Results of Sofosbuvir Plus Ribavirin in Patients With Hepatitis C Related Decompensated Cirrhosis

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Background: Sofosbuvir (SOF), a direct acting antiviral, has revolutionized the treatment of chronic Hepatitis C Virus (HCV) infection. However, data is scarce about efficacy of SOF plus Ribavirin (RBV) in Indian patients with decompensated cirrhosis. We evaluated the efficacy of SOF plus RBV in decompensated cirrhosis, and compared the outcome with compensated cirrhosis and non-cirrhotics. **Patients and methods:** Consecutive decompensated cirrhotic patients of chronic HCV with detectable HCV RNA were treated with 24-week course of SOF (400 mg) plus weight based RBV. Sustained Virological Response (SVR), Child Turcotte Pugh (CTP) and Model for Endstage Liver Disease (MELD) scores were assessed at 36 weeks (i.e. 12 weeks after completion of therapy). Non-cirrhotic chronic hepatitis C patients and patients with compensated cirrhosis treated with SOF plus RBV during the same period were used as controls. During the period of this study ledipasvir and daclatasvir were not available in India. **Results:** A total of 47 patients [median age 50 (29–82) years, 64% males] with decompensated cirrhosis were included as ‘cases’ in the study; while, 27 patients with compensated cirrhosis and 29 patients with chronic hepatitis were included as ‘controls’. Age, gender, HCV RNA levels, and genotype distribution were similar in cases and controls. The median CTP and MELD scores of cases were 8 (7–12) and 13 (6–25), respectively. Among cases 39 (83%) could complete the therapy, while 1 (2%) was intolerant and 7 (15%) died before completion of therapy. End of Treatment Response (ETR) was achieved in 37/39 (95%) cases. Of these, another 3 died before SVR, and 7 failed to achieve SVR, thus 27/34 (79%) could achieve SVR. Thus according to intention-to-treat analysis, only 27/47 (57%) cases could achieve SVR. In comparison, 24/28 (86%) compensated cirrhotics and 27/28 (96%) of chronic hepatitis achieved SVR. There was a significant improvement in mean CTP score in cases who achieved SVR ($P < 0.01$) compared to those who did not achieve SVR/ETR. On multivariate analysis the only independent factor influencing successful outcome patients was a serum albumin >3.5 g/dL. **Conclusions:** A 24-week course of SOF plus ribavirin in decompensated HCV cirrhosis could lead to SVR in only 57% of patients. The failure of therapy in 43% patients was either due to non-response, intolerance, or death. A serum albumin of more than 3.5 is associated with success of antiviral therapy. Thus an early initiation of antiviral therapy is recommended before decompensation sets in as it precludes successful outcome. (J CLIN EXP HEPATOL 2019;9:4–12)

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Abbreviations: CBC: Complete Blood Count; CHC: Chronic Hepatitis C; CTP: Child Turcotte Pugh; DAA: Direct-Acting Antivirals; ETR: End of Treatment Response; GFR: Glomerular Filtration Rate; HBsAg: Hepatitis B Surface Antigen; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; LFT: Liver Function Test; MELD: Model for Endstage Liver Disease; PegIFN: Pegylated Interferon; RFT: Renal Function Test; RNA: Ribonucleic Acid; RVR: Rapid Virological Response; SOF: Sofosbuvir; SVR: Sustained Virological Response; UGI: Upper Gastro-intestinal; USG: Ultrasonography

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It is estimated that around 170 million people worldwide are affected with the Hepatitis C Virus (HCV) infection.¹ HCV infection leads to a slowly progressive liver disease. Cirrhosis occurs usually around 20–30 years after the infection.² The rate of decompensation is 3.9% per year, and the Hepatocellular Carcinoma (HCC) rate is 3% per year.³ As most patients are asymptomatic for several years, early diagnosis remains a challenge. Stabilization of the liver functions is an important goal among both groups of compensated HCV infection and decompensated patients, who are not candidates for liver transplantation, whereas, prevention of HCV recurrence is the goal in post-liver transplantation patients.⁴

