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REVIEW

Differences in clinical outcomes among hepatitis C genotype 1-infected patients treated with peginterferon alpha-2a or peginterferon alpha-2b plus ribavirin: a meta-analysis

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Background: With the development of new direct acting antiviral (DAA) therapy for hepatitis C, the backbone peginterferon alpha used may be of importance in maximizing treatment outcomes. To this end, the rates of sustained virologic response (SVR), relapse, and treatment discontinuation among hepatitis C genotype 1-infected patients given peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin were determined using a meta-analysis.

Methods: Randomized trials examining peginterferon alpha-2a or peginterferon alpha-2b co-administered with ribavirin for 48 weeks were included. Data were extracted on SVR, relapse, and treatment discontinuations for treatment-naïve and treatment-experienced patients. Pooled proportions using fixed and random effects meta-analysis were calculated.

Results: Twenty-six trials provided data on patients treated with peginterferon alpha-2a plus ribavirin, and 19 trials provided data on patients treated with peginterferon alpha-2b plus ribavirin. Five trials were direct head-to-head evaluations. In the subset of trials that included head-to-head evaluations, no significant differences were observed between the two treatments for treatment-naïve (relative risk [RR]: 1.07, 95% confidence intervals [CI]: 0.97–1.18) and treatment-experienced patients (RR: 1.27, 95% CI: 0.58–2.77). Using only active trial arms, a larger proportion of the treatment-naïve patients who were provided peginterferon alpha-2a plus ribavirin achieved a SVR (47%), which is greater than that of treatment-naïve patients who were provided peginterferon alpha-2b plus ribavirin (40% SVR achievement); however, a larger proportion of treatment-experienced patients who were provided peginterferon alpha-2b plus ribavirin achieved a SVR (16%) when compared with treatment-experienced patients given peginterferon alpha-2a plus ribavirin (12% SVR achievement). A larger proportion of relapses occurred among both treatment-naïve and treatment-experienced patients given peginterferon alpha-2a plus ribavirin, when compared with treatment-naïve and treatment-experienced patients taking peginterferon alpha-2b plus ribavirin. The proportion of patients discontinuing treatment was greater among treatment-naïve patients taking peginterferon alpha-2a plus ribavirin, but smaller among treatment-experienced patients.

Conclusion: There are small differences in treatment outcomes for different types of peginterferon-alpha. Patient status and complexity of administration may differentiate clinical outcomes.

Keywords: hepatitis C, genotype 1, peginterferon, ribavirin, sustained virologic response, meta-analysis

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Introduction

The efficacy of peginterferon (also known as pegylated interferon) dosed concomitantly with ribavirin as a treatment for hepatitis C is influenced by patient clinical and genetic char-

acteristics, adherence, initial virologic response to treatment, and duration of therapy. It is possible that differences in treatment efficacy may also occur according to the type of peginterferon used (peginterferon alpha-2a or peginterferon alpha-2b). It is noteworthy that findings from a recently conducted large-scale randomized trial indicate that peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin do not differ significantly in terms of sustained virologic response (SVR) and tolerability when provided to treatment-naïve genotype 1-infected hepatitis C patients.[1] The finding from a single clinical trial, however, is rarely definitive.

Direct-acting antivirals (DAAs) in combination with peginterferon and ribavirin have dramatically improved treatment outcomes in patients infected with genotype 1 hepatitis C.[2,3] Despite the impact of these individual medications on treatment outcomes, it is possible that the specific peginterferon alpha used as a backbone may help to maximize the likelihood of therapeutic success, and therefore, this question remains relevant to current hepatitis C management. In the current study, the rate of SVR, treatment relapse, and treatment discontinuations in hepatitis C genotype 1-infected patients receiving either standard-dose peginterferon alpha-2a or peginterferon alpha-2b concomitantly with standard dose ribavirin were determined by applying a meta-analysis of all available treatment arms of the specified drug combinations from published randomized trials.

Methods

Eligibility

The arms of randomized trials involving standardized doses of peginterferon alpha-2a or peginterferon alpha-2b concomitantly administered with a standardized dose of ribavirin were included in the current study. Only trial arms that provided details on the number of genotype 1 patients allocated to treatment were included. Approved dosing standards were according to the European Association for the Study of the Liver (EASL) (alpha-2b 1.5 mcg per kg subcutaneously once weekly, alpha-2a 180 mcg subcutaneously once weekly, ribavirin total daily dose of 600–1400 mg depending upon weight). Trial arms were only included if they assessed 48 weeks of treatment administration. Studies had to be conducted in North America or Europe, as genotype 1 is the most common genotype in these regions.

Trial arms were excluded if they assessed loading doses and/or non-standardized doses of peginterferon or ribavirin, as were trials that recruited coinfected patients (eg, those with HIV or hepatitis B) and/or trials that exclusively recruited specific subgroups (eg, patients with compensated cirrhosis). Trial arms that included DAAs or additional hepatitis C medications were also excluded, as were any that did not break down outcomes exclusively for genotype 1 patients.

Search strategy

A search strategy was developed in consultation with a medical librarian. The included search terms were peginterferon OR peg-interferon OR pegylated interferon AND ribavirin AND hepatitis C. The search was limited to randomized trials in humans. Two investigators (EM and ED) searched independently, in duplicate, the following databases (from inception to week 32 [August 8–14], 2011): MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info, and Web of Science. Databases that include the full text of journals were also searched (*ScienceDirect* and *Ingenta*, including articles in full text from approximately 1700 journals since 1993). In addition, the bibliographies of published systematic reviews and relevant included trials were also searched. Searches were not limited by language, sex, or age.

Study selection

Two investigators (EM and ED) working independently, in duplicate, scanned all abstracts and obtained the full text reports of records indicating that the study was a randomized control trial evaluating peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin on the outcomes of interest. After obtaining full reports of the candidate studies, the same investigators independently assessed eligibility via full text review. Where required, a third investigator (CC) provided arbitration.

Data abstraction and endpoints

Two investigators (EM and ED) working independently, in duplicate, abstracted data. Data were abstracted only from the peginterferon-2a plus ribavirin or peginterferon-2b plus ribavirin treatment arms 48 weeks in length. Data on the primary outcome of interest (that is, SVR, which was defined as an undetectable HCV RNA at the end of the 24-week post therapy follow-up period) was abstracted, as well as data on the secondary outcomes of interest (the proportion of patients relapsing, which was defined as a recurrence of HCV RNA within the 24-week post therapy follow-up period), and the proportion of patients discontinuing treatment (defined as the discontinuation of all assigned study drugs during the set treatment period). The following study characteristics were also abstracted: study setting, study year, study

duration, and dosing regimens. Data were abstracted for both treatment-naïve patients (defined as patients with no exposure to peginterferon alpha plus ribavirin) and treatment-experienced patients (defined as patients with prior exposure to peginterferon alpha plus ribavirin).

