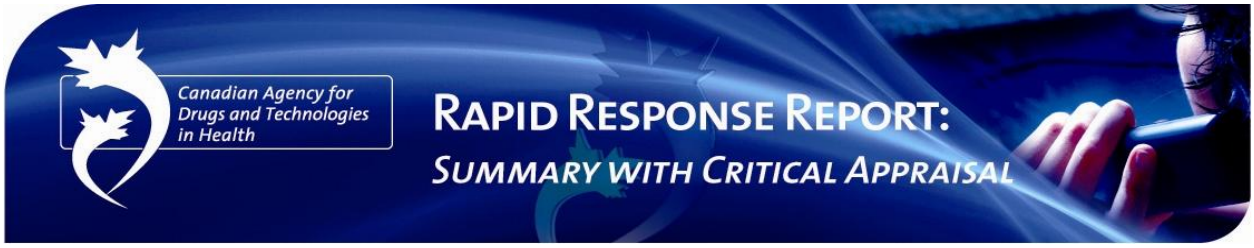


TITLE: Treatment of Anemia and Neutropenia in Patients with Chronic Hepatitis C Infection Treated with Peginterferon-Ribavirin Based Regimens With or Without Protease Inhibitors: A Review of the Clinical Evidence

DATE: 8 March 2012

CONTEXT AND POLICY ISSUES

Anemia and neutropenia are key adverse effects of combination therapy with peginterferon and ribavirin (PR) for chronic hepatitis C (CHC) infection. The main strategies used to manage these adverse effects include dose reduction of either peginterferon (neutropenia) or ribavirin (anemia) or addition of other drugs that can address these adverse effects. Granulocyte colony stimulating factors (G-CSFs) like filgrastim are used to treat or prevent neutropenia while erythropoietin (EPO) is used for anemia.

There are limitations to each approach. Dose reduction is a less costly option, at least in the immediate term, and is less likely to elicit adverse effects. However dose reduction also potentially increases risk of therapeutic failure. If the patient does fail therapy and needs to be retreated, it is possible that this strategy might prove more costly in the long run. On the other hand, use of G-CSFs or EPO to manage anemia or neutropenia adds considerable cost in the short run. There is also the issue of increased risk of harm to the patient, as the G-CSFs and EPO both carry a risk of adverse effects. Hence, there is a need to assess the evidence pertaining to the risks and benefits of each strategy.

This report was reviewed by a clinical expert in hepatology.

RESEARCH QUESTIONS

1. What is the comparative clinical efficacy and safety of erythropoietin versus ribavirin dose reduction for the treatment of anemia in patients with chronic hepatitis C infection who are treated with peginterferon and ribavirin (PR) with or without protease inhibitors?

2. What is the comparative clinical efficacy and safety of filgrastim versus interferon dose reduction for the treatment of neutropenia in patients with chronic hepatitis C infection who are treated with PR with or without protease inhibitors?

KEY MESSAGE

At present, there is no clear evidence that would suggest an advantage of one intervention (pharmacological intervention versus dose reduction) over another as a strategy for managing neutropenia in patients with chronic hepatitis C infection treated with PR. The evidence supporting the use of EPO versus ribavirin dose reduction in patients treated with PR who experience anemia is limited to small, underpowered studies. There is currently no evidence comparing pharmacological intervention with dose reduction in patients treated with protease inhibitor-PR regimens who experience anemia or neutropenia.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including MEDLINE, PubMed, EMBASE, The Cochrane Library (2011, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents. The search was not limited by publication date. The search was run on January 4, 2012. A supplemental limited literature search was performed on January 6, 2012 in MEDLINE and PubMed for publications addressing anemia or neutropenia while using peginterferon and ribavirin therapy.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with chronic hepatitis C genotype 1 infection
Intervention	Q1: Ribavirin dose reduction to manage anemia Q2: Filgrastim to manage neutropenia
Comparator	Q1: EPO to manage anemia Q2: Interferon dose reduction to manage neutropenia
Outcomes	Sustained virologic response (SVR); Safety, infection (neutropenia), quality of life, fatigue, hemoglobin
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials Emerging evidence (e.g. conference abstracts)

