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Treatment Efficacy of Sofosbuvir Containing Regimes in Chronic Hepatitis C, Genotype-3 Infected Patients in Indian Population - A Real World Experience

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Abstract: ***Background: Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. Chronic hepatitis C and its complications impose a substantial burden on affected patients, healthcare systems and society. The introduction of direct acting antiviral agents, in particular sofosbuvir (SOF), has revolutionized the treatment for chronic hepatitis C virus. With SOF-based regimens, we have achieved high cure rates, decreased the duration of treatment and IFN-free treatment regimens have been made possible. Aims and Objectives: To assess the treatment efficacy of sofosbuvir containing regimens in chronic hepatitis C infected patients of genotype 3 in Indian population. Materials and Methods: All the consecutive chronic hepatitis C, genotype 3 infected patients from outpatient and inpatient departments, fulfilling the inclusion and exclusion criteria were enrolled in the study. A total of 69 patients were included in study. Patients were divided into two groups. Those who received 24 weeks of Sofosbuvir plus Ribavirin (SR) belonged to group A with 39 patients, while those who received 12 weeks of Sofosbuvir plus Ribavirin plus peg interferon (SPR) belonged to group B with total of 30 patients. Patients were monitored by clinical and standard laboratory tests on follow up visit to OPD.HCV RNA was measured at baseline, 4 week and at the end of treatment. After the completion of treatment protocol, these patients were followed for further 12 weeks and then quantitative HCV RNA level was done to check SVR12. Results: The overall sustained virological response at 12 weeks (SVR12) was achieved in 87.2% in group A (SR). In cirrhotic patients SVR12 was achieved only in 66.7% while in non cirrhotic patients 93.3% have achieved SVR12.The overall sustained virological response at 12 weeks (SVR12) was achieved 90% in group B(SPR).In cirrhotic patients SVR12 was achieved 70% patients while all non cirrhotic 100% patients have achieved SVR12. Conclusion: Triple drug regimen (Sofosbuvir, Pegylated Interferon and Ribavirin) had showed a better overall treatment response than the dual regimen (Sofosbuvir and Ribavirin). Triple drug therapy could be still preferred in selected patients who are Interferon eligible with genotype 3 Hepatitis C related compensated Cirrhosis in our Indian population. The overall treatment response was relatively lower in cirrhotic patients.***

Keywords: Hepatitis C, Sofosbuvir, sustained virological response (SVR)

1. Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide.[1]Chronic hepatitis C and its complications (cirrhosis, liver failure, hepatocellular carcinoma (HCC) impose a substantial burden on affected patients, health care systems and society.[2,3]It is estimated that about 160 million people worldwide are affected by chronic hepatitis C.[2]India alone has an estimated burden of 8.6 million viraemic HCV carriers.[4]The high number of chronically infected individuals, the burden of disease, and the absence of a vaccine indicates that treatment will form part of the disease control. [5] The primary goal of HCV therapy is to cure the infection. The infection is cured in more than 99% of patients who achieve sustained virological (SVR). The SVR is generally associated with resolution of liver disease in patients without cirrhosis.6,7

The overall treatment options have evolved over the past two decades. Treatment of chronic hepatitis C infection started in the early 1990s with the use of recombinant interferon (IFN) alpha as monotherapy yielding dismal response rates. With the development of direct antivirals (DAAs) such as sofosbuvir, IFN-free treatment regimens have been made possible. With the use of second-generation DAAs, SVR rates of over 90% have been reported.[8]In genotype 3, the improvement in SVR rates is relatively suboptimal and is being considered the most difficult genotype to treat and thus representing a major challenge.[9]Sofosbuvir, a pangenotypic nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase, has been approved in January 2014.[10]In India sofosbuvir came in the market April 2015.There was not much published Indian data available about the efficacy of sofosbuvir containing regimens at that time. We conducted this prospective, observational study at our centre to show the efficacy of SOF-based regimens in our Indian population. Since the predominant genotypes of HCV in India are genotype 3, followed by genotype 1 as confirmed in various Indian studies [11] and genotype 3 is difficult to treat virus at present, we enrolled the genotype 3 patients in our study.

2. Aims and Objectives

1) To assess the treatment efficacy of sofosbuvir containing regimens in chronic hepatitis C infected patients of genotype 3 in Indian population.
2) To assess the treatment efficacy among the various subgroups of the treated patients.

