ORIGINAL ARTICLE

SOFOSBUVIR FOR THE TREATMENT OF HEPATITIS C GENOTYPE 3 INFECTED PATIENTS IN PAKISTAN

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Background: This study was conducted to determine the viral responses of patients with chronic infection of Hepatitis C virus treated with sofubuvir. **Methods:** This Quasi experimental study was conducted at Centre for Liver and Digestive Diseases, Holy Family Hospital, Rawalpindi from September 2014 to September 2016. 502 patients with HCV genotype 3 including treatment naive, non-responders or relapsers to previous interferon based therapy along with patients having decompensated cirrhosis (child class B or C) were included in the study. All patients were treated with Sofosbuvir 400 mg once daily along with Ribavirin for 6 months. Follow-up qualitative PCR (polymerase Chain Reaction) were performed at 4 weeks interval to assess RVR (Rapid virological Response), end of treatment to determine ETR (End of treatment response) and 3 months post treatment to determine SVR12 (Sustained viral response at 12 week). **Results:** 91% of the patients had become PCR negative at completion of four weeks of treatment with Sofosbuvir, whereas at completion of treatment 96.5% had attained a negative PCR. Sustained virological response at 12 weeks post therapy (SVR12) was attained in 85.5% of patients. No statistically significant associations were found with attainment status of RVR, ETR and SVR based on previous treatment status or presence of Decompensated liver disease. However, attainment of SVR was slightly more in females (*p* value=0.03). The serological profiles of patients whether they attained PCR at week 4, 24 of treatment or 12 weeks' post treatment did not exhibit any statistically significant difference. **Conclusion**: Sofosbuvir is effective in eradicating hepatitis C virus irrespective of previous treatment or liver fibrosis status in genotype 3 HCV Pakistani patients.

Keywords: Sofosbuvir; Hepatitis C virus; infection; Polymerase chain reaction; virology; Genotype

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INTRODUCTION

The global prevalence of Anti HCV is estimated to be about 1.6% with a viraemic prevalence of about 1.1% roughly accounting 80 million worldwide population.[1] Genotype 1 has got the highest global genotype distribution of about 46% followed by Genotype 3 with 22 %.[1] The natural history of the disease suggests that up to 85% patients remain HCV infected once they acquire acute hepatitis C infection.[2] That is why the treatment for hepatitis C is revolutionizing since 1986 when for the first-time interferon was used.[3] Till recent past, the standard treatment for Hepatitis C was a combination of pegylated interferon alfa and ribavirin for 48 weeks for genotype 1 and 24 weeks for genotype 2 and 3.[2] A breakthrough in the treatment was long awaited not only because of the unsatisfactory sustained viral response rate but also because of limited use due to side effects and contraindications.[4,5]

Sofosbuvir, a nucleotide analogue inhibitor of HCV NS5B polymerase, has been approved by FDA since 2013, in combination with pegylated interferon alfa and ribavirin for 12 weeks in genotype 1 or 4 and in combination with ribavirin for genotype 2 (12 weeks) or 3 (24 weeks) respectively.[6] Varying data has been shared so far around the globe, with maximum representation from the western world focusing on genotype 1.[7–9]

Pakistan being number 2 amongst the countries accounting for most of the global viremia has an anti-HCV prevalence of 6.7% with the commonest genotype 3 (79%).[1] VALENCE study conducted in Europe showed that among patients infected with HCV genotype 3, treatment with Sofosbuvir plus Ribavirin resulted in Rapid Virologic Response (RVR) of 99% and Sustained Virologic Response (SVR) of 85% respectively.[10]

The centre for Liver and Digestive diseases is one of the major centres in Pakistan where patients are evaluated and treated for Hepatitis C infection. No study has been published so far to determine the effectiveness of Sofosbuvir in Pakistani population; hence our study will be one of the pioneers to evaluate its effectiveness in Pakistani patients. In this study, viral responses of patients treated with Sofosbuvir were determined to provide evidence for this drug as an effective treatment modality, not only for treatment naïve patients but also for those who had either not responded or relapsed after treatment with interferons previously.

