

Role of Hematopoietic Growth Factors as Adjuncts in the Treatment of Chronic Hepatitis C Patients

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ABSTRACT

Drug-induced hematotoxicity is the most common reason for reducing the dose or withdrawing ribavirin (RBV) and interferon (IFN) therapy in chronic hepatitis C, which leads to the elimination of a possible cure for the patient. Traditionally, severe anemia and neutropenia have been considered as absolute contraindications to start antiviral therapy. This has not however, been the case since the advent of adjunct therapy with hematopoietic growth factors (erythropoietin (EPO) and granulocyte-colony stimulating factor (G-CSF)). Some recent landmark studies have used this adjunct therapy to help avoid antiviral dose reductions. Although the addition of this adjunct therapy has been shown to significantly increase the overall cost of the treatment, this extra cost is worth bearing if the infection is cured at the end of the day. Although more studies are needed to refine the true indications of this adjunct therapy, determine the best dose regimen, quantify the average extra cost and determine whether or not the addition of this therapy increases the sustained virological response rates achieved, the initial reports are encouraging. Therefore, although not recommended on a routine basis, some selected patients may be given the benefits of these factors. This article reviews the current literature on this subject and makes a few recommendations to help develop local guidelines.

Key Words: Chronic Hepatitis C, hematopoietic growth factors, hemolytic anemia, neutropenia

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Ribavirin (RBV)-induced hemolytic anemia and interferon (IFN)-induced neutropenia are two well known side effects of antiviral therapy in hepatitis C virus (HCV)-infected patients. Some studies have estimated that these side effects are responsible for dose reductions in almost 40%^[1,2] of the subjects with consequent 10-20%^[3-5] reductions in the virological responses achieved. One study incriminated pegylated interferon (PEG-IFN) as being directly responsible for suppressing hematopoiesis in all three cell lineages.^[6] Cirrhosis with hypersplenism, history of blood cell count drop with prior antiviral therapy, lower baseline cell counts (Hb level ≤ 13 g/dL; neutrophil count $\leq 2900/\text{mm}^3$; platelet count $<170\ 000/\text{mm}^3$) at the initiation of antiviral therapy, obesity and old age are considered to be the major risk factors for the development for hematotoxicity with RBV and IFN.^[7] Based on these observations, there is a renewed interest in the use of hematopoietic growth factors (HGFs) in patients undergoing antiviral therapy. Only a few studies have been conducted on the pros and cons of the use of HGFs, and data is still considered insufficient to recommend their routine use.^[8] This review article aims to discuss the current trends in the rationale, protocols and pros and cons of use of HGFs as an adjunct in the management of chronic hepatitis C. For this review, a literature search was made on 10/April/08 on PubMed, MEDLINE and EMBASE databases (key words: chronic hepatitis C, hemolytic anemia, neutropenia, and

hematopoietic growth factors), the public websites of the US Food and Drug Administration and erythropoiesis-stimulating agent (ESA) manufacturers, as well as safety advisories. American^[9] and Canadian^[8] consensus guidelines on the management of chronic hepatitis C, and American Society of Oncology guidelines on the use of Epoetin and Darbepoetin^[10] were also consulted.

ERYTHROPOIETIN

Anemia due to RBV,^[11] interferons,^[6] myelosuppression and relatively impaired endogenous HGF production is a major problem in patients receiving combination antiviral therapy.^[14] It appears to be the most common cause of dose reductions or discontinuation of combination therapy.^[15] It could be potentially life-threatening in patients with ischemic heart disease or cerebrovascular disease.^[16] In almost 25-30%^[17] of the subjects, reductions in RBV doses (primary strategy for anemia management) are required, which negatively impacts the sustained virological response (SVR) rates.^[3,18-21] In some recent studies, erythropoietin (EPO) use has been shown to attain pretreatment Hb levels in the majority of the patients, thus avoiding dose reductions/discontinuation of therapy.^[14,22-26] Besides increased erythropoiesis, EPO has also been shown to increase platelet counts.^[27] Although the initial results are encouraging, more

studies are needed to definitely recommend erythropoietin in *all* cases.

