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ORIGINAL ARTICLE

Comparison of Efficacy of Daily Sofosbuvir and Declatasvir with Alternate Day Sofosbuvir and Declatasvir in Hepatitis C Patients on Hemodialysis in Pakistani Population

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ABSTRACT

Objective: compare the efficacy of daily Sofosbuvir plus Declatasvir with alternate day Sofosbuvir and Declatasvir in HCV patients on hemodialysis.

Study design: Randomized clinical trial

Place and duration: department of general medicine Nishtar hospital, Multan from March 2020 to March 2021 in one year duration.

Methodology: A total of 260 patients were enrolled in study and divided into two groups (1 and 2) by convenient sampling technique. Non probability consecutive sampling technique was used. Group 1 treated with Sofosbuvir plus Declatasvir daily and group 2 was treated with alternate Sofosbuvir and Declatasvir. SPSS version 23.1 was used for data entry and analysis.

Results: The liver enzymes and hematological parameter were noted after 24th weeks. The mean differences at baseline and after 24th weeks within the groups was statistically significant, ($p<0.001$). Viral load detectable, RVR, ETR, and SVR at 24 weeks was 91.5% vs 88.5%, 98.5% vs 98.5% and 97.7% vs 90.8% respectively.

Conclusion: In Pakistani population hepatitis C virus is endemic like some other countries. In hemodialysis patients daily Sofosbuvir with daclatasvir is safe and effective with greater SVR as compare to Sofosbuvir with daclatasvir in alternate days even in genotype 3.

Keywords: Sofosbuvir, Daclatasvir, HCV, Hemodialysis, Genotype 1,2,3

INTRODUCTION

Prevalence of hepatitis "C" virus (HCV) patients on hemodialysis was about 60% in the world. Its spread through blood and nosocomial transmission is important factors that affect the incidence of HCV[1]. Dialysis patients are at higher risk of hepatocellular carcinoma, progressive cirrhosis, and increased rate of mortality. Some serious infections are also developed due to HCV infection especially in renal transplant patients[2]. Combination of ribavirin and pegylated interferon or interferon alone have been mainstay in patients of hemodialysis and HCV infection, but because of poor virologic response, prolong treatment, low tolerability, lesser efficacy, high association of side effects needs close monitoring supportive care[3].

Treatment of HCV infection have revolutionized with introduction of direct acting antiviral (DAAs) and their superior cure rates, SVR up to 90% or above, short treatment duration and tolerable adverse effects but their efficacy in hemodialysis patients is not well reported[4]. Combination of direct acting antiviral like Sofosbuvir plus Declatasvir with and without ribavirin is very useful and effective treatment modality even in immunocompromised and cirrhosis patients. These combination treatments also famous as interferon free therapies having potential reduction in HCV disease progression[5].

Many treatment options have been approved for end stage renal disease (ESRD) patients, pegylated interferon is one of them that have higher adverse effects and low SVR rates[6]. In terms of morbidity and mortality dialysis patients negatively impacted by HCV infection as compare to dialysis patients without HCV infection, effective treatment options required in these patients[7]. Treatment with Sofosbuvir has few side effects and leads to higher rate of SVR, but its use in patients with eGFR of ≥30 ml/min per 1.73 m^2 is restricted[8].

In severe renal impairment level of sofosbuvir is considerably higher and it's all metabolites excreted by the kidneys[9]. Another drug Daclatasvir strongly recommended in dialysis patients because of elimination and metabolism of its all components by the kidneys. Use of sofosbuvir and daclatasvir combination on daily basis and in alternate days is also famous for high SVR rate[10]. But data on its efficacy and tolerability is also limited, so this study was planned to compare the use these antiviral combinations on daily and alternate days in hemodialysis patients.

