INTRODUCTION
Chronic hepatitis C infection globally infects almost 3% population, nearly 170 million people worldwide and is estimated to result in 366,000 deaths annually. Approximately 10 million people have been infected with HCV in Pakistan and this is projected to increase dramatically over the next 20 years. The major hepatological consequence of hepatitis C virus infection is progression to cirrhosis in 10-20% of the patients and its potential complications: haemorrhage, hepatic insufficiency and primary liver cancer. Pakistan having an approximate population of 165 million and intermediate to high rates of infection is among the worst afflicted nations. Successful treatment of hepatitis C would have a major impact on health and healthcare costs depending on the proportion of patients treated and efficacy of treatment regimen.

Viral eradication is the only way to prevent disease progression. Treatment for hepatitis C has evolved from the use of interferon-α monotherapy to combination therapy with interferon ribavirin (IFN-RBV) and more recently to combination therapy with pegylated interferon alpha (PEG-IFNα) and RBV. Nowadays this is the standard initial treatment of chronic hepatitis C. Despite advances in treatment over past 18 years; a significant proportion of patients still do not respond to therapy. Thus the problem of refractory HCV infection is of significant magnitude. As new therapies with incremental improvement in sustained virologic response (SVR) have become available; large number of patients refractory to previous therapy are seeking re-treatment. Re-treatment of non-responders to IFN-α is generally associated with poor SVR rates, especially in HCV genotype 1 infected patients or patients with cirrhosis. Data from four large randomized controlled trial have shown that PEG-IFN alpha with or without ribavirin achieved significantly high SVR rates in comparison with standard IFN with or without ribavirin in naïve patients. Patients with an early virologic response (EVR) have a 70% probability of achieving a Sustained virological response (SVR), whereas those without such a response are unlikely to achieve SVR and most guidelines recommend discontinuation of treatment.

ABSTRACT
Objective: To determine the frequency of end treatment virologic response (ETR) with pegylated interferon alpha and ribavirin in treatment of chronic hepatitis C patients who failed to respond to interferon plus ribavirin therapy given for at least 24 weeks.
Study Design: Descriptive study.
Place and Duration of Study: Medical Unit-II, Benazir Bhutto Hospital, Shafi Clinic Rawalpindi and PAEC Hospital Islamabad, Pakistan, from July 2008 to June 2009.
Methodology: Patients with hepatitis C who were non-responders to previous treatment with standard interferon and ribavirin, were given Pegylated Interferon alpha plus ribavirin. Total duration of treatment was 24 weeks for genotypes 2 and 3 and 48 weeks for genotypes 1 and 4. The primary end point was undetectable HCV RNA by polymerase chain reaction assay at the completion of therapy.
Results: Out of the 44 enrolled patients, 24 (54.5%) were males and 20 (45.5%) were females. Mean age of patients was 45.2±7.14 years. HCV genotypes were 3 in 64%, 2 in 30% and 7% each had genotypes 1 and 4. Both the early virological response and end of treatment response was seen in 75% patients.
Conclusion: There was a high ETR rate of 75 in previous non-responders to conventional combination therapy. This high ETR as compared to international data is because of existence of favourable genotypes in our country which is encouraging in the treatment of non-responders.

Key words: Hepatitis C. Non-responders. Early virological response. End treatment response.
However, there is a large and growing pool of patients who have either failed to respond to an initial course of treatment or relapsed during follow-up after an initial favourable response. Therefore, defining the efficacy of re-treatment regimens is important.\textsuperscript{12}

The objective of this study was to determine the frequency of end treatment response (ETR) with PEG-IFN and RBV treatment in patients with chronic hepatitis C who failed to respond to standard IFN and RBV given for at least 24 weeks.

**METHODOLOGY**

This study was conducted at multiple centres over a period of one year from July 2008 to June 2009 in the twin cities of Rawalpindi and Islamabad at Medical Unit II, Benazir Bhutto Hospital, Shafi Clinic and Pakistan Atomic Energy Commission (PAEC) Hospital. Approval from the Hospitals' Ethics Committees was taken prior to conducting the study. Consecutive sampling was employed to select 44 patients. Non-responders were defined as having detectable HCV RNA in serum at 12 weeks or at the end of treatment with standard IFN and ribavirin. The primary end point was end treatment response (ETR), defined as an undetectable serum HCV RNA level at the end of treatment. EVR was defined as an undetectable serum HCV RNA level by week 12 of treatment. Anaemia was defined as haemoglobin level of ≤ 9 gm/dl, leucopenia ≤ 3,000 mm\(^3\) and thrombocytopenia ≤ 120,000/mm\(^3\). All laboratory tests were carried out at the respective hospital laboratory and the findings were reported by the consultant pathologist.

