INTRODUCTION
Infection with HCV affects an estimated 180 million people globally. It is a leading cause of chronic hepatitis, cirrhosis, and liver cancer and a primary indication for liver transplantation in the Western world. In Pakistan more than 10 million people suffer from hepatitis C constituting 3.6% of population. Genotype 3 is the most prevalent of the six genotypes in Pakistan. Since the approval of conventional interferon-based treatment for patients with hepatitis C in early 2000s, a 25 – 30% of patients did not respond to therapy. This will add to the alarmingly increasing pool of hard to treat patients with chronic hepatitis C. The progression of the disease could be more severe in these non-responders leading to early development of cirrhosis of liver and hepatocellular carcinoma. This has led to the necessity of retreatment of these patients with an effective regimen. Pegylated interferon and ribavirin combination treatment was approved for treatment of adults in 2002 and is the current standard of care for adults because of the capability of virus eradication in 80% treatment-naive patients. It is worthwhile to use these new agents in retreating patients who did not respond to conventional interferon-based treatment.

American Association for the Study of Liver Disease (AASLD) practice guidelines also recommend that retreatment with PEG-IFN plus ribavirin be considered for non-responders who underwent previous regimens of combination treatment using conventional interferon. It has now been proved that sustained virologic response, defined as reduction of serum HCV RNA to undetectable level 6 months after completion of treatment, will not only halt the disease progression but may reverse the fibrosis thereby reducing the chances of developing long-term complications such as cirrhosis of liver and hepatocellular carcinoma.

The purpose of this study was to determine the efficacy of combination of peg-interferon and ribavirin therapy in patients refractory to previous conventional interferon-based treatment and also determine the various factors influencing the sustained viral response (SVR) in patients with hepatitis C.

ORIGINAL ARTICLE

Efficacy of Peg-Interferon Based Treatment in Patients with Hepatitis C Refractory to Previous Conventional Interferon-Based Treatment
Samiullah Shaikh, Bikha Ram Devrajani and Musarat Kalhoro

ABSTRACT
Objective: To determine the efficacy of peg-interferon-based therapy in patients refractory to previous conventional interferon-based treatment and factors predicting sustained viral response (SVR).
Study Design: Analytical study.
Place and Duration of Study: Medical Unit IV, Liaquat University Hospital, Jamshoro, from July 2009 to June 2011.
Methodology: This study included consecutive patients of hepatitis C who were previously treated with conventional interferon-based treatment for 6 months but were either non-responders, relapsed or had virologic breakthrough and stage ≥ 2 with fibrosis on liver biopsy. All eligible patients were provided peg-interferon at the dosage of 180 µg weekly with ribavirin thrice a day for 6 months. Sustained Viral Response (SVR) was defined as absence of HCV RNA at 24th week after treatment. All data was processed on SPSS version 16.
Results: Out of 450 patients enrolled in the study, 192 were excluded from the study on the basis of minimal fibrosis (stage 0 and 1). Two hundred and fifty eight patients fulfilled the inclusion criteria and 247 completed the course of peg-interferon treatment. One hundred and sixty one (62.4%) were males and 97 (37.6%) were females. The mean age was 39.9 ± 6.1 years, haemoglobin was 11.49 ± 2.45 g/dl, platelet count was 127.2 ± 50.6 10^3/mm^3, ALT was 99 ± 65 IU/L. SVR was achieved in 84 (32.6%). The strong association was found between SVR and the pattern of response (p = 0.001), degree of fibrosis and early viral response (p = 0.001).
Conclusion: Peg-interferon based treatment is an effective and safe treatment option for patients refractory to conventional interferon-based treatment.

Key words: Hepatitis C. Non-responders. Relapsers. Peg-interferon.

