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ABSTRACT

Background: To determine the hematological safety profile of pegylated interferon plus ribavirin in treating chronic hepatitis C and the use of tissue stimulating growth factors. Methods: The study was conducted on 71 treatment naïve individuals with chronic hepatitis C treated with pegylated interferon plus ribavirin for 6 months. All subjects were analyzed for hematological side effects. Growth factors were given to counter the adverse effects. Consequent effects of growth factors and need for modification of antiviral therapy was observed. Results: Anemia was seen in 35.2% (n=25) individuals, 29.6% (n=21) developed thrombocytopenia while leukopenia was seen in 38% (n=27). Out of 9 individuals who required growth factors to counter the adverse effects, 7 (77.7%) had clinical improvement and did not require reduction in dose or discontinuation of therapy. All others tolerated the therapy well. Conclusion: Pegylated interferon combination therapy has tolerable spectrum of hematological side effects and the concomitant support by growth factors in those with profound log drop in cell lines can help to achieve the viral response without the need for reduction of dose or discontinuation of therapy. This could help achieve Sustained Virological Response (SVR) and End of Treatment Response (ETR) without jeopardizing the efficacy of interferon related to reduction of dose or discontinuation.

KEYWORDS: Pegylated interferon; anemia; leukopenia; thrombocytopenia; growth factors.

INTRODUCTION

Hepatitis C is comparable to a “viral time bomb”. According to WHO, 3 % of world population is affected with Hepatitis C Virus (HCV) and the yearly incidence of infection is 3 -4 million.[1] Interferon combination therapy has long being used in the treatment of chronic HCV infection.[2,3,4,5,6] The spectrum of hematological side effects experienced with pegylated interferon includes anemia, leukopenia and thrombocytopenia. All of these lead to poor quality of life, sub-optimal dosing or discontinuation of therapy.[2,3] To treat these hematological side effects, growth factors are routinely being used but their efficacy, safety and cost effectiveness is still unclear.[2,3,7,8] Furthermore, age is also an important contributing factor in considering the safety of this therapy.[9]

The objective of our study was to determine the frequency of hematological side effects of pegylated interferon combination therapy and describe its safety profile by evaluating its tolerability in treating chronic HCV infection. This is important because hematological side effects, particularly anemia, lead to poor adherence to therapy with subsequent lower response rates. Sufficient clinical data supporting the safe use of growth factors is not available. However, the use of these factors to support the therapy with the aim to achieve a better response rate seems promising.

MATERIAL AND METHODS

This study was approved by the Ethical Review Committee for Research, KRL Hospital Islamabad. All patients provided informed written consent. All the work was done in accordance with the ethical standards of the responsible committee on human experimentation and with the latest (2008) version of Helsinki Declaration of 1975.

Interferon naïve adults of both gender and all ages seen at liver clinic, KRL hospital with chronic Hepatitis C genotype-3 infection were eligible for enrolment and included in the study. Patients were required to have a detectable serum HCV RNA (ribonucleic acid) on Polymerase Chain Reaction (PCR) at pre-treatment visit. All patients provided informed consent. All the work was done in accordance with the ethical standards of the responsible committee on human experimentation and with the latest (2008) version of Helsinki Declaration of 1975.

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decompensated cirrhosis, other causes of liver disease and/or were Hepatitis B surface antigen or Human Immunodeficiency Virus positive. Alcoholics, patients with seizure disorders, cardiovascular disease, hemoglobinopathies, thyroid disease, clinically relevant depression or any other psychiatric disease were also excluded. Other exclusion criteria included hemophilia, poorly controlled diabetes, autoimmune disease, previous organ transplant and/or unable to use contraception.  

This single center, observational study was conducted at KRL hospital from August 2014 to August 2015. Patients who accepted the treatment were included in the study. The response to treatment was evaluated on the basis of Sustained Virological Response (SVR) and End of Treatment Response (ETR). Hematological side effects included new onset anemia, thrombocytopenia &/ or leukopenia during the course of treatment. The frequency of occurrence of these side effects was observed prospectively.

A total of 113 non-consecutive, treatment naïve, HCV RNA positive patients with chronic hepatitis C meeting the inclusion and exclusion criteria were given pegylated interferon alpha 2b 180 ug once weekly plus ribavirin (1000- 1200 mg/day) for 24 weeks. Intervventional therapy including growth factors i.e., erythropoietin, GM-CSF (Granulocyte Monocyte Colony Stimulating Factor) and/or Recombinant Interleukin (IL) - 11 were used to counter the side effects including a hemoglobin < 80 g/ l, a leukocyte count < 3 x 10^9 /l and a platelet count < 100 x 10^9 / l respectively. Growth factors were used in 9 individuals. Treatment was stopped in 2 of them due to serious hematological side effects including a hemoglobin level below 60 g/ L, leukocyte count below 1 x 10^9 /l and/ or platelet count below 40 x 10^9 / l despite interventional therapy and/ or presence of serious symptoms pertaining to these side effects. Rest of the 7 were able to complete the total duration of therapy without the need for significant reduction in dose of interferon or ribavirin. A total of 69 individuals were able to complete the total duration of therapy with regular follow-up. 62 of them did not require interventional therapy or significant reduction in dose. 42 individuals either did not come for follow-up or had missing data and were excluded from results. Presence or absence of hematological side effects was observed in 71 patients including the 2 with serious side effects.

