Role of Erythropoietin in Adherence to Antiviral Treatment in Hepatitis C

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Abstract

Background: To evaluate the role of low dose erythropoietin in the management of drug induced anemia and thus in adherence and continuation of antiviral treatment.

Methods: In this descriptive study 370 patients with chronic hepatitis C were included . All patients were given conventional Interferon Alpha-2b plus Ribavirin for 24 weeks. Haemoglobin estimation was done on day 0 and at 2 weekly interval for first month and then monthly for 5 months. Erythropoietin was given to patients with Hb level of 7 gm/dl and less. The study end points were to assess the Interferon maintenance and change in Hb.

Results: Out of the 370 patients treated with Interferon Alpha-2b plus Ribavirin, (n=31 patients) 8% were treated with erythropoietin. During erythropoietin treatment the Hb initial mean was 7 gm/dl and improvement of 2gm/dl or more than 2 gm/dl was the end point. In 3 patients, Hb dropped further inspite of erythropoietin treatment, while in 26 patients, Hb improved with erythropoietin treatment. The optimal dose of Ribavirin was maintained in 29 patients throughout the treatment. In 2 patients, Ribavirin dose was decreased due to anaemia not responding to erythropoietin.

Conclusion: Even low doses of erythropoietin are effective in improving or maintaining haemoglobin levels in patients with treatment induced anaemia . Reduction of severity of treatment-induced anaemia with erythropoietin has been shown to encourage adherence and to enable patients to remain on higher doses of antiviral treatment.

Key Words: HCV infection, Erythropoietin, Antiviral treatment (Interferon alpha 2-b plus Ribavirin).

Introduction

Hepatitis C virus (HCV) infection is increasingly recognized as a major health care problem, and is found frequently in Pakistani settings. Standard treatment for chronic HCV involves an interferon-based preparation and ribavirin for 24 to 48 weeks.

The goal of therapy is to prevent complications and death from HCV infection. Several types of virological responses may occur, labeled according to their timing relative to treatment. The most important is the sustained virological response (SVR), defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks following discontinuation of therapy. An early virological response (EVR) is defined as a _2 log reduction or complete absence of serum HCV RNA at week 12 of therapy compared with the baseline level. Failure to achieve an EVR is the most accurate predictor of not achieving an SVR. Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred to as an end-of treatment response (ETR). An ETR does not accurately predict that an SVR will be achieved but is necessary for it to occur.

Maximizing response rates to HCV therapy requires full treatment adherence to both Interferon and Ribavirin. Among the hematologic abnormalities associated with combination therapy, anemia is probably the most significant side effect. Significant anemia associated with ribavirin therapy can increase fatigue, has a demonstrable effect on quality of life, and is a frequent indication for dose reduction of ribavirin. A number of studies in patients undergoing therapy for hepatitis C have suggested that erythropoietin alfa can relieve many of the symptoms related to anemia.

Patients and Methods

This descriptive study was conducted from June 2005 to December 2008 at the Department of General Medicine, Federal Government Polyclinic, Islamabad. A total of 370 patients, with chronic hepatitis C, were included in the study. Patients included in this study were of both genders found out to be HCV positive on Qualitative PCR, had no contraindication to give Interferon Alpha like Low Hb (<10mg/dl), pancytopenia, moderate or severe depression or decompensated liver disease, Patients who had fall of Hb level of <7 mg/dl after starting Interferon treatment, no contraindication to start Erythropoietin like uncontrolled high blood pressure, or hypersensitivity. Patients with others causes of anaemia and no regular follow up were excluded from this study group. All patients were given conventional Interferon Alpha-2b plus Ribavirin for 24 weeks with definitive indication of treatment and no contraindication to the antiviral treatment.
Haemoglobin (Hb) levels were checked two weekly in all patients receiving antiviral treatment in first month of treatment and then once monthly thereafter. Cut off level of hemoglobin for the definition of anemia was set at the level of 12 gm/dl, below which all patients would be considered anemic. The patients who were candidates to receive Epo had Hb level of 7 gm/dl or below. The adherence to antiviral treatment was monitored in patients who had severe anemia for which they received Erythropoietin. Erythropoietin was given to all patients with Hb level of 7 gm/dl and below after ruling out other causes of anemia. A total dose of 4000 units subcutaneously three times per week was used. Pre treatment and post treatment HCV PCR were done to evaluate for early virological response (EVR), end of treatment response (ETR) and sustained viral response (SVR).

**Results**

Out of 370 patients, 188 (51%) were males and 182 (49%) were females. Anaemia was found in 267 (72%). Out of 267 patients who had anaemia, 165 (61.79%) had Hb level between 10 – 11.9 gm/dl (Table 1). Out of 267 patients 31 received erythropoietin. Out of these, 26 had an improvement in haemoglobin levels (Table 2). Twenty nine patients (99%) continued the treatment. Two patients who were admitted in the medical department for the treatment of anaemia with Hb of 4 gm/dl were excluded from study due to no regular follow up. EVR was achieved in 75% (p value .003) patients and ETR was achieved in 77% patients (p value 004). 69% patients achieved SVR (p value 007).

