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Review Article

Efficacy and Tolerability of Peginterferon α-2a and Peginterferon α-2b, Both plus Ribavirin, for Chronic Hepatitis C: A Meta-Analysis of Randomized Controlled Trials

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Background. The efficacy and tolerability of peginterferon α-2a and peginterferon α-2b in chronic hepatitis C (CHC) patients remain controversial. *Methods*. PubMed, Ovid, and Cochrane libraries were electronically searched until August 30, 2012. Studies that met the inclusion criteria were systematically evaluated by two reviewers independently. *Results*. The overall sustained virologic response (SVR) rate of the peginterferon α-2a group was significantly higher than that of the peginterferon α-2b group (46.7% versus 42.4%, P value = 0.01). The same tendency was observed for naïve, genotype 1/4, and genotype 2/3 patients. The early virologic response (EVR) and end-of-treatment response (ETR) rates were significantly higher in the peginterferon α-2a group than in the peginterferon α-2b group (56.1% versus 49.8%, $P < 0.0001$; 67.9% versus 56.6%, $P < 0.00001$, resp.). Peginterferon α-2a had a significantly lower discontinuation rate than peginterferon α-2b (27.9% versus 33.9%, $P < 0.0001$) in naïve patients. In both naïve CHC and hepatitis C virus genotype 1 patients, peginterferon α-2a had a higher relapse rate than peginterferon α-2b. *Conclusions*. Peginterferon α-2a has superior efficacy with higher EVR, ETR, and SVR than peginterferon α-2b for CHC patients, both plus ribavirin. Peginterferon α-2a might obtain a similar or even lower discontinuation rate than peginterferon α-2b. However, peginterferon α-2a had a higher relapse rate than peginterferon α-2b.

1. Introduction

The World Health Organization has estimated that up to 170 million people (approximately 3% of the world population) worldwide might be infected with hepatitis C virus (HCV). This virus is responsible for approximately 350,000 deaths every year. HCV is cleared spontaneously in only approximately 20% of individuals. Chronic infection frequently progresses to cirrhosis, end-stage liver disease, hepatocellular carcinoma, and death [1–4].

Currently, in many countries, the recommended therapy for chronic hepatitis C (CHC) is still the combination of peginterferon α and ribavirin [1, 2]. Two licensed products of peginterferon α are available: peginterferon α-2a (Pegasys, Hoffmann-La Roche, Nutley, NJ, USA) and peginterferon α-2b (Peg-Intron, Schering Plough Corp., Kenilworth, NJ, USA). However, differences in structural modifications and dosing (weight-adjusted versus fixed) between the two peginterferons may lead to various clinical outcomes. In addition, a recommendation about the two regimens has not been proposed in the current guidelines [5–11]. Although recent studies have compared the response rates obtained using the two peginterferons in CHC, they have failed to reach a consensus as to which treatment options are the most effective.

Some systematic reviews [12–15], which include meeting abstracts or HCV/HIV coinfected patients, concluded that peginterferon α-2a has higher sustained virologic response (SVR) than peginterferon α-2b in CHC but revealed that

both have similar safety. The virologic responses and tolerability of peginterferon plus ribavirin in HCV/HIV coinfected patients are substantially different from those in chronic HCV monoinfected patient. In addition, some reported meeting abstracts were found to be inadequate. Thus, we performed a meta-analysis of randomized controlled trials (RCTs) with critical inclusion and exclusion criteria to evaluate the efficacy and tolerability of the two regimens.

2. Materials and Methods

2.1. Search Strategy. We searched PubMed, Ovid, and Cochrane libraries until August 30, 2012. The following medical subject headings were used: "Hepatitis C, Chronic," "interferons," "peginterferon alfa/alpha/α-2a," "peginterferon alfa/alpha/α-2b," and "ribavirin." Electronic searches were supplemented with manual searches of reference lists of all retrieved review articles, primary studies, and abstracts from meetings to identify other studies not found in the electronic searches. The literature was searched by two authors (Z. Yang and L. Zhuang) independently.

2.2. Study Selection. Two authors independently selected trials and discussed them with each other when inconsistencies were found. Articles that meet the following criteria were included: (1) study types, randomized controlled trials; (2) participants, chronic HCV virus monoinfection patients either naïve or retreatment were randomly divided into two groups; (3) interventions, peginterferon α-2a and peginterferon α-2b, both plus ribavirin; (4) outcome measures, studies that used one or more of the following measurements were eligible: rapid virologic response (RVR), early virologic response (EVR), end-of-treatment virologic response (ETR), SVR, relapse rate, and discontinuation rate; and (5) full texts available.

Studies with the following situations were excluded: (1) followup period less than 6 months and (2) studies that included patients with other liver diseases (e.g., HBV infection, human immunodeficiency virus infection, and hepatocellular carcinoma) aside from HCV.

2.3. Quality Assessment. The methodological qualities of the included RCTs were assessed according to Cochrane Collaboration's tool described in Handbook version 5.1.0 [16]. Two authors (Z. G. Yang and L. Yang) assessed the quality independently, and inconsistency was discussed with a third review author (X. R. Chen) who acted as an arbiter.

2.4. Data Extraction. Two researchers read the full texts independently and extracted the following contents: publication data (first author's name, year of publication, and country of population studied), study design, sample size, patient characteristics (age, gender, body weight, distribution of genotype, and liver histology), treatment protocol (peginterferon type and dose, ribavirin dose), outcome measures (RVR, EVR, ETR, SVR, relapse rate, and discontinuation rate), and reasons for discontinuing combination therapy. Authors were contacted by e-mail for additional information if data were unavailable.