Sustained Virological Response (SVR) is tantamount to cure in anti-HCV treatment. SVR at present is defined as aviremia 12 weeks after the completion of antiviral therapy for chronic HCV infection.^{5–7} Till recently Interferon (IFN) based treatment was the standard of care in anti-HCV treatment. Direct Acting Antivirals (DAA) were the

major breakthrough in the treatment of HCV infection. Sofosbuvir (SOF) is an important DAA, present in almost all DAA regimens. Multiple studies have shown that the efficacy of IFN-free regimens, as studied in different phase-3 trials is >95% SVR rate in patients with chronic hepatitis and compensated cirrhosis.^{8,9} However data regarding efficacy of DAAs in decompensated cirrhosis patients is scarce, especially from India.

This study was undertaken to study the efficacy of SOF plus Ribavirin (RBV) in decompensated HCV cirrhosis patients from India.

PATIENTS AND METHODS

Study Setting

The study was conducted from May 2015 to June 2016, in patients attending inpatients or outpatients' department of Sir Ganga Ram Hospital, New Delhi. The Ethics Committee of the hospital approved the study and a written informed consent was obtained from all the participants. The study conformed to the Helsinki declaration of 1975 as revised in 1983.

Patients

Inclusion Criteria

Consecutive decompensated cirrhotic patients of chronic HCV with detectable HCV RNA were included in the study as 'cases'. Decompensated cirrhosis was defined as Child B or C with history of ascites, encephalopathy, Upper Gastro-intestinal (UGI) bleed secondary to varices, or jaundice. Non-cirrhotic chronic hepatitis C patients and patients with compensated cirrhosis treated with SOF plus RBV during the same period were used as 'controls'. Both cases and controls were ≥ 18 years old.

Exclusion Criteria

Patients with pregnancy; Glomerular Filtration Rate (GFR) less than 30 mL/min; HBV or Human Immunodeficiency Virus (HIV) co-infection; HCC; expected life span of less than one year due to various co-morbidities; refusal to participate; contraindication to the use of RBV; and patients on anticonvulsants (phenytoin, carbamazepine), rifabutin, rifampicin, amiodarone were excluded from the study.

Evaluation

Each patient underwent detailed evaluation in form of history, physical examination, and relevant investigations. History of previous upper and lower GI bleeds, hepatic encephalopathy, ascites, other co-morbidities like diabetes, hypertension, HIV, hepatitis B, chronic kidney disease, liver or kidney transplantation were obtained from all patients. History of current use of amiodarone, carbamazepine, phenytoin, rifampicin, and rifabutin were also obtained. Past history of medication use for HCV, its

details with outcome were taken. All patients underwent following investigations: Complete Blood Count (CBC), Liver Function Test (LFT), Renal Function Test (RFT), Hepatitis B Surface Antigen (HBsAg), HIV, Ultrasonography (USG) abdomen, Fibroscan, UGI endoscopy, HCV RNA quantitative analysis, and HCV genotype.

Treatment Protocol and Follow-up

All patients (cases and controls) were started with SOF and RBV with the intention of 24 weeks of treatment. During the period of this study Ledipasvir (LDV) and daclatasvir (DCV) were not available in India. Female patients of reproductive age group were cautioned not to become pregnant while receiving ribavirin containing antiviral regimens, and up to 6 months after stopping. Follow-up was done through direct patient visit, telephone call, or email. Follow up was done at 4, 12, 24, and 36 weeks (i.e. 12 week after treatment completion). During each visit patients were assessed for clinical improvement or deterioration and any adverse effects. In addition to these scheduled follow-ups, patients also visited or called as and when needed depending on patients' clinical status. The dose of RBV was modified on follow-up if patient developed anemia at any time.

Primary Objective

The primary objective of the study was to compare the SVR rate in cases and controls at 12 weeks from end of treatment.

Secondary Objectives

The secondary objectives of the study were to assess change in CTP and MELD scores at 12 weeks after completion of the treatment in decompensated cirrhosis and to study factors influencing achievement of SVR.

