ORIGINAL ARTICLE

Virological Responses in Chronic Hepatitis C Patients, Treated with Sofosbuvir and Declacavir Versus Sofosbuvir and Ribazole

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[1]Principal researcher, Drafting the article
[3]Literature review, Interpretation Statiscal Analysis

Article Info

Received: Feb 8,2018
Accepted: May 28, 2018

Funding Source: Nil
Conflict of Interest: Nil

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ABSTRACT

Objective: To determine the virological responses in chronic hepatitis c patients, treated with *sofosbuvir* and *declacavir* versus sofosbuvir and *ribavirin* at tertiary care Hospital

Study Design And Setting: This was a prospective comparative study and was carried out at the gastroenterology department of people's medical university Nawabshah.

Duration: One year from December 2016 to November 2017.

Methodology: All the patients diagnosed with chronic hepatitis C virus with detectable HCV RNA by PCR , age ranged 18 to 60 years either gender were selected. All the patients were divided in two groups according to treatment as; patients of group A were undergone treatment of *sofosbuvir* + *declacavir* and patients of group B were underwent treatment of sofosbuvir + *ribazole.* PCR for HCV RNA Quantitative had been performed for viral measurements at the completion of 4thweek (RVR), 12th week (EVR), 24th week (ETR) and after 24 weeks of treatment completion (SVR). All patients not complying with the treatment or developed any complication based on protocol investigations that lead to termination of treatment were excluded from the study. All the data was recorded in the proforma.

Results: Total 107 patients were selected, mean age of the patients was 36.46+11.34 years. Female was found in the majority as 58.9%. 80.4% patients were undergoing treatment of sofosbuvir+declacavir and 19.6% were underwent sofosbuvir+ribazole. Rapid viral load response (RVR), Early viral load response (EVR), End treatment response (ETR) and Sustained viral response (SVR) were s significantly more achieved in group A (sofosbuvir+declacavir) as compared to group B (sofosbuvir+ribazole) p-value 0.020, 0.020, 0.004 and 0.004 respectively. roup B (sofosbuvir+ribazole) 18 patients achieved out of 21. No significant difference was found in the mean of viral load in both groups after completion of treatment p-value 0.628.

Conclusion: It is concluded that both treatments showed good efficacy, but sofosbuvir+declacavir treatment achieved more significant Rapid viral load response (RVR), Early viral load response (EVR), End treatment response (ETR) and Sustained viral response (SVR) as compare to sofosbuvir+ribazole.

Keywords: Chronic HCV, sofosbuvir+declacavir, sofosbuvir+ribazole

Introduction

Current estimates suggest that approximately 180 million people worldwide are infected with hepatitis C virus (HCV) with the highest prevalence rates reported in Africa and Asia.[1,2] According to the World Health Organization (WHO), as many as 4 million new infections occur annually and more than 350, 000 people die from HCV related liver diseases each year.[2] Previous

Studies indicate that around, three to four million people are newly infected each year resulting in an estimated 350,000 deaths annually. Pakistan is estimated to have the second highest patient burden.[3,4] The natural history of the disease suggests that up to 85% patients remain HCV infected once they acquire acute hepatitis C infection.[2] That is why the treatment for hepatitis C is revolutionizing since 1986 when for the first-time interferon was used.[3] Till the recent past, the standard treatment for Hepatitis C was a combination of pegylated interferon alfa and ribavirin for 48 weeks for genotype 1 and 24 weeks for genotype 2 and 3.[2] A breakthrough in the treatment was long awaited not only because of the unsatisfactory sustained viral response rate but also because of limited use due to side effects and contraindications.[4,5]

