Original Article

"TREATMENT SUCCESS OF SOFOSBUVIR AND DACLATSVIR WITH OR WITHOUT RIBAVIRIN IN PATIENTS OF HEPATITIS C VIRUS"

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ABSTRACT

Background: To compare the frequency of responders achieving SVR12 after taking sofosbuvir and daclatasvir with vs without ribavirin.

Material and Methods: Total 180 patients meeting inclusion criteria were enrolled in the study from Department of Medicine, Government Teaching Hospital Shahdara, Lahore.This randomized controlled trial was conducted from March 25, 2021, to September 24, 2021. Treatment naive cases were given tablet sofosbuvir & daclatasvir for 12 weeks. Treatment-experienced and naive with cirrhosis were given ribavirin based on their body weight along with sofosbuvir and daclatasvir for 12 weeks. After 3 months of treatment, patients were called for follow up at 12th week post-treatment for HCV RNA PCR to see if patient has achieved SVR12 or not. Statistical analysis was performed using SPSS v25.0. Frequency of responders was compared using the Chi-square test. P-value less than or equal to 0.05 was considered statistically significant.

Results: In group-A, 54(60.0%) patients were males and 36(40%) patients were females. In group-B, 52(57.8%) patients were males and 38(42.2%) were females. The mean age in patients of group-A was 45.69±12.481 years while that was 44.99±14.590 years in group-B. In group-A (Sofosbuvir and daclatasvir with ribavirin), 81(90.0%) patients had a response rate and in group B (Sofosbuvir and daclatasvir), 65(72.2%) patients had a response rate with p-value (p=0.002).

Conclusion: It was concluded that sofosbuvir & daclatasvir with ribavirin was found more efficacious than sofosbuvir & daclatasvir alone in achieving SVR 12 in patients of chronic hepatitis C infection, so it will help in delaying disease process and improving quality of life, especially in the developing world.

Key Words: Sofosbuvir, Daclatasvir, Ribavirin, Hepatitis C

doi: https://doi.org/10.51127/JAMDCV5I2OA05

How to cite this:
Ather CAA, Nawaz M, Sulehria SB, Chaudary S, Mehmood Z, Rehman M. "Treatment success of sofosbuvir and daclatsvir with or without ribavirin in patients of hepatitis c virus"
JAMDC. 2023;5(2): 90-96
doi: https://doi.org/10.51127/JAMDCV5I2OA05

INTRODUCTION

Hepatitis C virus (HCV) is a single-stranded RNA virus. About 64 and 103 million people are chronically infected globally with HCV.[1] Chronic HCV poses a global threat, infecting more than 71 million people worldwide according to WHO report in 2015 with 400,000 deaths per year. HCV prevalence is highest in Central, South and East Asia more than 50% HCV infected cases belongs to Asian regions[2,3] National survey done in 2007-2008 in Pakistan reported 4.8% HCV prevalence.[4] Chronic HCV infection if untreated can lead to decompensated liver changes, extra-hepatic manifestations and hepatocellular carcinoma with early mortality.[5] Standard treatment for chronic HCV infection from the late 1990s to the early 2010s was a combination of

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peginterferon and ribavirin but they resulted in less viral clearance and more adverse effects. With the advent of science, new HCV treatment therapy with host targeting, oral and direct acting, anti-viral (DAA) agents have been recognized and approved by FDA in 2018. These newer drugs lead to early HCV elimination along with regression of hepatic fibrosis and hence decrease the risk of hepatocellular carcinoma.[6,7]

It has also been shown to be beneficial in the treatment of cryoglobulinemia associated with HCV, decreased cardiovascular events, and improved neurocognition.[8] Direct-acting, antiviral therapy includes several types of agents like HCV protease inhibitors, HCV polymerase inhibitors. Daclatasvir is a potent, pan genotypic NS5A inhibitor, it disrupts HCV replication complex formation. Sofosbuvir is a potent, pan genotypic, NS5B polymerase inhibitor thus inhibits HCV-RNA synthesis. Ribavirin is a guanosine analogue and works by immunomodulation and inhibits the initiation and elongation of RNA fragments.[9]