Exclusion Criteria

Health technology assessments, systematic reviews, and meta-analyses published before 2010 were excluded, as were duplicate publications of the same study. Studies that were included in selected systematic reviews were also excluded.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[1] The adequacy of randomization, allocation concealment, blinding (of patients, clinicians or health care providers, data collectors and outcome assessors), loss to follow-up, early stopping of trial, and description of intention-to-treat analysis were considered in the critical appraisal of the included randomized controlled trials (RCTs).

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 732 citations. Upon screening titles and abstracts, 718 citations were excluded and 14 potentially relevant articles were retrieved for full-text review. Of the 14 potentially relevant reports, 10 did not meet inclusion criteria. Four studies are included in this review. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart (Appendix 1).

No studies were found that addressed the question on effectiveness of ribavirin dose reduction versus erythropoietin for managing anemia in patients treated with one of the protease inhibitors. However, there were two open label RCTs (Talal 2011, Bertino 2010)[2,3] that addressed this question in patients receiving PR, rather than triple therapy, although the population in Talal was co-infected with HIV. An additional trial (Falasca 2010) was described by the authors as observational but appeared to have employed randomization to assign treatment.[4]

One systematic review (Tandon 2011) was identified that evaluated the clinical and cost-effectiveness of G-CSF versus PEG-IFN dose reduction for neutropenia associated with HCV therapy in treatment naïve adults.[5] The Talal trial also examined the use of G-CSF compared with interferon dose reduction for management of neutropenia.

Summary of Study Characteristics

Erythropoietin versus ribavirin dose reduction

In an open label randomized trial (N=103), Talal compared strategies for managing anemia and for managing neutropenia in adults with compensated CHC, co-infected with HIV-1, and being treated with PR. The two strategies were addition of EPO for anemia or G-CSF for neutropenia versus dose reduction (ribavirin reduction for anemia; PEG-IFN reduction for neutropenia).

The Bertino study began with all patients being treated with peginterferon (PEG-IFN) alpha-2a plus weight-based ribavirin (1000 to 1200 mg/day).[3] Patients who were responding to therapy and who had a reduction in hemoglobin >2 g/dL were randomized to receive either EPO-alpha (N=67) or to have their ribavirin dose reduced (N=67).

The authors of the Falasca paper described it as an observational study, however they also allude to patients being randomized to their assigned treatment group.[4] This was a single centre study, with all patients recruited from an infectious disease clinic in Italy. PR therapy-responsive patients (minimum 2 log reduction in hepatitis C virus [HCV] RNA) with evidence of anemia

(minimum 2.5 g/dL drop in hemoglobin) were assigned to receive either EPO-beta (N=22) or ribavirin dose reduction (N=20).

G-CSF versus interferon dose reduction

Tandon performed a systematic review of treatment-naïve adult patients on HCV-therapy (PR) induced neutropenia.[5] Included studies were to have compared administration of G-CSF (filgrastim or pegfilgrastim) or dose reduction or discontinuation of PEG-IFN therapy for management of neutropenia. The primary outcomes of interest were SVR and neutrophil count.

The open label RCT by Talal et al., described above, also examined the use of G-CSF compared with PEG-IFN dose reduction for managing neutropenia.[2]

Details of the characteristics of the included studies are provided in Appendix 2 and Appendix 3.

Summary of Critical Appraisal

Erythropoietin versus ribavirin dose reduction

The Talal study was limited by its sample size, which was reduced from the planned sample size of 200 patients after the study sponsor ended the study prematurely. Split among 4 groups, this led to a limited number of participants in each group, and potentially limited statistical power to detect differences between groups. The premature termination of enrollment is also a methodological concern, and there was no clear reason given for why the study was ended early.

