Efficacy of Daclatasvir and Half Dose Sofosbuvir in the Treatment of Hepatitis –C Virus Infection in Patients of Maintanance Hemodialysis-3 Years Trial in A Tertiary Renal Center

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Abstract

Background: *Hepatitis C virus (HCV) infection in end-stage renal disease (ESRD) heralds a bad outcome. Directly acting antiviral (DAA) drugs sofosbuvir along with daclatasvir are very effective in the management of HCV infection. Sofosbuvir is excreted mainly through the kidneys. There is sparse data worldwide on the use of sofosbuvir based drug regimens in ESRD patients having chronic hepatitis C (CHC) virus infection.This study was designed to evaluate the efficacy of half dose sofosbuvir in the management of HCV infection in ESRD patients on maintenance hemodialysis (MHD).*

Methods: *This clinical trial was conducted among 125 ESRD patients on MHD at Gonoshasthaya dialysis center, Dhanmondi, Dhaka from July 2019 to June 2022. Total 125 HCV positive patient with ESRD on MHD were included in this study; all the patients underwent HCV-RNA PCR test. Patients with detectable HCV RNA were observed for six months without antiviral drugs to identify the occurrence of spontaneous clearance of virus. Patients who had detectable HCV-RNA after six months were treated with sofosbuvir(200 mg) and daclatasvir (60 mg), irrespective of genotype. The drugs were given daily for 12 weeks. All the patients were on regular follow up at two weeks interval. Blood counts, liver function, creatinine phosphokinase and serum amylase values were evaluated periodically; virological response was assessed by HCV-RNA after 12 weeks of antiviral treatment.*

Results: *During the observation period, 29 (23.2%) patients had spontaneous virus clearance with an undetectable HCV-RNA. In the remaining 96 patients, the median HCV-RNA level was 2.76×10^4 (1.56×10^3– 1.89×10^6)I IU. Twelve weeks after the treatment, 91 (94.8%) patients achieved sustained virological response (SVR) with undetectable HCV-RNA. All patients tolerated the DAAs well and none of the patients reported any serious adverse events. No patient discontinued antiviral therapy due to side effects. Patients who attained SVR with DAA, after 6 months we repeated HCV-RNA in 30 patients, in majority of them (28, 93.3%), HCV-RNA were undetected but in 2 (6.7%) patients,HCV-RNA were detected again.*

Conclusion: *Daclatasvir along with half-dose sofosbuvir are safe and effective in the treatment of CHC patients with ESRD on MHD. Half dose sofosbuvir regimen can reduce the cost of treatment of HCV in ESRD patients in developing countries like Bangladesh, where cost is a significant barrier to HCV treatment.*

Key words: *ESRD, HCV, Sofosbuvir, Daclatasvir*

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Introduction:

The overall mortality in patients with end-stage renal disease (ESRD) and coexistent hepatitis C virus (HCV) infection is much higher than non-infected patients [1]. The worldwide prevalence of HCV infection in patients on hemodialysis is 13.5%, whereas only 3% in the general population [2]. Patients with severe renal insufficiency [eGFR < 30 mL/ min/1.73 m^2] including those on maintenance hemodialysis (MHD) are difficult to treat, as very few of directly acting antivirals (DAAs) are available for treatment of this group. Available approved regimens are limited to pegylated interferon with or without low-dose ribavirin, which is associated with poor tolerance, side effects, high dropout rates and dismal sustained virological response (SVR) rates [3-8].FDA-approved all-oral regimens of DAAs for patients with severe renal insufficiency with chronic hepatitis C (CHC) are elbasvir/grazoprevir, dasabuvir/ombitasvir and paritaprevir/ritonavir which is currently not available in Bangladeash [9-12]. Though FDA-approved all-oral regimens glecaprevir/ pibrentasviris now available in Bangladesh but due to its high price its use is very limited in poor dialysis patients.

Pangenotypic NS5B inhibitor sofosbuvir is excreted by the kidney and there are higher concentrations of active metabolite (GS461203) in ESRD patients. Several small studies have shown that sofosbuvir based regimens are safe in ESRD patients [13-17].

