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Predictors of Sustained Virological Response (SVR) to Pegylated Interferon A-2A and Ribavirin Combination Therapy in Patients with Chronic Hepatitis C

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Abstract:
Background: *Treatment of patients with chronic hepatitis C virus (HCV) infection remains suboptimal, with the current pegylated interferon (PEG-IFN) and ribavirin combination therapy providing sustained virological response (SVR) rates of 54-63%. A number of factors have been shown to be predictive of a sustained virological response. The aim of this study was to identify clinical and laboratory findings that can predict nonresponse to this treatment.* ***Methods:*** *A total of 64 patients with chronic HCV infection were treated with peginterferon α -2a and ribavirin from July 2004 to December 2011. To ensure comparability regarding peginterferon therapies, patients were analysed by several baseline variables. Univariate and multivariate logistic regression analyses were used to determine the effect of baseline variables and treatment modality on SVR.s.* ***Results:*** *Out of 64 patients studied (mean age 39.55±9.71 years; 50 male), 37/64 (57.81%) had an early virological response (EVR) and 46/64 (71.87%) had a SVR. On univariate analysis, absence of EVR, high baseline viral load, age >40 years, male sex and BMI>25kg/m2 were associated with lack of SVR. On multivariate analysis, EVR, baseline viral load, age and BMI>25kg/m2 were significant independent predictors of SVR.* ***Conclusion:*** *Absence of EVR, high baseline viral load, age >40 years and BMI>25kg/m2 are independent predictors of absence of SVR in patients with chronic HCV infection receiving PEG-IFN and ribavirin combination treatment.*
Keywords: *Hepatitis C virus (HCV), peginterferon and ribavirin, Sustained virological response (SVR), predictors.*

I. Introduction

Chronic infection with hepatitis C virus (HCV) is responsible for substantial morbidity and mortality worldwide1. Approximately 130 million people suffering from chronic hepatitis C are at risk of long-term complications such as liver cirrhosis and hepatocellular carcinoma. [1,2] Treatment with peginterferon plus ribavirin (RBV) is the current standard of care for patients with chronic hepatitis C. Data from pivotal trials demonstrated rates of sustained virological response (SVR) in 40–50% of genotype 1infected and in about 70–80% of genotype 2 and 3 infected individuals3. Despite improvements in treatment modalities that have increased SVR rates, treating chronic hepatitis C remains a challenge in certain populations such as those patients infected with hepatitis C virus (HCV) genotype 1, with high viral load (> 2 million copies/ml), cirrhosis etc.

Given the significant side-effects and healthcare costs associated with interferon therapies, identifying patients who are less likely to respond is highly desirable. Studies have demonstrated that an early virological

response is predictive of a SVR4. Patients who failed to achieve an early virologic response (EVR) had a lower likelihood of achieving SVR with an additional 12-36 weeks of treatment. EVR was found to be the single best predictor of SVR in HCV infected patients treated with peginterferon alfa-2a plus ribavirin.

Baseline factors that positively predict SVR to peginterferon alfa-2a plus ribavirin include HCV genotype (other than type 1), age (≤40 years), body weight (≤75 kg), lower baseline viral load (< 2 million copies/ml) and absence of cirrhosis/bridging fibrosis5,6. Identifying factors that predict EVR and SVR should further refine chronic hepatitis C virus treatment regimens. Recent evidence suggests that changes in haematologic parameters may be associated with virologic response to therapy7. Patients with a null response to peginterferon alfa-2a plus ribavirin demonstrated a smaller reduction in haematologic parameters than patients who achieved full virologic response, suggesting a systemic resistance to treatment.

Available data on the factors associated with achieving EVR and SVR in HCV infected patients treated with a standard regimen, consisting of peginterferon alfa-2a 180 µg/week plus ribavirin daily for 24- 48 weeks, is limited. Identifying these factors may provide information to optimize and/or individualize the treatment of HCV infected patients, thus improving antiviral response. We, therefore, analysed the data, examined the baseline and on-treatment factors associated with EVR and SVR to treatment with peginterferon alfa-2a plus ribavirin combination therapy in Bangladesh.

II. Methodology

Study population: This was a prospective study. The period of study was from July 2004 to December 2011 and place of study was department of Gastroenterology, BSMMU. All patients had detectable anti-HCV antibody and HCV RNA PCR in serum with normal or elevated ALT. HCV genotyping was performed by HCV-PCR reverse hybridisation (INNOLIPA) technique. All laboratory tests were performed prior to starting therapy. Patients were excluded from the study who had 1) HCV-related decompensated cirrhosis; defined as ascites, portosystemic encephalopathy, hepatorenal syndrome, hepatocellular carcinoma (HCC) and recurrent variceal bleed,2) concomitant HBV, HDV or HIV infection, 3) major psychiatric illness, 4) hemoglobin < 8 g/dL, neutrophil count <1500 cells/mL , platelet count < 85,000/dL (4), 5) serum creatinine >1.5mg/dL, 6) concomitant metabolic or autoimmune liver disease,7) post liver transplant patients, 8) pregnancy, 9) uncontrolled seizures, 10) severe heart disease or other absolute contraindications for the treatment. A total of 64 patients were selected for this study. Out of 64, thirty four(34) patients had genotype 3(a and b) infections,10 patients had 3 and 4 mixed , 8 patients had genotype 2b, 8 patients had genotype 1and 4 patients had genotype 4infections.All patients had received peginterferon α -2a (Inj. Pegasys; Roche Bangladesh LTD) 180 µg/week subcutaneously along with ribavirin (800mg in case of genotypes 2 or 3 and 1000-1200 mg in case of genotypes 1 and 4 infections according to body weight).

