

Treatment of Hepatitis C with Sofosbuvir in Combination with Ribavirin and Peg Interferon; a Prospective Study Highlighting the Sustained Virological Response

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Abstract

Objective: This study was intended to know the efficacy and safety of Sofosbuvir in combination with Ribavirin and Peg Interferon on the basis of sustained virological response.

Material and Methods: This was a prospective observational multicenter study with the use of non-probability convenient sampling technique. The duration of study was from January 2016 till July 2017. The study was conducted in lady reading hospital. The patients infected with HCV, belonging to both genders, and willing for treatment with standard interferon and Ribavirin were included in the study. The written consent was taken from all the patients with complete confidentiality of the data. HCV was diagnosed by detecting anti-HCV antibodies in serum with the help of Polymerase Chain Reaction (PCR). PCR was done at 12th week after the treatment and was classified as Sustained Virological Response (SVR). The therapy was categorized into dual containing Sofosbuvir and Ribavirin, triple containing Sofosbuvir, Ribavirin and Peg interferon. The dose of sofosbuvir, Ribavirin and Peg Interferon was 400 mg/OD, 1200 mg/OD and 180µg/OD respectively. All data was entered and analyzed on SPSS version 20.

Results: Total 386 patients were selected for the study including 172(45.5%) males and 214(54.5%) females with the male to female ratio of 1:1. They were divided into treatment naïve and experienced group with a frequency of 211(54.6%) and 175(45.4%). The frequency of genotypes of hepatitis C was found to be 4(1.9%), 1(0.5%), 2(0.9%), 1(0.5%), 178(84.3%), 20(9.5%), 3(1.4%) and 2(3.6%) for genotypes 1a, 2, 2a, 2b, 3, 3a, 3b and UT respectively in naïve patients and similarly it was 3(1.7%), 1(0.6%), 4(3.2%), 3(1.7%), 113(64.6%), 44(25.2%), 5(2.9%) and 2(1.1%) respectively in experienced group. The overall SVR achieved regardless of the dual and triple therapy in naïve patients was 200(94.7%) and in treatment experienced patients were 144(82.3%).

Conclusion: The Sofosbuvir is an effective drug for the achievement of sustained virological response in combination with Ribavirin and Peg Interferon. The uniformity in the high rates of achievement of SVR in dual and triple therapy suggests a powerful efficacy of Sofosbuvir in treating and eliminating the viral load in the patients infected with Hepatitis C Virus.

Keywords: Hepatitis C; Sofosbuvir; Sustained virological response

Introduction

Globally the infection of Hepatitis C Virus (HCV) has a huge prevalence [1-3]. About 170-200 million people are estimated to be chronically ill with hepatitis C virus [4]. It is in fact the leading cause of chronic liver disease and third most common cause of mortality in end stage renal disease patients [5]. The reported cases of HCV infection in Pakistan ranges range from 2.2-14% [6]. It is estimated that about 10 million people in Pakistan are infected with HCV [7]. With the prevalence rate 6.7%, 5%, 1.5%, 1.1% in Punjab, Sindh, Baluchistan and Khyber Pakhtunkhwa respectively [8].

The focus of researches done currently for the treatment of chronic HCV is on protease inhibitor that disrupt the cycle of viral replication. Some advanced proteases and polymerase inhibitors are already providing their ability for attaining a Sustained Viral Response (SVR), defined as the lack of HCV RNA in serum at the end of treatment and then six months later. The initial data appear with some positive results [9]. Improvement in histology of liver and the quality of health with low risk of HCC and liver related mortality is associated with attainment of SVR [10]. There is the co-relation of SVR with viral genotype, viral load, patient's age, BMI, race, environmental and other factors [11-13]. Patients who received 12 weeks treatment with the nucleotide polymerase inhibitors Sofosbuvir and combined with Ribavirin and Peg Interferon demonstrated to have higher sustained virologic response rates for genotypes 1, 2, 3, 4 and 6 in comparison with treatments that include only Peg Interferon and Rivavirin [14]. It is administered daily with or without meal at dosage of 400mg, and its response is effective against all HCV genotypes. Pharmacologically active uridine analog of triphosphate is formed by intracellular metabolism of Sofosbuvir which then integrated into HCV RNA by the NS5B RNA-dependent RNA polymerase (RdRp) acting as a chain terminator.