Statistical Analysis

Continuous data were expressed as median (range) and compared using Mann Whitney *U* test or Wilcoxon signed rank test. Categorical data were expressed as number (%) and compared using Fisher's exact test or Pearson Chi-square test. A *P* value <0.05 was considered significant. Statistical analysis was conducted using the SPSS 17.0 statistical package (SPSS Inc, Chicago, IL, USA).

RESULTS

Patients

From May 2015 to June 2016, a total of 55 patients with decompensated cirrhosis with HCV infection were screened for the study. However 8 patients were excluded due to following reasons: (i) GFR less than 30 mL/min ($n = 3$); (ii) HBsAg or HIV co-infection ($n = 2$); (iii) HCC ($n = 2$); and (iv) refusal to participate ($n = 1$). Thus

remaining 47 patients were included in the study as 'cases'. During the same duration, 28 patients of compensated cirrhosis due to HCV and 28 patients of non-cirrhotic Chronic Hepatitis C (CHC) were included in the study as 'controls'.

The baseline characteristics of included patients are given in Table 1. The age, gender distribution, genotype, HCV RNA, and prior treatment history were similar in cases and controls. The median CTP and MELD scores of cases were 8 (range 7–12) and 13 (6–25), respectively; and these were significantly worse than in controls. Ascites was present in 66% of cases, while none of the controls had ascites. Bilirubin, albumin, abnormal PT (INR), hemoglobin and platelet levels were significantly worse in cases as compared to controls.

Treatment and Results

All patients (cases and controls) were started with SOF and RBV with the intention of 24 weeks of treatment.

Among the 47 patient of decompensated cirrhosis group, one patient was intolerant to the antiviral therapy; hence, it was stopped. Remaining 46 patients continued with therapy, however, 7 patients died before completion of 24 weeks of treatment. The cause of these deaths were advanced liver disease. Thus a total of only 39 (83%) patients of 47 could complete the 24 weeks of treatment, and these were assessed for ETR. Thirty-seven out of 39 patients (95%) achieved ETR and 2 patients (5%) did not achieve ETR. During follow-up of next 12 weeks, additionally 3 patients died. Thus only 34 (92%) of 37 patients who had achieved ETR could be assessed for SVR. Of these 34 patients only 27 (79%) could achieve SVR and rest 7 (21%) could not achieve SVR.

Among controls, all 27/28 (96%) patients with compensated cirrhosis could complete 24 weeks of therapy, while one patient died due to development of rapid decompensation following HCC (which was not detected at

Table 1 Baseline Characteristics of HCV Patients Treated with Sofosbuvir + Ribavarin for 24 Weeks.

	Decompensated cirrhosis (n = 47, cases)	Compensated cirrhosis (n = 28, controls)	Chronic hepatitis (non-cirrhotic) (n = 28, controls)
Age	50 (29–82)	53 (26–76)	50 (18–65)
Gender			
Males	30 (64%)	23 (82%)	16 (57%)
Females	17 (36%)	5 (18%)	12 (43%)
Genotype			
1 and 4	10 (21%)	8 (29%)	8 (29%)
2 and 3	37 (79%)	20 (71%)	20 (71%)
HCV RNA	4×10^5 (3×10^1 – 9×10^6)	7×10^5 (6×10^3 – 3×10^7)	6×10^5 (2×10^3 – 2×10^7)
Prior treatment			
Treatment naïve	38 (81%)	24 (86%)	23 (82%)
Treatment experienced	9 (19%)	4 (14%)	5 (18%)
CTP score	8 (7–12)	5* (5–6)	5* (5–6)
MELD	13 (6–25)	7* (6–13)	6* (6–20)
Bilirubin	2.0 (0.4–12.0)	1.0* (0.3–2.1)	1.0* (0.4–1.5)
Albumin	2.9 (1.6–4.8)	3.6* (3.0–4.8)	3.6* (3.0–4.8)
INR	1.3 (0.9–3.6)	1.0* (1.0–1.7)	1.0* (0.8–1.4)
Hemoglobin	11 (7–16)	13* (7–16)	12* (9–17)
Platelets	106 (35–309)	170* (110–290)	184* (102–340)
Creatinine	1.0 (0.4–1.8)	1.0 (0.6–1.0)	0.8 (0.5–4.0)
Ascites			
Absent	16 (34%)	28* (100%)	28* (100%)
Present	31 (66%)	0 (0%)	0 (0%)
Encephalopathy			
Never had encephalopathy	42 (89%)	28 (100%)	28 (100%)
Had encephalopathy	5 (11%)	0 (0%)	0 (0%)
Variceal bleeding			
Never bled	42 (89%)	26 (93%)	29 (100%)
Past bleeder	5 (11%)	2 (7%)	0 (0%)

