

A meta-analysis that compares the use of either peginterferon- α 2a or peginterferon- α 2b plus ribavirin for HCV infection

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Background: Two kinds of peginterferons, peginterferon- α 2a (PEG-IFN- α 2a) and peginterferon- α 2b (PEG-IFN- α 2b), are used in the treatment of chronic hepatitis C virus (HCV) infection. However, it is unclear which is better in terms of virological responses and patient compliance. We conducted a meta-analysis to assess which peginterferon was better when used with ribavirin.

Methods: Relevant clinical trials were identified through the PubMed and EMBASE databases. Primary outcomes included early virological response (EVR), end of treatment response (ETR) and sustained virological response (SVR). Secondary outcomes included biochemical and histological responses and the discontinuation of treatment after adverse events. Meta-analysis was performed using fixed-effect or random-effect methods, depending on absence or presence of significant heterogeneity. Analyses were performed with Review Manager Version 4.2.2.

Results: Seven clinical trials were included that involved 3,526 patients in total; six were randomized clinical trials (RCTs) and one was nonrandomized. PEG-IFN- α 2a plus ribavirin was better than PEG-IFN- α 2b plus ribavirin with regards to ETR (relative risk [RR] = 1.21, 95% confidence interval [CI]: 1.14–1.28). This advantage was less obvious for EVR (RR = 1.12, 95% CI: 1.06–1.19) and SVR (RR = 1.10, 95% CI: 1.02–1.18). Patients who received PEG-IFN- α 2a were less likely to discontinue treatment for safety reasons (RR = 0.85, 95% CI: 0.52–1.38).

Conclusion: We demonstrated that PEG-IFN- α 2a was a better choice than PEG-IFN- α 2b in terms of virological responses.

Keywords: peginterferon- α 2a (PEG-IFN- α 2a), peginterferon- α 2b (PEG-IFN- α 2b), ribavirin, chronic hepatitis C virus (HCV) infection, treatment

Introduction

Hepatitis C virus (HCV) is a ribonucleic acid (RNA) virus that causes a wide range of liver diseases, including hepatitis, cirrhosis and hepatocellular carcinoma (HCC). In chronic HCV infection, a sustained response to treatment can be achieved with interferon alpha (IFN- α) in between 10% and 20% of patients.¹ The addition of ribavirin to this treatment results in a more than a twofold increase in sustained response rates.² The treatment with IFN- α has been improved by replacing IFN- α with pegylated interferon α (PEG-IFN- α) whose half-life is much longer. Two forms of PEG-IFN are applied clinically: PEG-IFN- α 2a is a branched molecule with a molecular mass of 40 kDa,³ and PEG-IFN- α 2b is a linear molecule with a molecular mass of 12 kDa. Nowadays, the standardized treatment for patients with chronic hepatitis C is PEG-IFN- α administered weekly plus daily ribavirin therapy for 48 consecutive weeks in the case of genotype 1 HCV infection and 24 weeks for genotypes 2 and 3. The efficacy of

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anti-viral treatment can be determined by the different viral response rates at different time points. Such parameters include rapid response rate (RVR; a reduction in HCV RNA levels by at least 2 log₁₀ from the baseline at week four of therapy), early virological response rate (EVR; a reduction in HCV RNA levels by at least 2 log₁₀ from the baseline at week 12 of therapy), end of treatment response (ETR; viral negativity at the end of treatment), sustained virological response (SVR, undetectable serum HCV RNA by a sensitive molecular assay 24 weeks after the end of therapy).⁴ The most important parameter is the SVR, which is the goal of anti-viral treatment.³

Although both forms of IFN- α are effective in the treatment of HCV infection, the differences between the efficacies of PEG-IFN- α 2a and PEG-IFN- α 2b are unclear. Some researchers believe that PEG-IFN- α 2b induces a better virological response during the first eight weeks of treatment,⁵ but others draw different conclusions.³ The aim of the present study was to elucidate whether there are any differences between the use of PEG-IFN- α 2a plus ribavirin or PEG-IFN- α 2b plus ribavirin in terms of EVR, ETR and SVR.

Materials and methods

Literature search and data extraction

Two independent reviewers searched the electronic databases of PubMed and EMBASE. Our searching strategy used a combination of “PEG-IFN OR peginterferon AND ribavirin AND HCV” with the limitation of being “clinical trial or randomized clinical trial (RCT) or controlled clinical trial”. Searching results had to be in English or Chinese. We also identified articles through bibliographies in relevant articles. We identified all the relevant outcomes of our researching by reading titles, abstract and full text. We also contacted authors of any articles which presented relevant information but not published. Unpublished data was accepted when the authors were kind enough to provide them.

Data was gathered and the methodological quality of each study was assessed by the two reviewers independently. Any dissents between the reviewers were resolved by discussion. The assessment of the quality of the trial included an evaluation of the randomization and blinding procedures. The data gathered included the following: age, gender, sample size, titer of HCV RNA before treatment, the regimen of intervention, the duration of follow-up, EVR, ETR, SVR, numbers of adverse events, and HCV genotype.