Anemia usually develops within the first four weeks of starting antiviral therapy and persists until the end of the course.^[15] Almost 40% patients suffer a drop in Hb concentration of ≥ 3 g/dL.^[15] Most published studies recommend RBV dose-reduction if Hb level falls to or below 10 g/dL. The dose-reduction should be gradual, *i.e.*, 800 mg/d for genotype 1 or 600 mg/d for genotype 2 or 3; further dose reductions to 600 mg/d or 400 mg/d for genotypes 1 and 2 or 3, respectively, should be done if Hb levels fail to rise after four weeks. The minimum effective dose of RBV appears to be 10.6 mg/kg/day;^[3] thus, any dose reduction below this level should be considered irrational. An Hb level of 8 g/dL warrants drug withdrawal (not dose reduction).

Possible indications for EPO therapy include a fall in Hb level by >4 g/dL, Hb levels of <11 g/dL, and patients developing symptoms and signs of anemia (palpitations, dyspnea, easy fatigability, pallor).^[14] If limited hematotoxicity (in the form of the above mentioned indications for EPO therapy) persists despite reducing the RBV dose to 10.6 mg/kg/day (the minimum effective dose),^[3] initiation of EPO therapy may be considered.

As is shown by data from the lead-in phase of the HALT-C trial, the most critical period when adequate RBV dosage is highly desirable to achieve reasonable early virological response (EVR) and SVR rates is the first 12 weeks of antiviral therapy.^[28] Dose reduction after 12-20 weeks may not be so crucial as far as effect on SVR rates is concerned.^[29] Based on this, it seems reasonable to believe that EPO therapy is most required during the first 12 weeks of RBV therapy to maintain adequate RBV dosage.

A recent paper^[30] demonstrated no change in SVR unless the overall dose of ribavirin falls below 60% of the recommended dose. It also showed that in patients who achieve an RVR (negative HCV RNA at week 4), even further reductions in the ribavirin dose may not impact SVR rates.

The US Food and Drug Administration-approved starting dose of epoetin is 150 U/kg three times per week or 40,000 U weekly subcutaneously; that of darbepoetin 2.25 μ g/kg weekly or 500 μ g every three weeks subcutaneously. Epoetin and darbepoetin are considered equivalent in therapeutic efficacy and safety.^[10,31] The health-related quality of life (HRQL) systematic review^[32] evaluated the effect of different dosing strategies on the safety and effectiveness of epoetin and darbepoetin. According to this review, there is no evidence to support doses or dosing schedules other than those recommended by FDA.^[10] The aim of EPO therapy should be to maintain an Hb level of >11 g/dL (return to the pretreatment level is not the aim).^[8] The first evidence of a response to EPO administration is an

increase in the reticulocyte counts within ten days.^[33] Since erythroid progenitors take several days to mature, a clinically significant increase in the hematocrit is usually not observed in less than two weeks and may require up to six weeks in some patients.^[34] If no response (*e.g.*, <1 - 2 g/dL rise in Hb or no diminution of transfusion requirements) occurs in 6-8 weeks despite an appropriate increase in the dose as per the US FDA-approved label, EPO therapy should be discontinued.^[10] Although some trials have used baseline concentrations of endogenous erythropoietin as predictors of response,^[32] the predictive power of such testing appears insufficient.^[35] Thus, it is not recommended to use endogenous erythropoietin testing either to justify initiation of ESAs or to predict response to ESAs.^[10]

If the rate of increase of hemoglobin content with ESA therapy is >1 g/dL over two weeks, EPO dose should be decreased. This is because a >1 g/dL rise in any two weeks during the course of the therapy has been associated with an increased risk of a thromboembolic phenomenon, predisposing the patient to myocardial infarction, stroke and even death.^[36] Also, according to the manufacturer's recommendation, an Hb level of ≥ 12 g/dL potentially increases the risk of thromboembolic phenomenon,^[37] thus warranting dose adjustment. Administering ESA to achieve a target Hb of >12 g/dL has been shown to increase the risk for death and serious cardiovascular events.^[38] This prompted the US FDA to add a black-box warning to the prescribing information for epoetin and darbepoetin in March 2007, instructing that the "dose should be adjusted for each patient to maintain the lowest Hb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL." Once an adequate Hb level (between 10-12 g/dL) is achieved, RBV dose can be increased to the optimum level. Once started, adjunct EPO therapy may be required until the end of the treatment.