Data analysis

In order to assess inter-rater reliability on inclusion of articles, the *Phi* statistic (φ) was calculated to provide a measure of inter-observer agreement independent of chance. The pooled weighted proportions were calculated by first stabilizing the variances of the raw proportions (r/n) using a Freeman–Tukey type arcsine square root transformation, and applying a fixed effects model. This was supplemented with a random effects model. While several methods of pooling proportions exist, the Freeman–Tukey method works well with both fixed and random effects meta-analyses and truncates at zero. This is a variance-stabilizing transformation that removes the dependence of the variance on the mean of the transformed proportion (ie, it corrects for over dispersion). Assessing heterogeneity in pooled proportions may be misleading, therefore the I^2 value is reported where applicable, and is interpreted with caution. In the case of trials that permitted a head-to-head evaluation, fixed and random effects relative risk meta-analyses were applied. Analyses were conducted using StatsDirect (v 2.5.2; StatsDirect Ltd, Cheshire, UK) and Comprehensive Meta-Analysis (v 2; Biostat, Englewood, NJ).

Results

Twenty-six trials provided data on patients treated with peginterferon alpha-2a plus ribavirin.[1,3–27] Eighteen of these trials were conducted among treatment-naïve patients,[1,3,10–23,26,27] and eight were conducted among treatment-experienced patients.[4–9,24,25] The characteristics of these trials are presented in Table 1. Nineteen trials provided data on patients treated with peginterferon alpha-2b plus ribavirin.[1,2,24–40] Thirteen of these trials were conducted among treatment-naïve patients,[1,2,26,27,32–40] and six were conducted among treatment-experienced patients.[24,25,28–31] The characteristics of these trials are presented in Table 2. Five trials were direct head-to-head evaluations of peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin.[1,24–27]

Forty-seven trials retrieved for detailed evaluation were excluded. The reasons for exclusion of these trials were that 20 assessed treatment combinations and/or treatment dosings that were not of interest,[41–52] twelve combined outcomes

Table 1 Trials reporting on outcomes among patients treated with peginterferon alpha-2a plus ribavirin

Trial	Region	Treatment duration (weeks)	Treatment experience	N	Peginterferon alpha-2a dose (μg/week)	Ribavirin dose (mg/day)
Fried et al[13]	International	48	Naïve	298	180	1000–1200
Hadziyannis et al[14]	International	48	Naïve	271	180	1000–1200
Herrine et al[5]	North America	48	Experienced	25	180	800–1000
Berg et al[4]	International	48	Experienced	35	180	1000–1200
Ferenci et al[11]	Europe	48	Naïve	95	180	1000–1200
Yenice et al[27]	Europe	48	Naïve	34	180	800–1200
Diago et al[10]	Europe	48	Naïve	475	180	1000–1200
Scotto et al[24]	Europe	48	Experienced	37	180	800–1200
Scotto et al[25]	Europe	48	Experienced	45	180	800–1200
von Wagner et al[21]	Europe	48	Naïve	352	180	1000–1200
Zeuzem et al[23]	International	48	Naïve	114	180	1000–1200
Hezode et al[15]	Europe	48	Naïve	82	180	1000–1200
Jensen et al[6]	International	48	Experienced	284	180	1000–1200
McHutchison et al[1]	North America	48	Naïve	1035	180	1000–1200
McHutchison et al[3]	North America	48	Naïve	75	180	1000–1200
Roberts et al[20]	Australia	48	Naïve	438	180	1000–1200
Rustgi et al[8]	North America	48	Experienced	104	180	1000–1200
Ferenci et al[12]	Europe	48	Naïve	127	180	1000–1200
Marcellin et al[17]	International	48	Naïve	212	180	1000–1200
McHutchison et al[7]	International	48	Experienced	114	180	1000–1200
Mendez-Navarro et al[18]	North America	48	Naïve	63	180	1000–1200
Reddy et al[19]	International	48	Naïve	189	180	1400–1600
Rumi et al[26]	Europe	48	Naïve	91	180	1000–1200
Zeuzem et al[22]	International	48	Naïve	441	180	1000–1200
Jacobson et al[16]	International	48	Naïve	361	180	1000–1200
Zeuzem et al[9]	International	48	Experienced	132	180	1000–1200

Table 2 Trials reporting on outcomes among patients treated with peginterferon alpha-2b plus ribavirin

Trial	Region	Treatment duration (weeks)	Treatment experience	N	Peginterferon alpha-2b dose (μg/kg/week)	Ribavirin dose (mg/day)
Scotto et al[38]	Europe	48	Naïve	26	1.5	800–1200
Mathew et al[30]	North America	48	Experienced	59	1.5	1000–1200
Maynard et al[31]	Europe	48	Experienced	82	1.5	800–1200
Yenice et al[27]	Europe	48	Naïve	34	1.5	800–1200
Jacobson et al[35]	North America	48	Naïve	1313	1.5	800–1400
Marcellin et al[29]	Europe	48	Experienced	3	1.5	800–1200
Shiffman et al[39]	North America	48	Naïve	48	1.5	800–1400
Sjogren et al[40]	North America	48	Naïve	29	1.5	1000–1200
Scotto et al[24]	Europe	48	Experienced	40	1.5	800–1200
Scotto et al[25]	Europe	48	Experienced	47	1.5	800–1200
Benhamou et al[32]	International	48	Naïve	226	1.5	1000–1200
Berg et al[33]	Europe	48	Naïve	225	1.5	800–1400
McHutchison et al[1]	North America	48	Naïve	1019	1.5	800–1400
Buti et al[34]	International	48	Naïve	86	1.5	800–1400
Kwo et al[36]	North America and Europe	48	Naïve	104	1.5	800–1400
Poordad et al[37]	North America	48	Naïve	70	1.5	800–1400
Rumi et al[26]	Europe	48	Naïve	87	1.5	800–1200
Bacon et al[28]	North America and Europe	48	Experienced	80	1.5	600–1400
Poordad et al[2]	North America and Europe	48	Naïve	344	1.5	600–1400

for genotype 1 with other genotypes,[53–64] nine did not provide extractable SVR data of interest,[65–73] and six assessed induction treatments.[74–79] Figure 1 shows a schematic of the trial selection process.

