Direct-acting antiviral therapies for hepatitis C genotype 1 infection: a multiple treatment comparison meta-analysis

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Received 13 August 2012 and in revised form 21 September 2012

Summary

Background: New direct-acting antiviral agents for hepatitis C genotype 1 infection, boceprevir and telaprevir, offer enhanced sustained virologic response (SVR) among both treatment-naive and treatment-experienced patients.

Aim: To determine the relative efficacy of the new direct-acting antiviral agents by applying a multiple treatment comparison meta-analysis.

Design: We included published Phase II and III randomized controlled trials evaluating head-to-head comparisons between boceprevir, telaprevir, peg-interferon alpha-2a with ribavirin and peg-interferon alpha-2b with ribavirin in hepatitis C genotype 1 patients. We applied Bayesian multiple treatment comparison meta-analysis.

Results: We included data from four boceprevir, three telaprevir and six peg-interferon alpha-2a plus ribavirin vs. peg-interferon alpha-2b plus ribavirin randomized controlled trials. Both boceprevir and telaprevir offer statistically superior outcomes for SVR, relapse and discontinuation due to adverse events than either peg-interferons among both treatment-naive and treatment-experienced patients. Among treatment-naive patients, clinical outcomes were similar for boceprevir and telaprevir, for SVR [odds ratio (OR) 0.90, 95% credible interval (95% CrI) 0.41–1.91] and for relapse (OR 1.09, 95% CrI 0.19–4.84). Similarly, among treatment-experienced patients, clinical outcomes were similar for boceprevir and telaprevir and for SVR (OR 1.45, 95% CrI 0.70–3.08) and for relapse (OR 0.35, 95% CrI 0.13–1.02). For treatment-naive patients receiving standard-duration therapy, telaprevir yielded lower rates of anemia and neutropenia, but higher rates of rash and pruritus. For treatment-experience patients, all adverse event rates were higher with telaprevir.

Discussion: Boceprevir and telaprevir exhibit similar effects among hepatitis C genotype 1 treatment-naive and treatment-experienced patients.

Introduction

Treatment for hepatitis C virus (HCV) infection is rapidly evolving, with several exciting new treatments developments, offering hope to both treatment-naive HCV patients and patients who had previously exhausted their treatment options. In particular, two direct-acting antiviral compounds, telaprevir (TVR)
and boceprevir (BOC) have recently been approved in Europe and North America for the treatment of HCV genotype 1 infection, the most common genotype in these regions.1,2

TVR, a linear peptidomimetic HCV non-structural 3 (NS3)/4A serine protease inhibitor, and BOC, a protease inhibitor that binds to the HCV NS3 active site, are now recommended for use in combination with peg-interferon alpha (peg-INF alpha) plus ribavirin (RIB) for HCV genotype 1 patients. Several large randomized trials demonstrate that both TVR and BOC, in combination with standard treatment, offer very favorable outcomes in terms of sustained virologic response (SVR). These benefits appear for both treatment-naive patients (those who have not received any drug therapy for their HCV infection)3–6 and treatment-experienced patients (those who have previously been treated for HCV and did not achieve a SVR to the therapy)7–9 when compared to standard therapy alone.

No direct head-to-head clinical trials have evaluated the superiority or non-inferiority of these new agents. A new statistical approach, termed ‘multiple treatment comparison’ (MTC) meta-analysis, allows an analysis of the comparative effectiveness of these agents compared with existing standard treatments to determine their relative effectiveness. This clinically useful tool allows the reader to determine the effectiveness of all examined interventions compared with each other.10 We aimed to evaluate the relative effectiveness of standard treatment with peg-INF alpha-2a or alpha-2b plus RIB and the new direct-acting antivirals, TVR and BOC, in combination with these standard treatments among HCV genotype 1 patients.

**Methods**

**Eligibility criteria**

We included published Phase II and III randomized controlled trials (RCTs) examining the efficacy and safety of peg-INF alpha-2a or peg-INF alpha-2b plus RIB, and TVR and BOC in combination with peg-INF alpha-2a or peg-INF alpha-2b plus RIB. We considered both standard-duration therapy and response-guided therapy regimens (refer to Table 1 for the definition of each standard-duration and response-guided regimen eligible).

Included RCTs must have had a common comparison so that a common comparator could be made. Only RCTs reporting outcomes predominantly for genotype 1 HCV infected adult patients were considered. A priori we were aware that some RCTs may provide outcomes for genotype 1 and genotype 4 patients combined. Where possible, we considered only outcomes for genotype 1 patients, but where not possible, we included the outcomes for genotype 1 and genotype 4 patients combined. Both treatment-naive and treatment-experienced populations were considered. We excluded trials conducted among co-infected patients (e.g. HIV and hepatitis B).

**Search strategy**

In consultation with a medical librarian, two investigators (K.T. and E.D.) conducted a comprehensive systematic search of the literature. The searches included the following terms: boceprevir, telaprevir, peginterferon, peg-interferon, pegylated interferon, ribavirin and hepatitis C. Each search was limited to RCTs in humans. Searches were not limited by language, sex or age. The searches were performed using the following databases [from inception to Week 4 of 2012 (23–29 January)]: MEDLINE (via PubMed), EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, PsychINFO and Web of Science (refer to Appendix 1 for an example of a full electronic search strategy utilized). The bibliographies of published systematic and narrative reviews and relevant included trials were also searched.

