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The outcome of Daclatasvir and low dose Sofosbuvir therapy in end-stage renal disease patients with hepatitis C virus infection

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Abstract. *Rapid progression of chronic kidney disease (CKD) is seen in patients with hepatitis C virus (HCV) infection compared with uninfected patients. Despite the high efficacy of direct-acting antivirals (DAAVs), their cost represents a limiting factor to their use in developing countries.*

Aim. This study aimed to evaluate the efficacy of low dose Sofosbuvir along with Daclatasvir in the management of HCV infection in end-stage renal disease (ESRD) patients.

Methods. A total of 82 HCV positive patients on ESRD were included in this study. The patients were observed for six months without antiviral drugs. Patients who remained seropositive were divided into two groups. The first group included 26 (37%) patients who were treated with half-dose Sofosbuvir 200 mg and Daclatasvir 60 mg and the second group consisted of 44 (63%) patients who have been treated with full-dose Sofosbuvir 400 mg and Velpatasvir 100 mg irrespective of HCV infection genotype for 12 weeks also.

Results. 12 (14%) patients became seronegative spontaneously. All patients (100%) of both groups achieved sustained virological response with undetectable HCV RNA in 12 weeks of the treatment. There were nonsignificant gastrointestinal side effects in the full dose Sofosbuvir group. All patients tolerated the DAAs well. No patient discontinued antiviral therapy due to side effects

Conclusion. In this study, the spontaneous seroconversion of HCV was 14%. Low-dose Sofosbuvir along with Daclatasvir was safe and as effective as full-dose Sofosbuvir and Velpatasvir in the treatment of HCV in ESRD patients. Low-dose Sofosbuvir regimen can be recommended for HCV infection treatment in ESRD patients.

Key words: *hepatitis C virus infection, direct-acting antiviral therapy, chronic kidney disease, end-stage renal disease.*

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Результат лікування Даклатасвіром та низькою дозою Софосбувіру пацієнтів з хронічною хворобою нирок V Д стадії та вірусним гепатитом С

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Резюме. Швидке прогресування хронічної хвороби нирок (ХХН) спостерігається у пацієнтів, інфікованих вірусом гепатиту С (HCV) порівняно з неінфікованими. Незважаючи на високу ефективність противірусних засобів прямої дії, їх вартість є обмежуючим фактором для застосування в країнах, що розвиваються.

Мета. Це дослідження мало на меті оцінити ефективність поєднаного застосування Даклатасвіру з низькою дозою Софосбувіру у лікуванні HCV-інфекції у пацієнтів ХХН V Д стадії.

Методи. У дослідження було включено 82 серопозитивних пацієнти з ХХН V Д стадії та вірусним гепатитом С. Період спостереження без противірусних засобів склав півроку. Пацієнтів, які залишились серопозитивними, поділили на дві групи. Перша група включала 26 (37%) пацієнтів, які отримували лікування половинною дозою Софосбувіру [200 мг] та Даклатасвіру (60 мг), до другої групи увійшли 44 (63%) пацієнти, які отримували повну дозу Софосбувіру (400 мг) та Велпатасвір (100 мг), незалежно від генотипу протягом 12 тижнів.

Результати. У 12 (14%) пацієнтів спостерігалась спонтанна ремісія HCV-інфекції. Усі пацієнти, які отримували противірусні засоби досягли стійкої вірусологічної відповіді: через 12 тижнів лікування РНК HCV не визначалась. У групі повної дози Софосбувіру не було помітних гастроінтестинальних побічних ефектів. Усі пацієнти добре переносили противірусні засоби прямої дії. Жоден пацієнт не припиняв протитивірусну терапію через побічні ефекти.

Висновки. У цьому дослідженні спонтанна HCV сероконверсія становила 14%. Низька доза Софосбувіру разом із Даклатасвіром була безпечною та такою ж ефективною, як повна доза Софосбувіру у поєднанні з Велпатасвіром у лікуванні вірусного гепатиту С у пацієнтів з ХХН V Д. Низька доза Софосбувіру може бути рекомендована для лікування вірусного гепатиту С у пацієнтів з ХХН V Д.

Ключові слова: вірусний гепатит С, противірусна терапія прямої дії, хронічна хвороба нирок, софосбувір, лікування.