Dosage of ribavirin was determined by body weight (1000 mg /day in patients less than 75 Kg; 1200 mg/day in patients greater than or equal to 75 Kg). During treatment patients were assessed as out-patients at 0, 2, 6, 12, 18 and 24 weeks. Their side effects were recorded prospectively and response to treatment was assessed via ETR at 24 weeks and via SVR at 48 weeks, both with Qualitative PCR for HCV RNA having lower limit of detection as 50 IU/ml. Patients who received at least 80% of pegylated dose and completed the duration of therapy were declared to have completed treatment.

Those with significant reduction in dose were described as the ones receiving < 80% of standard dose. PCR was carried out by Nested PCR. ETR was defined as negative qualitative PCR at end of treatment while SVR was defined as negative PCR six months after completion of therapy. Those achieving ETR &/ or SVR were designated as Complete Responders (CR) at respective points in time. Patients with positive PCR at end of treatment and also six months after treatment completion were declared as Non-Responders (NR), whereas, those with positive PCR at end of treatment and negative PCR, six months after completion of therapy were defined as Late Responders. Break-Through Non-Responders (BTNR) were the ones having reappearance of detectable HCV RNA once eradicated while on therapy. Relapse (R) was defined as negative end of treatment PCR but positive PCR after six months of completion of treatment. Definitions used were as per AASLD (American Association for the Study of Liver Diseases) guidelines.  

Baseline variables recorded at first presentation included age, gender, Body Mass Index (BMI), baseline levels for Alanine amino transferase (ALT), hemoglobin, leukocyte and platelet count. At each visit blood cell counts were measured and recorded. BMI was calculated using the patient’s height and weight according to the formula BMI (kg/m²) = (weight [kg]) / (height [m])².

For the purpose of this study, anemia was defined as an Hb < 120 g/l for women and < 135 g/l for men during therapy. Similarly, thrombocytopenia was defined as a platelet count < 150 x 10^9 / l & leukopenia as leukocyte count < 4x10^9 / l. Cut-off values for all cytopenias were in accordance with international standards.

Sample size was determined for hypothesis testing for the population proportion using WHO SS calculator. It was calculated to be 93 while keeping level of significance at 5%, power of test at 95% & reported frequency of anemia at 10.5-39 %. A non-probability sampling technique was used for patient selection.

The distribution of baseline characters & frequency of side effects were analyzed using simple descriptive statistics. All analyses were performed using SPSS version 16 (SPSS Inc. USA).

RESULTS

Male individuals constituted 26.8 % (n=19) of the population while 73.2% (n=52) were females. Mean age was 42.8 ± 9.45 years. Mean BMI was 26.50 ± 7.05 kg/ m². Mean baseline ALT was 71.44 ± 56.09 IU/ l. Mean hemoglobin was 13.26 ± 1.55 g/ l while platelet count was 249 ± 68 x 10^9 / l. Complete Responders at ETR and SVR were 82.6% (n=57) and 57.9% (n=40) respectively. [Table 1]

Out of the total population, 35.2% (n=25) individuals developed anemia, 29.6% (n=21) experienced...
thrombocytopenia while leukopenia was seen in 38% (n=27). Growth factors were used in 9 (12.6%) individuals. Treatment was stopped in 2 of them due to serious side effects. Rest of the 7 (77.7%) responded well and were able to complete the total duration of therapy without the need for significant reduction in dose of interferon or ribavirin. A total of 69 individuals were able to complete the total duration of therapy with regular follow-up. 62 of them did not require interventional therapy or significant reduction in dose. Erythropoietin was used in 44.4% (n=4) patients. GM-CSF was used in 33.3% (n=3) while 55.5% (n=5) patients required Recombinant IL-11. No adverse effect to the use of growth factors was observed. Overall spectrum of hematological side effects was quite tolerable and manageable. [Table 1]

Table 1: Outcome at EVR and SVR stage.

