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Original Article

Rapid Virological Response (RVR) of Daclatasvir and Sofosbuvir Plus Ribavirin in Non-Cirrhotic, Treatment-Naive Patients of Hepatitis C Virus Genotype 3

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Abstract

Background :To determine the efficacy of Daclatasvir and Sofosbuvir plus Ribavirin in achieving Rapid Virological Response (RVR) in patients of Hepatitis C genotype 3 who are non-cirrhotic and have not received any previous treatment.

Methods: In this descriptive case series study, 100 non cirrhotic, treatment-naïve patients of HCV genotype 3 were enrolled. Each patient was given oral tab Daclatasvir 60 mg once daily,tab Sofosbuvir once daily 400 mg and capsule Ribavirin 400 mg twice daily. HCV RNA PCR quantitative was obtained before treatment and repeated after completion of one month treatment with above mentioned drugs.

Results: Mean age of included patients was 42.7 ± 10.68 years (mean ± SD). Females were dominant(59%). The BMI was 26.07 ± 3.00 kg/m2. Out of 100 patients 87% patients achieved Rapid Virological Response (RVR).The data was stratified according to age, gender and BMI. There was no effect of these parameters on the final results.

Conclusion: Rapid Virological Response (RVR) of Daclatasvir plus Sofosbuvir and Ribavirin is impressive. However, more studies are required to ascertain the results.

Key Words: HCV, Genotype 3, RVR, Oral Direct Acting Antivirals , DAA, Daclatasvir, Sofosbuvir

Introduction

Hepatitis C is a rising and alarming global health problem. The hepatitis C virus can lead to acute and chronic hepatitis. According to World Health Organization (WHO), Chronic Hepatitis C has affected nearly 71 million people in the world, with about 399,000 deaths mainly due to its threatening complications such as cirrhosis and hepatocellular carcinoma (HCC).[1] Hepatitis C Virus has 6 homologous genotypes. Among which, HCV genotype 3 is much common in South East Asia , as compared with other five known genotypes.[2,3] Most common Genotype in Pakistan is 3a which is followed by 3b. [4]
Earlier, HCV infection was managed with interferons. However, these treatment regimens had low success rate against HCV infection, particularly against genotype 3, both because of their less efficacy and poor compliance to these regimens because of their adversity profile.[5-7] HCV genotype 3 has been found to be associated with markedly increasing risk of developing complications like cirrhosis and hepatocellular carcinoma if left untreated. [8,9]
With the recent advents in treatment regimens of HCV infection, the therapy for HCV genotype 3 has also been revolutionized in recent era. Both European Association for the Study of the Liver. (EASL) and American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD) now recommend oral Direct Acting Antivirals (DAA) as first line treatment for HCV infection, owing to their efficacy and compliance .[10,11]
The use of oral Direct Acting Antivirals (DAA) for treatment of HCV genotype 3 has been proved to be much efficacious in achieving Virological responses as compared to conventional interferons and PEG interferons.[12]
Uptil now, the most efficacious drugs trialed against HCV genotype 3 are Sofosbuvir and Daclatasvir.[13] Daclatasvir (DCV) inhibits HCV NS5A protein.[14] whereas Sofosbuvir (SOF) is an inhibitor of the HCV NS5B RNA polymerase.[15] These proteins play basic part in replication of viral RNA. Although the measure of efficacy of these drugs has been considered to be able to achieve the Sustained Virological Response (SVR) after treatment, researchers have also focused on response towards therapy in terms of Rapid Virological response, which has been defined as Achievement of undetectable Hepatitis C Virus RNA

by PCR quantitative 4 weeks after initiation of treatment with a lower limit of detection ≤ 25 IU/ml. This monitoring of Rapid Virological response is considered to be effective in monitoring response to therapy.[16] In one of these trials, it has been found that treatment of HCV genotype 3 infection with combination of Daclatasvir alongwith Sofosbuvir and Ribavirin has been reported to achieve Rapid Virological response (RVR) in 87% of cases in ALLY3+ trial.[17]

Patients and Methods

This case control study was done in Liver Clinic OPD of Medicine Unit II, Benazir Bhutto hospital from 01-01-2018 to 30-06-2018 over a period of six months .Among the patients presenting to liver clinic, Patients of HCV genotype 3 who were non-cirrhotic and had not taken any past treatment, were enrolled in study after informed consent. All patients in this study had pre-treatment HCV RNA Quantitative levels >1000 IU/L. Other inclusion criteria included age between 18-70 years, and BMI ≥ 18 kg/m^2. Exclusion Criteria included patients who had recieved any previous treatment for Hepatitis C Virus infection, or patients who had any evidence of Cirrhosis . Pregnant women and patients with Hepatitis B Virus, HIV co-infection and decompensated liver disease were also excluded. All included patients were given Oral Tab Daclatasvir 60 mg PO OD, Tab Sofosbuvir 400 mg PO Once daily, and Cap Ribavirin 400 mg PO twice daily as a protocol of treatment for HCV infection. HCV RNA PCR Quantitative levels were measured after completion of one month of treatment with these drugs to moniter the response to therapy and Rapid Virological Response (RVR) was calculated**.** All the categorical variables like gender, SVR were described as frequencies and percentages while for age, BMI which are continuous variables, mean and SD was calculated. Effect modifiers including age, gender, BMI were controlled by stratification. T-test was applied after stratification. p value of ≤ 0.05 was statistically considered significant.