2.5. Definitions. Chronic hepatitis C is defined by anti-HCV positive, HCV RNA positive as determined by a qualitative polymerase chain reaction (PCR) assay for more than 6 months. The primary outcome measure of efficacy of SVR was defined by a sensitive PCR assay as the absence of HCV RNA from serum at 24 weeks after completion of therapy. Secondary outcome measures of tolerability, including discontinuation rate, RVR, EVR, and ETR, were also determined. RVR was defined using a sensitive PCR assay as undetectable HCV RNA at 4 weeks after treatment. EVR was defined as ≥2 log reduction or complete absence of HCV RNA at 12 weeks after therapy compared with the baseline level. Undetectable virus at the end of either a 24-week or 48-week course of therapy was referred to as ETR. Virologic relapse refers to the reappearance of HCV RNA in serum after treatment was discontinued and ETR was documented.

2.6. Statistical Methods. Data were processed in accordance with the Cochrane Handbook [16]. Intervention effects were expressed with odds ratios (ORs) and associated 95% confidence intervals (CIs) for dichotomous data. By contrast, the effects were expressed with mean differences and 95% CIs for continuous data. Heterogeneity among studies was informally assessed by visual inspection of forest plots and formally estimated using χ^2 and I^2 tests (both $P > 0.05$; $I^2 < 50\%$ indicates no evidence of heterogeneity between the pooled studies) [17]. The fixed-effects model was first used for meta-analyses. The random-effects model was used in the presence of heterogeneity. Description analysis was performed when the quantitative data could not be pooled. Intention-to-treat (ITT) principle was used. Review Manage (v. 5.1; The Cochrane Collaboration) was used for data analysis.

3. Results

3.1. Study and Patient Characteristics. A total of 1166 abstracts of clinical trials were found and reviewed. Of these 1166 abstracts, 45 were retrieved, 6 [18–23] were excluded because they were published as abstract proceedings, 1 [24] was excluded because patients received monotherapy of peginterferon α-2a/2b at the first 4 weeks, 1 [25] was excluded because it was not designed randomly, 1 [26] was excluded because patients received 1.0 μg/kg peginterferon α-2b, 1 [27] was excluded because it included patients with HCV/HIV coinfection, and 1 [28] was excluded because duplicate data from the same medical center were published. Finally, 7 trials [5–11] met our inclusion criteria (Table 1).

Totally 1845 and 1823 patients were randomly treated with peginterferon α-2a and peginterferon α-2b, respectively, both plus ribavirin. The baseline characteristics of each study included in this meta-analysis are described in Table 2.

3.2. Methodological Quality Assessment. All studies included in this meta-analysis were described as randomized. Three

Table 1: Baseline characteristics of the included trials in this meta-analysis.

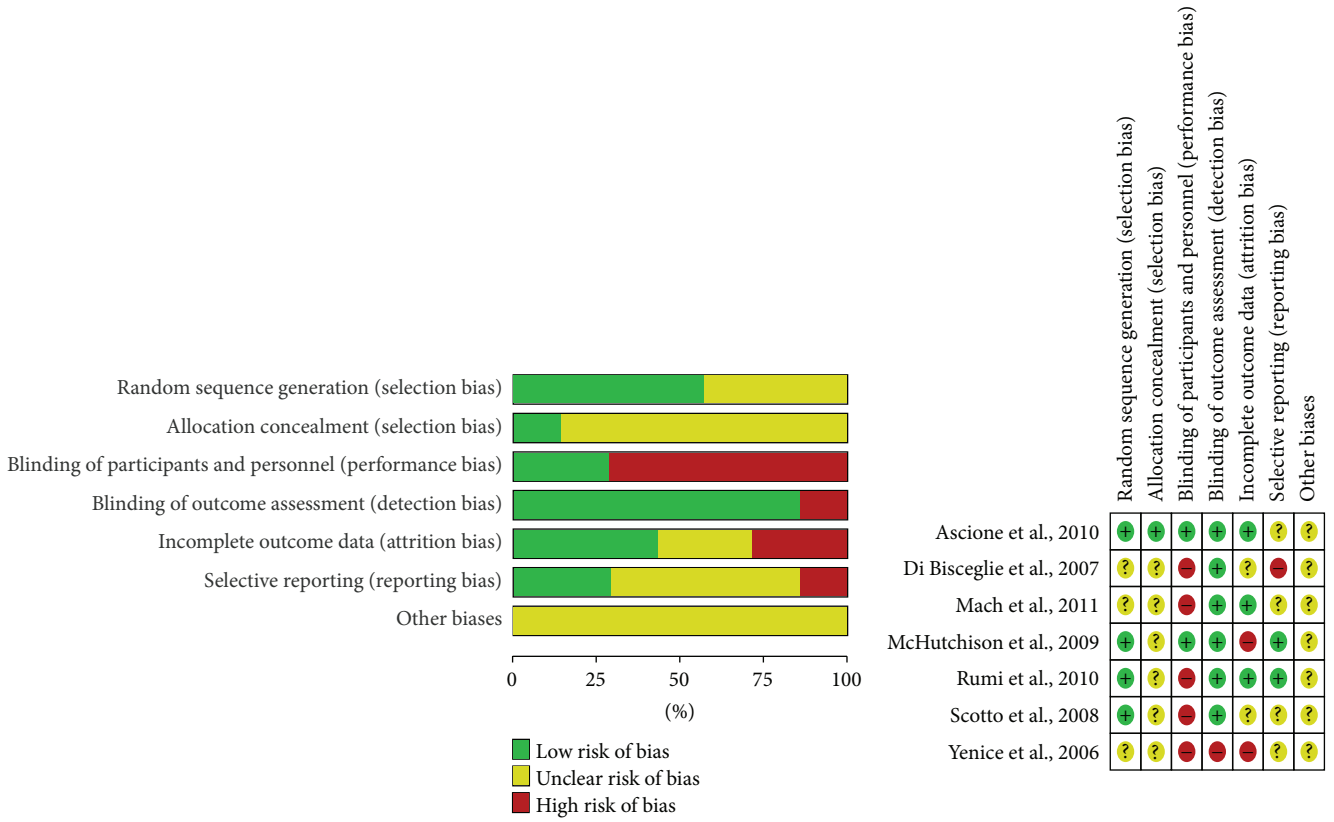
Study	Peginterferon	Ribavirin	Baseline treatment history	HCV genotype	Treatment in weeks	Country	Publication year	Study type
Yenice et al. [5]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	800–1200 mg/day	Naïve	1	24 or 48	Turkey	2006	RCT
Di Bisceglie et al. [6]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	1000–1200 mg/day	Naïve	1	12	USA	2007	RCT
Scotto et al. [7]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	15 mg/kg/day	Nonresponders	1,2,3,4	48	Italy	2008	RCT
McHutchison et al. [8]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	800–1400 mg/day	Naïve	1	24 or 48	IDEAL study team	2009	RCT
Rumi et al. [9]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	800–1200 mg/day	Naïve	1,2,3,4	24 or 48	Italy	2010	RCT
Ascione et al. [10]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	1000–1200 mg/day	Naïve	1,2,3,4	24 or 48	Italy	2010	RCT
Mach et al. [11]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	1000–1200 mg/day	Naïve	1b	48	Poland	2011	RCT

