ORIGINAL RESEARCH

A meta-analysis that compares the use of either peginterferon-α2a or peginterferon-α2b plus ribavirin for HCV infection

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Background: Two kinds of peginterferons, peginterferon-α2a (PEG-IFN-α2a) and peginterferon-α2b (PEG-IFN-α2b), 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-α2a plus ribavirin was better than PEG-IFN-α2b 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-α2a were less likely to discontinue treatment for safety reasons (RR = 0.85, 95% CI: 0.52–1.38).

Conclusion: We demonstrated that PEG-IFN-α2a was a better choice than PEG-IFN-α2b in terms of virological responses.

Keywords: peginterferon-α2a (PEG-IFN-α2a), peginterferon-α2b (PEG-IFN-α2b), 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-α2a is a branched molecule with a molecular mass of 40 kDa,[3] and PEG-IFN-α2b 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-α2a and PEG-IFN-α2b are unclear. Some researchers believe that PEG-IFN-α2b 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-α2a plus ribavirin or PEG-IFN-α2b 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-α2a plus ribavirin and PEG-IFN-α2b 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-α2b 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-α2a plus ribavirin, while 1,753 patients received PEG-IFN-α2b 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-α2b plus ribavirin.[14] The
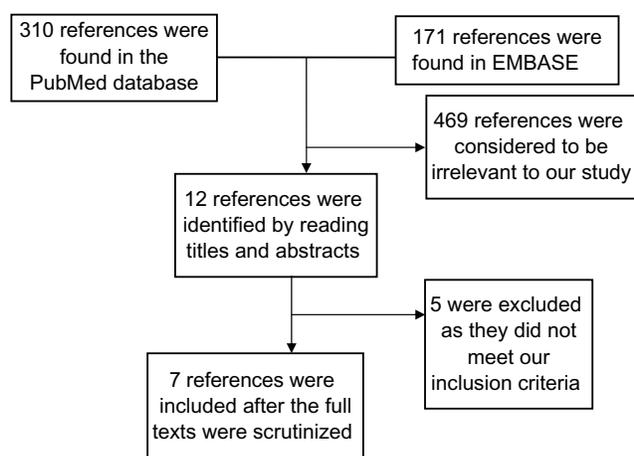
data from these patients was not included in meta-analysis (Table 1). All of the patients in the included studies were treatment-naïve. Six trials presented their exclusion criteria clearly for enrollment[11] and the other trial communicated their exclusion criteria to the authors of this present study 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-α2a and PEG-IFN-α2b, except for the IDEAL trial, which included a third treatment arm with a lower dose of PEG-IFN-α2b 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-α2a 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-α2b plus ribavirin group was higher than that in the group treated with PEG-IFN-α2a 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-α2a was 180 μg/week and 1.5 μg/kg/week was used of PEG-IFN-α2b; 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

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

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

Trial	PEG-IFN α2a + ribavirin				PEG-IFN α2b + 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 μg/week + ribavirin 800–1200 mg/day	89.5% (43/48)	NR	NR	1.5 μg/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 μg/week + ribavirin 800–1200 mg/day	NR	70.0% (28/40)	45.0% (18/40)	1.5 μg/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 μg/week + ribavirin 800–1200 mg/day	55.9% (33/59)	NR	50.8% (30/59)	1.5 μg/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 μg/week + ribavirin 1000–1200 mg/day	96.7% (29/30)	NR	93.3% (28/30)	1.5 μg/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
		66.1% (125/189)	NR	NR		63.35% (121/191)	NR	NR	Genotype 1	ND	ND
McHutchison et al 2009	180 μg/week + ribavirin 1000–1200 mg/day	45.0% (466/1035)	64.4% (667/1035)	40.9% (423/1035)	1.5 μg/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-α2b versus PEG-INF-α2a: P(EVR) = 0.01; P(ETR) < 0.001; P(SVR) = 0.57
					1.0 μg/kg/week + ribavirin 1000–1200 mg/day	36.0% (366/1016)	49.2% (500/1016)	38.0% (386/1016)		ND	
Ascione et al 2010	180 μg/week + ribavirin 1000–1200 mg/day	77.4% (72/93)	83.8% (134/160)	54.8% (51/93)	1.5 μg/kg/week + ribavirin 1000–1200 mg/day	66.7% (62/93)	64.4% (103/160)	39.8% (37/93)	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)	88.1% (59/67)		82.1% (55/67)		74.6% (50/67)	Genotype 2, 3		

