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VIROLOGICAL RESPONSE WITH PEGYLATED-INTERFERON ALPHA 2a 180 MICROGRAM-40 KD STUDY

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Abstract: **Several guiding principles for treatment of Hepatitis C have been developed by prestigious medical bodies worldwide. However these do not take into consideration about the local availability, technology and infrastructure of developing countries. The objective of this study was to determine the frequency of rapid virological response (RVR) and sustained virological response (SVR) in three categories of naïve, non-responders, and relapsers of HCV patients having genotype 2 and 3 treated with pegylated interferon alpha 2a and ribavirin. Methods: This descriptive clinical study was carried out at multiple places of Pakistan during Jan 2012 to Sep 2014. Hepatitis C patients categorized in three groups of naïve, relapsers, and non-responders treated with Pegylated Interferon alpha 2a 180 µg-40 kD+ribavirin for genotype 2 and 3, for 24 weeks. The primary endpoint was SVR and RVR after 24 weeks. Results: Out of the 1,046 patients, 59.3% were male and 40.7% were female. Mean age of patients was 43.57±6.1 years. HCV genotypes were 3 in 62%, and 2 in 38%. SVR was noticed in 76% naïve patients, 42.8% in non-responders, and 47.9% in relapsers. Conclusion: Pegylated-Interferon alpha 2a 180 µg-40 kD mixed with Ribavirin is clinically helpful and well endured in naïve, relapsers, and non responders with chronic Hepatitis C.**

Keywords: **Hepatitis C, treatment naïve, non-responders, relapsers, virological response.**

1. INTRODUCTION

Hepatitis C is an infectious liver disease caused by the single stranded RNA virus commonly known as Hepatitis C virus (HCV). Hepatitis C infection is endemic all around the world and it right now infects an assessed 175 million individuals overall.[1] Hepatitis C prevalence in the world is about 2.8% with an estimated infected population of more than 8.4 million. In Pakistan prevalence of Hepatitis C infection is much higher being about 4.9%. The prevalence of this disease is increasing to alarming proportions worldwide. The prevalence of anti-HCV antibody has been increased from 122 million in 1990 to 184 million in 2005 worldwide.[2]

Several guiding principles for treatment of Hepatitis C have been developed by prestigious medical bodies worldwide. However these do not take into consideration about the local availability, technology and infrastructure of developing countries. These rules incorporate alternative choices for clinicians with financial constrained, however, they are difficult to reach and inappropriate for some clinicians in developing nations.

In countries with low resources for health care for example in Pakistan, the total expenditure of HCV treatment is up to USD 1,500 per patient including diagnostic tests, physicians' fees, etc. This is the outside the reach of most patients in Pakistan where per capita income is approximately USD 2,800.[3]

Rapid virologic response (RVR), defined as 'an undetectable serum hepatitis C virus (HCV) RNA level at week 4 of treatment'. RVR is the current standard of care and a vital turning point in the treatment of patients who have chronic Hepatitis C by utilization of pegylated interferon-alfa and ribavirinis.[4] RVR is presently thought to be the strongest predictor of sustained virological reaction (SVR) in Hepatitis C infection (HCV) patients undergoing antiviral therapy. It can be utilized as a guide for duration of treatment in individual patient. The duration of treatment for HCV is based on HCV genotype: 24 weeks is prescribed for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4. HCV genotype is an imperative indicator of treatment response.[5]

SVR was defined as 'the absence of detectable HCV in blood 24 weeks after the completion of antiviral therapy'.[6] Interferon-based treatments is a basic determinant in accomplishing SVR in hepatitis C virus (HCV) genotype 2 and 3 infections.[7]

The rationale in treating HCV infection is to reduce virus-related complications and can be achieved by eradicating the virus if sustained viral response (SVR) is achieved. Patients who achieve SVR have clearance of the virus and the chances of virus reactivation are negligible. The incidence of liver necro-inflammation, fibrosis and hepatocellular carcinoma, poses a risk in patients of not achieving SVR.

The objective of this study was to determine the frequency of rapid virological response (RVR) and sustained virological response (SVR) in three categories of naïve, non-responders and relapsers of HCV patients having genotype 2 and 3 treated with pegylated interferon alpha 2a and ribavirin.

