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Original Article

Treatment Efficacy of Sofosbuvir and Ribavirin Combination at Two Weeks in Chronic Hepatitis C

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Abstract

Background:To determine the effectiveness of sofosbuvir plus ribavirin in terms of frequency of negative qualitative PCR at 2nd week of treatment in chronic hepatitis C patients with genotype 3.

Methods: In this case control study 60 patients with hepatitis C who were planned to receive sofobuvir and ribavarin combination therapy were included . Patients included were chronically infected with hepatitis C virus genotype 3 for whom treatment with peg-interferon is not an option and have contraindication for their use like decompensated liver disease, and patients are either non responder or relapsers to previous interferon based therapy. Pregnant or breast-feeding women, patients taking any of the medications which had interactions with sofosbuvir and patients who had not been compliant to sofosbuvir plus ribavirin therapy were excluded. Sofosbuvir was given in dose 400 mg once daily and ribavirin was given in dose of 400 or 600 twice daily(if weight <75kg or >75kg respectively). Patients were followed at 2nd week of treatment and qualitative PCR for HCV RNA was carried out

Results:Total sixty patients fulfilling the inclusion criteria were included in this study. Overall efficacy of sofosbuvir and ribavirin combination was 91. 7%. Majority of patients 55(91.7%) attained negative PCR for HCV RNA at2nd week of treatment).

Conclusion: Sofosbuvir plus ribavirin is an effective Treatment regimen as far as viral clearance at 2nd week of treatment is considered.

Key Words:Sofosbuvir, HCV RNA, Interferon, PCR

Introduction

The global prevalence of anti-HCV is 2.8% corresponding to >185 million infections. The prevalence of hepatitis C in Pakistan is 6.8% among adults. Progression to cirrhosis occurs in 20% of affected patients after about 20 years. Several treatment modalities are available for its treatment. Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV NS5B polymerase that is effective against HCV when it is administered in combination with Ribavirin Hepatitis C is a global health issue. It is one of the common causes of cirrhosis, end-stage liver disease and hepatocellular carcinoma and is the most common reason for liver transplant. Approximately 2.8% of the population is infected with hepatitis C worldwide.[1-4] Progression to cirrhosis occurs in 20% of affected patients after about 20 years . [5] Approximately3-6% of patients with cirrhosis will develop progressive liver failure, with a 1-5% annual risk of developing primary hepatocellular carcinoma.The nationwide prevalence of hepatitis C in Pakistan is 6.8% among adults, but it is much higher in certain regions of country . This indicates a great burden of the disease. [5-7]

In recent past, peginterferon plus ribavirin administered for 24 weeks was the standard treatment for patients with chronic hepatitis C.[8] But Interferon therapy is associated with multiple side effects and many patients with chronic hepatitis C infection are not eligible for interferon therapy due to advanced disease (like decompensated cirrhosis) or associated medical conditions while some have to discontinue treatment due to constitutional symptoms and hematologic abnormalities . [9] Some patients decline interferon therapy due to adverse effects and sub-cutaneous route of administration.[10] When studied in clinical trials, pegylated interferon in combination with ribavirin for 24 weeks, resulted in a sustained virological response in 70 to 85% of patients who had not received prior treatment and in 55 to 60% of those who had received treatment . [10]

Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV NS5B polymerase that is effective against HCV when it is administered in combination with Ribavirin.[8] It has better efficacy and safety profile than Interferon therapy.[11] In phase 3 trials involving patients with chronic hepatitis C infection, treatment with sofosbuvir with ribavirin for 12 weeks resulted in

rates of sustained virologic response of 78% among patients for whom pegylated interferon therapy was not possible because of contraindications or in whom unacceptable side effects developed. Among patients who had undergone previous therapy, rates of sustained virologic response were 50% among those who received 12 weeks of sofosbuvir plus ribavirin and 73% among those who received 16 weeks of the drug combination.[8] Another study showed that 91 % of patients who were not eligible for pegylated interferon and 81% of those who had undergone interferon based therapy attained negative PCR after two weeks of treatment.[10]