	180 μg/week + ribavirin 1000–1200 mg/day	180 μg/week + ribavirin 800 mg/day	Mixed	1.5 μg/kg/week + ribavirin 800–1200 mg/day	Mixed			
Rumi et al 2010	66% (60/91)	65% (59/91)	48% (44/91)	46% (40/87)	44% (38/87)	32% (28/87)	Genotype 1	ND	P(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(SVR) = 0.5
	97% (67/69)	96% (66/69)	96% (66/69)	95% (70/74)	93% (69/74)	82% (61/74)	Genotype 2	ND	P(SVR) = 0.01
	97% (33/34)	94% (32/34)	65% (22/32)	91% (29/32)	91% (29/32)	69% (22/32)	Genotype 3	ND	P(SVR) = 0.9
	80% (170/212)	78% (166/212)	66% (140/212)	69% (151/219)	67% (146/219)	54% (119/219)	Overall	OR = 1.71 (1.14–2.57)	P(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-α2b. 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-α2b plus ribavirin, PEG-IFN-α2a 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-α2a plus ribavirin were also slightly higher than those of the group treated with PEG-IFN-α2b 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-α2a plus ribavirin group was the same as that in the PEG-IFN-α2b 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-α2a 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-α2b 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-α2a plus ribavirin group compared to the PEG-IFN-α2b 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-α2b 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
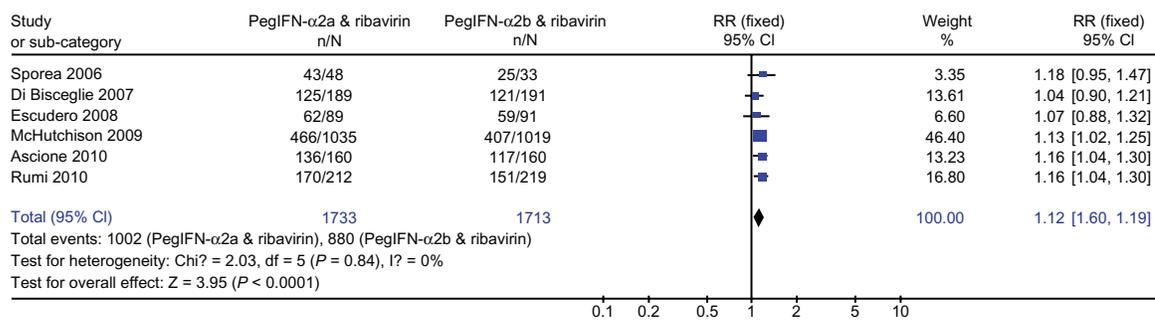
Table 2 The basic characteristics of four randomized clinical trials and one nonrandomized clinical trial that were included in this study (2)

Trial	Country	Study design	PEG-IFN-α2a and ribavirin			PEG-IFN-α2b and ribavirin			Follow up
			Mean age (year)	Male (%)	Initial viral load	Mean age (year)	Male (%)	Initial viral load	
Sporea et al 2006	Romania	Prospective head-to-head randomized trial	49.35	68.80%	1.10 ± 0.92 (MIU/mL)	49.06	78.80%	1.40 ± 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 nonrandomized open-label trial	44.4 ± 9.34	70.30%	5.9 ± 0.5 $(\log_{10}(\text{IU/mL}))$	43.6 ± 9.62	60.90%	5.8 ± 0.4 $(\log_{10}(\text{IU/mL}))$	64 weeks
Di Bisceglie et al 2007	USA	Prospective randomized open-label trial	46.9 ± 0.52	64.00%	6.5 ± 0.03 $(\log_{10}(\text{IU/mL}))$	48.4 ± 0.56	71.00%	6.5 ± 0.03 $(\log_{10}(\text{IU/mL}))$	12 weeks
McHutchison et al 2009	USA	Prospective head-to-head randomized trial	47.6 ± 8.2	59.20%	6.32 ± 0.70 $(\log_{10}(\text{IU/mL}))$	47.5 ± 7.8	60.20%	6.32 ± 0.69 $(\log_{10}(\text{IU/mL}))$	64 weeks
						47.5 ± 8.1	59.70%	6.32 ± 0.70 $(\log_{10}(\text{IU/mL}))$	
Ascione et al 2010	Italy	Prospective head-to-head, open-label, blinding, randomized trial	51.30	50.60%	570 (MIU/L)	48.9	58.80%	604 (MIU/L)	64 weeks
Rumi et al 2010	Italy	Prospective, head-to-head, open-label, randomized trial	51.6 ± 12.0	60.40%	2.6 ± 5.8 (MIU/L)	52.8 ± 12.0	54.80%	2.2 ± 4.7 (MIU/L)	64 weeks