**Data abstraction and endpoints**

Two investigators (K.T. and E.D.) working independently, in duplicate, abstracted data on the following efficacy outcomes: the proportion of patients achieving SVR (defined as an undetectable HCV RNA at the end of the 24-week post-therapy follow-up period), the proportion of patients relapsing (defined as a reoccurrence of HCV RNA within the 24-week post-therapy follow-up period) and the proportion of patients discontinuing treatment due to an adverse event (defined as the discontinuation of all assigned study drugs during the set treatment period due to an adverse event). Data were also abstracted for the following commonly reported hematological adverse events: anemia (generally defined as hemoglobin <100 g/l), neutropenia (generally defined as absolute neutrophil count <0.75 × 10⁹/l) and thrombocytopenia (generally defined as a platelet count <150 000/ml). Additionally, data were abstracted for the following commonly reported dermatological adverse events: rash (any, as reported by site investigators) and pruritus (any, as reported by site investigators). These data were only abstracted for the standard-duration therapy and response-guided therapy arms, as described earlier, among both treatment-naive and
treatment-experienced patients. Where necessary, we contacted the primary authors of the trial publications for clarifications on trial data, including study setting, participant inclusion criteria, therapy durations, outcomes data, and in the case where only an abstract was available, to ensure we were utilizing the most current and accurate data.

**Statistical analysis**

Our analysis applied a MTC method. This approach permits the calculation of the relative difference between treatments that have not been evaluated directly.\(^\text{11}\) Although statistically complex, this approach is now widely accepted by clinical guideline committees and health regulatory authorities.\(^\text{12}\) We applied a Bayesian analysis, which permits more sensitivity analyses than a usual frequentist analysis and is more conservative. We present our findings as odds ratios (ORs) and 95% credible intervals (95% CrIs), which are the Bayesian equivalent of confidence intervals.

We assess the following outcomes: SVR, relapse, discontinuation due to adverse events, anemia, neutropenia, thrombocytopenia, rash and pruritis. All outcomes are binary, and so, we modeled (log) ORs for the considered treatment comparisons using Bayesian MTC meta-analysis.\(^\text{13}\) The statistical technicalities of this approach are described elsewhere.\(^\text{11}\) For all six comparisons between the four treatments, we calculated median ORs and 95% CrIs from the Bayesian posterior distribution. To check agreement between pair-wise estimates and MTC estimates, we also conducted pair-wise random-effects meta-analysis for all pair-wise comparisons. K.T. and E.D. conducted all statistical analysis. All MTC analyses were conducted using WinBUGS (MRC Biostatistics Unit, Cambridge, UK). All pair-wise meta-analyses were conducted using StatDirect version 9.1.

**Results**

Table 2 provides the characteristics of the included RCTs. Figure 1 displays a schematic of the trial selection process. Six trials assessed peg-INF alpha-2a plus RIB vs. peg-INF alpha-2b plus RIB,\(^\text{14-19}\) three assessed TVR in combination with peg-INF alpha-2a or -2b plus RIB vs. peg-INF alpha-2a or -2b alone for 12 weeks,\(^\text{3,4,7}\) and four assessed BOC in combination with peg-INF alpha-2b plus RIB vs. peg-INF alpha-2b plus RIB alone.\(^\text{5,6,8,9}\) Of note, the TVR trials did not permit the use of erythropoietin therapy to treat anemia; however, at the discretion of the investigator, patients in the BOC trials could be prescribed erythropoietin if hemoglobin levels dropped below 10 g/dl.

| Regimen | Treatment | Dose | Course of treatment |
|---------|-----------|------|---------------------|
| Standard-duration therapy Peg-IFN alpha-2a + RIB | Peg-INF alpha-2a | 180 µg/week | Peg-IFN alpha-2a + RIB for 48 weeks |
| | Peg-INF alpha-2b | 1.5 µg/kg/week | Peg-IFN alpha-2b + RIB for 48 weeks |
| | RIB | 600–1400 mg/day | TVR combined with Peg-IFN alpha-2a or -2b + RIB for 12 weeks, followed by Peg-IFN alpha-2a or -2b alone for 36 weeks |
| TVR + Peg-IFN alpha-2a or -2b + RIB | TVR | 750 mg, three times a day | Peg-IFN alpha-2a or -2b + RIB for 12 weeks, followed by Peg-IFN alpha-2a or -2b alone for 36 weeks |
| | Peg-INF alpha-2a or -2b | Peg-INF alpha-2a 180 µg/week; Peg-INF alpha-2b 1.5 µg/kg/week | Peg-IFN alpha-2a or -2b for 44 weeks |
| | RIB | Peg-INF alpha-2a 180 µg/week; Peg-INF alpha-2b 1.5 µg/kg/week | Peg-IFN alpha-2a or -2b as well as BOC for 44 weeks |
| BOC + Peg-IFN alpha-2a or -2b + RIB | BOC | 800 mg, three times a day | Peg-IFN alpha-2a or -2b for 44 weeks |
| | Peg-INF alpha-2a or -2b | Peg-INF alpha-2a 180 µg/week; Peg-INF alpha-2b 1.5 µg/kg/week | Peg-IFN alpha-2a or -2b as well as BOC for 44 weeks |
| | RIB | Peg-INF alpha-2a 180 µg/week; Peg-INF alpha-2b 1.5 µg/kg/week | Peg-IFN alpha-2a or -2b as well as BOC for 44 weeks |