This study was intended to know the efficacy and safety of Sofosbuvir in combination with Ribavirin. Furthermore, it was aimed to evaluate the response to management of HCV infection

to PEG-IFN/RBV regimen by emphasizing on the virological and biochemical features.

Material and Methods

This was a prospective observational multicenter study with the use of non-probability convenient sampling technique. The duration of study was 1 year from January 2016 till December 2016. The study was conducted in Lady Reading Hospital. The patients infected with HCV, belonging to both genders, and willing for treatment with standard interferon and ribavirin were included in the study. Patients with co infection of hepatitis B virus and who had complications containing cirrhosis and having chronic disease like hypertension, diabetes and hypersensitivity to any of the product of Sofosbuvir, Ribavirin or Peg Interferon were excluded from the study. The written consent was taken from all the patients with complete confidentiality of the data.

The demographic variables like age and gender were documented. The genotype of the patient was categorized through PCR. PCR was done at 12th week after the treatment and was classified as Sustained Virological Response (SVR). The goal of the treatment was classified as achieved and not achieved. The patients with undetectable viral load were categorized to achieve the objective of the treatment. The patients were classified into treatment naïve and treatment experienced. A patient is said to be treatment naïve who did not had any treatment before. HCV was diagnosed by detecting anti-HCV antibodies in serum. HCV detection and its quantification was done with the help of Polymerase Chain Reaction (PCR). The therapy was categorized into dual containing Sofosbuvir and Ribavirin, triple containing Sofosbuvir, Ribavirin and Peg interferon. The dose of Sofosbuvir, Ribavirin and Peg Interferon was 400mg/OD, 1200 mg/OD and 180µcg/OD respectively.

Data Analysis

All data was entered and analyzed on SPSS version 20. Mean and standard deviation were calculated for the quantitative variables. Frequencies and percentages were measured for the qualitative variables. Chi-square test and paired t-test was used to assess the difference and the P value less than or equal to 0.05 was taken as significant.

Results

Total 386 patients were selected for the study including 172(45.5%) males and 214 (54.5%) females with the male to female ratio of 1:1. They were divided into treatment naïve and experienced group with a frequency of 211(54.6%) and 175(45.4%). The frequency of genotypes of hepatitis C was found to be 4(1.9%), 1(0.5%), 2(0.9%), 1(0.5%), 178(84.3%), 20(9.5%), 3(1.4%) and 2(3.6%) for genotypes 1a, 2, 2a, 2b, 3, 3a, 3b and UT respectively in naïve patients and similarly it was 3(1.7%), 1(0.6%), 4(3.2%), 3(1.7%), 113(64.6), 44(25.2%), 5(2.9%) and 2(1.1%) respectively. 196(92.8%) patients received double therapy (Sofosbuvir and Ribavirin) for the duration of 6 months and 15(7.2%) patients received triple therapy (Sofosbuvir, Ribavirin and Peg Interferon) in treatment naïve group for the duration of 3 months. Similarly 153(87.4%) patients received

double therapy (Sofosbuvir and Ribavirin) for the duration of 6 months and 22(12.6%) patients received triple therapy (Sofosbuvir, Ribavirin and Peg Interferon) for the duration of 3 months (Table 1).

Table 1: General analysis

Variable		Naïve (n=211)		Experienced	
		(n=175)			
		n	%	n	%
Gender	Male	100	47.4	72	41.2
	Female	111	52.6	103	58.8
Genotype	1a	4	1.9	3	1.7
	2	1	0.5	1	0.6
	2a	2	0.9	4	3.2
	2b	1	0.5	3	1.7
	3	178	84.3	113	64.6
	3a	20	9.5	44	25.2
	3b	3	1.4	5	2.9
	UT	2	3.6	2	1.1
Therapy	Dual therapy	196	92.8	153	87.4
	Triple therapy	15	7.2	22	12.6
Duration of treatment	3 months	15	7.2	22	12.6
	6 months	196	92.8	153	87.4

In our study we divided the patients on the basis of viral load as Achieved: those having undetectable viral load and Not achieved: those having detectable viral load. The SVR achieved in naïve patients with dual therapy was 185(94.4%) and was 15(100%) in patient receiving triple therapy. Similarly, the SVR achieved in inexperienced patients in dual therapy was 127(83%) and was 17(77.3%) in patient receiving triple therapy (Table 2).