METHODOLOGY

This randomized clinical trial was conducted in the department of general medicine Nishtar hospital, Multan from March 2020 to March 2021 in one year duration. Study was started after IRB approval from hospital ethical board and written informed consent from patients. Non probability consecutive sampling technique was used. A total of 260 diagnosed patients HCV infection (detected HCV RNA by PCR) and end stage renal disease (hemodialysis) were enrolled in the study. Patients with co-infection like HIV, HBV, HDV, terminally ill patients and decompensated cirrhosis were excluded from the study. Patients were divided into two groups (group 1 and 2) by convenient sampling technique. Patients in group 1 were given daily daclatasvir 60 mg and sofosbuvir 400mg and in group 2 patients were given daclatasvir 60mg and sofosbuvir 400mg on alternate days for time period of 12 weeks. Demographic data of all patients like age, gender and baseline investigation values like HCV RNA PCR, duration of disease, duration of dialysis, genotype (1,2,3) were noted by the researcher. Patients were classified as according to child pugh score and imaging studies as compensated cirrhosis or not. Cases cirrhosis cases were treated for 24 weeks.

Quantitative PCR for HCV viral load was performed at 4, 8 weeks, at end of treatment and after 12 weeks of completion of therapy, detectable limit was 12IU/ml. Primary outcome was SVR achievement which is labeled as undetectable viral load after 12 weeks of completion of treatment. Secondary outcome was undetectable viral load at completion of treatment which is also labeled as ETR (end of treatment response.

Statistical package for social sciences SPSS was used for data analysis, frequency (percentage) was calculated for nominal data like gender and mean SD was calculated for numerical data

like age. Student t test and chi square test were applied to see association among variables. P values ≤0.05 was taken as significant.

RESULTS

Two hundred and sixty patients were enrolled in this study. All the patients were further divided into two equal groups. No significant differences were found between demographic variables and groups, (p>0.001) but liver enzymes and hematological parameter were statistically significant in groups, (p<0.001). (Table. I).

The liver enzymes and hematological parameter were noted after 24th weeks. The mean differences at baseline and after 24th weeks within the groups was statistically significant, (p<0.001). (Table. II). Viral load detectable, RVR, ETR, and SVR were shown in table III.

Table 1: Demographic and baseline data of the study groups

Variable	Groups		p-value
	Group 1	Group 2	
Age (years)	50.82±10.56	52.24±9.29	>0.001
Gender			
Male	76 (58.5%)	86 (66.2%)	>0.001
Female	54 (41.5%)	44 (33.8%)	
Duration of hepatitis C (years)	5.06±1.28	5.09±1.28	>0.001
Duration of dialysis (years)	4.61±1.11	4.66±0.99	>0.001
HCV RNA PCR	5.59±2.03	5.79±2.01	>0.001
Genotype 1	45 (34.6%)	44 (33.8%)	>0.001
Genotype 2	5 (3.8%)	5 (3.8%)	>0.001
Genotype 3	71 (54.6%)	66 (50.8%)	>0.001
Cirrhosis	34 (26.2%)	33 (25.4%)	>0.001
Treatment experience	20 (15.4%)	13 (10.0%)	>0.001
Treatment withdrawal	19 (14.6%)	9 (6.9%)	>0.001
Aspartate Aminotransferase (U/L)	60.76±9.96	38.28±5.54	<0.001
Alanine Aminotransferase (U/L)	51.94±8.92	42.03±6.62	<0.001
Hemoglobin (g/dl)	10.24±1.12	12.36±2.08	<0.001
White Blood Cells×10^3/mm3	5.92±0.52	6.84±1.32	<0.001
Platelets×10^3/mm3	167.54±10.47	178.56±12.86	<0.001

Table 2: Comparison of liver enzymes and hematological parameter

Variable	Group	Baseline	24th week	p-value
Aspartate Aminotransferase (U/L)	1	60.76±9.96	48.12±13.41	<0.001
	2	38.28±5.54	22.15±5.54	<0.001
Alanine Aminotransferase (U/L)	1	51.94±8.92	47.71±8.56	<0.001
	2	42.03±6.62	20.72±4.74	<0.001
Hemoglobin (g/dl)	1	10.24±1.12	12.14±1.28	<0.001
	2	12.36±2.08	10.72±1.26	<0.001
White Blood Cells×10^3/mm3	1	5.92±0.52	6.89±1.14	<0.001
	2	6.84±1.32	5.89±1.04	<0.001
Platelets×10^3/mm3	1	167.54±10.47	172.19±12.74	<0.001
	2	178.56±12.86	184.74±13.64	<0.001