Oral combinations of direct-acting antivirals (DAAs) have become the standard of care for treating chronic HCV infection.[7,8] In clinical trials, rates of sustained virological response at post-treatment week 12 (SVR12) exceeding 90% have been reported for several drug combinations, with safety profiles superior to those of peginterferon-based regimens. However, advanced liver disease and concomitant medical conditions can adversely affect therapeutic responses and complicate the interpretation of results. Consequently, patients with such conditions are usually under-represented in clinical trials, and disease states encountered in clinical practice can differ in important ways from those permitted in randomized trials. Community-based programmes offer an important complement to registration studies by providing additional information concerning the therapeutic risk/benefit profile of a new regimen in a broader population.[9] It is reported that all oral direct-acting antivirals (DAAs) effectively treat chronic hepatitis C virus (HCV) infection, but response and complications of different regimens vary. Viral clearance achieved using different regimes were statistically the same. But triple drug and sofosbuvir with daclatasvir combination is having better SVR rates and more chances of decompensation than sofosbuvir and ribavirin combination.[10] No adequate data is available in the literature RVR and EVR in patients those were treated by sofosbuvir+ declacavir with ribavirin or without ribavirin. RVR and EVR mostly compared in peg-interferon based studies. Therefore this study has been conducted

Methodology

This was a prospective study and was carried out at gastroenterology department of people's medical university Nawabshah. This study was conducted with a duration of 1 one year from December 2016 to November 2017. All the patients diagnosed with chronic hepatitis C virus with detectable HCV RNA by PCR either gender were selected. All the patients with age ranged from 18 to 60 years were included.All the patient's with co-infection with HBV, CTP score > 9, known allergies to sofosbuvir or ribavirin, depressive illness not controlled on treatment, eGFR < 30 ml/min, and auto-immune hepatitis, alcoholic hepatitis, Wilson 's disease, HCC, haemochromatosis and pregnant or lactating females were excluded. Informed consent was taken from all the patients. All the patients were divided in two groups according to treatment as; patients of group A were undergone treatment of *sofosbuvir + declacavir* and patients of group B were underwent treatment of sofosbuvir + *ribazole.* CBC and LFT were checked at week 2 and then every 4 weeks depending upon the results. The patients who underwent the specified

treatment regimen were included and the data of study participants was taken from comprehensive patients individual records archived as a routine procedure and was entered in structured checklists for study variables for each study patient. PCR for HCV

RNA Quantitative had been performed for viral measurements at the completion of 4thweek (RVR), 12th week (EVR), 24th week (ETR) and after 24 weeks of treatment completion (SVR). All patients not complying with the treatment or developed any complication based on protocol investigations that lead to termination of treatment were excluded from the study.. All the data was recorded in the proforma.

Data Analysis: Data was entered in SPSS version 20. Mean and the standard deviation was calculated for quantitative variables like age. Frequency and percentage were calculated for categorical data like gender, educational status and frequency of hepatitis d virus. Chi square test was applied to compare the frequency of HDV with age groups, gender, and educational status, p-value less than 0.05 was considered as significant.

Results

Total 107 patients with detected of HCV RNA by PCR quantitative were selected in the study and underwent sofosbuvir treatment with combination two other treatments separately, mean age of the patients was (mean$\pm$SD = 36.46$\pm$11.34 years), and categorically most common age group was 18-30 years and 31-40 years with percentage of 35.5% and 31.8% respectively, while 23.4% patients were found with age group of 41-50 years and only 9.3% patients were with age of > 50 years. Females were found in the majority as 58.9% and male was found at 41.1%. According to the BMI most of the cases 82.2% were found with normal

BMI, 13.1% patients were overweight, 1.9% were obese, while 2.8% were underweight. Out of all cases, 11 patients were cirrhotic and the majority of patients 89.7% were non-cirrhotic. **Table I**

Table I: Demographic characteristics (n=107)

Basic characteristics	Frequency	%
Age groups		
18-30 years	38	35.5
31-40 years	34	31.8
41-50 years	25	23.4
>50 years	10	9.3
Total	107	100.0
Gender		
Male	44	41.1
Female	63	58.9
Total	107	100.0
BMI		
Normal	88	82.2
Overweight	14	13.1
Obese	2	1.9
Underweight	3	2.8
Total	107	100.0
Cirrhosis		
Cirrhotic	96	89.7
Non-cirrhotic	11	10.3
107	107	100.0
Mean age (mean+SD = 36.46+11.34 years)		