Before starting EPO therapy, it is important to rule out its contraindications. These include uncontrolled hypertension, iron deficiency anemia and known hypersensitivity to mammalian cell-derived products or human albumin. Prior to initiating EPO therapy, it is recommended to check the patient's serum iron and ferritin (should be at least 100 ng/mL) levels and transferrin saturation (should be at least 20%). Also, blood pressure should be adequately controlled and closely monitored during therapy. Although a well controlled seizure disorder is not considered to be a contraindication to antiviral therapy anymore, the safety and efficacy of EPO therapy in such cases have not been established. Also, it is not known whether or not it is safe to administer EPO in patients with underlying hematological disease (*e.g.*, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

Excessive hemolysis with resultant increased compensatory erythropoiesis causes increased consumption of iron, folic

acid and Vit B₁₂. Deficiency of these agents is an important cause of failure/difficulty to achieve/maintain target Hb and hematocrit levels in patients receiving EPO therapy. Thus, these agents should also be co-administered in anemia patients, if found deficient.^[39-41]

Currently, there is no consensus on the lower cut-off value of Hb level below which erythropoietin therapy should be commenced. In one randomized, double-blind study, Afdhal *et al.* proposed a cut-off value of 12 g/dL. Other studies have raised concerns on this value because of its cost-effectiveness.^[7] One study used a cut-off value of 10 g/dL.^[7] Whereas no local representative data is available on the normal levels of Hb in the Pakistani population, it appears that a cut-off value of 12 g/dL would practically mean giving HGF to >90% of our patients, which is definitely not cost-effective. It is suggested that probably an Hb level of ≤ 8g/d would be a more practicable marker to determine the need of HGF therapy in our population.

There are rare reports of development of pure-red-cell aplasia with epoetin-β therapy.^[42] Although no definite cause for this side effect is known, it appears to develop secondary to the presence of anti-EPO antibodies.^[43]

Erythropoiesis-stimulating agent (ESA) administration has been shown to increase the risks of venous thromboembolism (VTE)^[44-46] and mortality. In one study, VTE events occurred in 334 out of 4610 patients treated with ESA as compared to 173 VTE events among 3562 control patients (7.5 vs 4.9%; relative risk = 1.57; 95% CI: 1.31-1.87); the mortality risk was also increased (hazard ratio = 1.10; 95% CI: 1.01-1.20).^[47] As reported by a 2006 Cochrane Collaboration meta-analysis of 35 trials, epoetin or darbepoetin treatment was statistically significantly associated with increased risk for VTE events.^[48] Practically, it means that while ESA therapy may confer a transfusion-sparing effect, this therapy also increases the probability of patients developing VTE events including deep vein thromboses, pulmonary emboli, myocardial infarctions, strokes, or transient ischemic attacks. Caution must therefore be exercised in administering ESAs to patients who are particularly prone to develop VTE, *e.g.*, patients with past history of thromboses, surgery, and prolonged periods of immobilization or limited activity.^[10]

Erythropoiesis-stimulating agent administration has also been shown to have harmful effects on survival and/or tumor outcomes in cancer patients. Many recent trials (BEST,^[49] ENHANCE^[50] and EPO-CAN-20^[51]) have demonstrated higher mortality and significantly shorter locoregional progression-free survival and time in the epoetin arm than in the placebo arm. Notably, the majority of these trials targeted an Hb level of >12 g/dL. This further explains the need to achieve and maintain an Hb level that is just sufficient to avoid RBC transfusions, and not to exceed 12 g/dL.

Granulocyte colony-stimulating factor (G-CSF) / Filgrastim

G-CSF is a 175 amino acid, highly purified, nonglycosylated protein produced by recombinant technology in a lab strain of *E. coli* by the addition of a gene expressing the granulocyte colony-stimulating factor.^[52] It induces neutrophil production,^[53] differentiation^[54] and release from the bone marrow.^[55] Significant increases in the neutrophil counts can be observed within 24 h of G-CSF administration. It also appears to cause selected end-cell functional activation including enhanced phagocytic ability.^[56] Other cell lines are affected by negligible proportions, if at all. Neutrophil levels usually normalize within 1-7 days (average four days). Studies however, have not shown any survival benefit. It appears that no effect - positive or negative - is produced on disease progression. Also, despite neutropenia being common, infective episodes are extremely rare in treated HCV patients.

G-CSF is primarily used in patients with nonmyeloid cancers (myeloid hemopathy is a contraindication to use G-CSF), undergoing bone marrow-suppressive cytotoxic chemotherapy, or in patients undergoing myeloablative therapy before bone marrow transplantation. The aim is to reduce the incidence, severity and duration of neutropenia. Besides avoiding/correcting neutropenia, an additional effect of G-CSF is the mobilization of hematopoietic progenitor cells into the peripheral blood. These peripheral blood progenitor cells (PBPCs) may then be harvested and infused into patients undergoing cytotoxic chemotherapy, either alone or in addition to bone marrow transplantation, with consequent rapid and more adequate hematological recovery.

