Impact of erythropoietin on sustained virological response to peginterferon and ribavirin therapy for HCV infection: a systematic review and meta-analysis

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SUMMARY. Anaemia is a common complication of antiviral therapy for chronic hepatitis C virus (HCV) infection that necessitates dose reductions or therapy discontinuation. Administration of erythropoietin (EPO) is an alternative to ribavirin (RBV) dose reduction, but its advantage in terms of sustained virological response (SVR) has not been determined yet. In a systematic way, randomized studies were identified that evaluated the effect of EPO administration vs RBV dose reduction on virological response in patients who developed anaemia during anti-HCV therapy. The random-effects model was employed to run meta-analysis. SVR was set as the end point of interest. Data were abstracted from four studies containing 257 patients who developed anaemia during therapy. One hundred and twenty six subjects underwent RBV dose reduction. Patients who received EPO in response to haemoglobin drop had a significantly higher probability of achieving SVR compared with those who underwent RBV dose reduction because of anaemia (relative risk = 1.83 95% CI: 1.41–2.37). No heterogeneity was observed across study results ($I^2 = 0$). Publication bias assessment was nonsignificant. Our meta-analysis indicates that administration of EPO in patients who develop anaemia during anti-HCV therapy can considerably enhance SVR. Moreover, no adverse event of EPO administration was reported among included subjects.

Keywords: epoetin alpha, epoetin beta, erythropoietin, HCV.

INTRODUCTION

Hepatitis C virus (HCV) is an important cause of chronic liver disease. HCV accounts for 20% of acute hepatitis cases, 70% of all chronic hepatitis cases and 40% of all cases of liver cirrhosis [1]. As sustained virological response (SVR) to anti-HCV therapy avoids progression of liver fibrosis, decreases the risk of hepatocellular carcinoma and improves patients' survival, antiviral therapy is considered as a crucial option in the management of chronic HCV infection [2–5].

Current anti-HCV standard therapy is comprised of oral ribavirin (RBV) and peginterferon alpha-2a or alpha-2b. RBV dose during the treatment period and a patient's compliance with this drug are important factors in achieving SVR [6]. However, anaemia is the most challenging side-effect of RBV and is responsible for considerable numbers of dose reduction and treatment cessation [7]. Haemoglobin concentration has been reported to decrease to below 12 g/dL (mean decrease 3.7 g/dL) in 52% of patients receiving peginterferon alpha-2a and RBV combination therapy [Pegasys Package Insert, 2004]. Furthermore, significant anaemia (i.e. haemoglobin <10 g/dL) has been observed in 9–13% of these patients [8]. Although both interferon and RBV cause anaemia, RBV-induced haemolysis is generally identified as the main reason for dose reduction and treatment discontinuation [9].

Administration of recombinant human erythropoietin (EPO) is employed to maintain RBV dose, increase haemoglobin level and improve treatment compliance, whereas its impact in terms of SVR is not currently well elucidated [10–14]. Therefore, in this review, we aimed to draw a robust conclusion about the impact of EPO on SVR, by identifying, summarizing and pooling results of all available randomized clinical trials.

MATERIAL AND METHODS

Search methods for identification of studies

We searched electronic databases including Medline, Scopus, the Cochran Central Register of Controlled Trials and ISI for...
different combinations of ‘hepatitis C virus’ or ‘HCV’ with the following terms: ‘erythropoietin’, ‘EPO’, ‘Hematopoietic growth factor’, ‘darbepoetin’, ‘epoetin alpha’, ‘epoetin alfa’ and ‘epoetin beta’. Temporal limit was not applied to our search strategy.

Data collection and analysis

Titles and abstracts of all potentially relevant citations were screened by two authors separately (B. Behnava and S.V. Tabatabaei). After that, the full texts of all selected reports were retrieved and assessed according to our predefined inclusion and exclusion criteria. Data from studies that met our inclusion criteria were extracted by two investigators separately and were rechecked by the third one (S.M. Alavian). Finally, the decision about inclusion or exclusion of studies and predefined assumptions were made and agreed by all authors before running the meta-analysis. Moreover, data on characteristics from selected studies were abstracted using standard questionnaires.

Inclusion criteria

Randomized controlled studies of adults with chronic HCV infection were included if studied patients (i) received peginterferon alpha-2a 180 µg or peginterferon alpha-2b 1.5 µg/kg once weekly plus weight-based RBV, (ii) developed anaemia, defined as >2 or ≥2.5 g/dL haemoglobin drop from baseline or a haemoglobin level lower than 11 or 10 g/dL, (iii) were randomized to receive either EPO or RBV dose reduction for the management of anaemia during therapy or (iv) received subcutaneous epoetin alpha, epoetin beta or darbepoetin alpha at any dose and with/without dose modification depending on haematologic response in study group. The diagnosis of chronic HCV infection required a detectable HCV RNA value and duration of at least 6 months of infection. Articles in all languages that met the criteria were included. Inclusion of patients with previous history of treatment and dose modification of all studied medicines were allowed.

Studies were excluded if study patients (i) had decompensated liver disease, (ii) had positive seromarkers for HIV or HBV infection and (iii) had significant co-morbidities such as decompensated liver disease, autoimmune diseases, haemoglobinopathies and chronic kidney disease.