2. METHODS

This was a clinical study and conducted in Pakistan over a period from Jan 2012 to Sep 2014. The patients were included from Karachi, Hyderabad, and Sukkur in Sindh; Multan, Bahawalpur, Lahore, and Rawalpindi in Punjab; Peshawar in Khyber Pakhtunkhwa; and Islamabad in Federal Capital Territory. The Laboratories for virology were opted by the respective physicians. It was planned to document at least 1,000 HCV patients of genotype-2 and 3 infection under treatment of pegylated interferon-alpha 2a and ribavirin. The patients were categorized into three groups 1). Patients who were HCV positive but were not exposed to any treatment (Naïve). 2). Patients treated with conventional interferon (IFN) and Ribavirin but failed to achieve undetectable HCV RNA during and at the end of treatment (Non-responders). 3). Patients treated with conventional IFN and Ribavirin and accomplished ETR but subsequently relapsed and did not accomplish an SVR (Relapsers).

All patients with chronic Hepatitis C with compensated liver disease of any sex and age, with no contraindication to PEG-IFN/RBV were included in this study. All patients were checked for Hepatitis C genotype before entry into the study. Minimum haematologic criteria for entry included a haemoglobin >10 g/dl for females and >11 g/dl for males, WBC >3,000/mm^3 and platelet count >150,000/µl. 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 2a along with ribavirin (RBV) for 24 and 48 weeks based on genotype. Dose of RBV was adjusted according to weight; <75 Kg–1,000 mg/day, >75 Kg–1200 mg/day. Sequential monitoring of serum HCV RNA levels was done with qualitative polymerase chain-reaction assay.

The contraindications and possible side effects were considered during therapy. The therapy was solely based on medical reasons. The study centres were well equipped with diagnostic procedures and conducted all required investigations. Rapid Virological Response (RVR) after 4 week of treatment and Sustained Virological Response (SVR) at the end of treatment (24 weeks) were observed in the three groups.

Data for each patient was entered into a 'Master Sheet' designed using SPSS-16. Percentage frequencies of virological responses were computed within categories of naïve, non-responders and relapsers. 95% confidence intervals were also calculated for percentage frequencies. Individual virological responses were compared for three categories of patients by Chi-square test of proportions. The results were considered significant at $p<0.001$.

3. RESULTS

A total 1,046 HCV patients including 857 (82.0%) treatment-naïve, 91 (8.6%) non-responders and 98 (9.4%) Relapsers treated with pegylated interferon-α 2a and ribavirin was included in the study. There were 620 (59.3%) males and 426 (40.7%) females. The mean age of patients was 43.57± 6.1 year.

After four weeks of pegylated interferon α 2a and ribavirin, the RVR among naïve patients was 77.0%. The SVR after 24 weeks of treatment was 76% in naïve patients. Rapid viral response in non-responders was 42.8% patients. The non-responders who achieved SVR were 42.8%. Relapsers showed 77.5% RVR, and achieved 47.9% SVR at the end of treatment.

The naïve patients had a significantly higher SVR rate as compared with previous non-responders and previous relapsers (76% vs 42.8%, 47.9%, $p<0.001$), and a higher RVR rate as compared to non-responders (77% vs 42.8%, $p<0.01$). As for those who relapsed, non-responders and naïve patients the rates of rapid EVR (88.7%, 57.1% and 89.9%, $p<0.001$). The SVR among non-responders and relapsers were 42.8% and 47.9% respectively.

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Table.1: Treatment response of naïve, non-responders and relapsers in HCV patients (n=1,046)

Virological Response	Treatment Naïve n=857 (82.0%)	Non-responder n= 91 (8.6%)	Relapsers n=98 (9.4%)	Statistics
Rapid virological response (RVR)	660 (77.0)	39 (42.8)	76 (77.5)	Chi-square=50.67, *p*=0.001
Sustained virological response (SVR)	651 (76.0)	39 (42.8)	47 (47.9)	Chi-square=69.62, *p*=0.001

4. DISCUSSION

The RVR of the naïve, non-responders or relapsers patients were 77%, 42.8% and 77.5% respectively at 4th week. Umar *et al* also reported the RVR in treatment naïve, non-responder and relapsers as 74.5%, 55.8%, and 75% to previous therapy respectively.[8]