3. Materials and Methods

Study population: All the consecutive chronic hepatitis C, genotype 3 infected patients from outpatient and inpatient departments, fulfilling the inclusion and exclusion criteria were enrolled in the study from May 2015 to December 2016. Informed consent of the study participants was obtained in all cases. The study had approval of local Ethical Committee.

Study Design: It is a prospective, observational, non randomized study.

Sample Size: We screened 89 patients for the study and a total of 73 patients were included in study and for the final study analysis only 69 patients included.

Eligibility Criteria for study

Inclusion Criteria:
1) Chronic hepatitis C infected patients with genotype 3
2) Treatment naive and Treatment Experienced patients.
3) Non cirrhotic and well compensated cirrhotic patients
4) Detectable Base line HCV RNA

Exclusion Criteria:
1) Chronic liver disease of a non-HCV etiology.
2) Co Infection with hepatitis B virus or HIV
3) Contraindications to RBV and Interferon therapy
4) Patients with chronic kidney disease (Those having GFR<30ml/min)
5) Current or prior history of clinical hepatic decompensation (eg, ascites, jaundice, encephalopathy, or variceal haemorrhage)
6) Evidence of Hepatocellular carcinoma.

The enrolled patients were subjected to detailed history and physical examination to look for cirrhosis and any co morbid conditions. The various laboratory and imaging tests for assessment of cirrhosis and base line viral load were done before the commencement of treatment protocol. After discussing with patients and attendants about the efficacy ,safety ,duration of treatment and regimen of treatment, patients were divided into following two groups (A and B) as per patient and treating physician preferences and received treatment as per EASL 2015 guidelines at that time without any randomization[10].

a) Tab Sofosbuvir 400mg per day plus
Tab Ribavirin 1200mg if weight >75 kg, 1000mg if weight <75kg.
Treatment was given for 24 weeks.
OR
b) Tab Sofosbuvir 400mg per day plus
Tab Ribavirin 1200 mg if weight >75 kg,1000 mg if weight <75kg plus
Peg Interferon -α2a 180 microgram subcutaneously weekly.
Treatment was given for 12 weeks

During the treatment course patients were followed for drug compliance and any adverse drug event. Patients were monitored by clinical and standard laboratory tests on follow up visit to OPD. HCV RNA was measured at baseline, 4 week and at the end of treatment. After the completion of treatment protocol, these patients were followed for further 12 weeks and then quantitative HCV RNA level was done to check SVR12. SVR12 is defined as HCV RNA level < the lower limit of quantification (LLOQ, ie, ≤ 30 iu/m) 12 weeks after last dose of study drug [10].

Statistical methods and Data analysis
Statistical analysis was performed using software SPSS version 16.0. Results were expressed as mean± S.D. Qualitative data was tabulated in frequencies and percentages. Quantitative data was given in mean and standard deviation. The data was analysed by using following statistical tests:

Chi-Square test to detect significant P valve ($p<0.05$).

Clopper-pearson method: To see the SVR12 among different treatment groups and subgroups of patient.
Univariate analysis was done to assess response in relation to treatment.

Multivariate logistic- regression test to show relationship between a SVR12 and various demographic and baseline clinical characteristics.

4. Results

Group A-Dual Regimen:Sofosbouvir Plus Ribavirin(SR):(n=39)
Total of 39 patients were included in this group. The majority of patients were males 25(64.1%), with mean age in years was 57.8±6.The total number of cirrhosis patients were 9 (23.1%).The total number of treatment naive patients were 27(69.2%) while 12(30.8%) patients were treatment experienced .

Table 1: Overall treatment response at 4 weeks & SVR12

	Yes	No
Rapid virological response(RVR)	34 (87.2%)	05 (12.8%)
Sustained virlogical response (SVR 12)	34 (87.2%)	05 (12.8%)

The overall sustained virological response at 12 weeks(SVR12) was achieved in 34 (87.2%) out of 39 patients is shown in table 1.

Table 2: Treatment response (SVR12) in subgroups

Sub groups	*SVR 12*
Treatment naive (TN)	25 (92.6%)
Treatment Experienced (TE)	09 (75%)
Cirrhosis	06 (66.7%)
Non cirrhosis	28 (93.3%)

The treatment response in various subgroups is shown in table 2.In treatment naive group SVR12 was achieved in 25 of 27 patients (92.6%) while 09 of 12 (75%) patients

achieved SVR12 in treatment experienced group. In cirrhotic patients SVR12 was achieved only in 06 of 9 patients (66.7%) while in non cirrhotic patients28 of 30 (93.3%) have achieved SVR12.

