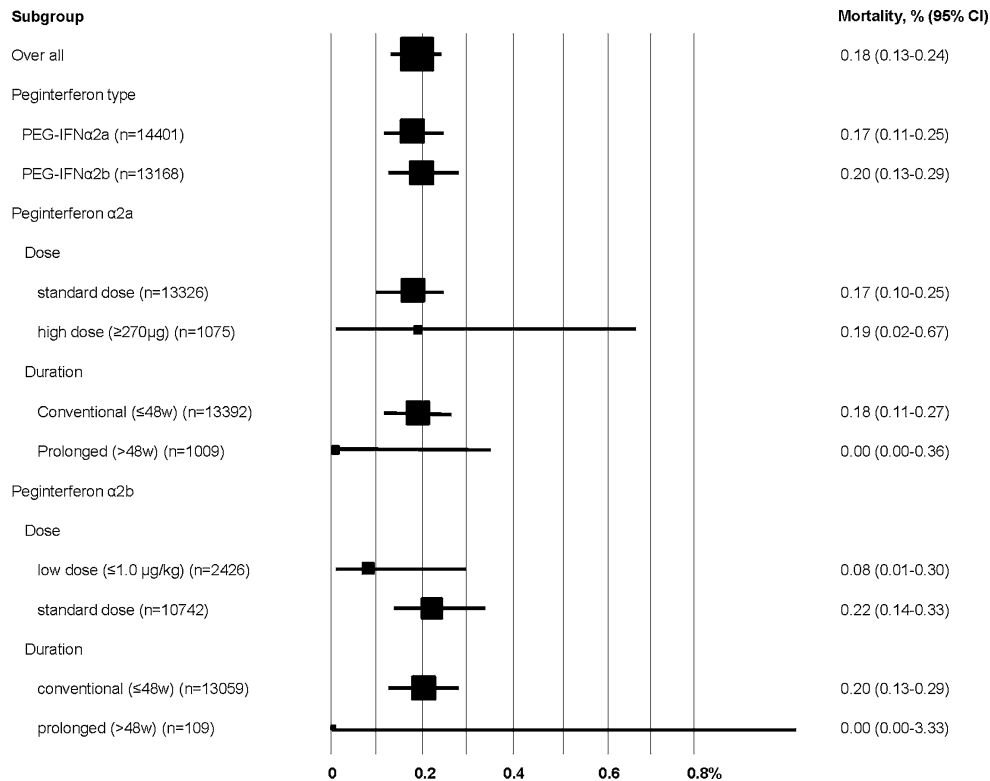
HCV hepatitis C virus, BW body weight, NR not reported

<sup>a</sup> Details of pegylated (Peg) interferon dose and duration of treatment are described in Supplementary Table 1