We observed that following re-treatment, the overall SVR rate in the 651 patients was 76%. A review of the literature shows that in patients infected with HCV, the reported SVR is 76% in cases treated with peg-IFN-α 2a plus RBV and 82% in cases treated with, and peg-IFN-α 2b plus RBV.[9,10] A meta-analysis demonstrated higher SVR rates treated for 24 weeks in genotype 2 compared to genotype 3 infected patients (74% vs 69%).[11] In treatment-naïve patients with chronic Hepatitis C, the SVR rate at 24 weeks of treatment was 56% in peginterferon-alpha-2a (40 kD) plus ribavirin.[12] ACCELERATE study reported a results of randomized trial in patients with genotype 2 or 3 infection that SVR rate was 62% in patients treated for 16 weeks with Peg-IFN-α 2a plus ribavirin (800 mg/day) as compared to 70% in patients treated for 24 weeks.[13] We found 42.8% SVR in non-responder patients and 47.9% in relapsers with genotype 2 and 3. Our results are supported by a Brazilian study which showed that the peginterferon alfa-2a (40 kD) plus ribavirin produced an SVR in 51% of relapsers and 26% of non-responders.[14] Another study showed that in case of non-responders extending the duration of re-treatment with peginterferon alfa-2a (40 kD) plus ribavirin to 72 weeks resulted in an SVR rate of 16%.[15]

The high SVR rates and sound tolerability in both treatment-naïve and treatment-experienced patients with chronic Hepatitis C with combination therapy are consistently reported by various randomized phase III trials. In this way peginterferon-alpha-2a (40 kD) in addition to ribavirin remains a significant treatment in patients with chronic Hepatitis C.[16]

Through the coming 5–10 years, the range of medicines accessible for HCV contamination will grow, and possibly without interferon regimens will turn into a reality. This may bring about a significant change in treatment achievement rate, shorter treatment time and an improved side-effects profile. It is, however, imperative that the way to accomplishment in low and middle income nations will be founded on valuing choices and the accessibility of generic compounds.[17]

5. CONCLUSION

Pegylated-interferon alpha 2a 180 µg-40 kD with Ribavirin is clinically compelling and very much tolerable in chronic Hepatitis C infection and indicated great reaction to accomplish maintained virological reaction in naïve, relapser and non-responder patients.

6. CONFLICT OF INTEREST

Finances to the patients for PCR RNA test twice were provided by Hilton Pharma. The authors declare no conflict of interest.

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APPENDIX - A

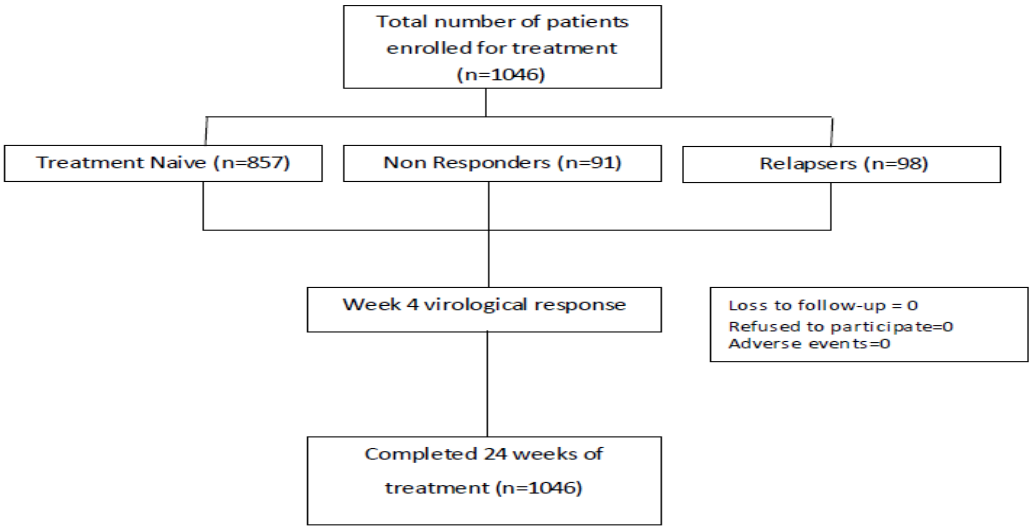

Figure.1: Flow diagram of patient enrolment and disposition of patients treated with PEG IFN α 2a+Ribavirin