Inclusion and exclusion criteria

Studies were included if they fulfilled these criteria:

1. All eligible references had to be controlled clinical or randomized controlled trials (RCT), which assessed and compared the effects of both regimens of PEG-IFN- α 2a plus ribavirin and PEG-IFN- α 2b plus ribavirin. Any articles that assessed only one treatment regimen were excluded. Detailed endpoints that related to patients had to be reported, irrespective of whether or not they had finished the course of treatment.
2. The diagnosis of chronic HCV infection had to be based on detectable levels of HCV RNA. The titers of HCV RNA had to be presented.
3. Baseline characteristics of patients had to include all aspects of information that related to the demographic features and the disease.
4. All subjects had to be treatment naïve at the commencement of the trial. If the cohort included patients who had undergone any treatment with IFN or ribavirin before enrollment into the trial, the data of treatment-naïve patients had to be able to be analyzed separately.
5. Patients enrolled had to be infected solely with HCV without any other co-existing hepatitis infection.
6. The full text of each reference had to be accessible.

Any reference with only the abstract published online was excluded. Any trials that did not exclude HCV-infected patients that were co-infected with HIV or any other hepatitis virus from their cohorts were also excluded from the systemic review.

Definition of main outcomes

Three primary outcome measures were identified. The first was the loss of detectable HCV RNA in serum for at least six months after the end of therapy as an assessment of SVR. The second was the decrease in the level of the viral titer by more than or equal to 2log₁₀ after 12 weeks of treatment which defined as EVR. Finally, undetectable serum HCV RNA at the end of treatment assessed the ETR. The secondary outcome measures included the biochemical response (normalization of transaminases), histological response (improvement of grading or staging scores of liver biopsies before treatment compared to after treatment), and the discontinuation of treatment due to a severe adverse event or events

Statistical analysis

We performed an intention-to-treat analysis that included all patients regardless of whether they completed the treatment course. We performed fixed-effects or random-effects

meta-analyses for all outcomes depending on what the heterogeneities were. The data of patients who lost to follow-up were also included by using the last observed response. The relative risks (RR) with 95% confidence intervals (CI) were calculated. Heterogeneity was explored with the use of χ^2 and I^2 tests. The statistical software used was Review Manager (Version 4.2.2 for Windows; The Cochrane Collaboration, Oxford, UK).

Results

Search results

We identified 310 references in PubMed and 171 references in EMBASE; of these, 469 were excluded according to the criteria described in Section 2.2 after the titles and abstracts were assessed. The full texts of the remaining 13 references were scrutinized. Five were excluded as they did not meet our inclusion criteria.⁵⁻⁹ Another one was excluded because of the incomparable dosage of PEG-IFN- α 2b applied.¹⁰ Seven studies were included^{3,11-16} (Figure 1). Six of these studies were randomly designed prospective head-to-head clinical trials (RCT). The remaining study was a nonrandomly designed head-to-head clinical trial.¹¹

Features of the trials

The number of participants included in our meta-analysis from all seven studies was 3,526 subjects. Of these, 1,773 patients were treated with PEG-IFN- α 2a plus ribavirin, while 1,753 patients received PEG-IFN- α 2b plus ribavirin. In the IDEAL trial (Individualized Dosing Efficacy vs flat dosing to Assess optimaL pegylated interferon therapy taken in USA, which was accepted by the FDA) 1,016 patients were treated with low-dose PEG-IFN- α 2b plus ribavirin.¹⁴ The

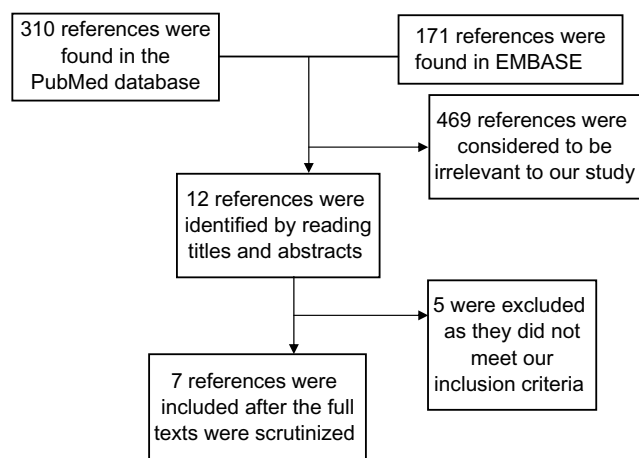


Figure 1 The quality of reporting of meta-analyses (QUOROM) chart for the meta-analysis.

data from these patients was not included in meta-analysis (Table 1). All of the patients in the included studies were treatment-naïve. Six trials presented their exclusion criteria clearly for enrollment¹¹ and the other trial communicated their exclusion criteria to the authors of this present study by email. Most of the studies assigned their subjects into two groups in a 1:1 ratio and applied standard treatment regimens of PEG-IFN- α 2a and PEG-IFN- α 2b, except for the IDEAL trial, which included a third treatment arm with a lower dose of PEG-IFN- α 2b plus ribavirin.¹⁴ However, the regimens of ribavirin were inconsistent among the trials (Table 1).