Adults ≥ 18 years age of either gender who were anti-HCV positive and non-responder to conventional IFN and RBV as detected by positive qualitative PCR for HCV-RNA were included in the study. Hepatitis C genotype was determined prior to entry into the study. Minimum haematologic criteria for entry included a haemoglobin > 10 g/dl for females and > 11 g/dl for males, WBC > 3000/mm\(^3\) and platelet count > 150,000/mml. Anti-HCV positive patients who had concurrent co-infection with hepatitis B virus, decompensated disease, neoplastic disease, severe cardiac or pulmonary disease, psychiatric disorder, or any other cause for liver disease e.g. haemochromatosis, Wilson's disease, alcohol or drug induced hepatitis were excluded from the study. There was no serum alanine aminotransferase (ALT) criterion for inclusion.

Informed consent was taken from all the study participants. All patients were given pegylated interferon (PEG-IFN) alpha along with ribavirin (RBV) for 24 and 48 weeks based on genotype. Dose of RBV was adjusted according to weight; < 75 kg - 1000 mg/day, > 75 kg - 1200 mg/day. Sequential monitoring of serum HCV RNA levels was done with qualitative polymerase-chain-reaction assay at week 4, 12, and at the end of treatment. Similarly haemoglobin levels, total leucocyte count, platelet count were checked monthly.

The use of granulocyte colony-stimulating factor and erythropoietin was permitted to manage clinically significant adverse events i.e. leucopenia and anaemia. All subjects with TLC < 2000/mm\(^3\) were given inj. Recombinant granulocyte colony stimulating factor (G-CSF) sub-cutaneously.

Data was analyzed by SPSS version 10. Descriptive statistics like mean and standard deviation was calculated for quantitative variables like age while frequency with percentages was used for qualitative data like gender, EVR, ETR, HCV genotype, anaemia, leucopenia and thrombocytopenia. Paired samples t-test was used to determine the difference in ALT at baseline and end of treatment, keeping p-value < 0.05.

**RESULTS**

A total of 44 patients were enrolled in the study, 24 (54.5%) were males and 20 (45.5%) were females. Mean age of patients was 45.25 ± 7.14 years, ranging from 26 to 65 years. HCV genotype 3 was found in 28 (63.6%), genotype 2 in 13 (29.5%) patients while 3 (6.8%) had genotype 1 and 4. Both EVR and ETR were seen in 33 (75%) patients and 69.2% genotype 2, 75% in genotype 3 and 100% in genotypes 1 and 4. None of the patients had breakthrough response. All patients completed the course without having any significant haematological complication. Leucopenia was seen in 33 (75%) patients and thrombocytopenia was seen in 18 (38.6%) cases. Thirty four patients had raised ALT i.e. > 40 U/L at the start of treatment; reduction was seen in 30 (68.18%) subjects which began at the end of first month of treatment. Mean ALT was 74.05 ± 51.965 U/L and 44.32 ± 32.865 U/L at 4 and 24 weeks respectively (p < 0.01).

**DISCUSSION**

Prevalence of hepatitis C is increasing worldwide; this infection refractory to previous therapy is common. Treatment of patients with refractory disease is difficult and less studied.\textsuperscript{9} With the advent of anti-viral therapies, more and more people are seeking treatment. Failure to maintain the SVR is an emerging issue with the use of conventional regimen. Therefore, it is important to study the effect of standard regimen on the early and end treatment virological response among non-responders as well as relapers. Trials of PEG IFN alpha in combination with RBV have established the superior efficacy of combination therapy over standard IFN and RBV.\textsuperscript{13} However, whether patients previously unresponsive to conventional interferon-based treatment...
regimens benefit from treatment with pegylated interferon-based regimens is less clear. As such limited data is available.\textsuperscript{8,10}

