

SVR12 is higher than SVR24 in treatment-naïve hepatitis C genotype I patients treated with peginterferon plus ribavirin

Kristian Thorlund^{1,2}

Eric Druyts^{3,4}

Edward J Mills^{1,4}

¹Stanford Prevention Research Center, Stanford University, Stanford, CA, USA; ²Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada; ³School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada; ⁴Faculty of Health Sciences, University of Ottawa, Ottawa, ON, Canada

Background: Randomized clinical trials (RCTs) of interventions for the hepatitis C virus have historically used sustained virological response (SVR) at 24 weeks after treatment (SVR24) as the key effect measure. However, recent RCTs investigating the efficacy of new direct acting agents (DAAs) have used SVR at 12 weeks after treatment (SVR12). While there is evidence to suggest SVR24 and SVR12 are similar in patients receiving new DAAs, this is unlikely to be true for patients receiving backbone peginterferon-ribavirin control treatment. Establishing the difference between SVR12 and SVR24 for patients receiving peginterferon-ribavirin treatment is therefore necessary to avoid biased interpretations of the benefits of newer DAAs.

Methods: We searched the MEDLINE®, Embase™, and Cochrane CENTRAL for RCTs with a peginterferon-ribavirin arm that used SVR24 and/or SVR12. As no RCTs reported on both, we pooled SVR12 and SVR24 proportions using conventional meta-analysis. Proportions were pooled separately for peginterferon alpha-2a and alpha-2b. Further, a Bayesian meta-regression model was employed to estimate the difference between SVR12 and SVR24.

Results: Thirty-five RCTs including a peginterferon arm were identified. Twenty-four trials included a peginterferon alpha-2a plus ribavirin arms, of which 20 reported SVR24 and five reported SVR12. Seventeen trials included a peginterferon alpha-2b plus ribavirin arm, of which 16 reported SVR24 and one reported SVR12. Using Bayesian meta-regression, the pooled SVR12 was 6% higher than SVR24 with peginterferon alpha-2a (53% versus 47%) and 5% higher with peginterferon alpha-2b (45% versus 40%) and 95% credible intervals (CrIs) were only marginally overlapping. The meta-regression also demonstrated a marginally significant relative risk of 1.13 (95% CrI 0.99–1.26) of SVR12 versus SVR24. The conventional pairwise meta-analyses were consistent with these findings.

Conclusion: Considering the relatively large difference observed between SVR12 and SVR24, it seems reasonable to insist that future clinical trials report both to allow for complete transparency and clarity in their interpretation.

Keywords: sustained virological response, meta-regression, direct acting antivirals

Background

Historically, Phase II and Phase III clinical trials of hepatitis C virus (HCV) treatments have defined sustained virological response (SVR) as an undetectable HCV RNA 24 weeks after end of treatment (SVR24). This definition of SVR has been used in all key randomized clinical trials (RCTs) of peginterferon plus ribavirin, telaprevir, and boceprevir. However, due to the high efficacy of newer direct acting agents (DAAs) (eg, faldaprevir, simeprevir, and sofosbuvir), clinical trials assessing these treatments have used SVR at 12 weeks after end of treatment (SVR12). In patients receiving these

Correspondence: Kristian Thorlund
Stanford Prevention Research Center,
Stanford University, Medical School
Office Building, 1265 Welch Road,
Stanford, CA 94305-5411, USA
Email thorlund@stanford.edu

newer agents, some RCTs have demonstrated nearly identical SVR12 and SVR24,^{1,2} and this has left trial researchers comfortable using SVR12 as the primary efficacy outcome. In addition, the impressively high SVRs observed in the recent clinical trials, along with the interferon-sparing properties of the newer agents, is surely sufficient to convince drug regulatory authorities. However, as the newer DAAs are slated to enter the market, decision-makers and clinicians will be faced with the challenge of deciding which agents are most likely to clear HCV, and for many Western countries, which agent(s) will be the most cost-effective to reimburse.

Since none of the newer agents have been compared head-to-head in RCTs, the best approach for establishing comparative efficacy between all agents is a technique commonly referred to as indirect treatment comparison (ITC) meta-analysis. ITC meta-analysis is a technique that is now widely recognized by health technology agencies worldwide. A key premise of ITC meta-analyses, however, is that all considered agents have been compared with the same control intervention using the same outcome measure. In the case of the DAAs, most newer agents have been compared with peginterferon plus ribavirin, but the efficacy of the first generation DAAs, telaprevir and boceprevir, have been established using SVR24; whereas the efficacy of the newer DAAs have predominantly been established using SVR12. Since decisions regarding the reimbursement of the newer DAAs will rely heavily on the results of ITC meta-analyses in most countries, and since the validity of ITC meta-analysis hinge on the similarity of SVR24 and SVR12 in patients receiving peginterferon plus ribavirin, it is highly important to establish whether this similarity in fact holds true. Further, since peginterferon plus ribavirin is considerably less potent than newer DAAs, and the end-of-treatment response is typically substantially higher than SVR24, there is reason to believe that SVR24 and SVR12 differ importantly in patients receiving peginterferon plus ribavirin. The extent to which SVR24 and SVR12 may differ needs to be established so decision-makers can appropriately account for the potential difference in their decision-making processes. In Table 1, we illustrate the potential bias that can occur on the relative efficacy estimates between DAAs and control peginterferon-ribavirin, when assuming that SVR12 and SVR24 are equal.