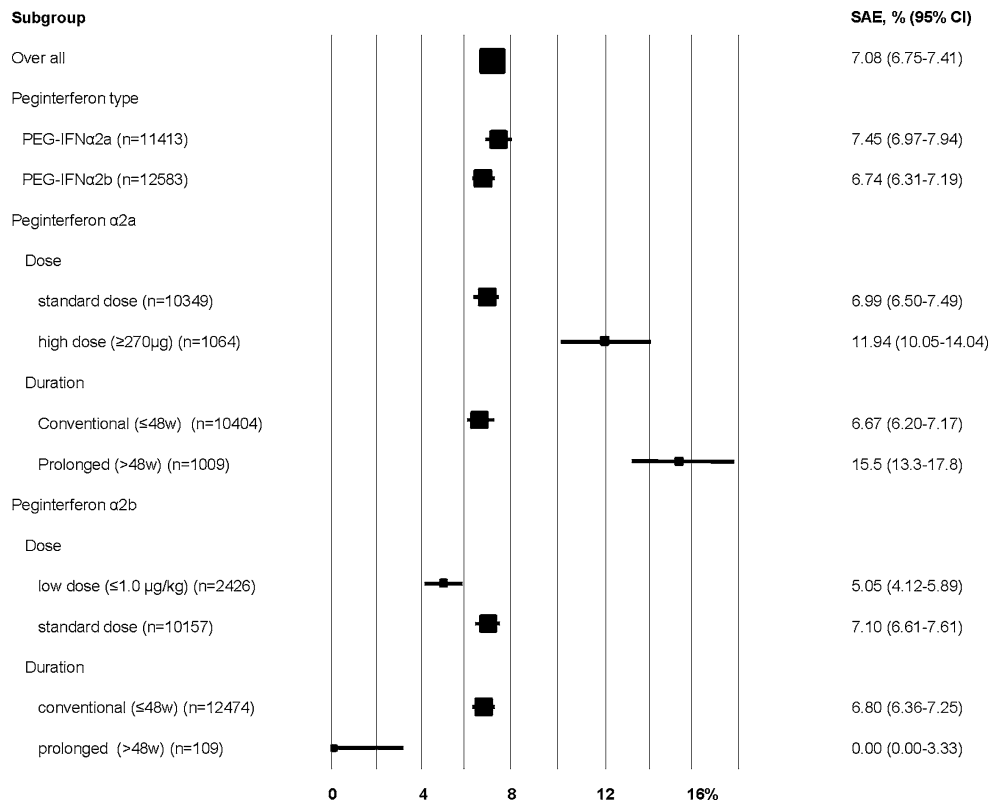
<sup>b</sup> Data values are expressed as medians



**Fig. 2** Forest plot of mortality, comparing treatment regimens. Sizes of the *boxes* reflect sample sizes, with the *bars* showing the 95 % confidence interval (CI)



**Fig. 3** Forest plot of SAEs, comparing treatment regimens. Sizes of the *boxes* reflect sample sizes, with the *bars* showing the 95 % confidence interval



Meta-regression analysis showed that greater body weight, an increased proportion of male patients, an increased proportion of HCV genotype 1, and an increased

proportion of Caucasian patients and decreased proportion of Asian patients were significantly associated with increased SAE rates (Table 2). There was no significant

association between increased SAE rates and the mean patient age or the proportion of African patients.

## Discussion

According to a report by the World Health Organization (WHO), age-specific annual death rates from all causes in individuals aged 45–49 years in the United States, Italy, and Japan (locations of the majority of our enrolled studies) were 409, 216, and 248 per 100000, respectively [11]. The crude mortality of 0.18 % (180 per 100000) found in the present study is low by comparison, even allowing for the biased population tolerable to PEG-IFN/RBV. Furthermore, the annual mortality rate could have been lower than the crude mortality rate, considering that the study period was longer than 1 year (including the follow-up period) in most enrolled studies. The annual treatment-related

mortality rate could have been lower than our finding of a treatment-related mortality of 0.06 %. However, the treatment-related mortality rate may be an underestimate, as assessment of the causal relationship between treatment and mortality can be subjective and/or biased. Nonetheless, these PEG-IFN/RBV-related mortality rates would be acceptable considering the high SVR rates and considering that SVR drastically reduces adverse events related to chronic hepatitis C infection. In the present study, the most common cause of mortality was suicide, and all of the suicides were considered as treatment-related. This finding should alert treating physicians when they are treating patients with a history of psychiatric illness.

Two types of PEG-IFNs (i.e., PEG-IFN alpha-2a and 2b) are approved for the treatment of chronic hepatitis C. PEG-IFN alpha-2a has a molecular mass of 40 kDa and PEG-IFN alpha-2b a mass of 12 kDa. In comparison with PEG-IFN alpha-2b, PEG-IFN alpha-2a is less effectively