All 18 trials assessing peginterferon alpha-2a plus ribavirin among treatment-naïve patients provided data on SVR;[1,3,10–23,26,27] eleven of these also provided data on the rate of relapse,[1,3,12,15–20,22,23] and twelve provided data on treatment discontinuations.[1,3,10,11,15,16,18–23] All 13 trials assessing peginterferon alpha-2b plus ribavirin among treatment-naïve patients provided data on SVR;[1,2,26,27,32–40] nine also provided data on the rate of relapse,[1,2,33–37,39,40] and seven provided

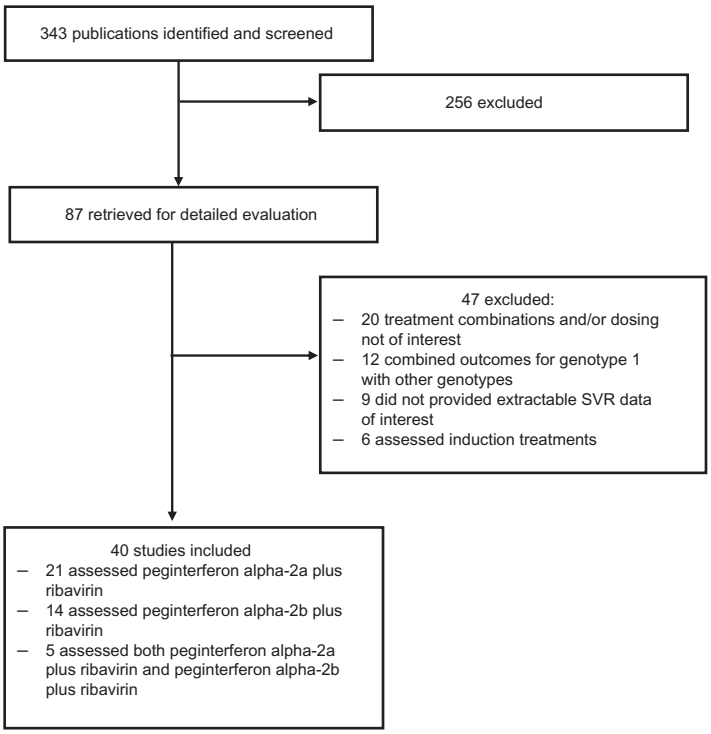

Figure 1 Study flow diagram.

Table 3 Fixed-effects proportional meta-analysis of sustained virologic response, relapse, and discontinuation for treatment-naïve patients

Treatment duration	Sustained virologic response			Relapse			Discontinuation		
	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)
Peginterferon alpha-2a plus ribavirin									
48 weeks	18	47% (45%–48%)	59% (21%–74%)	11	28% (26%–30%)	20% (0%–60%)	12	23% (21%–24%)	96% (95%–96%)
Peginterferon alpha-2b plus ribavirin									
48 weeks	13	40% (38%–41%)	35% (0%–65%)	9	23% (21%–25%)	76% (48%–86%)	7	19% (17%–21%)	96.7% (95%–97%)

Abbreviation: CI, confidence interval.

data on treatment discontinuations.[1,33,34,36–38,40] Table 3 shows the results of the fixed-effects proportional meta-analysis of SVR, relapse, and discontinuation for treatment-naïve patients (refer to the Appendix for the random-effects models). The pooled estimate of SVR among naïve patients treated for 48 weeks was 47% (95% confidence interval [CI]: 45%–48%) for those treated with peginterferon alpha-2a plus ribavirin, and 40% (95% CI: 38%–41%) for those treated with peginterferon alpha-2b plus ribavirin (Figure 2). The pooled rate of relapse was 28% (95% CI, 26%–30%) for naïve patients treated with peginterferon alpha-2a plus ribavirin for 48 weeks, and 23% (95% CI, 21%–25%) for those treated with peginterferon alpha-2b plus ribavirin for 48 weeks, and 28% (95% CI: 26%–30%) for those treated with peginterferon alpha-2b plus ribavirin for 48 weeks. The pooled discontinuation rate was 23% (95% CI: 21%–24%) and 19% (95% CI: 17%–21%) for naïve patients treated with peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin, respectively, for 48 weeks.

All eight trials assessing peginterferon alpha-2a plus ribavirin among treatment-experienced patients provided data on SVR;[4–9,24,25] two also provided data on the rate of relapse,[7,9] and three also provided data on treatment discontinuations.[7–9] All six trials assessing peginterferon alpha-2b plus ribavirin among treatment-experienced patients provided data on SVR;[24,25,28–31] one also provided data on the rate of relapse,[28]