The EVR rate was between 45.0% and 66.1% in genotype 1 HCV patients. In the group with HCV infections other than genotype 1, the EVR rate was as high as 96.7%. The ETR was between 44% and 70.0% in the group of genotype 1 patients, while in the nongenotype 1 group, the ETR was between 91% and 96%. Between 32.5% and 50.8% patients infected with genotype 1 HCV achieved SVR at six months after treatment, while approximately 90% patients with nongenotype 1 HCV achieved SVR.

Among all the subjects enrolled the rate of male is between 27.0% and 70.0% (Table 2). There were 1,051 male patients in the PEG-IFN- α 2a plus ribavirin group while, there were 1,054 male ones in the other group. The age of the subjects ranged from 43.6 to 52.8 years (Table 2). Six references reported the levels of the viral load. In most cases, the viral load levels were similar between the treatment groups except for the report by Sporea et al in which the viral level of subjects in the PEG-IFN- α 2b plus ribavirin group was higher than that in the group treated with PEG-IFN- α 2a plus ribavirin. With regards to the follow-up period, two of the seven references followed their subjects for 12 weeks. They only reported the EVR. The other five studies followed patients up for 64 weeks (48 weeks treatment added with 24 more weeks follow-up to assess SVR) (Table 2). Three trials enrolled patients that were only infected with the HCV genotype 1. Another three trials reported the distribution of all genotypes. One report did not mention the specific genotypes of their subjects (Table 1).

The standard dose of PEG-IFN- α 2a was 180 μ g/week and 1.5 μ g/kg/week was used of PEG-IFN- α 2b; these dosages were used by all trials. The dose of ribavirin ranged from 800 to 1400 mg per day, according to the body weight of patients.

Methodological quality of the trials

Six of the seven enrolled trials were RCTs. Three trials reported the details of the random allocation of patients.¹⁴⁻¹⁶ The IDEAL trial conducted a double-blinded trial with

Table 1 The basic characteristics of four randomized clinical trials and one nonrandomized clinical trial that were included in this study (1)

Trial	PEG-IFN α 2a + ribavirin				PEG-IFN α 2b + ribavirin				Genotype	OR/RR/RD (95% CI)	P value
	Dose	EVR(n/N)	ETR(n/N)	SVR(n/N)	Dose	EVR(n/N)	ETR(n/N)	SVR(n/N)			
Sporea et al 2006	180 μ g/week + ribavirin 800–1200 mg/day	89.5% (43/48)	NR	NR	1.5 μ g/kg/week + ribavirin 800–1200 mg/day	75.7% (25/33)	NR	NR	NR	OR = 2.75 (0.81–9.33) RR = 1.18 (0.95–1.46)	0.61
Yenice et al 2006	180 μ g/week + ribavirin 800–1200 mg/day	NR	70.0% (28/40)	45.0% (18/40)	1.5 μ g/kg/week + ribavirin 800–1200 mg/day	NR	67.5% (27/40)	32.5% (13/40)	Genotype 1	ND	P(ETR) = 0.79; P(SVR) = 0.239
Escudero et al 2008	180 μ g/week + ribavirin 800–1200 mg/day	55.9% (33/59)	NR	50.8% (30/59)	1.5 μ g/kg/week + ribavirin 800–1200 mg/day	50.0% (29/58)	NR	46.6% (27/58)	Genotype 1	ND	P(SVR) = 0.73
Di Bisceglie et al 2007	180 μ g/week + ribavirin 1000–1200 mg/day	96.7% (29/30)	NR	93.3% (28/30)	1.5 μ g/kg/week + ribavirin 800–1400 mg/day	90.9% (30/33)	NR	87.9% (29/33)	Genotype 2, 3, 4	ND	P(SVR) > 0.63
McHutchison et al 2009	180 μ g/week + ribavirin 1000–1200 mg/day	45.0% (466/1035)	64.4% (667/1035)	40.9% (423/1035)	1.5 μ g/kg/week + ribavirin 800–1400 mg/day	63.35% (121/191)	NR	NR	Genotype 1	ND	ND
McHutchison et al 2009	180 μ g/week + ribavirin 1000–1200 mg/day	45.0% (466/1035)	64.4% (667/1035)	40.9% (423/1035)	1.5 μ g/kg/week + ribavirin 800–1400 mg/day	39.9% (407/1019)	53.2% (542/1019)	39.8% (406/1019)	Genotype 1	ND	Standard dose PEG-IFN- α 2b versus PEG-IFN- α 2a: P(EVR) = 0.01; P(ETR) < 0.001; P(SVR) = 0.57
Ascione et al 2010	180 μ g/week + ribavirin 1000–1200 mg/day	77.4% (72/93)	83.8% (134/160)	54.8% (51/93)	1.0 μ g/kg/week + ribavirin 1000–1200 mg/day	36.0% (366/1016)	49.2% (500/1016)	38.0% (386/1016)	Genotype 1, 4	RD(EVR) = 12% (2.9%–21%); RD(ETR) = 19.4% (9.8%–28.5%); RD(SVR) = 14.4% (3.7%–24.6%)	P(EVR) = 0.009, P(ETR) < 0.0001, P(SVR) = 0.008
		95.5% (64/67)		88.1% (59/67)		82.1% (55/67)		74.6% (50/67)	Genotype 2, 3		