* $P < 0.05$ in comparison to decompensated cirrhosis.

baseline). All the remaining 27 patients (100%) who completed therapy achieved ETR. After 12 week follow up 24/27 (89%) could achieve SVR and 3/27 (11%) could not achieve SVR. Of 28 patients with chronic hepatitis (non-cirrhotics), all (100%) could complete 24 weeks of therapy. These 28 patients were assessed for ETR and 27 (96%) achieved ETR; and of these 27 patients assessed for SVR, all of them (100%) achieved SVR.

Thus according to intention-to-treat analysis only 27 (57%) out of 47 decompensated cirrhotics (cases) could achieve SVR and the rest 20 (43%) failed therapy either due to non-response, intolerance or death. In contrast 24/28 (86%) of compensated cirrhotics and 27/28 (96%) of chronic hepatitis were able to achieve SVR (Figure 1).

Factors Influencing Success of Therapy

Out of the total cohort of 103 patients (47 cases and 56 controls), 78 (76%) had successfully achieved SVR, while rest 25 (24%) failed the therapy due to following reasons: non-response ($n = 13$), intolerance to therapy ($n = 1$), and death ($n = 11$). Various baseline factors were analyzed to determine which factors were associated with success of therapy (Table 2). On univariate analysis, following factors were found to be associated with success of therapy: low CTP score, low MELD score, low bilirubin levels, high albumin levels, low INR, absence of ascites, and absence of decompensation (Table 2). When these factors were entered into multivariate analysis by binary logistic regression (Table 3), only high albumin level was found to be independently associated with success of therapy [odds ratio 2.1 (95% CI 1.2, 3.9)]. When ROC curve was prepared to find out the utility of serum albumin level in predicting the success of therapy the Area Under ROC Curve (AUROC) was 0.716 (95% CI 0.604, 0.828; $P = 0.001$). The maximum value of Youden's index corresponded

to a serum albumin level of 3.5 g/dL. Thus a cut-off level of ≥ 3.5 g/dL of serum albumin best predicted the success of therapy with a Positive Pressure Ventilation of 91% (95% CI 79%, 96%) (Table 4 and Figure 2).

Causes of Deaths

In the whole cohort of 103 patients, a total of 11 (11%) patients had died during the study period. Ten (90%) of these deaths had occurred in the decompensated cirrhosis group and one death occurred in the control group due to decompensation. The causes of deaths in the decompensated cirrhosis were complications of end-stage liver disease (hepatorenal syndrome, sepsis, hepatic encephalopathy, and multi-organ failure). On comparison of baseline factors between patients who died ($n = 10$) and those who survived ($n = 37$) in the decompensated cirrhosis group, it was found that none of the baseline parameter was significantly different.

Changes in CTP and MELD Scores

The baseline CTP score in patients with decompensated cirrhosis was 8 (range 7–12) and MELD was 13 (6–25). There was significant improvement in CTP and MELD score in patients who achieved SVR ($n = 27$); while there was no improvement in CTP and MELD scores of surviving patients who did not achieve SVR ($n = 10$) (Figure 3).

DISCUSSION

To summarize the results, our study showed that a 24-week course of SOF plus ribavirin in decompensated HCV cirrhosis could lead to SVR in only 57% of patients. In comparison, 86% of compensated cirrhotics and 96% of chronic hepatitis could achieve SVR. The failure of therapy in 43% of decompensated cirrhosis patients was either due

Figure 1 Flow of patients.