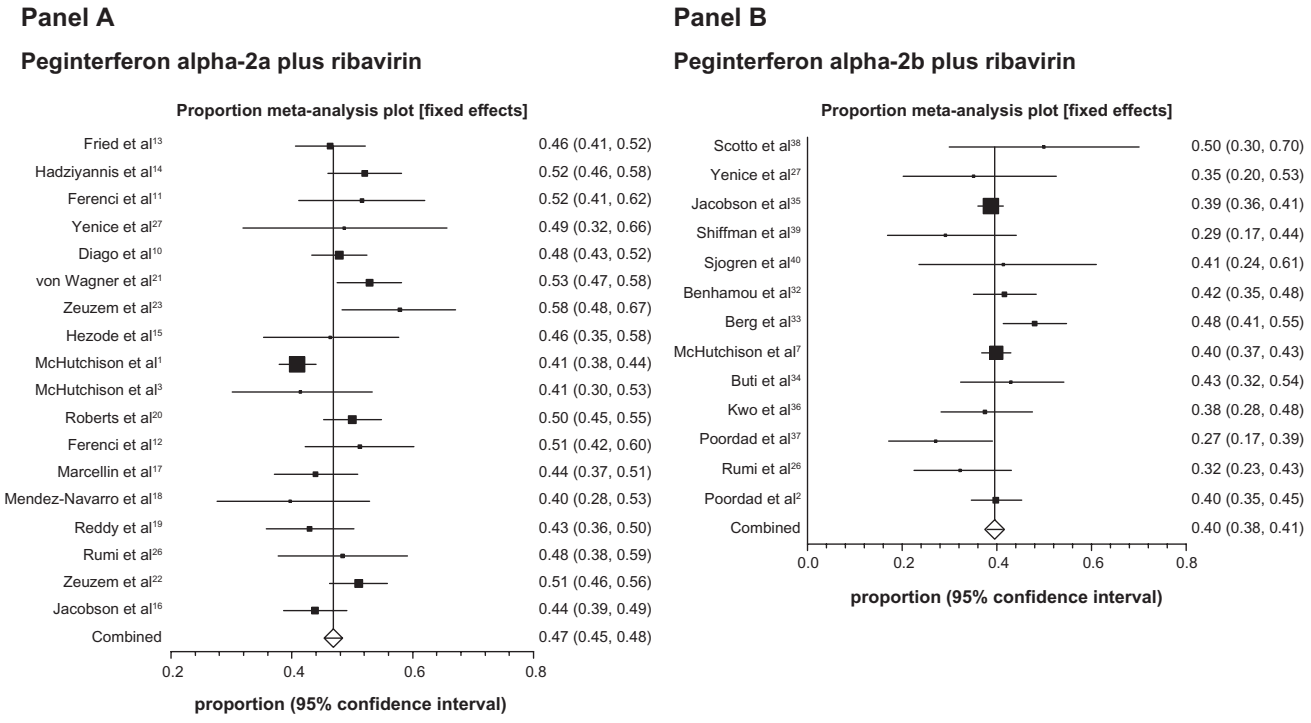

Figure 2 Fixed-effects proportional meta-analysis of sustained virologic response for treatment naïve-patients provided peginterferon alpha-2a plus ribavirin (**panel A**) or peginterferon alpha-2b plus ribavirin (**panel B**) for 48 weeks.

Table 4 Fixed-effects proportional meta-analysis of sustained virologic response, relapse, and discontinuation for treatment-experienced patients

Treatment duration	Sustained virologic response			Relapse			Discontinuation		
	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)
Peginterferon alpha-2a plus ribavirin									
48 weeks	8	12% (10%–14%)	86.7% (77%–92%)	2	60% (49%–70%)	NA	3	40% (35%–45%)	96% (94%–97%)
Peginterferon alpha-2b plus ribavirin									
48 weeks	1	16% (12%–20%)	0% (0%–61%)	1	33% (21%–46%)	NA	1	71% (64%–78%)	NA

Abbreviations: CI, confidence interval; NA, not applicable.

and one provided data on treatment discontinuations.[28] Table 4 shows the results of the fixed-effects proportional meta-analysis of SVR, relapse, and discontinuation for treatment-experienced patients (refer to the Appendix for the random-effects models). Pooled SVR estimates for experienced patients treated with peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin for 48 weeks were 12% (95% CI: 10%–14%) and 16% (95% CI: 12%–20%), respectively (Figure 3). The pooled rate of relapse was 60% (95% CI: 49%–70%) for experienced patients treated with peginterferon alpha-2a plus ribavirin for 48 weeks, and 33% (95% CI: 21%–46%) for those treated with peginterferon alpha-2b plus ribavirin for 48 weeks. Discontinuation of all treatments occurred in 40% (95% CI: 35%–45%) and 71% (95% CI: 64%–78%) of experienced patients treated with peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin, respectively, for 48 weeks.

Three trials provided data on SVR in head-to-head evaluations of peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin among treatment-naïve patients.[1,26,27] Another two trials provided this data in head-to-head evaluations of peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin among treatment-experienced patients.[24,25] Table 5 presents the results of the fixed-effects direct comparison meta-analysis of SVR for patients treated with peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin for 48 weeks (refer to the Appendix for the random-effects model). This analysis shows that there are no differences between peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin in terms of SVR for both treatment-naïve patients and treatment-experienced patients. There were insufficient data available to allow for a direct comparison of peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin for relapse and discontinuation of treatment.

Discussion

The results of the current study indicate that 47% of treatment-naïve patients provided with peginterferon

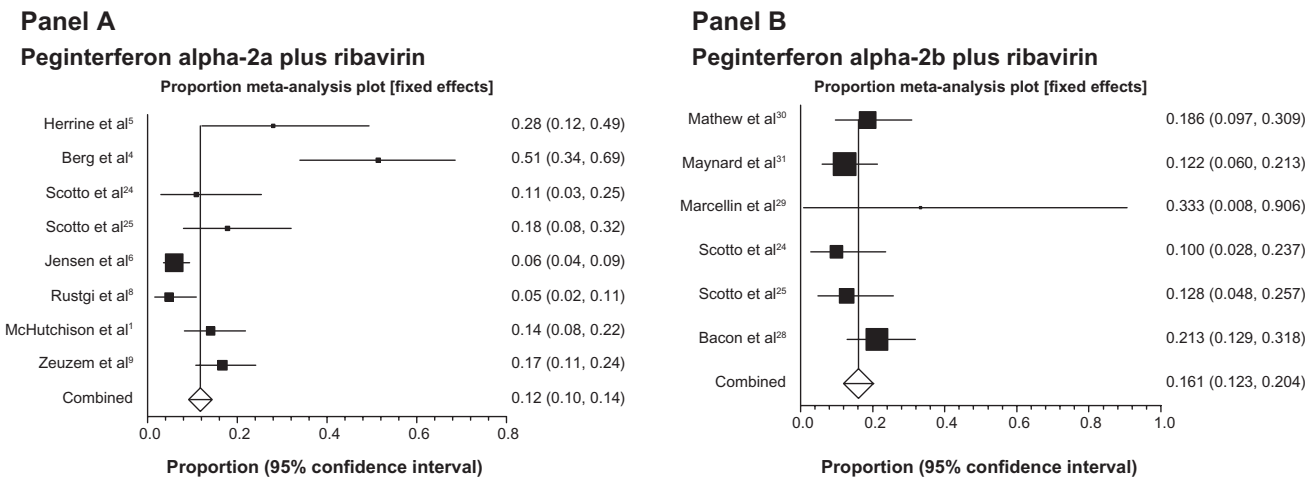

Figure 3 Fixed-effects proportional meta-analysis of sustained virologic response for treatment experienced-patients provided peginterferon alpha-2a plus ribavirin (**panel A**) or peginterferon alpha-2b plus ribavirin (**panel B**) for 48 weeks.

