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EFFICACY OF SOFOSBUVIR/DACLATASVIR IN CIRRHOTIC AND NON-CIRRHOTIC PATIENTS WITH HCV GENOTYPE 4 INFECTION AT A SPECIALIST HOSPITAL.

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Abstract:

Introduction: Untreated Hepatitis C virus infection can lead to cirrhosis, hepatocellular cancer and even death and increases liver disease related morbidity and mortality worldwide. Treatment with Direct Acting Antivirals offer cure over 90% with fewer side effects. Daclatasvir (DCV) and Sofosbuvir (SOF) combination in HCV GT4 infection has imparted higher rates of SVR after treatment with great tolerability.

This study assesses the effectiveness of this regimen in eradication of the HCV GT4 infection in treatment-naïve patients.

Methods: A retrospective study, conducted in our center between June 2017 and December 2020. Treatment protocol was given in treatment-naive HCV GT4 infected cirrhotics and noncirrhotics participants who were later followed for a total of 24 weeks for safety and efficacy of SOF-DCV. Data was analyzed using SPSS, and figures created using MS-Excel.

Results: We analyzed data of 124 participants with HCV GT 4 infection. Mean age was (54.04 +/- 16.39) Treatment regimen was given to 39 cirrhotic (F4) and 85 non-cirrhotic(F0-F3). SVR was seen

in 98% of participants with tolerable side effects and improved MELD scores as fall in percentage seen from 46.1% to 40.5% in participant's with MELD>10.
Discussion: This retrospective study confirms that SOF-DCV is safe and effective treatment regimen in HCV GT4 patients. The findings are consistent with findings of multiple clinical trials. Our study was conducted exclusively on HCV genotype 4 with good number of participants. Treatment completion was followed by high SVR12 rated and improvement in prognostic markers of liver disease in participants with compensated cirrhosis.
Conclusion: SOF-DCV combination showed efficacy in achieving the SVR12 in Child-Pugh B cirrhotic and noncirrhotic population with a favorable safety profile.

Keywords: Hepatitis, Cirrhosis, Daclatasvir, Sofosbuvir, Sustained virological response

Introduction

Hepatitis C virus (HCV) infection is one of a pre-eminent cause of chronic liver disease across the globe. HCV- associated chronic hepatitis if not timely treated can progress to potentially lifethreatening complications of liver disease that leads to cirrhosis, hepatocellular carcinoma, liver failure, and death. Several extra hepatic manifestations are associated with HCV infection and elimination of HCV infection reduces morbidity and all-cause mortality. There are six prevalent HCV genotypes globally and include genotype 1 (1a and 1b), 2,3,4,5 and 6
Exact data on the prevalence of HCV infection in Saudi Arabia is currently unavailable, as most HCV research was conducted over 10 years ago. The rate of prevalence recorded for Saudi Arabia in various studies ranges from 0.22 to 1.1% [1,2]. The most prevalent genotype (GT) is HCV GT4, followed by HCV GT1[3].The objective of HCV therapy is to cure the infection by achieving sutained virolgical response (SVR) i.e. undetectable HCV RNA after 12 weeks of treatment completion. Newly approved Direct-Acting antivirals (DAAs) which inhibit HCV non-structural proteins are associated with high SVR rates
Daclatasvir (DCV) is a potent pan-genotypic inhibitor of the HCV NS5A protein and Sofosbuvir (SOF) is a pan-genotypic nucleotide analogue inhibitor of the HCV NS5B RNA polymerase. [4, 5] These inhibitors are administered as a single fixed-dose combination, which has been approved for the treatment of HCV GT1 and GT4 infections in treatment-naïve compensated cirrhotic and non-cirrhotic patients and patients for whom prior therapy has failed.[6]

METHODS

Study Design:

This is a retrospective study which was conducted at King Fahad Specialist Hospital, Buraidah, between June 2017 and December 2020, in accordance with Good Clinical Practice guidelines and approved by regional institutional review boards and regulating agencies. The final manuscript was reviewed and approved by all research authors. A fixed - dose tablet of DCV 60 mg plus SOF 400 mg was given to all participants for 12 weeks, and all participants were followed up for another 12 weeks to track their SVR status and monitor for side effects or adverse effects related to the treatment. Dose modifications were not allowed, and the study was terminated 12 weeks after completion of treatment.

