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Original Research Article

Assessment of efficacy and safety of daclatasvir, sofusbuvir and ribavirin regimen for 12 weeks as compared to daclatasvir and sofusbuvir combination regimen for 24 weeks in decompensated cirrhotic patients due to hepatitis C virus genotype 3 infection

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ABSTRACT

Background: Assessment of efficacy and safety of daclatasvir+sofosbuvir+ribavirin (DCV+ SOF+ RBV) for 12 weeks as compare to daclatasvir and sofusbuvir for 24 weeks in decompensated cirrhotic patients due to hepatitis C virus (HCV) genotype 3 infection.
Methods: An observational, prospective, COHORT study over 1 year, in decompensated cirrhosis due to G3-HCV infected adult patients. Treatment was a combination of sofosbuvir 400 mg/day+daclatasvir 60 mg/day, with or without a weight-adjusted dosing of ribavirin for 12 or 24 weeks. The primary efficacy endpoint was sustained virologic response rates 12 weeks after therapy (SVR 12). The primary safety endpoint was treatment withdrawal rates secondary to severe adverse events.
Results: The 32 patients were screened and 2 were excluded, one patient due to associated HBV+, one patient due to severe anemia. 30 patients were randomized. All 30 randomized patients were divided into two groups. Group 1 was given SOF+DCV+RBV for 12 weeks while group 2 patients were given SOF+DCV for 24 weeks. 81.8% of the participants in the group1 achieved SVR 12. The 90.9% of the participants in the group 2 achieved SVR12 (p=1). No other patient or treatment basal variables influenced the treatment effectiveness. No patient treatment withdrawal secondary to severe adverse events was observed.
Conclusions: Both the regimen SOF+DCV with or without RBV are highly efficacious and safe. Addition of RBV can reduce the treatment duration to 12 weeks, and it will further improve compliance and more convenient for the patients.

Keywords: HCV decompensated cirrhosis, Genotype 3, Sofosbuvir, Daclatasvir, Ribavirin

INTRODUCTION

The prevalence rates of hepatitis C virus (HCV) and HCV genotype (GT) distribution around the Asia-Pacific region were well described in a recent study.[1] Estimated HCV infection rates in the general populations were 0.1-14.7% in the Asia-Pacific region.[1] Overall GT1 is most commonly distribute GT worldwide followed by GT3. In India, GT3 is the most common GT that is about 63% followed by GT1. The majority of patients who acquire HCV do not spontaneously clear the virus and develop chronic HCV infection. Chronic infection results in liver fibrosis and ultimately cirrhosis in a subset of patients, although the rate of disease progression is variable. Patients who develop cirrhosis are at further risk for complicating events (such as variceal hemorrhage, ascites, and encephalopathy) and hepatocellular carcinoma, although many patients with compensated cirrhosis remain stable for years.

In the past, interferon (IFN)-based treatment was the only effective treatment option for HCV but it is having a low

sustained virological response (SVR) rate (50%) and with several reported unwanted effects).

The addition of DAAs was a breakthrough in HCV treatment worldwide, these drugs having a function of inhibition in the replication cycle of the HCV. The three-drug classes of direct-acting antivirals, inhibitors of NS3/NS4A protease, NS5A complex and NS5B polymerase was approved by food and drug administration (FDA). More than 90% of SVR rates can be achieved by drug combinations from these approved three-classes of DAAs. The advent of DAAs undoubtedly revolutionized the treatment both in terms of safety and efficacy however genotype 3 is still thought to be difficult to treat genotype. With the availability of DAAs, the rates of SVR and virological cure have vastly increased across all HCV genotypes for treatment- naïve patients as well as for treatment-experienced patients, especially for patients with cirrhosis, where cure has been difficult and where side effects to interferon-based regimens were difficult to tolerate and often precipitated decompensation.