According to the treatment regimen 80.4% patients were underwent treatment of sofosbuvir+declacavir and 19.6% were underwent sofosbuvir+ribazole. **Figure 1**

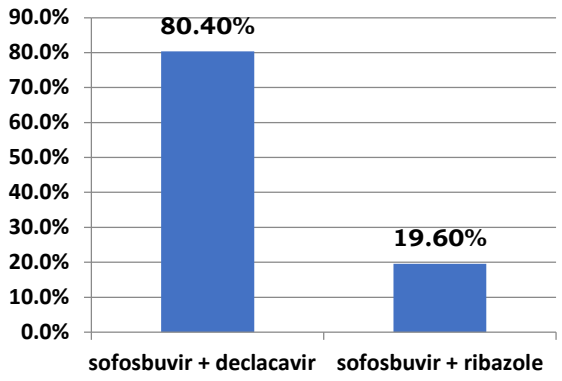

Figure 1. Patients distribution according to treatment regimen (n=107)

In this study on assessment of virological response according to the treatment regimen, Rapid viral load response (RVR) was achieved in both and significantly more achieved in group A (sofosbuvir+declacavir) as compared to group B (sofosbuvir+ribazole) p-value 0.020. Early viral load response (EVR) was also achieved by most of the cases, while significantly more in group A (sofosbuvir+declacavir) as compared to group B (sofosbuvir+ribazole) p-value 0.020. End treatment response (ETR) significantly more achieved by group A (sofosbuvir+declacavir) as 85 cases out of 86 and only 1 cases not achieved, while 18 cases achieved of group B (sofosbuvir+ribazole) out of 21, p-value 0.004. Sustained viral response (SVR) was also significantly more achieved by the patients of group A (sofosbuvir+declacavir) as 85 cases out of 86 and in group B (sofosbuvir+ribazole) 18 patients achieved out of 21. **Table II**

Table II: Virological response according to a regimen of treatment (n=107)

Viral response	Treatment regimen		
	sofosbuvir and declacavir	sofosbuvir and ribazole	P-value
Rapid viral load response (RVR)			
Achieved	84	18	
Not achieved	2	3	0.020
Total	86	21	
Early viral load response (EVR)			
Achieved	84	18	
Not achieved	2	3	0.020
Total	86	21	
End treatment response (ETR)			
Achieved	85	18	
Not achieved	1	3	0.004
Total	86	21	
Sustained viral response (SVR)			
Achieved	85	18	
Not achieved	1	3	0.004
Total	86	21	

In this study, no significant difference was found in the mean of viral load in both groups after completion of treatment as mean of viral load in group A (sofosbuvir+declacavir) was 972.31±185, and viral load mean in group B (sofosbuvir+ribazole) was 120.40±135.6, p-value 0.628. **Table III.**

Table III: Patients distribution according to viral after complete treatment (n=107)

Treatment regimen	N	Mean±SD	P-value
sofosbuvir and declacavir	86	972.31±185.2	0.628

Table III: Patients distribution according to viral after complete treatment (n=107)

Treatment regimen	N	Mean±SD	P-value
sofosbuvir and declacavir	86	972.31±185.2	0.628
sofosbuvir and ribazole	21	120.40±135.6	

Discussion

Sofosbuvir treatment represents the 1st step towards the new era in treatment of patients with chronic hepatitis C, since it is 1st approved direct acting antiviral agents with the big genetic barrier and potent activity against all HCV genotypes.[11,12] Additionally it is excellent according to safety, even when it is given with advanced liver disease and higher risk of complications. It has excellent pharmacokinetic profile allowing its administration as one tablet daily and has rather limited potential for drug-drug interactions.[12] In this study 107 patients were comparatively treated with sofosbuvir+declacavir and sofosbuvir+ribazole. Both groups showed good efficacy, but patients of sofosbuvir+declacavir (group) showed significant achievement of Rapid viral load response (RVR), Early viral load response (EVR), End treatment response (ETR) and Sustained viral response (SVR) as compare to group B (sofosbuvir+ribazole) p-value 0.020, 0.020, 0.004 and 0.004 respectively p-value 0.020, 0.020, 0.004 and 0.004 respectively. In the favor of these findings Kutala BK et al[13] reported that the combination of SOF+DCV has shown more efficacy as compared to SOF+RBV (p=0.035