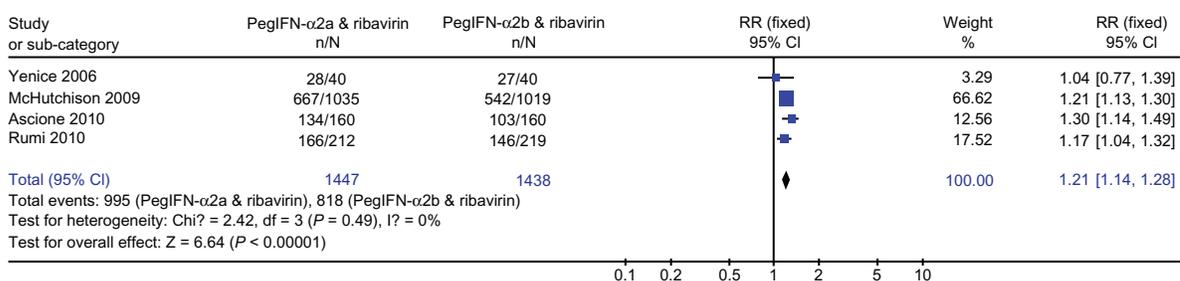**Abbreviation:** NR, nonreported.

A EVR

Review: peginterferon-α2a with ribavirin versus peginterferon with ribavirin
Comparison: 01 Virological responses
Outcome: 01 EVR (all genotypes)

Study or sub-category	PegIFN-α2a & ribavirin n/N	PegIFN-α2b & ribavirin n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Sporea 2006	43/48	25/33		3.35	1.18 [0.95, 1.47]
Di Bisceglie 2007	125/189	121/191		13.61	1.04 [0.90, 1.21]
Escudero 2008	62/89	59/91		6.60	1.07 [0.88, 1.32]
McHutchison 2009	466/1035	407/1019		46.40	1.13 [1.02, 1.25]
Ascione 2010	136/160	117/160		13.23	1.16 [1.04, 1.30]
Rumi 2010	170/212	151/219		16.80	1.16 [1.04, 1.30]
Total (95% CI)	1733	1713		100.00	1.12 [1.60, 1.19]

Total events: 1002 (PegIFN-α2a & ribavirin), 880 (PegIFN-α2b & ribavirin)
Test for heterogeneity: Chi? = 2.03, df = 5 (P = 0.84), I? = 0%
Test for overall effect: Z = 3.95 (P < 0.0001)

0.1 0.2 0.5 1 2 5 10

B ETR

Review: peginterferon-α2a with ribavirin versus peginterferon with ribavirin
Comparison: 01 Virological responses
Outcome: 03 ETR (all genotypes)

Study or sub-category	PegIFN-α2a & ribavirin n/N	PegIFN-α2b & ribavirin n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Yenice 2006	28/40	27/40		3.29	1.04 [0.77, 1.39]
McHutchison 2009	667/1035	542/1019		66.62	1.21 [1.13, 1.30]
Ascione 2010	134/160	103/160		12.56	1.30 [1.14, 1.49]
Rumi 2010	166/212	146/219		17.52	1.17 [1.04, 1.32]
Total (95% CI)	1447	1438		100.00	1.21 [1.14, 1.28]

