Original Article

Comparison Of Sofosbuvir Plus Daclatsvir With Sofosbuvir Alone In Achieving Svr In Dialysis Dependent Chronic Hepatitis C Patients

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Abstract

Introduction: According to current guidelines of Infectious Diseases Society of America (IDSA), hepatitis C of all genotypes in dialysis population is recommended to treat with Glecaprevir 300mg/ Pibrentasvir 120mg given for 8 to 16 weeks. Due to commercial unavailability of these drugs in Pakistan, we have compared two alternative regimes, Sofosbuvir+Daclatsvir and Sofosbuvir alone in HCV confirmed subjects on hemodialysis.

Objective: To compare the efficacy of Sofosbuvir + Daclatasvir and Sofosbuvir alone in treating HCV patient on hemodialysis. It is a Randomized controlled trial spanned on Six months at Department of Nephrology, PIMS Islamabad.

Subjects and Methods: In the present randomized controlled trial, a total of one hundred and eight (n=108) patients of either gender on hemodialysis and diagnosed as HCV positive were enrolled. All the patients were between age ranges 18 to 65 years and had an HCV RNA level of ≥100,000 IU/mL. All the enrolled patients were treatment naïve patients. All the enrolled patients were randomly divided into two groups by lottery method. Patients in Group A were given the combination of Sofosbuvir and Daclatasvir while patients in group B were treated with Sofosbuvir alone in dialysis department. The outcomes of the study were determined in terms of viral load detected at 3 months and sustained virological response (SVR) at six months.

Results: There were 50.0% (n=27/54) males and 50.0% (n=27/54) females in group A and there were 53.7% (n=29/54) males and 46.3% (n=25/54) females in group B. Mean age of group A patients was 42.8 years ± 12.1 SD and mean age of group B patients was 47.2 years ± 10.7 SD. Mean duration of dialysis in group A patients was 28.3 months ± 25.7 SD and mean duration of dialysis in group B patients was 24.3 years ± 17.3 SD. In group A, 7.4% (n=4/54) had no baseline comorbidity, 5.6% (n=3/54) had hypertension, 55.6% (n=30/54) had diabetes, 1.9% (n=1/54) had IHD and 29.6% (n=16/54) had multiple comorbidities at baseline. The percentages in group B were 14.8% (n=8/54), 1.9% (n=1/54), 53.7% (n=19/54), 1.9% (n=1/54) and 27.8% (n=15/54), respectively. Three months after start of treatment, viral load was not detected in 98.1% (n=53/54) of patients in group A and 96.3% (n=52/54) of patients in group B (P=0.558). At six month after the start of treatment, SVR was achieved in 98.1% (n=53/54) of patients in group A and 96.3% (n=52/54) of patients in group B (P=0.558).

Conclusions: Efficacy of treatment was found better at 3 and 6 months of treatment in patients who were treated with combination of Sofosbuvir and Daclatasvir (group A) when compared those treated with Sofosbuvir alone. The difference, however, was not statistically significant.

INTRODUCTION

There is a strong relationship between chronic hepatitis C infection and several glomerular diseases including mixed cryoglobulinemia, membranous nephropathy, membrano-proliferative glomerulonephritis and polyarteritis nodosa along with non-renal complications like arthalgia. HCV related morbidity and mortality are growing on account that 2007, HCV-related deaths inside the United States had exceeded those from human immunodeficiency virus (HIV) infection. [i,ii]

