END TREATMENT VIROLOGICAL RESPONSE IN NON-RESPONDER TO CONVENTIONAL THERAPY: USE OF PEGYLATED INTERFERONE IN HCV GENOTYPE 3 PATIENTS

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ABSTRACT

Hepatitis C virus (HCV) infection is one of all chronic liver disease which affecting the approximate 160 million population globally. As per WHO reported data, the HCV disease burden in Pakistan reaches to 4.9%.

Method: The study was conducted with 147 patients in Medical out-patient of Saidu Teaching Hospital Swat. After taking informed consent, the cross-sectional data was collected post completion of pegylated interferon alfa-2a at a dose of 180ug weekly with a weight-based dosage of ribavirin (For < 75 kg: 1000 mg/day, For > 75 kg: 1200 mg/day).

Patient included as per eligibility criteria, both gender aged 18-60years with chronic hepatitis C genotype 3 patients and non-responders to 24-week therapy of interferon and ribavirin. End of Treatment Virological Response (ETR) was observed in patients who had the end of treatment qualitative PCR. The collected data were analyzed through SPSS v. 20.0.

Results: The mean (± SD) age of HCV patients was 34.7 (± 8.38) with a range of 21-49 years. In all, 109 (74%) were males, 38 (25.9%) were females. Out of all, 28 (19%) patients were diabetic and 21 (14%) were Chronic Renal Failure. There was no patient found with ischemic heart disease and with thyroid disease.

Out of 147 patients, end treatment response was achieved in 119 (81%) patients. In this study, ETR was found signifi- cantly associated at p=0.007 with less than 40 years of age and 85% ETR was achieved in non-chronic renal failure patients (p=0.003)

Conclusion: Pegylated interferon alfa2b plus weight-based ribavirin is effective especially in the younger age population and non- chronic renal failure patients.

INTRODUCTION

Hepatitis C virus (HCV) infection is one of all chronic liver disease which has affected approximately
160 million population globally. The epidemic of newly diagnosed patient globally is around 3 to 4 million per annum from which 130 – 170 million are chronically affected. As per WHO reported data, the HCV disease burden in Pakistan reached 4.9%[1].

Through studies, it was observed that the major causes of prevailing HCV disease among Pakistani population are not only parental route but this also in- cludes non-parental transmission. The use of injection among Pakistani people is very common with the rate of 0.9-8.5 per person/year and the practice of unsteril- ized, contaminated and non-disposable injections are usually found in the society. The transmission through shaving, piercing, tattooing, intrafamilial transmission, dental or medical procedures including dialysis and blood transfusion, are also the contributing factor in spreading the disease[2].

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Prevent complication is the prime therapy goal for HCV treatment which basically accomplished by using infections' eradication. Hence, the outcomes of HCV RNA testing can measure the therapy response. The HCV RNA detection in serum or plasma can be made possible via a sensitive, qualitative or quantitative or both technique of Polymerase Chain Reaction. Re- lapser are those who showed undetectable serum HCV RNA at 12 week or at end of treatment with standard care of treatment but failed to achieve SVR whereas non-responders are those who failed to achieve decline in 2 log HCV RNA IU/ml after 12 week therapy or show detectable HCV RNA during treatment of 24 week ther- apy[5].

In 1991, Food and Drug Administration first time approved Interferon for treatment for HCV followed by a combination of ribavirin in 1998. In 2001, Pegylated Interferon approved in combination with ribavirin which showed the standard of care till 2011 with 50-70% SVR rate[6].

As per reported data in EASL, 65-82% of Geno- type 3 patient achieved SVR with pegylated IFN-a and ribavirin therapy[5] whereas the rate of ETR was reported differently in different studies. In some studies, 46% of ETR has reported among patients who failed to eradi-

cate the hepatitis C virus with monotherapy of Interferon and some studies reported 25.7% ETR. The highest ETR was found in previous studies with treatment of peg IFN is 75% in refractory patients with 69.2% in genotype 2, 75% in genotype 3 and 100% with genotype 1 and 4[7].