Table 3: The predictors for treatment response (SVR12).Multivariate Analysis

Factors	*SVR 12*		*p value*
	Yes	*No*	
Cirrhosis			0.03*
Yes	6	3	
No	28	2	
Treatment history			0.1
Treatment Naive	25	2	
Treatment Experienced	9	3	
Age			0.2
<65 years	32	4	
>65 years	2	1	
Sex			0.8
Male	22	3	
Female	12	2	
BMI			--
<30 kg/m^2	34	5	
>30 kg/m^2	--	--	
HCV RNA Log 10			0.8
<6 log	15	2	
≥ 6 log	19	3	

* Statistically significant (p<0.05)

Multivariate analysis was done to show the factors predicting the response (SVR12) is shown in table no 3.Only cirrhosis was significant predictor for response (SVR12).

Group B-Triple Regimen: Sofosbuvir Plus Ribavirin Plus Peg interferon (SPR):(n=30)

Total no of patients were 30 in this group. The majority of patients were males 23(76.7%), with mean age in years 56.2±9.08.The total number of cirrhosis patients were 10(33.3%).The total number of treatment naive patients were 22(73.3.%) while 8 (26.7%) patients were treatment experienced .

Table 4: The overall treatment response at 4weeks and 12 weeks (SVR12):

	Yes	No
RVR	27 (90%)	03 (10%)
SVR 12	27 (90%)	03 (10%)

The overall sustained virological response at 12 weeks (SVR12) was achieved in 27 of 30 patients (90%) is shown in table 4.

Table 5: Treatment response (SVR12) in subgroups:

Sub groups	*SVR 12*
Treatment naive (TN)	21 (95.4%)
Treatment Experienced (TE)	06 (75%)
Cirrhosis	07 (70%)
Non cirrhosis	20 (100%)

The treatment response in various subgroups is shown in table 5. In treatment naive group SVR12 was achieved in 21 of 22 patients (95.4%), while 6 of 8 patients (75%) patients achieved SVR12 in treatment experienced group. In cirrhotic patients SVR12 was achieved only in 7 (70%) patients while all non cirrhotic 20 (100%) patients have achieved SVR12.

Table 6: The predictors for treatment response (SVR12), Multivariate Analysis:

Factors	SVR 12		p value
	Yes	**No**	
Cirrhosis			0.009*
Yes	7	3	
No	20	--	
Treatment history			0.09
Treatment Naive	21	1	
Treatment Experienced	6	2	
Age			0.4
<65 years	23	2	
>65 years	4	1	
Sex			0.6
Male	21	2	
Female	6	1	
BMI			--
<30 kg/m^2	25	3	
>30 kg/m^2	--	--	
HCV RNA Log 10			0.3
<6 log	17	1	
≥ 6 log	10	2	

*Statistically significant (p<0.05)

Multivariate analysis was done to show the factors predicting overall response (SVR12) are shown in table no 6.Only cirrhosis was the significant predictor for SVR12.

Table 7: Comparison of response (SVR 12) among both groups

Group	Regimen		p value
	S.R (39)	SPR (30)	
Overall	34 (87.2%)	27 (90%)	0.7
Treatment Naive	25	21	0.6
Treatment Experienced	09	06	0.7
Cirrhosis	06	07	0.4
No cirrhosis	28	20	0.6

The overall response of treatment was high in both the groups. The overall response was higher in interferon containing regimen as compared to interferon free regimen but the difference was statistically insignificant.

5. Discussion

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease world wide .[1]Chronic hepatitis C and its complications impose a substantial burden on affected patients, healthcare systems and society.[2,3]The introduction of direct acting antiviral agents, in particular sofosbuvir (SOF), has revolutionized the treatment for chronic hepatitis C virus. With SOF-based regimens, we have achieved high cure rates and decreased the duration of treatment. In this prospective observational study, we compared our real-world experience with SOF-based regimens to the results reported by Phase 3 trials.