Results

100 patients were included in this study. Mean age of included patients was 42.70 ± 10.68 years (mean ± SD). The age was further distributed into two categories. Out of 100 patients, 59% were females and 41% were males**.** The BMI in study group was 26.07 ± 3.00 kg/m^2. Majority (87%) achieved Rapid Virological Response (RVR) (Figure 1). Data was stratified according to age, gender and BMI. There was no effect of these parameters on the final results (Table 1).

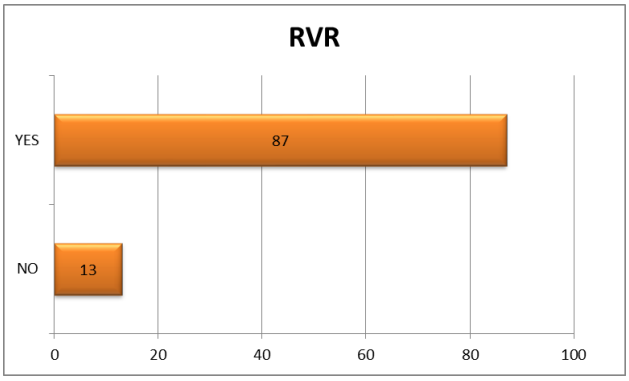

Figure 1. Virological response in hepatitis C patients

Table 1. RVR status after stratification

Parameter		RVR		P value
		Yes	No	
Age	<50 years	61	09	0.949[a]
	>50 years	26	04	
Gender	Male	36	05	0.844[a]
	Female	51	08	
BMI	<25	33	04	0.622[a]
	>25	54	09	

Discussion

Although, in few parts of the world, blood screening and many preventive measures have decreased the incidence of Hepatitis C Virus but still HCV infection is a considerable global health issue. The many genotypes of HCV, and rapid rate of mutations, have created difficulty in the development of effective medications. The older drugs like interferons and ribavirin have been replaced by new oral direct acting antiviral agents, in which Daclatasvir and Sofosbuvir are considerable in treatment of Hepatitis C Virus genotype 3.[18]

The effectiveness of new oral Direct Acting Antivirals is determined by frequency of attainment of Sustained Virological response after treatment. Rapid virological response has also been considered to be an effective parameter to estimate and assess the response to antiviral agents therapy, but its role in predicting the response of ongoing treatment is yet to be established.[16]

ALLY 3+ trial done for evaluation of response of Daclatasvir with Sofosbuvir and Ribavirin in HCV genotype 3 depicted 83% of patients receiving 12

weeks treatment achieved RVR. Rapid Virological Response in our study was 87%, although our study did not include the cirrhotic patients as opposed to ALLY 3+ trial.[12,13] In another study done by Goel et al, in 2017 a cohort of 160 patients was analyzed for RVR, ETR and SVR. The results showed RVR to be 91.3% in that cohort.[19] RVR of patients was also evaluated in a study done by Hill A et al, which reported RVR to be achieved in 84% of study population .[20] In a meta-analysis done by using databases of PUBMED , WANFANG, CNKI, EMBASE and COCHRANE the data of 1100 patients of Genotype 1 to 4 was assessed for achievement of virological responses after use of DAAs. This meta-analysis also concluded Daclastavir to be superior in achieving RVR and SVR . [21]

In another meta-analysis mainly done for HCV genotype 1, RVR has been reported as an outcome in the evaluating response of DAA as an indirect comparison.[22] Sperl J et al. reported combination of Sofosbuvir and Daclatasvir to be highly effective in patients of haemodialysis, and Saint-Laurent et al. reported this combination to be both efficacious and cost effective.[23,24,] In a study , done in Italy, Combination therapy for HCV genotype 3 treatment with Daclatasvir + sofosbuvir + Ribavirin for 12 weeks was found more efficacious to Sofosbuvir plus ribavirin therapy for 6 months. Cost effectiveness of DCV and SOF combination therapies has also been established in various other studies. In our setups, these drugs are being rapidly introduced, however cost effectiveness was not evaluated. [25-27] Pakistani studies suggested rate of virological responses of Daclastavir using combination to be above 80% in Pakistan. [28,29,30] Present study is mainly focused on evaluation of efficacy of Daclatasvir with Sofosbuvir and Ribavirin in achieving Rapid Virological response. However patients need to be followed to determine End of Treatment response (ETR) and Sustained Virological Response (SVR) as a part of 12 week treatment regimen. RVR measurement during course of therapy can serve as useful tool to predict response to DAA therapy as well as it can help to evaluate the cases of treatment relapse during course of therapy.

Conclusion

1.The efficacy of Daclatasvir with Sofosbuvir plus Ribavirin in achieving Rapid Virological Response is impressive.

2. It is required to ascertain efficacy of oral direct acting anti-virals in cirrhotic and treatment experienced/relapsed patients .

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