**Table 1: Haemoglobin levels in chronic hepatitis C patients**

<table>
<thead>
<tr>
<th>Haemoglobin (g/dl)</th>
<th>No(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-10</td>
<td>165 (61)</td>
</tr>
<tr>
<td>&lt;10-8</td>
<td>60 (22)</td>
</tr>
<tr>
<td>&lt;8-6</td>
<td>32(12)</td>
</tr>
<tr>
<td>&lt;6</td>
<td>10(4)</td>
</tr>
</tbody>
</table>

**Discussion**

Treating Hepatitis C patients is still a challenge due to the high rate of adverse events. Among the adverse events of treatment, RBV induced haemolytic anaemia is of particular importance as it accounts for up to 36% of HCV treatment interruptions. Recombinant human erythropoietin (EPO), as adjuvant therapy during peg IFN and RBV therapy, is suggested in cases with treatment associated anaemia ad guidelines are suggested.

**Table 2: Chronic Hepatitis C and Erythropoietin Therapy**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>370</td>
</tr>
<tr>
<td>Patients who developed anaemia</td>
<td>267</td>
</tr>
<tr>
<td>Patients who received Erythropoietin</td>
<td>31</td>
</tr>
<tr>
<td>Hb improvement by Erythropoietin</td>
<td>26</td>
</tr>
<tr>
<td>No response to Erythropoietin</td>
<td>3</td>
</tr>
<tr>
<td>Ribavirin dose maintained while on Erythropoietin</td>
<td>29</td>
</tr>
<tr>
<td>Ribavirin dose decreased while on Erythropoietin</td>
<td>2</td>
</tr>
<tr>
<td>Early virological response (EVR)*</td>
<td>75%</td>
</tr>
<tr>
<td>End of Treatment Response**</td>
<td>77%</td>
</tr>
<tr>
<td>Sustained Viral Response (SVR)***</td>
<td>69%</td>
</tr>
</tbody>
</table>

*EVR=Early Virological Response. It means HCV RNA cannot be detected in the blood at week 12 of treatment (complete EVR) or HCV RNA drops by more than 2 logs (100 times) from the baseline level by week 12 (partial EVR). Not reaching EVR predicts a low likelihood of achieving viral cure;**ETR=End of Treatment Response. It means HCV RNA is not detected in the blood at the end of treatment.***SVR=Sustained Viral Response. It means HCV RNA is not detected six months after treatment ends.

Recombinant EPO (erythropoietin alfa), is a preparation of a physiological endogenous erythroid growth factor, and most clinicians are familiar with its use in the treatment of anaemia in chronic renal failure and end-stage renal disease. In terms of efficacy, under the ideal conditions of a clinical trial, it cannot be disputed that EPO improves hemoglobin levels in the setting of HCV treatment. Quality of life scores have also been reported to be better in those receiving EPO compared with those who did not. Studies revealed significant improvement in Hb levels in those who received EPO. Epoetin α in the treatment of HCV may not only increase but maintains hemoglobin levels in many patients without requiring RBV dose reduction or discontinuation.

In present study, a high incidence (72%) of patients had experienced anaemia out of which 11% had severe anaemia due to antiviral therapy but erythropoietin therapy for severe anaemia in these patients was significantly correlated with achieving ETR & SVR. Another aspect of the study which needs attention here is that we gave EPO to very selective patients (only 8%) who had Hb level below 7gm/dl although according to other International studies available, patients received EPO on Hb level of 10gm/dl and below instead of 7gm/dl and below as we chose. The reason for selecting such a low level of Hb for initiation of EPO is that being in a third world country with limited resources, we need to reserve EPO only
for severely anaemic patients keeping in view the high cost of EPO. In present study a dose of 4000 units thrice weekly was used. Treatment was discontinued in less 1% patients due to anaemia and statistically significant number of patients continued treatment even with Hb below 7gm/dl. The reason could be that our population either doesn’t develop constitutional symptoms or they have a good tolerance for this level of low Hb. Not only this but our patients also showed a good response to low doses of erythropoietin therapy as shown by percentage of people who achieved EVR, ETR and SVR. In our study, drop of Hb was from 12 gm/dl. So in this way, a drop of between 3 and 5 gm/dl from the set standard of 12gm/dl, means Hb of below 9 and 7 gm/dl respectively as compared to drop of same ranges from 14-16gms/dl, which is between 11 -13gms/dl and below 9-11gms in the international study, which is a near normal Hb level for our population. 16

In present study the dose of Ribavirin, in patients developing anemia is contrary to an assumption to reduce the dose.17 This could further increase the SVR rates in our study along with EPO use. Internationally recommended dose of erythropoietin is 40,000 Units subcutaneously once weekly. We used small doses of erythropoietin that is 4000 Units subcutaneously 3 times weekly, which is supported by a trial, in which a similar dose of erythropoietin was used. 18

**Conclusion**

Even low doses of erythropoietin are effective in improving or maintaining the haemoglobin level in patients of hepatitis C who develop treatment induced anaemia

**References**