ORIGINAL ARTICLE

EARLY PREDICTABILITY OF VIROLOGICAL RESPONSE IN PATIENTS OF CHRONIC HEPATITIS-C WITH GENOTYPE-3, TREATED WITH PEGYLATED INTERFERON AND RIBAVIRIN

Mohammad Umar, **Hamamat-ul-Bushra Khaar, Sameera Abbas Khan, Masood Ahmed, Saima Ambreen, Zahid Mahmood Minhas, Madeeha Nazar**
Department of Medicine, Rawalpindi Medical College, Rawalpindi, Pakistan

Background: This study was conducted to assess the early predictability of virological response in chronic hepatitis-C patients (Genotype-3), treated with pegylated interferon alpha-2a and ribavirin with an objective of determining predictive values of Rapid Virological Response (RVR) and Early Virological Response (ETR) on Sustained Virological Response (SVR). **Method:** This cross sectional study was conducted in January 2014, at Holy Family Hospital, Rawalpindi by inclusion of 582 patients of chronic hepatitis being treated with Pegylated Interferon α 2b and ribavirin. Based on Polymerase Chain Reaction (PCR) for HCV RNA Qualitative on 4th, 12th and 24th week of treatment regimen, RVR, EVR and End treatment Response (ETR) was assessed respectively whereas 24th week post treatment PCR concluded as SVR. Effect of treatment was determined as proportions for responses in total and then compared for treatment naïve, responders and relapsers to previous conventional therapy using Chi square test. Positive and Negative Predictive Values were also calculated. **Results:** Qualitative PCR for HCV revealed that 281 (69.2%) achieved RVR where 60.3% attained SVR. PPV and NPV of RVR in study population were 67.41% and 44.45% respectively and 66.29% and 57.14% respectively for EVR. Statistically significant differences in RVR, EVR and ETR were observed in patients based on conventional treatment response. **Conclusion:** Attainment of RVR is a prospect to categorize patients appropriate for abridged treatment and this study supported the evidence that failure to achieve EVR was congruent with failure to achieve SVR.
Keywords: Hepatitis-C Virus, Rapid Virologic Response, Early Virologic Response, Positive Predictive Value, Negative Predictive Value, Pegylated Interferon, Ribavirin, conventional Interferon treatment naive, relapsers, non-repsonders

INTRODUCTION

The viral kinetics monitoring in patients of Hepatitis-C Virus (HCV) during treatment is an important management strategy that enables to predict the response. Early predictability can not only lead to improvement in patient outcomes but also cost effectiveness through optimization of therapy. The goal of therapy in patients of chronic HCV Infection is attainment of sustained virological response (SVR), depicting eradication of virus from the body, and improved histological outcome.[1] The recent protocols involve assessment of the viral load at baseline, followed by injections of Pegylated interferon administered weekly and daily ribavirin therapy prolonging from 12 weeks to one year depending on patient response.[2,3] The viral load is re-assessed at 4 and 12 weeks to see the patient's response to treatment.[4] Recent studies suggest that serum HCV RNA determined at 4 weeks of therapy is rapid virological response (RVR) that is a strong predictor of SVR, and therapy can be shortened in patient who achieves it. Similarly there are studies to validate the fact that treatment should only be continued beyond 12 weeks in patients with a 2 log 10 reductions in serum HCV RNA. These patients are said to have achieved early virological response (EVR). Discontinuation of treatment is recommended in patients who could not attain EVR, as they are not likely to benefit much from it.[5] Although many studies have been conducted to show that Pegylated Interferon with Ribavirin plays very promising role in virus eradication, however, no conclusive evidence of the applicability of RVR and EVR as predictors of sustained virological response has yet been coined.

The study was conducted with the objectives to determine the predictive values of RVR and EVR for SVR and to compare predictive values of RVR and EVR in treatment naïve, non-responder and those relapsed to conventional Interferon therapy, treated with Pegylated interferon and Ribavirin for 24 weeks. This study relates the therapy outcomes with virological responses as predictors with particular interest in RVR and EVR. Identification of treatment predictors will have direct clinical utility in selecting the potentially suitable candidates and also deciding the treatment duration in our population.

MATERIAL AND METHODS

This was a cross-sectional study conducted with 582 diagnosed patients of Hepatitis-C virus, confirmed positive on PCR for HCV RNA Qualitative (Genotype-3) who attended the Liver Clinic at Holy Family Hospital during the period of June 2008 till December 2013.The liver clinic at Holy Family Hospital is specified for patients with hepatic ailments with an average weekly turnover of 300.