Bertino was limited by a small sample size (N=67 in each comparison group) and by lack of blinding. The small sample size limits the statistical power of the trial, and the lack of blinding increases the risk of bias. For example, patients being managed with addition of EPO might have been more adherent with their therapy, as they would be less concerned about anemia worsening.

The major issue with Falasca was unclear description of study design. The authors described it as an observational study, and only once mentioned that patients were randomized into their assigned groups. Therefore it was not entirely clear whether this was a randomized controlled trial. If it was randomized, no details were provided about the method of randomization. The study was carried out at a single centre in Italy, and this may reduce the generalizability of the study to the Canadian setting. As with the other studies, the sample size was small, potentially limiting statistical power.

G-CSF versus interferon dose reduction

From a methodological standpoint, the Tandon systematic review was well-conducted, with only minor weaknesses that are common to many systematic reviews. The main limitation of the review was the lack of high quality studies identified. One RCT was identified, and this study lacked adequate power to properly address the research question. The remainder of the studies were retrospective cohort studies or case series.

Critical appraisal of the Talal RCT is described above.

A summary of the strengths and limitations of each publication is provided in Appendix 4.

Summary of Findings

Erythropoietin versus ribavirin dose reduction

In Talal, use of EPO did not differ significantly with respect to SVR rates compared with ribavirin dose reduction. In anemic patients, the percentage of patients with SVR was 29% with EPO and 21% with ribavirin dose reduction (P = 0.92).

In Bertino, there was a statistically significant improvement in SVR rates for patients whose anemia was managed with addition of EPO compared to patients managed with ribavirin dose reduction (60% versus 34%, P < 0.01). Hemoglobin levels were higher at end of treatment in patients receiving EPO versus patients having their ribavirin dose reduced (13.8 g/dL versus 11.5 g/dL), although it was not reported whether this was a statistically significant difference. The authors also reported that quality of life scores were superior with addition of EPO versus those patients who reduced their ribavirin dose.

The SVR findings in Falasca supported those of the other studies. A larger proportion of patients managed with EPO achieved SVR compared with patients whose anemia was managed with ribavirin dose reduction (82% versus 45%, P = 0.03), and this difference was statistically significant. Hemoglobin levels at end of treatment were similar between patients managed with EPO versus those managed with ribavirin dose reduction.

G-CSF versus interferon dose reduction

One recent (2011) systematic review included studies of treatment-naïve adult patients with HCV therapy-induced neutropenia. The single RCT (Sharvadze et al) included in this review enrolled 41 patients, but did report a numerically higher SVR rate among patients who received G-CSF versus patients who had a PEG-IFN dose reduction, although this difference was not statistically significant (RR of 2.07 [95% confidence interval: 0.89 to 4.82], P = 0.12). The remainder of the studies were non-RCTs, and therefore represent poorer quality evidence. SVR rates were not reported in many of these studies; where reported, use of EPO for anemia and G-CSF for neutropenia typically elicited higher SVR rates than observed with dose reduction strategies.

In the RCT by Talal et al, SVR responses did not differ significantly with the use of G-CSFs compared with dose reduction strategies among patients with neutropenia: the SVR rate was 40% with G-CSF and 20% with IFN dose reduction. Although this difference was not statistically significant (P = 0.46), it is likely that there was limited statistical power given the small sample sizes (N=10 and N=15 in each group, respectively).[2]

Limitations

There is limited evidence to support any conclusions for either of the research questions in this report. This is the case both for protease inhibitor-PR therapy and for PR regimens. The small number of trials that were identified either had small sample sizes and important methodological

limitations, or were non-randomized designs. Furthermore, there were little data reported for outcomes other than SVR.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence with respect to the relative benefits of ribavirin dose reduction versus use of EPO to manage anemia, or IFN dose reduction versus use of G-CSFs to manage neutropenia, in patients with CHC infection treated with PR regimens is limited to a few small RCTs and a number of observational studies. In two studies there was a statistically significant improvement in SVR rates for patients with anemia managed with EPO versus ribavirin dose reduction, and a statistically non-significant trend towards higher SVR rates with EPO in a third study. A systematic review and RCT of G-CSF versus interferon dose reduction in patients experiencing neutropenia both found statistically non-significant trends towards higher SVR rates in patients treated with G-CSF. A RCT comparing EPO with ribavirin dose reduction among patients treated with boceprevir-PR has recently been completed, but results from this study have not yet been reported.[6]

