



Response to combination of sofosbuvir and daclatasvir in chronic hepatitis C infection.

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ABSTRACT... Objectives: To determine efficacy of sofosbuvir and daclatasvir in the treatment of chronic hepatitis C infection. **Study Design:** Experimental study. **Setting:** Hepatitis Clinic, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan. **Period:** June to December 2018. **Material & Methods:** Five hundred patients having chronic hepatitis C infection including those with compensated cirrhosis were included in the study. They were given sofosbuvir 400 mg daily and daclatasvir 60 mg daily. Weight based ribavirin was added if patient has evidence of cirrhosis. Treatment duration was 12 weeks for non-cirrhotic and 24 weeks for cirrhotics. End of treatment response (ETR) was recorded. **Results:** Mean age of the included patients was 41 ± 11.69 with range from 8 to 82 years, while 217 (43.4 %) patients were male and 283 (56.6 %) were female. Cirrhosis was present in 59 (11.8 %) patients; among these 35.6 % were in Child A and 64.4 % in early Child B. End of treatment response occurred in 491 (98.2 %) patients and there was no significant difference in ETR between male and female patients, and between cirrhotic and non-cirrhotic. Similarly, there was no significant difference in age between those having ETR and those having no ETR. Fatigue was experienced by 13.2 % and headache by 4.2 % patients. **Conclusion:** The combination of sofosbuvir and daclatasvir has high response rate in chronic hepatitis C patients of our population.

Key words:

Compensated Cirrhosis, Daclatasvir, End of Treatment Response, Hepatitis C, Sofosbuvir.

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INTRODUCTION

Globally, about 100 million population have anti-HCV antibodies positive and 70 million people are suffering from chronic hepatitis C.¹ The most common cause of cirrhosis in our population is hepatitis C virus (HCV) infection. In southern part of Punjab, prevalence of hepatitis C infectivity was 8 to 24 %.^{2,3} After an acute infection, 50 – 85 % patients develop chronic hepatitis C.⁴ Cirrhosis develops after 20 years among 16 % of these patients.⁵ Cirrhotic patients develop hepatocellular carcinoma (HCC) at a rate of upto 3 % per year.⁶

Keeping in view these life threatening sequel of hepatitis C infection, it is important to detect and treat these patients at an early stage, before development of cirrhosis which is irreversible. Chronic hepatitis C patients had been treated with Interferon alpha since late 1980s⁷ with little

benefit⁸, even after prolonging the treatment duration from 24 to 48 weeks⁹ but addition of ribavirin resulted in greater efficacy (SVR rose from 6 to 40 %).^{10,11} Replacement of interferon with pegylated interferon further improved the SVR rate (54 – 61 %).¹² In addition to low response rate, this regimen had high profile of side effects.^{13,14} Boceprevir and telaprevir, directly acting antivirals (DAAs), were used in 2011 and these improved response rate to 65 – 75 %^{15,16} but had to be given with pegylated interferon plus ribavirin and again had higher side effect profile. New oral DAAs became available since 2013 which have higher efficacy and lower rate of side effects. Two combinations are available in Pakistan: sofosbuvir and daclatasvir, sofosbuvir and velpatasvir; both have response rates of 95 to 100 %.^{7,17,18} Both of these combinations are pangenomic.

Sofosbuvir along with daclatasvir are being prescribed to our patients due to their availability and low cost. As the efficacy of hepatitis C treatment varies with genotype and other patient factors, we carried out this study to look for the success rate of this combination in our local population.

Our study had the objective of determining the response rate of sofosbuvir plus daclatasvir in patients of chronic hepatitis C virus infection.

MATERIAL & METHODS

This was an experimental study conducted at Hepatitis clinic, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan from June 2018 up to December 2018.

Five hundred patients having chronic hepatitis C who attended our outpatient clinic for treatment were included in our study. Both patients without cirrhosis and those with compensated cirrhosis were included. For inclusion patients had to be treatment naïve. Exclusion criteria were decompensated cirrhosis, previously treated patients, co-infection with HIV, pregnancy, concomitant fatty liver disease, alcoholism, renal failure, and presence of liver cancer.

Every patient enrolled in the study was specially asked about the presenting complaints and associated symptoms, current usage of drugs and the presence of comorbidities. Routine blood tests were advised including complete blood count (CBC), prothrombin time (PT), liver function tests (LFTs), albumin and creatinine. Qualitative PCR for HCV RNA was sent and ultrasound abdomen was done.

Included patients were given sofosbuvir one tablet of 400 mg once per day and daclatasvir tablet of 60 mg once per day. Ribavirin was added according to the weight of the patient (500 mg twice daily for those having weight less than 75 kg and 600 mg twice daily for those having weight more than 75 kg) if there was clinical, biochemical and ultrasonographic evidence of cirrhosis. Treatment was given for 12 weeks in non-cirrhotic and for 24 weeks in those having cirrhosis. After

completion of treatment duration, qualitative HCV RNA (PCR) was advised and result of end of treatment response (ETR) recorded. Side effects of drugs were also noted.