| Response-guided therapy TVR + Peg-IFN alpha-2a or -2b + RIB | TVR | 750 mg, three times a day | Peg-IFN alpha-2a or -2b for 12 weeks, followed by Peg-IFN alpha-2a or -2b alone for 12 weeks if HCV RNA was undetectable at any time between Weeks 4 and 12 |
| | Peg-INF alpha-2a or -2b | Peg-INF alpha-2a 180 µg/week; Peg-INF alpha-2b 1.5 µg/kg/week | Peg-IFN alpha-2a or -2b alone for 12 weeks if HCV RNA was undetectable at any time between Weeks 4 and 12 |
| | RIB | Peg-INF alpha-2a 180 µg/week; Peg-INF alpha-2b 1.5 µg/kg/week | Peg-IFN alpha-2a or -2b alone for 12 weeks if HCV RNA was undetectable at any time between Weeks 4 and 12 |
| BOC + Peg-IFN alpha-2a or -2b + RIB | BOC | 800 mg, three times a day | Peg-IFN alpha-2a or -2b for 36 weeks if HCV RNA was undetectable between Weeks 8 and 24 or for 44 weeks if HCV RNA was detectable at any time between Weeks 8 and 24 |
| | Peg-INF alpha-2a or -2b | Peg-INF alpha-2a 180 µg/week; Peg-INF alpha-2b 1.5 µg/kg/week | Peg-IFN alpha-2a or -2b alone for 36 weeks if HCV RNA was undetectable between Weeks 8 and 24 or for 44 weeks if HCV RNA was detectable at any time between Weeks 8 and 24 |
| Trial publications     | Region                        | Experience in the treatment | Regimen          | Treatment                               | No. of patients (n) |
|-----------------------|-------------------------------|-----------------------------|------------------|-----------------------------------------|---------------------|
| Bacon *et al.*, 2011$^8$ | North America and Europe     | Experienced                 | Standard-duration | BOC + peg-IFN alpha-2b + RIB            | 161                 |
|                       |                               |                             | Response-guided   | BOC + peg-IFN alpha-2b + RIB            | 162                 |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2b + RIB                 | 80                  |
| Flamm *et al.*, 2011$^9$ | North America                | Experienced                 | Standard-duration | BOC + peg-IFN alpha-2a + RIB            | 134                 |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2a + RIB                 | 67                  |
| Jacobson *et al.*, 2011$^3$ | International               | Naïve                       | Standard-duration | TVR + peg-IFN alpha-2a + RIB           | 361                 |
|                       |                               |                             | Response-guided   | TVR + peg-IFN alpha-2a + RIB           | 363                 |
| Poordad *et al.*, 2011$^6$ | North America and Europe     | Naïve                       | Standard-duration | BOC + peg-IFN alpha-2b + RIB            | 366                 |
|                       |                               |                             | Response-guided   | BOC + peg-IFN alpha-2b + RIB            | 368                 |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2a + RIB                 | 363                 |
| Zeuzem *et al.*, 2011$^7$ | International                | Experienced                 | Standard-duration | TVR + peg-IFN alpha-2a + RIB           | 132                 |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2a + RIB                 | 266                 |
| Ascione *et al.*, 2010$^{14}$ | Europe                     | Naïve                       | Standard-duration | Peg-IFN alpha-2a + RIB                 | 93                  |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2b + RIB                 | 93                  |
| Kwo *et al.*, 2010$^5$  | North America and Europe     | Naïve                       | Standard-duration | BOC + peg-IFN alpha-2b + RIB            | 103                 |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2b + RIB                 | 104                 |
| Rumi *et al.*, 2010$^{15}$ | Europe                       | Naïve                       | Standard-duration | Peg-IFN alpha-2a + RIB                 | 91                  |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2b + RIB                 | 87                  |
| McHutchison *et al.*, 2009$^4$ | North America              | Naïve                       | Standard-duration | TVR + peg-IFN alpha-2a + RIB           | 75                  |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2a + RIB                 | 79                  |
| McHutchison *et al.*, 2009$^{16}$ | North America              | Naïve                       | Standard-duration | Peg-IFN alpha-2a + RIB                 | 1035                |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2b + RIB                 | 1019                |
| Scotto *et al.*, 2008$^{17}$ | Europe                      | Experienced                 | Standard-duration | Peg-IFN alpha-2a + RIB                 | 45                  |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2b + RIB                 | 47                  |
| Scotto *et al.*, 2008$^{18}$ | Europe                      | Experienced                 | Standard-duration | Peg-IFN alpha-2a + RIB                 | 37                  |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2b + RIB                 | 40                  |
| Yenice *et al.*, 2005$^{19}$ | Europe                      | Naïve                       | Standard-duration | Peg-IFN alpha-2a + RIB                 | 40                  |
|                       |                               |                             | Standard-duration | Peg-IFN alpha-2b + RIB                 | 40                  |
Nineteen trials extracted for detailed evaluation were excluded for the following reasons: 12 were Phase I trials examining pharmacokinetics, tolerability or safety (nine of which assessed TVR and three of which assessed BOC),20–31 three did not examine a standard-duration or response-guided therapy arm (each of which assessed TVR),32–34 three did not examine a control treatment nor common comparator (each of which assessed TVR)35–37 and one did not examine the outcomes of interest specifically for genotype 1 or genotype 1/4 (which assessed TVR).38 Refer to Table A1 for a list of the excluded trials.

For treatment-naive patients, TVR and BOC were linked through the head-to-head comparisons of peg-INF alpha-2a plus RIB and peg-INF alpha-2b plus RIB for all efficacy measures (Figure 2A). For treatment-experienced patients, head-to-head comparisons of peg-INF alpha-2a plus RIB and peg-INF alpha-2b plus RIB were not available, and thus, TVR and BOC were linked through the assumption that peg-INF alpha-2a plus RIB and peg-INF alpha-2b plus RIB were similar in terms of efficacy and safety (Figure 2B).