An Indian study showed over 90% SVR12 achievement with all oral-DAA therapy.[10] Similarly 12 week treatment with sofosbuvir and daclatasvir resulted in 90% SVR12 in treatment naive patients, 86% in treatment experienced, while 96% in patients without cirrhosis and 63% in cirrhotic having HCV genotype 3 but with treatment relapse in 16 patients.[11] Comparable SVR12 results were observed in two treatment groups in large real world cohort study regardless of liver status or prior treatment.[12] This therapy almost exhibited similar results in HCV mono-infected, HIV co-infected, and fibrotic cases except decompensated cases having less virological clearance.[13,14] The SVR12 rate was 97.5% in group without ribavirin and 87.7% in group with Ribavirin.[15] this study aims to assess the response of HCV infected patients treated with sofosbuvir and daclatasvir with or without ribavirin. It may represent different response in our population due to ethnic differences or comparable with other Asian groups showing high SVR rates.[14] It may show different responses in our elderly population due to different prevalent diseases as compared to a study by Tamer Elbaz.[15] No recently published local data is available regarding this. It may provide local evidence regarding DAA therapy and may add productive data to the existing body of knowledge and help for further research work. Patients who achieved SVR12 with treatment i.e Sustained Virological Response 12 (SVR12) the endpoint of treatment defined by undetectable levels of HCV RNA in blood 12 weeks after the end of therapy as assessed by a sensitive molecular method like PCR with a lower limit of detection at 15 IU/ml. HCV patients who were treated successfully with sofosbuvir and daclatasvir with or without ribavirin and achieved SVR 12 will be labelled responders while HCV patients who did still show detectable viral load on HCV PCR 12 weeks after the end of treatment will be labelled as non-responders. There is a difference in the frequency of responders after treatment with sofosbuvir and daclatasvir with vs. without ribavirin in hepatitis C infected patients.

MATERIAL AND METHODS

It was conducted in the Department of Medicine, at Government Teaching Hospital Shahdara, Lahore. It was performed from March 25, 2021 to September 24, 2021. It was a randomized controlled trial. Non-probability consecutive sampling technique was used. A sample of size 180 (90 in each group) was calculated according to the WHO formula with an expected SVR12 rate 87.7% in sofosbuvir and daclatasvir with the ribavirin group and 97.5% in sofosbuvir and daclatasvir without ribavirin group at 12 weeks in patients with hepatitis C virus infection with 80% power of the test and 5% level of significance.[15] Patients between the ages of 18 and 90 with detectable HCV RNA burden on quantitative HCV RNA PCR with a lower limit of detection at 15 IU/ml and positive anti-HCV antibodies on screening were included while patients with diagnosed hepatocellular carcinoma or any other malignancy, having concomitantly Hepatitis B or HIV with HCV, those who are currently

on interferons or other oral anti-viral drugs, those of chronic renal disease (with serum creatinine > 2.5mg/dl), with any organ transplantation, on haemodialysis, pregnant females and critically sick patients in ICU were ***excluded***. After approval from the ethical committee of the Hospital, informed consent was taken from 180 patients meeting the inclusion criteria as mentioned above and they were enrolled in a study from the Outdoor Department of Medicine, Government Teaching Hospital Shahdara, Lahore.

These patients were given treatment according to EASL recommendations 2018. Patients who taking anti-viral therapy for the first time in life were labelled as treatment naive cases and it was the control group of the study. Those who had taken interferons, ribavirin or DAA therapy in past but hadn't achieved SVR12 were labelled as treatment experienced cases. Treatment naive cases were given tablet sofosbuvir (Sofos, Genix Pharma, Karachi, Pakistan, 400mg orally once daily) and daclatasvir (Daclit, Genix Pharma, Karachi, Pakistan 60mg orally once daily) for 12 weeks. Treatment experienced and naive with cirrhosis were given ribavirin based on their body weight (Ribavil, Genix Pharma, Karachi, Pakistan 1200mg or 1000mg orally daily if greater than 75kg and 75kg or less body weight respectively) along with sofosbuvir 400mg orally daily and daclatasvir 60mg orally daily for 12 weeks. Data were collected from patients on the first visit including their age, gender, baseline viral load on quantitative HCV RNA PCR, treatment naive or treatment experienced cases. Treatment was prescribed as above and entered on proforma and patients were followed monthly for 3 months for checking treatment compliance, adverse effects and supply of next month's drugs.