**Table 2** Meta-regression analysis for continuous variables

Variables	Slope <sup>a</sup>	Standard error	P value
Mean age, per year increase			
All studies ( <i>N</i> = 100)	−0.00244	0.00380	0.52
Alpha-2a ( <i>N</i> = 60)	−0.00049	0.00513	0.93
Alpha-2b ( <i>N</i> = 40)	−0.00203	0.00488	0.68
Mean body weight, per 1 kg increase			
All studies ( <i>N</i> = 95)	0.00343	0.00147	0.02
Alpha-2a ( <i>N</i> = 64)	0.00584	0.00242	0.02
Alpha-2b ( <i>N</i> = 31)	0.00067	0.00178	0.71
Proportion of male patients, per 1 % increase			
All studies ( <i>N</i> = 125)	0.00305	0.00130	0.02
Alpha-2a ( <i>N</i> = 73)	0.00218	0.00182	0.23
Alpha-2b ( <i>N</i> = 52)	0.00257	0.00166	0.13
Proportion of Caucasian patients, per 1 % increase			
All studies ( <i>N</i> = 75)	0.00167	0.00043	<0.001
Alpha-2a ( <i>N</i> = 46)	0.00102	0.00062	0.11
Alpha-2b ( <i>N</i> = 29)	0.00201	0.00061	0.003
Proportion of African patients, per 1 % increase			
All studies ( <i>N</i> = 72)	−0.00092	0.00113	0.42
Alpha-2a ( <i>N</i> = 41)	0.00781	0.00394	0.55
Alpha-2b ( <i>N</i> = 31)	−0.00030	0.00109	0.79
Proportion of Asian patients, per 1 % increase			
All studies ( <i>N</i> = 58)	−0.00092	0.00042	0.03
Alpha-2a ( <i>N</i> = 32)	−0.00042	0.00061	0.50
Alpha-2b ( <i>N</i> = 26)	−0.00106	0.00053	0.06
Proportion of genotype 1 patients, per 1 % increase			
All studies ( <i>N</i> = 129)	0.00143	0.00036	<0.001
Alpha-2a ( <i>N</i> = 73)	0.00179	0.00048	<0.001
Alpha-2b ( <i>N</i> = 56)	0.00075	0.00046	0.104

<sup>a</sup> Slope values indicate increases (decreases) in the rates of serious adverse events (SAEs) per unit. For example, a 1-year increase in mean age in a study results in 0.00464 (0.464 %) decrease in the SAE rate

cleared by the kidneys and therefore has a longer half-life. In fact, pharmacokinetic analysis in 22 patients showed that PEG-IFN alpha-2a was still detectable in 10 patients 168 h after the administration of 180 µg/week, whereas the administration of 1.0 µg/kg/week of PEG-IFN alpha-2b was undetectable in 11 of 12 patients at the same time point [12]. PEG-IFN alpha-2a is thought to be more effective than PEG-IFN alpha-2b because of its longer half-life. A recent meta-analysis showed a higher SVR rate after treatment with PEG-IFN alpha-2a than after treatment with PEG-IFN alpha-2b [13]. On the other hand, the half-life of each PEG-IFN may be related to its safety profile. However, among studies that have directly compared the safety of the two PEG-IFNs, only one reported a significant difference between SAE rates for PEG-IFN alpha-2a and PEG-IFN alpha-2b (11.7 vs. 8.6 %,  $P = 0.02$ ) [14–18]. The inability of the other studies to detect such a difference may have been due to small sample sizes. In fact, a difference in SAE rates between the two PEG-IFNs was observed in pooled samples in our study.

Increasing the dose intensity of PEG-IFN and prolonging treatment duration have been attempted to achieve higher IFN levels in blood for longer periods, eventually resulting in a higher SVR rate. Treatment dose and duration are also expected to be related to the safety profile. The higher SAE rates in regimens with more intensive dosing observed for PEG-IFN alpha-2a and 2b and longer treatment duration observed for PEG-IFN alpha-2a support this hypothesis. The higher SAE rates in regimens with longer treatment duration were not observed for PEG-IFN alpha-2b, probably due to small sample sizes in regimens with longer treatment duration of PEG-IFN alpha-2b.