INTRODUCTION
Infection with HCV affects an estimated 180 million people globally. It is a leading cause of chronic hepatitis, cirrhosis, and liver cancer and a primary indication for liver transplantation in the Western world. In Pakistan more than 10 million people suffer from hepatitis C constituting 3.6% of population. Genotype 3 is the most prevalent of the six genotypes in Pakistan. Since the approval of conventional interferon-based treatment for patients with hepatitis C in early 2000s, a 25 – 30% of patients did not respond to therapy. This will add to the alarmingly increasing pool of hard to treat patients with chronic hepatitis C. The progression of the disease could be more severe in these non-responders leading to early development of cirrhosis of liver and hepatocellular carcinoma. This has led to the necessity of retreatment of these patients with an effective regimen. Pegylated interferon and ribavirin combination treatment was approved for treatment of adults in 2002 and is the current standard of care for adults because of the capability of virus eradication in 80% treatment-naive patients. It is worthwhile to use these new agents in retreating patients who did not respond to conventional interferon-based treatment.

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The purpose of this study was to determine the efficacy of combination of peg-interferon and ribavirin therapy in patients refractory to previous conventional interferon-based treatment and also determine the various factors influencing the sustained viral response (SVR) in patients with hepatitis C.
METHODOLOGY
This analytical study included consecutive patients of hepatitis C who were previously treated with conventional interferon-based treatment for 6 months but were either non-responders, relapsed or had virologic breakthrough response and ≥ 2 stage fibrosis on biopsy. The study was conducted at the Medical Unit IV of Liaquat University Hospital, Jamshoro, Pakistan, from July 2009 to June 2011. The study was conducted in conformance with the principles of the Declaration of Helsinki. The institutional review board of the hospital approved the protocol and consent forms. All participants provided written informed consent. Patients were labelled as non-responders if they had detectable HCV RNA during previous treatment. Patients with relapse had undetectable HCV RNA during treatment which re-appeared after discontinuation of treatment. Patients with virologic breakthrough were those who had achieved undetectable HCV RNA levels in serum during treatment initially although serum HCV RNA eventually re-appeared later on with ongoing treatment.

Patients with mild fibrosis (stage 0 and 1 fibrosis) were excluded from the study according to ASSLD guidelines. Pregnant or breast feeding women patients with haemoglobin < 10 g/dl, neutrophil count < 1500 cells/mm³ or platelet count < 50,000 cells/mm³, hypothyroidism or hyperthyroidism, hepatitis B, hepatitis C, illicit drug abusers, alcoholics, patients with features consistent with decompensated cirrhosis of liver such as ascites, history of bleeding from oesophageal varices and patients with hepatocellular carcinoma were also excluded from the study.

Liver biopsy was performed in all patients under local anaesthesia by a trained person after taking consent and fully explaining the procedure to patients. Biopsy was performed using cutting biopsy needle (14-gauge) under ultrasound guidance. Specimen size greater than 10 mm and containing more than 5 portal tracts was considered as adequate sample. All patients tolerated the procedure well without development of any major complications such as requirement of blood transfusion, hypotension or biliary peritonitis. A single qualified histopathologist, who was unaware about the clinical data, assessed the biopsy slides. Fibrosis stage was determined according to the METAVIR group scoring system as F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = few septa; F3 = numerous septa without cirrhosis; or F4 = cirrhosis.

All eligible patients were provided peg-interferon at the dosage of 180 µg weekly with weight-based dosage of ribavirin (800 mg for 65 kg; 1000 mg for 65 – 85 kg; 1200 mg for 85 – 105 kg, and 1400 mg for 105 – 125 kg) for 6 months by Hepatitis Prevention and Control Program, launched on the initiative of Sindh Chief Minister. This program initiated by the Government of Sindh, Pakistan, provides free conventional interferon based treatment to naive hepatitis C patients as well as peg-interferon-based treatment to non-responders, relapers and patients with breakthrough response. This program covers 55.24 million population of the Sindh province.

All patients were assessed clinically and biochemically before starting the treatment and then monthly during the treatment period. Haemoglobin, ALT (alanine aminotransferase) and platelet count were done in Liaquat University Research Laboratory. Qualitative HCV RNA by PCR was done at 12th and 24th week of treatment and then 24th week after treatment from Liaquat University Molecular Laboratory. BMI of all patients were calculated by formula of body weight (kgs)/height in meters. Patients were divided into BMI ≤ 30 kg/m² and > 30 kg/m². Early virologic response (EVR) was defined as negative HCV-RNA by PCR at 12th week of treatment. Sustained Viral Response (SVR) was defined as absence of HCV RNA at 24th week after treatment.