Participants

The participants included male and female patients 18 years and older with HCV infection, any level of detectable HCV RNA, and a documented HCV GT 4 infection. All cirrhotic participants were assigned a Child–Pugh (CP) score based on clinical and laboratory data and MELD based on laboratory data. Cirrhosis and non-cirrhosis was defined by clinical, radiological features and liver stiffness assessed by Transient elastography with a value >12.5kpa and <12.5 kpa respectively, within six months of screening [7-9]. None of our patients found to have Renal disease, HCC, coinfection with HBV or HIV and previous treatment history with pegylated interferon or DAA therapy, hence they were not included in the study

Assessment and analysis:

The primary endpoint was to achieve SVR after 12 weeks of completing the treatment (SVR12), which is defined as HCV RNA <15 IU/mL(lower limit of quantitation = 15 IU/mL, lower limit of detection = 15 IU/mL). Efficacy is presented for the intention-to-treat population, which includes all participants who received ≥1 dose of study medication.

The model for end-stage liver disease (MELD) score and the CP score were analyzed at baseline and at follow-up week 24. Evaluation of safety was done by monitoring for adverse events and serious adverse events, with serious adverse events defined as events that may lead to treatment discontinuation or death .Analysis of laboratory abnormalities included grade 3/4 laboratory abnormality, defined as alanine aminotransferase (ALT) or aspartate aminotransferse (AST) 5 times the upper limit of normal (ULN) and total bilirubin level >2.6 mg/dL, and hemoglobin value of less than 8.9 g/dl.

Statistical analysis was done using the Statistical Program for Social Analysis (SPSS version 22.0). Baseline patient characteristics are presented in numbers and percentages. A 95% confidence interval plot was plotted using the Clopper–Pearson method to assess the baseline patient characteristics that may affect SVR12. On-treatment and off-treatment viral response rates are presented in numbers and percentages. Confidence interval was calculated for changes in CHILD and MELD score. Safety profile summary was shown in number and percentages

RESULTS

Sample Demography:

In our study, we assessed data of 124 treatment navie participants with HCV GT4 infection. Of the 124 participants, 72 were female and 52 were male. The mean age was 54.04+/-16.39 for SOF-DCV sample subjects, with a predilection for a higher mean age in the cirrhotic subjects at 60.00 ± 11.07. There were 39(25.9%) cirrhotic participants with predominant CP class B7 and 85(74.1%) non-cirrhotic participants. In cirrhotic participants approximately 21 participants (42.8%) had a pretreatment MELD score of <10 and a pretreatment MELD score of >10 were found in 18 participants (57.1%). Pretreatment HCV RNA levels were >1000000 IU/ml in 96 participants (77.4%), and only 28 participants (22.6%) had HCV RNA levels of <1000000 IU/ml.

Treatment Regimens:

DCV 60 mg + SOF 400 mg was administered once daily were given to 124 patients for 12 weeks. Twelve weeks after completion of the treatment, 98 % of the participants had undetectable HCV RNA levels. All patients underwent treatment for 12 weeks and were followed up for 24 weeks, Two patients with cirrhosis and CP class B8 with viral load > 10000 IU/ml had relapses during follow-up week 12.Treatment was not discontinued in any patient due to adverse event or serious adverse event.