As mortality and SAE during PEG-IFN/RBV treatment are rare, most studies reported no such events. Therefore, the proportion calculated using the DerSimonian and Laird weight for the random-effect model showed considerable discrepancies between crude and pooled rates. In fact, pooled and treatment-related mortalities calculated using the random-effects (DerSimonian and Laird) model were 0.30 % (0.24–0.37 %) and 0.17 % (0.12–0.22 %), respectively, which were considerably different from the crude rates of each outcome (data not shown). Thus, we adopted crude instead of pooled rates for mortality and SAE.

Our meta-regression analysis showed a significant association between increased SAEs and HCV genotype 1. It is plausible that patients with genotype 1, which is difficult to treat, received a higher dose and longer duration of treatment. This is consistent with the results of the subgroup analysis.

A significant positive association between the SAE rate and the proportion of Caucasian patients, and an inverse relationship between SAEs and the proportion of Asian patients were also observed. This result may suggest a role

of genetic diversity in the mechanisms underlying the adverse effects of PEG-IFN/RBV. Indeed, inosine triphosphate pyrophosphatase (*ITPA*) gene variants are associated with RBV-induced hemolytic anemia, and genetic polymorphisms near the interleukin-28B (*IL-28B*) gene were reported to be associated with response to HCV treatment with PEG-IFN and RBV, and the frequency of the variants differed between ethnic groups [19, 20].

We found that greater body weight was associated with a higher SAE rate. Of note, in the PEG-IFN alpha-2a-based regimen, the starting dose was fixed regardless of body weight; thus, with the PEG-IFN alpha-2a regimen, there might have been an overdose for patients of lower weight, leading to SAEs. However, whether such overdosing occurred was not clear in this study because there was a positive correlation between body weight and the SAE rate in patients receiving the PEG-IFN alpha-2a regimen. The reason for this positive relationship remains unclear; however, it may be because obesity is itself associated with various medical comorbidities.

We also found that an increased proportion of male patients in a study was associated with a higher SAE rate. It has been reported that female gender was an independent factor contributing to severe anemia [21], so the reason for the present finding of the increased proportion of male patients remains unclear; it may be correlated with increased body weight which caused a higher SAE rate. However, whether the proportions of individuals with obesity differed between male and female patients is not clear, because data on body mass index was often lacking.

In the present study increased mean age was not associated with a higher SAE rate, whereas discontinuation, dose reduction, and grade 3 adverse events were more frequent in older patients in previous studies [22, 23]. The lack of an association between mean age and the SAE rate in the present study could be due in part to the patients' mean age of 45.9 years, and the proportion of patients over 60 being small. Low-risk patients tend to be included in RCTs. This is one of the limitations of this study.

Recently, the use of HCV nonstructural 3/4A serine protease inhibitors combined with PEG-IFN and RBV were reported to achieve higher SVR rates in genotype 1 patients compared with conventional PEG-IFN/RBV. These triple therapies are considered to be the next standard of care for chronic hepatitis C [24, 25]. Adverse events during triple therapies could include those related to PEG-IFN/RBV, as these regimens include PEG-IFN/RBV.

We extracted only RCTs for our analysis in order to obtain highly reliable data and minimize the influence of recall bias because RCTs are prospectively designed, and SAEs should be defined a priori. However, several limitations are still worth noting. The latent limitation of this study is inter-study variability in the definition of SAE. The

precise meaning of ‘serious’ has not been determined, and some discrepancies between studies exist. These discrepancies may diminish the accuracy of the pooled SAE rate in this study. Second, even by choosing only RCTs, we could not completely exclude the influence of publication bias.

Overall, PEG-IFN/RBV treatment is relatively safe, with low mortality, considering the fact that chronic hepatitis C patients carry a high risk of cirrhosis and HCC. Nevertheless, the SAE rate with this treatment is not negligible and the development of safer regimens should be, and is, encouraged.

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