Due to the known benefits of G-CSF in neutropenia patients, it has been tried in some recent studies in HCV-infected patients undergoing IFN therapy. The most common cause of interferon dose reductions in HCV-infected patients is IFN-induced neutropenia.^[5] Some 30-50% of the subjects develop neutropenia within 1-2 weeks of starting the therapy.^[3-5] The frequency appears to be higher with PEG-IFN when compared with nonPEG-IFN.^[6,57] Reasonable results have been obtained when G-CSF has been tried in some studies^[7] to avoid IFN dose reductions.

The current recommendation is to reduce the IFN dose if the neutrophil count falls to $<0.5 \times 10^9/L$, and discontinue it if it falls to $<0.3 \times 10^9/L$.⁸ The minimum effective dose of PEG-IFN appears to be 1 μg/kg/week. G-CSF therapy may be considered if neutrophil counts remain $<0.5 \times 10^9/L$ despite reducing the PEG-IFN dose to the minimum effective level.

G-CSF is commercially available in the form of sterile, clear, colorless, preservative-free liquid for parenteral administration. The product is available in single-use vials

and prefilled syringes containing either 300 mcg or 480 mcg Filgrastim at a fill volume of 1.0 or 1.6 mL, respectively. A suggested dose regimen is starting G-CSF therapy at a dose of 300 mcg subcutaneously (SQ) once weekly, and then adjusting the dose as per the response/requirement. The aim should be to maintain a neutrophil count of ≥ 1000 cells/ μ L (return to the pretreatment level is not the aim). Whereas most patients respond adequately to a G-CSF dose of 300 mcg SQ once weekly, almost 1/3rd of all cases require dose adjustments. Some patients may require up to 480 mcg Filgrastim SQ thrice weekly; others may only need 150 mcg Filgrastim SQ once weekly. Complete blood counts should be taken twice or thrice weekly to judge the response to therapy. Once an adequate neutrophil count is achieved, IFN dose can be increased to the optimal level. Once started, adjunct G-CSF therapy may be required until the end of the treatment. In one study,^[7] the median duration of G-CSF therapy was 20 weeks (range: 9-45).

No international consensus currently exists on the lower cut-off value of neutrophil counts below which the risk of development of serious infections is high enough to warrant initiation of G-CSF therapy.^[58,59] Whether or not neutropenia increases the risk of infection is also debatable. One study showed an average fall of 34% in the neutrophil count with no documented or suspected ensuing bacterial infection.^[60] Another study demonstrated that infections neither correlate with the nadir of neutrophil count ($< 1,000$ or $> 750/\text{mm}^3$) nor with the magnitude of neutrophil count fall from the baseline.^[59] This is in contrast to the observations made in immunodeficient cirrhotics,^[61] HIV carriers^[62] and liver transplant patients,^[63] in whom prolonged neutropenia has been associated with the development of bacterial infections warranting the cessation of antiviral therapy. The frequency of development of superadded bacterial infection secondary to neutropenia appears to be lower in the black population.^[60] Also, these patients have an intrinsically low white cell count before treatment. Hence, the lower cut-off value ought to be lower in black patients. Interestingly, Puoti *et al.* demonstrated that the frequency of nonrespiratory infections may increase with PEG-IFN therapy, independent of the neutrophil count.^[64]

G-CSF is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, including Filgrastim or any of its components. However, in general, this drug is generally well tolerated. Common side effects include bone/muscle aches and nausea and vomiting. The frequency of bone/muscle aches can be reduced by giving G-CSF either two days before or two days after interferon injection.^[65] Rarely, splenomegaly and spontaneous splenic rupture have also been reported with G-CSF use. Thus, any patient reporting with left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture. If neutropenic patients receiving G-CSF develop fever, dyspnoea and lung infiltrates, they

should be evaluated for the possibility of adult respiratory distress syndrome (ARDS). Development of ARDS warrants immediate cessation of G-CSF therapy until the resolution of the symptoms.