Table 2: Baseline characteristics in the two groups of peginterferon α-2a and peginterferon α-2b in this meta-analysis.

Study	Peginterferon group	Total patients	Mean age (years)	Gender (male/female)	HCV genotype (1/2/3/4)	F3-4 OR cirrhosis, N (%)	Body weight (kg)	BMI (kg/m^2)
Yenice et al. [5]	α-2a	37	49.95	13/24	37/0/0/0	NA	NA	NA
	α-2b	37	50.84	10/27	37/0/0/0	NA	NA	NA
Di Bisceglie et al. [6]	α-2a	189	46.9 ± 0.52	121/68	189/0/0/0	28 (14.8)	86.5 ± 1.34	29.2 ± 0.44
	α-2b	191	48.4 ± 0.56	136/55	191/0/0/0	29 (15.2)	85.4 ± 1.32	28.5 ± 0.42
Scotto et al. [7]	α-2a	71	45.86 ± 9.33	42/29	45/6/8/12	13 (18.3)	80.7	18.5–24.9 (n = 32), 25–29.9 (n = 34), ≥30 (n = 5)
	α-2b	72	47.82 ± 9.61	40/32	47/5/9/11	13 (18.1)	78.9	18.5–24.9 (n = 35), 25–29.9 (n = 30), ≥30 (n = 7)
McHutchison et al. [8]	α-2a	1035	47.6 ± 8.2	613/422	1035/0/0/0	110 (10.6)	82.8 ± 16.6	NA
	α-2b	1019	47.5 ± 7.8	613/406	1019/0/0/0	111 (10.9)	84.0 ± 16.5	NA
Rumi et al. [9]	α-2a	212	51.6 ± 12.0	128/84	91/69/34/18	43 (20.3)†	72.2 ± 14.6	25.5 ± 4.4
	α-2b	219	52.8 ± 12.0	120/99	87/74/32/26	39 (17.8)†	68.9 ± 12.0	24.8 ± 3.7
Ascione et al. [10]	α-2a	160	51.3 ± 10.3	81/79	89/49/18/4	33 (20.6)	70.4 ± 10.6	25.5 ± 3.1
	α-2b	160	48.9 ± 11.3	94/66	92/50/17/1	26 (16.3)	69.9 ± 10.7	25.3 ± 3.0
Mach et al. [11]	α-2a	138	45.2 ± 10.5	80/58	138/0/0/0	13 (9.4)	NA	24.5 ± 0.9
	α-2b	122	44.2 ± 13.6	73/49	122/0/0/0	12 (9.8)	NA	25.1 ± 1.3

NA: not available; BMI: Body mass index; †Ishak score S5, 6.
F0–4 (F0: no fibrosis; F1: portal fibrosis without septa; F2: portal fibrosis with few septa; F3: numerous septa without cirrhosis; F4: cirrhosis).
All baseline characteristics were comparative between the two groups.

studies [5, 6, 11] did not report the method of randomization, but randomization was adequate in other studies [7–10]. Among these studies, two were randomized by a computer-generated randomization list [9, 10], one was randomized by an interactive voice system [8], and the study by Scotto et al. was randomized by a table of random numbers [7]. One study revealed that the randomization list was not available to the treating physicians. Double blinding was described in one trial by McHutchison et al. [8]. And, Ascione et al. [10] designed a study where the physician received the report on the allocation of each patient from an independent researcher who knew nothing about the patient except for the genotype. The statistical analyses in one study by Yenice et al. [5] were not based on ITT, and more than 20% of the participants in the study by McHutchison et al. were lost to followup, both of which were considered as high risk in the item of



(a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

(b) Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Figure 1: Risk of bias assessment.

incomplete outcome data. No descriptions of lost to followup were found in the two studies by Di Bisceglie et al. [6] and Scotto et al. [7], thus accounting for the ambiguity in the item of incomplete outcome. No patient was lost to followup in the study by Ascione et al., and the other studies described the lost to followup participants, which were balanced between the two groups and considered low risk. Selective reporting was found in the study by Di Bisceglie et al. because it failed to include the expected results (e.g., SVR rate) for such a study. The other potential biases were unclear in these trials (Figure 1).

3.3. Virologic Responses. The overall SVR rates for CHC patients treated with peginterferon α-2a plus ribavirin and CHC patients treated with peginterferon α-2b plus ribavirin were 46.7% (773/1656), and 42.4% (692/1632), respectively (OR = 1.20, 95% CI = 1.04–1.38, and $P = 0.01$; Figure 2(a)). For naïve patients with no interferon experience, subgroup analysis found that the SVR rate was significantly higher in the peginterferon α-2a group than in the peginterferon α-2b group (47.9% versus 43.5%, OR = 1.20, 95% CI = 1.04–1.39, $P = 0.01$, Figure 2(b)). For genotype 1/4 patients, peginterferon α-2a could obtain a higher SVR than peginterferon α-2b (42.2% versus 38.3%, OR = 1.17, 95% CI = 1.01–1.36, $P = 0.03$, Figure 2(c)). For CHC patients with genotype 2/3, peginterferon α-2a might achieve a higher SVR rate than peginterferon α-2b (82.6% versus 74.3%, OR = 1.71, 95% CI = 1.01–2.89, and $P = 0.04$; Figure 2(d)).

