Original article

Sofosbuvir plus daclatasvir without ribavirin for the treatment of chronic hepatitis C in patients with decompensated liver disease

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ABSTRACT

Background: In chronic hepatitis C infection, hepatic decompensation remained a contraindication to treatment for many years. The direct-acting antiviral drugs have shown high treatment success even in decompensated liver disease. This study aims to assess the response and safety profile of Sofosbuvir and Daclatasvir in patients of decompensated cirrhosis with chronic hepatitis C.

Patients and methods: It was a prospective observational study conducted at the Gastroenterology Department of Gujranwala Medical College/ DHQ Teaching Hospital, Gujranwala from February 2016 to December 2017. Consecutive patients of hepatitis C with decompensated cirrhosis were enrolled in the study. Sofosbuvir 400mg and Daclatasvir 60mg were given to all patients without ribavirin for a period of 24 weeks. Sustained virologic was taken as a primary endpoint.

Results: A total of 140 patients were included in our study, 122 patients (87%) completed the study, 08 patients (5.7%) were lost to follow up, treatment discontinuation was seen in 06 patients (4.2%) & 04 patients (2.8%) died during the study. 110 patients (90.2%) achieved end treatment response (ETR), 12 patients (9.8%) remained treatment non-responder, 100 patients (82%) achieved sustained virological response (SVR12) and 10 patients (8%) had a relapse of HCV infection.

Conclusion: Once-daily oral Sofosbuvir plus Daclatasvir without Ribavirin achieved overall high rates of sustained virologic response in patients with chronic HCV have decompensated liver disease.

Keywords:
Direct Acting Antivirals, Chronic Hepatitis C Infection (HCV), Decompensated Liver Disease, Sustained Virological Response (SVR)

INTRODUCTION

Chronic Hepatitis C has emerged as a global health problem and according to an estimation of about 3% of the world's population is infected with this virus.[1] Almost 130-185 million peoples are infected worldwide and 350,000 people die each year due to its complications.[1,2] In the United States, hepatitis C virus (HCV)-related cirrhosis is the major indications of liver transplantation and it accounts for 35-40% of all cases.[3] In the coming years, the burden of decompensated cirrhosis is supposed to be high due to the worldwide prevalence of hepatitis C infection.[4] For a long time, interferon therapy was the only treatment option of hepatitis C infection and it was contraindicated in decompensated cirrhotics. The only treatment option for this group of patients was liver transplantation. Recently, better insight into the hepatitis C virus genome has enabled the development of multiple direct acting antiviral agents (DAAs).[5] These new drugs block the virus replication at different critical points and have high sustained virologic response rates (> 90%). These new direct-acting anti-viral drugs have made this possible to treat HCV infection in decompensated liver disease for which previously there was no treatment.[6] Daclatasvir and sofosbuvir (a pan-genotypic regimen) along with ribavirin has shown higher sustained virologic response rates in treating hepatitis C infection in decompensated liver disease.[7] Daclatasvir inhibits NS5A while Sofosbuvir is an NS5B polymerase inhibitor. Both the drugs have good safety profiles and the ease of once-daily dosing, with less significant side effects.[8] Though the use of ribavirin along with this combination is said to improve the overall sustained virological response (SVR), but it has many hemotoxic adverse effects in patients with decompensated cirrhosis.[9,10] The current study was designed to determine the response and safety profile of daclatasvir and sofosbuvir combination without using ribavirin in patients of chronic hepatitis C with decompensated cirrhosis.