After 3 months of treatment, patients were called for follow up at 12^{th} week post-treatment for HCV RNA PCR to see if the patient has achieved SVR12 or not and their results were entered on her/his proforma. Responders were labelled (as per operational definition).

All the data were collected and analysed by the trainee himself and all the investigations were done from the hospital laboratory and reported by the same fellow pathologist having five years' experience to eliminate bias and confounding variables were controlled by exclusion. Patients who did not achieve SVR12 were advised further workup and retreatment. Statistical analysis was performed using SPSS version 25.0. Mean and standard deviation was calculated for quantitative variables like age and viral load. Frequency and percentage were calculated for gender, treatment naive and treatment experienced cases, responders and non-responders. The frequency of responders was compared using the Chi-square test. Data were stratified for age, gender, treatment naïve vs. already treatment taken for the two treatment groups. Poststratification, the Chi-square test was applied and p-value less than or equal to 0.05 was considered statistically significant.

RESULTS

In this study, we enrolled 180 patients (90 in each group) with hepatitis C virus. In group-A (Sofosbuvir and daclatasvir with ribavirin), 54(60.0%) patients were males and 36(40.0%) patients were females. In group-B (Sofosbuvir and daclatasvir), 52(57.8%) patients were males and 38(42.2%) patients were females

The mean age of patients in Group-A (Sofosbuvir and daclatasvir with ribavirin) was 45.69±12.481 years and 44.99±14.590 years in Group B (Sofosbuvir and daclatasvir). In Group-A (Sofosbuvir and daclatasvir with ribavirin),

63(70.0%) patients had ages ≤50 years and 27(30.0%) patients had >50 years. In Group-B (Sofosbuvir and daclatasvir),

64(71.1%) patients had ages ≤50 years and 26(28.9%) patients had >50 years

In group-A, 61(67.8%) patients had new treatment and 29(32.2%) patients had experienced treatment. In-group-B, 64(71.1%) patients had new treatment and 26(28.9%) patients had experienced treatment **(Table-1)**.

In Group-A (Sofosbuvir and daclatasvir with ribavirin), 81(90.0%) patients had a response rate and in Group B (Sofosbuvir and daclatasvir), 65(72.2%) patients had a response rate with p-value (p=0.002) **(Table-2)**. According to the stratification of responders between groups concerning gender, there is a significant difference in responders between groups of either gender (p<0.05) . According to the stratification of responders between groups concerning age, there is a significant difference in responders between groups in either age group (p<0.05) . According to the stratification of responders between groups concerning the treatment group, there is a significant difference in efficacy between groups in the treatment group (p<0.05) **(Table-3)**.

Table-1: Comparison of treatment group distribution between groups

Treatment group	Groups		Total
	Sofosbuvir and daclatasvir with ribavirin	Sofosbuvir and daclatasvir	
New	61	64	125
	67.8%	71.1%	69.4%
Experienced	29	26	55
	32.2%	28.9%	30.6%
Total	90	90	180
	100.0%	100.0%	100%

Table-2: Comparison of responders between groups

Responders	Groups		Total	p-value
	Sofosbuvir and daclatasvir with ribavirin	Sofosbuvir and daclatasvir		
Yes	81	65	146	0.002
	90.0%	72.2%	81.1%	
No	9	25	34	
	10.0%	27.8%	18.9%	
Total	90	90	180	
	100.0%	100.0%	100%	

Table-3: Stratification of responders between groups concerning treatment group

Treatment group	Responders	Groups		Total	p-value
		Sofosbuvir and daclatasvir with ribavirin	Sofosbuvir and daclatasvir		
New	Yes	57	42	99	0.001
		93.4%	65.6%	79.2%	
	No	4	22	26	
		6.6%	34.4%	20.8%	
	Total	61	64	125	
		100.0%	100.0%	100%	
Experienced	Yes	24	23	47	0.549
		82.8%	88.5%	85.5%	
	No	5	3	8	
		17.2%	11.5%	14.5%	
	Total	29	26	55	
		100.0%	100.0%	100%	