According to the ALLY 3+ trial, the combination of sofosbuvir and daclatasvir in genotype 3 patients is safe and efficacious with an SVR 12 of 92 percenatges in treatment naïve and 89% in treatment-experienced patients respectively.[2] The combination has minimal drug-drug interactions and has safely been tried in patients with a liver transplant, renal transplants, and HIV co-infected patients as well.[3] Current recommendations for treatment of HCV GT 3 decompensated cirrhosis include either the sofosbuvir+velpatasvir±ribavirin or the SOF+DCV+RBV regimens.[4]

With India being a developing country, the price of DAAs is a major issue. The treatment cost of sofosbuvir and velpatasvir-containing regimen is about double of sofosbuvir and daclatasvir containing regimens. According to the ASALD guideline, if ribavirin is added to SOF+DCV treatment, duration should be reduced to 12 weeks from 24 weeks.[4] Our study is one such effort to compare the efficacy, safety of daclatasvir, sofosbuvir and Ribavirin regimen for 12 weeks as compared to daclatasvir and sofosbuvir regimen for 24 weeks in decompensated cirrhotic patients due to HCV genotype 3 infection in the Indian population.

METHODS

This prospective, randomized study was conducted in the PG Department of Medicine, GSVM Medical College, Kanpur from December 2019 to October 2021 on male and female patients age 18-65 years with decompensated cirrhosis due to GT3 HCV infections, eligible to receive sofosbuvir/daclatasvir/ ribavirin fixed-dose combination. Patients with CLD due to non-HCV etiology, coinfection with HBV or HIV, HCC, haemoglobin less than 8.5 g/dl, and patients with ESRD (eGFR <45 ml/min/1.73 m^2) were excluded from the study.

Decompensated cirrhosis was defined by the development of jaundice, ascites, variceal hemorrhage, hepatic encephalopathy, or a calculated CTP (child Turcotte Pugh) score of 10 to 15 (CTP Class C). The 16 patients received open-label treatment with (Daclatasvir) DCV 60 mg and (Sofosbuvir) SOF 400 mg once daily with or without food, plus weight-based (Ribavirin) RBV (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg) taken twice daily as a divided dose with food other 14 patients received only DCV with SOF without RBV (Figure 1). Dose reduction of RBV was permitted at investigator discretion for patients with low haemoglobin (≤10 g/dl) or creatinine clearance <50 ml/min. Patients were randomized 1:1 using an interactive voice response system to receive treatment for 12 or 24 weeks, with a subsequent 12-weeks follow-up period. Randomization was stratified by fibrosis stage (advanced fibrosis or cirrhosis, as defined above), with an enrolment of advanced fibrosis capped at 40%.

Statistical analysis

Study was done using non parametric test (Wilcoxon-Mann-Whitney-U test) with SPSS 23 version software. statistical value p<0.05 analyzed.

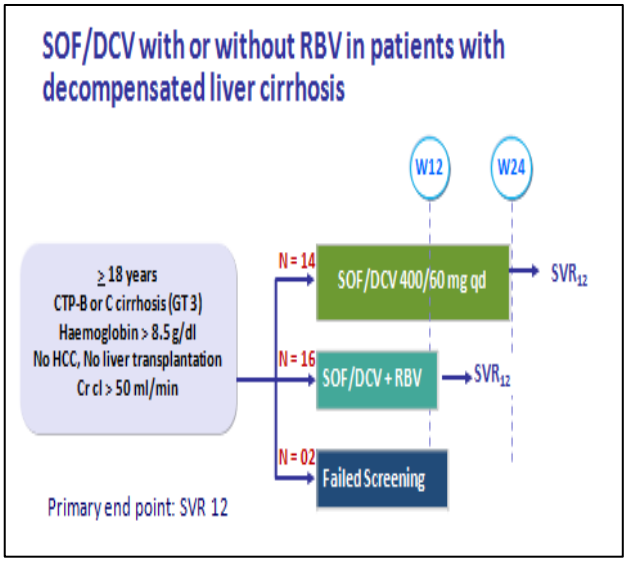

Figure 1: SOF/ DCV with or without RBV in patients with decompensated liver cirrhosis.