Table 3 presents the ORs and 95% CrIs for the efficacy measures, SVR, relapse to treatment and discontinuation due to adverse events. For treatment-naive patients receiving standard-duration therapy, TVR and BOC were statistically comparable in terms of SVR and relapse, as indicated by the wide 95% CrIs (note that data on discontinuations due to adverse events were not available among naive patients provided standard-duration therapy). Similarly, for treatment-experienced patients on standard-duration therapy, TVR and BOC were statistically comparable, in terms of SVR, relapse and discontinuations due to adverse events, as indicated by the wide 95% CrIs. Furthermore, for treatment-naive patients receiving response-guided therapy, TVR and BOC were also statistically comparable, in terms of SVR, relapse and discontinuations due to adverse events, as indicated by the wide 95% CrIs (note that no trial reported on treatment-experienced patients receiving response-guided therapy). Finally, TVR and BOC both yielded higher SVR rates, lower relapse rates and higher discontinuation rates than the two peg-INF alpha plus RIB regimens. Table A2 presents the corresponding pair-wise comparisons from the pair-wise random-effects meta-analyses.

Table 4 presents the ORs and 95% CrIs for adverse events of anemia, neutropenia, rash and pruritus. For treatment-naive patients receiving standard-duration therapy, TVR yielded lower rates of anemia and neutropenia, but higher rates of rash and pruritus. The 95% CrI for rash did not include 1, suggesting statistical evidence of higher incidence of rash episodes in patients treated with TVR compared with BOC. For treatment-experienced patients, all adverse event rates were higher with TVR. For treatment-naive patients receiving response-guided therapy, TVR and BOC yielded comparable rates of anemia and neutropenia, and TVR yielded higher rates of rash and pruritus. The 95% CrI for rash did not include 1, suggesting statistical evidence of higher incidence of rash episodes in patients treated with TVR compared with BOC. Table A3 presents the corresponding pair-wise comparisons from the pair-wise random-effects meta-analyses.

Although thrombocytopenia was not consistently reported in the trial publications of TVR or BOC, combined data from all trials were available in the US Food and Drug Administration (FDA) reports.39,40 For TVR, 18 of 1823 (1.0%) patients randomized to a treatment arm containing TVR were diagnosed with thrombocytopenia, whereas 1 of 764 (0.1%) patients randomized to a matched placebo arm was diagnosed with thrombocytopenia. For BOC, 49 of 1057 (4.6%) patients randomized to a treatment arm containing BOC were diagnosed with thrombocytopenia, whereas 7 of 443 (1.6%) patients randomized to a matched placebo arm were diagnosed with thrombocytopenia. These proportions correspond to an OR of 3.36 (95% CrI
Note, however, that this OR represents the comparative risk of thrombocytopenia across both naive and experienced patients receiving either standard-dose duration therapy or response-guided therapy.

**Discussion**

Our study demonstrates that both new direct-acting agents offer favorable outcomes over standard therapy for the treatment of genotype 1 HCV infection. Clinically important outcomes, including SVR, relapse and discontinuation of treatment due to adverse events appear to be similar between the two direct-acting agents and are clearly superior over the standard therapies examined for both standard-dose duration therapy and response-guided therapy regimens. Our findings should be of interest to clinicians and patients who are seeking either the most effective options for first-line therapies or exploring options among more experienced patients.

The decision to use one specific HCV peg-IFN alpha or direct-acting antiviral over another is based on multiple parameters, including SVR rate, relapse rate, discontinuation rate due to adverse events, side-effect profile, dosing regimen, pill count, resistance risk, likelihood of shortened therapy utilizing a treatment (RGT) approach to therapy, patient characteristics (e.g. physical, behavioral and genetic) and cost. Our analysis suggests that SVR, relapse rate and discontinuation rate due to adverse events can be removed from this decision algorithm in genotype 1-infected populations as these key outcomes of HCV therapy, based on currently available data, are similar between TVR and BOC containing regimens and between the peg-IFN alpha-based treatments. Overall, our analyses suggest that the

| Table 3 | ORs and 95% CrIs for the three efficacy measures |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Comparison in the treatment | SVR, OR (95% CrI) | Relapse, OR (95% CrI) | Discontinuation due to adverse events, OR (95% CrI) |
| Treatment-naïve patients on standard-duration therapy<sup>a</sup> | | | |
| TVR + peg-IFN alpha + RIB vs. BOC + peg-IFN alpha + RIB | 1.11 (0.23–5.68) | 1.09 (0.19–4.83) | – |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 2.94 (0.80–5.77) | 0.19 (0.04–0.76) | – |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 2.65 (0.89–7.06) | 0.18 (0.09–0.31) | – |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 4.22 (1.09–8.67) | 0.29 (0.04–1.18) | – |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 3.77 (1.69–4.97) | 0.27 (0.16–0.44) | – |
| Peg-IFN alpha-2a + RIB vs. peg-IFN alpha-2b + RIB | 1.42 (0.83–2.93) | 0.67 (0.52–0.86) | – |
| Treatment-experienced patients on standard-duration therapy<sup>b</sup> | | | |
| TVR + peg-IFN alpha + RIB vs. BOC + peg-IFN alpha + RIB | 1.45 (0.70–3.08) | 0.35 (0.13–1.02) | 0.44 (0.11–1.63) |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha + RIB | 10.4 (6.10–18.4) | 0.10 (0.05–0.18) | 3.01 (1.47–7.19) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha + RIB | 7.17 (4.52–11.5) | 0.27 (0.13–0.58) | 6.80 (2.59–24.7) |
| Treatment-naïve patients on response-guided therapy<sup>c</sup> | | | |
| TVR + peg-IFN alpha + RIB vs. BOC + peg-IFN alpha + RIB | 1.54 (0.95–2.07) | 0.99 (0.47–2.12) | 1.11 (0.53–2.32) |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 3.80 (2.77–5.21) | 0.24 (0.15–0.37) | 1.43 (0.81–2.60) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 2.47 (1.76–3.46) | 0.23 (0.13–0.43) | 1.30 (0.86–1.99) |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 4.40 (3.01–6.28) | 0.36 (0.21–0.60) | 1.42 (0.85–2.43) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 2.85 (2.12–3.86) | 0.36 (0.20–0.62) | 1.28 (0.79–2.13) |
| Peg-IFN alpha-2a + RIB vs. peg-IFN alpha-2b + RIB | 1.42 (0.83–2.93) | 1.50 (0.16–1.94) | 0.99 (0.77–1.27) |