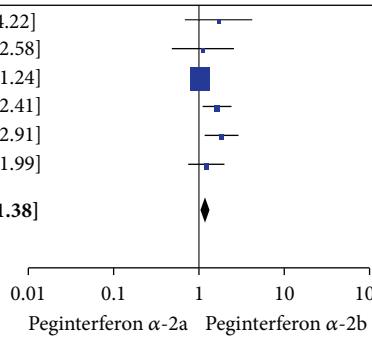
Only three studies [6, 8, 9] reported the RVR rate in patients who received peginterferons plus ribavirin. No difference in RVR rate was found between the two regimens (23.2% versus 23.4%, OR = 1.01, 95% CI = 0.83–1.23, and $P = 0.91$; Figure 3(a)). However, patients treated with peginterferon α-2a could achieve significantly higher EVR rates than those treated with peginterferon α-2b (56.1% versus 49.8%, OR = 1.32, 95% CI = 1.15–1.52, and $P < 0.0001$; Figure 3(b)). Meta-analysis of RCTs [5, 7–11] by a fixed-effects model ($P = 0.17$, $I^2 = 36\%$) revealed that, compared with peginterferon α-2b, peginterferon α-2a increased the ETR rate significantly in patients with chronic hepatitis C (67.9% versus 56.6%, OR = 1.66, 95% CI = 1.43–1.92, and $P < 0.00001$; Figure 3(c)).

3.4. Discontinuation Rate and Dose Modification. All the patients that did not complete the treatment duration were considered as discontinuing therapy, either for adverse events or nonsafety reasons. Of the studies included in this meta-analysis, two [6, 7] reported the number of patients who withdrew from therapy for nonsafety reasons, whereas one

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	18	40	13	40	2%	1.7 [0.68, 4.22]
Scotto et al., 2008	14	71	13	72	2.9%	1.11 [0.48, 2.58]
McHutchison et al., 2009	423	1035	406	1019	68.1%	1.04 [0.87, 1.24]
Rumi et al., 2010	140	212	119	219	11.2%	1.63 [1.11, 2.41]
Ascione et al., 2010	110	160	87	160	7.6%	1.85 [1.17, 2.91]
Mach et al., 2011	68	138	54	122	8.2%	1.22 [0.75, 1.99]
Total (95% CI)		**1656**		**1632**	**100%**	**1.2 [1.04, 1.38]**
Total events	773		692			

Heterogeneity: $\chi^2 = 8.84$, df = 5 ($P = 0.12$); $I^2 = 43\%$

Test for overall effect: $Z = 2.56$ ($P = 0.01$)

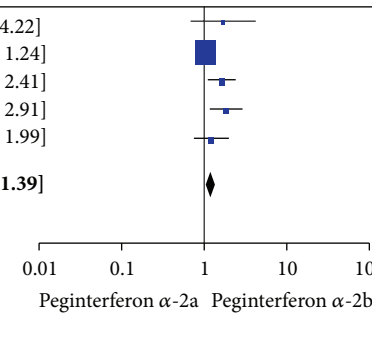


(a) The overall SVR rate of CHC patients treated with the two types of peginterferons

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	18	40	13	40	2.1%	1.7 [0.68, 4.22]
McHutchison et al., 2009	423	1035	406	1019	70.1%	1.04 [0.87, 1.24]
Rumi et al., 2010	140	212	119	219	11.5%	1.63 [1.11, 2.41]
Ascione et al., 2010	110	160	87	160	7.9%	1.85 [1.17, 2.91]
Mach et al., 2011	68	138	54	122	8.4%	1.22 [0.75, 1.99]
Total (95% CI)		**1585**		**1560**	**100%**	**1.2 [1.04, 1.39]**
Total events	759		679			

Heterogeneity: $\chi^2 = 8.81$, df = 4 ($P = 0.07$); $I^2 = 55\%$

Test for overall effect: $Z = 2.55$ ($P = 0.01$)

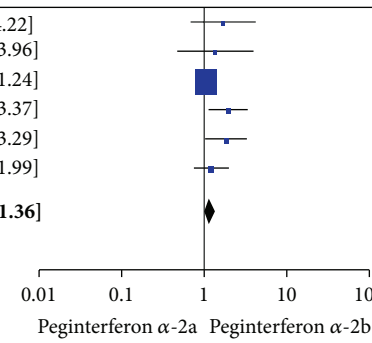


(b) The SVR rate of naïve CHC patients

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	18	40	13	40	2.2%	1.7 [0.68, 4.22]
Scotto et al., 2008	9	57	7	58	1.8%	1.37 [0.47, 3.96]
McHutchison et al., 2009	423	1035	406	1019	75.8%	1.04 [0.87, 1.24]
Rumi et al., 2010	52	109	36	113	5.8%	1.95 [1.13, 3.37]
Ascione et al., 2010	51	93	37	93	5.2%	1.84 [1.03, 3.29]
Mach et al., 2011	68	138	54	122	9.1%	1.22 [0.75, 1.99]
Total (95% CI)		**1472**		**1445**	**100%**	**1.17 [1.01, 1.36]**
Total events	621		553			

Heterogeneity: $\chi^2 = 8.06$, df = 5 ($P = 0.15$); $I^2 = 38\%$

Test for overall effect: $Z = 2.12$ ($P = 0.03$)