Table 5 Fixed-effects direct comparison meta-analysis of sustained virologic response for patients treated with peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin

Treatment duration	Peginterferon alpha-2a plus ribavirin			Peginterferon alpha-2b plus ribavirin			Direct comparison
	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)	RR
Treatment-naïve patients							
48 weeks	3	42% (39%–45%)	26% (0%–79%)	3	39% (36%–42%)	8% (0%–75%)	1.07 (0.97–1.18)
Treatment-experienced patients							
48 weeks	2	15% (8%–24%)	NA	2	12% (6%–20%)	NA	1.27 (0.58–2.77)

Abbreviations: CI, confidence interval; NA, not applicable; RR, relative risk.

alpha-2a plus ribavirin for 48 weeks achieved a SVR compared to 40% of treatment-naïve patients provided with peginterferon alpha-2b plus ribavirin for 48 weeks. For treatment-experienced patients, 12% dosed with peginterferon alpha-2a plus ribavirin for 48 weeks achieved a SVR compared to 16% who received peginterferon alpha-2b plus ribavirin. Among the subset of trials that included head-to-head evaluations of peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin, the current study's direct meta-analysis revealed no significant differences between treatments.

The current study's results indicate that a greater proportion of treatment-naïve patients receiving peginterferon alpha-2a plus ribavirin relapsed, when compared to those dosed with peginterferon alpha-2b plus ribavirin (28% and 23%, respectively). Similarly, a greater proportion of treatment-experienced patients relapsed following peginterferion alpha-2a plus ribavirin as compared to peginterferion alpha-2b plus ribavirin (60% and 33%, respectively). A low relapse rate is desirable following completion of a long and difficult course of antiviral therapy so this characteristic is a key parameter guiding the selection of peginterferon alpha.

The proportion of treatment-naïve patients discontinuing therapy was similar among peginterferon alpha-2a plus ribavirin recipients and those dosed with peginterferon alpha-2b plus ribavirin (23% and 19%, respectively). In contrast, the proportion of treatment-experienced patients discontinuing therapy was lower among those provided with peginterferon alpha-2a plus ribavirin than those provided peginterferon alpha-2b plus ribavirin (40% and 71%, respectively). It appears that this difference is primarily driven by greater on-treatment virologic clearance with peginterferon alpha-2a and, as a consequence, fewer patients interrupting their therapy for viral non-response criteria.

DAAs in combination with peginterferon alpha and ribavirin have dramatically improved SVR rates in genotype 1-infected treatment recipients.[2,3] Although the individual DAA used contributes significantly to the likelihood of success, peginterferon alpha plays a critical role in early virologic response and treatment outcomes. It is plausible that specific peginterferon alpha characteristics, including slope of early viral decay, timing of viral clearance, and relapse rate, may all influence the likelihood of success with DAA therapy utilizing a peginterferon alpha backbone. In the IDEAL study, a higher proportion of peginterferon alpha-2a recipients achieved early virologic clearance.[1] This may be important in minimizing the likelihood of DAA resistance developing during the early period of combination therapy dosing. A lower relapse rate was observed with peginterferon alpha-2b recipients. It remains to be determined whether this is also seen when combined with DAA therapy. Preliminary studies with boceprevir and telaprevir suggest that the impact of individual peginterferon alphas may be minimal.[46,80] However, larger studies are required to fully resolve this question.

There are limitations to the current study's analysis that should be considered when interpreting these results. Although there were large numbers of patients enrolled in many of the included trials, the power to differentiate across interventions may be a limitation. Data were combined from multiple trials which were not identical in their recruitment procedures, study design, or analysis plans. However, this is true of all meta-analyses,[81] and medical professionals were consulted at the outset to ensure that it was appropriate to pool these trials. The analysis of treatment-experienced patients is limited in that outcomes were not separately assessed for prior relapsers and null responders. However, in non-trial clinical practice, the history of prior on-treatment virologic response to treatment is often incomplete or missing. Therefore, the composite estimates provided for treatment-experienced patients in the current analysis are of clinical utility.

The current study's evaluation of head-to-head trials suggest equivalence in terms of SVR for those provided with peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin. However, the pooled analysis suggests a small benefit in terms of SVR with peginterferon alpha-2a plus ribavirin. This could be a result of a systemic

bias in the design of peginterferon alpha-2a trials to recruit 'better patients' for treatment (eg, less fibrosis, lower body weight, or more ribavirin per weight), and there may be better promotion of, or support for, patients to remain adherent. It is plausible that peginterferon alpha-2b trials are systematically designed to mandate more frequent or greater dose reductions of peginterferon alpha or ribavirin for side-effect management, which may reduce on-treatment viral response, increase post treatment relapse, and reduce SVR. Furthermore, if the side-effect profile for peginterferon alpha-2a is 'better' than peginterferon alpha-2b, this would promote adherence and maximize dosing resulting in superior SVR result. All of these issues are difficult to control for given insufficient reporting of this information.

Other meta-analyses assessing head-to-head evaluations of peginterferon alpha-2a and peginterferon alpha-2b have found comparable results to the current study, where peginterferon alpha-2a plus ribavirin is slightly favorable to peginterferon alpha-2b plus ribavirin in terms of SVR.[82–84] It is important to recognize, however, that the current meta-analysis differs from others in many important ways. Most notably, the inclusion criteria utilized in other meta-analyses were much broader than those of the current study, including, for example, trials that assessed induction-based treatment regimens, trials that assessed genotypes 3 and 4, and, in the case of Awad et al, trials that included patients coinfected with HIV.[83]

In conclusion, the current study identified small differences in patient outcomes according to the type of peginterferon alpha used in the treatment of hepatitis C. The information provided by this study may be of relevance to the interpretation of trial results evaluating peginterferon alpha in combination with DAAs, and in the selection of the peginterferon alpha backbone for future combination therapies.

Disclosure

The authors report no conflicts of interest in this work.