Rumi et al 2010	180 μ g/week + ribavirin 1000–1200 mg/day	66% (60/91)	65% (59/91)	48% (44/91)	1.5 μ g/kg/week + ribavirin 800–1200 mg/day	46% (40/87)	44% (38/87)	32% (28/87)	Genotype 1	ND	$P(\text{SVR}) = 0.04$
		55.6% (10/18)	50% (9/18)	44% (8/18)		46.2% (12/26)	38.5% (10/26)	30.8% (8/26)	Genotype 4	ND	$P(\text{SVR}) = 0.5$
	180 μ g/week + ribavirin 800 mg/day	97% (67/69)	96% (66/69)	96% (66/69)		95% (70/74)	93% (69/74)	82% (61/74)	Genotype 2	ND	$P(\text{SVR}) = 0.01$
	Mixed	97% (33/34)	94% (32/34)	65% (22/32)		91% (29/32)	91% (29/32)	69% (22/32)	Genotype 3	ND	$P(\text{SVR}) = 0.9$
		80% (170/212)	78% (166/212)	66% (140/212)	Mixed	69% (151/219)	67% (146/219)	54% (119/219)	Overall	OR = 1.71 (1.14–2.57)	$P(\text{SVR}) = 0.02$

Abbreviations: OR, odds ratio; RR, relative risk; NR, nonreported; ND, non-done; N, total number of subjects enrolled; n, number of patients with specific viral response; EVR, early viral response; ETR, end of treatment response; SVR, sustained viral response.

regards to the dose of PEG-IFN- α 2b. One trial reported the concealment of allocation.¹⁵ The five other studies did not mention their blinding status or procedures. None of the four RCTs reported the adequate concealment of subject allocation. Among all of the seven enrolled trials, five were open-label studies; one of these five was a non-RCT.

Viral response

Compared with PEG-IFN- α 2b plus ribavirin, PEG-IFN- α 2a plus ribavirin led to a slightly higher EVR (RR = 1.12, 95% CI: 1.06–1.19, n = 6 trials; Figure 2A), a higher ETR (RR = 1.21, 95% CI: 1.14–1.28, n = 4 trials; Figure 2B), and a similar level of SVR (RR = 1.10, 95% CI: 1.02–1.18, n = 5 trials; Figure 2C) between the two groups. When the patients were stratified according to the genotypes of their HCV infection, the EVR and ETR among the genotype 1 patients treated with PEG-IFN- α 2a plus ribavirin were also slightly higher than those of the group treated with PEG-IFN- α 2b plus ribavirin group (EVR: RR = 1.13, 95% CI: 1.05–1.22, n = 5 trials; ETR: RR = 1.22, 95% CI: 1.14–1.31, n = 3 trials; Figure 3A, 3B). The SVR in the PEG-IFN- α 2a plus ribavirin group was the same as that in the PEG-IFN- α 2b plus ribavirin group (RR = 1.07, 95% CI: 0.97–1.18, n = 4 trials; Figure 3C).

Adverse events

Six trials reported the numbers of patients who discontinued the treatment for adverse events.^{3,12–16} In the PEG-IFN- α 2a plus ribavirin group, 172 patients did not complete their treatment for safety reasons, while there were 182 patients who discontinued treatment in the PEG-IFN- α 2b group. Therefore, the RR of the discontinuation of treatment for safety reasons was 0.85 (95% CI: 0.52–1.38, n = 6 trials; Figure 4).

Two trials reported the number of patients who received a dose reduction of ribavirin.^{14,16} According to these reports, the two regimens did not incur significantly different rates of the dose reduction (data not shown).

Other common adverse events were also reported in three trials. The rates of fever, headache, and nausea were lower in the PEG-IFN- α 2a plus ribavirin group compared to the PEG-IFN- α 2b plus ribavirin group (fever: RR = 0.56, 95% CI: 0.42–0.75; headache: RR = 0.87, 95% CI: 0.80–0.94; nausea: RR = 0.87, 95% CI: 0.79–0.96; n = 3 trials). On the other hand, the rates of depression and rash were not significantly lower in the PEG-IFN- α 2b plus ribavirin group (depression: RR = 0.88, 95% CI: 0.77–1.01; n = 4 trials; rash: RR = 1.16, 95% CI: 0.72–1.89; n = 3 trials). Rates of other

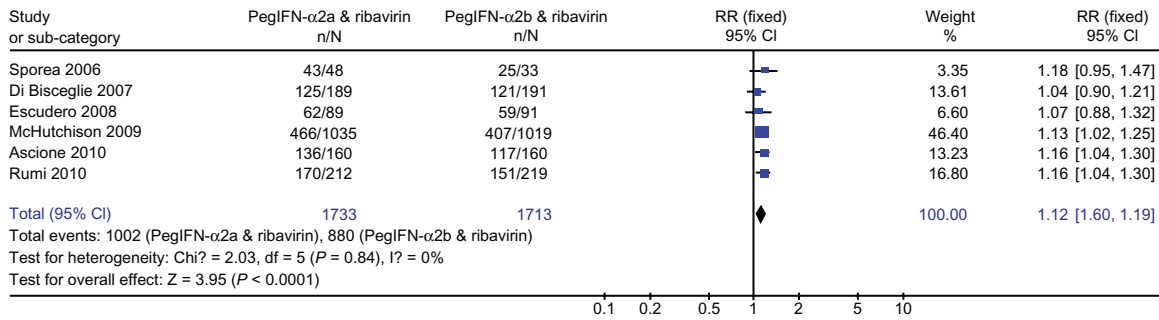
Table 2 The basic characteristics of four: randomized clinical trials and one nonrandomized clinical trial that were included in this study (2)