Currently, no clinical trials including a peginterferon plus ribavirin arm have reported both SVR12 and SVR24. However, several trials have reported SVR24, and a number of trials investigating newer DAAs include a peginterferon plus ribavirin arm and report on SVR12. To compare SVR24

Table 1 Illustration of potential bias associated with assuming SVR12 and SVR24 are equal

| |
|---|
| One trial has compared telaprevir with peginterferon alpha-2a plus ribavirin. The SVR24 for telaprevir 75% and the SVR24 in the control arm is 47%. The resulting relative risk is $RR = 75\%/47\% = 1.60$. |
| One trial has compared a new direct acting agent with peginterferon alpha-2a plus ribavirin. The SVR12 for the new direct acting agent is 90% and the SVR12 in the control arm is 53%. The resulting relative risk is $RR = 90\%/53\% = 1.70$. |
| The relative risk for telaprevir and the new direct acting agent thus appear highly similar. However, assuming second trial had also measured SVR24 and the control group SVR24 was also 47%, the resulting relative risk would be $RR = 90\%/47\% = 1.91$, which is considerably higher than 1.60. |

Abbreviations: SVR12, sustained virological response at 12 weeks after treatment; SVR24, sustained virological response at 24 weeks after treatment; RR, relative risk.

and SVR12 in patients receiving peginterferon plus ribavirin we therefore undertook a systematic review of clinical trials including a peginterferon plus ribavirin arm that reported either SVR24 or SVR12.

Methods

Trial eligibility criteria

We included RCTs involving standard doses of peginterferon alpha-2a or alpha-2b administered in combination with ribavirin for 48 weeks to treatment-naïve patients. Standard doses were determined according to EASL (European Association for the Study of the Liver) (alpha-2b 1.5 µg per kg subcutaneously once weekly, alpha-2a 180 µg subcutaneously once weekly, ribavirin total daily dose of 600–1400 mg depending on patient weight). We included clinical trials that reported SVR for HCV genotype 1. We arbitrarily allowed for combined reporting for genotype 1 and 4 if the proportion of genotype 4 patients did not exceed 10%. We only considered studies conducted in North America or Europe and excluded trials administering non-standardized doses, including patients with co-infections (eg, HIV [human immunodeficiency virus]) or comorbidities (eg, cirrhosis).

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. We searched the following databases (from inception to week 31 [July 29–August 4], 2013): MEDLINE®,

Embase™, and Cochrane CENTRAL. We also identified relevant published systematic reviews in our search and scanned their bibliographies for additional relevant trials. Lastly, we scanned the abstract books from the 2012 and 2013 annual meetings of AASLD (American Association for the Study of Liver Disease) and of EASL, respectively.^{3,4}

Study selection and data extraction

Two investigators (KT and ED) scanned all abstracts and potentially eligible full text articles independently for eligibility. Disagreements were resolved by discussion with a third reviewer (EJM). Data extraction was also performed independently and in duplicate by two investigators (KT and ED). Data items included the trial region, year of publication, peginterferon type, peginterferon dose, ribavirin dose, number of patients, and number of patients achieving SVR (either 12 or 24).

Data analysis

To explore the potential differences between SVR24 and SVR12, we plotted the extracted proportions (and 95% confidence intervals) of each outcome for all eligible clinical trials using forest plots. Forest plots were constructed separately for peginterferon alpha-2a and alpha-2b as these two peginterferon treatments have previously been demonstrated to yield different SVR proportions.^{5–7} We also pooled the proportions across trials using a DerSimonian-Laird random-effects model.⁸ This was done by pooling *logit* transformed proportions to preserve symmetry and normality of the mean. To assess combinability of the retrieved proportions, we estimated the degree of heterogeneity in each pairwise meta-analysis using the I^2 measure for heterogeneity.⁹ To estimate whether SVR12 and SVR24 were different, we performed a Bayesian random-effects meta-regression of SVR proportions (and associated 95% credible intervals [CrIs]).¹⁰ (Note that the code used for the Bayesian analyses is provided in the Supplementary material.) This Bayesian regression model also concomitantly controlled for type of peginterferon. All analyses were conducted using WinBUGS version 1.4.3 (WinBUGS, Cambridge, UK).¹¹