Hepatitis c virus (HCV) infection is the usual viral contamination that influences patients on maintenance hemodialysis (MHD).[iii] Nosocomial transmission and transmission through blood and blood components are 2 essential factors that have an effect on HCV occurrence. Hepatitis c virus (HCV) infection is the usual viral contamination that influences patients on maintenance hemodialysis (MHD).[iv]Prevalence of hepatitis C in hemodialysis patients in Pakistan is 23.7%-56.6%. Previously chronic Hepatitis C infection was treated with peginterferon alpha/ ribavirin with disappointing results and low tolerability in dialysis population. According to current guidelines of Infectious Diseases Society of America (IDSA), hepatitis C of all genotypes in dialysis population is recommended to treat with Glecaprevir 300mg/ Pibrentasvir 120mg given for 8 to 16 weeks.[v] Unfortunately, these drugs are not commercially available in Pakistan. Sofosbuvir is a nucleotide analogue HCV NS5B polymerase inhibitor eliminated primarily from kidneys (80%) and feces (0.5%) and some of it is removed from dialysis as well. Daclatasvir is a HCV NS5A inhibitor, eliminated primarily from feces (88%) and urine (6.6%). Velpatasvir a HCV NS5A inhibitor is also commercially available in Pakistan and eliminated from feces (94%) and urine (14%) but we have chosen Daclatsvir for our study as it has less renal clearance compared to Velpatsavir. Hepatitis C virus (HCV) infection is more common in dialysis patients than in healthy populations. The Dialysis Outcomes and Practice Patterns Study (DOPPS) reported an overall prevalence of 9.9% among adult hemodialysis patients randomly selected from dialysis facilities in high- and middle-income countries (France, Germany, Italy, Japan, Spain, the United Kingdom, China, Russia, Sweden, Belgium, Turkey, Gulf countries, and the United States).[vi] HCV infection is more common among dialysis patients in resource-limited countries, with an approximate incidence of 4.4 cases in 100 patient-years compared with 1 in 100 patients-years in resource-rich countries.[vii,viii,ix,x,xi]

Duration and mode of Dialysis, Characteristics of the Dialysis Unit, number of blood transfusions, The risk is also higher among patients who are dialyzed in close proximity to HCV-infected patients.[xii] Other risk factors include a history of organ transplantation, injection drug use, and male gender.[xiii] A history of injection drug use was present in 30% of anti-HCV antibody-positive patients receiving hemodialysis. [xiv] The management of HCV in adults with significant kidney disease (ie, estimated glomerular filtration rate <30 mL/min per 1.73 m^2) has undergone substantial changes with the availability of new direct-acting antiviral agents and will likely continue to evolve as more data accumulate. As the treatment paradigm for HCV infection has moved away from interferon-containing regimens in all patients, including those with kidney disease and mixed cryoglobulinemia, case reports and series have emerged demonstrating the efficacy of newer direct-acting antiviral agents in the treatment of HCV and mixed cryoglobulinemia.[xv,xvi,xvii,xviii]

Regimen selection: eGFR ≥30 mL/min per 1.73 m2 — Regimen selection is the same as that for patients without renal impairment. For most HCV antiviral agents, dose adjustments are not required for patients with an eGFR ≥30 mL/min per 1.73 m^2. However, in the uncommon case that ribavirin is used for treatment in such patients, the dose is adjusted. It is given orally at alternating doses of 200 and 400 mg every other day.

eGFR<30 mL/min per 1.73 m2 or on dialysis — Data on the safety direct-acting antivirals (DAAs) in the setting of severe renal impairment or dialysis (hemodialysis or peritoneal dialysis) are evolving. Given the significant potential for adverse effects with the combination of peginterferon and ribavirin, an interferon-free, combination DAA-based regimen is recommended in these patients.

OBJECTIVE: To compare the efficacy of Sofosbuvir + Daclatasvir and Sofosbuvir alone in treating HCV patient on hemodialysis

