INTRODUCTION

Hepatitis C Virus (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 performed.1 Hepatitis C Virus (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 Hepatitis C Virus (HCV) infection is increasing rapidly. Viral eradication is the only way to prevent disease progression. A recent National Institute of Health (NIH) consensus guideline recommended treatment with Pegylated interferon and ribavirin. Those with total leukocyte count (TLC) <4000/cmm were given injection Granulocyte-Colony Stimulating Factor (G-CSF) according to severity of leucopenia. Response to therapy was noted and dose titration was done accordingly.

RESULTS: A total of 208 patients were enrolled in the study with 99 (48%) males and 109 (52%) females. Total leukocyte count (TLC) < 4000/cmm was observed in 78 (37.5%) cases. Conventional interferon induced leucopenia was seen in 60 out of 172 (35%) cases. Pegylated interferon induced leucopenia was seen in 18 out of 36 (50%) cases. Patients on Pegylated interferon had more severe leucopenia as compared to those on conventional interferon. Granulocyte-Colony Stimulating Factor (G-CSF) administration resulted in an increase in mean total leukocyte count from 2300 to 5200/cmm. No patient required antiviral dose reduction or discontinuation.

Conclusion: Recombinant Granulocyte-Colony Stimulating Factor (G-CSF) administration tends to manage leucopenia, which is a common adverse effect of antiviral treatment for hepatitis C.

Key words: Hepatitis C, Leucopenia, Interferons, Enzyme-linked immunosorbent assay.

METHODOLOGY

This observational study was conducted at Shafi Clinic, Rawalpindi. A total of 208 patients were selected by non-probability purposive sampling from July 2005 to July 2007. All patients of either gender, 18 years of age with positive Polymerase Chain Reaction (PCR) and positive HCV-RNA by Enzyme Linked Immunosorbent Assay (ELISA) method were included in the study. Standard combination therapy was given to all i.e. interferon and ribavirin. Those with total leukocyte count (TLC) <4000/cmm were given injection Granulocyte-Colony Stimulating Factor (G-CSF) according to severity of leucopenia. Response to therapy was noted and dose titration was done accordingly.

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positive for Hepatitis C Virus (HCV) by Enzyme Linked Immunosorbent Assay (ELISA) method with no contraindications to interferon or ribavirin (non-pregnant ladies) and baseline total leucocyte count (TLC) >4000/cubic millimeter and hemoglobin (Hb) >10g/dl, were included. Informed written consent was taken from all the patients. All patients were genotype 2 or 3. All were treated for 6 months. Patients, who were initially assigned to conventional interferon, and who were non-responders among them, were given pegylated interferon. No patient ended up needing Erythropoietin or blood transfusion. Complete baseline labs including complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), blood sugar random (BSR), thyroid function tests (TFTs) and ultrasound (USG) abdomen were done before enrollment of the patients. Standard combination therapy was given to all i.e. interferon and ribavirin in standard doses.11,12 Most of the patients were given conventional interferon because of its low cost.

Follow-up was done initially 2-weekly for 3 months and then monthly till the end of treatment. Blood complete picture and alkaline transferase (ALT) repeated at each follow-up to look for any complication. In patients, who developed leucopenia, Granulocyte-Colony Stimulating Factor (G-CSF) was administered according to severity i.e., If Total Leukocyte Count (TLC) was 3000/cmm, Inj. Recombinant Granulocyte-Colony Stimulating Factor (G-CSF) was given subcutaneously (S/C) once a week. If TLC was 2000/cmm, Inj. Recombinant Granulocyte-Colony Stimulating Factor (G-CSF) was given twice-a-week. If TLC was < 2000/cmm, then Inj. Recombinant Granulocyte-Colony Stimulating Factor (G-CSF) was administered thrice-a-week. Response to treatment was noted and dose titration done accordingly. Treatment was stopped at the end of 6 months by repeating Polymerase Chain Reaction (PCR).

All patients completed their 6 months treatment. There was no effect on Hb level by the use of Inj. G-CSF.

All the data collected was analyzed by SPSS version 15. Descriptive statistics like mean and standard deviation for quantitative data and frequency with percentages for qualitative data was used.

**RESULTS**

A total of 208 patients were included in the study, in which 99 (48%) were males and 109 (52%) were female patients. One hundred seventy two (82.7%) patients received conventional interferon (IFN) and 36 (17.3%) patients received pegylated interferon (IFN). The mean age of the patients was 42.5 years with maximum patients in the age group of 41 to 60 years (Table I). Range was 18 to 65 years.