References

1. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med*. 2009;361(6):580–593.
2. Poordad F, McCone J, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364(13):1195–1206.
3. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med*. 2009;360(18):1827–1838.
4. Berg C, Goncales FL, Bernstein DE, et al. Re-treatment of chronic hepatitis C patients after relapse: efficacy of peginterferon-alpha-2a (40 kDa) and ribavirin. *J Viral Hepat*. 2006;13(7):435–440.
5. Herrine SK, Brown RS, Bernstein DE, Ondovik MS, Lentz E, Te H. Peginterferon alpha-2a combination therapies in chronic hepatitis C patients who relapsed after or had a viral breakthrough on therapy with standard interferon alpha-2b plus ribavirin: a pilot study of efficacy and safety. *Dig Dis Sci*. 2005;50(4):719–726.
6. Jensen DM, Marcellin P, Freilich B, et al. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial. *Ann Intern Med*. 2009;150(8):528–540.
7. McHutchison JG, Manns MP, Muir AJ, et al. Telaprevir for previously treated chronic HCV infection. *N Engl J Med*. 2010;362(14):1292–1303.
8. Rustgi VK, Lee WM, Lawitz E, et al. Merimepodib, pegylated interferon, and ribavirin in genotype 1 chronic hepatitis C pegylated interferon and ribavirin nonresponders. *Hepatology*. 2009;50(6):1719–1726.
9. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med*. 2011;364(25):2417–2428.
10. Diago M, Olveira A, Solà R, et al. Treatment of chronic hepatitis C genotype 1 with peginterferon-alpha 2a (40 kDa) plus ribavirin under routine clinical practice in Spain: early prediction of sustained virological response rate. *Aliment Pharmacol Ther*. 2007;25(8):899–906.
11. Ferenci P, Formann E, Laferl H, et al. Randomized, double-blind, placebo-controlled study of peginterferon alfa-2a (40 KD) plus ribavirin. with or without amantadine in treatment-naive patients with-chronic hepatitis C genotype 1 infection. *J Hepatol*. 2006;44(2):275–282.
12. Ferenci P, Laferl H, Scherzer TM, et al. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. *Gastroenterology*. 2010;138(2):503–512.
13. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347(13):975–982.
14. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004;140(5):346–355.
15. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med*. 2009;360(18):1839–1850.
16. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011;364(25):2405–2416.
17. Marcellin P, Gish RG, Gitlin N, et al. Safety and efficacy of viramidine versus ribavirin in ViSER2: Randomized, double-blind study in therapy-naive hepatitis C patients. *J Hepatol*. 2010;52(1):32–38.
18. Méndez-Navarro J, Chirino RA, Corey KE, et al. A randomized controlled trial of double versus triple therapy with amantadine for genotype 1 chronic hepatitis C in Latino patients. *Dig Dis Sci*. 2010;55(9):2629–2635.
19. Reddy KR, Shiffman ML, Rodriguez-Torres M, et al. Induction pegylated interferon alfa-2a and high dose ribavirin do not increase SVR in heavy patients with HCV genotype 1 and high viral loads. *Gastroenterology*. 2010;139(6):1972–1983.
20. Roberts SK, Weltman MD, Crawford DHG, et al. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. *Hepatology*. 2009;50(4):1045–1055.
21. von Wagner M, Hofmann WP, Teuber G, et al. Placebo-controlled trial of 400 mg amantadine combined with peginterferon alfa-2a and ribavirin for 48 weeks in chronic hepatitis C virus-1 infection. *Hepatology*. 2008;48(5):1404–1411.
22. Zeuzem S, Sulkowski MS, Lawitz EJ, et al. Albinterferon Alfa-2b was not inferior to pegylated interferon-α in a randomized trial of patients with chronic hepatitis C virus genotype 1. *Gastroenterology*. 2010;139(4):1257–1266.
23. Zeuzem S, Yoshida EM, Benhamou Y, et al. Albinterferon alfa-2b dosed every two or four weeks in interferon-naive patients with genotype 1 chronic hepatitis C. *Hepatology*. 2008;48(2):407–417.