MATERIAL AND METHODS

This open-label, quasi experimental study was carried out at centre for Liver and Digestive Diseases, Holy Family Hospital, Rawalpindi after ethical approval of the Institutional research forum of Rawalpindi

Medical College. Patients were enrolled from September 2014 through September 2016, with ages above 18 years and had chronic infection with HCV genotype 3, with HCV RNA levels detectable by PCR regardless of whether they were treatment naïve or had experienced Interferon in the past. The treatment experienced patients included both treatment relapse and non-responders. Treatment relapse patients included the ones with reappearance of HCV RNA in serum after therapy was discontinued whereas non-responders were those who failed to clear HCV RNA from serum after 24 weeks of therapy. After written informed consent and baseline evaluation, all included patients were offered Sofosbuvir 400mg once daily along with weight based Ribavirin for a period of 24 weeks. Follow-up PCRs were performed at four weeks' interval to assess the RVR (Rapid Virological Response), end of treatment to determine ETR (End of treatment response) and 3 months' post treatment to determine SVR_{12} (Sustained viral response at 12 week). Amongst 502 study participants, PCR of 426 patients was available at fourth week of treatment, 116 patients at completion of treatment and 55 patients at 12 weeks' post treatment respectively. Amongst all patients 85 were having child class B or above.

Since the patients were included through non-probability consecutive sampling technique and in addition it was a single group study, lacking any control group based on ethical grounds, hence it was a quasi-experiment. Keeping the expected proportion of patients with attainment of SVR in Genotype 3 patients as 99% according to recent VALENCE study[10], the absolute precision as 0.9% and the level of confidence as 95%, the minimally required sample size was estimated to be 470 through WHO sample size calculator. One patient expired during study due to non-hepatic cause whereas two did not comply with the treatment fully.

All the data was entered and analysed in SPSS v.22. In addition to descriptive statistics, Independent samples *t*-test was applied at 5% level of significance to compare the age and haemoglobin levels (Hb) of patients who attained negative PCR with those who did not. For Alanine Transaminase levels (ALT), Platelet counts and total leukocyte counts (TLC), Median and inter-quartile ranges (IQR) were estimated and Mann Whitney U test was applied at 5% level, since frequency distribution was not normal.

Pearson's Chi Square test was applied at 5% level of significance to compare proportions of the patients who attained RVR, ETR or SVR 12 or not, based on gender and previous treatment status and *p*-values equal to or less than 0.05 were considered statistically significant. For cross tabulations where more than 10% of cells had expected counts less than 5, Fischer Exact test was applied at 5% level of significance. Relative risks were also calculated for the failure to attainment of negative PCR at week 4, at end of treatment and 3 months' post treatment along with 95% Confidence intervals using MedCalc software. Exclusion of value of 1.00 from the confidence intervals determined the statistical significance.

RESULTS

A total of 502 patients were included in the study having genotype 3 amongst which 219 (43.6%) were males and 283 (56.4%) were females. The mean age of participants was 46.84 years (±10.49 years), while their baseline serum profile showed mean ALT as 84.19 IU/l (±58.73 IU/l), mean haemoglobin level as 13.15 (±2.22 mg/dl, mean serum platelet count as 171804.07 (±93935.22) and total leukocyte count as 6998.46 (±5731.19).

Study participants who were naïve to any previous Interferon treatment were 291 (58%) while amongst remaining 211 (42.03%) patients who had experienced Interferon treatment previously, 86 (40.75%) were non-responders while 125 (59.24%) were relapsers.

Amongst 502 patients' PCR of 426 patients was available at completion of four weeks and 388 (91%) had become PCR negative at completion of four weeks of treatment while PCR of 116 patients was available at completion of treatment amongst whom 112 (96.5%) had attained a negative PCR. Sustained virological response at 12-week post therapy (SVR12) was evaluated in 55 patients out of which 47 (85.5%) were PCR negative. The distribution of virological responses in study participants based on previous treatment status is displayed in figure I and no statistically significant difference was observed in patients whether attained RVR, ETR or SVR 12 or not, based on previous treatment status with all *p*-values >0.05. The serological assessment of the patients and age profile at the baseline of the patients were also compared amongst patients who attained negative PCR, at week four, at end of therapy and twelve weeks post treatment and no statistically significant difference was found amongst the groups;2 with *p*-values more than 0.05. (Table-1)