The mean age of study participants was 45.25 ± 7.14 years which was almost the same as reported in previous studies. Gender distribution was also somewhat similar to previous studies which have reported as 65-78% males.\textsuperscript{14,15}

HCV genotypes prevalent in Pakistan include 2 and 3. This study also showed that 64% patients had genotype 3 while 30% had genotype 2. Fortunately these types are responsive to the conventional treatment with an SVR of about 76% respectively. However, there is still a big population of non-responders or relapers. Qazi \textit{et al.} reported the prevalence of genotype 3 to be 71\%.\textsuperscript{13,16} Other studies reported the prevalence of genotype 2 and 3 to be between 6-47\%.\textsuperscript{14,17} The most predominant HCV genotype is genotype 3 in 87\%,\textsuperscript{16,18} followed by genotypes 1 and 5. Non-responders had genotype 1 infection 87\% in a study done in Canada.\textsuperscript{17}

The results of this study also showed that re-treatment of refractory patients of hepatitis C with pegylated interferon resulted in 75\% of patients achieving both EVR and ETR. It was 69.2\% in genotype 2, 75\% genotype 3 and 100 \% in genotypes 1 and 4. This figure is quite high as compared to worldwide studies, though another local study also reported the same ETR.\textsuperscript{15} Hadziyannis \textit{et al.} reported an overall EVR of 52\%; ETR of 18\% among combination therapy non-responders and 43\% ETR among IFN monotherapy non-responders.\textsuperscript{12} Better response rates were seen for both genotype,\textsuperscript{10} Krawitt \textit{et al.} in his study found an ETR of 46\% among non-responders, 29\% for genotype 1 and 86\% for genotypes 2 and 3. Similar trend was seen with regards to SVR 29\% for genotype I patients compared to 58\% for genotypes 2 and 3 patients. Moucari \textit{et al.} in his study on retreatment of prior non-responders reported an EVR of 34.6\%, ETR of 25.7\% and SVR of 13\%.\textsuperscript{6,8} An EVR of 58\% and ETR response of 53\% is documented in a study done in USA in 2006.\textsuperscript{9} Studies have also shown no significant association of genotype with response or with early response.\textsuperscript{19}

Second important result seen in this study is that all those patients who achieved EVR; also achieved ETR. Parise and colleagues showed that 78\% of relapers achieved ETR and 51\% achieved SVR; 57\% of non-responders ETR and 26\% achieved SVR.\textsuperscript{21} Moucari \textit{et al.} also showed a great positive predictive value of EVR on SVR.\textsuperscript{8} A recent study showed an EVR of 53\% among non-responders.\textsuperscript{20} Non-responders showed 57\% ETR and 26\% SVR among Brazilian patients who were previous responder. Relapers are most likely to respond to a course of peginterferon/ribavirin combination therapy, whereas previous non-responders can also achieve significant rates of SVR, particularly those infected with genotype.\textsuperscript{21,22} In another study the efficacy SVR was achieved in 86.76\% patients at the end of follow-up, while the secondary efficacy parameter SVR at the ETR was achieved in 77.27\% of patients.\textsuperscript{21} Furthermore, early virologic response at week 8 and week 12 of treatment had similar predictive value for SVR.\textsuperscript{23} The mean ALT value reported in other studies was much higher compared to this study, with the total of 93.68\% of patients having elevated ALT level.\textsuperscript{24}

Results of this study show that retreatment of patients with refractory hepatitis C infection with PEG-IFN-α is well-tolerated and gives modest response rates. Though these are encouraging but due to the small sample size, results cannot be generalized. Due to the high cost of treatment and the laboratory tests we could not check viral load; instead qualitative PCR was done. However, it was exclusively done in non-responders, whereas most of other studies are on both relapers and non-responders. Follow-up of these patients for SVR would help to determine the positive predictive value of ETR. It is still needed to conduct studies on larger scale by using all viral kinetics in order to fully understand the importance of retreatment in the rapidly expanding population of non-responders in this setup.

**CONCLUSION**

EVR is the most important predictor of achieving ETR. PEG-IFN-α with RBV is effective in treatment of non-responders to conventional combination therapy. This high ETR as compared to international data, is because of favourable genotypes 2 and 3 in our country. These good results would create hope in treatment refractory cases in our environment of rapidly expanding population of chronic hepatitis C.

**REFERENCES**