24. Scotto G, Fazio V, Fornabaio C, et al. Early and sustained virological response in non-responders with chronic hepatitis C: a randomized open-label study of pegylated interferon-alpha-2a versus pegylated interferon-alpha-2b. *Drugs*. 2008;68(6):791–801.
25. Scotto G, Fazio V, Fornabaio C, et al. Peg-interferon alpha-2a versus Peg-interferon alpha-2b in nonresponders with HCV active chronic hepatitis: a pilot study. *J Interferon Cytokine Res*. 2008;28(10):623–629.
26. Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. *Gastroenterology*. 2010;138(1):108–115.
27. Yenice N, Mehtap O, Gümrah M, Arican N. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. *Turk J Gastroenterol*. 2006;17(2):94–98.
28. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364(13):1207–1217.
29. Marcellin P, Horsmans Y, Nevens F, et al. Phase 2 study of the combination of merimepodib with peginterferon-alpha 2b, and ribavirin in nonresponders to previous therapy for chronic hepatitis C. *J Hepatol*. 2007;47(4):476–483.
30. Mathew A, Peiffer LP, Rhoades K, McGarrity T. Sustained viral response to pegylated interferon alpha-2b and ribavirin in chronic hepatitis C refractory to prior treatment. *Dig Dis Sci*. 2006;51(11):1956–1961.
31. Maynard M, Pradat P, Bailly F, et al. Amantadine triple therapy for non-responder hepatitis C patients. Clues for controversies (ANRS HC 03 BITRI). *J Hepatol*. 2006;44(3):484–490.
32. Benhamou Y, Afdhal NH, Nelson DR, et al. A phase III study of the safety and efficacy of viramidine versus ribavirin in treatment-naïve patients with chronic hepatitis C: ViSER1 results. *Hepatology*. 2009;50(3):717–726.
33. Berg T, Weich V, Teuber G, et al. Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients. *Hepatology*. 2009;50(2):369–377.
34. Buti M, Lurie Y, Zakharova NG, et al. Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response. *Hepatology*. 2010;52(4):1201–1207.
35. Jacobson IM, Brown RS Jr, Freilich B, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology*. 2007;46(4):971–981.
36. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet*. 2010;376(9742):705–716.
37. Poordad F, Lawitz E, Shiffman ML, et al. Virologic response rates of weight-based taribavirin versus ribavirin in treatment-naive patients with genotype 1 chronic hepatitis C. *Hepatology*. 2010;52(4):1208–1215.
38. Scotto G, Fazio V, Palumbo E, Cibelli DC, Saracino A, Angarano G. Treatment of genotype 1b HCV-related chronic hepatitis: efficacy and toxicity of three different interferon alfa-2b/ribavirin combined regimens in naive patients. *New Microbiol*. 2005;28(1):23–29.
39. Shiffman ML, Salvatore J, Hubbard S, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. *Hepatology*. 2007;46(2):371–379.
40. Sjogren MH, Sjogren R, Lyons MF, et al. Antiviral response of HCV genotype 1 to consensus interferon and ribavirin versus pegylated interferon and ribavirin. *Dig Dis Sci*. 2007;52(6):1540–1547.
41. Bacon BR, Shiffman ML, Mendes F, et al. Retreating chronic hepatitis C with daily interferon alfacon-1/ribavirin after nonresponse to pegylated interferon/ribavirin: DIRECT results. *Hepatology*. 2009;49(6):1838–1846.
42. Braga EL, Lyra AC, Nascimento L, Netto E, Kalabrik L, Lyra LGC. Daily interferon induction regimen using different manufactured interferons (alpha-2A or alpha-2B) in combination with ribavirin for treatment of chronic hepatitis C: a prospective randomized study. *Arq Gastroenterol*. 2006;43(4):275–279.
43. Di Bisceglie AM, Shiffman ML, Everson GT, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med*. 2008;359(23):2429–2441.
44. Fargion S, Borzio M, Maraschi A, Cargnel A, Gruppo Epatologico Lombardo. Triple antiviral therapy in HCV positive patients who failed prior combination therapy. *World J Gastroenterol*. 2006;12(33):5293–5300.
45. Ho SB, Aqel B, Dieperink E, et al. US multicenter pilot study of daily consensus interferon (CIFN) plus ribavirin for "difficult-to-treat" HCV genotype 1 patients. *Dig Dis Sci*. 2011;56(3):880–888.
46. Marcellin P, Forns X, Goeser T, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. *Gastroenterology*. 2011;140(2):459–468.
47. McHutchison JG, Patel K, Schiff ER, et al. Clinical trial: interferon alpha-2b continuous long-term therapy vs repeated 24-week cycles for re-treating chronic hepatitis C. *Aliment Pharmacol Ther*. 2008;27(5):422–432.
48. Peck-Radosavljevic M, Boletis J, Besisik F, et al. Low-dose peginterferon alfa-2a is safe and produces a sustained virologic response in patients with chronic hepatitis C and end-stage renal disease. *Clin Gastroenterol Hepatol*. 2011;9(3):242–248.
49. Pellicano R, Craxi A, Almasio PL, et al. Interferon beta-1a alone or in combination with ribavirin: a randomized trial to compare efficacy and safety in chronic hepatitis C. *World J Gastroenterol*. 2005;11(29):4484–4489.
50. Wright M, Grieve R, Roberts J, Main J, Thomas HC, UK Mild Hepatitis C Trial Investigators. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess*. 2006;10(21):1–113.
51. Horsmans Y, Colle I, Van Vlierberghe H, et al. Weekly pegylated interferon alpha-2b vs daily interferon a-2b versus standard regimen of interferon a-2b in the treatment of patients with chronic hepatitis C virus infection. *Acta Gastroenterol Belg*. 2008;71(3):293–297.
52. Roffi L, Colloredo G, Pioltelli P, et al. Pegylated interferon-alpha 2b plus ribavirin: an efficacious and well-tolerated treatment regimen for patients with hepatitis C virus related histologically proven cirrhosis. *Antiv Ther*. 2008;13(5):663–673.
53. Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. *Gastroenterology*. 2010;138(1):116–122.
54. Bergmann JF, Vrolijk JM, van der Schaar P, et al. Gamma-glutamyltransferase and rapid virological response as predictors of successful treatment with experimental or standard peginterferon-alpha-2b in chronic hepatitis C non-responders. *Liver Int*. 2007;27(9):1217–1225.
55. Brady DE, Torres DM, An JW, Ward JA, Lawitz E, Harrison SA. Induction pegylated interferon alfa-2b in combination with ribavirin in patients with genotypes 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study. *Clin Gastroenterol Hepatol*. 2010;8(1):66–71.
56. Ciancio A, Picciotto A, Giordanino C, et al. A randomized trial of pegylated-interferon-alpha 2a plus ribavirin with or without amantadine in the re-treatment of patients with chronic hepatitis C not responding to standard interferon and ribavirin. *Aliment Pharmacol Ther*. 2006;24(7):1079–1086.
57. Crespo M, Sauleda S, Esteban JI, et al. Peginterferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin for chronic hepatitis C in HIV-coinfected patients. *J Viral Hepat*. 2007;14(4):228–238.
58. Falasca K, Ucciferri C, Mancino P, Gorgoretti V, Pizzigallo E, Vecchiet J. Use of epoetin beta during combination therapy of infection with hepatitis c virus with ribavirin improves a sustained viral response. *J Med Virol*. 2010;82(1):49–56.
59. Gish RG, Arora S, Rajender Reddy K, et al. Virological response and safety outcomes in therapy-naive patients treated for chronic hepatitis C with taribavirin or ribavirin in combination with pegylated interferon alfa-2a: a randomized, phase 2 study. *J Hepatol*. 2007;47(1):51–59.