Trial	Country	Study design	PEG-IFN- α 2a and ribavirin			PEG-IFN- α 2b and ribavirin			Follow up
			Mean age (year)	Male (%)	Initial viral load (MIU/mL)	Mean age (year)	Male (%)	Initial viral load	
Sporea et al 2006	Romania	Prospective head-to-head randomized trial	49.35	68.80%	1.10 \pm 0.92 (MIU/mL)	49.06	78.80%	1.40 \pm 1.98 (MIU/mL)	12 weeks
Yenice et al 2006	Turkey	Prospective head-to-head randomized trial	Male: 48.2 vs Female: 50.9	35.10%	NR	Male: 50.8 vs Female: 50.85	27.00%	NR	64 weeks
Escudero et al 2008	Spain	Prospective head-to-head non-randomized open-label trial	44.4 \pm 9.34	70.30%	5.9 \pm 0.5 (log ₁₀ (IU/mL))	43.6 \pm 9.62	60.90%	5.8 \pm 0.4 (log ₁₀ (IU/mL))	64 weeks
Di Bisceglie et al 2007	USA	Prospective randomized open-label trial	46.9 \pm 0.52	64.00%	6.5 \pm 0.03 (log ₁₀ (IU/mL))	48.4 \pm 0.56	71.00%	6.5 \pm 0.03 (log ₁₀ (IU/mL))	12 weeks
McHutchison et al 2009	USA	Prospective head-to-head randomized trial	47.6 \pm 8.2	59.20%	6.32 \pm 0.70 (log ₁₀ (IU/mL))	47.5 \pm 7.8	60.20%	6.32 \pm 0.69 (log ₁₀ (IU/mL))	64 weeks
Ascione et al 2010	Italy	Prospective head-to-head, open-label, blinding, randomized trial	51.30	50.60%	570 (MIU/L)	47.5 \pm 8.1	59.70%	6.32 \pm 0.70 (log ₁₀ (IU/mL)) 604 (MIU/L)	64 weeks
Rumi et al 2010	Italy	Prospective, head-to-head, open-label, randomized trial	51.6 \pm 12.0	60.40%	2.6 \pm 5.8 (MIU/L)	52.8 \pm 12.0	54.80%	2.2 \pm 4.7 (MIU/L)	64 weeks

Abbreviation: NR, nonreported.

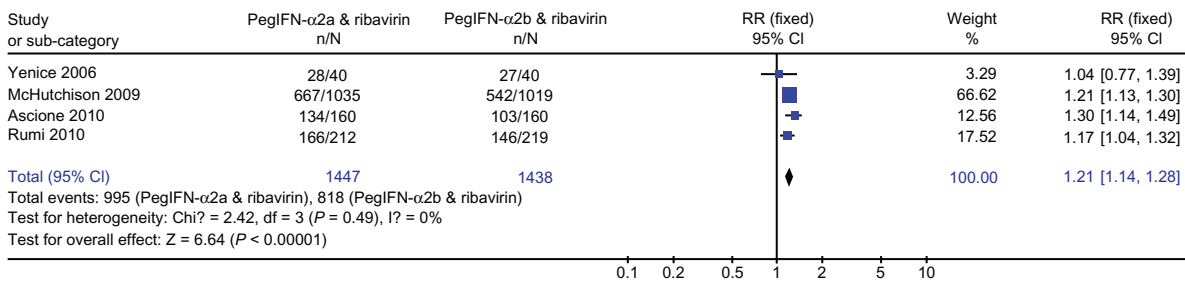
A EVR

Review: peginterferon- α 2a with ribavirin versus peginterferon with ribavirin
 Comparison: 01 Virological responses
 Outcome: 01 EVR (all genotypes)



B ETR

Review: peginterferon- α 2a with ribavirin versus peginterferon with ribavirin
 Comparison: 01 Virological responses
 Outcome: 03 ETR (all genotypes)



C SVR

Review: peginterferon- α 2a with ribavirin versus peginterferon with ribavirin
 Comparison: 01 Virological responses
 Outcome: 05 SVR (all genotypes)