ORs > 1 indicate higher rates in the first treatment group.
<sup>a</sup>Random effects MTC model including head-to-head comparison of the two peg-interferons.
<sup>b</sup>Fixed-effect MTC model assuming equal effects of the two peg-interferons.
<sup>c</sup>Fixed-effect MTC model including head-to-head comparison of the two peg-interferons.
Treatment-naive patients on response-guided therapy have been appropriate for this analysis. This pair-wise meta-analysis permit, which would not allow for a more powerful exploration of treatment differences than new in the clinical literature and allows for a more direct comparisons. We recognize that both methods provide stronger inferences than adjusted direct comparisons. We included all published studies evaluating the head-to-head comparisons of the two peg-interferons.

There are several important strengths to consider in our analysis. First, our analysis permits inferences into differences in treatment effects that had not been evaluated directly. This approach is relatively new in the clinical literature and allows for a more powerful exploration of treatment differences than pair-wise meta-analysis permit, which would not have been appropriate for this analysis. This method provides stronger inferences than adjusted in direct comparisons. We recognize that both direct-acting agents were provided on top of standard treatment. We examined whether the choice of peg-IFN alpha affects the treatment outcomes of patients and found that they did not matter in a clinically important manner.

There are also certain limitations to consider in our analysis. We included all published studies evaluating the head-to-head comparisons of interventions in our network. In some circumstances, these were small. For example, the number of trials contributing to the analysis of experienced patients may provide less precise estimates than if we had a larger number of trials. For experienced patients, we were unable to determine the outcomes of relapse or discontinuation due to non-reporting in the primary studies. Furthermore, the boceprevir trials conducted among experienced patients did not recruit null responders, but the telaprevir trials did. In this regard, the treatment-experienced populations are dissimilar, and the results may slightly underestimate the efficacy of telaprevir and/or slightly overestimate the efficacy of boceprevir in the prior non-response subgroup of patients. We estimated the additive effects of each direct-acting agent on top of the chosen peg-IFN alpha used in each trial and did not demonstrate a statistically significant benefit of peg-IFN alpha choice. There is some reason to believe that the choice of peg-IFN alpha will differ in our results indicate that anemia is slightly increased with TVR and moderately increased with BOC, it should be recognized that erythropoietin, used for the management of anemia, was not permitted in the TVR trials. This difference in erythropoietin use could have affected the proportions of patients discontinuing due to anemia.

### Table 4 ORs and 95% CrIs for the four adverse outcomes

| Comparison in the treatment | Anemia, OR (95% CrI) | Neutropenia, OR (95% CrI) | Rash, OR (95% CrI) | Pruritus, OR (95% CrI) |
|-----------------------------|---------------------|--------------------------|------------------|---------------------|
| **Treatment-naive patients on standard-duration therapy**<sup>a</sup> | | | | |
| TVR + peg-IFN alpha + RIB vs. BOC + peg-IFN alpha + RIB | 0.44 (0.23–1.03) | 0.86 (0.38–1.98) | 3.09 (1.45–6.65) | 2.37 (0.80–7.07) |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 1.13 (0.56–2.31) | 1.01 (0.48–2.15) | 2.22 (1.15–4.23) | 2.35 (1.18–4.89) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 2.41 (1.74–3.31) | 1.16 (0.80–1.67) | 0.72 (0.48–1.07) | 1.00 (0.43–2.27) |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 1.11 (0.53–2.33) | 1.32 (0.62–2.85) | 3.06 (1.57–5.99) | 2.20 (0.79–6.29) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 2.35 (1.80–3.08) | 1.53 (1.19–2.09) | 0.99 (0.70–1.40) | 0.93 (0.67–1.29) |
| Peg-IFN alpha-2a + RIB vs. peg-IFN alpha-2b + RIB | 0.98 (0.82–1.17) | 1.32 (0.99–1.60) | 1.37 (1.13–1.68) | 0.93 (0.44–2.04) |
| **Treatment-experienced patients on standard-duration therapy**<sup>b</sup> | | | | |
| TVR + peg-IFN alpha + RIB vs. BOC + peg-IFN alpha + RIB | 1.65 (0.83–3.37) | 1.72 (0.67–4.38) | 1.13 (0.47–2.67) | 2.52 (1.09–5.70) |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha + RIB | 2.42 (1.40–4.73) | 1.41 (0.76–2.77) | 2.57 (1.56–4.32) | 2.88 (1.86–4.58) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha + RIB | 1.46 (0.96–2.21) | 0.81 (0.43–1.64) | 2.28 (1.17–4.71) | 1.15 (0.57–2.31) |
| **Treatment-naive patients on response-guided therapy**<sup>a</sup> | | | | |
| TVR + peg-IFN alpha + RIB vs. BOC + peg-IFN alpha + RIB | 0.94 (0.60–1.52) | 0.96 (0.57–1.61) | 2.17 (1.32–3.52) | 1.07 (0.44–2.68) |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 2.27 (1.69–3.07) | 1.20 (0.81–1.75) | 1.79 (1.35–2.40) | 1.07 (0.48–2.52) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 2.40 (1.69–3.42) | 1.24 (0.87–1.75) | 0.83 (0.57–1.23) | 0.99 (0.71–1.40) |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 2.22 (1.56–3.15) | 0.91 (0.65–1.27) | 2.47 (1.75–3.52) | 1.19 (0.91–1.57) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 2.35 (1.73–3.19) | 0.94 (0.63–1.40) | 1.14 (0.82–1.60) | 1.11 (0.46–2.55) |
| Peg-IFN alpha-2a + RIB vs. peg-IFN alpha-2b + RIB | 0.98 (0.82–1.17) | 0.75 (0.62–0.92) | 1.37 (1.12–1.68) | 0.92 (0.42–2.06) |