MATERIALS AND METHODS

Randomized controlled trial held at Department of Nephrology, PIMS, Islamabad for 9 months duration. We used WHO calculator for the estimation of sample size with following parameters:
Confidence Level : 5%, Test power: 80%, Anticipated population proportion (rate of SVR achieved at 12 weeks in combination group) P1 = 100%[xix] ,Anticipated population proportion (rate of SVR achieved at 12 weeks in sofosbuvir alone group) P2 = 86.7%[xx] ,Sample size: 54 in either group and a total of 54+54=108
Sample technique: The sampling was two staged. On first step a total of 108 patients were selected by non-probability consecutive sampling. In second stage, they were divided into 2 equal groups of 54 patients randomly by lottery method.
Inclusion criteria: Patients on hemodialysis and diagnosed as HCV positive in ELISA/PCR.
All patients with 18 to 65 years of age and had chronic HCV (all genotype) infection with an HCV RNA level of 100,000 IU per milliliter or higher. All those patients who were treatment naive
Exclusion criteria: All patients allergic to these drugs. Patients with chronic liver disease other than HCV infection and coinfection with HIV or hepatitis B virus. Patients who will not give written consent to participate. Pregnancy. Psychiatric Illness. Malignancy. Sepsis. Advanced liver disease.

DATA COLLECTION PROCEDURE

After taking permission from the Hospital Ethical Committee this study was conducted at the Nephrology department (dialysis unit) of PIMS. Informed written consent was taken from all Participants. A proforma was filled and after taking complete history & fulfilling the inclusion & exclusion criteria, all patients on dialysis who were Hepatitis C positive on screening were sent for ELISA and if it was positive, then PCR Quantitative (viral load) and Qualitative (for genotype) was done. The sizeable quantitative PCR (viral load) patients were divided into two random groups, that is Group A and Group B. Patients in Group A were given the combination of sofosbuvir (400mg-5 days a week) and Daclatasvir (60 mg daily) while patients in group B were treated with Sofosbuvir (400mg-5 days a week) alone in dialysis department to see the response of drugs. Demographic features were recorded; including age and gender. Past medical history, cause of renal failure and co-morbid, previous treatment with interferon alpha or ribavirin were also recorded. All biochemical tests including (complete blood picture, liver function tests, renal function tests, ECG, echocardiogram, blood sugars and fasting lipid profile) were done at the start of the therapy and then repeated monthly for 3 months during treatment. HCV RNA (viral load) and genotype was done at the start of the therapy. Viral load was repeated at the end of therapy i.e 3 months and 24 weeks after the stoppage of treatment. The data was entered on a standardized Performa

DATA ANALYSIS PROCEDURE

Data were entered and analyzed using SPSS version 23. Mean and standard deviation were calculated for quantitative variables (age, duration of dialysis, viral load at start of therapy and then at 3 months of therapy and 6 months post therapy.) Frequencies and percentages were calculated for qualitative variables (gender, comorbid and response to drugs at 3 and 6 months). Effect of drug (Efficacy) was determined in terms of Sustained Viral Response (SVR) achieved at the end of 6 months of therapy. Chi-square test was applied to compare efficacy of both groups at 3 and 6 months. A $p \leq 0.05$ was taken as statistically significant.

RESULTS

Demographic Features of Study Population: In the present randomized controlled trial, a total of one hundred and eight (n=108) patients of either gender on hemodialysis and diagnosed as HCV positive were enrolled. All the patients were between age ranges 18 to 65 years and had an HCV RNA level of ≥100,000 IU/mL. All the enrolled patients were treatment naïve patients. All the enrolled patients were randomly divided into two groups by lottery method. Patients in Group A were given the combination of Sofosbuvir and Daclatasvir while patients in group B were treated with Sofosbuvir alone in dialysis department. The outcomes of the study were determined in terms of viral load detected at 3 months and SVR at six months. There were 50.0% (n=27/54) males and 50.0% (n=27/54) females in

group A and there were 53.7% (n=29/54) males and 46.3% (n=25/54) females in group B. Mean age of group A patients was 42.8 years ± 12.1 SD and mean age of group B patients was 47.2 years ± 10.7 SD

Baseline Patient Characteristics : Mean duration of dialysis in group A patients was 28.3 months ± 25.7 SD and mean duration of dialysis in group B patients was 24.3 years ± 17.3 SD In group A, 7.4% (n=4/54) had no baseline comorbidity, 5.6% (n=3/54) had hypertension, 55.6% (n=30/54) had diabetes, 1.9% (n=1/54) had IHD and 29.6% (n=16/54) had multiple comorbidities at baseline. The percentages in group B were 14.8% (n=8/54), 1.9% (n=1/54), 53.7% (n=19/54), 1.9% (n=1/54) and 27.8% (n=15/54), respectively.