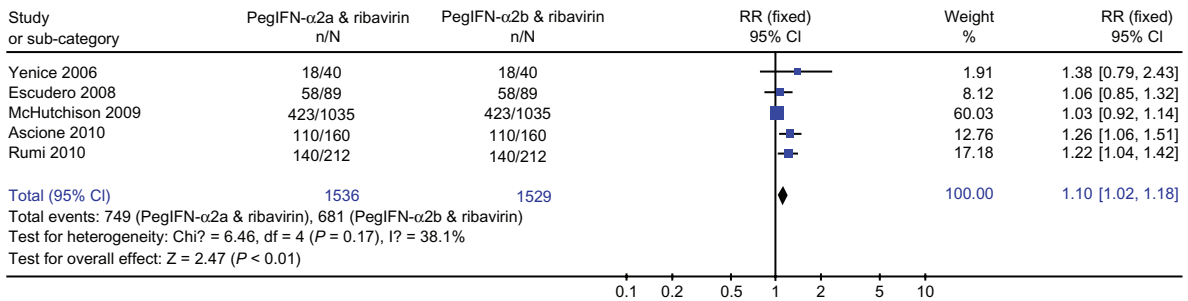


Figure 2 Meta-analysis of trials that assessed the effect of PEG-IFN- α 2a plus ribavirin versus PEG-IFN- α 2b plus ribavirin on viral responses (**A**: EVR; **B**: ETR; **C**: SVR), regardless of the HCV genotype.

adverse events were not significantly different between the two treatment groups.

Discussion

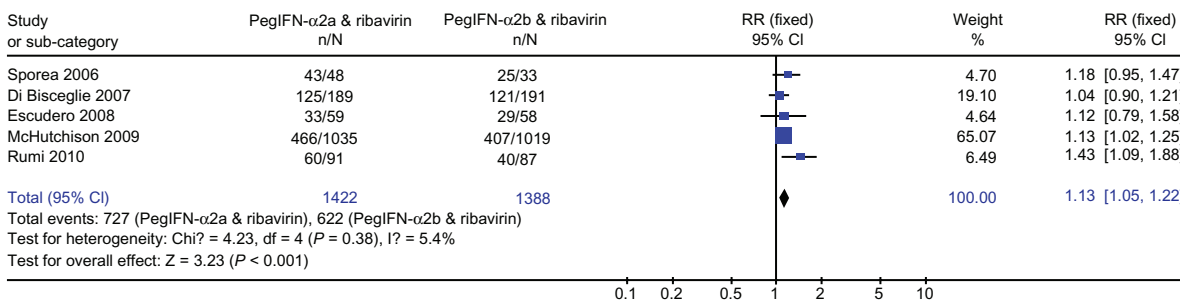
In this meta-analysis, we demonstrated the regimen of PEG-IFN- α 2a plus ribavirin led to slightly better rates of EVR and ETR compared with the use of PEG-IFN- α 2b plus ribavirin in patients with HCV infections. On the other hand, the two treatment regimens did not differ significantly with regards to the SVR. PEG-IFN- α 2b plus ribavirin incurred higher rates of common adverse events in most cases

except for a lower rate of rash, although this result was not statistically significant. However, the number of patients that discontinued treatment due to adverse events in the PEG-IFN- α 2a plus ribavirin group was slightly lower than the number in the group treated with PEG-IFN- α 2b, although this difference was not significant. Because of the lack of data, no comparison was possible between the histological and biochemical benefits of the two treatment regimens.

The limitations of this meta-analysis included the small number of trials that could be included, small cohort sizes in most of the studies, a short duration of follow-up, the lack of

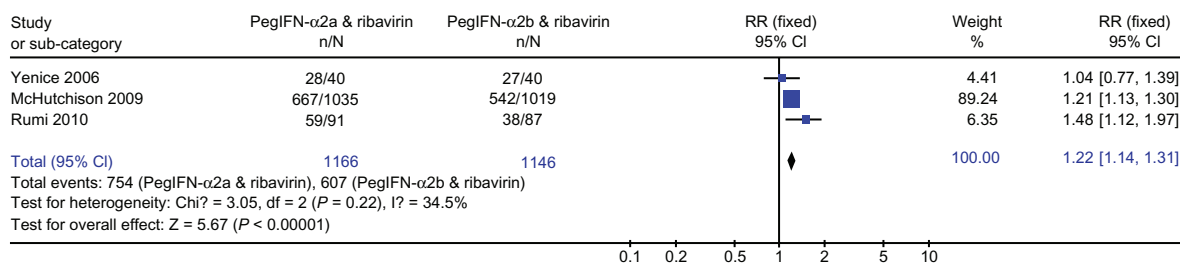
A EVR

Review: peginterferon- α 2a with ribavirin versus peginterferon with ribavirin
 Comparison: 01 Virological responses
 Outcome: 02 EVR (genotype 1)



B ETR

Review: peginterferon- α 2a with ribavirin versus peginterferon with ribavirin
 Comparison: 01 Virological responses
 Outcome: 04 ETR (genotype 1)



C SVR

Review: peginterferon- α 2a with ribavirin versus peginterferon with ribavirin
 Comparison: 01 Virological responses
 Outcome: 06 SVR (genotype 1)