The comparison of risk of failure to attain negative PCR and proportions of patients who attained negative PCR with those with positive PCR, at three points of time on follow up was also executed based on gender and previous treatment status that revealed no statistically significant difference in groups except that attainment of SVR

was comparatively higher in female patients as compared to male patients (*p*-value 0.03). (Table-2) As regards adverse effects, in patients treated with Sofosbuvir plus Ribavirin, fatigue and generalized weakness remained the most common adverse effect. It was observed in 136 (27.09%) patients. Other side effects were fever in 45 patients (8.9%), dry cough in 27 (5.3%), oral ulcers in 4 (0.7 %), rash and pruritis in 14 (2.7%) patient. However, 75 patients (14.9 %) complained to have myalgias and 12 patients (2.3%) suffered from headache during treatment regimen. Anaemia related to Ribavarin is seen in 28 patients (5.5%). Amongst all patients, 163 (32.4%) confirmed to have experienced none of the side effects related to therapy. Amongst all 502 patients, 85 (16.9%) of patients had decompensated liver disease and distribution of patients attaining or not attaining RVR, ETR or SVR_{12} in 85 patients with decompensated liver disease is displayed in figure-2

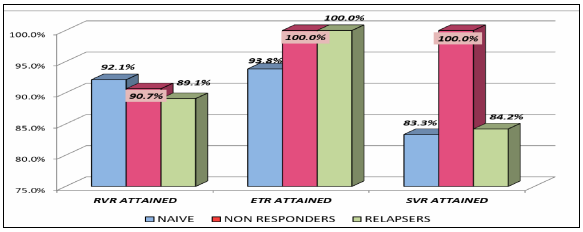

Figure-1: Bar chart displaying the distribution of patients attaining RVR, ETR and SVR, according to their previous treatment status.

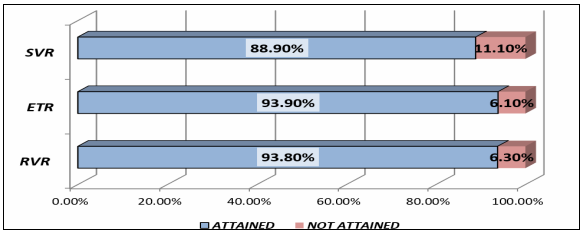

Figure-2: A bar chart exhibiting the attainment of RVR, ETR and SVR in 85 patients with decompensated liver disease

Table-1: The comparison of baseline haematological & biochemical profile and ages of patients who attained or did not attain negative PCR, at week 4, 24 after initiation of treatment and 12 weeks post treatment.

Profile	PCR	Week 4		Week 24		Week 12 post treatment	
		Mean (±SD)	*p*-value	Mean (±SD)	*p*-value	Mean (±SD)	*p*-value
Age In years	Positive	46.09 (±9.56)	0.90	47.25 (±4.34)	0.96	46.55 (±8.60)	0.54
	Negative	46.32 (±10.74)		47.54 (±9.29)		48.50 (±7.11)	
Haemoglobin levels (G/DL)	Positive	13.29 (±2.20)	0.77 *p*-value	11.43 (±1.67)	0. 21 *p*-value	12.06 (±2.70)	0.92 *p*-value
	Negative	13.17 (±2.26)		10.86 (±2.24)		12.16 (±1.75)	
		Median (IQR)		Median (IQR)		Median (IQR)	
Alanine transaminase levels (IU/L)	Positive	78.00 (64.50)	0.34	66.00 (31.37)	0.85	66.00 (55.00)	0.98
	Negative	69.00 (57.00)		72 (47.50)		66.00 (58.00)	
Total leukocyte count	Positive	6000.00 (4550.00)	0.92	5900.00 (1000.00)	0.77	5900.00 (5900.00)	0.82
	Negative	6370.00 (2500.00)		6300.00 (2980.00)		63;200 (3410.00)	
Platelet count	Positive	162000.00 (131500.00)	0.85	77500.00 (53000.00)	0.21	82000.00 (203750.00)	0.41
	Negative	159000.00 (119750.00)		117000.00 (95000.00)		119000.00 (132000.00)	

Table-2: The comparison of gender and previous treatment status of patients who attained or did not attain negative PCR, at week 4 (n=414), week 24 (n=97) and 12 weeks post treatment (n=55) after initiation of treatment