In this study, we determine the frequency of ETR in HCV genotype 3 patients who received pegylated interferon and ribavirin, previously non-responder to conventional interferon and ribavirin.

METHOD

The study was conducted with 147 patients in Medical out-patient of Saidu Teaching Hospital Swat. After taking informed consent, the cross-sectional data was collected post completion of pegylated interferon alfa-2a at a dose of 180ug weekly with a weight-based dosage of ribavirin (For < 75 kg: 1000 mg/day, For > 75 kg: 1200 mg/day).

Patient included as per eligibility criteria, both gender aged 18-60 years with Chronic HCV genotype 3 positive patients diagnosed via PCR and non-responders to 24-week therapy of interferon and ribavirin.

The data on diabetes mellitus, ischemic heart disease, thyroid disorder and chronic renal failure were also recorded. End Treatment virological Response (ETR) was observed in a patient who had qualitative PCR.

The Probability sampling was applied using simple random sampling technique. The sample size of the study was 147, using 75% rate of ETR with pegylated interferon and ribavirin in chronic hepatitis C genotype 3 non-responders to conventional interferon and ribavirin, with 7% of margin of error and 95% confidence level with WHO software.

The mean and standard deviation were calculated for quantitative data includes age, while frequency with percentages will be used to present qualitative facts like gender, ETR, HCV genotype. Cross-tabulation and chi-square were calculated to show the association of ETR with age and non-chronic renal failure patients. The recorded data turned into SPSS v.20 to analyze data.

RESULTS

Total 147 recruited patients were diagnosed with HCV genotype 3. All the recruited patients were non-responders to standard care of treatment.

The mean (± SD) age of HCV patients was 34.7 (± 8.38) with a range of 21-49 years old. In all, 109 (74%) were male, 38 (25.9%) were female. Out of all, 28 (19%) patients were diabetic and 21 (14%) were Chronic Renal Failure. There was no patient found with ischemic heart disease or with thyroid disease.

Out of 147 patients, end treatment response was achieved in 119 (81%) patients (see figure 1). Descriptive of age-wise stratification along with baseline characteristics are shown in table 1. Among ≤40 age group, 87.5% achieved ETR and 69.2% of > 40-year-old achieved ETR which found significantly associated at p=0.007 with less than 40 years of age.

Among Diabetic patients, 21 (75%) achieved ETR at week 24. Whereas among non-chronic renal failure patients, 85% ETR was achieved at p=0.003. Gender & other baseline variables do not show any significant association.

DISCUSSION

Un til r ecently, the standard of care for chronic hepatitis C was a combination of pegylated interferon-a and ribavirin. In registration trials, the genotype 1 infection was considered more difficult to treat, with SVR rates between 42-46% in treatment na€ıve patients, whereas genotypes 2 and 3 were con-considered more favourable, with SVR rates of 76-82%. Un til r ecently, the standard of care for chronic hepatitis C was a combination of pegylated interferon-a and ribavirin. In registration trials, the genotype 1 infection was considered more difficult to treat, with SVR rates between 42-46% in treatment- na€ıve patients, whereas genotypes 2 and 3 were con- considered more favourable, with SVR rates of 76-82%.

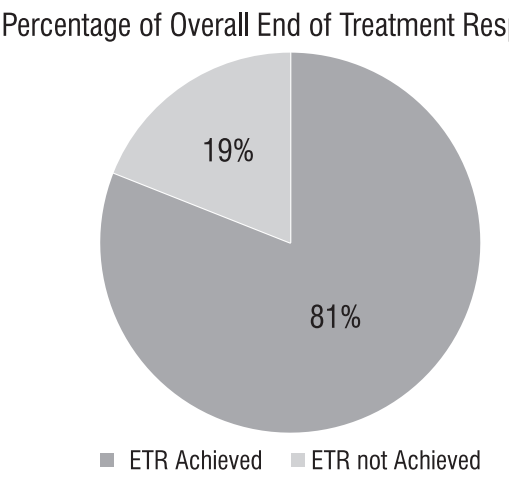

Figure 1: Overall End of Treatment Response

Table 1: Baseline Characteristics

Gender	n (%)
Female	38 (25.9)
Male	38 (25.9)
Age	
≤40	95 (64.6)
>40	52 (35.4)
Diabetes	28 (19.0)
Chronic Renal Failure	21 (14.3)