The mean of baseline PCR of dual and triple therapy was 832654.23±99218.01 and 774668.69±93060.06 respectively. The mean SVR of dual and triple therapy was 0.34±0.93 and 0.19±0.70 respectively. The significant relationship exists between these combinations of therapy and PCR showing *p-value* of <0.001 (Table 3).

The overall SVR achieved regardless of the dual and triple therapy in naïve patients was 200(94.7%) and in treatment experienced patients were 144(82.3%) (Figure 1).

Discussion

Viral hepatitis creates a burden as public health problem in multiple areas of the world. Therefore there is a need to approve worldwide approach to attain the eradication of hepatitis. The mixed approach of this study has assessed the management of hepatitis in accordance with the achievement of the sustained virological response, thus helpful for the reduction in the disease burden.

Table 2: Showing the qualitative comparison of Sustained Virological Response (SVR) in experience and naïve patients

	Naïve (n=211)				Experienced (n=175)			
	Achieved		Not Achieved		Achieved		Not Achieved	
	n	(%)	n	(%)	n	(%)	n	(%)
Dual therapy	185	94.4	11	5.6	127	83	26	17
Triple therapy	15	100	0	0	17	77.3	5	22.7

Table 3: Showing the quantitative comparison of combination of therapy and Sustained Virological Response (SVR)

Combination of Therapies	PCR				P-Value
	Baseline		SVR		
	Mean	STD	Mean	STD	
Dual therapy	832654.2	99218.01	0.34	0.93	<0.001
Triple therapy	774668.7	93060.06	15.8	50.29	

The achievement of RVR in patients infected with chronic HCV depends on the genotype of virus. Several studies have documented that patients infected with HCV genotype 2 (G2) or genotype 3(G3) who have attain RVR, the reduction in duration of treatment up to 12-16 weeks was effective. As an indicator for the duration of treatment that is extended or short treatment duration, RVR can be used in patient with HCV G1.16 One of the study showed that the rate of SVR achieved at 12 week after treatment with Sofosbuvir and Ribavirin was about 83% excluding the patients who lost to follow up or discontinue the therapy. SVR at 12th week rates were 91% and 80% in previously untreated and in treated patients respectively [17]. Another study documented that with the help of dual therapy (Sofosbuvir plus Ribavirin) SVR was achieved in 100% and 68% of treatment naïve and in treatment experienced patients respectively that were infected with chronic HCV (either genotype 2 or 3) [18,19]. One of the study showed that SVR among patients taking dual therapy was 78% while in those who have acquired treatment previously was 50% at 12 weeks [20]. The findings of the above studies are in accordance with our study which established the SVR at 12th week was achieved in 94.7 % of the cases in treatment naïve patients and 82.3% of the patients in experienced group, excluding the loss to follow up or the patients who discontinued the therapy.

Another study showed that in HCV G1 patients, SVR in treatment-experienced patients taking dual therapy was poor