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS ONE [Internet]. 2007 [cited 2012 Feb 8];2(12):e1350. Available from: http://dx.plos.org/10.1371/journal.pone.0001350

2. Talal AH, Liu RC, Zeremski M, Dimova R, Dove L, Pearce D, et al. Randomized trial comparing dose reduction and growth factor supplementation for management of hematological side effects in HIV/hepatitis C virus patients receiving pegylated-interferon and ribavirin. J Acquir Immune Defic Syndr. 2011 Nov 1;58(3):261-8.

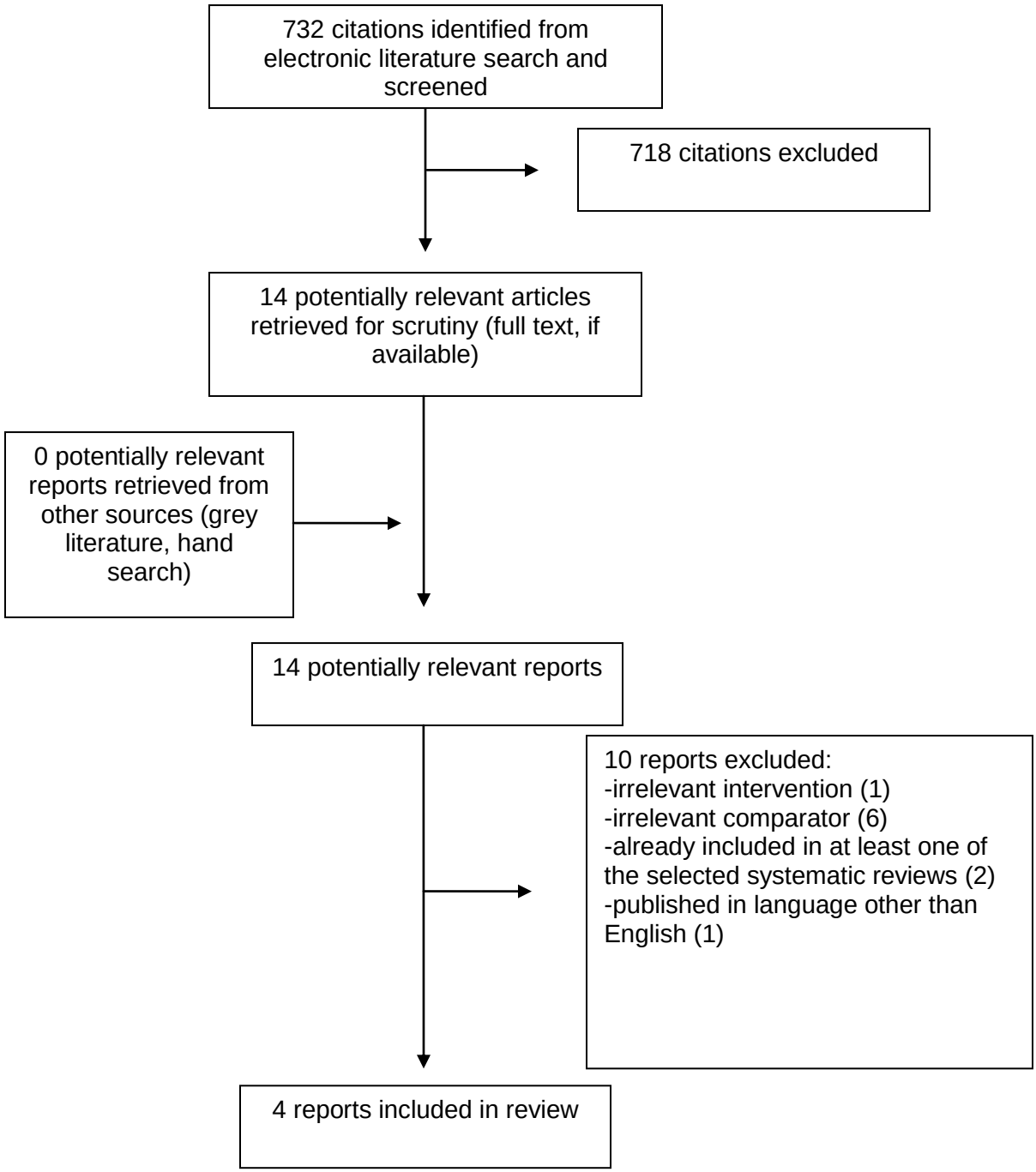
3. Bertino G, Ardiri A, Boemi PM, Calvagno GS, Ruggeri IM, Speranza A, et al. Epoetin alpha improves the response to antiviral treatment in HCV-related chronic hepatitis. Eur J Clin Pharmacol. 2010 Oct;66(10):1055-63.