Efficacy:

SVR was observed in 98% of participants (table2). Two patients with cirrhosis and CP class B8 had relapse during follow-up week 12. Improvements in the MELD score were observed in 59.5% of the participants with MELD score of less than 10. No treatment failure was observed during follow up week 12. A subgroup analysis of SVR rates revealed lower SVR rate in participants with a higher CP scores .Similarly lower SVR rates were observed in participants with meld score greater than10. Higher SVR rates were noted in participants with MELD scores lower than 10. Variables such as age and baseline viral load were not predictive of SVR12, however female participants showed lower SVR rates as compared to males.

Change in MELD and CP scores:

At follow up week 24, Post-treatment MELD scores showed improvement with 59.5% of the sample recording MELD scores of less than 10 and 40.5% maintained a score of more than 10 (table 3).CP

score was decreased by 2 point in 5 participants, and 67.6% of participants had CP score of B7 and 32.4% had a score of B8 (table 4).

Safety:

Treatment related adverse events were noted in 4.8% (Table 5) of participants while no serious adverse events or laboratory abnormality that can result in treatment discontinuation was observed in any participant. There was no death or hepatic decompensation during treatment and on follow-up. 5.1% cirrhotic participants reported fatigue, while 2.3% of noncirrhotic participants reported headache, nausea and insomnia. All treatment related adverse effects were subsided upon treatment discontinuation.

Discussion:

In this open label, retrospective study, SOF-DCV efficacy was demonstrated with 98% of the study sample achieving SVR12 after completing the treatment course while two patients with cirrhosis had relapse during follow-up week 12. Both cirrhotic and non-cirrhotic were equally responsive to the regimen. Only 4.8% of participants reported treatment related adverse effects which disappeared on treatment completion. These findings provide evidence that both regiments are safe and effective.

The efficacy of SVR12 in HIV-HCV GT4 infection was reported as SVR12 of 92% after 12 weeks of SOF-DCV in a total of 50 patients [(10)]. SVR12 achieved was 98% and 96% in patients receiving sofosbuvir plus ledipasvir and sofosbuvir plus daclatasvir in 100patients with HCV GT4.[(11)] Large real world GT4 cohort, the French temporary authorization (ATU) program, data analyzed for GT4 showed the SVR 12 for DCV-SOF was 84% (53/63patients).[12] In ALLY 1 trial, SVR 12 was 100%(4/4) HCV GT4 patients with advanced cirrhosis who were treated with DCV/SOF and RBV for 12 weeks.[13]

However the efficacy was almost equal when compared to open label trial that included 82 treatment-naïve GT1 infected patients treated with SOF and DCV SVR 12 was 95 & 100% with or without RBV respectively. Similarly, in a study of HIV and HCV coinfected patients, 12 weeks of DCV plus SOF resulted in SVR rates of 97% among treatment-naïve (n = 83)[14].

Our study has a more exclusive area of interest, as we assessed HCV GT4 responsiveness to a treatment protocol with a sample size of 124 patients However, the limitations of the study are as follows, single center and it is retrospective, and no liver biopsy and post treatment participants could not be observed for long term complication (relapse and HCC).

Conclusion:

In this retrospective study, SOF-DCV combination is highly effective in achieving SVR12 in cirrhotics and non cirrhotics treatment naïve patients with HCV GT 4 infection. This regimen also showed decline in MELD scores and child pugh B score in cirrhotics with a favorable tolerability profile.

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Table 1: Participants demographics and baseline characteristics

Charcateristics n- 85(74.1%)	**Noncirrhotics** n – 39(25.9%)	**Cirrhotics**
Sex		
Female	47(55%)	25(71.4%)
Male	38(45%)	14(28.6%)
HCV GT		
4	85(100%)	39(100%)
Treatment Status		
Naïve	85(100%)	39(100%)
Viral Load		
<1000000 IU/ml	26(17.5%)	13(28.6%)
>1000000 IU/ml	69(82.5%)	26(71.4%)
Child Pugh score		
7	-	20(50%)
8	-	14(35.7%)
9	-	5(14.3%)
MELD Score		
<10	-	21(53.9%)
>10	-	18(46.1%)