Assessment of response to antiviral therapy: The therapeutic responses were assessed as follows: (i) early virological response (EVR) defined as ≥ 2-log10 decrease from baseline in HCV RNA after 12 weeks therapy, (ii) end of treatment response (ETR) defined as undetectable HCV RNA in serum at the completion of treatment which was assessed at 24 and 48 weeks depending on the duration of treatment (in case of genotype 2 and 3 infections , it was at 24 weeks and in case of genotype 1 and 4 infections , it was at 48 weeks) (iii) sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after completion of antiviral therapy.

Monitoring and follow-up of patients: Patients were assessed in our follow up clinic, initially 2 weekly for 1 month then 4 weeklies until the end of treatment. After completion of treatment follow-up visits were conducted at weeks 12 and 24. Physical signs for hepatic decompensation, adverse effects of antiviral therapy, complete blood count and ALT were recorded on each visit. ALT and HCV RNA were tested at weeks 12, at end of treatment (24 or 24 weeks according to genotypes) and 24 weeks after completion of treatment. Data were analysed to determine the predictors of SVR outcome.

Statistical Analysis: Data were analysed using SPSS for windows, version 16.0(SPSS Inc, Chicago, Illinois, USA). Results were presented as mean ± standard deviation for quantitative variables and frequencies (percentages) for qualitative variables. Age, gender, BMI, baseline hemoglobin, total leukocyte count (TLC), platelet count, prothrombin time (PT), total bilirubin, albumin, alanine amino-transaminase (ALT), and EVR were considered potential predicting factors for SVR. To assess the association between SVR and categorical variables, the Chi-square or Fisher exact test was used, where appropriate. Further, to assess the difference in proportions of the SVR and non-SVR groups and quantitative variables, the independent sample t-test was used.

To evaluate potential predicting factors for SVR, univariate and multivariate logistic regression analyses were performed. Factors that were significant in the univariate analysis were used in the multiple logistic regression

models. Variables those are significant at 10% level of significance are considered as predictor variables while SVR is the Predicted variable.

III. Result

This observational cross-sectional study was conducted in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. From July 2004 to December 2011, 72 patients received anti-viral therapy for HCV. Out of 72, 64 patients fulfilled the eligibility criteria and were treated with peginterferon and ribavirin. Over all, there were 50 (78%) male and 14(22%) female patients; the mean age of the patients was 39.55 ±9.71 years. The mean body mass index (BMI) was 23.54±2.41 kg/m2. Other characteristics and baseline laboratory parameters of patients are described in Table 1

Table1: Baseline characteristics of study subjects.

Parameter	Value	
	N	%
Gender		
Male	50	78.0
Female	14	22.0
Genotypes		
3(a, b)	34	
1(a, b)	8	
3 and 4 mixed	10	
2b	8	
4	4	
Fatty liver	6	9.37
Cirrhosis	4	6.24
Baseline virological load		
High virological load (>2 million copies/ml)	10	
Low virological load (<2million copies/ml)	24	
	Mean±SD	
Age (in Year)	39.55±9.71	
BMI (kg/m^2)	23.54±2.41)	
Hemoglobin(mg/dl)	12.94±1.67	
TLC count$x10^9/L$	6.36±1.98	
Platelet count$x10^9/L$	220.45±66.67	
Prothombin time	13.71±2.54	
Total bilirubin(mg/dL)	0.97±.33	
ALT(IU/mL)	86.78±23.87	
Albumin(mg/dL)	3.67±0.43	

When the demographic features and baseline characteristics were compared between patients who had and who had not achieved SVR there was statistically significant difference observed in the age, BMI and baseline viral load. On univariate analysis, younger age, female gender, lower BMI, lower baseline viral load and achievement of EVR were found to be significant predicting factors for SVR [**Table 2]**.

On multivariate logistic regression analysis, younger age, lower BMI, lower baseline viral load and EVR were found to be significant positive predicting factors for SVR [**Table 3].** Although sex was significant in bi- variate case, it was insignificant in multiple case.