Study assessments

HCV genotype or subtype was determined using the real time HCV genotype II assay (Abbott molecular, Abbott Park, IL). Levels of HCV RNA in patient plasma were assessed at the screening, at end of treatment (ETR) at weeks 12, and 24 week (in the 24-week treatment group only) and at 12 weeks post-treatment (SVR-12) using the HCV COBAS TaqMan test (version 2.0; Roche molecular systems, Pleasanton, CA) with a lower limit of quantitation (LLOQ) of 25 IU/ml. Virological response was defined as HCV RNA below the LLOQ with no target RNA detected (HCV RNA<LLOQTND). Safety and tolerability were

assessed through AE reporting, clinical laboratory tests, vital signs and physical examinations.

Virological failure was defined as a virological breakthrough (an on-treatment increase in HCV RNA of at least 1 log 10 IU/ml above nadir or confirmed HCV RNA≥LLOQ if previous <LLOQTD/TND), relapse (any confirmed HCV-RNA measurement ≥LLOQ during post-treatment follow-up subsequent to an on-treatment response <LLOQ without target RNA detected (<LLOQTND) at the end-of-treatment visit) or any other HCV-RNA measurement ≥LLOQ that did not meet the criteria for virological breakthrough or relapse.

RESULTS

Baseline characteristics of study

Patients 16 (53.3%) of the participants had group 1, 14 (46.7%) of the participants had group 2. The mean age (Years) was 46.87±9.05. 32 patients were screened and 2 were excluded, one patient due to associated HBV+, one patient due to severe anemia. The 30 patients were randomized. All 30 randomized patients were divided into two groups. Group 1 was given SOF+DCV+RBV for 12 weeks while group 2 patients were given SOF+DCV for 24 weeks (Figure 2).

Table 1: Association between group and parameters.

Parameters	Group 1, (n=16) (%)	Group 2, (n=14) (%)	P value
Age (years)	45.12±8.67	48.86±9.37	
31-40	5 (31.2)	4 (28.6)	
41-50	7 (43.8)	3 (21.4)	0.3181
51-60	3 (18.8)	5 (35.7)	
61-70	1 (6.2)	2 (14.3)	
Gender			
Male	9 (56.2)	7 (50)	0.7323
Female	7 (43.8)	7 (50)	
HCV RNA (IU/ml) (baseline)	50367647.12±186341384.97	1820963.93±6350921.02	0.3341
Ascites			
Grade 1	2 (12.5)	3 (21.4)	
Grade 2	5 (31.2)	5 (35.7)	0.8872
Grade 3	5 (31.2)	3 (21.4)	
Grade 4	4 (25)	3 (21.4)	
HE			
Grade 0	9 (56.2)	5 (35.7)	
Grade 1	6 (37.5)	8 (57.1)	0.7172
Grade 2	1 (6.2)	1 (7.1)	
S. bilirubin (mg/dl)	4.27±3.18	2.66±1.62	0.2041
S. albumin (g/dl)	2.93±0.39	2.94±0.43	0.9831
INR	1.51±0.28	1.40±0.23	0.3351
CTP score	10.25±1.95	9.71±1.59	0.3861
CTP class			
B	5 (31.2)	6 (42.9)	0.5103
C	11 (68.8)	8 (57.1)	
Hemoglobin, (g/dl) (baseline)	9.41±2.19	9.64±0.96	0.7391
Ribavirin dose (mg) (baseline)	1012.50±136.01	-	-
Duration of treatment (weeks)* **	11.25±1.77	23.43±2.14	<0.0011
Analysed for SVR at 12 weeks (yes)	11 (68.8)	11 (78.6)	0.6892
SVR at 12 weeks achieved (yes)	9 (81.8)	10 (90.9)	1.0002
Blood transfusion required (yes)	2 (12.5)	1 (7.1)	1.0002
Ribavirin dose reduction (yes)	3 (18.8)	0 (NaN%)	1.0003
SAE leading to discontinuation (yes)	2 (12.5)	0 (0)	0.4852
Lost to follow up (yes)	1 (6.2)	1 (7.1)	1.0002
Death (yes)	0 (0)	0 (0)	1.0003
Adverse effects: insomnia (yes)	3 (18.8)	1 (7.1)	0.6022
Adverse effects: headache (yes)	3 (18.8)	1 (7.1)	0.6022
Adverse effects: fatigue (yes)	7 (43.8)	6 (42.9)	0.9613
Adverse effects: irritability (yes)	3 (18.8)	1 (7.1)	0.6022
Adverse effects: diarroea (yes)	4 (25)	2 (14.3)	0.6572
Adverse effects: dyspnea (yes)	2 (12.5)	1 (7.1)	1.0002

***Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U test, 2: Fisher's exact test, 3: Chi-Squared test.

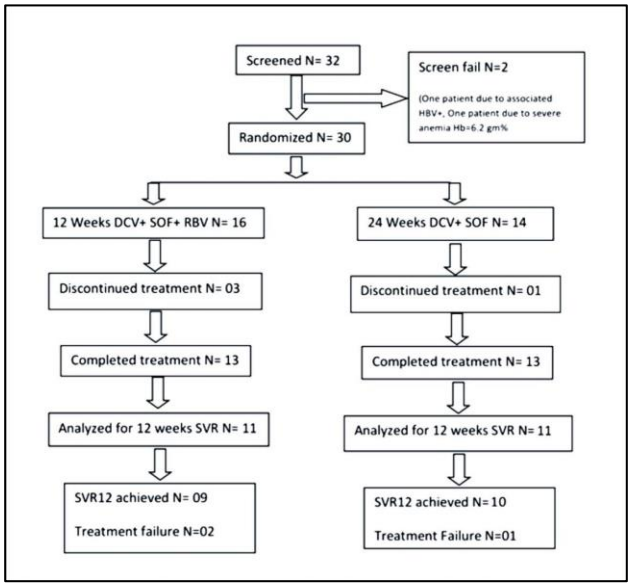

Figure 2: Summary of the screened patients.

Effectiveness and outcomes

Majority of patients achieved virologic response at the end of treatment but 2 patients in group 1 and 1 patient in group 2 did not achieve the SVR 12 although this was insignificant. There was no significant difference between the various groups in terms of SVR 12 achieved between the two groups. The 81.8% of the participants in the group1 achieved SVR 12 while 90.9% of the participants in the group 2 achieved SVR at 12 weeks. The 12.5% in group 1 required blood transfusion (BT) while in group 2 only 10% required BT although it was insignificant. Other potential baseline patients or treatment factors that could influence treatment effectiveness have not been identified, so no significant differences had been seen in SVR12 according to patients gender, basal HCV viral load, platelets, or albumin levels, bilirubin levels, CTP score or treatment duration.

Table 2: Association between group and SVR at 12 weeks achieved, (n=22).

SVR at 12 weeks achieved	Groups (%)		Total (%)
	1	2	
Yes	9 (81.8)	10 (90.9)	19 (86.4)
No	2 (18.2)	1 (9.1)	3 (13.6)
Total	11 (100)	11 (100)	22 (100)

Table 3: Association between group and BT required, (n=30).

BT required	Groups (%)		Total (%)
	1	2	
Yes	2 (12.5)	1 (7.1)	3 (10)
No	14 (87.5)	13 (92.9)	27 (90)
Total	16 (100)	14 (100)	30 (100)

Safety outcomes

During follow only very few patients had serious adverse reactions. The average of severe adverse event leading to discontinuation of treatment was 6.7% which was insignificant, while only 18.8% of patients required dose reduction ribavirin which again was very insignificant and there were 6.7% of patients were lost to follow up and there was no any death reported during follow up of the study DCV-SOF-RBV was well tolerated. There were few SAEs leading to discontinuation of treatment. Four patients had insomnia, headache, irritability, 13 patients had fatigue and 6 patients had diarrhoea. A summary of AEs is shown in Table. The 12.5% of the participants group1 had SAE leading to discontinuation. No participants in the group: 2 had SAE leading to discontinuation.