Based on complete review of the patient's record conducted in January 2014, all study participants were first categorized as Treatment Naïve or treatment experienced patients to Conventional interferon therapy for 24 weeks (including Non responder and Relapser). Later they had undergone treatment with Pegylated Interferon α2 b the dose being 1.5 μg/kg body weight per week, and ribavirin at a dosage of 800 mg/day. All the patients received treatment for 24 weeks irrespective of their previous treatment status.

The patients who underwent the specified treatment regimen were included and the data of study participants was taken from comprehensive patients individual records archived as a routine procedure and was entered in structured checklists for study variables for each study patient. PCR for HCV RNA Qualitative had been performed for viral measurements at completion of 4th week (RVR), 12th week (EVR), 24th week (ETR) and after 24 weeks of treatment completion (SVR). All patients not complying with the treatment or developed any complication based on protocol investigations that lead to termination of treatment were excluded from the study. The following operational definitions were used in this study:

RVR, (Rapid Virological Response): PCR done at 4 weeks of regimen and RVR positives are those who tested negative for HCV RNA by PCR at 4weeks and vice versa.

EVR, Early Virological Response: PCR done at 12 weeks of regimen and EVR positives are those who tested negative for HCV RNA by PCR (or/and ≥2 log reduction) at 12 weeks and vice versa.

ETR, End Treatment Response: PCR done at 24 weeks of therapy and ETR positives are those who tested negative for HCV RNA by PCR and vice versa.

SVR, Sustained Viral Response: Undetectable serum HCV RNA, after 24 weeks of post treatment.

All the data was entered and analyzed using PASW statistics (version 19. SPSS). Frequencies and Proportions were calculated for categorical variables like gender, pretreatment status and whether they attained RVR, EVR, ETR and SVR. To determine any associations of pretreatment status with virological responses after pegylated Interferon with Ribavarin, Chi square test at 5% level of significance was applied and also to validate the homogeneity of the baseline characteristics of the study participants.

The predictive values of RVR and EVR for SVR were calculated using positive and Negative Predictive values. Positive predictive value (PPV) was taken as the probability of achieving SVR in patients who tested positive RVR and EVR whereas Negative predictive value (NPV) was probability of not achieving SVR in those who tested negative for RVR and EVR.

Limited availability of all viral responses concurrently in study participants restricted our predictive analysis to variable groups of patients. The patients for whom PCR after baseline was not available at any stage (i.e., after 4th, 12th week of treatment or 24 weeks post treatment) he/she was excluded from the analysis of positive and negative predictive values for PCR of that specific time (RVR or EVR) for SVR. For example if a patient had got her/his RVR and SVR done but not EVR, that patient was included only in analysis of PPV and NPV of RVR for SVR but excluded for predictive values of EVR and vice versa. Hence the study participants were not excluded based on absence of RVR but were included for Predictive values of EVR if their EVR and SVR was available. Predictive values of ETR for SVR were not calculated.

RESULTS

A total 582 patients, 416 (71.5%) treatment naïve and 166 (28.5%) conventional treatment experienced patients fulfilled the selection criteria. Amongst all, 296 (50.9%) were males whereas 286 (49.1%) were females (P-value 0.22). Mean age of all participants was 40.43±9.622 years. The mean ages based on treatment exhibited no variability based on age (p-value 0.23). Majority of the participants (83.7%) were married. Chi squared test with p-values >0.05 demonstrated the homogeneity of these baseline characteristics in study participants based on the status of their previous treatment exposure.

The virological responses recorded for study participants are exhibited in figure-1. Based on their previous treatment status, i.e., treatment naïve, non-responders or relapsers, the distribution of virological characteristics of the patients are given in table-1. At 4th week of therapy, 406 /582 (69.8%) patients went for PCR for HCV RNA.284/406 (70.0%) were Treatment Naïve and 122 (30.0%) were Treatment Experienced.

Among them, 281 (69.2%) were RVR positive. RVR was observed in 74.5%, 55.8% and 75% in each group of treatment naïve, non-responder

and relapsers to previous therapy respectively (*p*=0.003).