60. Helbling B, Jochum W, Stamenic I, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. *J Viral Hepat*. 2006;13(11):762–769.
61. Lodato F, Azzaroli F, Brillanti S, et al. Higher doses of peginterferon alpha-2b administered twice weekly improve sustained virological response in difficult-to-treat patients with chronic hepatitis C: results of a pilot randomized study. *J Viral Hepat*. 2005;12(5):536–542.
62. Mangia A, Ricci GL, Persico M, et al. A randomized controlled trial of pegylated interferon alpha-2a (40 KD) or interferon alpha-2a plus ribavirin and amantadine vs interferon alpha-2a and ribavirin in treatment-naive patients with chronic hepatitis C. *J Viral Hepat*. 2005;12(3):292–299.
63. Meyer-Wyss B, Rich P, Egger H, et al. Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5 microg/kg) combined with ribavirin in interferon-naïve patients with chronic hepatitis C and up to moderate fibrosis. *J Viral Hepat*. 2006;13(7):457–465.
64. Nevens F, Van Vlierberghe H, D'Heygere F, et al. A randomized, open-label, multicenter study evaluating the efficacy of peginterferon alfa-2a versus interferon alfa-2a, in combination with ribavirin, in naïve and relapsed chronic hepatitis C patients. *Acta Gastroenterol Belg*. 2010;73(2):223–228.
65. Di Bisceglie AM, Ghalib RH, Hamzeh FM, Rustgi VK. Early virologic response after peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin treatment in patients with chronic hepatitis C. *J Viral Hepat*. 2007;14(10):721–729.
66. Homoncik M, Sieghart W, Formann E, et al. Erythropoietin treatment is associated with more severe thrombocytopenia in patients with chronic hepatitis C undergoing antiviral therapy. *Am J Gastroenterol*. 2006;101(10):2275–2282.
67. Pockros PJ, Nelson D, Godofsky E, et al. R1626 plus peginterferon alfa-2a provides potent suppression of hepatitis C virus RNA and significant antiviral synergy in combination with ribavirin. *Hepatology*. 2008;48(2):385–397.
68. Sporea I, Danila M, Sirli R, Popescu A, Laza A, Baditoiu L. Comparative study concerning the efficacy of Peg-IFN alpha-2a versus Peg-IFN alpha-2b on the early virological response (EVR) in patients with chronic viral C hepatitis. *J Gastrointestin Liver Dis*. 2006;15(2):125–130.
69. Cheng WSC, Roberts SK, McCaughan G, et al. Low virological response and high relapse rates in hepatitis C genotype 1 patients with advanced fibrosis despite adequate therapeutic dosing. *J Hepatol*. 2010;53(4):616–623.
70. Mangia A, Minerva N, Bacca D, et al. Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. *Hepatology*. 2008;47(1):43–50.
71. Langlet P, D'Heygere F, Henrion J, et al. Clinical trial: a randomized trial of pegylated-interferon-alpha-2a plus ribavirin with or without amantadine in treatment-naive or relapsing chronic hepatitis C patients. *Aliment Pharmacol Ther*. 2009;30(4):352–363.
72. Mimidis K, Papadopoulos VP, Elefsiniotis I, et al. Hepatitis C virus survival curve analysis in naive patients treated with peginterferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of peginterferon and predictability of sustained viral response from early virologic data. *J Gastrointestin Liver Dis*. 2006;15(3):213–219.
73. Napoli N, Giannelli G, Antonaci A, Antonaci S. The use of different Peg-interferon alpha-2b regimens plus ribavirin in HCV-1b-infected patients after rapid virological response does not affect the achievement of sustained virological response. *J Viral Hepat*. 2008;15(4):300–304.
74. Angelico M, Koehler-Horst B, Piccolo P, et al. Peginterferon alpha-2a and ribavirin versus peginterferon alpha-2a monotherapy in early virological responders and peginterferon alpha-2a and ribavirin versus peginterferon alpha-2a, ribavirin and amantadine triple therapy in early virological nonresponders: the SMIEC II trial in naïve patients with chronic hepatitis C. *Eur J Gastroenterol Hepatol*. 2008;20(7):680–687.
75. Bronowicki JP, Ouzan D, Asselah T, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. *Gastroenterology*. 2006;131(4):1040–1048.
76. Bruno S, Cammà C, Di Marco V, et al. Peginterferon alfa-2b plus ribavirin for naive patients with genotype 1 chronic hepatitis C: a randomized controlled trial. *J Hepatol*. 2004;41(3):474–481.
77. Carr C, Hollinger FB, Yoffe B, et al. Efficacy of interferon alpha-2b induction therapy before retreatment for chronic hepatitis C. *Liver Int*. 2007;27(8):1111–1118.
78. van Soest H, van der Schaar PJ, Koek GH, et al. No beneficial effects of amantadine in treatment of chronic hepatitis C patients. *Dig Liver Dis*. 2010;42(7):496–502.
79. Zeuzem S, Pawlotsky JM, Lukasiewicz E, et al. International, multicenter, randomized, controlled study comparing dynamically individualized versus standard treatment in patients with chronic hepatitis C. *J Hepatol*. 2005;43(2):250–257.
80. Flamm S, Lawitz E, Jacobson I, et al. High sustained virological response (SVR) among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir (BOC) plus peginterferon alfa-2a/ribavirin. *J Hepatol*. 2011;54:S541–S542.
81. Moayyedi P. Meta-analysis: Can we mix apples and oranges? *Am J Gastroenterol*. 2004;99(12):2297–2301.
82. Alavian S, Behnava B, Tabatabaei. The comparative efficacy and safety of peginterferon alpha-2a vs 2b for the treatment of chronic HCV infection: A Meta-Analysis. *Hepat Mon*. 2010;10(2):121–131.
83. Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alpha-2b in chronic hepatitis c: systematic review of randomized trials. *Hepatology*. 2010;51(4):1176–1184.
84. Singal A, Jampana S, Anand B. Peginterferon alfa-2a is superior to peginterferon alfa-2b in the treatment of naïve patients with hepatitis C virus infection: meta-analysis of randomized controlled trials. *Dig Dis Sci*. 2011;56(8):2221–2226.

Appendix

Table A Random-effects proportional meta-analysis of sustained virologic response, relapse, and discontinuation for treatment-naïve patients

Treatment duration	Sustained virologic response			Relapse			Discontinuation		
	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)
Peginterferon alpha-2a plus ribavirin									
48 weeks	18	48% (45%–50%)	59% (21%–74%)	11	28% (25%–30%)	20% (0%–60%)	15	26% (20%–34%)	96% (95%–96%)
Peginterferon alpha-2b plus ribavirin									
48 weeks	13	40% (37%–42%)	35% (0%–65%)	9	24% (19%–29%)	76% (48%–86%)	7	31% (16%–48%)	96.7% (95%–97%)

Abbreviation: CI, confidence interval.

Table B Random-effects proportional meta-analysis of sustained virologic response, relapse, and discontinuation for treatment-experienced patients

Treatment duration	Sustained virologic response			Relapse			Discontinuation		
	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)
Peginterferon alpha-2a plus ribavirin									
48 weeks	8	17% (9%–25%)	86.7% (77%–92%)	2	60% (48%–71%)	NA	3	40% (15%–68%)	96% (94%–97%)
Peginterferon alpha-2b plus ribavirin									
48 weeks	1	16% (12%–20%)	0% (0%–61%)	1	33% (21%–46%)	NA	1	71% (64%–78%)	NA

Abbreviations: CI, confidence interval; NA, not applicable.

Table C Random-effects direct comparison meta-analysis of sustained virologic response for patients treated with peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin

Treatment duration	Peginterferon alpha-2a plus ribavirin			Peginterferon alpha-2b plus ribavirin			Direct comparison
	Arms	Proportion (95% CI)	I^2 (95% CI)	Arms	Proportion (95% CI)	I^2 (95% CI)	RR
Treatment-naïve patients							
48 weeks	3	43% (38%–48%)	26% (0%–79%)	3	39% (35%–42%)	8% (0%–75%)	1.21 (0.91–1.60)
Treatment-experienced patients							
48 weeks	2	15% (8%–24%)	NA	2	12% (6%–20%)	NA	1.27 (0.58–2.78)

Abbreviations: CI, confidence interval; NA, not applicable; RR, relative risk.