Table 4: Summary of adverse effects.

Adverse effects	Yes (%)	No (%)
Insomnia	4 (13.3)	26 (86.7)
Headache	4 (13.3)	26 (86.7)
Fatigue	13 (43.3)	17 (56.7)
Irritability	4 (13.3)	26 (86.7)
Diarrhea	6 (20)	24 (80)
Dyspnea	3 (10)	27 (90)

DISCUSSION

DAAs has revolutionised the treatment of HCV, however HCV genotype 3 was difficult to treat. DAAs regimen achieved higher rates of SVR as compared to interferon-based therapy. There was a drastic decline in the prices of DAAs due to its generic availability in developing countries. In our study, we only included difficult to treat a population that was only decompensated cirrhotic patient with mean serum bilirubin 3.52±2.66, mean albumin was 2.93±0.40, mean INR 1.46±0.26, 36.7% had CTP B and 63.3% had CTP class C. The mean haemoglobin was 9.52±1.70. This study demonstrated a high level of efficacy and safety with DCV-SOF With or without RBV administered for 12 or 24 weeks to a challenging group of genotype 3-infected decompensated cirrhotic patients. In this difficult-to-treat patient cohort, the overall SVR 12 rate was 86.4% and observed SVR12 did not differ with 12 versus 24 weeks of treatment. The SVR 12 in group 1 was 81.6% and in group 2 was 90.9% but this finding was insignificant (p=SVR 12 were broadly comparable across subgroups and did not decline with a high baseline viral load. In group 1, 12.5% of patients required BT while oil group 2 it was only 7.1% but the Study was insignificant (p=1). The 12.5% of patients had a severe adverse reaction in group 1 which lead to ribavirin discontinuation and 18.8% of the patients required ribavirin dose reduction and again the study was insignificant. Both the regimens were highly efficacious, safe, and tolerable with insignificant adverse reactions. The efficacy of the SOF+DCV±RBV regimen for HCV genotype patients has been evaluated in the phase 3 studies (ALLY 3 and ALLY3+). In ALLY 3 a

total of 101 treatment-naive patients received SOF+DCV therapy for 12 weeks and the SVR 12 was 90%. But this was significant lower in cirrhotic patients in which SVR 12 was 63% ALLY-3+ is the first randomized study to optimize interferon-free treatment response in genotype 3-infected patients with cirrhosis. In this study patients with advanced fibrosis or cirrhosis received SOF+DCV+RBV therapy for 12 and 16 weeks. The high SVR 12 rate among patients with cirrhosis, irrespective of previous treatment experience, compares favourably with the 63% SVR 12 rate achieved in patients with cirrhosis in the earlier ALLY-3 study and strongly suggests a benefit to adding RBV to DCV-SOF in this patient group.[2] Poordad et al also concluded 12 weeks of oral treatment with the combination of daclatasvir with sofosbuvir and ribavirin achieved high SVR rates across multiple genotypes.[5]

However, in our study addition of ribavirin shows no benefit in achieving SVR 12 it may be due to less sample size.