Group A-Dual Regimen: SOF Plus Ribavirin (SR)

Total number of patients was 39 in this group, the majority of patients were males 25 (64.1%). The mean age in years was 57.8±6. Treatment experienced patients were 12

(30.8%).Total number of cirrhotic patients were 9 (23.1%).The overall treatment response (SVR12) was achieved in 34 of 39 patients(87.2%) which is almost comparable with phase III clinical trials and other recently conducted clinical studies. The comparison between our study and those of phase III trials and other studies is shown in table 8:

Table 8: The comparison between our study and those of phase III trials and other studies- SR Group:

Response	Our Study	Valence Study[12]	Boson Study[13]	Ingiliz et al[16]	Chulanov et al[14]	Christina et al[19]	Shalimar et al[21]	Anurag et al[17]
SVR12 overall	87.2%	85%	84%	91%	90%	79%	91%	89.4%

The SVR12 achieved in various subgroups is shown in table 9.In cirrhotic patients out of 9 only 6 (66.7%) achieved SVR12while in non cirrhotic patients out of 30, 28 (93.3%) achieved SVR which is statistically significant. Our results are almost similar with the two recently conducted Indian studies by Shalimar et al and Bubun et al. The overall response in our cirrhotic group response was low as compared with phase 3 trials but consistent with clinical studies while in non cirrhotic group response rate was comparable with that of phase III trials and other clinical studies.

The SVR12 was achieved in 25 (92.6%) patients out 27 in treatment naive group while in treatment experienced group 9 (75%) out of 12 patients achieved SVR .The response rate in treatment naive patients was comparable as showed in phase III trials while response was low in treatment experienced group as compared with phase III trials which was probably because, most of our treatment experienced patients were cirrhotic patients. Overall our treatment naive patients had better treatment response as compared to treatment experienced group though this difference was not statistically significant.

Table 9: The comparison of SVR12 achieved in various subgroups – SR Group:

Sub group	Our study SVR12 (%)	Valence study[12] SVR12(%)	Boson study[13] SVR12 (%)	Bubin et al[20]	Shalimar et al[21]
Cirrhosis	66.7%	62-92% (TE-TN)	79%	66.7%	68%
Non cirrhosis	93.3%	87-95% (TE-TN)	87%	93%	91%
Treatment Naive	92.6%	94%	88%		
Treatment Exper.	75%	79%	80%		

The multivariate analysis was done to show the factors predicting the overall response SVR12.Only cirrhosis was the statistically significant factor($p < 0.03$)for those who did not achieve SVR12. In phase III trials they also showed cirrhosis was only significant factor for inferior response. Christina J etal[29] in his recently conducted real world study also showed that cirrhosis was the significant factor for the inferior response.

Group B -Triple regime: Sofosbuvir + Ribavarin + IFN (SPR group):

The total no of patients were 30 in this group. The majority of the patients were males 23 (76.7%) . The mean age in years was 56.20 ±9.The treatment naive patients were 22(73.3%) while 8 (26.7%) patients were treatment experienced. Total no of cirrhotic patients were 10 (33.3%).

The overall response (SVR12)was achieved in 27 (90%) patients out of 30 in SPR group which is almost comparable with phase III clinical trials and various other recently conducted clinical studies is shown in table 10.

Table 10: The comparison between our study and those of phase III trials and other studies – SPR Group:

Response	Our Study	Boson[13]	Ingiliz et al[16]	Alqahtani *et al*[15]	Dalgard etal[18]	Bubun et al[20]
SVR12	90%	93%	94%	89%	92%	89%

The SVR12 achieved in various subgroups is shown in table 11.In cirrhotic patients 7(70%) out of 10 achieved SVR12 while all non cirrhotic patients 20(100%) have achieved SVR which is statistically significant ($p<0.009$). Similar response was shown in recently conducted Indian study by Bubun etal[30].The overall response in our cirrhotic group was low as compared with phase 3 trial (Boson)while in non cirrhotic group response rate was high as shown in phase III trial.

In treatment naive group the SVR12 was achieved in 21 (95.4%) out 22 while in treatment experienced group 6(75%) out 8 patients achieved SVR12.The response rate in treatment naive patients was comparable as shown in phase III trial (Boson). Response rate was low in treatment experienced group as compared with phase III trial (Boson) which was probably because most of our treatment experienced patients were cirrhotic patients.