The data was analyzed by using software SPSS version 25. After describing as frequency and percentage, the qualitative data was analyzed using Chi-square test. Mean \pm SD and range were used to express the quantitative data which was analyzed by Student's t-test. A p value of < 0.05 was considered as having statistical significance. Analysis was done for whole of study population and also for non-cirrhotic and cirrhotic groups separately.

Approval for study protocol was taken from Institutional Review Board and Ethical Committee.

RESULTS

Female patients were more than male and the patients included had mean age of about 42 years (Table-I). Fifty nine % (295) patients were in fourth or fifth decade of life. Male patients have mean age of 42.31 ± 12.96 years and female have mean age of 41.64 ± 10.64 . The difference between their ages was not of statistical significance ($p = 0.529$). About 12 % (59) patients were cirrhotic. Among these, 21 (35.6 %) had Child A and 38 (64.4 %) had Child B cirrhosis. Eleven (18.64 %) cirrhotic had ascites. Cirrhotic were older than non-cirrhotic (mean ages 46.34 ± 9.46 vs 41.34 ± 12.96) and this difference was significant ($p = 0.002$).

Variables	Results
Age in years \pm SD (range)	41.93 ± 11.70 (8 to 82 years)
Gender	
Male	217 (43.4 %)
Female	283 (56.6 %)
Non-cirrhotic	441 (88.2 %)
Cirrhotic	59 (11.8 %)

Table-I. Demographic features of 500 patients

HCV RNA PCR negativity after completion of treatment i.e., ETR was observed in 491 patients (98.2 %). Mean age of responders was 41.90 ± 11.61 and of non-responders $43.78 \pm$

16.26 ($p = 0.633$). The response rate was not significantly different in male and female patients, and between cirrhotic and non-cirrhotic (Table-II). Sixty six patients (13.2 %) complained of fatigue and 21 patients (4.2 %) had headache. Among 59 cirrhotic patients who were given ribavirin, 11 (18.64 %) developed cough and mild breathlessness on exertion which responded to symptomatic treatment. Ten of these patients (16.95 %) had drop in hemoglobin below 10 g/dl for which dose of ribavirin had to be adjusted. None of the serious side effects occurred requiring treatment discontinuation.

Dependent Variable	ETR		P-Value
	Yes	No	
Gender			
Male	211	6	0.186
Female	280	3	
Cirrhosis			
Not present	433	8	1.000
Present	58	1	

Table-II. ETR – gender wise and according to presence of cirrhosis

DISCUSSION

Sofosbuvir, a NS5B inhibitor, was the first oral DAA¹⁹ that drastically changed the treatment of hepatitis C.²⁰ It was followed by development of many other DAAs. It has good efficacy against all genotypes of hepatitis C.²¹ In our country genotype 3 accounts for more than 80 % of hepatitis C patients.^{22,23} This genotype is considered to be less responsive to DAAs.²⁴ Sofosbuvir was initially used with ribavirin for genotype 2 and 3 patients. In Fission and Positron trials, SVR with this combination in genotype 3 were 56 % and 61 % respectively.^{25,26} In Pakistan SVR with it was 83 %.²⁰ Daclatasvir is NS5A inhibitor and used along with sofosbuvir for genotype 2 and 3 patients. This combination is proved to be more effective than sofosbuvir with ribavirin.²⁷

In ALLY-3 study, sofosbuvir plus daclatasvir were given without ribavirin to hepatitis C genotype 3 treatment naïve patients for 12 weeks. Overall, ETR was > 99 % and SVR12 90 % (96 % for patients having no cirrhosis and 63 % for those having cirrhosis).¹⁸ In another study, this combination

was given with or without ribavirin for 24 weeks to treatment naïve patients of genotypes 1, 2 and 3. SVR12 were 98 %, 92 % and 89 % respectively.²⁸ Poordad et al gave this combination with ribavirin to cirrhotic hepatitis C patients for 12 weeks. SVR12 for genotypes 1, 2, 3 and 4 were 82 %, 80 %, 83 % and 100 % respectively.²⁹ Considering local data, when sofosbuvir and daclatasvir combination was given, overall both end of treatment response and SVR24 were 98.84 %.³⁰ About 10 % of these patients were cirrhotics. Similarly, Azmat A, et al showed a ETR of 98.8 % and SVR12/24 of 96.25 %.⁷ All of their patients were of genotype 3. Our result (ETR 98.2 %) is similar to local studies. It indicates that hepatitis C patients in Pakistani population respond better to sofosbuvir and daclatasvir.

We did not check genotype status of the patients due to cost issue but we assume that genotype 3 would be most common as all local studies favor this finding.^{22,23} We could not determine SVR12 as most of our patients lost in follow up but as our ETR is similar to that of other local studies,^{7,30} it can be assumed that SVR will also be similar to them. Side effects profile and tolerability of drugs in our study were same as in other local and international studies.^{7,28}

CONCLUSION

The combination of two DAAs, sofosbuvir and daclatasvir, is very effective for the treatment of chronic hepatitis C patients of Southern Punjab like other regions of our country. These drugs have good tolerability and generally safe to use.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
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2	M. Israr ul Haq	Conception of idea, data collection, data analysis, interpretation of results, proof reading.	
3	Ghulam Abbas	Conception of idea, data collection, Data analysis, Interpretation of results.	