Original Article

Combination of Sofosburvir and Daclatsvir in the treatment of Hepatitis C Genotype 2 and Genotype 3

Ziauddin[1], Inayat Ullah[1], Shah Zeb[2], Shahabuddin Zia[3], Dawood Khan[1] and Muhammad Abbas[2]

ABSTRACT

Objective: To see the result of combination of Sofosburvir and Daclatsvir in the treatment of Hepatitis C Genotype 2 and Genotype 3

Study Design: Observational intent-to-treat study

Place and Duration of Study: This study was conducted at the Department of Medicine, Lady Reading Hospital, Peshawar from January 2020 to December 2020.

Materials and Methods: 172 HCV patients i.e., HCV genotype 2 and genotype 3were included. Qualitative PCR including genotyping were done for all these patients. Liver status was evaluated through ultrasound. All patients were given combination of Sofosbuvir 400mg OD and Daclatasvir 60mg OD ± Ribavirin 400mg TDS. SVR was obtained at 12 weeks. Data was analyzed by SPSS version 22.

Results: Among 172 patients, 76 (44.2%) were males and 96 (55.8%) were females. The mean age was 40.84 years ± 12.0 SD. In these patients, 52(30.2%) patients and 120 (69.8%) were HCV genotype 2 and genotype 2 respectively. Among these patients, 86.1% of patients with HCV genotype 3 and 84.1% of HCV genotype 2 patients achieved SVR at 12 weeks. Sixty percent of the cirrhotic patients and 91.2% of those patients who had previously experienced treatment, obtained SVR at 12 weeks. Ninety-two percent male patients and 94.8% of female patients obtained SVR at 12 weeks.

Conclusion: Combination of Daclatasvir and Sofosbuvir with or without Ribavirin (DCV+SOF±RBV) have impressive results in achieving SVR at week 12 while treating HCV genotype 2,3.

Key Words: Chronic HCV, genotype 3, genotype 2, Sofosbuvir, Daclatasvir

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INTRODUCTION

It has been estimated that around 71 million people are infected with chronic hepatitis C globally with an estimated prevalence is 2.5% (1.8% to 5.6%). Globally, genotype 3 is the second most common strain, responsible for 30% of HCV infection, followed by genotype 2 (9%), genotype 4 (8%), and genotype 6 (5%). In Pakistan, HCV prevalence is 3.8% (92.8%-3.9%) with genotype 3(79%) and genotype 2(2.6%)[1-4].

1. Department of Medicine, Lady Reading Hospital, MTI, Peshawar.
2. Department of Medicine, Mardan Medical Complex (MTI) Mardan.
3. Khyber Medical University, Peshawar.

Correspondence: Dr. InayatUllah, Assistant Professor of Medicine, Lady Reading Hospital, MTI, Peshawar.
Contact No: 0300-5963571
Email: drabadat78@yahoo.com

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Direct-acting antiviral agents (DAAs) have shown excellent results by providing high rates of SVR in patients infected with any subtype of HCV[5].

Sofosbuvir, an NS5B polymerase inhibitor, has been evaluated in combination with Daclatasvir, an NS5A inhibitor, for clinical trials in the treatment of CHC genotype 2 and genotype 3 with 92% to 100% SVR at 12 or 24 weeks for genotype 2 and 86% to 97% SVR in genotype 3 patients[6]. These patients experienced this combination as treatment- naïve or have already experienced Ribavirin or pig interferon. In patients with liver cirrhosis, the SVR rates are usually 70% to 89% with 12 to 24 weeks with SOF+DAV±RBV[7,8].

This above-mentioned combination is effective in other subtypes of HCV, making it possible to eliminate hepatitis C from the world as aimed by WHO till 2030 defined as a 90% reduction in new cases and 65% reduction in mortality[9,10]. However, in resource-poor countries, this achievement seems to be difficult due to affordability issues[11].

In this study, we had given the combination of Sofosbuvir and Daclatasvir with or without Ribavirin to the patients infected with CHC genotype 2 and genotype 3 and obtained the SVR at 12 weeks.