Table 11: The comparison of SVR12 achieved in various subgroups – SPR Group:

Subgroup SVR12(%)	Our study SVR 12(%)	Boson study[13] SVR12(%)	Bubun etal[20]
Cirrhosis	70%	88%	66.7%
Non cirrhosis	100%	95%	93%
Treatment naive	95.4%	95%	
Treatment experienced	75%	91%	

There were 5 patients in SR group who did not achieve SVR(non responders) . They also had not achieved RVR, but had shown a reduction of viral load. The possible explanation for it could be that out of the 5 patients, 3 patients were having advanced fibrosis (high APRI score) and were treatment experienced i.e. they had earlier not responded to Pegylated Interferon and Ribavirin combination. The other 2 patients were treatment experienced who didn't achieve SVR in interferon based therapy. Poor compliance (missed drug dose) could be another reason for non response as duration of treatment is longer in SR group. In SPR group, three patients had not achieved SVR though they also had shown a reduction of viral load during treatment course. All of them probably had

advanced fibrosis (high APRI score) and were treatment experienced(failure).Though treatment experience was not shown significant factor for the inferior response in phase III trials, in our study overall treatment experienced group patients have responded less as compared to treatment naive group although statistically insignificant. Small sample size may have contributed to the difference. Treatment experience may still be the significant factor for the inferior response in SOF based regimens in real world setting.

The overall treatment response was low in our cirrhotic group included in both the regimens as compared with phase III trials but our results were consistent with two recently conducted Indian studies by Bubun et al[30] and Shalimar etal [32]-a real world experience. All those cirrhotic patients who didn't respond in both groups seem to have compensated cirrhosis but actually could have advanced fibrosis(high APRI) as biopsy was not done and this could be the possible reason for inferior response. Our cirrhotic patients were mostly treatment experienced patients who didn't respond with interferon based therapy.

The other important feature in our study is that there was high concordance (100%) between RVR and SVR12 in both the groups as showed by Ruchir et al[25] in recently conducted study. So the pre-treatment HCV RNA and demonstrating its absence at 12 weeks after the end of therapy may suffice in treatment with Sofosbuvir especially in the resource poor countries like India.RVR and ETR may not be tested routinely.

The results of our study have shown that patients with genotype 3 HCV achieve overall superior rates of SVR with 12 weeks of sofosbuvir plus peginterferon and ribavirin than they do with 24 weeks of sofosbuvir and ribavirin although statistically insignificant. This could be due to small sample size in our study and non randomization. Numerically superior SVR 12 rates were also observed across all major subgroups of genotype 3 patients who received triple therapy as compared with those receiving IFN-free treatment.

Newer all-oral, ribavirin-free treatments for chronic HCV have been approved since this study, along with ongoing efforts to develop a pan-genotypic drug. With the rapid development of more effective and tolerable treatments, the SOF-based regimens discussed here have been replaced with newer options to treat chronic HCV in the west, although these regimens may still remain relevant in developing countries like India. Yet, this study highlights the importance of evaluating efficacy (ie, Will this treatment work under ideal circumstances?).We also provide data for future analyses of HCV treatment among our multiethnic population. This study also paves the way for more research, in genotype 3 HCV infection, which though was initially considered to be easy to treat with high SVR, is now considered the most difficult to treat. With the development of new drugs like DAA acting at different viral targets, the future holds promise.

6. Conclusion

1) Sofosbuvir containing regimens have an overall good treatment efficacy in hepatitis C genotype-3 patients in our Indian population.
2) Triple drug regimen containing Sofosbuvir, Pegylated Interferon and Ribavirin had showed a better overall treatment response than the dual regimen containing Sofosbuvir and Ribavirin group. Triple drug therapy could be still preferred in selected patients who are Interferon eligible with genotype 3 Hepatitis C related compensated Cirrhosis in our Indian population.
3) The overall treatment response was relatively lower in cirrhotic patients in both the regimens as shown in earlier studies.
4) Sofosbuvir with Ribavirin is still a treatment option with the available newer regimens in Indian population who are Interferon ineligible.
5) There was high concordance (100%) between RVR and SVR12. So checking the pre-treatment HCV RNA and demonstrating its absence at 12 weeks after the end of therapy may suffice in treatment with Sofosbuvir especially in the resource poor countries like India.

Abbreviations

HCV Hepatitis C virus
HCC Hepatocellular Carcinoma
CHB Chronic Hepatitis B
ALT Alanine aminotransferase
HCV Hepatitis C virus
SVR Sustained Virological Response
SVR12 Sustained Virological Response at 12 weeks.
RVR Rapid virological Response
DAA Direct Antivirals
SOF Sofosbuvir
SR group Sofosbuvir and Ribavirin group
SPR group Sofosbuvir , Ribavirin and peg interferon group
RBV Ribavirin
PEG-IFNα Pegylated Interferon α
CBC Complete Blood Count
LFT Liver Function Test
TSH Thyroid Stimulating Hormone

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