End points of interest

Our primary end point of interest was SVR, defined as undetectable HCV RNA 6 months after treatment cessation.

Source of support

This meta-analysis was not supported by any pharmaceutical company or government agency or grants from other sources.

Data synthesis

All analyses were performed in Mix 2.0 professional software for meta-analysis in Excel [15]. Data on all included patients were analysed based on the intention-to-treat principle, irrespective of compliance or follow-up. To manage missing data, we used worst-case scenario analysis, and because we had a positive outcome (virological response), all missing data were counted as nonresponder. The results are presented as relative risk (RR) with 95% confidence interval.

The meta-analysis was performed using the random-effects model of DerSimonian and Laird [16]. The estimate of heterogeneity was taken from the Mantel–Haenszel model. Study results were considered heterogeneous if the resultant P-value was <0.1 [17]. I² was also used to provide a measure of the degree of inconsistency between the studies’ results [18]. Furthermore, publication bias assessment was carried out using Harbord’s modified test [19].

RESULTS

Our search strategy yielded 58 unique citations that included four randomized clinical trials [20–23], three prospective [12,24,25] and two retrospective studies [25,26] that evaluated the effect of EPO on SVR. Nonrandomized studies were excluded. Three studies by Falasca, Sharvadze and Bertino et al. randomized patients who developed anaemia to EPO recipients and patients with RBV dose reduction as standard care, whereas Shiffman et al. randomized patients to EPO recipients and placebo recipients from the beginning of study. To compare EPO vs RBV dose reduction, from Shiffman et al.’s study, only data of patients who developed anaemia in either the erythropoietin support group or control group were included in the analyses. Overall, 257 unique patients were included of whom 131 patients had received EPO and 126 subjects had undergone RBV dose reduction.

Study characteristics

Table 1 shows the characteristics of included studies. All studies were published as full text in peer-review journals between 2006 and 2010. One study was from United States, two from Italy and one from Georgia. In all studies, patients received weight-based RBV accompanying peginterferon alpha-2a or 2b. None of the randomized trials were double-blinded, and the method of concealment was unclear in all RCTs. Bertino and Shiffman had used computer-generated random numbers; however, the method of random number sequence generation was unknown in Sharvadze and Falasca et al.’s study. Table 2 shows predefined protocols for EPO adjuvant therapy and RBV dose reduction in control groups.
Patient characteristics

Table 3 shows baseline characteristics of included patients. Approximately two-thirds of included patients had genotype 1 infection. Sharvadze et al. had not reported history of anti-HCV therapy in their subjects; however, in other studies, only treatment-naïve patients were eligible for inclusion. Baseline characteristics of included patients were available in Falasca and Bertino et al.’s studies. In Sharvadze and Bertino et al.’s study, all patients who received EPO normalized haemoglobin level and did not need further RBV dose reduction. In Shiffman et al.’s study, patients who dropped haemoglobin despite EPO therapy vs those who developed anaemia without haematologic support are compared.

Comparative sustained virological response rate of anaemia patients who received erythropoietin vs standard care

Patients who developed anaemia and received EPO as adjuvant therapy had a significantly higher rate of SVR compared with those who underwent ribavirin dose reduction.

![Fig. 1](image-url)  
Comparative chance of achieving sustained virological response in anaemia patients who received erythropoietin compared with those who underwent ribavirin dose reduction.
compared with those with anaemia who underwent RBV dose reduction as standard care with RR of 1.83 (95% CI 1.41–2.37). SVR occurred in 88 of 131 (67%) from the former group and 46 of 126 (37%) from the latter group. No heterogeneity was observed between study results ($P = 0.88$, $I^2 = 0$). Figure 1 shows the summary estimates with 95% CI of included studies and pooled RR for likelihood of SVR in patients who received EPO vs those who received standard care. As presented in Fig. 2, the pooled estimate was not dependent on any single study. Publication bias assessment was nonsignificant for this analysis ($P = 0.29$) (Fig. 3).

**DISCUSSION**

Our meta-analysis suggests that administration of EPO agents to avoid further RBV dose reduction or treatment discontinuation significantly improves SVR compared with
patients who underwent standard care. This finding is completely compatible with results of studies that evaluated the effect of RBV dose adjustment on virological response [27,28]. In spite of unclear risk of bias across included studies owing to lack of adequate methodological reporting, we believe that we can have high confidence in our findings because of the following reasons: (i) absence of statistical heterogeneity among study results despite different treatment protocols, (ii) statistically significant results despite very limited statistical power, (iii) absence of publication bias that indicates it is unlikely that unidentified studies in grey literature can alter the pooled result, and, last but not least, (iv) a robust pooled estimate by exclusion of studies in grey literature can considerably enhance SVR. No adverse event of EPO administration was reported among included patients, owing to the small number of included subjects, the full safety of EPO use during anti-HCV therapy could not be assured in this review.

CONCLUSION

Our meta-analysis determined that administration of EPO in patients who developed anaemia during anti-HCV combination therapy can considerably enhance SVR. No adverse event of EPO administration was reported among included subjects.

AUTHOR CONTRIBUTIONS

All authors were responsible for design, concept and writing of the manuscript, for literature search, and for retrieving data.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript.

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