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Factors Influencing the Response of Sofosbuvir and Ribavirin Therapy in Chronic Hepatitis C Patient, In Punjab, Pakistan

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ABSTRACT

Background & Aims: Chronic Hepatitis C is a viral infection that affects the human liver. In past, pegylated interferon with ribavirin was the only option to treat it. But now, Sofosbuvir appeared as a miracle drug. The objective of this study was to determine pertinent factors influencing the response of Sofosbuvir and Ribavirin Therapy in chronic Hepatitis C patients. **Methodology:** Patients with chronic hepatitis C were treated with Sofosbuvir plus ribavirin for 24 weeks with routine follow up. The response to therapy was checked using PCR test at 4and 24 weeks of treatment, called RVR and ETR, respectively. Pertinent factors influencing the response to therapy were analyzed descriptively and analytically using SPSS version 15. Bivariate analysis was applied to determine the significant association of different factors with RVR. **Results:** Sample size was n=100 patients, out of which, 48 (48%) were males and 52 (52%) were females. Mean age of patients was 45.68±10.71 years. RVR was found in 91 (91%) cases while ETR in 95 (95%) cases. 88% cases had genotype 3a.Different factors were compared with RVR, however, only the ALT normalization in first month of treatment was found statistically significant (p=0.003). **Conclusion**: The response of Chronic Hepatitis C patients to Sofosbuvir plus Ribavirin therapy, at both RVR and ETR stages, was found magical, 91% and 95% respectively. Genotype 3a was the predominant type of virus in the studied patients. One pertinent factor, ALT normalization in 1st month of treatment was found significantly associated with RVR.

INTRODUCTION

Chronic Hepatitis C is a global problem, wherein about 8-10 million patients from Pakistan are infected[1-2]. In past, pegylated interferon with ribavirin was the only but less beneficial option to treat it[3]. Now, several Direct Acting Antivirals (DAA)[4] are available, among which Sofosbuvir is a miracle drug[5]. Sofosbuvir is Hepatitis C virus (HCV) Polymerase Inhibitor, that is given orally at the dose of 400mg once daily along with Ribavirin[6]. The responses to this drug are excellent[7-8].The response of therapy is measured in terms of Rapid Virological Response (RVR), defined as negative HCV-Polymerase chain reaction (PCR) test at week 4 of treatment; End Treatment Response (ETR), defined as negative HCV-PCR at the end of treatment and Sustained Virological response (SVR), defined as negative HCV-PCR 6 months after completion of therapy[9]. Factors associated with poor response to interferon therapy are known and include age, obesity, prior interferon therapy, presence of cirrhosis and unfavorable genotype[10]. Studies to evaluate such factors which could influence the response to new emerging therapy like sofosbuvir are scarce, which promoted the authors to undertake this study.

The objective of this study was to determine factors influencing response of Sofosbuvir and Ribavirin Therapy in chronic Hepatitis C patients.

METHODOLOGY

A prospective analysis of patients with chronic hepatitis C, who were treated with Sofosbuvir and ribavirin from January 2015 to December 2015 at Liver Clinic, 250 Shadman, Lahore, Pakistan, was done. All chronic hepatitis C patients aged 5 years and above with positive HCVRNA were included in the study. Patients with decompensated liver disease and child pug score >12, pregnancy, HIV and/or HBV co-infection and renal dysfunction with creatinine clearance <50 mL /minute were excluded. Both patients with cirrhosis and without cirrhosis were included. The history of diabetes mellitus and prior interferon therapy was also noted. All patients were given combination of sofosbuvir and ribavirin for 24 weeks. Sofosbuvir was given in a dose of 400mgdaily while ribavirinwas given 1000 mg in divided doses for patients weighing less than 70 kg and 1200 mg for those weighing 70 kg and above[7]. Both drugs were started and stopped at the same time. All patients were assessed in an outpatient basis for safety, tolerance, and efficacy at every month during treatment. Biochemical and hematological testing

was done every 4 weeks for whole 24 week therapy, and serum HCV-RNA testing was performed at week 4 and at end of treatment to see for RVR and ETR respectively.