Only 107 (18.4%) patients had both RVR and SVR done. PPV and NPV were observed to be 67.41% and 44.45%. The PPV were 72.97%, 37.5% and 42.8% in treatment naïve, non-responder and relapser to previous therapy respectively. The NPV was 40.0%, 50.0% and 100% in treatment naïve, non-responder and relapsers (Figure-2). The SVR rates 56.1% (n=60) who had achieved RVR were not significantly different from 9.3% (n=10) of patients who had not achieved RVR (chi=0.931, *p*-value=0.33)

At 12th week of therapy, 356/582 (61.2%) patients who went for PCR for HCV RNA.251 (70.5%) were Treatment Naïve and 105 (29.5%) were Treatment Experienced.

Among them, 245 (68.8%) had negative PCR for HCV RNA.EVR was observed in 71.7%, 59.1% and 83.3% within treatment naïve, non-responder and relapser to previous therapy respectively (*p*=0.045).

Only 103/582 (17.7%) patients had both EVR and SVR. PPV and NPV were observed to be 66.29% and 57.14%.The PPV were 68.49%, 55.55% and 57.1% in treatment naïve, non-responder to conventional interferon and relapser to previous therapy patients. The NPV was 54.54% and 100% in treatment naïve and non-responder to previous therapy respectively (Figure-3). The NPV could not be calculated in relapsers as none of the patient was observed to be non EVR and non SVR at the same time (unavailability of true negatives). The SVR rates 57.3% (n=59) who had achieved EVR were not significantly different from those 5.8% (n=6) of patients who had not attained EVR (chi=2.854, *p*-value=0.09).

At 24th week of therapy, 352 /582 (60.5%) patients went for PCR for HCV RNA. 265 (75.3%) were Treatment Naïve and 87 (24.8 .0%) were Treatment Experienced. Among them, 261 (74.1%) were ETR positive. ETR was observed in 77.7%, 59.3% and 71.4% within treatment naïve, non-responder and relapsers respectively (*p*=0.013).

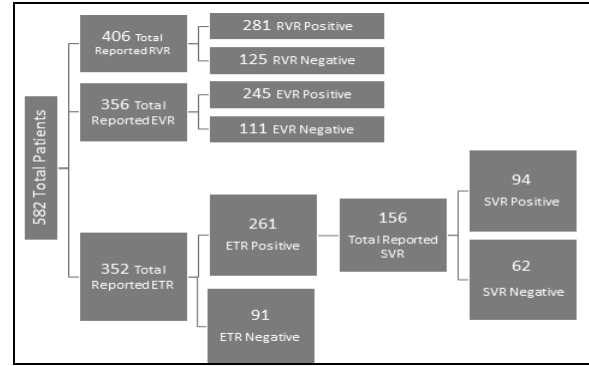Only 156 (26.8%) patients had both ETR and SVR done. SVR rate was found to be 60.3% in all participants.

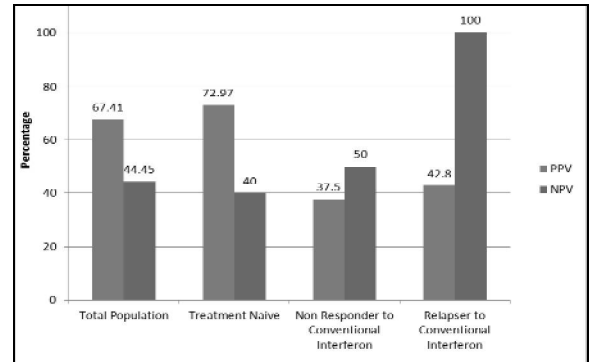**Figure-1:Virological Responses of the study participants**
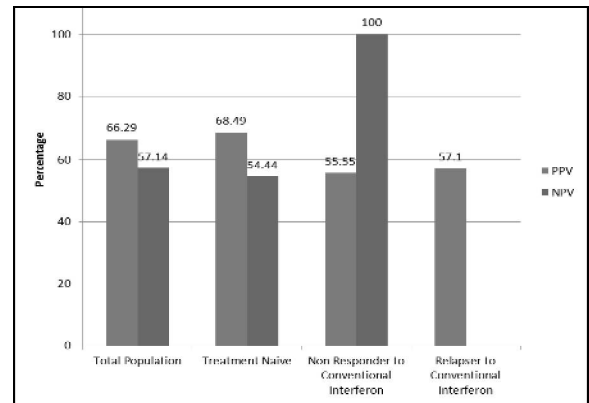