Table 4: Pre and post-treatment Child Pugh scores

CP Class	**Pre–treatment CP scores**	**Post –treatment CP scores**
B7	20(51.3%)	25(67.6%)
B8	14(35.9%)	12(32.4%)
B9	5(12.8%)	0(0%)
Total	39(100%)	37(100%)

Table 3: Pre and post -treatment MELD scores

MELD scores	Pre treatment MELD score	Post treatment MELD score
<10	21(53.9%)	22(59.5%)
>10	18(46.1%)	15(40.5%)
Total	39(100%)	37(100%)

Table 2: Sustained virolgical response SVR 12 (95% Confidence Interval)

Variables	n/N	% Confidence Interval
All	122/124	98%(94-99)
Sex		
Female	70/72	97%(90-99)
Male	52/52	100%(93-100)
HCV genotype		
GT4	122/124	98%(94-99)
Treatment status		
Naïve	122/124	98%(94-99)
Baseline HCV RNA level		
<1000000 IU/ml	28/28	100%(87-100)
>1000000 IU/ml	94/96	97%(92-99)
Child-Pugh score		
7	20 /20	100 %(83-100)
8	12 /14	86% (57-98)
9	5 / 5	100%(47-100)
MELD score		
<10	21/21	100 % (83-100)
>10	16/18	89% (65-99)

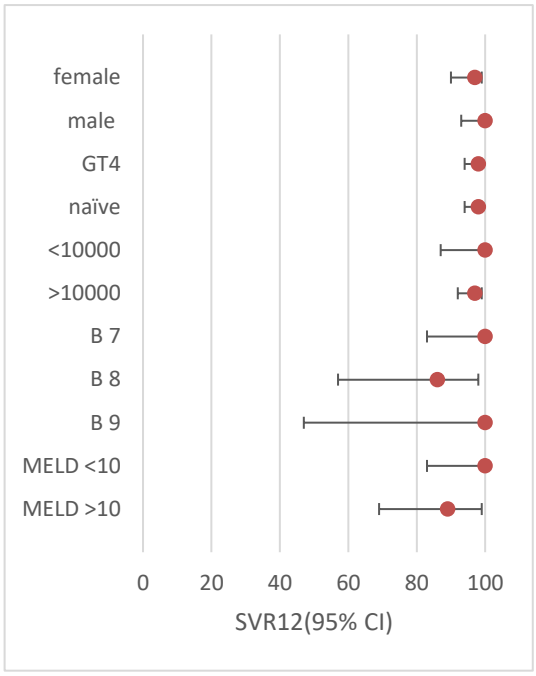

Table 5: Adverse Events during treatment and follow -up

Variables	Noncirrhotic n=85	Cirrhotic n=39	All participants n=124
Adverse events AEs			
Nausea and headache	2 (2.3%)	0 (0.0%)	2(1.6%)
Fatigue	0 (0.0%)	2(5.1%)	2(1.6%)
Insomnia	2 (2.3%)	0 (0.0%)	2(1.6%)
Treatment related AEs	4(4.7%)	2(5.1%)	6 (4.8%)
Serious adverse events/Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment discontinuation due AEs	0 (0.0%)	0 (0.0%)	0 (0.0%)
Laboratory abnormalities	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALT/AST elevation 1.1-2.5 x baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade ¾ laboratory abnormalities			
Total bilirubin elevation >2.6	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALT/AST elevation >5 ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hemoglobin (< 8.9-7 g/dL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hemoglobin (< 7 g/dL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
WBC (< 1500/mm^3)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphocytes(< 500/mm^3)	0 (0.0%)	0 (0.0%)	0 (0.0%)

NOTE: Values are presented as n (%);
AEs- adverse events; ALT- alanine aminotransferase; AST- aspartate aminotransfersae