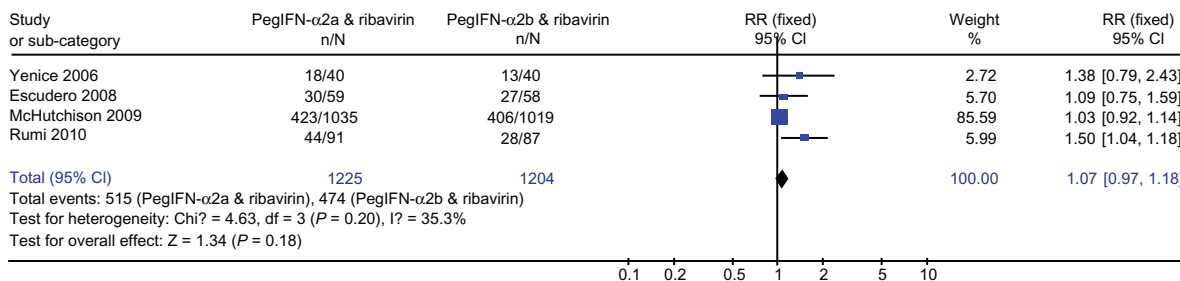


Figure 3 Meta-analysis of trials on the effect of PEG-IFN- α 2a plus ribavirin versus PEG-IFN- α 2b plus ribavirin on viral responses (A: EVR; B: ETR; C: SVR) when all of the patients were infected by genotype 1 of HCV.

information with regards to the histological and biochemical response to treatment, the low level of methodological quality (including inadequate allocation sequence generation, inadequate allocation concealment, and a lack of double-blinding in most studies), and inconsistent ribavirin treatment regimens adopted by different trials. All of these could lead to false conclusions (type I and II errors) being made and all studies could have been affected by publication biases.

With regards to these limitations, most of the trials included in this study enrolled small cohorts (less than 200 subjects). Only the IDEAL trial had a large sample size with more than 1,000 subjects in each treatment arm.¹⁴

For this reason, the IDEAL trial usually had a much larger weighting than others in our statistical calculations. The conclusions of our meta-analysis therefore resemble, to some extent, the outcomes of the IDEAL study. The publication bias and systematic deviations within the IDEAL trial could not be concealed by this meta-analysis.

Secondly, in order to assess the benefits of any medication for HCV infection, which can be lifelong in most cases, long-term follow-up and the collection of comprehensive information are both required. However, the longest duration of follow-up was only 64 weeks in the present study, which was just long enough to assess the SVR.

Review: peginterferon- α 2a with ribavirin versus peginterferon with ribavirin
 Comparison: 02 Adverse events
 Outcome: 01 Discontinuation of treatment for safety reasons

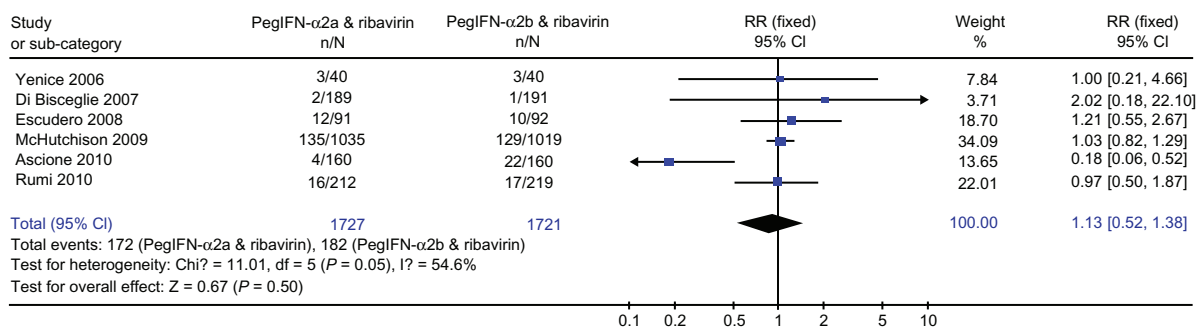


Figure 4 Meta-analysis of six trials on the numbers of patients that discontinued treatment because of adverse events; the groups that received PEG-IFN- α 2a plus ribavirin or PEG-IFN- α 2b plus ribavirin were compared, regardless of the HCV genotype.

Among the trials included in this study, only one reported data of biochemical responses,¹¹ no significant differences were observed in this study. Because most patients were reluctant to accept a second liver biopsy after treatment, no authors reported any data with regards to the histological responses.

Furthermore, the methodological quality of the trials included was not high. Three trials reported adequate allocation sequence generation.^{15,16} One of these mentioned allocation concealment, which was not double-blinded.¹⁵ Inadequate statistic power weakens the reliability of the outcomes of a meta-analysis. The identified differences between PEG-IFN- α 2a and PEG-IFN- α 2b may reflect publication biases or biases due to low methodological quality. Our trial number is too small to do any analysis of publication bias.

Pharmacokinetics of PEG-IFN- α 2a and PEG-IFN- α 2b may influence response rates. According to their different dosages the serum exposure of PEG-IFN- α 2a was 16-fold greater than PEG-IFN- α 2b. And the serum concentration of PEG-IFN- α 2a was more stable than PEG-IFN- α 2b. When the patient body weight increased the serum exposure of PEG-IFN- α 2a decreased for it was given as a fixed dose.⁵ Nevertheless, a higher dose of PEG-IFN- α 2a didn't necessarily lead to a significantly higher SVR of obese patients.¹⁷ With further research the dosage of PEG-IFN- α 2a may be improved in future.