Table 3: Distribution of Viral load, RVR, ETR &SVR

Viral load detectable	Groups			
	Group 1		Group 2	
	Yes N (%)	No N (%)	Yes N (%)	No N (%)
4th week (RVR)	11 (8.5)	119 (91.5)	15 (11.5)	115 (88.5)
8th week	5 (3.8)	125 (96.2)	5 (3.8)	125 (96.2)
12th week (ETR)	2 (1.5)	128 (98.5)	2 (1.5)	128 (98.5)
24th week (SVR)	3 (2.3)	127 (97.7)	12 (9.2)	118 (90.8)

DISCUSSION

HCV is endemic in Pakistani population, about 6.8% people are infected and its sero-prevalence is increasing 40% every year[11]. Currently, daily dose of Sofosbuvir with daclatasvir reported as associated with greater SVR in HCV patients of genotype 1, 2 and 3, but patients of end stage renal disease are less likely to receive this therapy. Some other direct acting antivirals are available that can be used to attain greater efficacy in patients of chronic kidney disease (CKD) but not available in Pakistan[12].

In a recent meta-analysis conducted by Li T et al[13] reported that SVR up to 66.7% to 98.3% with use of DAAs in patients of hemodialysis patients but with use of Sofosbuvir based treatment SVR reported 89.4%. These results are consistent with our study findings, SVR 97.7% with daily Sofosbuvir and 90.8% with alternate Sofosbuvir plus daclatasvir. Another similar study was conducted by Cheema et al[14] in 2019 and reported that patients with hemodialysis can better managed with daily Sofosbuvir and daclatasvir as compare to alternate therapy with similar combination as SVR at 24 weeks was 100% in daily and 82.3% with alternate therapy.

In our study most of patients from genotype 3 in both groups 54.6% vs 50.8% in daily therapy and alternate group respectively. In another Pakistani study conducted by Umer et al[15] reported similar findings, 63.8% patients having genotype 3, 2.7% with genotype 2. HCV seroprevalence was 6.8% in Pakistani population. In an Indian study conducted by Agarwal et al[16] on HCV positive patients who were on hemodialysis and end stage renal disease and found 64.5% patients with genotype 1 and 29% with genotype 3. Treatment was given daily SOF+Ribavirin, alternate day SOF+ribavirin, daily SOF+daclatasvir and alternate day SOF/daclatasvir for 12 weeks, after 12 weeks SVR was observed 95.2%.

Desnoyer et al[17] conducted prospective study and evaluate the efficacy of Sofosbuvir daily dosing and 3 times in a week in combination with daclatasvir, ribavirin and ledipasvir in hemodialysis patients. No inactive metabolites were observed accumulated along with hemodialysis and other drugs. SVR was calculated 83% without any serious adverse effects in daily dosing group. Gane et al[18] conducted an observation on 10 patients of renal impairment, among them 1 having genotype 3 and 9 with genotype 1. Dose was daily Sofosbuvir and at the study only 40% SVR concluded.

Ram et al[19] compared two regimen Sofosbuvir 400mg and 200mg in combination with simeprevir on 15 hemodialysis patients. Overall SVR was 87% and no major adverse effects noted, both doses were having same efficacy and safety. Garimella et al[20] conducted a study on effectiveness of DAAs in hemodialysis patients and reported that tolerability and efficacy of Sofosbuvir is good enough but data is limited to conclude recommend findings.

CONCLUSION

In Pakistani population hepatitis C virus is endemic like some other countries. In hemodialysis patients daily Sofosbuvir with daclatasvir is safe and effective with greater SVR as compare to Sofosbuvir with daclatasvir in alternate days even in genotype 3.

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