Results

A total of 35 clinical trials were eligible and included in the analyses.^{12–45} Twenty-four trials included a peginterferon alpha-2a plus ribavirin arms,^{12–33} of which 20 reported SVR24^{12–28} and five reported SVR12^{29–33} (one reported on both²⁹). Seventeen trials include a peginterferon alpha-2b plus ribavirin arm,^{31,34–45} of which 16 reported SVR24^{34–45}

and one reported SVR12.³¹ The characteristics of all clinical trials and peginterferon treatments are presented in Table 2. Figure 1 shows a schematic of the trial selection process.

Table 3 presents the pooled SVR12 and SVR24 proportions associated with peginterferon alpha-2a and peginterferon alpha-2b under the conventional DerSimonian-Laird pairwise meta-analysis and the Bayesian meta-regression. Figure 2 displays the forest plot of SVR24 and SVR12 proportions associated with peginterferon alpha-2a arms, as well as the pooled SVR24 and SVR12 proportions for these subgroups. The pooled SVR12 was 6% higher than SVR24 with peginterferon alpha-2a, and 95% confidence intervals were not overlapping. The degree of heterogeneity in both meta-analyses was $I^2=0\%$ in the meta-analysis of SVR12 proportions and $I^2=65\%$ in the meta-analysis of SVR24 proportions. The pooled SVR12 was 3% higher than SVR24 with peginterferon alpha-2b in the conventional meta-analysis and 5% higher in the Bayesian meta-regression. In the conventional meta-analysis where all data were analyzed separately, the 95% confidence intervals were overlapping. However, in the Bayesian meta-regression where all data were analyzed simultaneously and the relative risk between SVR12 and SVR24 was assumed equal for the two peginterferons, the 95% CrIs were only slightly overlapping. From the Bayesian meta-regression the relative risk between SVR12 and SVR24 (assumed equal for the two peginterferons) was $RR=1.13$ (95% CrI 0.99–1.26). That is, the Bayesian meta-regression provided marginally statistically significant evidence that the SVR12 is, on average, 13% relatively higher than SVR24.

Discussion

Our findings indicate that SVR12 is higher than SVR24 in HCV genotype 1 patients treated with peginterferon plus ribavirin. This difference holds true for both peginterferon alpha-2a and peginterferon alpha-2b. These findings do not come as a surprise as it has long been known that end-of-treatment response with peginterferon-ribavirin treatment is larger than SVR24, and that the loss of viral response in patients after end of treatment occurs gradually during the 24-week follow-up period.

Our findings have implications for the interpretation of current and future RCTs comparing new DAAs with backbone peginterferon-ribavirin alone. In particular, newer direct acting agents may erroneously be interpreted as only exhibiting moderate benefit over backbone peginterferon-ribavirin treatment if SVR is assessed at 12 weeks after treatment and the assumption is made that SVR12 and SVR24 are identical. ITC meta-analysis and network meta-analysis

Table 2 Characteristics of the additional single-arm peginterferon alpha-2a and alpha-2b data included in the analyses

