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 patients (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

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. 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. 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 F 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 al13 | International | 48                         | Naïve                | 298| 180                                  | 1000–1200                |
| Hadziyannis et al14 | International | 48                         | Naïve                | 271| 180                                  | 1000–1200                |
| Herrine et al15 | North America | 48                         | Experienced          | 25 | 180                                  | 800–1000                 |
| Berg et al16   | International | 48                         | Experienced          | 35 | 180                                  | 1000–1200                |
| Ferenci et al17 | Europe      | 48                         | Naïve                | 95 | 180                                  | 1000–1200                |
| Yenice et al18 | Europe      | 48                         | Naïve                | 34 | 180                                  | 800–1200                 |
| Diago et al19  | Europe      | 48                         | Naïve                | 475| 180                                  | 1000–1200                |
| Scotto et al20 | Europe      | 48                         | Experienced          | 37 | 180                                  | 800–1200                 |
| Scotto et al21 | Europe      | 48                         | Experienced          | 45 | 180                                  | 800–1200                 |
| von Wagner et al22 | Europe      | 48                         | Naïve                | 352| 180                                  | 1000–1200                |
| Zeuzem et al23 | International | 48                         | Naïve                | 114| 180                                  | 1000–1200                |
| Hezode et al24 | Europe      | 48                         | Naïve                | 82 | 180                                  | 1000–1200                |
| Jensen et al25 | International | 48                         | Experienced          | 284| 180                                  | 1000–1200                |
| McHutchison et al26 | North America | 48                         | Naïve                | 1035| 180                                 | 1000–1200                |
| Roberts et al27 | North America | 48                         | Naïve                | 75 | 180                                  | 1000–1200                |
| Rustgi et al28 | Australia   | 48                         | Naïve                | 438| 180                                  | 1000–1200                |
| Ferenci et al29 | North America | 48                         | Experienced          | 104| 180                                  | 1000–1200                |
| Marcellin et al30 | North America | 48                         | Naïve                | 127| 180                                  | 1000–1200                |
| McHutchison et al31 | International | 48                         | Naïve                | 212| 180                                  | 1000–1200                |
| Mendez-Navarro et al32 | North America | 48                         | Naïve                | 63 | 180                                  | 1000–1200                |
| Reddy et al33 | International | 48                         | Naïve                | 189| 180                                  | 1400–1600                |
| Rumi et al34 | Europe      | 48                         | Naïve                | 91 | 180                                  | 1000–1200                |
| Zeuzem et al35 | International | 48                         | Naïve                | 441| 180                                  | 1000–1200                |
| Jacobson et al36 | International | 48                         | Naïve                | 361| 180                                  | 1000–1200                |
| Zeuzem et al37 | International | 48                         | Experienced          | 132| 180                                  | 1000–1200                |
for genotype 1 with other genotypes, nine did not provide extractable SVR data of interest, and six assessed induction treatments. 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; eleven of these also provided data on the rate of relapse, and twelve provided data on treatment discontinuations. All 13 trials assessing peginterferon alpha-2b plus ribavirin among treatment-naïve patients provided data on SVR, nine also provided data on the rate of relapse, and seven provided data on treatment discontinuations.