ORs > 1 indicate higher rates in the first treatment group.

<sup>a</sup>Fixed effects MTC model including head-to-head comparison of the two peg-interferons.

<sup>b</sup>Fixed effect MTC model assuming equal effects of the two peg-interferons.
The statistical approach that we employed is widely accepted by agencies such as the UK National Institutes of Clinical Excellence, the Canadian Drug Safety and Effectiveness Network and the US Agency for Healthcare Research and Quality. However, many clinicians may be unfamiliar with this approach and few guides are available to critically appraise such studies. The MTC meta-analysis relies on many of the same assumptions as a standard pair-wise meta-analysis. There is a necessary consideration that the trials of each agent are sufficiently similar to pool together in terms of populations, interventions and outcomes. A further necessary consideration is that these similarities exist across the different agents. Finally, there is a necessary consideration that indirect comparisons and direct comparisons yield consistent outcomes, a finding that can be assessed statistically when both direct and indirect evidence are available for the same interventions (in this case, in the peg-INF alpha plus RIB treatments). The largest analysis that has examined the coherence between direct and indirect comparisons of trials, published in 2011, found that there was inconsistency in only 14% of evaluations.

In summary, both of the new direct-acting protease inhibitors available to treat HCV infections yield superior treatment outcomes when added to the peg-INF and RIB combinations alone and thus provide exciting new opportunities for hepatitis C control. Given their similar efficacy, selection of regimen to treat individuals with hepatitis C infection should include specific considerations such as tolerance and cost.

Acknowledgements
Study planning (C.C., R.L., K.T., E.D., A.C.E.K., S.Y. and E.J.M.); study conduct (C.C., R.L., K.T., E.D., A.C.E.K., S.Y. and E.J.M.); analysis (K.T. and E.D.); study writing (C.C., R.L., K.T., E.D., A.C.E.K., S.Y. and E.M.J.); and agreement of submission of article (C.C., R.L., K.T., E.D., A.C.E.K., S.Y. and E.J.M.).

Funding
This study was initiated and conducted by the academic researchers. We approached Merck & Co. for funding and received funding based on a submitted protocol. Merck & Co. had no involvement in the choice of analysis, interpretation of the results or choice to submit. Dr A.C.E.K. was an employee of Merck, Sharp & Dohme at the time this study was conducted and assisted with content expertise and access to data. He had no role in choices regarding the interpretation or decision to submit this article.

Conflict of interest: None declared.

References
1. Poordad F, Khungar V. Emerging therapeutic options in hepatitis C virus infection. Am J Manag Care 2011; 17(Suppl. 4):S123–30.
2. Ciesek S, Manns MP. Hepatitis in 2010: the dawn of a new era in HCV therapy. Nat Rev Gastroenterol Hepatol 2011; 8:69–71.
3. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011; 364:2405–16.
4. McHutchison JG, Eversion GT, Gordon SC, Jacobson IM, Sulkowski M, Kaufman R, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009; 360:1827–38.
5. Kwo PY, Lawitz EJ, McCone J, Schill ER, Vierling JM, Pound D, 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; 376:705–16.
6. Poordad F, McCone J, Bacon B, Bruno S, Manns M, Sulkowski M, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011; 364:1195–206.
7. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011; 364:2417–28.
8. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364:1207–17.
9. Flamm S, Lawitz E, Jacobson I, Rubin R, Bourliere M, Hezode C, 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:S535–46.
10. Cooper NJ, Peters J, Lai MC, Juni P, Wandel S, Palmer S, et al. How valuable are multiple treatment comparison methods in evidence-based health-care evaluation? Value Health 2011; 14:371–80.
11. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004; 23:3105–24.
12. Sutton A, Ades AE, Cooper N, Abrams K. Use of indirect and mixed treatment comparisons for technology assessment. Pharmaco Economics 2008; 26:753–67.
13. Sutton AJ, Higgins JP. Recent developments in meta-analysis. Stat Med 2008; 27:625–50.
14. Ascione A, De Luca M, Tartaglione M, Lampasi F, Di Costanzo G, Lanza A, 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; 138:116–22.
15. Rumi MG, Aghemo A, Prati GM, D’Ambrosio R, Donato MF, Soffredini R, et al. Randomized study of peginterferon-alpha 2a plus ribavirin vs peginterferon-alpha 2b plus...
29. Sarrazin C, Kieffer T, Bartels D, Hanzelka B, Mu¨hU, et al. Peg-interferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009; 361:580–93.

