COMMENTS

ROLE OF GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF)/FILGRASTIM AS AN ADJUNCT IN CHRONIC HEPATITIS C MANAGEMENT

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ABSTRACT

Drug-induced hematotoxicity is the commonest reason for reducing the dose or withdrawing interferon (IFN) therapy in a case of chronic hepatitis C thus depriving the patient of a possible cure. Traditionally, severe neutropenia has been considered an absolute contraindication to start antiviral therapy. Since the advent of adjunct therapy with Granulocyte-colony stimulating factor, the same is not true any more. Some recent landmark studies have used this adjunct therapy to help avoid antiviral dose reductions. Although, addition of this adjunct therapy has been shown to significantly increase the overall cost of the treatment, if the infection is cured at the end of the day, this extra cost is worth bearing. 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 validate that whether or not the addition of this therapy increases the sustained virologic response rates achieved, the initial reports are encouraging. Therefore, although not recommended on routine basis, some selected patients may be given the benefits of these factors. In this article, a review of the current literature on this subject is given followed by few suggested recommendations at the end to help develop local guidelines.

Keywords: Chronic Hepatitis C. Neutropenia. Hematopoietic growth factors. Granulocyte-colony stimulating factor.

INTRODUCTION

Ribavirin(RBV)-induced hemolytic anemia and Interferon(IFN)-induced neutropenia are two well known side effects of antiviral therapy in 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 virologic responses achieved. One study incriminated pegylated interferon (PEG-IFN) as 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 2900/mm3; platelet count <170,000/mm3) 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 so far been done on the pros and cons of HGFs use, 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 granulocyte-colony stimulating factor (G-CSF) use as an adjunct in the management of chronic hepatitis C. For this review, a literature search

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was made on 20/Oct/08 on PubMed, MEDLINE and EMBASE databases (key words: chronic hepatitis C, neutropenia, hematopoietic growth factors and granulocyte-colony stimulating factor), the public Web site of the US Food and Drug Administration and Erythropoiesis-stimulating agents (ESAs) manufacturers, and safety advisories. American[9] and Canadian[8] consensus guidelines on the management of chronic hepatitis C were also consulted.

DISCUSSION:

G-CSF is a 175 amino acid, highly purified, non-glycosylated protein produced by recombinant technology in a lab strain of E. Coli by the addition of a gene for the Granulocyte colony-stimulating factor.[10] It induces neutrophil production,[11] differentiation[12] and release from the bone marrow.[13] Significant increase in the neutrophil counts can be observed within 24hrs of G-CSF administration. It also appears to cause selected end-cell functional activation including enhanced phagocytic ability.[14] Other cell lines are affected by negligible proportions, if at all. Neutrophil levels usually normalize within 1-7 days (average 4 days). Studies, however, have not shown any survival benefit. It appears that no effect – positive or negative - is produced on disease progression and despite the fact that neutropenia is common, infective episodes are extremely rare in treated HCV patients.

G-CSF is primarily used in patients with nonmyeloid cancers (myeloid haemopathy 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 mobilization of the hematopoietic progenitor cells into the peripheral blood. These peripheral blood progenitor cells (PBPC) 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.

Because of 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 commonest 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 as compared to the non-PEG-IFN.[6,15] G-CSF has been tried in some studies[7] with reasonable results to avoid IFN dose reductions.

The current recommendation[8] is to reduce IFN dose if neutrophil count falls to $<0.5x10^9$/L, and discontinue it if it falls to $<0.3x10^9$/L. The minimum effective dose of PEG-IFN appears to be 1 µg/kg/wk. If despite reducing the PEG-IFN dose to the minimum effective level, neutrophil counts of $<0.5x10^9$/L persist, G-CSF therapy may be considered.

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 filled volume of 1.0 mL or 1.6 mL, respectively. Suggested starting dose regimen of G-CSF is 300µg SQ once weekly and then adjusting the dose as per response/requirement. The aim should be to maintain a neutrophil count of =1000cells/µL (return to the pretreatment level is not the aim). Most patients adequately respond to a G-CSF dose of 300µg SQ once weekly, whereas 1/3rd cases require dose adjustments. Some patients may require up to 480µg Filgrastim SQ thrice weekly; others may only need 150µg Filgrastim SQ once weekly. Complete blood counts should be asked twice or thrice weekly and response to therapy judged. After the adequate neutrophil count is achieved, IFN dose can be increased to the optimum level. Once started, adjunct G-CSF therapy may be required till 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 count after which the risk of development of serious infections is high enough to warrant initiation of G-CSF therapy.[16-17]

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 bacterial infection.[18] Another study demonstrated that infections neither correlate with the nadir of neutrophil count (<1,000 or >750/mm^3) nor with the magnitude of neutrophil count fall from the baseline.[17] This is in contrast to the observations made in the immunodeficient cirrhotics[19], HIV carriers[20] and liver-transplant patients[21] in which prolonged neutropenia has been associated with the development of bacterial infections warranting cessation of antiviral therapy. The frequency of development of superadded bacterial infection, secondary to neutropenia appears to be lower in blacks.[18] These patients also have an intrinsic low white cell count prior to starting treatment. Thus the lower cut-off value ought to be lower in blacks. Interestingly, as demonstrated by Puoti et al, the frequency of non-respiratory infections may increase with PEG-IFN therapy, independent of the neutrophil count.[22]

G-CSF is considered contraindicated in patients with known hypersensitivity to E coli-derived proteins including Filgrastim or any of its components.

This drug is generally well tolerated. Common side effects include bone/muscle aches, nausea and vomiting. The frequency of bone/muscle aches can be reduced by giving G-CSF either 2 days before or 2 days after interferon injection.[23] 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. Neutropenic patients receiving G-CSF, if develop, fever, dyspnoea or lung infiltrates, should be evaluated for the possibility of adult respiratory distress syndrome (ARDS). Development of ARDS warrants immediate cessation of G-CSF therapy till the resolution of the symptoms. There are conflicting reports regarding the cost effectiveness of HGF therapy. One study reported an increase in the final cost by 43% with adjunct biotherapy with EPO and G-CSF,[7] whereas another study suggested that since HGF therapy increases therapeutic compliance, improves quality of life, and avoids complications of chronic liver disease, compared to the standard care, it is cost effective.[24] A cost analysis using a decision analysis model demonstrated that G-CSF use in HCV-infected genotype 1 cases is cost effectice, especially when given in a dose of 300µg SQ once weekly.[25] Most published, cost-effectiveness studies assume that, once started, patients continue to take HGF's for the remaining hepatitis C therapy. In significant percentage of patients' withdrawal of HGF therapy may be possible much earlier without negatively affecting the SVR rates. This makes HGF therapy even more cost-effective.

CONCLUSION:

Despite the data being limited, it appears that HGF therapy improves the quality of life (QOL) across many domains (physical, mental and social).[26,27] Due to 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, adjunct therapy with HGFs where indicated, helps avoiding antiviral dose reductions and attain optimum adherence (defined as the administration of bitherapy in an optimum dose i.e. PEG-IFN =1 g/kg/wk and RBV =10.6 mg/kg/day for more than 80% of the prescribed duration). The possible net effect may be, attainment of higher SVR rates, although more studies are needed to validate it. Studies have shown that HGF therapy is generally well tolerated. Further studies are needed to determine the lower cut-off values of neutrophil count after which G-CSF therapy should be started. More studies are also needed to establish the right dosages and cost effectiveness of HGF therapy.

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