Continuous variables such as age, ALT levels, platelet count were computed as mean ± SD and categorical variables such as genders, pattern of response, sustained viral response (SVR), stage of fibrosis and early virologic response were expressed as frequency with percentage. Chi-square test was performed to assess the effects of these independent variables such as pattern of response, stage of fibrosis and early virologic response and BMI on sustained viral response. A p-value of 0.05 was considered statistically significant. All data was processed on Statistical Package for Social Sciences (SPSS) version 16.

RESULTS
Out of the 450 patients enrolled in the study, 192 were excluded from the study on the basis of minimal fibrosis (stages 0 and 1). Two hundred and fifty-eight patients fulfilled the inclusion criteria and 247 completed the course of peg-interferon treatment, whereas 11 patients were dropped due to peg-interferon induced complications during study period. The mean age was 39.9 ± 6.0 years, mean haemoglobin (g/dl) was 11.49 ± 2.45, platelet count (10⁹/mm³) was 127.2 ± 50.6, ALT (IU/L) 99.6 ± 33.3. One hundred and sixty-one (62.4%) were males and 97 (37.6%) females. ALT ≤ 40 IU/L was found in 131 (53%) patients and SGPT ≥ 40 (IU/L) in 127 (49.2%) patients. Fibrosis stage 2 was present in 169 (65.5%), stage 3 in 66 (25.6%) and stage 4 in 23 (8.9%) patients. Among 258 relapsers were 110 (42.6%), non-responders 95 (36.8%) and breakthrough response in 53 (20.5%) patients. Body mass index (BMI) was > 30 kg/m² in 161 (62.4%) patients and < 30 kg/m² in 97 (37.6%) patients. Early viral response was attained by 137/258 (53.1%) patients and sustained viral response was achieved by 84/258 (32.6%) patients. Table I shows
the baseline characteristics of patients included in study. Strong relation was found between SVR and the pattern of response \((p = 0.001)\) as 51/110 (46.3%) relapers, 20/53 (37.7%) patients with breakthrough response and 13/95 (13.6%) non-responders achieved sustained viral response. Another factor predicting the sustained viral response was degree of fibrosis at the time of liver biopsy \((p = 0.001)\) as 71/169 (42.0%) patients in F2, 10/66 (15.1%) in F3 and 3/23 (13.0%) in F4 showed sustained viral response. EVR strongly predicted the sustained viral response \((p = 0.001)\) as 51/110 (46.3%) relapers, 20/32 (62.5%) with breakthrough response and 13/48 (27.08%) non-responders patients with early viral response achieved sustained viral response. No significant association was found between BMI and SVR \((p = 0.39)\) as 32/97 (32.9%) patients \(\leq 30\) achieved SVR whereas 52/161 (32.2%) patients \(\geq 30\) achieved SVR as shown in Table II.

**DISCUSSION**

This study demonstrated that PEG-IFN based treatment resulted in sustained viral response in 32.6% patients in whom previous combination therapy with IFN alpha/ribavirin had failed to eradicate HCV infection. Gonçales et al. in their study consisting of 40 patients observed sustained viral response in 40% of patients with genotype 3.16 Krawitt et al. in their study found 55% response rate in patients retreated with peg-interferon therapy.17 The reason for high response rate in Krawitt study was due to inclusion of only relapsers in the study whereas we have included all categories of non-responders. Poynard et al. in EPIC study demonstrated a SVR of 22% in 294 patients with genotype 3.18 The reason for lower response rate in EPIC study was that majority of patients included were of fibrosis stage III and IV whereas in our study majority of patients were in stage II fibrosis. Another reason for lower response was that in this study patients with previous combination therapy with IFN alpha/ribavirin were included whereas EPIC study included patients with previous combination therapy with IFN alpha/ribavirin as well as previous PEG-IFN and ribavirin therapy.