Total events: 995 (PegIFN-α2a & ribavirin), 818 (PegIFN-α2b & ribavirin)
Test for heterogeneity: Chi? = 2.42, df = 3 (P = 0.49), I? = 0%
Test for overall effect: Z = 6.64 (P < 0.00001)
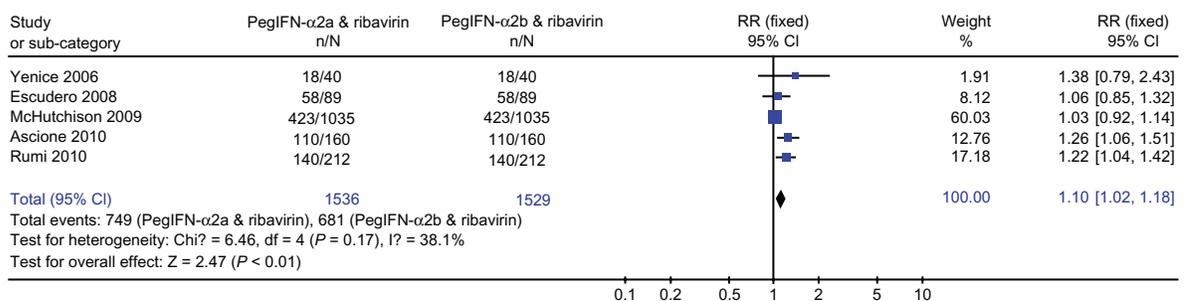
0.1 0.2 0.5 1 2 5 10

C SVR

Review: peginterferon-α2a with ribavirin versus peginterferon with ribavirin
Comparison: 01 Virological responses
Outcome: 05 SVR (all genotypes)

Study or sub-category	PegIFN-α2a & ribavirin n/N	PegIFN-α2b & ribavirin n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Yenice 2006	18/40	18/40		1.91	1.38 [0.79, 2.43]
Escudero 2008	58/89	58/89		8.12	1.06 [0.85, 1.32]
McHutchison 2009	423/1035	423/1035		60.03	1.03 [0.92, 1.14]
Ascione 2010	110/160	110/160		12.76	1.26 [1.06, 1.51]
Rumi 2010	140/212	140/212		17.18	1.22 [1.04, 1.42]
Total (95% CI)	1536	1529		100.00	1.10 [1.02, 1.18]

Total events: 749 (PegIFN-α2a & ribavirin), 681 (PegIFN-α2b & ribavirin)
Test for heterogeneity: Chi? = 6.46, df = 4 (P = 0.17), I? = 38.1%
Test for overall effect: Z = 2.47 (P < 0.01)

0.1 0.2 0.5 1 2 5 10

Figure 2 Meta-analysis of trials that assessed the effect of PEG-IFN-α2a plus ribavirin versus PEG-IFN-α2b 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.
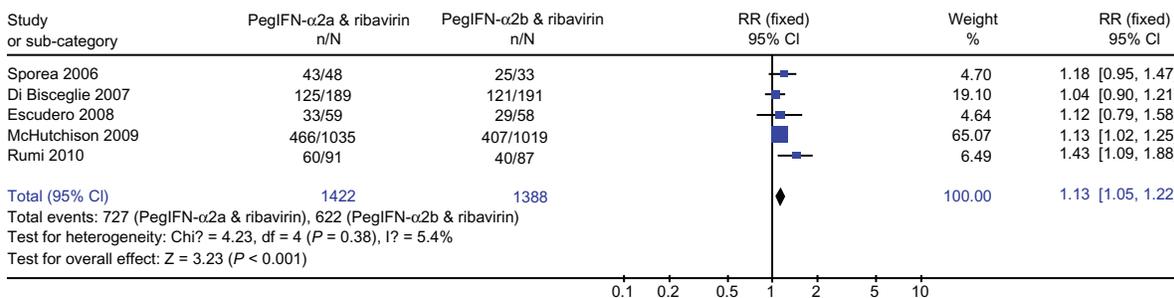
Discussion

In this meta-analysis, we demonstrated the regimen of PEG-IFN-α2a plus ribavirin led to slightly better rates of EVR and ETR compared with the use of PEG-IFN-α2b 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-α2b 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-α2a plus ribavirin group was slightly lower than the number in the group treated with PEG-IFN-α2b, 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
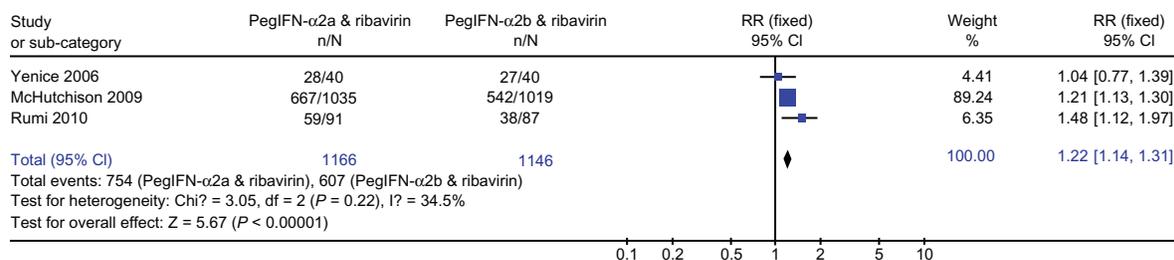
A EVR