Table 2 Univariate Analysis of Factors Influencing Success of therapy.

	Successful therapy (i.e. achieved SVR) (n = 78)	Failed therapy* (n = 25)	P value
Age	51 (25–82)	50 (18–68)	0.951
Gender			0.806
Males	52 (67%)	18 (72%)	
Females	26 (33%)	7 (28%)	
Genotype			1.000
1 and 4	20 (26%)	6 (24%)	
2 and 3	58 (74%)	19 (76%)	
HCV RNA	5×10^5 (3×10^4 – 3×10^7)	5×10^5 (6×10^3 – 7×10^6)	0.940
Prior treatment			1.000
Treatment naïve	64 (82%)	21 (84%)	
Treatment experienced	14 (18%)	4 (16%)	
CTP score	6 (5–11)	7 (5–12)	<0.001
MELD	7 (6–22)	13 (6–25)	<0.001
Bilirubin	1.0 (0.3–8.0)	2.0 (0.3–12.0)	0.002
Albumin	3.4 (1.6–4.8)	3.1 (1.3–4.7)	0.001
INR	1.0 (0.8–2.2)	1.3 (1.0–3.6)	0.002
Hemoglobin	12 (8–17)	11 (7–15)	0.177
Platelets	168 (67–340)	107 (35–309)	0.076
Creatinine	1.0 (0.5–4.0)	0.9 (0.4–1.6)	0.283
Ascites			0.011
Absent	60 (77%)	12 (48%)	
Present	18 (23%)	13 (52%)	
Encephalopathy			0.091
Never had encephalopathy	76 (97%)	22 (88%)	
Had encephalopathy	2 (3%)	3 (12%)	
Variceal bleeding			0.676
Never bled	73 (94%)	23 (92%)	
Past bleeder	5 (6%)	2 (8%)	
Groups			<0.001
Decompensated cirrhosis	27 (35%)	20 (80%)	
Controls	51 (65%)	5 (20%)	

*Failed therapy patients include those who failed to achieve SVR or ETR (non-responders), those who were intolerant to therapy, and those who died.

Table 3 Multivariate Analysis by Binary Logistic Regression of Factors Influencing Success of Therapy.

	B	S.E.	Wald	df	P value	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
CTP score	0.181	0.269	0.456	1	0.500	1.199	0.708	2.030
Decompensated cirrhosis	−1.504	0.984	2.339	1	0.126	0.222	0.032	1.527
MELD score	0.179	0.164	1.199	1	0.274	1.197	0.868	1.650
Bilirubin	−0.342	0.228	2.240	1	0.134	0.711	0.454	1.112
Albumin	0.764	0.304	6.343	1	0.012	2.148	1.185	3.894
INR	−2.378	1.600	2.208	1	0.137	0.093	0.004	2.135
No ascites	0.020	0.606	0.001	1	0.974	1.020	0.311	3.348

Table 4 Predictive Values of Serum Albumin Level of ≥ 3.5 g/dL for Predicting Success of Anti-viral Therapy.

Serum albumin (g/dL)	Successful therapy (n)	Failed therapy (n)	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	LR+ (95% CI)	LR- (95% CI)
≥ 3.5	39	4	43							
<3.5	39	21	60	50% (38–62%)	84% (64–95%)	91% (79–96%)	35% (29–42%)	77% (72–82%)	3.1 (1.2–7.9)	0.6 (0.4–0.8)
Total	78	25	103							

to non-response, intolerance, or death. We also showed that a serum albumin of more than 3.5 is associated with success of antiviral therapy. Successful antiviral therapy also leads to improvement in liver functions in terms of CTP and MELD scores. Thus we suggest that an early initiation of antiviral therapy is recommended before decompensation sets in, and precludes successful outcome.