| Trial | No of patients | Genotype | Experimental intervention | Peginterferon arm | SVR12 | SVR24 |
|---------------------------------|----------------|----------|---------------------------|-------------------|-------|-------|
| Fried et al ¹² | 298 | I | Peginterferon alpha-2a | Alpha-2a | – | 46.3% |
| Hadziyannis et al ¹³ | 271 | I | Peginterferon alpha-2a | Alpha-2a | – | 52.0% |
| Ferenci et al ¹⁴ | 95 | I | Peginterferon alpha-2a | Alpha-2a | – | 51.6% |
| Diago et al ¹⁵ | 475 | I | Peginterferon alpha-2a | Alpha-2a | – | 47.8% |
| von Wagner et al ¹⁶ | 352 | I | Peginterferon alpha-2a | Alpha-2a | – | 52.8% |
| Zeuzem et al ¹⁷ | 114 | I | Peginterferon alpha-2a | Alpha-2a | – | 57.9% |
| Hezode et al ¹⁸ | 82 | I | Peginterferon alpha-2a | Alpha-2a | – | 46.3% |
| Roberts et al ¹⁹ | 438 | I | Peginterferon alpha-2a | Alpha-2a | – | 50.0% |
| Marcellin et al ²⁰ | 212 | I | Peginterferon alpha-2a | Alpha-2a | – | 43.9% |
| Zeuzem et al ²¹ | 441 | I | Peginterferon alpha-2a | Alpha-2a | – | 51.0% |
| Ascione et al ²² | 93 | I,4 | Both peginterferons | Alpha-2a | – | 54.8% |
| McHutchison et al ²³ | 1,035 | I | Both peginterferons | Alpha-2a | – | 40.9% |
| Rumi et al ²⁴ | 91 | I | Both peginterferons | Alpha-2a | – | 48.4% |
| Yenice et al ²⁵ | 40 | I | Both peginterferons | Alpha-2a | – | 45.0% |
| McHutchison et al ²⁶ | 75 | I | Telaprevir | Alpha-2a | – | 41.3% |
| Jacobson et al ²⁷ | 361 | I | Telaprevir | Alpha-2a | – | 43.8% |
| Bronowicki et al ²⁸ | 11 | I | Asunaprevir | Alpha-2a | – | 45.4% |
| Bronowicki et al ²⁹ | 53 | I | Asunaprevir | Alpha-2a | 52.8% | 45.0% |
| Sulkowski et al ³⁰ | 71 | I | Faldaprevir | Alpha-2a | 56.3% | – |
| Manns et al ³¹ | 50 | I | Simeprevir | Alpha-2a | 62.0% | – |
| Jacobson et al ³² | 132 | I | Simeprevir | Alpha-2a | 50.0% | – |
| Lawitz et al ³³ | 26 | I | Sofosbuvir | Alpha-2a | 57.7% | – |
| Benhamou et al ³⁴ | 226 | I | Peginterferon alpha-2b | Alpha-2b | – | 41.6% |
| Berg et al ³⁵ | 225 | I | Peginterferon alpha-2b | Alpha-2b | – | 48.0% |
| Brady et al ³⁶ | 311 | I,4 | Peginterferon alpha-2b | Alpha-2b | – | 29.6% |
| Buti et al ³⁷ | 86 | I | Peginterferon alpha-2b | Alpha-2b | – | 43.0% |
| Jacobson et al ³⁸ | 1,313 | I | Peginterferon alpha-2b | Alpha-2b | – | 38.7% |
| Kumada et al ³⁹ | 31 | I | Peginterferon alpha-2b | Alpha-2b | – | 49.2% |
| Poordad et al ⁴⁰ | 70 | I | Peginterferon alpha-2b | Alpha-2b | – | 27.1% |
| Scotto et al ⁴¹ | 26 | I | Peginterferon alpha-2b | Alpha-2b | – | 50.0% |
| Shiffman et al ⁴² | 48 | I | Peginterferon alpha-2b | Alpha-2b | – | 29.2% |
| Sjogren et al ⁴³ | 29 | I | Peginterferon alpha-2b | Alpha-2b | – | 41.4% |
| Ascione et al ²² | 93 | I,4 | Both peginterferons | Alpha-2b | – | 39.8% |
| McHutchison et al ²³ | 1,019 | I | Both peginterferons | Alpha-2b | – | 39.8% |
| Rumi et al ²⁴ | 87 | I | Both peginterferons | Alpha-2b | – | 32.2% |
| Yenice et al ²⁵ | 40 | I | Both peginterferons | Alpha-2b | – | 32.5% |
| Kwo et al ⁴⁴ | 104 | I | Boceprevir | Alpha-2b | – | 37.5% |
| Poordad et al ⁴⁵ | 363 | I | Boceprevir | Alpha-2b | – | 37.8% |
| Manns et al ³¹ | 80 | I | Simeprevir | Alpha-2b | 42.5% | – |

Abbreviations: SVR12, sustained virological response at 12 weeks after treatment; SVR24, sustained virological response at 24 weeks after treatment.

informing comparative efficacy of newer DAAs may also become biased if a mixture of SVR12 and SVR24 control responses are used in the analysis.

There are strengths and limitations to consider in our analysis. Strengths include the systematic inclusion of all relevant clinical trials allowing for a well informed analysis. Further, our analysis was designed specifically for this project using a Bayesian approach that recognizes differences in effect sizes across arms, thereby allowing greater precision to detect differences. Weaknesses of our study include the fact that publication bias inherently exists as the trials have been completed but do not report on both 12- and

24-week SVR. Newer DAAs in particular have had their trials completed but are, as yet, unavailable in published form. Lastly, our results are based on separated single-arm evidence, and while the considerable amount of data adds to the reliability of our results, confirmations of our findings will be required from randomized clinical trials that report both SVR12 and SVR24. In this vein, we should note that our findings stand in contrast to a recent retrospective observational study by Martinot-Peignoux which found a close to 100% agreement between SVR12 and SVR24 in patients receiving either of the two peginterferons.⁴⁶ This study, however, included several genotype 2 and 3 patients