A strong association was found between sustained viral response and the pattern of response in this study as the response rate was higher in relapers as compared to non-responders. Sherman et al. in their study of 59 patients with genotype 3 demonstrated SVR in 55% in previous relapers and 23% in non-responders to conventional interferon-based treatment.19 Shiffman and colleagues in HALT-C trial (hepatitis C antiviral long-term treatment against cirrhosis), the largest study so far which included 406 non-responder patients to previous standard interferon-based treatment with advanced fibrosis or cirrhosis observed a 54% sustained viral response in genotype 3.20 Parise et al. found the highest response rate so far with 46% SVR in non-responders and 70% in relapers of non-genotype-1 patients.21 Jacobson and colleagues assessed the efficacy of retreatment with combination PEG-IFN and RBV therapy in patients unresponsive to combination IFN-RBV treatment or who relapsed despite combination therapy in 321 patients observed a 8% SVR in the combination-therapy non-responders, and 42% in the combination-therapy relapers when they were randomized to receive either PEG-IFN 2b 1.5 µg/kg/wk plus RBV 800 mg/day or PEG-IFN 2b 1.0 µg/kg/wk plus RBV 1000-1200 mg/day.9
Another factor influencing the outcome of the patients in this study was stage of fibrosis at the time of starting the retreatment as 51/169 (42.0%) patients in F2 showed SVR as comparison to 10/66 (15.1%) in F3 and 3/22 (13.0%) in F4. According to Dieterich and colleagues patients with mild fibrosis on liver biopsy (F0, F1 and F2) responded well to retreatment as compared to those with bridging fibrosis/cirrhosis (F3 and F4). A poor response rate was observed in the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial which recruited 1,046 patients with advanced fibrosis (Ishak fibrosis scores of 3 to 6) which is equal to Metavir score of 3 and 4. All patients included did not respond to conventional interferon based treatment and were treated with peg-interferon alpha-2a and ribavirin. It was shown that advanced fibrosis at the start of retreatment was an important predictor of poor response. This observation was independent of age, HCV genotype and type of prior therapy. In EPIC3 study which comprised 604 patients out which 71% had stage 3/4 Metavir score, a response rate of 22% was demonstrated in these patients showing a direct relationship between the SVR and degree of fibrosis at the start of retreatment. In contrast to the present and other studies, Gonçalves et al. did not observe a statistically significant impact of degree of fibrosis on SVR. They found SVR of 25% in patients with Metavir score of F0, F1 and F2 as comparison to 35% SVR in patients with advanced fibrosis (Metavir score 3 and 4). Early viral response (EVR) has been found an important predictor of SVR in this study as (p = 0.001) as 51/79 (64.55%) relapers, 20/32 (62.5%) with breakthrough response and 13/48 (27.08%) non-responders with early viral response achieved sustained viral response. Shiffman et al. in HALT-C study also showed that patients not achieving EVR are highly unlikely to achieve SVR making EVR an important predictor of SVR as seen in this study. Fried et al. also observed that 3% of patients will achieve SVR if they have not achieved EVR whereas 65% patients who had EVR at 12th week of treatment will achieve SVR.

In this study, no influence of BMI was found on SVR. Conjeevaram in a study of 401 patients did not find high BMI as a significant factor for poor outcome in patients on interferon based treatment. Pattullo et al. also confirmed this finding in their study of 134 patients. According to them BMI has no influence on SVR if ribavirin is prescribed according to body weight as done in this study. The results could be different if quantitative PCR had been done after 12th week of treatment to include those patients as responders who achieved 2-log reduction in viral load. Genotyping was not done according to guideline of Pakistan Society of Gastroenterology which advocates that because of preponderance of genotype 3 in Pakistan, it should not be done on routine basis. It is possible that some of the patients might be of genotype I which need 48 weeks of treatment.

CONCLUSION
This study demonstrated that peg-interferon based treatment is an effective and safe treatment option for patients unresponsive to conventional interferon based treatment. It is important to select the population before starting the treatment as the sustained viral response rate is much higher in relapers with fibrosis stage II who achieved EVR.

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REFERENCES