The regimen of ribavirin can also affect the viral response.¹⁸ The SVR improved with higher doses of ribavirin. On the other hand, higher dosages of ribavirin can lead to higher rates of anemia and the requirement for dose reductions.¹⁹ It was obvious that the ribavirin regimens and ribavirin dose reduction rules of different trials were distinct. Also, three of the trials did not even mention their dose

reduction rules and criteria.^{3,11,12} The inconsistent regimens of ribavirin between the two treatment arms might have affected the virological responses to the two treatment regimens. This was considered to be one of the reasons as to why the conclusions of IDEAL trial were inconsistent from the two other trials in the same year.²⁰ It also may be related to why the significantly higher EVR and ETR after PEG-IFN- α 2a treatment did not lead to a consequentially higher SVR in the IDEAL trial.²⁰ We speculate that fixed dosages of ribavirin and rules for dose reduction are necessary to erase this confounding factor.

The ages and the levels of virus load of patients enrolled were matched between the treatment arms in most trials. One trial reported a higher virus titer in PEG-IFN- α 2b group.¹¹ We had no reasons to consider there were any significant confounding factors. However, since the lower viral load is one of the predictors of SVR,⁶ the distinct viral load levels in different trials could be a source of variations among their outcomes.

Gender, race (non-Caucasian versus Caucasian) and cirrhotic status were believed to affect the outcomes of treatment.²¹ There were equal numbers of male/female patients treated by two treatment regimens, the gender rate was not a likely source of bias of treatment outcome. Among all seven trials, there were two studies that stratified their subjects by races and ethnicity. The IDEAL trial reported that, among black patients, the SVR to PEG-IFN- α 2a plus ribavirin was higher than the other treatment regimen (RR = 1.13, 95% CI: 0.80–1.61). According to the other trial, the EVR of black patients was also higher when they received PEG-IFN- α 2a plus ribavirin (RR = 1.31, 95% CI: 0.80–2.16). It also seemed that nonblack patients enjoyed higher levels of EVR and SVR than their black counterparts (EVR: RR = 1.39, 95% CI: 1.08–1.77;

SVR: RR = 1.79, 95% CI: 1.49–2.15). Because of the differences in terms of the virological response among different races and the large weight of the IDEAL trial, among whose subjects there were approximately 20% black patients, it may be a confounding factor that affected the outcomes of our analysis. It is believed that the gene region encoding interleukin 28 B (IL28B) is associated with SVR.²² Recently, Ge and his colleagues reported a genetic polymorphism rs12979860 leading to better response, whose frequency is much higher among European-Americans compared with African-Americans. This polymorphism explains half of the difference in response rate between the two ethnic groups.²³ However, the impact of race on the virological response to treatment will require further studies to be fully elucidated.

It is also believed that the cirrhotic status is a factor that affects the virological response.²⁴ A higher stage of fibrosis is a predictor of a lower rate of SVR. Nevertheless, the exact impacts of cirrhotic status on the efficacy of specific medications are still unknown. Therefore, we have no way of knowing the true impacts of the cirrhotic status on our conclusions, although most trials designed their two treatment arms with similar average fibrosis scores.

We assessed seven trials among which six were RCTs and four were open-label studies. All the subjects enrolled were treatment naïve. Most of them were infected by genotype 1 HCV. As a standard treatment regimen, the combination of PEG-IFN- α 2a or PEG-IFN- α 2b plus ribavirin was the most effective (80% of patients with genotype 2 or 3 HCV and 45% of patients with genotype 1 or 4 patients achieved SVR).²⁵ These two treatment regimens led to very similar effects. According to our meta-analysis, PEG-IFN- α 2a was slightly more effective than PEG-IFN- α 2b on achieving EVR and ETR. Nevertheless, this better early performance of PEG-IFN- α 2a did not last for a long period. When assessing the SVR, it is difficult to discern any differences. As the RRs could be affected by the biases and drawbacks discussed above, we believe that if there are any possible differences between these two treatment regimens, further trials have to be done in order to confirm them.

Adverse events were observed less frequently among patients treated with PEG-IFN- α 2a, though the numbers of patients that suffered from a rash were slightly higher in this treatment group (data not shown). Based on this fact, PEG-IFN- α 2a may be considered as a better choice, as it may lead to a better level of patient compliance. However, since it was possible that a reduction in the neutrophil count was

a predictor of SVR,¹⁹ the relationship between the efficacies of peginterferon and adverse events needs to be evaluated carefully.

In our review, the number of nongenotype-1 patients was small. The conclusions presented above were based on a population that consisted of more than 95% patients with genotype 1 HCV. To investigate the effects of the two treatment regimens on a population with other HCV genotypes, a clinical trial should be conducted that focuses on a cohort of nongenotype 1 patients, which is large enough to have a reliable statistical power.

Due to the lack of data, our review did not assess the histological and biochemical responses of patients after receiving these two treatment regimens. The trials that were included did not report any histological improvement after treatment. If there were any possible differences of the histological or biochemical responses between PEG-IFN- α 2a and PEG-IFN- α 2b, a more detailed trial with a longer period of follow-up is necessary in order to discern them.

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Disclosure

The authors report no conflicts of interest in this work.

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