Treatment-Induced Anaemia in Hepatitis C Patients and Role of Erythropoietin in its Management

Nadim Iqbal Sheikh, Anila Nisar, Shahzad Manzoor, M. Shoaib Shafi, Shahid Abbasi, Bushra Kahoot, Iffat Sultana

Department of Medicine, Rawalpindi General Hospital and Rawalpindi Medical College, Rawalpindi

Abstract

Background: To study the incidence of anaemia during antiviral treatment and the effectiveness of erythropoietin to correct it.

Methods: This prospective, observational study included 208 subjects with PCR positive for HCV RNA who presented in Shafi Clinic Rawalpindi. Duration of the study was 2 years. All patients were given antiviral treatment including interferon and ribavirin. Baseline Hb and all other laboratory parameters were checked. Any drop in Hb after initiation of therapy was noted. Patients who had Hb < 10g/dl were given inj erythropoietin for correction of anaemia.

Results: Of the 208 patients, 99 were males (48%) and 107 (52%) females. 172 patients (82.7%) were given conventional interferon whereas 38 patients (17.3%) were given PEG-IFN along with ribavirin. Anaemia ie Hb less than 10g/dl developed in 38 cases (18.5%). Hb <8g/dl developed in 7 cases (3.4%). Out of these 38 cases; 30 patients had received conventional interferon whereas 8 patients had received PEG-IFN. Mean drop in Hb was from 11.5 to 6.0 g/dl mostly seen between 2-4 weeks. All patients were given inj Epo. All had significant increase in Hb upto 11.5 +/− 0.2 g/dl over 6-8 weeks. No patient required treatment discontinuation because of anaemia.

Conclusion: It is concluded that anaemia is a common adverse effect of antiviral treatment. Recombinant human erythropoietin alpha is very effective to counter this problem without requiring blood transfusion or dose reduction. It allows adherence and maintenance of critical dose level producing optimal HCV treatment.

Introduction

HCV is currently the most common cause of cirrhosis and end-stage liver disease. It is responsible for more than 50% of liver transplants being performed1. HCV infects almost 3% of world’s population i.e., 170 million people 2. About 10-20% of chronically infected persons progress to cirrhosis over an average of 20 years 3, 4. Prevalence of HCV infection is increasing worldwide. Viral eradication is the only way to prevent disease progression. A recent NIH consensus guideline recommended treatment with pegylated interferon and ribavirin for patients with HCV-RNA viral loads higher than 50 copies per ml; a liver biopsy with portal or bridging fibrosis and at least moderate inflammation and necrosis 5. Recommended doses of drugs for antiviral treatment are: 6, 7.

Conventional IFN: 3 MIU S/C thrice a week.
PEG-IFN α 2b (Pegintron): 1.5 mcg per kg S/C once weekly.
PEG-IFN α 2a (Pegasys): 180 mcg S/C once weekly.

Ribavirin capsule according to body weight:

- <55 kg → 400 mg 1+1 daily
- 55-75 kg → 500 mg 1+1 daily
- >75 kg → 400 mg 1+1+1 daily

Anaemia, leucopenia and thrombocytopenia are among the numerous side effects of currently available antiviral treatment 8, 9. Ribavirin and interferon both cause anaemia. Ribavirin causes anaemia by extravascular hemolysis and suppression of erythropoiesis by downregulation of Epo receptors 10, 11. Interferon causes anaemia by suppression of hematopoietic progenitor cell proliferation, activation of programmed cell death in erythroid progenitor cells 12 and provocation of immune hemolysis and impairment of renal function If Hb level falls below 10g/ dl, ribavirin dose should be reduced by 200 to 400 mg/day. If it drops to below 8.5 g/dl; ribavirin should be discontinued 6, 7.

Anaemia tends to occur less frequently with PEG-IFN than with non-pegylated IFN 13. When combination therapy is used, Hb less than 11g/dl occurs in 25 to 30% of patients 14. Anaemia is more pronounced with combination therapy than with IFN-alpha monotherapy 13. Most important factors in successful eradication of HCV are adherence to therapy and dose maintenance. 13 Anaemia accounts for about 36% of
discontinuation of combination therapy (8.8% of all cases). Recombinant human erythropoietin therapy represents an alternative to ribavirin dose reduction or discontinuation. We conducted a study to note the incidence of anaemia during combination therapy and to determine the effect of erythropoietin on correction of anaemia.