DISCUSSION

The use of drugs known as direct acting antivirals (DAAs) has truly revolutionized the way that chronic HCV is treated, but their high market costs have long been a cause for grave worry. This is even though every effort has been made to give patients, particularly those in developing countries, access to these medications at affordable prices.[16] One such strategy that has significantly lowered the cost of DAAs is the decision to permit generic drugs in around 101 developing nations[17], but the safety and efficacy of these generics constituted a significant problem that requires scientific analysis. At the end of the course of treatment, the overall SVR12

rate was 81.1%. Similar to this, patient subgroups with characteristics that are regarded as being significantly more challenging to treat, like decompensated chronic liver disease and genotype 3 HCV infection with decompensated chronic liver disease, demonstrated substantial SVR12 rates. Patients with Child-Pugh C had lower SVR12 rates, which is consistent with past studies, and as a result, markers of advanced liver disease, such as a low platelet count or low serum albumin level, were linked to a higher risk of treatment failure.[18] However, a significant percentage of this gap was caused by pre-existing severe chronic liver disease rather than poor virological efficiency. After excluding individuals who had a non-virological failure, the majority of them died from advanced chronic liver disease. Those with decompensated chronic liver disease had a 90% SVR12 rate. All Child-Pugh classes had similar rates and advanced chronic liver disease signs did not significantly increase the probability of virological failure.

The study's results are excellent and strikingly similar to data that is widely available. Contrary to this research, ALLY 3+, a top study that evaluated sofosbuvir and daclatasvir in individuals with genotype 3 reported an SVR12 of 90%. SVR12 is 86.01% in chronic liver disease that has decompensated and 87.01% in chronic liver disease that has received therapy, according to this study.[19] In another study, the same combination was used to treat genotype 3 HCV patients, and the outcomes showed an overall SVR12 of 88%, 92% in patients who had never received treatment, 84% in those who did, and 89% in cirrhotics.[20] In patients with genotype 3, a trial from Iran showed the efficacy of generic daclatasvir and sofosbuvir, although their outcomes were significantly better with an SVR12 of 98%. Additionally, they only include cirrhotic individuals in their trial, and a 12-week course of the generic medication costs roughly $1,890.[21]

In Indian research, all oral-DAA medications achieved an SVR12 of above 90%.[10] Similar to this, a 12-week course of sofosbuvir plus daclatasvir therapy produced 90% SVR12 in patients who were treatment naive, 86% in patients who had received previous therapy, 96% in patients without cirrhosis, 63% in cirrhotics with HCV genotype 3 and treatment relapse in 16 individuals.

Regardless of liver function or prior therapy, comparable SVR12 results were seen in two treatment groups in a significant real-world cohort trial.[12] Except for decompensated individuals having poorer virological clearance, this therapy almost produced equivalent results in HCV mono-infected, HIV co-infected, fibrotic cases.[13,14] The SVR12 rate was 87.7% in the group receiving ribavirin against 97.5% in the group not receiving it.[15] Daclatasvir and sofosbuvir were generally well tolerated, both with and without ribavirin, and their safety profile was comparable to that of phase III trial results. Even though a large number of patients had severe chronic liver disease—a population that frequently has decreased tolerance to HCV therapy, particularly those involving injectable interferon— no unusual safety events were discovered. There were very few cases of treatment termination due to adverse events and it is not surprising that in a population with advanced chronic liver disease, the majority of serious adverse events and treatment termination were most likely brought on by the disease's natural course rather than medication. Safety results were largely comparable between the two medication groups, except for a higher incidence of typically moderate haematological events, such as hemolysis resulting in anaemia, in the ribavirin group.

CONCLUSION

To achieve SVR 12 in patients with chronic hepatitis C infection, sofosbuvir and daclatasvir with ribavirin were found to be more effective than sofosbuvir and daclatasvir alone. This will aid in slowing the progression of the disease and enhancing the quality of life, particularly in the developing world.

AUTHOR'S CONTRIBUTION

CAAA: Supervised the research
MN: Data collection and analysis
SBS: Prepared the manuscript
SC: Final review of the article
ZM: Data analysis
MR: Help in data analysis and SPSS

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