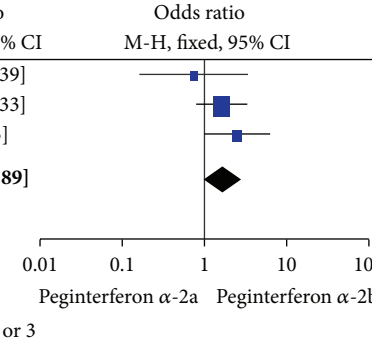


(c) The SVR rate of CHC patients with HCV genotype 1 or 4

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Scotto et al., 2008	5	14	6	14	17.7%	0.74 [0.16, 3.39]
Rumi et al., 2010	88	103	83	106	54.8%	1.63 [0.79, 3.33]
Ascione et al., 2010	59	67	50	67	27.5%	2.51 [1, 6.3]
Total (95% CI)		**184**		**187**	**100%**	**1.71 [1.01, 2.89]**
Total events	152		139			

Heterogeneity: $\chi^2 = 1.84$, df = 2 ($P = 0.4$); $I^2 = 0\%$

Test for overall effect: $Z = 2.01$ ($P = 0.04$)

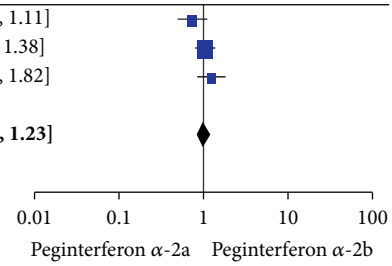


(d) The SVR rate of CHC patients with HCV genotype 2 or 3

Figure 2: SVR rates of chronic hepatitis C patients who received the two regimens of peginterferon α-2a and peginterferon α-2b, both plus ribavirin.

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Di Bisceglie et al., 2007	79	189	94	191	26.7%	0.74 [0.49, 1.11]
McHutchison et al., 2009	123	1035	116	1019	50.5%	1.05 [0.8, 1.38]
Rumi et al., 2010	132	212	125	219	22.8%	1.24 [0.84, 1.82]
Total (95% CI)		**1436**		**1429**	**100%**	**1.01 [0.83, 1.23]**
Total events	334		335			

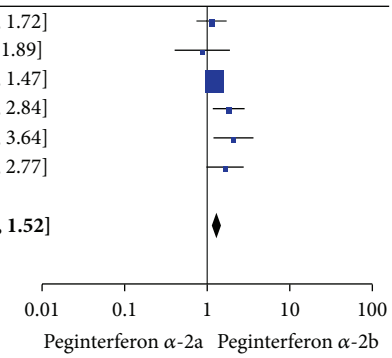
Heterogeneity: $\chi^2 = 3.42$, df = 2 ($P = 0.18$); $I^2 = 41\%$
Test for overall effect: $Z = 0.11$ ($P = 0.91$)



(a) RVR rate comparison

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Di Bisceglie et al., 2007	125	189	121	191	11.7%	1.13 [0.74, 1.72]
Scotto et al., 2008	16	71	18	72	4%	0.87 [0.4, 1.89]
McHutchison et al., 2009	466	1035	407	1019	64.6%	1.23 [1.03, 1.47]
Rumi et al., 2010	170	212	151	219	8.4%	1.82 [1.17, 2.84]
Ascione et al., 2010	136	160	117	160	5%	2.08 [1.19, 3.64]
Mach et al., 2011	99	138	74	122	6.4%	1.65 [0.98, 2.77]
Total (95% CI)		**1805**		**1783**	**100%**	**1.32 [1.15, 1.52]**
Total events	1012		888			

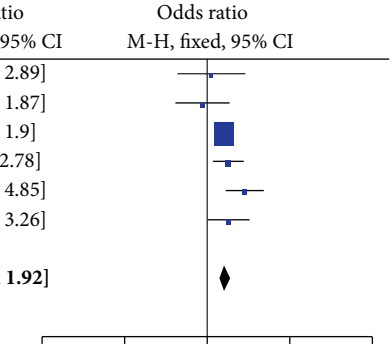
Heterogeneity: $\chi^2 = 7.54$, df = 5 ($P = 0.18$); $I^2 = 34\%$
Test for overall effect: $Z = 3.98$ ($P < 0.0001$)



(b) EVR rate comparison

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	28	40	27	40	2.9%	1.12 [0.44, 2.89]
Scotto et al., 2008	17	71	19	72	5.1%	0.88 [0.41, 1.87]
McHutchison et al., 2009	667	1035	542	1019	69%	1.6 [1.34, 1.9]
Rumi et al., 2010	166	212	146	219	11.1%	1.8 [1.17, 2.78]
Ascione et al., 2010	134	160	103	160	6%	2.85 [1.68, 4.85]
Mach et al., 2011	113	138	87	122	5.9%	1.82 [1.01, 3.26]
Total (95% CI)		**1656**		**1632**	**100%**	**1.66 [1.43, 1.92]**
Total events	1125		924			

Heterogeneity: $\chi^2 = 7.81$, df = 5 ($P = 0.17$); $I^2 = 36\%$
Test for overall effect: $Z = 6.78$ ($P < 0.00001$)



(c) ETR rate comparison

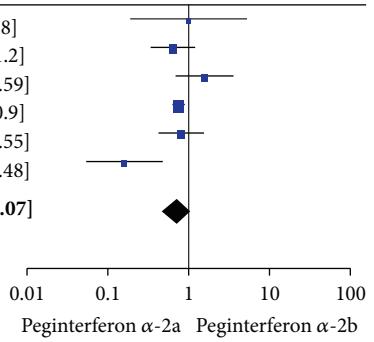
Figure 3: The RVR, EVR, and ETR rates of CHC patients treated with the two regimens.

[11] did not provide the exact discontinuation number of patients. Meta-analysis of RCTs [5–10] by a random-effects model ($P = 0.05$, $I^2 = 55\%$) revealed that peginterferon α-2a and peginterferon α-2b had a similar discontinuation rate for CHC patients, including naïve and retreatment ones with any HCV genotype ($P = 0.11$, Figure 4(a)). By contrast, meta-analysis of RCTs [5, 6, 8–10] by a fixed-effects model ($P = 0.09$, $I^2 = 50\%$) revealed that peginterferon α-2a had a significantly lower discontinuation rate than peginterferon α-2b for naïve CHC patients (27.9% versus 33.9%, OR = 0.71, 95% CI = 0.61–0.84, and $P < 0.0001$; Figure 4(b)).