Week	Patients Characteristics		PCR positive		PCR negative		Relative risk of failure to attain negative PCR		
			f	%	f	%	RR	95% CI	*p*-value
Week 4 of treatment	Gender	Female	18	9.4	173	90.6	1.10	0.60–2.03	0.72
		Male	20	8.5	215	91.5			
	Treatment Naïve	Yes	19	7.9	222	72.1	0.76	0.41–1.40	0.39
		No	19	10.3	166	89.7			
	Previous Treatment Status	Non-responders	7	9.3	68	90.7	0.85	0.35–2.07	0.72
		Relapsers	12	10.9	98	89.1			
Week 24 of treatment	Gender	Female	0	0	45	100	0.17	0.00–3.15	0.23
		Male	4	5.6	67	94.4			
	Treatment Naïve	Yes	4	6.2	61	93.8	7.09	0.39–128.75	0.18
		No	0	0	51	100			
	Previous Treatment Status	Non-responders	0	0	15	100	2.31	0.04–111.52	0.67
		Relapsers	0	0	36	100			
12 Weeks post -treatment	Gender	Female	1	3.2	30	96.8	0.11	0.01–0.83	0.03*
		Male	7	29.2	17	70.8			
	Treatment Naïve	Yes	5	16.7	25	83.3	1.38	0.36–5.24	0.62
		No	3	12.0	22	88.0			
	Previous Treatment Status	Non-responders	0	0	6	100	0.40	0.02–6.95	0.53
		Relapsers	3	15.8	16	84.2			

Statistically significant with *p*-value<0.05 f=Frequency, %=Percentages, RR=Relative Risk, 95% CI=95% Confidence Intervals for RR

Table-3: Characteristics of patients not achieving SVR12

Age	Gender	ALT	PCR[IU/ml]	Status	DCLD	RVR	ETR
43	M	55	282377	Naïve	No	Attained	Not attained
45	M	77	4671750	Naïve	Yes	Not Attained	Not Attained
53	M	89	66613	Naïve	No	Not Available	Not Attained
40	M		3260010	Relapser	No	Attained	Attained
48	M	54	407407	Naïve	Yes	Not Available	Not Attained
46	M	72	399299	Naïve	No	Not Available	Attained
50	F	36	2000000	Relapser	No	Attained	Attained
63	M	75	393656	Relapser	No	Not Available	Attained

DISCUSSION

With the advent of direct acting anti-virals, an era of all oral regimens has been introduced, Sofasbuvir being the first one to gain worldwide exposure is a NS5B non-nucleoside polymerase inhibitor.[11] Being the polymerase inhibitor it has got pan-genotypic effect. Several significant studies from west are available to evaluate the effectiveness of Sofosbuvir for different genotypes but data is relatively scarce for genotype 3 as it is more prevalent in eastern countries.[1] Few clinical trials available in literature for genotype 3, includes FISSION, FUSION, POSITRON, ALLY-3 and BOSON studies suggesting good acceptance of the drug but hints for a longer duration of therapy.[12–16] 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.[10]

In our study, all 502 patients were included irrespective of the fact, whether they were previously treated or not. Patients with advanced cirrhosis were also included. In our study, maximum patients have data based upon RVR, but studies have proved RVR to be a good predictor for SVR.[17] Subsequently we will evaluate the results with SVR as more patients will complete their therapy, in next phase of this existent study.

The treatment naïve group has shown the RVR of about 92% and SVR_{12} of 83.3% respectively. This response is irrespective of cirrhosis. In VALENCE trial the SVR for treatment naïve non-cirrhotic patients was 93% and cirrhotic patients was 92% respectively and the results are quite comparable with our study. A multi-centre RESiP trial from Pakistan involving more than 5000 patients with 94% genotype 3 patients showed a SVR12 of 97% in non-cirrhotic and 89% cirrhotic treatment naïve patients respectively.[18]

As evident by the VALENCE trial the basic problem is to deal with the treatment experienced patients especially those who have already developed cirrhosis. The SVR in this group was only 60%.[13] Treatment experienced patients include both failures and relapsers to IFN/Peg-IFN along with Ribavirin in the past. Data from different studies in Pakistan using PEG-IFN+RBV showed a SVR ranging from 57.6–75%.[19–22] The results were even poor (SVR 27% only) for patients who failed to respond to IFN initially and subsequently treated with PEG-IFN.[23] Therefore a huge number of patients were waiting for this breakthrough in HCV treatment. But VALENCE trial results proved to be discouraging especially for cirrhotics. Contrarily our study has shown a good response in treatment experienced patients including cirrhotics with a RVR of about 90% and SVR12 of 86.3% respectively. RESiP study from Pakistan also showed a SVR12 of about 86% in treatment experienced cirrhotic patients.[18] This difference of result is very promising for the patients in eastern countries where new DAAs are not readily available and choices are limited. Furthermore, removing the SOF/RBV combination from AASLD updated guidelines can also be questioned especially for genotype 3 patients.[24]