In November 2019, the FDA changed the label for sofosbuvir-based regimens to allow their use in patients with kidney disease, even those with low eGFR (eGFR d"30 mL/min) or undergoing dialysis. Studies have shown that sofosbuvir does not worsen eGFR in CKD patients, nor linked to an increased risk of ESRD [18]; also there is no association between sofosbuvir and changes in eGFR levels during and after treatment [19]

In the present study, we evaluated the efficacy of using half-dose sofosbuvir (200 mg/day) in treatment of hepatitis C infection in patients with ESRD on MHD.

Methods:

This clinical trial was conducted among 125 ESRD patients on MHD at Gonoshasthaya dialysis center, Dhanmondi, Dhaka from July 2019 to June 2022. Only adult patients (age >18 years) on MHD for at least 3 months were included in this study. Purposive sampling was done among the patients who fulfilled the selection criteria. Written informed consent was taken from every patient. The research protocol was approved by the Gonoshasthaya Nagar Hospital ethical committee.

We included 125 patients with CHC with ESRD on MHD. None of the patients was co-infected with hepatitis B or human immunodeficiency virus. All the patients underwent HCV-RNA PCR test.Patients with detectable HCV-RNA were observed for six months without any antiviral drugs. Patients who had detectable HCV-RNA after 6 months (96 patients) were treated with half-dose sofosbuvir [200 mg] and daclatasvir (60 mg), daily for12 weeks. The proposed dose of 200 mg of sofosbuvir was obtained by splitting the standard 400 mg pill into two halves with each half being administered on consecutive days. A complete evaluation of the pretreatment HCV status including HCV-RNA, baseline liver and renal functions and extent of liver disease was assessed by ultrasonography was carefully reviewed and recorded during enrollment to study.

Patients were followed up with complete hemogram, serum amylase, creatinine phosphokinase, liver and renal function tests at 2 weeks interval and at the end of treatment at 12 weeks. Hepatitis C viral load was checked at 12 weeks post-treatment for sustained virological response (SVR 12). The virological cure or SVR12 was defined as undetectable HCV-RNA 12 weeks after end of treatment [9, 20]. Side effects, if any, were recorded by the treating physician in the patient's clinical record file.

Data analysis was done by Statistical Package for Social Science (SPSS-24). Results are presented as tables and diagrams. We used mean (M), standard deviation (SD), median (Me) and interquartile range (Q25, Q75) of the data in thisstudy. A p value <0.05 was considered significant.

Results:

Total 125 patients with CHC with ESRD on MHD were selected randomly in this study.None of the patients was co-infected with hepatitis B or human immunodeficiency virus. Patients were observed for six months without antiviral drugs to observe the occurrence of spontaneous clearance of virus. During the observation period of six months, 29 patients (23.20%) became HCV-RNA negative spontaneously (Figure 1).

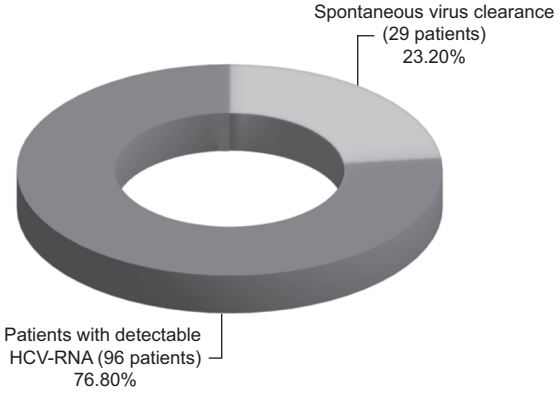

Fig.-1: *Percentage of spontaneous virus clearance in studied population*

Ninety six patients had detectable HCV-RNA after six months. Among them 53 (55.20%) were female and 43 (44.80%) were male. Mean age of the patients was 44.50± 11.78 years. The underlying common etiology of CKD in this study were diabetic nephropathy in 42 (43.75%), chronic glomerulonephritis in 33 (34.37%), and hypertensive nephropathy in 21 (21.88%) patients.