OUTCOMES OF TREATMENT

Three months after start of treatment, viral load was not detected in 98.1% (n=53/54) of patients in group A and 96.3% (n=52/54) of patients in group B (P=0.558). At six month after the start of treatment, SVR was achieved in 98.1% (n=53/54) of patients in group A and 96.3% (n=52/54) of patients in group B (P=0.558).

Efficacy of treatment was found better at 3 and 6 months of treatment in patients who were treated with combination of Sofosbuvir and Daclatasvir (group A) when compared those treated with Sofosbuvir alone. The difference, however, was not statistically significant.

DISCUSSION

According to current guidelines of Infectious Diseases Society of America (IDSA), hepatitis C of all genotypes in dialysis population is recommended to treat with Glecaprevir 300mg/ Pibrentasvir 120mg given for 8 to 16 weeks. Due to commercial unavailability of these drugs in Pakistan, we have compared two alternative regimes, Sofosbuvir+Daclatsvir and Sofosbuvir alone in HCV confirmed subjects on hemodialysis. A total of one hundred and eight (n=108) patients of either gender on hemodialysis and diagnosed as HCV positive were enrolled in the present trial. All the patients were between age range 18 to 65 years and had an HCV RNA level of ≥100,000 IU/mL. All the enrolled patients were treatment naïve patients. All the enrolled patients were randomly divided into two groups by lottery method. Patients in Group A were given the combination of Sofosbuvir and Daclatasvir while patients in group B were treated with Sofosbuvir alone in dialysis department. The outcomes of the study were determined in terms of viral load detected at 3 months and sustained virological response (SVR) at six months. Our results showed that mean age of group A patients was 42.8 years ± 12.1 SD and mean age of group B patients was 47.2 years ± 10.7 SD. Mean duration of dialysis in group A patients was 28.3 months ± 25.7 SD and mean duration of dialysis in group B patients was 24.3 years ± 17.3 SD. Three months after start of treatment, viral load was not detected in 98.1% (n=53/54) of patients in group A and 96.3% (n=52/54) of patients in group B (P=0.558). At six month after the start of treatment, SVR was achieved in 98.1% (n=53/54) of patients in group A and 96.3% (n=52/54) of patients in group B (P=0.558).

For patients on hemodialysis the treatment decisions are based on a case-by-case basis whether to provide these patients with HCV treatment or not. Assessment of life expectancy is important as in many cases the renal disease is not associated with HCV, i.e, HCV is diagnosed incidentally. Moreover these patients have significant comorbidities, like diabetes mellitus, hypertension, and cardiovascular disease, which have contributed to the development of or coexist with chronic kidney disease (CKD). In the setting of advanced CKD and with such competing comorbidities, it is difficult to determine whether treatment of chronic HCV infection would actually provide the patient with a survival benefit. In contrast, patients with HCV-related renal disease are likely to experience improvement in renal function and symptoms related to renal failure with successful treatment. Treatment is warranted even if life expectancy may otherwise be limited due to other comorbidities. In the present study we did a very careful selection of patients. We enrolled those who had chronic HCV (all genotype) infection with an HCV RNA level of 100,000 IU per milliliter or higher. Moreover, all those patients were treatment naïve patients.