MATERIALS AND METHODS

In this open-label, phase II observational intent-to-treat study, 172 patients were enrolled which was conducted at the department of medicine Lady Reading Hospital, Peshawar from January 2020 to December 2020. Patients aged >18 years and both gender were included. Those patients who did not experience treatment or those who experienced treatment, both, were included. Informed consent was taken from all the patients and data was collected on the predesigned preform. PCR HCV was done for all of the patients. Liver status was evaluated through ultrasound by CPSP qualified radiologist. All the patients were allowed for baseline investigations including full blood counts, liver functions, and renal functions tests. All the patients were given SOF + DCV ± RBV for 12 weeks. Those patients who had experienced treatment before or those who had cirrhotic liver on ultrasound were given SOF + DCV + RBV while the rest of the patients who had not experienced treatment or who had normal liver on ultrasound were given SOF + DCV. All the patients who had given this particular regime were planned for PCR at 12 weeks. All the data were entered into and analyzed by SPSS version 22. Mean and standard deviation were calculated for numerical variables while percentages and frequencies were calculated for categorical variables. For comparison of categorical variables, Chi-square test was applied while student t-test was applied for comparison of numerical variables. Statistical significance level was considered as $p < 0.05$.

RESULTS

Among these 172 patients, 76 (44.2%) were males and 96 (55.8%) were females. Mean age 40 ± 12.23 years. Ninety-one patients (53%) were in young aged group, defined as aged 18-40 years. Seventy-one patients (41.3%) were in middle-aged group (40-60 years). While 10 patients (5.7%) were in elderly-aged group i.e., aged >60 years. Among these patients, 120 (69.8%) patients were infected with HCV genotype 3 and 52 (30.2%) patients were infected with HCV genotype 2. Among these 172 patients, 138 (80.2%) patients did not experienced treatment while 34 (19.8%) patients experienced treatment either with Sofosbuvir + Ribavirin or with interferon. On ultrasound, 157 patients (91.3%) had normal liver status while 15 (8.7%) patients had cirrhotic liver. Among these 172 patients treated with SOF + DCV ± RBV, 161 patients (93.6%) had SVR at 12 weeks, while the remaining 11 patients (6.4%) did not achieve SVR at 12 weeks. Among the 120 patients with HCV genotype 3, 114 patients (95%) achieve SVR at 12 weeks while the remaining 6 patients (5%) didn't achieve SVR at 12 weeks. While those 52 patients infected with HCV genotype 2, 47 patients (90.4%) achieve SVR at 12 weeks while the remaining 5 patients (9.6%) did not achieve SVR at 12 weeks.

Table No.1: Distribution of patients

Gender wise distribution	Males 76 (44.2%)	172 (100%)
	Females 96 (55.8%)	
Genotype wise distribution	genotype3 HCV 120 (69.8%)	172 (100%)
	Genotype 2 HCV 52 (30.2%)	
Aged wise distribution	Young aged (18-40 years) 91 (53%)	172 (100%)
	Middle-aged (41-60 years) 71(41.3%)	
	Elderly aged (>60 years) 10 (5.7%)	
Treatment experienced	Did not experience Rx 138 (80.2%)	172 (100%)
	Experienced Rx 34 (19.8%)	
Liver status on ultrasound	Normal liver 157 (91.3%)	172 (100%)
	Cirrhotic liver 15 (8.7%)	

Table No.2: Results of the study

Patients	SVR at 12 weeks	Did not achieve SVR at 12 weeks
172 patients (100%) in total	161 patients (93.6%)	11 patients (6.4%)
HCV Genotype 3	114 patients (95%)	6 patients (5%)
HCV genotype 2	47 patients (90.4%)	5 patients (9.6%)
157 patients with Normal liver US status	152 patients (96.8%)	5 patients (3.2%)
Cirrhotic liver on US 15 patients	9 Patients (60%)	6 patients (40%)
Treatment not experienced 138	130 patients (94.2%)	8 patients (5.8%)
Treatment experienced 34	31 patients (91.2%)	3 patients (8.8%)
Male patients 76	70 patients (92%)	6 patients (8%)
Female patients 96	91 patients (94.8%)	5 patients (5.2%)

In both HCV genotype 2 and genotype 3, SVR results were tested with age and sex but the results were statistically not significant. Among the 157 patients having normal liver status on ultrasound 152 (96.81%) achieved SVR at week 12 while the remaining 5 patients (3.19%) did not achieve SVR at week 12. Among 15 cirrhotic patients, 9 patients (60%) achieve

SVR at week 12 while the remaining 6 patients (40%) didn't achieve SVR at week 12. Among 138 patients who did not experience treatment before, 130 patients (94.2%) achieve SVR at week 12 while the remaining 8 patients (5.8%) did not achieve SVR at week 12. Among those 34 patients who experienced treatment either with SOF + RBV or with interferon, 31 patients (91.2%) achieve SVR at week 12 while the remaining 3 patients (8.8%) did not achieve SVR at week 12. In gender-wise distribution, 70 male patients (92%) achieve SVR while 6 patients (8%) didn't achieve SVR at week 12. In females, 91 patients (94.8%) achieve SVR while 5 patients (5.2%) did not achieve SVR at week 12. Among the 11 non-responder patients, 3 (27.3%) were in young-age group (18-40 years), 7 patients (63.6%) were in middle-aged group (40-60 years) while one patient (9.1%) was in elderly-aged group (>60 years). The most common adverse events were headache, fatigue, nausea, and skin rashes.