Conflict of interest: The authors declared no conflict of interest exists.
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SUBJECTS AND METHODS

This study was carried out at the Gastroenterology Department of DHQ Teaching Hospital Gujranwala /Gujranwala Medical College from February 2016 to December 2017. The non-probability consecutive sampling technique was used to include the patients. The sample size of 140 was calculated using a 90% confidence level, a 5% margin of error, and taking an expected outcome of 85%.[13,14] Patients of both genders aged 18 to 60 years were included. Patients having HCV viral load > 20 IU/ml on Real-Time PCR and type 3 genotype were included in the study. Decompensated cirrhosis was defined by present or past evidence of ascites on ultrasound, gastric or esophageal varices on upper GI endoscopy and / or hepatic encephalopathy. Both treatment-naive and previously treated patients were enrolled in our study. Patients with positive HIV and Hepatitis B serology were excluded from the study. Patients with Hb < 10 g/dL, platelet < 30,000/mm3, serum bilirubin > 3 mg/DL, ALT & AST > 5 times normal & creatinine > 2 mg/dl were also excluded from the study. The Serum HCV-RNA level was assessed using a polymerase chain reaction. After approval from the institutional review board, informed consent obtained & demographic data, history, and clinical examination were recorded. All the patients were given Sofosbuvir plus Daclatasvir for 24 weeks without ribavirin. Baseline laboratory tests and physical examinations were performed before starting the treatment, fortnightly during the first month and then monthly throughout the treatment. HCV RNA levels were assessed quantitatively, before starting the treatment, week 24, and then 12 weeks after completing the treatment. Adverse effects of drugs were noted during the study. SVR12 (HCV RNA below 20 IU/ml) was the primary endpoint of the study. SPSS version 22 was used for the statistical analysis. Mean and standard deviation were calculated for quantitative variables. Frequency and percentage were calculated for qualitative variables. A Chi-square test was used to compare the variables before and after the treatment. $P < 0.05$ was taken as statistically significant.

RESULTS

A total of 140 patients of Chronic HCV with decompensated liver disease were enrolled and treated at our department of Gastroenterology from February 2016 to December 2017. Their mean age (±SD) was 51.44 years (±7.32). Eighty-two patients (58.5%) were males and fifty-eight patients (41.4%) were females. Table 1 summarizes the laboratory parameters of the study patients. One hundred and four patients (74%) were treatment-naive and thirty-six patients (25%) were treatment-experienced (including both non-responders and relapsers). Among the treatment-experienced patients, 26 patients had used interferon or peginterferon with ribavirin while 10 patients had to use sofosbuvir plus ribavirin. After starting treatment, 8 patients (5.7%) were lost during follow-up, Treatment discontinuation was seen in 6 patients (4.3%) because of severe adverse events like severe fatigue, persistent vomiting, severe diarrhea, mental status alteration. 4 patients (2.8%) died during the study unrelated to the therapy (03 patients because of complications of advanced liver disease and 01 patients due to cerebrovascular accident). A total of 122 patients (87%) completed their treatment course. 110 patients (90.2%) achieved end treatment response (ETR) after 24 weeks of treatment and 12 patients (9.8%) were treatment nonresponses. A total of 100 patients (82%) achieved SVR, while 10 patients (8%) had a relapse of HCV infection. Table 2 summarizes the virological response of patients. All patients tolerated medications well with minor side effects like mild fatigue (32%), headache (27%), transient diarrhea (15%), nausea, and vomiting (12%). Mean pre-treatment ALT /AST were 55.3 IU/L & 60.9 IU/L, and mean post-treatment ALT/AST were 38.3 IU/L & 33.8 IU/L. Statistically significant reductions were observed after treatment in ALT and AST levels (< 0.005). Figure 1 summarizes the virological response rate of study participants.

Table 1. Laboratory parameters of patients (N=140)

Parameter	Value	p-value
HCV RNA PCR IU/ml		
Mean [Range]	358995 [2563-5856358]	
Child-Pugh class (%)		
A	46 (32.8)	
B	70 (50)	
C	24 (17.1)	
Treatment history (%)		
Naive	104 (74)	
Rx Experienced	36 (25)	
Mean ALT (SD)		
Pre-treatment	55.3 (23.77)	0.035
Post-treatment	38.3 (13.87)	
Mean AST (SD)		
Pre-treatment	60.9 (19.28)	0.029
Post-treatment	33.8 (13.63)	
Mean bilirubin mg/dl (SD)		
Pre-treatment	1.72 (0.58)	0.153
Post-treatment	1.56 (0.42)	