Table 2: Results of Bi-variate Logistic Regression: (Logistic Regressions fitted for SVR vs Age, SVR vs BMI, SVR vs Fatty Liver, SVR vs Sex separately)

Parameter	SVR (n=46)	Non-SVR (n=18)	Odds Ratio	95% C.I(L.L,H.L)	P -value
Age	36.78(8.02)	46.61(10.31)	1.122	(1.044, 1.206)	0.002*
Sex(Female)	26.09%	5.56%	0.149	(0.018,1.240)	0.078**
BMI	22.77(1.67)	25.50(2.92)	1.727	(1.259,2.371)	0.001*
Fatty Liver	0(0%)	6(33.33%)	0.00	(0.00,0.00)	0.999
Cirrhosis	0(0%)	4(22.22%)	0.00	(0.00,0.00)	0.999

Genotype					
3(a,b)	64.70%	35.3%	1.00	(0.621,1.609)	1.000
Non 3	100%	------			
Viral load (<2 million copies/ml)	97%	50%	22.00	(4.053,119.426)	0.000*
EVR	57.81	47.19	32.889	(6.376,169.645)	0.000*
ALT	84.74±50.11	89.96±32.16	0.99	(0.98,1.009)	0.62
Prothrombin time	13.38±1.33	14.16±6.43	0.95	(0.83,1.08)	0.49
Albumin	3.49±0.47	3.48±0.50	1.05	(0.38,2.92)	0.91

*Indicates the corresponding variables are significant at 5% level of significance
** Indicates the corresponding variable is significant at 10% level of significance

Table 3: Results of Multiple Logistic Regression of variables associated with SVR (Here we fit Logistic Regression for SVR vs Age, BMI, Viral Load, EVR, Sex)

Parameter	Odds Ratio	95% C.I (L.L,H.L)	P -value
Age	1.095	(0.988,1.213)	**0.083****
BMI	1.437	(0.967,2.137)	**0.073****
Viral Load (<2 million)	24.575	(1.954,309.043)	**0.013***
EVR	8.645	(1.184,63.138)	**0.033***
Sex	0.144	(0.005,4.396)	**0.267**

IV. Discussion

This well-documented study of patients treated with peginterferon alpha -2a plus ribavirin in clinical practice identified a number of independent positive and negative predictors of SVR including HCV genotype, baseline viral load, age, gender, EVR, BMI >25 kg/m2, presense of fatty liver and cirrhosis. Many of these factors have been identified previously under study conditions, and this study confirms their relevance in daily clinical practice.

In our Study, the predictive factors for absence of SVR included absence of EVR, high baseline viral load, older age, female gender and BMI >25 kg/m2. In this study, absence of EVR was the most significant predictor associated with an absence of SVR. Previous studies have reported EVR at 12 weeks to be a significant predictor of SVR4,7. In a study of 511 patients, Davis et al found that all subjects who failed to achieve EVR at 12 weeks also failed to achieve SVR8.

Steatosis has previously been found to be an independent predictor of poor response to therapy in patietns with chronic HCV infection9-10. One suggested explanation is that the pharmacodynamics of interferon in patients with steatosis may be altered leading to a poor reponse in patients with chronic HCV infection. Also it is possible that by targeting steatosis we may be able to improve the SVR patients with chronic HCV infection. In pivotal trials of peginterferon plus ribavirin, the presence of cirrhosis was associated with a lower rate of SVR and absence of cirrhosis has been shown to be an independent positive predictor of SVR11-12. In this study, although all the patients with steatosis(n=6) and cirrhosis(n=4) did not achieve SVR which is similar to the findings of other studies,these predictors were not found to be statistically significant on univariate and multivariate logistic regression analyses.

In previous studies,other host factors such as old age, male gender and presence of obesity have been correlated with a poor response6,7. In a study of 253 patients in Toronto, obesity(BMI=30Kg/m2) was an independent negative predictor of response to hepatitis C treatment.13 . In the current study, age greater than 40 years, male gender, BMI > 25kg /m2 were significant negative predictive variables for SVR.

Viral factors that have also been associated with poor response rates include HCV genotype and pre-treatment viral load. Several studies have shown genotype 1 to be a significant predictor of non-response to therapy14. HCV genotype 2 and 3 infection and low baseline viral load are important and well-known positive predictors of response in chronic hepatitis C identified in a number of clinical studies15,16.In our study genotype 3(a and b) had poor response(64.70%) in comparison with other studies who reported response rate of 70-80%.This poor response could be due to selection bias or this may be due to the fact that genotype 3 patients of Bangladesh are poor responders.On the other hand, while response rate of genotype 1 and 4 are reported to be 40-50%, we got response rate of 100%. As the sample size was very small, it is difficult to comment regarding the cause of this favourable response.In our study, high baseline viral load was also a negative predictor for SVR.

No association was observed with haemogram, albumin, prothombin time and ALT level.

There were several limitations of this study. We diagnosed fatty liver and cirrhosis by ultrasonogram, liver biopsy was not done. So histological condition was not properly evaluated.Also,number of patients in this study was small. So a further study incorporating a larger population is necessary to validate this results.

Limitations of the study

The present study was conducted in a very short period due to time constraints limitations. The small sample size was also a limitation of the present study.

V. Conclusion

Absence of EVR, high baseline viral load, older age, BMI >25 kg/m2 are independent negative predictors of sustained viral response rates of patients with chronic HCV infection receiving peginterferon α-2a and ribavirin combination treatment in Bangladesh.

VI. Recommendation

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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