Review: peginterferon-α2a with ribavirin versus peginterferon with ribavirin
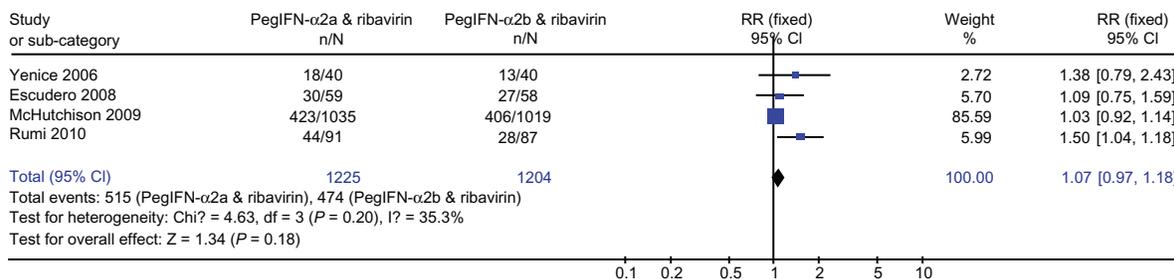Comparison: 01 Virological responses
Outcome: 02 EVR (genotype 1)

Study or sub-category	PegIFN-α2a & ribavirin n/N	PegIFN-α2b & ribavirin n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Sporea 2006	43/48	25/33		4.70	1.18 [0.95, 1.47]
Di Bisceglie 2007	125/189	121/191		19.10	1.04 [0.90, 1.21]
Escudero 2008	33/59	29/58		4.64	1.12 [0.79, 1.58]
McHutchison 2009	466/1035	407/1019		65.07	1.13 [1.02, 1.25]
Rumi 2010	60/91	40/87		6.49	1.43 [1.09, 1.88]
Total (95% CI)	**1422**	**1388**		**100.00**	**1.13 [1.05, 1.22]**

Total events: 727 (PegIFN-α2a & ribavirin), 622 (PegIFN-α2b & ribavirin)
Test for heterogeneity: Chi² = 4.23, df = 4 (P = 0.38), I² = 5.4%
Test for overall effect: Z = 3.23 (P < 0.001)

0.1 0.2 0.5 1 2 5 10

B ETR

Review: peginterferon-α2a with ribavirin versus peginterferon with ribavirin
Comparison: 01 Virological responses
Outcome: 04 ETR (genotype 1)

Study or sub-category	PegIFN-α2a & ribavirin n/N	PegIFN-α2b & ribavirin n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Yenice 2006	28/40	27/40		4.41	1.04 [0.77, 1.39]
McHutchison 2009	667/1035	542/1019		89.24	1.21 [1.13, 1.30]
Rumi 2010	59/91	38/87		6.35	1.48 [1.12, 1.97]
Total (95% CI)	**1166**	**1146**		**100.00**	**1.22 [1.14, 1.31]**

Total events: 754 (PegIFN-α2a & ribavirin), 607 (PegIFN-α2b & ribavirin)
Test for heterogeneity: Chi² = 3.05, df = 2 (P = 0.22), I² = 34.5%
Test for overall effect: Z = 5.67 (P < 0.00001)

0.1 0.2 0.5 1 2 5 10

C SVR

Review: peginterferon-α2a with ribavirin versus peginterferon with ribavirin
Comparison: 01 Virological responses
Outcome: 06 SVR (genotype 1)

Study or sub-category	PegIFN-α2a & ribavirin n/N	PegIFN-α2b & ribavirin n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Yenice 2006	18/40	13/40		2.72	1.38 [0.79, 2.43]
Escudero 2008	30/59	27/58		5.70	1.09 [0.75, 1.59]
McHutchison 2009	423/1035	406/1019		85.59	1.03 [0.92, 1.14]
Rumi 2010	44/91	28/87		5.99	1.50 [1.04, 1.18]
Total (95% CI)	**1225**	**1204**		**100.00**	**1.07 [0.97, 1.18]**