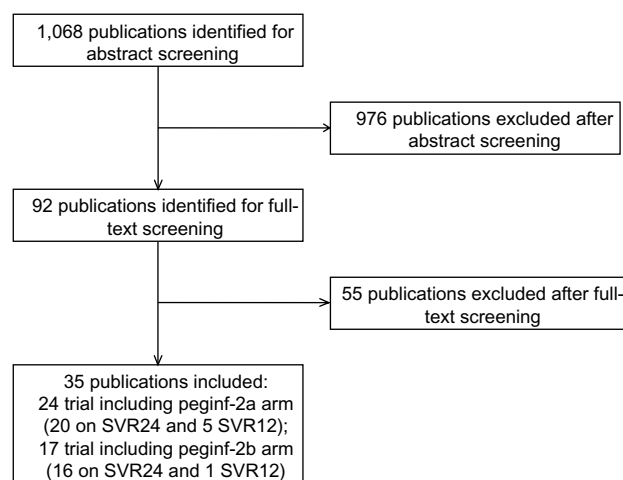


Figure 1 Study flow diagram.

Abbreviations: peginf, peginterferon; SVR12, sustained virological response at 12 weeks after treatment; SVR24, sustained virological response at 24 weeks after treatment.

as well and previous relapsers and non-responders, and so, the populations are not fully comparable. The SVR24 in the study by Martinot-Peignoux was 71%, in contrast to the 35%–55% in all the RCTs included in our analysis. The study by Martinot-Peignoux used a highly sensitive assay with a lower level of detection of 9.6 IU/mL, and one can thus speculate that use of older less sensitive assays (eg, Copas Amplicor with 50 IU/mL lower level of detection) may be the cause of differences between SVR12 and SVR24. However, a subgroup analysis by RCTs using highly sensitive assays (defined as <20 IU/mL) versus “moderately” sensitive assays (actualized as 50 IU/mL or higher, although defined as >20 IU/mL) showed nearly identical SVR24 (results not shown). All trials reporting SVR12 used highly sensitive assays. In fact, the pooled proportions of highly sensitive assay SVR24 estimates were further from the SVR12 estimates than the pooled

Table 3 The pooled SVR12 and SVR24 proportions associated with peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin

| SVR time point | Peginterferon type | Conventional Meta-analysis | Bayesian Meta-regression |
|----------------|--------------------|----------------------------|--------------------------|
| SVR12 | Alpha-2a | 54% (49%–59%) | 53% (46%–59%) |
| SVR24 | Alpha-2a | 49% (46%–51%) | 47% (45%–49%) |
| SVR12 | Alpha-2b | 43% (33%–53%) | 45% (39%–53%) |
| SVR24 | Alpha-2b | 40% (38%–41%) | 40% (38%–43%) |

Notes: Proportions obtained with conventional pairwise meta-analysis of proportions, and with Bayesian meta-regression. The 95% confidence intervals and credible intervals are presented in parenthesis for the conventional meta-analysis and Bayesian meta-regression, respectively.

Abbreviations: SVR, sustained virological response; SVR12, SVR at 12 weeks after treatment; SVR24, SVR at 24 weeks after treatment.

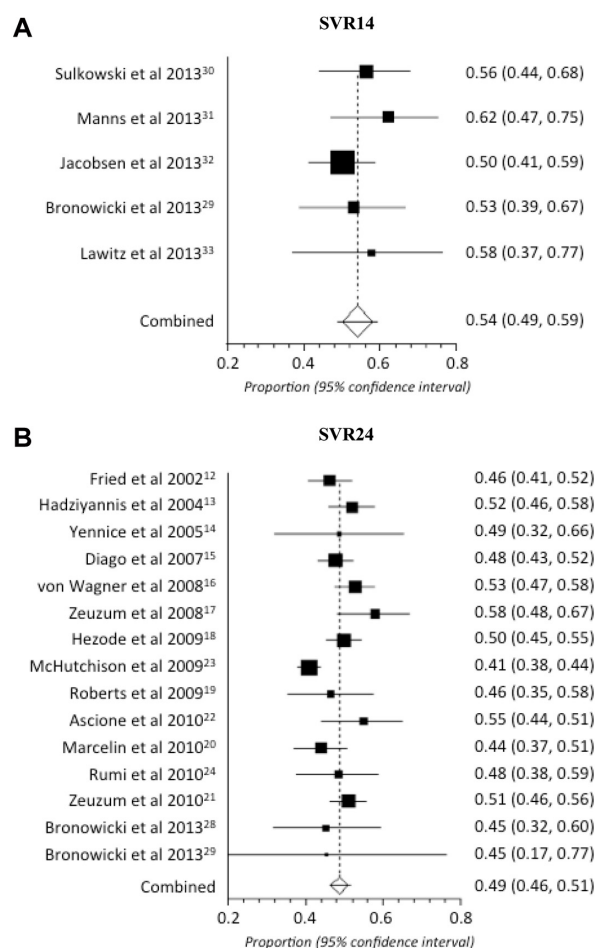


Figure 2 Forest plots of RCT peginterferon alpha-2a arms informing SVR12 (A) and SVR24 (B) proportions.