Although there is an overall scarcity of data on anti-HCV therapy in patients with renal disease, there is growing evidence on these of various regimens in such patients. An understanding of the pharmacology of the different agents in this populations, as well as data from patients without renal disease, all support the following suggestions for regimen selection, according to eGFR. Data on the safety DAAs in the setting of severe renal impairment or dialysis

(hemodialysis or peritoneal dialysis) are evolving. For all patients with severe renal impairment, the pangenotypic DAA regimen of glecaprevir-pibrentasvir is preferred. It has documented efficacy and safety in this population and, unlike some of the alternatives, can be used for all genotypes without the need for NS5A resistance-associated substitution (RAS) testing or ribavirin. If glecaprevir-pibrentasvir is not an option, the main alternative is a sofosbuvir-containing regimen (eg, sofosbuvir-velpatasvir) prescribed by an expert in HCV management. European clinical practice guidelines recommend that sofosbuvir with velpatasvir or daclatasvir can be used if there is an urgent need to treat genotype 2- or 3-infected patients with eGFR<30 mL/min per 1.73 m^2 or on hemodialysis (with ribavirin 200 mg/day for genotype 3); if used, kidney function should be closely monitored, as it could decline on therapy.[69,70] Velpatasvir is commercially available in Pakistan but we have chosen Daclatsvir for our study as it has less renal clearance compared to Velpatsavir. Patients in Group A were given the combination of sofosbuvir (400mg-5 days a week) and Daclatasvir (60 mg daily) while patients in group B were treated with Sofosbuvir (400mg-5 days a week) alone.

Present study results demonstrated that efficacy of treatment was found better at 3 and 6 months of treatment in patients who were treated with combination of Sofosbuvir and Daclatasvir when compared those treated with Sofosbuvir alone. The difference, however, was not statistically significant (P>0.05). It has been reported in previous studies that sofosbuvir based therapy leads to high rates of SVR with few side effects,[xxi] however, its use is restricted in patients who have eGFR of ≤30 ml/min per 1.73 m^2. The active metabolite of sofosbuvir is eliminated by the kidneys and levels of sofosbuvir are substantially higher in patients with severe renal impairment.[xxii] Daclatasvir has been recommended for treatment of patients with severe renal disease, as its components are metabolized mainly by the liver. Direct acting antivirals including Sofosbuvir in combination with Daclatasvir, with or without ribavirin is highly effective in treating HCV infection in patients with or without cirrhosis.[xxiii,xxiv] Currently, little data on the treatment of HCV in hemodialysis patients with DAAs (sofosbuvir based regimens) are available.[xxv] A pharmacologic analysis did not identify clinically significant increases in daclatasvir levels among patients with eGFR ≤30 mL/min per 1.73 m^2 or on dialysis.[86] However, daclatasvir is usually given in combination with sofosbuvir, and this combination has not been well studied in patients with eGFR<30 mL/min per 1.73 m^2.[87] In a recent study from India,[xxvi] that included treatment-naïve haemodialysis, HCV infected patients. Patients were treated with different frequency of drug usage, like daily SOF/Ribavirin, every other day SOF /ribavirin, daily SOF/daclatasvir and every other day SOF/daclatasvir for 12 weeks. 95.2% achieved SVR. There was no impact of genotype on SVR. Treatment with daily daclatasvir and daily sofosbuvir yielded a 93.3% (14/15) SVR, compared to 100% (6/6) SVR with daily daclatasvir and alternate day sofosbuvir.

In a study among local population, Cheema SR et al prospectively enrolled patients with hepatitis-C on maintenance hemodialysis and randomized 36 patients equally into group 1 who received 400 mg daily sofosbuvir/ 60 mg daily daclatasvir and group 2 who received thrice a week 400 mg Sofosbuvir and daily 60 mg daclatasvir for 12 weeks. HCV viral load was assessed at week 4, 8, at end of therapy and 12 weeks after treatment. Their results demonstrated all patients in both groups achieved undetectable viral load at 12th week. Overall 29/36 (80.55%) patients achieved SVR (group 1 = 15/18; group 2 = 14/18) and as per-protocol analysis overall 29/32 (90.62%) patients achieved SVR (group 1 = 15/15; group 2 = 14/17).[xxvii] Authors concluded that direct acting antiviral therapy using sofosbuvir and declatsavir is highly effective and tolerable given daily in patients with HCV on maintenance hemodialysis.

