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REVIEW

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.

Abbreviations: EPO, erythropoietin; HCV, hepatitis C virus; RBV, ribavirin; RR, relative risk; SVR, sustained virological response.

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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]. I^2 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 erythropoietic 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 Scharvadze and Falasca *et al.*'s study. Table 2 shows predefined protocols for EPO adjuvant therapy and RBV dose reduction in control groups.

Table 1 Study characteristics

References	Samples' origin	Publication year	Randomization	Allocation concealment	Blinding	Treatment regimen
Falasca *et al.* [20]	Italy	2010	Unclear	Unclear	No	PEG-α-2a PEG-α-2b
Sharvadze *et al.* [21]	Georgia	2006	Unclear	Unclear	No	PEG-α-2a PEG-α-2b
Shiffman *et al.* [22]	US	2007	Computer-generated	Unclear	No	PEG-α-2b
Bertino *et al.* [23]	Italy	2010	Computer-generated	Unclear	No	PEG-α-2a

Table 2 Protocols of EPO adjuvant therapy and ribavirin dose reduction

References	Protocol for EPO therapy	Protocol for ribavirin dose reduction
Falasca *et al.* [20]	Adjusted dose 30 000 IU, EPO-β QW or 2QW	From 1200/1000/800 to 600 mg
Sharvadze *et al.* [21]	Fixed dose 40 000 IU, EPO-α QW	From 1000/1200 to 800/600 mg
Shiffman *et al.* [22]	Adjusted dose 20 000 – 60 000 IU EPO-α QW	200 mg in each step from 800/1000/1200/1400/1600 mg
Bertino *et al.* [23]	Fixed dose 10 000 IU, EPO-α 2QW	From 1200/1000 to 1000/800 mg

EPO, erythropoietin.

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

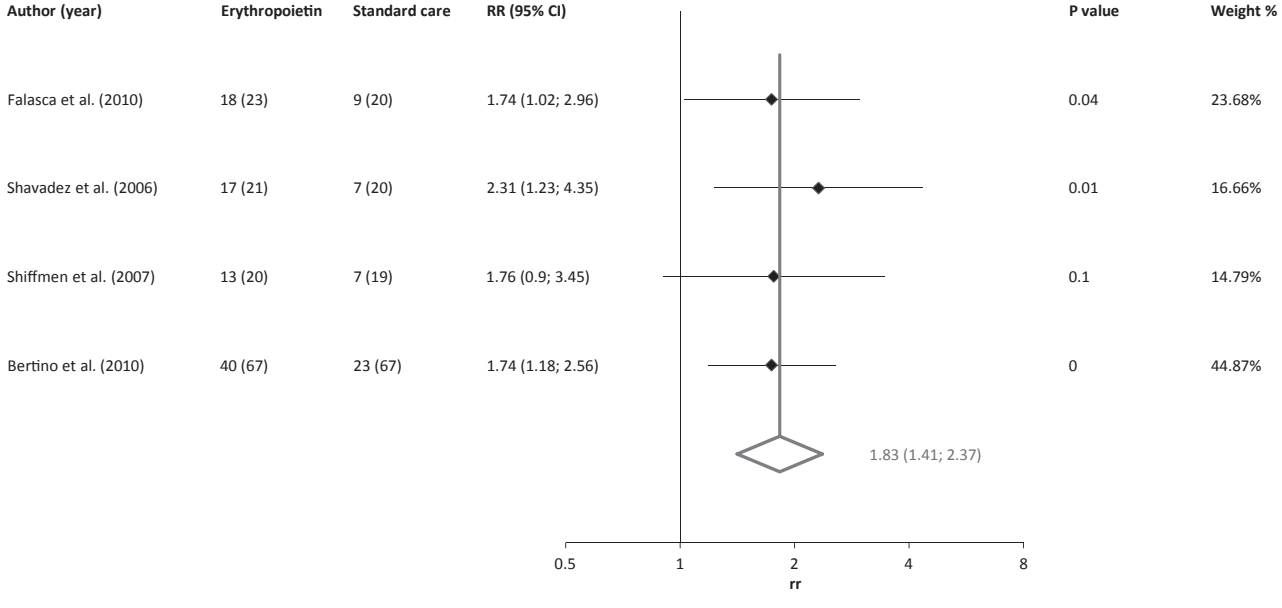

Fig. 1 Comparative chance of achieving sustained virological response in anaemia patients who received erythropoietin compared with those who underwent ribavirin dose reduction.