In this study, leucopenia i.e. Total Leukocyte Count (TLC) < 4000/cmm was seen in 78 cases. Conventional interferon induced leucopenia was seen in 60 (35%) cases and pegylated interferon induced leucopenia was seen in 18 out of 36 cases i.e. 50% cases. Out of them, 36 (46%) had mild leucopenia (TLC 4000/cmm), 34 (44%) had moderate leucopenia (TLC 3000/cmm) and 8 (10%) had severe leucopenia (TLC <2000/cmm) (Figure 1). This leucopenia was mostly observed at the end of second month of treatment (Figure 2).

### Table I: Age distribution of patients receiving conventional interferon (172/208 patients) and pegylated interferon (36/208 patients).

<table>
<thead>
<tr>
<th>Age of patients</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 years</td>
<td>1</td>
</tr>
<tr>
<td>21-30 years</td>
<td>32</td>
</tr>
<tr>
<td>31-40 years</td>
<td>60</td>
</tr>
<tr>
<td>41-50 years</td>
<td>79</td>
</tr>
<tr>
<td>51-60 years</td>
<td>30</td>
</tr>
<tr>
<td>61-65 years</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>208</strong></td>
</tr>
</tbody>
</table>

All these patients were given Inj. Recombinant Granulocyte-Colony Stimulating Factor (G-CSF). Sixty (35%) patients required Inj. Recombinant Granulocyte-Colony Stimulating Factor (G-CSF) in thrice weekly dosage whereas rest of the patients received weekly dose regimens.

After initiation of Inj. Recombinant Granulocyte-Colony Stimulating Factor (G-CSF), mean leucocyte count increased from 2300 to 5200 per cmm in 6 months.

There was a gradual drop in total leukocyte count during treatment from second to seventh week, which was countered by administering Inj. Recombinant Granulocyte-Colony Stimulating Factor (G-CSF) so that all patients were able to complete the desired duration of treatment.

**DISCUSSION**

Hepatitis C is one of the most common infections worldwide.1 The advent of new antiviral treatment regimens have proved to be very effective in achieving Sustained Viral Response (SVR). However, these medications have significant adverse effects. Hematological toxicity includes anemia, leucopenia and thrombocytopenia.11 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.12-14 For achieving
SVR, dose maintenance and treatment adherence are essential. Another study by Fukuda et al. also shows that long-term use of Interferon-Alpha produces negative feedback on G-CSF production. Neutropenia is more commonly seen with pegylated interferon.

The present study shows significant frequency of leucopenia during antiviral therapy i.e 37.5%. Eight patients developed severe leucopenia with cell count < 2000/cmm. One patient had a TLC of 1200/cmm with absolute neutrophil count of 720/cmm. This study shows that about 50% of the patients who used pegylated interferon became leucopenic as compared to 35% with conventional interferon. It is also evident by previously conducted studies of Manns, Fried and Raymond. Recombinant human G-CSF enhances granulopoiesis and stimulates production of multipotent hematopoietic progenitor cells and mature granulocytes.

Addition of G-CSF during treatment increases mean and peak white cell count. There are no guidelines for its use in HCV infected population but the rationale for it is predicted on its success in patients with cancer who are receiving chemotherapy. Various studies have proved its effectiveness in hepatitis C treatment. Although the exact dose of G-CSF is not fully established, it is suggested that a typical dose be 300 micrograms SC 2-3 times per week with dose titration as needed to maintain ANC of > or =750 cells per cmm. G-CSF was administered to all those patients who developed leucopenia according to given doses. All the patients responded well with a significant increase in mean TLC. No adverse effects were noted. There were some individual variations to response but overall none needed dose reduction or discontinuation after starting Inj. Recombinant Granulocyte-Colony Stimulating Factor (G-CSF). Another study also showed similar results with the use of G-CSF. However, in this study, inj. Recombinant Granulocyte-Colony Stimulating Factor (G-CSF) was started with antiviral therapy to avoid dose reduction.

The main limitation of this study was lack of randomization and controls, being a case-series. Randomized-controlled trials can establish the role of G-CSF.

CONCLUSION
It is concluded that leucopenia is a common adverse effect of antiviral treatment, seen mostly with the use of Pegylated interferon. Injectable Recombinant Granulocyte-Colony Stimulating Factor (G-CSF) can be effective to combat leucopenia, allowing adherence and maintenance of critical dose level, producing optimal hepatitis C virus treatment.

REFERENCES