No adequate data of peginterferon α or ribavirin dose reduction were reported in the studies by Yenice et al. [5], Di Bisceglie et al. [6], Ascione et al. [10], and Mach et al. [11]. However, the same dose reduction was applied for both arms in two studies [6, 10]. For the modification of peginterferon dose, meta-analysis of RCTs [7–9] by a fixed-effects model ($P = 0.26$, $I^2 = 25\%$) indicated no difference in the two types of peginterferons (22.2% versus 20.7%, OR = 1.09, 95% CI = 0.90–1.31, and $P = 0.40$; Figure 4(c)). For the reduction of ribavirin dose, meta-analysis of RCTs [5, 7–9] by a fixed-effects model ($P = 0.76$, $I^2 = 0\%$) revealed no statistical

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, random, 95% CI
Yenice et al., 2006	3	40	3	40	5.1%	1 [0.19, 5.28]
Di Bisceglie et al., 2007	18	189	27	191	19%	0.64 [0.34, 1.2]
Scotto et al., 2008	17	71	12	72	14.3%	1.57 [0.69, 3.59]
McHutchison et al., 2009	414	1035	479	1019	33.1%	0.75 [0.63, 0.9]
Ascione et al., 2010	18	212	23	224	18.6%	0.81 [0.42, 1.55]
Rumi et al., 2010	4	160	22	160	9.9%	0.16 [0.05, 0.48]
Total (95% CI)		**1707**		**1706**	**100%**	**0.72 [0.48, 1.07]**
Total events	474		566			

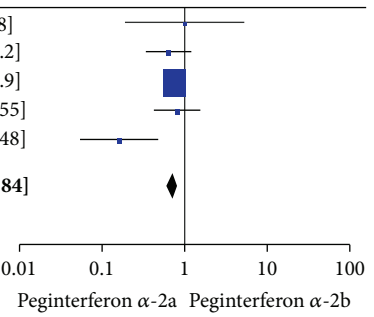
Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 11.21$, df = 5 ($P = 0.05$); $I^2 = 55\%$
Test for overall effect: $Z = 1.62$ ($P = 0.11$)



(a) The overall discontinuation rate

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	3	40	3	40	0.8%	1 [0.19, 5.28]
Di Bisceglie et al., 2007	18	189	27	191	6.8%	0.64 [0.34, 1.2]
McHutchison et al., 2009	414	1035	479	1019	80.8%	0.75 [0.63, 0.9]
Rumi et al., 2010	18	212	23	224	5.7%	0.81 [0.42, 1.55]
Ascione et al., 2010	4	160	22	160	6%	0.16 [0.05, 0.48]
Total (95% CI)		**1636**		**1634**	**100%**	**0.71 [0.61, 0.84]**
Total events	457		554			

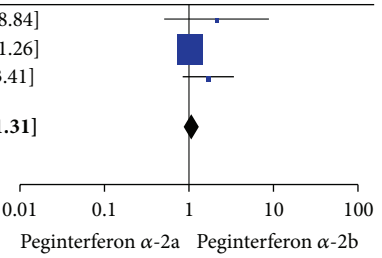
Heterogeneity: $\chi^2 = 7.94$, df = 4 ($P = 0.09$); $I^2 = 50\%$
Test for overall effect: $Z = 4.14$ ($P < 0.0001$)



(b) The discontinuation rate of naïve CHC patients treated with the two types of peginterferons

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Scotto et al., 2008	6	71	3	72	1.3%	2.12 [0.51, 8.84]
McHutchison et al., 2009	264	1035	254	1019	92.7%	1.03 [0.85, 1.26]
Rumi et al., 2010	22	212	14	219	6%	1.7 [0.84, 3.41]
Total (95% CI)		**1318**		**1310**	**100%**	**1.09 [0.9, 1.31]**
Total events	292		271			

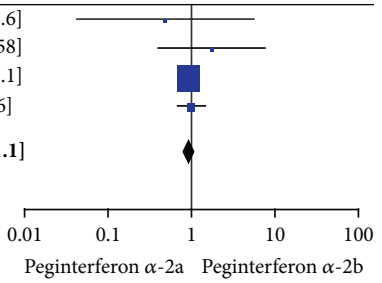
Heterogeneity: $\chi^2 = 2.67$, df = 2 ($P = 0.26$); $I^2 = 25\%$
Test for overall effect: $Z = 0.85$ ($P = 0.4$)



(c) Peginterferon dose modification of CHC patients treated with the two types of peginterferons

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	1	40	2	40	0.7%	0.49 [0.04, 5.6]
Scotto et al., 2008	5	71	3	72	0.9%	1.74 [0.4, 7.58]
McHutchison et al., 2009	322	1035	338	1019	80.2%	0.91 [0.76, 1.1]
Rumi et al., 2010	119	212	123	219	18.1%	1[0.68, 1.46]
Total (95% CI)		**1358**		**1350**	**100%**	**0.93 [0.79, 1.1]**
Total events	447		466			

Heterogeneity: $\chi^2 = 1.16$, df = 3 ($P = 0.76$); $I^2 = 0\%$
Test for overall effect: $Z = 0.85$ ($P = 0.4$)

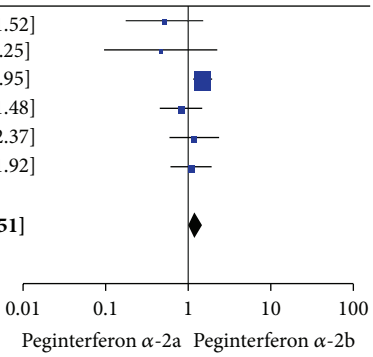


(d) Ribavirin dose modification of CHC patients treated with the two types of peginterferons

Figure 4: The discontinuation rates and drugs modification of CHC patients who received the two regimens.