Total events: 515 (PegIFN-α2a & ribavirin), 474 (PegIFN-α2b & ribavirin)
Test for heterogeneity: Chi² = 4.63, df = 3 (P = 0.20), I² = 35.3%
Test for overall effect: Z = 1.34 (P = 0.18)

0.1 0.2 0.5 1 2 5 10

Figure 3 Meta-analysis of trials on the effect of PEG-IFN-α2a plus ribavirin versus PEG-IFN-α2b plus ribavirin on viral responses (**A**: EVR; **B**: ETR; **C**: SVR) when all of the patients were infected by genotype 1 of HCV.
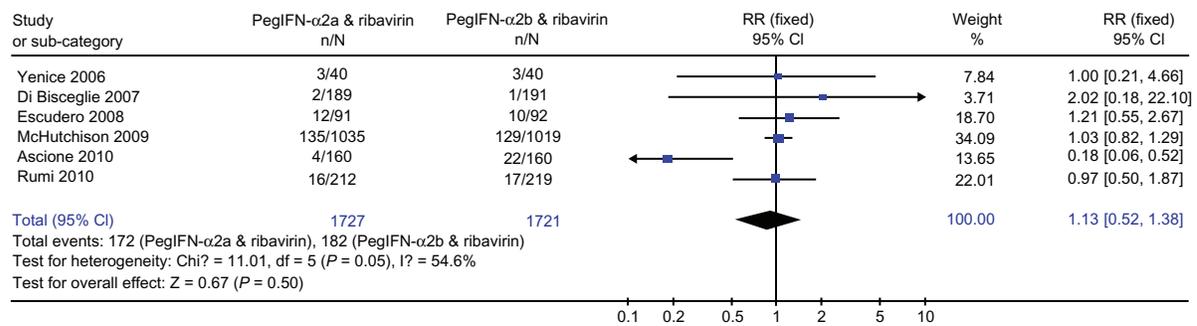
information with regards to the histological and biochemical response to treatment, the low level of methodological quality (including inadequate allocation sequence generation, inadequate allocation concealment, and a lack of double-blinding in most studies), and inconsistent ribavirin treatment regimens 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-α2a with ribavirin versus peginterferon with ribavirin
Comparison:	02 Adverse events
Outcome:	01 Discontinuation of treatment for safety reasons

Study or sub-category	PegIFN-α2a & ribavirin n/N	PegIFN-α2b & ribavirin n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Yenice 2006	3/40	3/40		7.84	1.00 [0.21, 4.66]
Di Bisceglie 2007	2/189	1/191		3.71	2.02 [0.18, 22.10]
Escudero 2008	12/91	10/92		18.70	1.21 [0.55, 2.67]
McHutchison 2009	135/1035	129/1019		34.09	1.03 [0.82, 1.29]
Ascione 2010	4/160	22/160		13.65	0.18 [0.06, 0.52]
Rumi 2010	16/212	17/219		22.01	0.97 [0.50, 1.87]
Total (95% CI)	1727	1721		100.00	1.13 [0.52, 1.38]

Total events: 172 (PegIFN-α2a & ribavirin), 182 (PegIFN-α2b & ribavirin)
Test for heterogeneity: Chi² = 11.01, df = 5 (P = 0.05), I² = 54.6%
Test for overall effect: Z = 0.67 (P = 0.50)

0.1 0.2 0.5 1 2 5 10

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-α2a plus ribavirin or PEG-IFN-α2b 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-α2a and PEG-IFN-α2b 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-α2a and PEG-IFN-α2b may influence response rates. According to their different dosages the serum exposure of PEG-IFN-α2a was 16-fold greater than PEG-IFN-α2b. And the serum concentration of PEG-IFN-α2a was more stable than PEG-IFN-α2b. When the patient body weight increased the serum exposure of PEG-IFN-α2a decreased for it was given as a fixed dose.[5] Nevertheless, a higher dose of PEG-IFN-α2a didn't necessarily lead to a significantly higher SVR of obese patients.[17] With further research the dosage of PEG-IFN-α2a 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-α2a 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-α2b 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-α2a 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-α2a 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-α2a or PEG-IFN-α2b 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-α2a was slightly more effective than PEG-IFN-α2b on achieving EVR and ETR. Nevertheless, this better early performance of PEG-IFN- α2a 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-α2a, 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-α2a 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 nongenetype-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-α2a and PEG-IFN-α2b, a more detailed trial with a longer period of follow-up is necessary in order to discern them.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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