Among them 56 patients (58.34%)were on thrice weekly hemodialysis and 40 patients (41.66%)were on twice weekly hemodialysis session. Mean duration of hemodialysis was 1.6 years (0.7 -6 years).

Ninety six patients with detectable HCV-RNA irrespective of genotype were treated with half-dose sofosbuvir (200 mg) and daclatasvir (60 mg), daily for 12 weeks.

The median HCV-RNA level in all 96 studied patients was 2.76×10^4 (1.56×10^3– 1.89×10^6)IU. Nineteen patients(19.79%) had evidence of compensated chronic liver disease(CLD) at the time of enrollment to study and 100% patients were treatment naïve. Ninety one patients(94.80%) achieved SVR with undetectable HCV-RNA after 12 weeks (Figure 2).

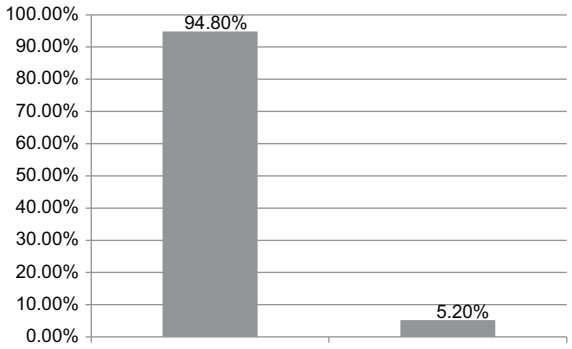

Fig.-2: *Virological response in studied hemodialysis patients after 12 weeks of the antiviral treatment*

There were no significant differences in biochemical parameters in pre- and post-treatment in patients treated with half dose sofosbuvir and daclatasvir shown in table-I.

Table-I

Changes in biochemical parameters pre- and post-treatment in half dose sofosbuvir and daclatasvir group

Investigations	Pretreatment	Post-treatment	*P* value
Hemoglobin(g/dl) (Mean± SD)	9.32±1.2	9.40±1.3	0.533
Bilirubin(mg/dl) Mean(Range)	0.82(0.58-1.1)	0.85(0.3-1.08)	0.785
AST U/L) (Mean, Range)	56.23(19-290)	43.87(27-187)	0.786
ALT U/L) (Mean, Range)	52.5(23-345)	47.23(26-187)	0.635
Albumin (gm/dl) (Mean± SD)	3.87±0.64	3.89±0.43	0.832
Creatinine phosphokinase(CPK:U/L) (Mean± SD)	93.32±2.1	89.58±1.7	0.757
Serum Amylase(U/L) (Mean± SD)	162±1.9	149±1.7	0.657

All patients tolerated the DAAs well and none of the patients reported any serious adverse events (Figure 3). No patient discontinued antiviral therapy due to side effects.

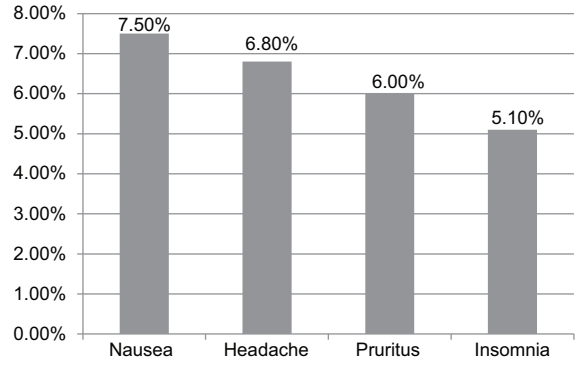

Fig.-3: *Percentage of antiviral side effects in studied population*

Patients who attained SVR with DAA, after 6 months we repeated HCV-RNA in 30 patients, in majority of them (28, 93.3%) HCV-RNA were undetected but in 2 patients(6.7%) HCV-RNA was detected again.