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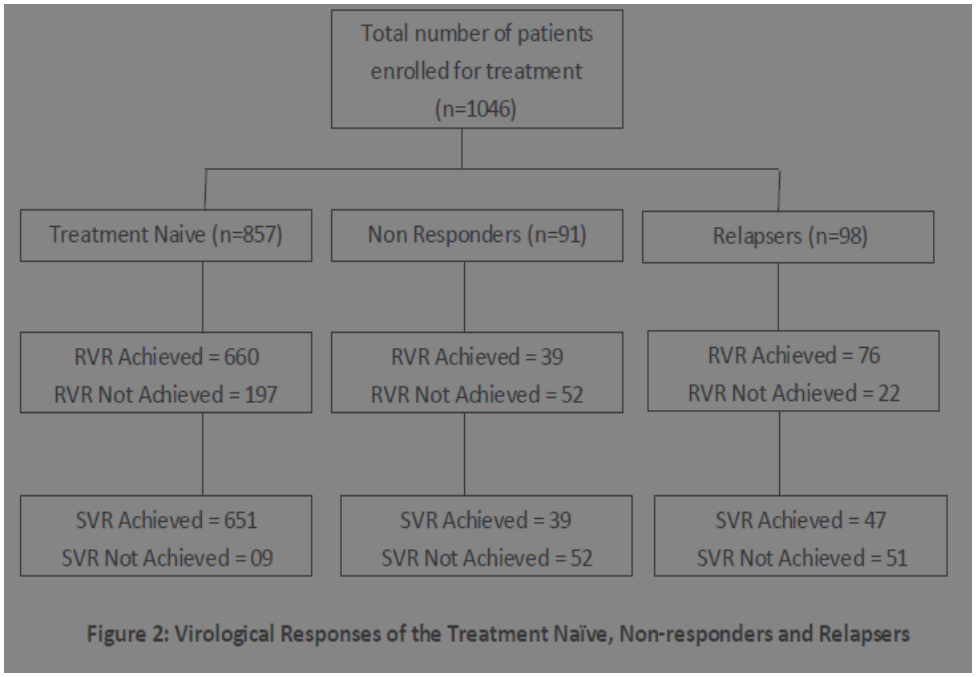

Figure 2: Virological Responses of the Treatment Naïve, Non-responders and Relapsers

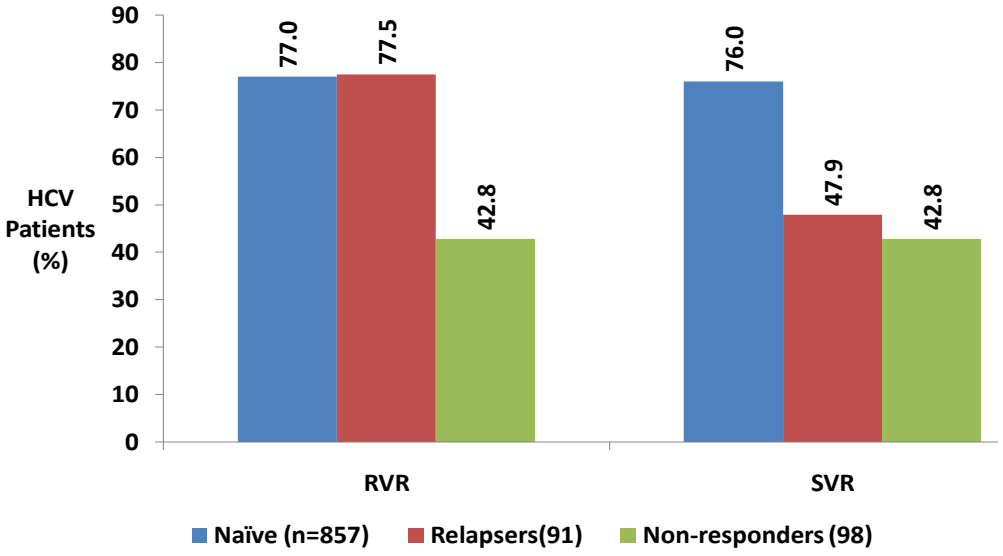

Figure.3: Virological response of the treatment naïve, non-responder, and relapser hepatitis C patients