Abbreviations: RCT, randomized controlled trial; SVR12, sustained virological response at 12 weeks after treatment; SVR24, sustained virological response at 24 weeks after treatment.

proportions of the “moderately” sensitive assays. Considering that in the only RCT that reported both SVRs,²⁹ the SVR12 was 51.8% and the SVR24 was 45.0%; and considering that our meta-analytic evidence is based on a large set of homogenous trials including a total of over 10,000 patients, it seems reasonable to suggest that limited confidence should be placed on the findings of the study by Martinot-Peignoux.

Considering the relatively large difference observed between SVR12 and SVR24, it seems reasonable to insist that future clinical trials report both outcome measures to allow for complete transparency and clarity in their interpretation.

Acknowledgments

We are grateful to Kabir Toor for his assistance with late-stage data extraction and proof reading of the manuscript.

Disclosure

Kristian Thorlund and Edward J Mills have previously consulted with Merck, Pfizer, Novartis, Janssen, and Gilead on systematic review issues. In addition, they have received grants from the Canadian Institutes of Health Research (CIHR) and consulted to the Canadian Agency for Drugs and Technology in Health and US Agency for Healthcare Research and Quality (AHRQ). Kristian Thorlund's salary is supported by CIHR. Edward J Mills' salary is supported by a CIHR Canada Research Chair. Eric Druyts does not have any potential competing interests. No funding was received for this study.

References

- Manns M, Vierling JM, Bacon BR, et al. High sustained viral response at 12- and 24-week follow-up of MK-7152 with pegylated interferon alpha-2a and ribavirin in HCV genotype 1 treatment-naïve non-cirrhotic patients. *J Hepatol*. 2013;58(Suppl N1):1.
- Lawitz E, Gane E, Lalezari J, et al. High concordance of SVR4, SVR12, SVR24 in patients with HCV infection who have received treatment with sofosbuvir. *The International Liver Congress*. 2013; Amsterdam, The Netherlands, April 24–28, 2013(P848).
- AASLD Abstracts. *Hepatology*. 2012;56(Suppl 4).
- The international liver congress 2013 abstract book. *J Hepatol*. 2013;58(Suppl N1).
- Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Glud 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.
- 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 peginterferon alpha-2b plus ribavirin: a meta-analysis. *Clin Exp Gastroenterol*. 2012;5:11–21.
- Thorlund K, Thabane L, Mills EJ. Modelling heterogeneity variances in multiple treatment comparison meta-analysis – are informative priors the better solution? *BMC Med Res Methodol*. 2013;13:2.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
- Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity–subgroups, meta-regression, bias, and bias-adjustment. *Med Decis Making*. 2013;33(5):618–640.
- Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: evolution, critique and future directions. *Stat Med*. 2009;28(25):3049–3067.
- Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347(13):975–982.
- 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.
- Ferenci P, Formann E, Laferl H, et al. Randomized, double-blind, placebo-controlled study of peginterferon alpha-2a (40 KD) plus ribavirin with or without amantadine in treatment-naïve patients with chronic hepatitis C genotype 1 infection. *J Hepatol*. 2006;44(2):275–282.
- Diago M, Oliveira A, Sola R, et al. Treatment of chronic hepatitis C genotype 1 with peginterferon-alpha2a (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.
- von Wagner M, Hofmann WP, Teuber G, et al. Placebo-controlled trial of 400 mg amantadine combined with peginterferon alpha-2a and ribavirin for 48 weeks in chronic hepatitis C virus-1 infection. *Hepatology*. 2008;48(5):1404–1411.
- Zeuzem S, Yoshida EM, Benhamou Y, et al. Albinterferon alpha-2b dosed every two or four weeks in interferon-naïve patients with genotype 1 chronic hepatitis C. *Hepatology*. 2008;48(2):407–417.
- 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.
- Roberts SK, Weltman MD, Crawford DH, et al. Impact of high-dose peginterferon alpha-2 A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. *Hepatology*. 2009;50(4):1045–1055.
- Marcellin P, Gish RG, Gitlin N, et al. Safety and efficacy of viramidine versus ribavirin in ViSER2: randomized, double-blind study in therapy-naïve hepatitis C patients. *J Hepatol*. 2010;52(1):32–38.
- Zeuzem S, Sulkowski MS, Lawitz EJ, et al. Albinterferon Alfa-2b was not inferior to pegylated interferon-alpha in a randomized trial of patients with chronic hepatitis C virus genotype 1. *Gastroenterology*. 2010;139(4):1257–1266.
- Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alpha-2a plus ribavirin is more effective than peginterferon alpha-2b plus ribavirin for treating chronic hepatitis C virus infection. *Gastroenterology*. 2010;138(1):116–122.
- McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alpha-2b or alpha-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med*. 2009;361(6):580–593.
- Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha 2a plus ribavirin vs peginterferon-alpha 2b plus ribavirin in chronic hepatitis C. *Gastroenterology*. 2010;138(1):108–115.
- 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;17:5.
- 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.
- 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.
- Bronowicki JP, Pol S, Thuluvath PJ, et al. Randomized study of asunaprevir plus peginterferon alpha and ribavirin for previously untreated genotype 1 chronic hepatitis C. *Antivir Ther*. Epub June 26, 2013.
- Bronowicki JP, Ratzliff V, Gadano A, et al. Asunaprevir with peginterferon-alpha and ribavirin in treatment-naïve patients with genotype-1 or -4 chronic hepatitis C: SVR24 results from a randomized phase 2b study (AI447016). *J Hepatol*. 2013;58(Suppl N1):S574.
- Sulkowski MS, Asselah T, Lalezari J, et al. Faldaprevir combined with pegylated interferon alpha-2a and ribavirin in treatment-naïve patients with chronic genotype 1 HCV: SILEN-C1 trial. *Hepatology*. 2013;57(6):2143–2154.
- Manns M, Marcellin P, Poordad F, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype-1 infection in treatment-naïve patients: results from QUEST-2 a phase III trial. *J Hepatol*. 2013;58(Suppl N1):S258.
- Jacobson I, Dore GJ, Foster GR, et al. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype-1 infection in treatment-naïve patients: results from QUEST-1, a phase III trial. *J Hepatol*. 2013;58(Suppl N1):1.
- Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alpha-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis*. 2013;13(5):401–408.
- 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.