4. Falasca K, Ucciferri C, Mancino P, Gorgoretti V, Pizzigallo E, Vecchiet J. Use of epoetin beta during combination therapy of infection with hepatitis C virus with ribavirin improves a sustained viral response. J Med Virol. 2010 Jan;82(1):49-56.

5. Tandon P, Doucette K, Fassbender K, Vandermeer B, Durec T, Dryden DM. Granulocyte colony-stimulating factor for hepatitis C therapy-associated neutropenia: systematic review and economic evaluation. J Viral Hepat. 2011 Jul;18(7):e381-e393.

6. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01023035, Boceprevir/peginterferon/ribavirin for chronic hepatitis C: erythropoietin use versus ribavirin dose reduction for anemia (P06086 AM2); 2011 Nov 22 [cited 2012 Feb 29]. Available from: http://clinicaltrials.gov/ct2/show/NCT01023035

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Systematic Reviews

First author, country, publication year	Eligibility criteria	Included study designs	Included studies
Tandon 2011[5] Canada	**Population:** treatment-naïve adult patients with HCV therapy-induced neutropenia **Intervention:** comparison of the administration of G-CSF (filgrastim or pegfilgrastim) or dose reduction or discontinuation of therapy for management **Outcomes:** SVR, neutrophil count; secondary: infections, adverse effects, HRQOL, long term survival	RCTs and observational studies	19 studies: One RCT Three retrospective cohort studies 15 case series

G-CSF=granulocyte colony-stimulating factor; **HCV**=hepatitis C virus; **HRQOL**=health-related quality of life; **RCT**=randomized controlled trial; **SVR**=sustained virologic response

Appendix 3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)
Talal 2011[2] USA	OL RCT N=103 (planned N=200 but study discontinued prematurely by sponsor)	Adults 26-66 years old with compensated CHC and HIV-1 PR naïve ≥CD4+ 100 cells/mm^3 No rhEPO and G-CSF in the 30 days immediately preceding the study Excluded patients with significant hematologic abnormalities at baseline: Neutropenia (ANC <1200 x 10^3 cells/µL) Thrombocytopenia (<70 x 10^3 cells/µL)	For anemia: rhEPO 40,000 Units per week For neutropenia: G-CSF 5 µg/kg/d twice weekly	Dose reduction: For anemia: RBV reduction For neutropenia: PEG-IFN reduction
Bertino 2010[3] Italy	OL RCT N=134 randomized into the comparative phase of the study	Adults ≥18 years of age, HCV genotype 1b Baseline Hb >13 (men) or >12 (women) Liver histology of chronic hepatitis (Ishak ≤13) Excluded patients with HIV-1	For patients with reduction in baseline Hb >2g/dL: EPO-alpha 10000 IU twice weekly	For patients with reduction in baseline Hb >2g/dL: RBV reduction
Falasca 2010[4] Italy (single centre)	Observational/RCT N=42	Patients with CHC treated with PR and experiencing ≥2 log decline in HCV during the first month of therapy and a >2.5 g/dL fall in Hb from baseline and Hb <11 g/dL	EPO-beta 30000 U	RBV reduced to 600mg daily