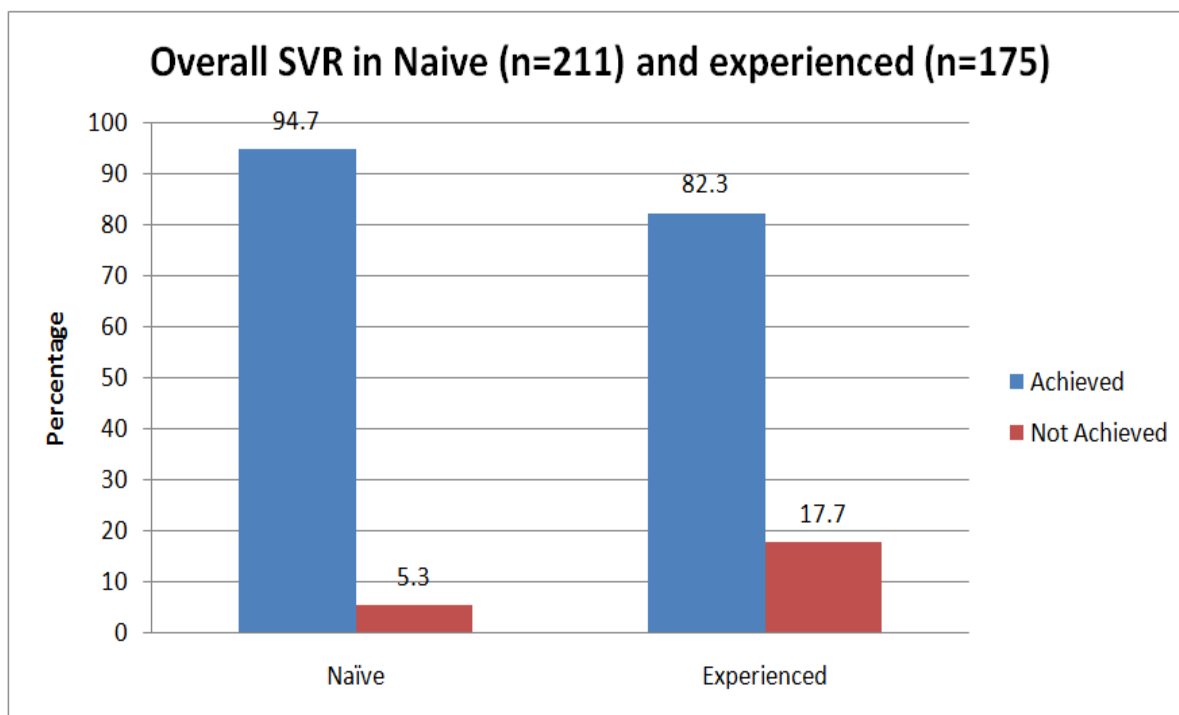


Figure 1: Showing the overall sustained virological response in naïve and experienced patients

[19]. One of the study showed that rate of SVR at 12th week in patients with HCV genotype G2 and G3 were 96% and 83% respectively that is better in patients with HCV genotype G2 than G3 in patients receiving triple therapy (Sofosbuvir, Ribavirin and Peg-interferon)[21]. Another study presented that RVR and SVR in patients with decompensated cirrhosis among patients taking triple therapy were 93.6% and 88.8 % respectively [22]. In another study from meta-analysis of 757 patients, 411 were selected for studies that were having HCV infection revealed that SVR rate for triple regimen was 88.54% [23]. The study carried out in Egypt indicated that triple therapy is better than dual therapy as SVR was 94% in triple therapy while 83% in dual therapy [24]. Another study documented the rate of SVR12 among patients receiving triple therapy having genotype 2 and 3 were 94% and 93% respectively [25]. The recent studies have established that there was a significant association between the RVR and the SVR at 12th week, with 100% (38/38) of those who had RVR achieving a final SVR at 12th week [26,27]. The conclusion of the above studies are in agreement with our study which recognized that the SVR at 12th week was achieved in 100 % of cases with the triple therapy in naïve patients and 77.3% in experienced patients. Furthermore triple therapy is better in terms of achievement of SVR than the dual therapy. The mixed approach in this study has assured that we have assessed wide perspective of the treatment with Sofosbuvirin combination with Ribavirin and Peg Interferon. However the study might not be immune from the selection bias because of the unknown outcome related to the attainment of SVR in patients who loss to follow up. In view of the valuations of this study and to what extend these results are comparable to the other treatment options would be enlightening to discover further facts about the balanced approach in treating the patients of hepatitis C.

Conclusion

The Sofosbuvir is an effective drug for the achievement of sustained virological response in combination with Ribavirin and Peg Interferon. The uniformity in the high rates of achievement of SVR in dual and triple therapy suggests a powerful efficacy of Sofosbuvir in treating and eliminating the viral load in the patients infected with Hepatitis C Virus.

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