DCV-SOF, with or without RBV, is currently the only regimen option recommended by both U.S. treatment guidelines (American association for the study of liver diseases /infectious diseases society of America/ international antiviral society USA recommendations and European guidelines (European association for the study of the liver recommendations) for use in all genotype 3-infected patients irrespective of HCV treatment experience or cirrhosis status. Both guidelines recommend 12 weeks of DCV-SOF without RBV for patients without cirrhosis, and this recommendation is supported by the similarly high (≥96%) SVR12 rates noted in this.[4,6] The patient group with and without RBV in ALLY-3 and ALLY-3+. Recommendations for RBV use and treatment duration in genotype 3-infected patients with cirrhosis differ between U.S. and EU guidelines and are based on limited empirical data. The results of ALLY-3+ suggest that 12 or 16 weeks of DCV-SOF-RBV is an effective therapeutic option for both HCV treatment-naïve and treatment-experienced patients with compensated cirrhosis. The SVR 12 rates observed are similar to those noted recently for genotype 3-infected patients with cirrhosis treated with SOF and the investigational agent velpatasvir, suggesting that a 100% response rate may be hard to achieve in this difficult-to-treat patient group.

The optimal duration of treatment for some genotype 3 patient groups-such as those with decompensated cirrhosis or patients with cirrhosis for whom RBV may be contraindicated. Unrandomized, real-world observations for 24 weeks of DCV-SOF with and without RBV have recently been reported from interim analyses of two European early access programs that provided DCV ahead of its marketing authorization to patients with advanced liver disease and no other HCV treatment options. The French “Authorisations temporaires d'Utilisation” (ATU) program observed an SVR 12 rate of 86% for 24 weeks of DCV-SOF without RBV in 135 genotype 3-infected patients with cirrhosis (mostly child-Pugh A [85%] or B [13%]), with no incremental benefit observed in a similar group of 53 patients with cirrhosis treated for 24 weeks with DCV-SOF-RBV (SVR12 of 81%).[8] Similar results were observed in the multicentre European compassionate use program for a group of 71 genotype 3-infected patients with cirrhosis, most of whom were treated for 24 weeks, where SVR12 rates were 88% on DCV-SOF and 86% on DCV-SOF-RBV.[9]

Finally, another observational study evaluated the SVR rates in patients with compensated or decompensated cirrhosis with HCV genotype 3 infection treated for 24 weeks with SOF plus DCV with or without RBV. Among those treated with SOF plus DCV, SVR rates were 100% for child-Pugh A (19 of 19), 80% for child-Pugh B (12 of 15), and 75% for child-Pugh C (6 of 8). Conversely, among those who added RBV, response rates were 85% (11 of 13) for child-Pugh A, 86% (12 of 14) for child-Pugh B, and 100% (2 of 2) for child-Pugh.[7]

In all the above studies it's clearly shown that SOF+DCV for 12 weeks provides very high SVR in non-cirrhotic patients (94-97%) but with cirrhosis, the overall SVR is 59% to 69% which is very unsatisfactory, while in our study the SVR achieved through this combination is very impressive which is 90.9% in decompensated cirrhotic patients. In all the above studies, it's also shown that the addition of RBV increases SVR rates to above 80%, and extending treatment to 24 weeks raises SVR to 90%. while in our study the SVR12 achieved after the addition of ribavirin is only 81.8%, this may be due to the less sample size of the patients, for cirrhotic patients, the optimal duration or the best regimen still remains uncertain.

Limitation

Further studies with a large number of patients are required to answer this question.

CONCLUSION

The combination of SOF+ DCV for 24 weeks showed a high SVR of 90.9% in decompensated cirrhotic patients, but this regimen has an inconveniently longer treatment duration which can increase cost and reduced compliance of the patients. The addition of ribavirin to SOF+DCV provides SVR12 of 81.8%, which is lower than the above regimen this may be due to because low sample size and more no. Of CTP-C patients in this group but this was insignificant. But with the addition of ribavirin, the duration of treatment can be reduced to 12 weeks and still achieve good SVR12 and it will further increase the patient's convenience and compliance and reduced cost. With the addition of ribavirin to SOF+DCV, only 12.5% of patients had SAE which lead to the discontinuation of an RBV which is insignificant, suggesting ribavirin can be safely added to the SOF+DCV and reduced the duration of the treatment and thereby its cost.

Both the regimens are safe and highly efficacious but it still remains unclear about the best regimen in decompensated cirrhotic patients due to HCV genotype 3 infection.

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