**Patients and Methods**

It was a prospective observational study. Patients with PCR + ve for HCV - RNA presenting in Shafi Clinic Rawalpindi with age between 18 to 65 years were included in the study. Duration of study was 2 years i.e. from July 2005 to July 2007. Sample size was 208 patients. A simple convenient sampling technique was used.

Patients with any major comorbidity e.g., IHD or CRF, those with HCC, those with CTP-class C or any contraindication to INF or ribavirin were not included. Similarly pregnant ladies and those with baseline TLC < 3000/cmm and baseline Hb < 8g/dl were excluded from the study.

Patients who were lost to final follow-up were also not included.

Complete baseline tests including CBC, LFTs, RFTs, BSR, TFTs and USG abdomen were done before enrollment. Serotyping of HCV was not done in all patients because of affordability problems. Also the common serotypes in our region are 2 and 3 mostly. These serotypes are very much responsive to conventional interferon. Standard combination therapy was given to all i.e., interferon and ribavirin.

Most of the patients were given conventional interferon because of its low cost.

Follow up was done initially 2 weekly for 2-3 months and then monthly till end of treatment. Blood CP and ALT were repeated at each follow up to look for any complication.

In patients who developed anaemia, Inj. Erythropoietin was administered according to severity of anaemia i.e., Hb < 8 g/dl inj Epo 4000 units SC twice a week. Hb > 8 g/dl but < 10 g/dl inj Epo 4000 units SC once weekly. Response to treatment was noted and dose titration done accordingly. Treatment stopped at the end of six months by repeating PCR.

**Results**

Total patients were 208 of which males were 99 (48%) and females 109 (52%). Age ranged from 18 to 65 years with maximum patients aged between 30 to 50 years (Fig.1)

Patients who received conventional IFN were 172 (82.7%) and those who received pegylated IFN were 36 (17.3%). Serotyping was done in 133 cases only. It revealed 100 cases of Serotype 3, 32 cases of untypable serotype and 1 case of Serotype 2b.

Anaemia ie Hb less than 10 g/dl occurred in 38 cases out of 208 (18.5%). Hb drop to less than 8 g/dl was seen in 7 cases (3.4%). Out of these 38 cases, 30 patients were on conventional IFN (80%) and 8 patients were on PEG-IFN (20%), both in combination with ribavirin.

Hb < 8 g/dl was seen in 7 cases, all on conventional IFN. Hb > 8 but < 10g/dl was seen in 31 cases including 8 using PEG-IFN (Fig. 2).

Thus anaemia observed in 2 Groups was as follows: Conventional IFN = 30 / 172 x 100 = 17.4 %

PEG-IFN = 8 / 36 x 100 = 22.2%

Mean drop in Hb was from 11.5 to 6.0g/dl. Maximum decline was seen about 2-4 weeks after
antiviral treatment. (Fig.3). All these patients were given Inj Epo according to dose mentioned above. All the patients had a significant increase in Hb over a period of 6-8 weeks. Hb levels rose back to 11.5 +/- 0.2. No patient required blood transfusion or discontinuation of therapy. All patients were able to complete desired dose and duration of therapy.

**Fig. 3: Change in Haemoglobin levels**

Discussion

Anaemia, leucopenia and thrombocytopenia are common adverse effects of antiviral treatment. These side effects compromise treatment adherence and dose maintenance. Response rate is lower for patients who do not complete their treatment course or who receive < 80% of the intended dose for < 80% of the intended time 16-19.

In clinical trials, significant anaemia (Hb < 10 g/ dl) has been observed in 9-13% of patients. Moderate anaemia (Hb < 11 g/dl) may be seen in 30% of cases9. Recombinant human Epo allows correction of anaemia without treatment discontinuation or blood transfusion 20-22. It acts like endogenous Epo.

Though there are no official guidelines for its use in HCV treatment associated anaemia but studies have proven it very beneficial13. In comparison with non-pharmacological treatment ie dose reduction or blood transfusion, Epo improves Hb level more effectively. Percentage of patients who were able to maintain > 10.6 mg / kg/ day of ribavirin dose was also significantly greater in Epo group 22.

Conclusion

It is concluded that anaemia is a common adverse effect of antiviral treatment. Recombinant human erythropoietin alpha is very effective to counter this problem without requiring blood transfusion or dose reduction. It allows adherence and maintenance of critical dose level producing optimal HCV treatment.

References