28. Kieffer T, Sarrazin C, Miller J, Welker M, Forestier N, 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; 68:791–801.

27. Forestier N, Reesink H, Weegink C, McNair L, Kieffer T, al et. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009; 360:1839–50.

26. Lawitz E, Rodriguez-Torres M, Muir A, Kieffer T, McNair L, et al. Peg-interferon alfa-2a versus peginterferon alfa-2b. Scand J Gastroenterol 2006; 41:94–8.

25. Gelderbloom H, Zeuzem S, Weegink C, Forestier N, McNair L, Purdy S, et al. Inflammatory markers neopterin and alanine aminotransferase in HCV patients treated with HCV NS3/4A protease inhibitor telaprevir (VX-950) and/or peginterferon alfa-2a. Scand J Gastroenterol 2008; 43:1122–7.

24. Curry S, Jiu P, Tong Y. Analysis of HCV resistance mutations during combination therapy with protease inhibitor boceprevir and PEG-IFN alpha-2b using TaqMan mismatch amplification mutation assay. J Virol Methods 2008; 153:156–62.

23. Susser S, Welsch C, Wang Y, Zettler M, Domingues F, Karey U, et al. Characterization of resistance to the protease inhibitor bocaprevir in hepatitis C virus-infected patients. Hepatology 2009; 50:1709–18.

22. Adiwijaya B, Hare B, Caron P, Randle J, Neumann A, Gupta S, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010; 362:1292–303.

21. Guedj J, Perelson A. Second-phase hepatitis C virus RNA decline during telaprevir-based therapy increases with drug effectiveness: implications for treatment duration. Hepatology 2011; 53:1801–8.

20. Garg V, van Heeswijk R, Lee J, Alves K, Nadkarni P, Luo X. Peg-interferon alpha-2a or-2b plus ribavirin reduces HCV RNA in patients with chronic hepatitis C. J Hepatol 2009; 50:1292–303.

19. Yenice N, Mehtap O, Gumrah M, Arican N. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. Turk J Gastroenterol 2006; 17:94–7.

18. Scotto G, Fazio V, Fornabaio C, Tartaglia A, Di Tullio R, Scotto G, et al. Rapid decline of wild-type hepatitis C virus on telaprevir treatment. Antivir Ther 2009; 14:591–5.

17. Everson G, Flamm S, Afdhal N, Nelson D, Sulkowski M, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med 2011; 365:1014–24.

16. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Goovers T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009; 360:1839–50.

15. Marcellin P, Forns X, Goeser T, Perelson A, Everson 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; 140:459–68.

14. Muir A, Poordad F, McHutchison J, Shiffman M, Berg T, Forns X, et al. Telaprevir alone or with peginterferon and ribavirin reduces HCV RNA in patients with chronic genotype 2 but not genotype 3 infections. Gastroenterology 2011; 141:881–9.

13. Antiviral Drugs Advisory Committee, US Food and Drug Administration. Telaprevir, FDA Advisory Committee Briefing Document, April 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf (1 August 2012, date last accessed).

12. Division of Antiviral Products (DAVP), US Food and Drug Administration. Boceprevir, FDA Advisory Committee Briefing Document, April 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/AntiviralDrugsAdvisoryCommittee/ucm252341.pdf (1 August 2012, date last accessed).

11. Cooper CL, Druyts E, Thorlund K, Nachega JB, El Khoury AC, O’Regan C, et al. Boceprevir and telaprevir for the treatment of chronic hepatitis C genotype 1 infection: an indirect comparison meta-analysis. Ther Clin Risk Manag 2012; 8:105–30.

10. Mills EJ, Chenet M, O’Regan C, Thorlund K. Estimating the power of indirect comparisons: a simulation study. PLoS One 2011; 6:e16237.

9. Druyts E, Mills EJ, Nachega J, O’Regan C, Cooper CL. Differences in clinical outcomes among hepatitis C genotype 1-infected patients treated with peginterferon alpha-2a or protease inhibitor, plus pegylated interferon alpha-2b for genotype 1 nonresponders. Gastroenterology 2007; 132:1270–8.

8. Reesink H, Zeuzem S, Weegink C, Forestier N, van Vliet A, van de Wetering de Rooy J, et al. Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase IIb, placebo-controlled, randomized study. Gastroenterology 2006; 131:997–1002.

7. Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010; 362:1292–303.
peginterferon alpha-2b plus ribavirin: a meta-analysis. *Clin Exp Gastroenterol* 2012; 5:11–21.

44. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010; 340:c117.

45. Mills E, Bansback N, Ghement I, Thorlund K, Kelly S, Puhan M, et al. Multiple treatment comparison meta-analyses: a step forward into complexity. *Clin Epidemiol* 2011; 3:193–202.

46. Song F, Xiong T, Parekh-Bhurke S, Loke YK, Sutton AJ, Eastwood AJ, et al. Inconsistency between direct and indirect comparisons of competing interventions: meta-epidemiological study. *BMJ* 2011; 343:d4909.

