ORIGINAL RESEARCH PAPER

Volume-8 | Issue-4 | April-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFICACY OF SOFOSBUVIR PLUS RIBAVIRIN WITH PEGINTERFERON-ALFA IN PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 3 INFECTION IN INDIAN POPULATION.

Gastroenterology

Hilal Ahmed Tali* Department of Gastroenterology & Hepatology, Yashoda Hospital, Hyderabad *Corresponding Author

Rubiya Ryhan Department of Immunohematology and Transfusion Medicine GMC, Srinagar

Irshad Ahmad Tali Department of Gynae and Obstetrics GMC, Srinagar

Falak Ara Department of Anaesthesia GMC, Srinagar

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 plus ribavarin with peginterferon-alfa in chronic hepatitis C infected patients of genotype 3.

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 30 patients were included in study. Patients received 12 weeks treatment of Sofosbuvir plus Ribavirin plus peg interferon (SPR). 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 90%.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. The overall treatment response was relatively lower in cirrhotic patients. Triple drug therapy could be still alternative treatment regimen for hepatitis C with genotype 3 patients who are Interferon eligible .

KEYWORDS

Hepatitis C, Sofosbuvir, sustained virological response (SVR)

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.

AIMS AND OBJECTIVES

1. To assess the treatment efficacy of sofosbuvir plus ribavarin with peginterferon-alfa in chronic hepatitis C infected patients of genotype 3.
2. To assess the treatment efficacy among the various subgroups of the treated patients.

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 study.

SAMPLE SIZE:

1. We screened 39 patients for the study and a total of 30 patients were included in study.

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 following

treatment protocol as per EASL 2015 guidelines at that time [10].
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.

RESULTS

Total no of patients were 30 in study. 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 1. The overall treatment response at 4weeks (RVR) 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 1.

Table 2.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 2. 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 3.The predictors for treatment response (SVR12), Multivariate Analysis:

FACTORS	SVR 12		p value
	Yes	No	
Cirrhosis Yes No	07 20	03 --	0.009*
Treatment history Treatment Naive Treatment Experienced	21 06	01 02	0.09
Age <65 years >65 years	23 04	02 01	0.4
Sex Male Female	21 06	02 01	0.6
BMI <30 kg/m2 >30 kg/m2	25 --	03 --	--
HCV RNA Log 10 <6 log ≥ 6 log	17 10	01 02	0.3

* Statistically significant ($p<0.05$)

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

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. The total no of patients were 30 in study. 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 4.

Table-4 The comparison between our study and those of phase III trials and other studies:

Response	OurStudy	Boson[12]	Ingiliz et al[14]	Alqahtani et al[13]	Dalgard etal[15]	Bubun et al[16]
SVR12	90%	93%	94%	89%	92%	89%

The SVR12 achieved in various subgroups is shown in table 5.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[16].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-5 The comparison of SVR12 achieved in various subgroups

Subgroup SVR12(%)	Our study SVR12(%)	Boson study12 SVR12(%)	Bubun etal16
Cirrhosis	70%	88%	66.7%
Non cirrhosis	100%	95%	93%
Treatment naive	95.4%	95%	
Treatment experienced	75%	91%	

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 as compared with phase III trials but our results were consistent with two recently conducted Indian studies by Bubun et al[16] -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 as showed by **Ruchir** et al[17] 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.

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.

CONCLUSION

1. Triple drug regimen containing Sofosbuvir, Pegylated Interferon and Ribavirin had showed a better overall treatment response.Triple drug therapy could be still alternative treatment regimen for hepatitis C with genotype 3 patients who are Interferon eligible .
2. The overall treatment response was relatively lower in cirrhotic patients.
3. 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
SPR 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

REFERENCES

1. Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect 2011;17:107–115.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection.J Hepatol. 2014;60(2):392–420.
3. Dugum M, O'Shea R. Hepatitis C virus: here comes all-oral treatment. Cleve Clin J Med. 2014;81(3):159–72.
4. Hatzakis A, Chulanov V, Gadano AC, Bergin C, Ben-Ari Z, Mossong J, et al. The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm – Volume 2. J Viral Hepat 2015;22 Suppl 1:26-45.
5. Westbrook RH, Dusheiko G. Natural history of hepatitis C. Journal of Hepatology. 2014 Nov;61(1, Supplement):S58–68.
6. Arase Y, Kobayashi M, Suzuki F, Suzuki Y, Kawamura Y, Akuta N, et al. Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. Hepatology 2013;57:964–973.
7. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al.Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis.JAMA 2012;308:2584–2593.
8. Bansal S, Singal AK, McGuire BM, Anand BS . Impact of all oral anti-hepatitis C virus therapy: A meta-analysis. World J Hepatol 2015;7:806-13.
9. Javier Ampuero, K Rajender Reddy, Manuel Romero-Gomez.Hepatitis C virus genotype 3: Meta-analysis on sustained virologic response rates with currently available treatment options. World J Gastroenterol 2016 June 14; 22(22): 5285-5292.
10. EASL -Clinical Practice Guidelines [Internet].[cited 2015 Aug 9].Available from:http://www.easl.eu/research/our-contributions/ clinical-practiceguidelines/detail/recommendations-on-treatment-of-hepatitis-c-2015/report/6.
11. Raghuraman S, Shaji RV, Sridharan G, Radhakrishnan S, Chandy G, Ramakrishna BS, et al. Distribution of the different genotypes of HCV among patients attending a tertiary care hospital in south India. J Clin Virol. 2003 Jan;26(1):61–9.
12. Foster GR, Pianko S, Brown A, Forton D, Nahass RG, George J,et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment experienced patients with cirrhosis and hepatitis C virus genotype2 infection. Gastroenterology 2015; 149: 1462-1470.
13. Alqahtani S, Zeuzem S, Manns M, Kuo A, Di Bisceglie AM,Reddy R, Mailliard M, O'Leary J, Pockros P, Kwo PY, Lim JK,Vargas HE, Fried MW, Nelson D, Sulkowski MS. Safety and effectiveness of sofosbuvir-based regimens for the treatment of hepatitis C genotype 3 and 4 infections: Interim analysis of a prospective, observational study. J Hepatol 2015; 62: S652.
14. Ingiliz P, Christensen S, Hueppe D, Lutz T, Schewe K, BoeseckeC, Simon KG, Schmutz G, Baumgarten A, Busch H, Maussemail S.German multicenter cohort on sofosbuvir-based treatments in HCV mono- and HIV/HCV co-infected patients (GECOSO). J Hepatol 2015; 62: S650.
15. Dalgard O, Weis N, Noraberg G, Isaksen K, Oevrehus A,Skalshoj Skjar M, Weiland O. Sofosbuvir containing regimes to patients with HCV genotype 3 infection. A scandinavian real-life experience. J Hepatol 2015; 62: S287.
16. Bubun patel,Sukanya,Raghavendra,nayana Joshi,Rohit,Ajit kumar et al. DAAs in genotypes 2 and 3 of chronic hepatittis C- a real world experience. Journal of Clinical and Experimental Hepatology . July 2016 ; Vol. 6 (S1):S8–S22.
17. Patel R, Chaubal A, Parikh P, Rathi C, Ingle M, Prabha Sawant.(2016) Is Testing for Rapid Virological Response (RVR) Necessary in the Present Era of Treatment of Hepatitis C? : An Analysis from South Asia. Gastroenterol Pancreatol Liver Disord 3(5): 1-4.