Figure 2. Predictive Values of RVR

Figure 3. Predictive Values of EVR

Table-1: Virological Characteristics of Patients

Virological responses		n (%)	Treatment Naïve f (%)	Treatment experienced		χ -statistic *p*-values
				Non Responders f (%)	Relapsers f (%)	
RVR N=406	Achieved	281 (100%)	209 (74.4%)	57 (20.3%)	15 (5.3%)	11.37
	Not achieved	125 (100%)	75 (60%)	45 (36%)	5 (4%)	**0.003**
EVR N=356	Achieved	245 (100%)	180 (73.5%)	55 (22.4%)	10 (4.1%)	6.21
	Not achieved	125 (100%)	71 (64%)	38 (34.2%)	2 (1.8%)	0.04*
ETR N=352	Achieved	261 (100%)	206 (78.9%)	35 (13.4%)	20 (7.7%)	8.65
	Not achieved	91 (100%)	59 (64.8%)	24 (26.4%)	8 (8.8%)	**0.01***
SVR N=182	Achieved	110 (100%)	92 (83.3%)	8 (7.3%)	10 (9.1%)	4.40
	Not achieved	72 (100%)	51 (70.8%)	8 (11.1%)	13 (18.1%)	**0.11**

N=patients with respective virological response, n=total number of participants in each group, f=frequency,%=percentages *statistically significant, ** highly statistically significant

DISCUSSION

Our study, conducted in a large patient population of 582 patients infected with HCV includes both the Treatment Naïve (N=416) and 166 Treatment experienced patients (Relapsers and Non responders to previous conventional). The results of this study demonstrate that Rapid virological Response observed in 65.4% of the total population, is highly predictive of attaining of SVR. PPV of 72.97% is highest in treatment Naïve group. Interestingly the NPV in Relapser to previous therapy is 100%. Conversely, failure to achieve EVR, observed in 31.2% of overall population is observed to be a strong predictor of non-SVR, the highest NPV of 100% in non-responder to previous therapy.

Our SVR is not very different to a meta-analysis done in 2008 on genotype 2 and 3 with reported SVR of 745 and 68% respectively.[6] This study has very high SVR Rates as compared to 7.81% in males and 8.15% in females as was done in a study in Baluchistan.[7] Though it is also done in Pakistan with almost similar conditions and problems. This study has far lower SVR as was reported as 80% done in genotype-2 patients' specifically[8] and another showing SVR of 75%[9] or 80%.[10] Previously research conducted on HCV infected patients with genotype-2 and 3, exhibited SVR ranging from 79–84 treated for 24–48 weeks.[11–13]

Our study replicates the findings as done by Mangia *et al*[14] and Delgard *et al*[15] showing high RVR in general population from 31–100%, and PPV ranging from 69–100%.[16] These all researches were done based on Peg interferon treatment based on all genotypes separately; however, our study catered genotype-3 patients specifically, to avoid confounding effect. We also had a major shift in calculating the NPV of 100% in relapser to previous therapy group and could not compare with any preexisting study.

This study supports the evidence that "failure to attain EVR is a consistent indicator of failure to attain SVR" as was concluded by Fred P[16], Davis *et al*[17], Sanaa *et al*[18], Hasan F *et al*[19], showing 26–60% non EVR in general population, PPV of 36–100% and NPV, of 96–100%.

Non-reporting of virological responses was the major limitation which compromised the validity of the study. Only 27% of the study participants reported all the virological responses till SVR but still inclusion of an enormous sample still allowed determination of attainment of RVR, EVR and ETR in variable groups with ample size.

However this study can play a role in opening pavements for further research that can contribute substantially in defining optimal treatment duration and predictors of SVR in patients with HCV.

CONCLUSIONS

The NPV of RVR (no RVR and no SVR) was generally low except in relapser to previous therapy and thus may be considered to stop treatment in this group, however further studies are recommended to augment the findings. Achievement of RVR epitomizes a prospect in classifying patients apposite for abridged treatment duration and can also contribute in motivating patients resulting in better compliance.

Conflict Of Interest: None

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Address for Correspondence:

Dr. Mohammad Umar, Department of Medicine, Rawalpindi Medical College, Rawalpindi, Pakistan
Cell: +92-333-5118283, +92-300-9553830
Email: researchunitrmc@gmail.com