**Appendix 1**

**Search strategy used in PubMed**

(((peginterferon) OR peg-interferon) OR pegylated interferon AND (Humans[Mesh] AND Randomized Controlled Trial[ptyp]))) OR (((telaprevir AND (Humans[Mesh] AND Randomized Controlled Trial[ptyp]))) AND (hepatitis c AND (Humans[Mesh] AND Randomized Controlled Trial[ptyp]))) OR (((boceprevir AND (Humans[Mesh] AND Randomized Controlled Trial[ptyp]))) AND (hepatitis c AND (Humans[Mesh] AND Randomized Controlled Trial[ptyp]))) AND (ribavirin AND (Humans[Mesh] AND Randomized Controlled Trial[ptyp]))) AND (hepatitis c AND (Humans[Mesh] AND Randomized Controlled Trial[ptyp]))) AND (hepatitis c AND (Humans[Mesh] AND Randomized Controlled Trial[ptyp])))

**Table A1** Trials excluded after detailed evaluation

| Trial publications          | Reason for exclusion                                                                 |
|-----------------------------|--------------------------------------------------------------------------------------|
| Foster et al., 201138       | Examined patients with genotypes 2 and 3                                             |
| Garg et al., 201120         | Examined Phase I trial data                                                          |
| Guedj and Perelson, 201121  | Examined Phase I trial data                                                          |
| Kumada et al., 201132       | Did not examine a standard-duration therapy nor response-guided therapy regimen of interest |
| Marcellin et al., 201135    | Did not examine a control treatment nor common comparator treatment                   |
| McHutchison et al., 201033  | Did not examine a standard-duration therapy nor response-guided therapy regimen of interest |
| Muir et al., 201136         | Did not examine a control treatment nor common comparator treatment                   |
| Sherman et al., 201137      | Did not examine a control treatment nor common comparator treatment                   |
| Adiwijaya et al., 200932    | Examined Phase I trial data                                                          |
| Hezode et al., 200934       | Did not examine a standard-duration therapy nor response-guided therapy regimen of interest |
| Susser et al., 200935       | Examined Phase I trial data                                                          |
| Curry et al., 200836        | Examined Phase I trial data                                                          |
| Gelderblom et al., 200625   | Examined Phase I trial data                                                          |
| Lawitz et al., 200826       | Examined Phase I trial data                                                          |
| Forestier et al., 200727    | Examined Phase I trial data                                                          |
| Kieffer et al., 200728      | Examined Phase I trial data                                                          |
| Sarrazin et al., 200729     | Examined Phase I trial data                                                          |
| Sarrazin et al., 200730     | Examined Phase I trial data                                                          |
| Reesink et al., 200631      | Examined Phase I trial data                                                          |
### Table A2  ORs and 95% CIs for the direct comparisons

| Comparison in the treatment | SVR, OR (95% CI) | Relapse, OR (95% CI) | Discontinuation due to adverse events, OR (95% CI) |
|-----------------------------|------------------|----------------------|-----------------------------------------------|
| **Treatment-naïve patients on standard-duration therapy** | | | |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 2.89 (1.82–4.60) | 0.21 (0.08–0.57) | 1.42 (0.98–2.06) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 3.68 (2.50–5.42) | 0.21 (0.06–0.79) | 1.07 (0.74–1.54) |
| Peg-IFN alpha-2a + RIB vs. peg-IFN alpha-2b + RIB | 1.46 (0.98–2.19) | 1.50 (1.16–1.93) | 0.93 (0.59–1.46) |
| **Treatment-experienced patients on standard-duration therapy** | | | |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha+ RIB | 9.00 (6.22–13.02) | 0.10 (0.06–0.16) | 2.91 (1.67–5.07) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha + RIB | 7.08 (4.46–11.26) | 0.27 (0.13–0.57) | 5.61 (1.94–16.17) |
| **Treatment-naïve patients on response-guided therapy** | | | |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha+ RIB | 3.78 (3.03–4.73) | 0.24 (0.17–0.34) | 1.42 (0.98–2.06) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha + RIB | 2.85 (2.30–3.52) | 0.36 (0.25–0.53) | 0.75 (0.56–1.01) |

ORs > 1 indicate higher rates in the first treatment group. CI, confidence interval.

### Table A3  ORs and 95% CIs for the direct comparisons

| Comparison in the treatment | Anemia, OR (95% CI) | Neutropenia, OR (95% CI) | Rash, OR (95% CI) | Pruritus, OR (95% CI) |
|-----------------------------|---------------------|--------------------------|-------------------|----------------------|
| **Treatment-naïve patients on standard-duration therapy** | | | | |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha-2a + RIB | 1.13 (0.69–1.86) | 1.00 (0.59–1.69) | 2.20 (1.39–3.47) | 2.32 (1.41–3.82) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha-2b + RIB | 2.31 (1.79–3.07) | 1.93 (0.76–4.91) | 0.99 (0.78–1.26) | 0.93 (0.74–1.18) |
| Peg-IFN alpha-2a + RIB vs. peg-IFN alpha-2b + RIB | 0.98 (0.82–1.17) | 1.32 (1.09–1.59) | 1.37 (1.19–1.58) | 0.93 (0.54–1.60) |
| **Treatment-experienced patients on standard-duration therapy** | | | | |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha+ RIB | 2.37 (1.61–3.47) | 0.20 (0.13–0.31) | 2.54 (1.78–3.62) | 2.88 (2.09–3.96) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha + RIB | 1.44 (0.27–7.74) | 0.82 (0.51–1.32) | 2.19 (1.09–4.41) | 1.12 (0.69–1.84) |
| **Treatment-naïve patients on response-guided therapy** | | | | |
| TVR + peg-IFN alpha + RIB vs. peg-IFN alpha+ RIB | 2.46 (1.94–3.12) | 0.70 (0.53–0.93) | 1.79 (1.43–2.25) | 1.75 (1.42–2.15) |
| BOC + peg-IFN alpha + RIB vs. peg-IFN alpha + RIB | 2.34 (1.89–2.90) | 1.24 (0.97–1.58) | 1.14 (0.90–1.45) | 0.84 (0.66–1.06) |

ORs > 1 indicate higher rates in the first treatment group. CI, confidence interval.