35. 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.
36. 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. e1.
37. 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.
38. 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.
39. Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peginterferon and ribavirin for treatment-naïve patients chronically infected with HCV of genotype 1 in Japan. *J Hepatol*. 2012;56(1):78–84.
40. Poordad F, Lawitz E, Shiffman ML, et al. Virologic response rates of weight-based taribavirin versus ribavirin in treatment-naïve patients with genotype 1 chronic hepatitis C. *Hepatology*. 2010;52(4):1208–1215.
41. 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 naïve patients. *New Microbiol*. 2005;28(1):23–29.
42. 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.
43. Sjogren MH, Sjogren R Jr, 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.
44. 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-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet*. 2010;376(9742):705–716.
45. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364(13):1195–1206.
46. Martinot-Peignoux M, Stern C, Maylin S, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. *Hepatology*. 2010;51(4):1122–1126.

Supplementary material

WinBUGS code and data for the Bayesian meta-regression.

```
## model begins

model{

#####
## Modelling of Peg-2a and Peg-2b SVR24 and SVR12 ##
#####

## Assigning priors for regression parameters

mu.peg ~ dnorm(0,.001)      # Mean logit peg-2a SVR12
coef.pb ~ dnorm(0,.001)    # Log OR offset from peg-2a to peg-2b
coef.24 ~ dnorm(0,.001)    # Log OR offset from SVR12 to SVR24

## looping over trial SVRs

for(i in 1:n.1)
{
  # Random effects logit link of SVR
  logit(p.p[i])<-mu[s[i]] + coef.pb*p2b.p[i] + coef.24*svr24.p[i]

  # binomial likelihood for number of patients with SVR
  r.p[i]~dbin(p.p[i],n.p[i])
}

## looping over trial baseline SVR (peg-2a SVR12)

for(j in 1:ns.1)
{
  # random-effects modelling of baseline Peg SVR
  mu[j] ~ dnorm(mu.peg, tau.b)
}

## Prior and deterministic equations for between-trial variance (random-effects term)
sd.b~dgamma(.01,.01)I(,1)
var.b<-pow(sd.b,2)
tau.b>-1/pow(sd.b,2)

## Conversions to effect measures of interest
logit(SVR2A12) <- mu.peg      # back transform to proportions (SVR12
                             # for peg-2a)
logit(SVR2B12) <- mu.peg + coef.pb  # back transform to proportions (SVR12
                             # for peg-2b)
```



```

logit(SVR2A24) <- mu.peg + coef.24          # back transform to proportions (SVR24
                                           for peg-2a)
logit(SVR2B24) <- mu.peg + coef.pb + coef.24 # back transform to proportions
                                           (SVR24 for peg-2b)
RRAB12 <- SVR2A12/SVR2B12                # RR of peg-2a vs peg-2b for SVR12
RRAB24 <- SVR2A24/SVR2B24                # RR of peg-2a vs peg-2b for SVR24
RR1224A <- SVR2A12/SVR2A24               # RR of SVR12 vs SVR24 for peg-2a
RR1224B <- SVR2B12/SVR2B24               # RR of SVR24 vs SVR24 for peg-2a

}
## model ends
## Complete data set for Bayesian meta-regression ##

## number of trials and arms

list(ns.1=35, n.1=41)