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	10	28	14	27	5.5%	0.52 [0.18, 1.52]
Scotto et al., 2008	3	17	6	19	2.8%	0.46 [0.1, 2.25]
McHutchison et al., 2009	193	612	123	523	54.7%	1.5 [1.15, 1.95]
Rumi et al., 2010	26	166	27	146	14.6%	0.82 [0.45, 1.48]
Ascione et al., 2010	24	134	16	103	8.9%	1.19 [0.59, 2.37]
Mach et al., 2011	45	113	33	87	13.5%	1.08 [0.61, 1.92]
Total (95% CI)		**1070**		**905**	**100%**	**1.23 [1, 1.51]**
Total events	301		219			

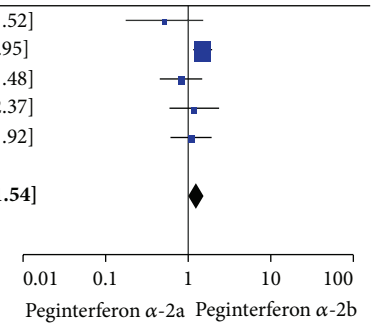
Heterogeneity: $\chi^2 = 8.1$, df = 5 ($P = 0.15$); $I^2 = 38\%$
Test for overall effect: $Z = 2$ ($P = 0.05$)



(a) The overall relapse comparison

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	10	28	14	27	5.7%	0.52 [0.18, 1.52]
McHutchison et al., 2009	193	612	123	523	56.2%	1.5 [1.15, 1.95]
Rumi et al., 2010	26	166	27	146	15%	0.82 [0.45, 1.48]
Ascione et al., 2010	24	134	16	103	9.2%	1.19 [0.59, 2.37]
Mach et al., 2011	45	113	33	87	13.9%	1.08 [0.61, 1.92]
Total (95% CI)		**1053**		**886**	**100%**	**1.25 [1.02, 1.54]**
Total events	298		213			

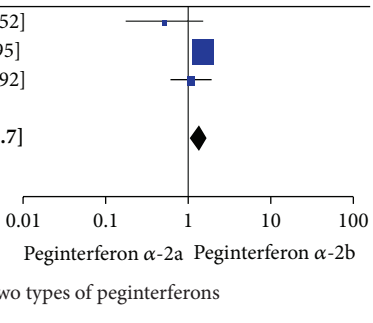
Heterogeneity: $\chi^2 = 6.61$, df = 4 ($P = 0.16$); $I^2 = 39\%$
Test for overall effect: $Z = 2.15$ ($P = 0.03$)



(b) The relapse rate of naïve CHC patients treated with the two types of peginterferons

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	10	28	14	27	7.5%	0.52 [0.18, 1.52]
McHutchison et al., 2009	193	612	123	523	74.2%	1.5 [1.15, 1.95]
Mach et al., 2011	45	113	33	87	18.3%	1.08 [0.61, 1.92]
Total (95% CI)		**753**		**637**	**100%**	**1.35 [1.07, 1.7]**
Total events	248		170			

Heterogeneity: $\chi^2 = 4.21$, df = 2 ($P = 0.12$); $I^2 = 52\%$
Test for overall effect: $Z = 2.51$ ($P = 0.01$)



(c) The relapse rate of CHC patients with HCV genotype 1 or 4 treated with the two types of peginterferons

Figure 5: The relapse rate of CHC patients who received the two regimens.

difference between the two groups (32.9% versus 34.5%, OR = 0.93, 95% CI = 0.79–1.10, and $P = 0.40$; Figure 4(d)).

3.5. Relapse Rate. No difference in relapse rate for CHC patients treated with the two regimens was noted in the meta-analysis of RCTs [5, 7–11] by a fixed-effects model (28.1% versus 24.2%, OR = 1.23, 95% CI = 1.00–1.51, and $P = 0.05$; Figure 5(a)). However, subgroup analysis showed that, for naïve CHC patients, peginterferon α-2a obtained a higher relapse rate than peginterferon α-2b (28.3% versus 24.0%, OR = 1.25, 95% CI = 1.02–1.54, and $P = 0.03$; Figure 5(b)). For HCV genotype 1 patients, peginterferon α-2a had a higher relapse rate than peginterferon α-2b (32.9% versus 26.7%, OR = 1.35, 95% CI = 1.07–1.70, and $P = 0.01$; Figure 5(c)).

4. Discussion

Most previous meta-analyses concluded that peginterferon α-2a has higher SVR rate than peginterferon α-2b in CHC patients, but no difference in the safety profile was noted [12–15]. However, a recent meta-analysis has revealed that these two types of peginterferons have similar effects on RVR, SVR, and tolerability [29]. Moreover, the above analyses included either meeting abstracts or coinfected patients of HIV/HCV,

which may have an impact on the conclusions. In the present meta-analysis, we included more RCTs and restricted our trial analyses to full papers. We excluded abstracts because they did not contain adequate details of patients and outcomes.

Interferon-based therapy could lower the risk of cirrhosis and hepatocellular carcinoma and improve the survival of CHC patients who have an SVR with a large possibility through eradicating HCV and cutting liver fibrosis procession. Our analysis showed that peginterferon α-2a might achieve a higher SVR rate than peginterferon α-2b, including nonresponders. Subgroup analysis revealed that peginterferon α-2a was also more effective than peginterferon α-2b for HCV genotype 1 or 4 patients or treatment-naïve patients. However, these two types of peginterferons had similar SVR effects on HCV genotype 2 or 3 patients. These analyses indicated a difference in antiviral activity between the two therapeutic regimens. A previous study [30] proved that combination therapy with peginterferon α-2a is an independent pretreatment predictor of SVR (OR = 1.88, 95% CI = 1.20–2.96). Peginterferon α-2a achieves higher SVR rates than peginterferon α-2b in patients infected with HCV-1 and HCV-2; however, the two therapeutic regimens obtain similar SVR rates in patients infected with HCV-3 and HCV-4 [9]. Our results indicated that patients with genotype 2 or 3 had similar SVR rates in both groups. Given that the patients included in this meta-analysis mostly had HCV genotype 1 or 4, only less than 200 patients in each group were infected with HCV genotype 2 or 3; high-quality trials with a large sample size are needed to estimate the efficacy of the two regimens for genotype 2 or 3 CHC patients, especially for the comparison of the therapeutic efficacy in each genotype stratum.