Since 1990, IFN based regime were the main stay of treatment with a very low SVR. Since 2001 Peg IFN was in use in CHC with a SVR of 50%.¹⁰ Even then almost 75% of the HCV patients remained devoid of antiviral therapy because of varying reasons. Treatment in the decompensated liver disease remained an area of research interest, where use of IFN is either contraindicated or patients are intolerant. In a previous study done from our center published in 2015, we had shown that cirrhosis was the most common presentation of HCV (56%), and only 45% were eligible for Peg-IFN based treatment.¹¹ Thus the introduction of IFN-free treatment regimens was the need of hour in country like India, where majority of HCV patients present late in the course of their disease.

Availability of DAAs was the major breakthrough in HCV treatment. The structure of HCV virus consists of structural and nonstructural proteins. DAAs target molecular protein structures specific to HCV thereby hindering viral replication. Bocepravir and telepravir, the first DAAs, were available since 2011.¹² FDA approved SOF in 2013.¹³ Currently there are four categories of DAAs: NS5A, NS5B,

NS3/4A, and protease inhibitors. NS5A inhibitors available include LDV, ombitasvir (ABT-267) and DCV. SOF (GS-7977) is a NS5B inhibitor.^{14,15} The efficacy of SOF based regimens was studied in different phase 3 clinical trials, these IFN-free regimens have shown an SVR >90%.⁸

The 24-week course of SOF plus ribavirin treatment in our study gives an SVR of 96% in chronic hepatitis, 93% in the compensated cirrhotics, and 57% in the decompensated cirrhotics. These results match with the results of various phase 3 trials worldwide. In the study by Osinusi et al. that included G1 patients with unfavorable treatment characteristics, treated with 24 weeks, the overall SVR was 68%.¹⁶ In VALANCE trial, SVR in G3 patients with 24 weeks of treatment was 85% overall, 91% in non-cirrhotics, and 68% in the cirrhotics.¹⁷ In the study by Doss et al. study, SVR in G4 was overall 90%, 93% in non-cirrhotics, and 78% in the cirrhotics.¹⁸ In the study by Ruane et al. in G4 group, SVR was 93% overall.¹⁹ In the BOSON study, SVR in G2 was 100% and in G3 84%.²⁰ The SVR12 in one of the other study, patients without cirrhosis was 91.0% and 92.9% for 12 or 16 weeks of therapy, respectively. In patients with cirrhosis treated for 12 or 16 weeks, SVR12 was 79.0% and 83%.²¹ In the study by Sood et al., 44.8% were cirrhotics, 14.3% were decompensated. Overall SVR was 95.8%. SVR rates did not differ among different genotypes but were higher in non-cirrhotics.²²

In advanced HCV related liver diseases, data are scarce, both from western world and from India, regarding the efficacy of 24 weeks of SOF plus ribavirin; especially in terms of, stage of disease, improvement achievable in measurable amount (i.e. improvement in CTP score or MELD scores), and opportunity to delist from liver transplantation waiting list, after achieving the SVR. While the SVR rate in our study in this group was 57%; we were able to show secondary gains with SVR, i.e. improvement in the CTP and MELD score in SVR achievers compared to failure group. With less infrequent side effects of DAA, our study proved the safety of these medications in the advanced liver disease. Initial evidence for improvement in liver function in decompensated cirrhosis came from Afdhal et al., who showed that 48 weeks treatment with SOF/RBV gave SVR12 rate of 72% and led to significant improvement in ascites, encephalopathy, CTP and MELD scores in the majority. However, only Child's status A and B patients were included; there were no Child's C patients in this trial.²³ In the study conducted in Pakistan by

Figure 2 ROC curve for serum albumin as a predictor of successful therapy.

Figure 3 Change in CTP and MELD scores in decompensated cirrhosis group.