DISCUSSION

The introduction of direct-acting antiviral drugs has brought a revolution in the management of chronic hepatitis C. Treating the infection before the onset of

Table 2. Virological response rates of HCV treatment in decompensated liver disease

Parameter	Frequency (*n*)	Percentage
Treatment completed	**122**	**87.1**
Treatment non- completed	18	12.9
Lost to follow up	08	5.7
Left due to S/E	06	4.3
Death	04	2.9
End Rx Response (%)	**110**	**90.2**
Treatment naive	88	72.1
Treatment experienced	22	18.0
Non-responders (%)	**12**	**9.8**
Treatment naive	04	3.3
IFN Experienced	08	6.5
Sustained virologic response (%)	**100**	**82**
Treatment naive	82	67.2
Treatment experienced	18	14.8
Relapse (%)	**10**	**8.2**
Treatment naive	06	4.9
Treatment experienced	04	3.3

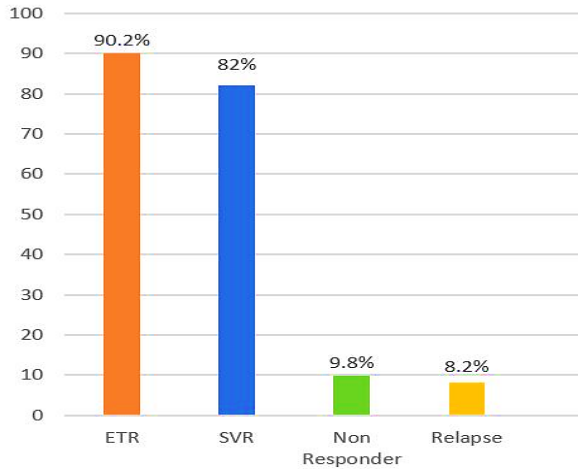

Figure 1. Virological response rates of study participants

decompensation has shown clear benefits.[11] However, limited data is available regarding similar benefits of treatment in decompensated cirrhotic patients after the elimination of HCV infection as are seen after the elimination of HBV infection.[12] In our study, a sustained virologic response of 82% was achieved with sofosbuvir and daclatasvir combination without ribavirin in decompensated cirrhotic patients. It also showed that achieving sustained virological response is associated with statistically significant improvements in ALT & AST levels, suggesting that eradication of the disease has beneficial effects on liver function and inflammation. Our results are similar to a study conducted by Christophe Hezode et al in France in 2017. Their study showed overall SVR12 of 86% in patients with an advanced liver disease where sofosbuvir plus daclatasvir was used for 24 weeks while it was 80% in other groups where ribavirin was also used. No added benefit of ribavirin in achieving SVR12 was observed in this study.[13] Only 1% of the patients had severe adverse events and stopped the treatment. A similar study performed on the European population by Jim Yong et al in 2017 showed an overall SVR of 87 % in patients with advanced liver disease who received 24-week treatment of sofosbuvir and daclatasvir without ribavirin.[14] Another study performed in Gothe University Hospital Germany in 2016 by Tania et al showed overall SVR12 of 91% in patients with advanced cirrhosis treated with sofosbuvir and daclatasvir for 24 weeks without ribavirin.[15] The safety profile of our study regimen was also favorable and consistent with that observed in clinical trials.[16] However, long term follow-up may be needed to assess the possible long-term benefits after achieving SVR, such as decreased incidence of hepatocellular carcinoma, reduced liver-related mortality, decreased need for liver transplantation, and reversibility of liver failure.

CONCLUSION

Ribavirin free treatment with sofosbuvir and daclatasvir for 24 weeks is a safe and efficient treatment strategy for patients with decompensated liver disease. This combination achieved a high overall sustained virologic response without any significant adverse events.

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