During data interpretation, normal values for ALT used as <30 IU/L for men and <19 IU/L for women,[11], while normal range of total serum bilirubin was taken as 0.2–1.2 mg/dL[3].The descriptive analysis of the collected data was done by SPSS version 15. Gender, History of diabetes mellitus, Prior interferon therapy, HCV genotyping, Liver cirrhosis, decrease in Hb> 2 g/dl in 1st month of treatment, ALT normalization, rise in Bilirubin in 1st month of treatment, RVR & ETR were the qualitative variables, while age, weight, baseline Hb, baseline ALT, baseline serum bilirubin, Hb at week 4 of treatment, ALT at week 4 of treatment and Serum bilirubin at week 4 of treatment were quantitative variables. Investigational data was interpreted in negative or positive values. For quantitative variables, means and standard deviations were calculated and for qualitative variables, frequencies and percentages were computed. In order to determine the significant relation of different factors with RVR, bivariate analysis was performed. For chi-square test, a p-value of equal to or less than 0.05 was taken as significant. Odd ratio with 95% confidence intervals (CI) was also calculated for each association.

RESULTS

A total of 100 cases were treated with a combination of Sofosbuvir and ribavirin. Forty-eight cases (48%) were male and 52 (52%) female. Age ranged from 22-70 years, with a mean value of 45.68 + 10.71 years (Table 1). During analysis, importantly, it was observed that out of 100 patients, 91(91%) achieved RVR and 95(95%) achieved ETR. Moreover, in order to analyze the significant factors which affect the RVR, chi-square analysis was performed. Different factors like the gender of patients, age, weight, history of diabetes, history of prior interferon therapy, HCV Genotyping, presence of Liver cirrhosis, decrease in Hb, ALT normalization and rise in serum bilirubin during first month of treatment were studied (Table 2). Out of which only ALT normalization in first month of treatment was found significant. Among patients who had ALT normalization in first month of treatment, 100% (49 out of 49) achieved RVR, while among those who had no ALT normalization in first month of treatment, 82.35% (42 out of 51) achieved RVR. This association was statistically significant (p=0.003). This is an important finding which also manifests that 18% chance of achieving RVR increases with ALT normalization at week 4

of therapy. However, the association of RVR with other factors including gender of patients, age, weight, history of diabetes, history of prior interferon therapy, HCV Genotyping, presence of Liver cirrhosis, decrease in Hb and rise in serum bilirubin during first month of treatment was statistically not significant (Table 2).

Table 1: Descriptive Statistics of Quantitative Variables (n=100)

Quantitative variables	Minimum	Maximum	Mean± SD
Age (years)	22	70	45.68±10.71
Weight (Kg)	47	113	73.38±12.80
Hb at start of treatment(g/dl)	8.9	17.3	12.78±1.86
ALT at start of treatment(IU/L)	12	623	84.49±84.73
Serum Bilirubin at start of treatment(mg/dl)	0.2	4.6	1.02±0.77
Hb at week4 of treatment(g/dl)	6.5	14.4	10.96±1.60
ALT at week4 of treatment(IU/L)	11	122	31.28±19.31
Serum Bilirubin at week4 of treatment(mg/dl)	0.1	5.5	0.98±0.69

Hb=Hemoglobin; ALT= Alanine Aminotransferase; WBC=White Blood Cells

Table 2: Comparison of factors associated with Rapid Virological Response(n=100)