Patients and Methods

This case control study was conducted in center for Liver and Digestive Diseases (CLD), Holy Family Hospital, (HFH) Rawalpindi, from October 2015 to September 2016. Sample size was calculated using WHO calculator. Total of 60 patients who met the following criteria were included in the study: adults greater than 18 years of age and less than 80 years, detectable HCV viremia by qualitative PCR before start of treatment,genotype 3 infection, who gave written informed consent to participate in the study,patients chronically infected with hepatitis C virus genotype 3 for whom treatment with peg-interferon is not an option and have contraindication for their use like decompensated liver disease, and patients are either non responder orrelapsers to previous interferon based therapy. Pregnant or breast-feeding women,patients taking any of the medications which hadinteractions with sofosbuvir such as, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, tipranavir/ritonavir and patients who had not been compliant to sofosbuvir plus ribavirin therapy were excluded. Sofosbuvir was given in dose 400 mg once daily and ribavirin was given in dose of 400 or 600 twice daily(if weight <75kg or >75kg respectively). Patients were followed at 2nd week of treatment and qualitative PCR for HCV RNA was carried out.For categorical variables, like gender, status of patients as treatment failure or not eligible for interferon therapy and status of effectiveness of treatment at two weeks of treatment) frequencies and percentages were calculated. For continuous variables like age, duration of illness, time since interferon treatment, mean along with standard deviation were calculated. All the effect modifiers like age, gender were controlled by stratification; post stratification chi square test was applied.

Results

Mean age was 48.9 ±7.843 years (Table 1). Mean and standard deviation for duration of illness was 45.27 months (±18.88 months)(Table 2). Majority of patients (91.9%) attained negative PCR(Table 3).In majority of patients either belonging to age group up to 50 years or above 50 years, with no statistically significant difference in attainment based on gender (p-value=1.00) (Table 4). When attainment of negative PCR of patients at week 2 was analyzed according to previous treatment status of the patients, negative PCR was found 100% in patients who were naïve. Based on previous treatment status of patients, 20% were treatment naïve patients, 21.7% were non responder to interferon therapy and 58.3% had relapsed after interferon based treatment(Table5).

Table 1: Demographic profile

Descriptive statistics	total in years	Gender groups		Age groups	
		Male	Female	Upto 50 years	Above 50 years
Mean	48.90	48.62	49.35	43.50	55.96
Std. Deviation	7.84	7.99	7.75	5.28	4.103
Range	32	32	29	16	15
Minimum	34	34	34	34	51
Maximum	66	66	63	50	66

Table 2: Duration of illness and time since interferon treatment

	Duration of illness (in months)	Time since interferon treatment (in months)
Mean	45.27	35.8
Standard deviation	18.88	12.22

Table 3: Attainment status of PCR in study participants according to the gender

Gender group	Attainment status of PCR		Total	p-value
	Negative	Positive		
Females	20 (87.0%)	3 (24.0%)	23 (100%)	0.38
Males	35 (94.6%)	2 (5.4%)	37 (100%)	

Total	55 (91.7%)	5 (8.3%)	60 (100%)	

Table 4: Attainment status of PCR in study participants according to the age

Age Group	Attainment status of PCR		Total	p-value
	Negative	Positive		
Upto 50 years	31 (91.2%)	3 (8.8%)	34 (100%)	1.00
Above 50 years	24 (92.3%)	2 (7.7%)	26 (100%)	
Total	55 (91.7%)	5 (8.3%)	60 100%)	

Table 5: Response to treatment according to previous treatment status

Previous treatment status	PCR status at 2 weeks of treatment	
	Positive	Negative
Naïve (n=12)	12 (100%)	0 (0%)
Non-Responders (13)	12 (92.3%)	1 (7.7%)
Relapsers (n=35)	31 (88.6%)	4 (11.4%)