In this study mean age of the patients was (mean±SD = 36.46±11.34 years), and categorically most common age group was 18-30 years and 31-40 years with percentage of 35.5% and 31.8% respectively. On other in the study of Umar M et al[14] reported that amongst all, 296 (50.9%) were males whereas 286 (49.1%) were females (P-value 0.22). Mean age of all participants was 40.43±9.622 years. While inconsistently we found female in majority as 58.9% and male were 41.1%. In another study of Sarwar S et al[15] reported that mean age was 49.4 (±12.1) years with male to female ratio of 1.1 (114/102)

In this study on assessment of virological response according to treatment regimen, Rapid viral load response (RVR) was achieved in both groups and significantly more achieved in group A (sofosbuvir+declacavir) as compare to group B (sofosbuvir+ribazole) p-value 0.020. In this study Early viral load response (EVR) was also achieved by most of the cases, while significantly more in group A (sofosbuvir+declacavir) as compare to group B (sofosbuvir+ribazole) p-value 0.020. No more data is available in the literature RVR and EVR in patients those were treated by sofosbuvir+ declacavir with ribavirin or without ribavirin. RVR and EVR mostly compared in peg-interferon based studies, as Mangia *et al*[16] and Delgard *et al*[17] showing high RVR in general population from 31–100%, and PPV ranging from 69–100%.16 These all researches were done based on Peg interferon treatment based on all genotypes separately.

In the current study end treatment response (ETR) significantly more achieved by group A (sofosbuvir+declacavir) as 85 cases out of 86 and only 1 cases not achieved, while 18 cases achieved of group B (sofosbuvir+ribazole) out of 21, p-value 0.004. On another hand in the study of Siddique MS et al[18] stated that patients treated with Sofosbuvir have shown excellent results with 99.5% achievement of RVR, 99% ETR of patients treated and SVR 98.5%. Other studies have shown higher rates of SVR in patients treated with interferon-free combinations in genotypes 1 and 2 especially with the very good safety profile and favorable outcomes and without resistance in both cirrhotics and non-cirrhotics.[19]

In this series sustained viral response (SVR) was also significantly more achieved by the patients of group A (sofosbuvir+declacavir) as 85 cases out of 86 and in group B (sofosbuvir+ribazole) 18 patients achieved out of 21. Similarly in the study of El-Khayat H et al[20] reported that sustained virological response at 12 weeks after the end of treatment (SVR12) rate was 92% in naïve cirrhotic patients and 87% in previously treated patients. In our series SVR 98.7% which is high as compare other published studies, this may because in our study decompensated cirrhotic patients were not included. Comparable findings were found in the study of Omar H et al[21] reported that overall, 95.1% achieved SVR12 (95.4% among patients treated without RBV and 94.7% for patients treated with RBV, P= .32. On other hand Welzel TM et[22] reported that overall, SVR12 was achieved by 91%), including 92% of patients treated with DCV+SOF and 89% of those treated with DCV+SOF+RBV. Shiha G et al[23] reported that sustained viral response after 12 weeks of end of treatment (SVR12) was achieved in 96.6% of the patients receiving 12 weeks of DCV + SOF treatment, in 95.7% of the patients receiving 12 weeks of DCV + SOF + RBV, in 93.3% of those receiving 24 weeks of DCV + SOF, and in 92.2% of patients receiving 24 weeks of DCV + SOF + RBV treatment as well as SVR12 rate was significantly higher in patients with no cirrhosis receiving DCV + SOF only for 12 weeks or 24 weeks.

Conclusion

It is concluded that both treatments showed good efficacy, but sofosbuvir+declacavir treatment achieved more significant Rapid viral load response (RVR), Early viral load response (EVR), End treatment response (ETR) and Sustained viral response (SVR) as compare to sofosbuvir+ribazole. While no significanr difference was is mean of viral load in both groups.

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