## s[] is the study number
## p2b.p is in indicator function for whether the peginterferon is alpha-2b (=1)
  or alpha-2a (=0)
## r.p[] is the number of patients with SVR
## n.p[] is the number of patients
svr24.p[] is an indicator function for whether SVR is SVR24 (=1) or SVR12 (=0)

s[]  p2b.p[]  r.p[]  n.p[]  svr24.p[]
1    0        51    93    1      ## Ascione 2010
1    1        37    93    1      ## Ascione 2010
2    0       423   1035   1      ## IDEAL 2009
2    1       406   1019   1      ## IDEAL 2009
3    0        44    91    1      ## Rumi 2010
3    1        28    87    1      ## Rumi 2010
4    0        18    40    1      ## Yenice 2010
4    1        13    40    1      ## Yenice 2010
5    0        38   298    1      ## Fried 2002
6    0       141   271    1      ## Hadziyannis 2004
7    0        49    95    1      ## Ferenci 2006
8    0       227   475    1      ## Diago 2007
9    0       186   352    1      ## von Wagner 2008
10   0        66   114    1      ## Zeuzem 2008
11   0        38    82    1      ## Herzode 2009
12   0       219   438    1      ## Roberts 2009
13   0        93   212    1      ## Marcellin 2010
14   0       225   441    1      ## Zeuzem 2010
15   0        31    85    1      ## Pockros 2013
16   1       145   348    1      ## Manns 2001

```

| | | | | | |
|----|---|-----|-----|---|---|
| 17 | 1 | 13 | 26 | 1 | ## Scotto 2005 |
| 18 | 1 | 171 | 427 | 1 | ## Jacobson 2007 |
| 19 | 1 | 14 | 48 | 1 | ## Shiffman 2007 |
| 20 | 1 | 12 | 29 | 1 | ## Sjogren 2007 |
| 21 | 1 | 94 | 226 | 1 | ## Benhamou 2009 |
| 22 | 1 | 108 | 225 | 1 | ## Berg 2009 |
| 23 | 1 | 92 | 311 | 1 | ## Brady 2010 |
| 24 | 1 | 37 | 86 | 1 | ## Buti 2010 |
| 25 | 1 | 19 | 70 | 1 | ## Poordad 2010 |
| 26 | 0 | 40 | 71 | 1 | ## Sulkowski 2013 – Faldaprevir (Hepatology) |
| 27 | 0 | 31 | 50 | 0 | ## Manns 2013 – EASL (Simeprevir RCT) |
| 27 | 1 | 34 | 80 | 0 | ## Manns 2013 – EASL (Simeprevir RCT) |
| 28 | 0 | 66 | 132 | 0 | ## Jacobsen 2013 – EASL (Simeprevir RCT) |
| 29 | 0 | 28 | 53 | 0 | ## Bronowicki 2013 – EASL (Asunaprevir RCT) |
| 29 | 0 | 24 | 53 | 1 | ## Bronowicki 2013 – EASL (Asunaprevir RCT) |
| 30 | 0 | 5 | 11 | 0 | ## Bronowicki 2013 – Antivir Ther (Asunaprevir) |
| 31 | 1 | 39 | 104 | 1 | ## Kwo 2010 (boceprevir) |
| 32 | 1 | 137 | 363 | 1 | ## Poordad 2011 (boceprevir) |
| 33 | 0 | 31 | 75 | 1 | ## McHutchinson 2009 (telaprevir) |
| 34 | 0 | 158 | 361 | 1 | ## Jacobson 2011 (telaprevir) |
| 35 | 0 | 15 | 26 | 0 | ## Lawitz 2013 (sofosbuvir) |

END

Clinical Epidemiology

Dovepress

Publish your work in this journal

Clinical Epidemiology is an international, peer-reviewed, open access journal focusing on disease and drug epidemiology, identification of risk factors and screening procedures to develop optimal preventative initiatives and programs. Specific topics include: diagnosis, prognosis, treatment, screening, prevention, risk factor modification, systematic

reviews, risk & safety of medical interventions, epidemiology & biostatistical methods, evaluation of guidelines, translational medicine, health policies & economic evaluations. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use.

Submit your manuscript here: <http://www.dovepress.com/clinical-epidemiology-journal>