Predictors/Categories	RVR		Total	p-value	Odd ratio with 95% Confidence interval
	Achieved	Not-achieved			
Gender: Male	42 (46.2%)	6 (66.7%)	48	0.305	0.429 (0.101-1.820)
Female	49 (53.8%)	3 (33.3%)	52		
Age (years**) :** <45	35 (38.5%)	5 (55.6%)	40	0.478	2.00 (0.503-7.957)
>45	56 (61.5%)	4 (44.4%)	60		
Weight (Kg) : <70	30 (33.0%)	5 (55.6%)	35	0.271	2.542 (0.636-10.159)
>70	61 (67.0%)	4 (44.4%)	65		
History of Diabetes: Yes	27 (29.7%)	0 (0%)	27	0.108	0.877 (0.804-0.955)
No	64 (70.3%)	9 (100%)	73		
History of Prior Interferon Therapy: Yes	42 (46.2%)	3 (33.3%)	45	0.508	1.714 (0.404-7.278)
No	49 (53.8%)	6 (66.7%)	55		
HCV Genotyping: 3a	79 (86.8%)	9 (100%)	88	0.595	0.898 (0.837-0.963)
Non-3a	12 (13.2%)	0 (0%)	12		
Liver status: Non-Cirrhosis	46	7 (77.8%)	53	0.167	3.424 (0.675-17.376)

Cirrhosis	(50.5%) 45 (49.5%)	2 (22.2%)	47		
Decrease in Hb> 2g/dl in 1st month of treatment: Yes No	39 (42.9%) 52 (57.1%)	5 (55.6%) 4 (44.4%)	44 56	0.501	0.600 (0.151-2.382)
ALT normalization in 1st month of treatment: Yes No	49 (53.8%) 42 (46.2%)	0 (0%) 9 (100%)	49 51	0.003	0.824 (0.725-0.935)
Rise in Bilirubin in 1st month of treatment: Yes No	39 (42.9%) 52 (57.1%)	3 (33.3%) 6 (66.7%)	42 58	0.730	1.500 (0.353-6.374)

RVR= Rapid Virological response;Hb=Hemoglobin; ALT= Alanine Aminotransferase; HCV= Hepatitis C virus

DISCUSSION

Various baseline factors have been studied in the past for their predictive value regarding response to Interferon plus ribavirin therapy[12-13], reportedly as such not local as well as international studies for sofosbuvir plus ribavirin is found in literature.

In comparison to interferon plus ribavirin therapy, where a big proportion of patients were lost to follow due to compliance and adverse events[14], here in our study follow-upby the patients was 100% due to high response rate and low adverse reactions of sofosbuvir and ribavirin therapy. For the same combination of Sofosbuvir plus ribavirin therapy, the compliance rate was 99% in its original trial[5].Hence, the compliance of the patients was good in our peoples as well.

Unlike interferon[12-13],the response to sofosbuvir plus ribavirin therapy was not affected by host baseline factors, such as age, weight and extent of liver disease as well as viral baseline factors such as HCV genotype in our study.

In this study, ALT normalization in first month of therapy was predictive of loss of HCV viremia i.e. achievement of RVR as determined by HCV-PCR testing. This may point the worth of the so cheap testing of ALT that may escape the need of an additional PCR testing at week 4 of therapy in addition to ETR.

We also know that Sofosbuvir plus ribavirin therapy for 24 weeks is not recommended by international guidelines in HCV genotype 1 and is called as suboptimal for genotype 3 cirrhotic patients[6]. However, in our study the response rates (RVR and ETR) were so high (91% and95% respectively) and response rate of cases with genotype non-3a was 100%. Further cirrhotic patients responded 3.424 times more than non-cirrhotic patients. So that for our people recommendations should be reconsidered by local authorities on the basis of local data. Further studies may facilitate to solve the issue.

CONCLUSION AND RECOMMENDATIONS

This study concluded that response to sofosbuvir plus ribavirin therapy was excellent in our population for all hepatitis C genotypes. Dominant HCV genotype among patients was 3a. Among the factors predictive of response, only ALT normalization in first month of treatment was found significantly associated with rapid Virological response. While monitoring the response of the treatment of hepatitis C patients, cheap testing of ALT may escape the need of very expensive PCR testing at the week 4 of therapy.

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