In summary, the theme derived from the present study results and review of literature on the subject is that if glecaprevir-pibrentasvir is not an option, the main alternative is a sofosbuvir-containing regimen (eg, sofosbuvir-velpatasvir or sofosbuvir- daclatasvir) in patients with HCV on maintenance hemodialysis. High rates (>95%) of achived SVR has been reported. We found similar results in the present study. Current study has several strengths. Firstly, it was the designed as randomized controlled trial with highly stringent inclusion/exclusion criteria. Secondly, we compared two different sofosbuvir based regimens and found both of them effective. Finally, we assessed the patients at multiple followup (3 months and 6 months) that enabled us to monitor viral load and overall wellness of enrolled subjects at different time intervals. Present study has some limitation too. We feel the sample size was relatively smaller, yet sufficient enough to draw the inference and secondly we studied single dose regimens (sofosbuvir 400mg-5 days a week, and Daclatasvir 60 mg daily) in the present study. We suggest future studies with

larger sample size and taking into account variable doses of the same regimen. We also suggest to explore further sofosbuvir based regimens in combinations with other available treatment options.

CONCLUSIONS: Efficacy of treatment was found better at 3 and 6 months of treatment in patients who were treated with combination of Sofosbuvir and Daclatasvir when compared those treated with Sofosbuvir alone. The difference, however, was not statistically significant.
We suggest future studies with larger sample size and taking into account variable doses of the same regimen. We also suggest exploring further sofosbuvir based regimens in combinations with other available treatment options.

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GENDER	GROUP		TOTAL
	SOFOSBUVIR+DACLATSVIR	SOFOSBUVIR ALONE	
MALES	27	29	56
	50.0%	53.7%	51.9%
FEMALES	27	25	52
	50.0%	46.3%	48.1%
TOTAL	54	54	108
	100.0%	100.0%	100.0%

Table 1: Gender distribution in both groups

GROUP	MEAN AGE (YEARS)	STD. DEVIATION
SOFOSBUVIR+ DACLATSVIR	42.8	12.1
SOFOSBUVIR ALONE	47.2	10.7

Table 2: Age distribution in both groups

GROUP	MEAN DURATION (MONTHS)	STD. DEVIATION
SOFOSBUVIR+ DACLATSVIR	28.3	25.7
SOFOSBUVIR ALONE	24.3	17.3

Table 3: Duration of dialysis in both groups

COMORBIDITIES	GROUP		TOTAL
	SOFOSBUVIR+DACLATSVIR	SOFOSBUVIR ALONE	
NONE	4	8	12
	7.4%	14.8%	11.1%
HTN	3	1	4
	5.6%	1.9%	3.7%
DM	30	29	59
	55.6%	53.7%	54.6%
IHD	1	1	2
	1.9%	1.9%	1.9%
MULTIPLE	16	15	31
	29.6%	27.8%	28.7%
TOTAL	54	54	108
	100.0%	100.0%	100.0%

Table 4: Baseline comorbidities in both groups

VIRAL LOAD AT 3 MONTHS	**GROUP**		**TOTAL**	**P-VALUE CHI-SQUARE**
	SOFOSBUVIR+ DACLATSVIR	**SOFOSBUVIR ALONE**		
NOT-DETECTED	53	52	105	0.558
	98.1%	96.3%	97.2%	
DETECTED	1	2	3	
	1.9%	3.7%	2.8%	
TOTAL	54	54	108	
	100.0%	100.0%	100.0%	

Table 5: Viral load at 3 months in both groups

SVR	**GROUP**		**TOTAL**	**P-VALUE CHI-SQUARE**
	SOFOSBUVIR+ DACLATSVIR	**SOFOSBUVIR ALONE**		
ACHIEVED	53	52	105	0.558
	98.1%	96.3%	97.2%	
NOT-ACHIEVED	1	2	3	
	1.9%	3.7%	2.8%	
TOTAL	54	54	108	
	100.0%	100.0%	100.0%	

Table 6: SVR at 6 months in both groups