### 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 | Europe | 48 | Naïve | 26 | 1.5 | 800–1200 |
| Mathew et al | North America | 48 | Experienced | 59 | 1.5 | 1000–1200 |
| Maynard et al | Europe | 48 | Experienced | 82 | 1.5 | 800–1200 |
| Yenice et al | Europe | 48 | Naïve | 34 | 1.5 | 800–1200 |
| Jacobson et al | North America | 48 | Naïve | 1313 | 1.5 | 800–1400 |
| Marcellin et al | Europe | 48 | Experienced | 3 | 1.5 | 800–1200 |
| Shiffman et al | North America | 48 | Naïve | 48 | 1.5 | 800–1400 |
| Sjogren et al | North America | 48 | Naïve | 29 | 1.5 | 1000–1200 |
| Scotto et al | Europe | 48 | Experienced | 40 | 1.5 | 800–1200 |
| Scotto et al | Europe | 48 | Experienced | 47 | 1.5 | 800–1200 |
| Benhamou et al | International | 48 | Naïve | 226 | 1.5 | 1000–1200 |
| Berg et al | Europe | 48 | Naïve | 225 | 1.5 | 800–1400 |
| McHutchison et al | North America | 48 | Naïve | 1019 | 1.5 | 800–1400 |
| Buti et al | International | 48 | Naïve | 86 | 1.5 | 800–1400 |
| Kwo et al | North America and Europe | 48 | Naïve | 104 | 1.5 | 800–1400 |
| Poordad et al | North America | 48 | Naïve | 70 | 1.5 | 800–1400 |
| Rumit et al | Europe | 48 | Naïve | 87 | 1.5 | 800–1200 |
| Bacon et al | North America and Europe | 48 | Experienced | 80 | 1.5 | 600–1400 |
| Poordad et al | North America and Europe | 48 | Naïve | 344 | 1.5 | 600–1400 |

Figure 1 Study flow diagram.
data on treatment discontinuations.\textsuperscript{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. 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;\textsuperscript{4–9,24,25} two also provided data on the rate of relapse,\textsuperscript{7,9} and three also provided data on treatment discontinuations.\textsuperscript{7–9} All six trials assessing peginterferon alpha-2b plus ribavirin among treatment-experienced patients provided data on SVR;\textsuperscript{24,25,28–31} one also provided data on the rate of relapse.\textsuperscript{28}

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 |
|--------------------|-----------------------------|---------|----------------|
| Peginterferon alpha-2a plus ribavirin | | | |
| 48 weeks | 18 | 47% (45%–48%) | 11 | 28% (26%–30%) | 12 | 23% (21%–24%) |
| Peginterferon alpha-2b plus ribavirin | | | |
| 48 weeks | 13 | 40% (38%–41%) | 9 | 23% (21%–25%) | 7 | 19% (17%–21%) |

**Panel A**

Peginterferon alpha-2a plus ribavirin

**Panel B**

Peginterferon alpha-2b plus ribavirin

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 |
|--------------------|------------------------------|---------|-----------------|
| Peginterferon alpha-2a plus ribavirin |                         |         |                 |
| 48 weeks           | Peginterferon alpha-2a plus ribavirin | 8 | 12% (10%–14%) | 2 | 60% (49%–70%) | 3 | 40% (35%–45%) |
| Peginterferon alpha-2b plus ribavirin |                         |         |                 |
| 48 weeks           | Peginterferon alpha-2b plus ribavirin | 1 | 16% (12%–20%) | 1 | 33% (21%–46%) | 1 | 71% (64%–78%) |

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-naive 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-naive 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-naive patients provided with peginterferon

![Figure 3](image_url) 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.
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 peginterferon alpha-2a plus ribavirin as compared to peginterferon 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. 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. 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. 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, 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

| Treatment duration | Peginterferon alpha-2a plus ribavirin | Peginterferon alpha-2b plus ribavirin | Direct comparison |
|--------------------|--------------------------------------|--------------------------------------|-------------------|
|                    | Arms | Proportion (95% CI) | I² | Proportion (95% CI) | I² | Proportion (95% CI) | I² | RR (95% CI) |
| 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.
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. 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.

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.

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## 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 |
|--------------------|------------------------------|---------|-----------------|
| Peginterferon alpha-2a plus ribavirin | | | |
| 48 weeks | 18 | 48% (45%–50%) | 59% (21%–74%) |
| Peginterferon alpha-2b plus ribavirin | | | |
| 48 weeks | 13 | 40% (37%–42%) | 35% (0%–65%) |

**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 |
|--------------------|------------------------------|---------|-----------------|
| Peginterferon alpha-2a plus ribavirin | | | |
| 48 weeks | 8 | 17% (9%–25%) | 60% (48%–71%) |
| Peginterferon alpha-2b plus ribavirin | | | |
| 48 weeks | 1 | 16% (12%–20%) | 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 |
|--------------------|--------------------------------------|--------------------------------------|-------------------|
| 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.