ANC=absolute neutrophil count; **CHC**=chronic hepatitis C; **G-CSF**=granulocyte colony-stimulating factor; **Hb**=hemoglobin; **HCV**=hepatitis C virus; **HIV**=human immunodeficiency virus; **HRQOL**=health-related quality of life; **IU**=international units; **OL**=open label; **PEG-IFN**=pegylated interferon; **PR**=peginterferon-ribavirin; **RBV**=ribavirin; **RCT**=randomized controlled trial; **rhEPO**=recombinant human erythropoietin; **SVR**=sustained virologic response

Appendix 4: Summary of Study Strengths and Limitations

First Author, Publication Year, Design	Strengths	Limitations
Tandon 2011[5] Systematic review	• Duplicate screening performed • Research question and inclusion criteria provided • Multiple databases searched • No restrictions on language • Characteristics of included studies provided • Quality assessment performed and taken into account in conclusions • Conflict of interest declared	• Excluded studies not listed • Publication bias not assessed
Talal 2011[2] RCT	• Central randomization	• Underpowered • Generalizability to the research question (co-infection) • Study prematurely halted • Lack of blinding
Bertino 2010[3] RCT	• Central randomization	• Underpowered • Lack of blinding
Falasca 2010[4] Observational/RCT		• Underpowered • Lack of blinding • Randomization not described (also described as 'observational study') • Single centre

Appendix 5: Summary of Main Study Findings and Author Conclusions

First author, publication year	Main findings	Author conclusions
Systematic review		
Tandon 2011[5]	From one RCT: SVR: G-CSF: 12/22 (55%) DR/DC: 5/19 (26%) RR of 2.07 [95% confidence interval: 0.89 to 4.82], P = 0.12	"While administration of G-CSF may enable patients to remain on or resume optimal HCV therapy, there was weak evidence that this improves the likelihood of SVR compared with dose reduction. Adverse effects of G-CSF are mild. The economic evaluation was inconclusive." (p. e381)
Randomized controlled trials		
Talal 2011[2]	SVR: Anemia: EPO: 7/24 DR: 4/19 P = 0.92 Neutropenia: G-CSF: 4/10 DR: 3/15 P = 0.46	"Growth factor supplementation and dose reduction do not seem to differ as management strategies for anemia and neutropenia in HIV/HCV-coinfected individuals treated with PEG-IFN/RBV." (p. 261)
Bertino 2010[3]	SVR: EPO: 60% DR: 34% Control: 60%* P < 0.01 Hemoglobin at end of therapy: EPO: 13.8 ±1.2 g/dL DR: 11.5 ±0.8 g/dL P = NR *the control group had no developed anemia, therefore were not randomized into the study	"In patients with 1b HCV-related chronic hepatitis who develop anemia during antiviral treatment, administration of epoetin alpha increases hemoglobin levels and the end-of-treatment rate and sustains virological response by improving treatment adherence." (p. 1055)
Falasca 2010[4]	SVR: EPO: 18/22 (82%) DR: 9/20 (45%) P = 0.03 Mean ±SD Hemoglobin at end of treatment, g/dL: EPO: 11.4 ±1.2 DR: 11.3 ±1.3	"Administration of epoetin-beta increases sustained viral response rates among patients developing anemia, because the standard dose of ribavirin is maintained, thereby reducing the side effects of antiviral treatment." (p. 49)

DR=dose reduction**; EPO**=erythropoietin**; G-CSF**=granulocyte colony-stimulating factor; **HCV**=hepatitis C virus; **HRQOL**=health-related quality of life; **NR**=not reported; **RBV**=ribavirin; **RCT**=randomized controlled trial; **SVR**=sustained virologic response