Discussion

Chronic Active Hepatitis C (CHC) can go undetected for years, and once the symptoms do appear, liver damage has already begun.[12] In advanced stages of cirrhosis, liver transplantation is typically the only treatment option.[13,14] In the last few years, the standard of care for untreated CHC patients has changed from dual therapy with peginterferon and ribavirin to triple treatment with peginterferon, ribavirin plus protease inhibitors (PI) such as telaprevir or boceprevir.[15] Although fairly effective compared to the older dual therapy, this triple therapy does not achieve more than a 75 % sustained virologic response (SVR) , which is defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the end of treatment. Once SVR is achieved, relapse is very unlikely. [16] However, injected interferon can lead to severe side effects such as fatigue, depression, and emotional liability.[17]

With the advent of Direct acting anti-virals, an era of all oral regimen has been introduced, sofosbuvir being the first one to gain worldwide exposure. Several clinical trials are now available in literature for genotype 3, including FISSION, FUSION, POSITRON, ALLY-3, BOSON, studies suggesting good acceptance of the drug but hints for a longer duration of therapy.[10, 11, 18-20] The most recent VALENCE trial shows a SVR of 93% in treatment naïve and 77% in treatment experienced patients after a 24 week drug use in combination with ribavirin.[21] In December 2013, U.S. Food and Drug Administration FDA approved sofosbuvir as a new component of interferon-free oral regimen for treating chronic hepatitis C. The drug eliminates the need for some patients to take interferon, specifically patients with genotypes 2 and 3.[22]

We checked effectiveness of sofosbuvir plus ribavirin in terms of frequency of negative qualitative PCR at 2nd week of treatment. We found that at 2 weeks of treatment this drug regimen is 83% effective in chronic hepatitis C patients with respect of 95% confidence interval in our sample size.Results of our study showed, with this drug regimen, 91.7% patients had cleared virus just in 2 weeks while 5 patients (8.3%) still had detectable virus RNA after 2 weeks of treatment. These results are similar to Neutrino and Fision trial and other studies.[8, 10, 11]

Frequency of negative qualitative PCR was calculated in both gender and in both age groups (upto 50 years and above 50 years). The results were same in both groups. No significant difference was observed in male and female patients. Similarly age didn't affect attainment of negative PCR. These results are also similar to other studies.[8, 10]We also calculated frequency of negative qualitative PCR at 2 weeks in different sub types of genotype 3. Our study showed statistically no difference in different sub types of genotype 3 in terms of viral clearance. Difference was not statistically significant among naive, non-responders and relapsers. Previous treatment status didn't affect viral clearance assessed at 2nd week. Although in our study 100% of naïve patients achieved viral clearance at 2nd week and 88.6 % of relapsers achieved negative PCR but the difference was not statistically significant (p-value >0.05). Present study showed that sofosbuvirv plus ribavirin in above mentioned doses is 83% effective in chronic hepatitis C patients with respect of 95% confidence interval in our sample. (95% CI, p value 0.045). This result is statistically significant with p value 0.045. (<0.05). Studies have shown that rapid viral clearance is best predictor of SVR.[23] For those patients who have not responded to the sofosbuvir/ribavirin combination several other options can be considered. LONESTAR-2 study has showed better results (SVR 83%) with the addition of pegalated interferon in the above

combination.[24] But this option can only be used for interferon eligible patients. Another strategy is to add additional DAAs to the regimen as already approved for Genotype 1. A recent small study have evaluated sofosbuvir and daclatasvir in Genotype 3 patients but the results in cirrhotic patients are not satisfactory with 58% SVR in treatment naïve and 69% treatment experienced cirrhotic patients.[18] Another trial adding Ladipasvir to Sofosbuvir/Ribavirin combination for 12 weeks has shown a 73% SVR amongst genotype 3 patients.[25]

Conclusion

Sofosbuvir plus ribavirin is an effective treatment regimen as far as viral clearance at 2nd week of treatment is considered.

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