Table 2: End of Treatment Response

	ETR Not Achieved	ETR Achieved	P value
Age grouping			
≤40	12 (12.6%)	83 (87.4%)	0.007
>40	16 (30.8%)	36 (69.2%)	
Chronic Renal Failure			
Chronic renal failure patient	9(42.9%)	12 (57.1%)	0.003
Non- chronic renal failure patient	19(15.1%)	107(84.9%)	
Gender			
Female	7(18.4%)	31(81.6%)	0.909
Male	21(19.3%)	88(80.7%)	
Diabetes Miletus (DM)			
DM patient	7(25%)	21(75%)	0.373
Non- DM patient	21(17.6%)	98(82.4%)	

Our studies showed pegylated interferon and ribavirin is effective in achieving end treatment response among 81% non-responder patients to Interferon therapy. The results are comparable with the other studies published on pegylated interferon conducted in Pakistan. Aziz, Sina, et al. study showed 83.8% ETR and 87.1% SVR was achieved in treatment naïve patient[10]. Ali, Shafqut, et al. showed 80% response rate (EVR) was achieved at 12 weeks and 94% SVR at week 24[11]. Study with standard interferon therapy reported that 67.5% of patients achieved ETR and 130 (35.5%) failed to do so in a naïve patient[12]. Another study reported 74.62% end of therapy response (ETR) and 25.38% failed to eradicate the virus from their body[13]. SVR rate is nearly twice with alone pegylated interferon than standard interferon for 48-week therapy of HCV regardless of relapse rates which remain higher with pegylated interferon. Moreover, Genotype 1 patients found to be non-responders in most of the cases[14,15]. It was found from the studies that the inclusion of ribavirin decreases the relapse cases[16,17].

In this study, the proportion of greater than 40 years of age group is less than the younger population. A similar observation has found in other studies. A study published in China showed that the older age group 50-59 has the higher incidence of HCV Infection[18] whereas in Brazil the age group of 45- 60 years patients are more prevalent with more advanced disease[19].

For the management of HCV, the genotyping determination is very important. Hadziyannis et al. reported an overall SVR 48 is 63% in genotype 1 patient[20]. Krawitt et al in his study found that Genotype 2 has higher end of treatment (100%) and sustained virologic response (93%) in contrast to genotype 3 (93 and 79%, respectively)[21]. Like other studies[13], we missed observing variables such as Early Virological Response or Sustained Virological Response.

Till 2015, the pegylated interferon and ribavirin combination was considered as a standard therapy for HCV patients because of unavailability of direct-acting antivirals in Pakistan and sales data of pegylated interferon of various pharmaceuticals show that this molecule is still in use for the treatment of Chronic HCV. Genotype 1 is still considered hard to treat group in all but genotype 3 is now not considered as easy to treat genotype anymore due to increased morbidity and mortality in health care system[22]. Now, the therapy goal extended from preventing HCV complications (hepatic or extrahepatic disease) to improve quality of life and prevent onward transmission[23]. From 2018 onwards, EASL recommended interferon (IFN)-free, ribavirin-free regimen to provide efficacy with safety and tolerability inpatient HCV infected with cirrhosis and in compensated and decompensated including treatment naïve or treatment experienced. In order to treat successfully, measurement of HCV RNA should be performed in a specified time point (Baseline, 12 weeks and 24 weeks) along with the monitoring of safety profile[23].

Studies with recent updates in HCV treatment with long-term follow up can better depict the current situation of HCV.

CONCLUSION

Pegylated interferon alfa2b plus weight-based ribavirin is effective especially in the younger age population and non- chronic renal failure patients.

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