<table>
<thead>
<tr>
<th>Categories of outcome</th>
<th>Response categories</th>
<th>Complete Responders n (%)</th>
<th>Break-Through Non Responders n (%)</th>
<th>Non- Responders n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome at ETR stage</td>
<td></td>
<td>57 (82.6)</td>
<td>2 (2.8)</td>
<td>10 (14.5)</td>
</tr>
<tr>
<td>Outcome at SVR stage</td>
<td></td>
<td>40 (57.9)</td>
<td>17 (24.6)</td>
<td>12 (17.4)</td>
</tr>
</tbody>
</table>

Table 1: Response to interferon therapy at ETR and SVR stage; ETR=End of Treatment response; SVR=Sustained Virological Response.

Figure 1: Comparison of hematological side effects of antiviral therapy in our study with local literature; conventional versus pegylated interferon.

Hematological side effects of interferon include anemia, thrombocytopenia and leukopenia. They lead to poor quality of life, suboptimal dosing or even discontinuation of therapy ultimately leading to low SVR rates. To treat these hematological side effects, erythropoietic growth factors like Epoetin are being used in clinical trials that effectively increase hemoglobin by stimulating bone marrow. Other cell lines are improved by respective growth factors that improve adherence to the therapy and hence SVR but efficacy, safety and cost effectiveness of these growth factors is unclear. Patient age is also an important contributing factor to determine safety to interferon combination therapy as older patients have

DISCUSSUION

‘Interferon and ribavirin’ combination therapy is the standard of treatment for HCV. Both of them have challenging side effects. SVR is lower for patients who do not complete the entire course or less than 80 % of intended dose.
decreased cardiac and pulmonary functions and so are less resistant to anemia and pneumonitis caused by combination therapy. The older age group also has a higher rate of treatment discontinuation, adverse events and a lower SVR compared to middle aged and younger population.\(^9\)

During the course of treatment in our study, 35.2\% (n=25) individuals developed anemia, 29.6\% (n=21) experienced thrombocytopenia while leukopenia was seen in 38\% (n=27). Leukopenia and anemia were the most common side effects. Treatment was stopped in 2.81\% (n=2) individuals due to serious hematological side effects. Erythropoietin, GM-CSF and/or Recombinant IL-11 were needed to counter the side effects in 12.6\% (n=9) individuals. 77.7\% (n=7) of them did not need the reduction of dose of interferon or ribavirin and responded well to the growth factors. No adverse events were observed with the use of growth factors. This helped in achieving the recommended dosing schedule and thus preventing inadequate dosage to be a contributing factor towards reduced response rate. No interventional therapy was required in 87.32\% (n=62) patients in our study. [Table 1]

As a whole, the frequency of serious hematological side effects was quite low i-e., 2.8\% (n=2) with pegylated interferon combination therapy. The tolerance to this mode of treatment was quite good. Keeping in view the judicious use of pegylated interferon in an HCV epidemic country like Pakistan, our study showed that hematological side effects do not hamper the primary goal of achieving response to treatment for HCV. Moreover, the use of growth factors with the aim to prevent dose reduction or discontinuation of therapy was successful in 77.7\% (n=7) of those receiving them.

The role of growth factors, to our knowledge, has never been studied in Pakistan and we are the first ones to make such an attempt. In addition, the description of frequency of side effects experienced with interferon is also limited in the local literature. Hayat et al. (2009) concluded that hematological side effects of interferon therapy (conventional) are generally tolerable but they can still result in adverse outcomes at times.\(^9\) The counteracting endogenous production of growth factors is insufficient to tackle the serious side effects. We further extended this literature on interferon by studying these effects for pegylated interferon. This causes reduction of antiviral dose resulting in delivery of insufficient dose. Hayat et al. (2009) further suggested that super-physiological doses of growth factors can help reduce the hematological toxicities enabling the patients to receive full doses of antivirals.\(^9\) A comparison of our results (pegylated interferon) regarding hematological side effects with the results of Hayat et al. (conventional) is shown in figure -1.

Based on our observation, we conclude that pegylated interferon combination therapy for treatment of HCV is a safe mode of treatment when administered under strict follow-up with serial monitoring of cell counts. We also conclude that concomitant use of growth factors to counter the side effects is a good option to prevent both a reduction in dose as well as discontinuation of therapy. Such measures can improve the clinical outcome as a whole.

**CONCLUSION**

Pegylated interferon combination therapy has tolerable spectrum of hematological side effects and the concomitant support by growth factors in those with profound log drop in cell lines can help to achieve the viral response without the need for reduction of dose or discontinuation of therapy. This could help achieve Sustained Virological Response (SVR) and End of Treatment Response (ETR) without jeopardizing the efficacy of interferon related to reduction of dose or discontinuation.

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**CONFLICT OF INTEREST**

The authors declare that they do not have any conflict of interest regarding this work.

**REFERENCES**