DISCUSSION

HCV is considered to be endemic in Pakistan and an estimated 6.8% of the Pakistani population is infected with HCV which is around 40% increase in seroprevalence of HCV in recent years[12]. Data suggests that SOF based oral regimens are considered to be the most effective in the treatment of HCV and once-daily regimen of sofosbuvir/daclatasvir is associated with high SVR rates among patients infected with HCV genotype 1,2 and 3[13,14]. The results of this study show that sofosbuvir/daclatasvir± ribavirin are effective in the treatment of chronic HCV genotype 2 and 3, both in naïve and treatment-experienced as well as cirrhotic patients.

Results of a meta-analysis conducted by Li T et al. suggest that SVR rates for DAAs are 66.7 to 98.3%. The results of our study are consistent with it[15]. (table #2)

In our study, the cure rate for HCV genotype 2 and genotype 3 was 90.4% and 95% respectively by achieving SVR at 12 weeks which is consistent with the results of Belperio PS et al. They concluded in their study that the cure rate for HCV genotype 2 and genotype 3 was 94% and 90% respectively. We also concluded that Ribavirin does not affect the cure rates which is also consistent with Belperio PS et al[16]. In our study, SVR rates were low in cirrhotic patients i.e. 60% SVR at 12 weeks VS 94.2% in treatment-naïve patients and in treatment-experienced patients i.e. SVR 91.2% VS 94.2% at 12 weeks which is also consistent with Belperio PS et al.

Wehmeyer MH et al conducted a multicenter study on a different treatment regimens of HCV genotype 3. They achieved an SVR of 90% at 12 weeks which is consistent with the results of our study. They also concluded that daclatasvir/sofosbuvir ± ribavirin is effective in treating-naïve, cirrhotic and treatment-experienced HCV genotype 3 patients which is also consistent with the conclusion of our study[17].

Tacke F et al conducted a cohort study on the treatment of HCV genotype 2 and concluded that patients treated with daclatasvir/sofosbuvir ± ribavirin achieved SVR up to 90% which is consistent with the results of our study. They also concluded that SVR rates were low in cirrhotic patients which supports the results of this study as well[18].

Sulkowski MS et al. Concluded in their study that the single daily regimen of Sofosbuvir/Daclatasvir had 92% and 89% SVR in HCV genotypes 2 and 3 respectively which is also consistent with the results of our study[19].

Moshyk A et al. Concluded in their study that Sofosbuvir/Daclatasvir combination was effective in treating chronic HCV treatment-experienced patients which is consistent with the results of our study and found in cost effective comparatively[20].

Zanaga LP et al. concluded in their study that the combination of Sofosbuvir and Daclatasvir had an SVR of 59-69% in chronic HCV genotype 3 cirrhotic patients which is consistent with the results of our study[21].

Mushtaq S et al. Conducted a study on the treatment of chronic HCV and concluded that Sofosbuvir/ Daclatasvir + Ribavirin had SVR of 94% in chronic HCV genotype 3 patients which is consistent with the results of our study. They also concluded that SVR was lower in patients with advanced liver diseases which is again consistent with our study[22].

CONCLUSION

Generic Sofosbuvir /Daclatasvir + ribavirin achieve high SVR rates in chronic HCV genotype 2 and 3. This combination is safe, effective and well-tolerated in patients with liver cirrhosis as well.

RECOMMENDATIONS: Further studies with large sample size are recommended for clarifying this regimen further and for optimal duration particularly in patients with liver cirrhosis.

Author's Contribution:

Concept & Design of Study:	Ziauddin,
Drafting:	Inayat Ullah, Shah Zeb
Data Analysis:	Shahabuddin Zia, Dawood Khan and Muhammad Abbas
Revisiting Critically:	Ziauddin, Inayat Ullah
Final Approval of version:	Ziauddin,

Conflict of Interest: The study has no conflict of interest to declare by any author.

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