Discussions:

In our study total 125 HCV positive patient on ESRD on MHD underwent HCV-RNA PCR test. All patients with detectable HCV-RNA were observed for six months without antiviral drugs to observe the occurrence of spontaneous clearance of virus. During the observation period, 29 patients (23.20%) had spontaneous virus clearance with a undetectable HCV-RNA. The remaining 96 patients got half dose sofosbvir (200mg) and daclatasvir (60 mg), irrespective of genotype daily for 12 weeks. Twelve weeks after the treatment (94.8%) 91 patients achieved SVR with undetectable HCV-RNA.

Sofosbuvir is an NS5B polymerase inhibitor and is metabolized intracellularly and forms the active metabolite GS-461203, followed by dephosphorylation resulting in the inactive compound GS-331007. GS-331007 is primarily renal excreted (78% of the administered dose)[13-15]. So, increased metabolite levels in patients with renal impairment and its efficacy and safety remains an important issue.

There are few studies on using full dose sofosbuvir, half dose sofosbuvir, full dose sofosbuvir in alternate days[21-23]. A meta-analysis comparing two subgroups of patients who received either a full dose of sofosbuvir (400 mg per day) or a decreased dose found that the SVR rate was 97.1% (95% confidence interval 92.1-99.9%) for the full-dose group and 96.2% (95% confidence interval 88.3-100%) for the decreased-dose group. The difference between these two groups was not statistically significant, as indicated by the p-value of 0.72. [24]

Daclatasvir is an NS5A inhibitor that is administered at a dosage of 60 mg/day. This drug is highly bound to plasma proteins (99%). It is metabolized in liver (CYP3A4) and is a substrate of P-gp. Biliary excretion is the major route of elimination[14]. Studies have showed that no dose adjustments of daclatasvir are necessary in patients with renal impairment[25,26].

In our study, after treating 96 patients of ESRD on MHD irrespective of genotype with half dose (200mg)sofosbuvir and full dose (60mg)daclatasvir for 12 weeks, 91 patients (94.8%) achieved SVR at 12 weeks. Near similar to our experience,Taneja et al.[27] showed in their study 65 patients of CKD eGFR<30ml/min/1.73m^2 received half dose sofosbuvir and full dose daclatasvir and all patients attained SVR. Chowdhury et al.[23] showed in their study among 14 patients 2 patients were treated with sofosbuvir (400 mg) in alternate days and daclatasvir daily these 2 patients also attained sustained virological response at 12 weeks. Mostafi et al[28] also showed in their study 100% patients achieved SVR with undetectable HCV-RNA in 12 weeks who got half dose sofosbuvir and full dose daclatasvir.

In our study, half dose sofosbuvir and full dose daclatasvir were well tolerated by ESRD patients and there were no major side effects and no treatment discontinuation. Similar result is seen in Taneja et al. [27]. Several small studies and case reports have shown that both low-dose (200 mg) and normal-dose (400 mg) sofosbuvir were overall well-tolerated[16, 29]. All the patients in our study tolerated this regimen well without any major side effects; several case series have also showed good safety profile of half dose sofosbuvir[21-23,28-31] like our study.

In our study there were no significant difference in before and after treatment with antivirals in levels of hemoglobin, liver function test, creatinine-phosphokinase and serum amylase level. Mostafi et al.[28]

also showed in their study there were no significant differences in biochemical parameters in pre and post-treatment biochemical parametersin HD patients treated with the half-dose sofosbuvir and daclatasvir.

Patients who attained SVR with DAA, after 6 months, we repeated HCV-RNA in 30 patients, in majority of them (93.34%) HCV-RNA were undetected but in 2 patients(6.66%) HCV-RNA were detected again.

The efficacy and safety of half dose sofosbuvir (200mg) with daclatasvir(60mg) in patients of ESRD is established in our study but the main limitation of our study are having small sample size, genotyping was not done in our patients. However, for the increased need of treatment in this difficult to treat group our study can be reliable one for further future larger studies.

Conclusion:

In hepatitis C seropositive patientsdaclatasvir along with half-dose sofosbuvir are safe,well-tolerated and effective in the treatment of CHC patients with ESRD on MHD. Thus, half dose sofosbuvir regimen can be recommended in the treatment of HCV in ESRD patients in the developing countries which can reduce the financial burden by reducing the treatment cost of poor dialysis patients.

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