There are conflicting reports regarding the cost-effectiveness of HGF therapy. Whereas one study reported an increase in the final cost by 43% with adjunct biotherapy with EPO and G-CSF7, another study suggested that as HGF therapy increases therapeutic compliance, improves quality of life, and avoids complications of chronic liver disease compared to the standard care, it is actually cost-effective.^[66] Another study^[67] showed that the cost per additional quality-adjusted life-year was \$34,793 and \$60,600 for genotype 1 and \$33,832 and \$64,311 for genotypes 2 or 3 for darbepoetin and epoetin, respectively. The net conclusion was that EPO therapy, **especially darbepoetin therapy**, is cost-effective for genotypes 1, 2 and 3. A cost analysis using a decision analysis model demonstrated that G-CSF use in HCV-infected genotype 1 cases is cost-effective, especially when given at a dose of 300 mcg SQ once weekly.^[17] Most published cost-effectiveness studies assume that once started, patients continue to take HGFs for the remainder of hepatitis C therapy. However, the reality is that in a significant percentage of patients, withdrawal of HGF therapy may be possible much earlier without negatively affecting the SVR rates. In fact, in one study,^[7] the median duration of EPO treatment was 24 weeks (range: 6-39). This makes HGF therapy even more cost-effective. One study showed that RBV dose reduction after 20 weeks of therapy does not significantly affect the final SVR rates achieved^[28] even in nonresponders. If this finding is validated by other studies, it would mean that most patients would require HGF therapy only during the first 20 weeks, which still makes this option cost-effective.

IFN-induced thrombocytopenia and its treatment

IFN therapy is also known to cause a 10-50% fall in platelet counts. This fall is clinically insignificant in most cases. Possible mechanisms include decreased platelet production (due to relative thrombopoietin deficiency^[68] and virus-induced bone marrow suppression^[69,70]) and increased peripheral destruction of platelets (both immune-mediated^[71] and due to portal hypertension and hypersplenism)^[72]. Thrombocytopenia appears to be more severe with PEG-IFN/RBV combination therapy as compared to IFN/RBV therapy. It is worst with PEG-IFN monotherapy^[5] suggesting that some reactive thrombocytosis may be occurring secondary to RBV-induced anaemia.

The current recommendation is to reduce the IFN dose if the platelet count falls to $< 30 \times 10^9/\text{L}$, and discontinue if it falls to $< 20 \times 10^9/\text{L}$.⁸ The minimum effective dose of PEG-IFN appears to be 1 mcg/kg/week. G-CSF therapy may be considered if platelet counts remain $< 30 \times 10^9/\text{L}$ in spite of reducing the PEG-IFN dose to the minimal effective level.

Recently, an oral thrombopoietin-receptor agonist, Eltrombopag (SB-497115, GlaxoSmithKline), has been shown to stimulate megakaryocyte proliferation and differentiation and to cause dose-dependent increases in platelet counts in chimpanzees and humans.^[73-76] A similar dose-dependent increase in platelet counts has been demonstrated by Eltrombopag in patients with chronic immune thrombocytopenic purpura.^[77] In one study,^[78] whereas only 6% of HCV-related cirrhotics in the placebo group completed the 12 weeks antiviral course, the same was completed by 36, 53, and 65% of patients receiving 30 mg, 50 mg, and 75 mg of eltrombopag, respectively. Although the study was small and thus underpowered, the most commonly reported side effects (headache, dry mouth, abdominal pain, and nausea) were of insufficient severity to require discontinuation of the drug. Despite the encouraging initial results, further confirmation of the therapeutic efficacy and safety of eltrombopag in phase 3 trials involving standard-duration courses of peginterferon and ribavirin is required.

CONCLUSION

Despite data being limited, it appears that HGF therapy improves the quality of life (QOL) across many domains (physical, mental, and social).^[14,22] Although there is lack of SVR data, *no respectable association recommends the routine use of HGF therapy*. Based on the current evidence, it is quite reasonable to believe that, where indicated, adjunct therapy with HGFs helps to avoid antiviral dose reductions and attain *optimum adherence* (defined as the administration of bitherapy in an optimal dose, *i.e.*, PEG-IFN ≥ 1 mcg/kg/week and RBV ≥ 10.6 mg/kg/day for more than 80% of the prescribed duration). The possible net effect may be the attainment of higher SVR rates although more studies are needed to validate this. Studies have shown that HGF therapy is generally well tolerated. Further studies are needed to determine the lower cut-off values of Hb and neutrophil counts below which EPO/G-CSF therapy should be started. Also, more studies are needed to establish the right dosages and cost-effectiveness of HGF therapy.

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