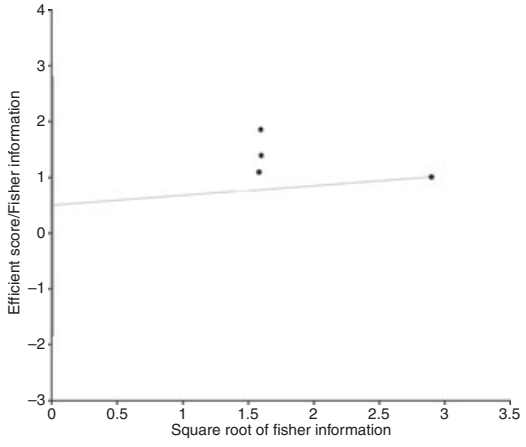

Fig. 2 Simple exclusion sensitivity analysis.

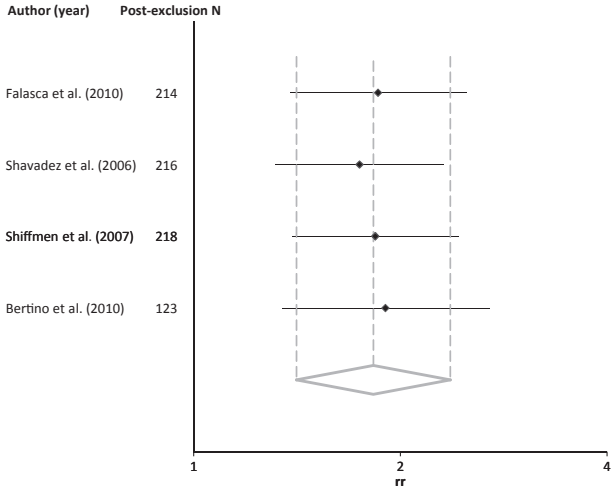

Fig. 3 Harbord's regression line to assess significant funnel plot asymmetry.

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

Table 3 Patient characteristics

References	Men		Age		ALT (IU/L)		Viral load (IU/mL)		Genotype 1	
	EPO	SOC	EPO	SOC	EPO	SOC	EPO	SOC	EPO	SOC
Falasca *et al.* [20]	22.7%	35%	47.5 ± 10.6	48.6 ± 15.0	116.5 ± 131.2	117.4 ± 87.7	67.9 ± 37.2 × 104 cp/mL	69.5 ± 46.2 × 104 cp/mL	68.2%	75%
Sharvadze *et al.* [21]	NR	NR	NR	NR	NR	NR	NR	NR	100%	
Shiffman *et al.* [22]*									100%	
Bertino *et al.* [23]	50.5%		48.0 ± 1.1		139 ± 3.0		6.40 ± 0.86 $\log_{10}$ IU/mL		100%	

EPO, erythropoietin; SOC, standard of care; NR, not reported.
*As only a subgroup of patients, who developed anaemia, was included, the data provided by authors could not represent baseline characteristics of included patients.

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 sensitivity analysis that implies the final estimate was not dependent on any single study result. A higher rate of SVR among patients who developed anaemia despite EPO adjuvant therapy compared with other anaemia patients without EPO adjuvant therapy in Shiffman *et al.*'s study could be due to lower rate of treatment discontinuation, lower RBV dose reduction and tolerance for higher dose of RBV in the high-dose RBV group. Furthermore, in Bertoni *et al.*'s study, despite EPO usage, none of the patients who received standard care achieved haemoglobin increase. In addition, only in the adjuvant therapy group, the '80/80/80 rule' was respected (administration of at least 80% of the dose of peg-IFN and RBV for at least 80% of the treatment time). These patients had exactly the same rate of SVR as the control group (without anaemia and treated with full dose of RBV). These findings were in line with other included study results.

Erythropoietic agents might not be completely safe. Hypertension, headache, reaction at injection site, increased numbers of platelets in the blood, severe thrombocytopenia and antibody-mediated pure red cell aplasia during anti-HCV therapy are rare complications of EPO adjuvant therapy [29–32]. Although none of the included studies reported any adverse events attributable to EPO 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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