Sarwar et al., the study design was similar to our study. There were 51.9% cirrhotics and 17.1% were decompensated. SVR in cirrhotics was 75.4%, in non-cirrhotics was 93%, in decompensated was 68.8%. This study also showed that there was a statistically significant difference among the SVR achievers and failed patients with respect to baseline serum albumin, presence or absence of cirrhosis and CTP scores.²⁴ In the study by Reddy et al., the treatment of decompensated HCV patients with different regimens, including SOF and RBV showed that these drugs are safe and efficacious in this group with a SVR of 75% in G2. This study showed that lesser the MELD, higher the response rate. In this study serum bilirubin, albumin, MELD scores were improved in significant proportion of patients who achieved SVR.²⁵ In the study by Foster, an impact of DAA in decompensated patients, overall viral clearance was achieved in 81.6% (90.5% with genotype 1 and 68.8% with genotype 3). MELD scores also improved in treated patients.²⁶

Host and viral factors predictive of SVR have been studied in the IFN-era and also in the DAA-era. In the IFN plus ribavirin related regimens, the genotype, the pretreatment viral load, virological response during the treatment, age, sex, race, degree of fibrosis, IL 28B

polymorphisms, insulin resistance, vitamin D status, liver cirrhosis stage, all considered as individual factors predicting the response to treatment.²⁷ The same does not hold good in the DAA era. The most important factor that affects the response rate in the DAA era is liver status. Both chronic hepatitis and the compensated cirrhotics showed a better SVR rate than the decompensated cirrhotics in our study. In NEUTRINO trial, the variables associated with therapy response were cirrhosis, IL28B (rs12979860) genotype and ribavirin exposure. In FISSION study, the predictive factors associated with SVR12 were HCV genotype, presence of cirrhosis, HCV-RNA viral load at baseline and ribavirin exposure. In both NEUTRINO and FISSION trials known variables such as older age, black race (self-reported), body mass index ≥ 30 kg/m² that are commonly associated with failure of previous IFN-based treatments were not associated with SVR.²⁸

In the present study, in the univariate analysis, CTP, MELD, bilirubin, INR, albumin, were considered as a predictors of response. On multivariate analysis, only the serum albumin pretreatment, was the independent factor predictive of response. The area under ROC curve for pretreatment serum albumin was 0.716. We found that if the serum albumin levels were >3.5 before the

treatment, higher rates of SVR can be predicted. Our results were consistent with results from other studies. In the study of Foster, an impact of DAA in decompensated patients, baseline serum albumin, serum sodium and age came out as predictive factors of response to therapy. Patients with initial serum albumin <35 g/L, aged >65 or with low (<135 mmol/L) baseline serum sodium concentrations were least likely to benefit from therapy.²⁶ In the study conducted in Pakistan by Sarwar et al., serum albumin of <3.5 g/dL and CTP score >6 was seen in the failed candidates.²⁴

The results from treatment with double DAA regime using ledspavir and daclatasavir are more promising as per the phase 3 and real time experiences from western population in both compensated and decompensated group.^{29,30} SOLAR 2, ALLY 1 studies in the decompensated HCV, treated with daclatasavir or ledspavir along with the SOF and RBV showed an overall good SVR (85–88% in G1 and 57% in G4).^{31,32} The SOLAR-2 study could also show improvement of MELD- and Child–Pugh scores in the treated patients. The same were not available in India when this study was undertaken. The results from pan-genotypic regime using the valpatasavir is still further area of interest, which can avoid the need of genotyping, cost burden to patients.^{33,34} The same has just been launched in India, and results are awaited.

There are two limitations in our study. First, this study was conducted when only SOF was available in India. With the availability of newer DAAs like LDV, daclatasavir and valpatasavir, the SVR rate in decompensated cirrhosis is expected to be much better. Second limitation is small sample size. We recommend a further study on larger sample size to validate the findings of our study.

In conclusion, patients with decompensated cirrhosis show a poorer response to antiviral therapy and a 24-week course of SOF plus ribavirin could lead to SVR in only 57% of patients. The reasons for failure of therapy in these patients are non-response, intolerance, and death due to advanced liver disease. Of all characteristics of poor liver function in decompensated cirrhosis, we found that serum albumin is a good surrogate marker for expected success or failure of therapy. A serum albumin of more than 3.5 g/dL is associated with success of antiviral therapy. Successful antiviral therapy also leads to improvement in liver functions. Thus we propose that an early initiation of antiviral therapy is essential before decompensation sets in and precludes successful outcome.

CONFLICTS OF INTEREST

The authors have none to declare.

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