Similarly our data regarding decompensated cirrhosis is also very encouraging as compared to international data. HCV-TARGET study evaluated the Sofosbuvir based regimens for GT3 and only 39% SVR12 were observed.[25] Contrarily in our study 93.6% patients with decompensated cirrhosis have achieved RVR and 88.8% have achieved SVR12 respectively. As the SVR data regarding DCLD patients only comprises 20 patients, therefore more data is required to establish a definitive conclusion.

Sofosbuvir and Ribavirin combination has shown a good safety profile in both cirrhotic and non-cirrhotic patients in our population. No serious side effects have been reported. Only complaints the patients come up with were fatigue, generalized weakness, myalgias, fever, dry cough and headaches. All these side effects were easily manageable. Even Ribavirin related anaemia was easily managed either by holding the drug temporarily or reducing the dose. Only two patients required blood transfusion. In none of the patients, treatment needs to be stopped. Younossi *et al*. in a study also showed similar side effects and a good safety profile.[26]

In our study we also included the haematological and biochemical parameters of the patients undergoing Sofosbuvir/Ribavirin therapy, including Haemoglobin, Leucocyte counts, Platelet counts and Liver function tests. But none of the

parameters showed any significant influence on the outcome of the therapy.

About 8 patients out of 52 were unable to achieve SVR12, 5 of them were treatment naïve and 3 were relapsers. Surprisingly 7 out of 8 were males. A number of studies in the past have showed gender disparity in achieving SVR after interferon therapy. Belci *et al*. in a study showed a significantly higher SVR in women age <50.[27] Similarly a meta-analysis by Bhattacharya *et al*. showed higher SVR in pre-menopausal women.[28] Even in our study the only female patient who didn't achieve SVR was 50 years old. Probable explanation for this gender biasedness can be a more active Interferon signalling in the presence of estrogen.[29] Weather this explanation is applicable on DAAs as well needs further investigation. Martin *et al*. proved that DAAs apart from their direct action of HCV also boosts the immune system to fight against the virus, the mechanism very similar to that of interferons.[30,31]

All 3 relapsers have attained ETR and then relapsed again, suggesting that the viral pool in these patients had DAA mutant variants as well. Interferon resistance is not based upon mutations related to non-structural proteins like NS3 to NS5B[29], which are the main targets of DAAs. The association in our study signifies that the wild type virus that was initially resistant to Interferon responded well to DAAS but the patients had low levels of resistant viral variants to DAAs as well that causes the relapse after stopping the treatment and thus became detectable once the competing environment with wild type was over.[32] (Table-3)

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 Interferons in the above combination.[33] But this option can only be used for interferon eligible patients and is no more recommended by AASLD guidelines.[24] Another strategy is to add additional DAAs to the regimen but currently none are available in Pakistan. A recent small study has 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.[14] Another trial adding Ladipasvir to Sofosbuvir/Ribavirin combination for 12 weeks has shown a 73% SVR amongst genotype 3 patients.[34]

Our study has shown better SVR results than any of these combinations and so far these results are quite promising for eastern populations where availability of newer DAAs will remain an issue. More data will further reveal the efficiency of SOF and its usefulness in the treatment of Pakistani HCV patients. Furthermore, we will be able to update the national guidelines considering our own local issues.

CONCLUSION

Sofosbuvir is effective in treating genotype 3 HCV patients especially in eastern population, irrespective of their previous treatment status, age or serological status. With attainment of SVR in 84.6% of patients, Sofosbuvir is a safe and cost effective treatment modality for HCV patients in Pakistan. Female patients seem to have an edge in attaining SVR but further data is required to establish a definite relationship.

Conflict of interest: None

AUTHORS' CONTRIBUTION

TSA: performed Literature review, and contributed in formulating introduction, data analysis and discussion. MU: conceived the research question, performed literature review and contributed in introduction and discussion formulation. HTBK: contributed in literature review, introduction and discussion formulation. FA: formulated the research methodology, performed data analysis and formulated the results. AN: contributed in literature review, introduction and data collection. GN, SA, MO: contributed in data collection and data entry.

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