Further analysis showed that no significant difference in RVR rate was found in the patients treated with the two peginterferon-α-based regimens. However, peginterferon α-2a could achieve higher EVR and ETR rates in CHC patients than peginterferon α-2b. Early eradication of HCV is important to the therapeutic resolution of CHC, and RVR remains the most notable on-treatment response predictor of SVR. Moreover, the present guidelines concluded that the absence of EVR is the most robust means of identifying nonresponders. Approximately 97%–100% of the treatment-naïve patients with HCV genotype 1 infection who did not reach EVR failed to elicit SVR. Thus, patients without EVR can discontinue therapy early without compromising their chance to elicit SVR [1, 2]. This finding might be associated with the potentially higher SVR rate of patients treated with peginterferon α-2a. ETR does not accurately predict the occurrence of SVR; however, ETR is necessary for SVR to take place [1, 2, 31].

Our meta-analysis of RCTs [5–10] suggests that the two peginterferons may be comparable with regard to any reasons leading to treatment discontinuation, including naïve and retreatment patients with any HCV genotype. However, for naïve CHC patients, peginterferon α-2a had a significantly lower discontinuation rate than peginterferon α-2b. Previous meta-analyses [12–15] concluded that peginterferon α-2a has a similar safety profile as peginterferon α-2b. Given that our results were based on ITT analysis, all patients who withdrew therapy were considered as treatment discontinuation, either for adverse events or nonsafety reasons. The reason above may explain why our analysis of discontinuation rate in naïve CHC patients conflicted with those of the previous studies.

Although peginterferon α-2a should achieve higher virologic responses and gain lower discontinuation rate, peginterferon α-2a had a higher relapse rate than peginterferon α-2b. The high relapse rate with peginterferon α-2a was a novelty, as in previous studies. Relapse rates ranged from 17% to 25% for peginterferon α-2a in patients with HCV genotype 1 [32, 33], which is significantly lower than the 31.5% reported in the IDEAL study [8]. These findings were not supported by two randomized studies that reported no difference in relapse rate between the two regimens [9, 10]. Many factors might have contributed to the difference in the findings above. Some of these factors include differences in epidemiological and genetic characteristics, mean body weight, distribution of genotype CC in the IL28B polymorphism, and ribavirin dose reduction schemes applied to the two regimens [34]. Maintaining a high ribavirin dose (≥12 mg/kg/day) during the full treatment period can lead to suppression of relapse in HCV-1 patients responding to peginterferon α-2b plus ribavirin. Ribavirin dosing seems to be instrumental in preventing posttreatment relapse [35], and ribavirin concentration in the later stages of treatment is an important marker for discriminating relapse [34, 36]. In the present meta-analysis, no significant difference in peginterferon and/or ribavirin dose reduction was found between the two groups. However, in the IDEAL study by McHutchison et al. [8], the dose reduction for the peginterferon α-2b arm occurred in two steps. The first step was a reduction of either 200 mg (in patients receiving 800 mg/day–1,200 mg/day of ribavirin) or 400 mg (in patients receiving 1,400 mg/day). The second step was reduction by another 200 mg, if required for resolution of the adverse event. For the peginterferon α-2a arm, the dose was reduced to 600 mg/day. The abrupt reduction of ribavirin dose to 600 mg/day might have played a crucial role in the high relapse rates observed in patients receiving the peginterferon α-2a regimen [8–10, 34].

Therefore, the peginterferon α-2a regimen holds a slight advantage in terms of virologic responses and discontinuation rates compared with the peginterferon α-2b regimen. This advantage may be considered as a direct consequence of the better pharmacokinetic profile of peginterferon α-2a than peginterferon α-2b. The pharmacodynamic properties of peginterferon α-2a allow slower absorption and elimination than peginterferon α-2b. Therefore, maximum concentrations occur later with peginterferon α-2a than with peginterferon α-2b. Peginterferon α-2b is associated with fluctuating blood levels and rapid rise and fall in the blood level because of the relatively rapid release of interferon α-2b molecule [37–39]. Previous studies [38, 40] showed that the concentration of peginterferon α-2b did not remain stable over the week as a whole. At the end of the week, serum interferon could not be detected in most patients treated with peginterferon α-2b. When interferon was no longer detectable in the serum, the viral load increased until the next interferon injection. This phenomenon increases the potential for more side effects and reduces the efficacy of the

drug. Peginterferon α-2b is distributed widely in the body fluids and tissues [14, 39]. By contrast, peginterferon α-2a is distributed predominantly to the blood and interstitial fluid, resulting in high drug concentrations in the liver. The reduced clearance of peginterferon α-2a, as a consequence of metabolism via nonspecific proteases, provides significant, consistent, and measurable therapeutic plasma levels even at the end of the weekly dosing period [41]. These differences between the two types of peginterferons should lead to better compliance and superior safety of peginterferon α-2a [14].

In conclusion, current evidence suggests that peginterferon α-2a has superior efficacy with higher EVR, ETR, and SVR than peginterferon α-2b for CHC patients, both plus ribavirin. Peginterferon α-2a might obtain similar or even lower discontinuation rate than peginterferon α-2b. However, peginterferon α-2a had a higher relapse rate than peginterferon α-2b. Further trials must focus on the comparison of the two types of peginterferons in terms of achieving SVR and clinically relevant outcomes, such as liver-related cirrhosis, hepatocellular carcinoma, mortality, and morbidity.

Abbreviations

CHC: Chronic hepatitis C
HCV: Hepatitis C virus
RVR: Rapid virologic response
EVR: Early virologic response
ETR: End-of-treatment virologic response
SVR: Sustained virologic response
CI: Confidence interval.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

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