Introduction. The worldwide prevalence of hepatitis C virus (HCV) infection in hemodialysis (HD) patients is 13.5%, whereas only 3% in the general population [1]. The overall mortality in patients with end-stage renal disease (ESRD) and coexistent HCV infection is also much higher than non-infected patients [2]. The availability of directly acting antivirals (DAA) for the treatment of chronic hepatitis C infection has transformed the management of HCV infection. However, patients with ESRD are difficult to treat due to a limited number of directly acting antivirals (DAAs) available for the treatment of this subgroup. The only FDA-approved all-oral regimens of DAAs for ESRD patients are Elbasvir/Grazoprevir, Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir, and Glecaprevir/Pibrentasvir, which are currently not available in Bangladesh [3-6]. Thus, 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 [7-12].

In general, there is limited scientific data on the role of DAAs in patients with chronic kidney disease (CKD). The pan-genotypic NS5B inhibitor Sofosbuvir is excreted by the kidney and there are higher concentrations of the active metabolite (GS461203) in ESRD patients. Thus, Sofosbuvir is currently not recommended for HCV infection treatment in CKD and HD patients [13]. However, several small studies have shown that Sofosbuvir based regimens are safe in ESRD patients [14-18].

The present study **aimed** to describe our experience of using half-dose Sofosbuvir (200 mg/day) with usual doses of Daclatasvir (60 mg) in the treatment of hepatitis C infection in HD patients.

Materials and Methods. This prospective study was conducted among the HD patients at Gonoshasthaya dialysis center, Dhanmondi, Dhaka from October 2018 to September 2019. Only adult patients (age >18 years) on HD for at least 3 months were included in this

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study. Purposive sampling was done among the patients who fulfilled the selection criteria.

The research protocol was duly approved by the Gonoshasthaya Nagar Hospital ethical committee (Trial Registration Number: GBRAB/105/2019). Informed consent was taken from every patient before the trial.

We included 82 HD patients with CHC. None of the patients was co-infected with hepatitis B or human immunodeficiency virus. The patients were observed for six months without antiviral medicine.

46 (65.7%) patients were on thrice-weekly hemodialysis and 24 (34.28%) patients were on twice-weekly hemodialysis session. (Due to financial constrain some of our patients are taking twice weekly hemodialysis) The mean duration of HD was 2.7 years (0.5 -7 years).

70 seropositive patients were randomly divided into two groups. The first group included 26 (37%) patients who were treated with half-dose Sofosbuvir 200 mg and Daclatasvir 60 mg, given daily for 12 weeks irrespective of CHC genotype. The second group consisted of 44 (63%) patients who were treated with full-dose Sofosbuvir 400 mg and Velpatasvir 100 mg, given daily for 12 weeks irrespective of CHC genotype also.

A complete evaluation of the pretreatment HCV status including HCV RNA, baseline liver and renal functions, and extent of liver disease assessed by ultrasonography was carefully reviewed and recorded.

Patients were followed up with complete hemogram, liver and renal function tests after the end of treatment at 12 weeks. HCV load was checked at 12 weeks post-treatment for a sustained virological response (SVR 12) in both groups. The virological cure or SVR12 was defined as undetectable HCV RNA 12 weeks after the end of treatment [3, 19]. Side effects if any were recorded by the treating physician in the patients' clinical record file.

Data analysis was done by Statistical Package for Social Science (SPSS-24). The 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 this study and methods of their comparison. P-value <0.05 was considered significant.

Results: A total of 82 HD patients with CHC were included in the study. During the observation period of six months, 12 patients (14%) became seronegative spontaneously, 70 (86%) patients remained seropositive after six months. Among them, 40 (57.2%) were female and 30 (42.8%) were male. The average age of the patients was 43.70 ± 12.01 years. The main CKD etiology were diabetic nephropathy in 28 (40%) patients, chronic glomerulonephritis in 22 (31.4%), and hypertensive nephropathy in 20 (28.57%) patients.

The median HCV RNA level in all 70 studied patients was 2.35 × 104 (1.06 × 103– 1.73 × 106) IU. 23% of patients had evidence of cirrhosis, and 100% of patients were treatment naïve.

There were no significant differences in biochemical parameters in pre and post-treatment examination in HD patients treated with the half-dose Sofosbuvir and Daclatasvir (Table 1) and full-dose Sofosbuvir and Velpatasvir group (Table 2).

Table 1

Pre- and post-treatment changes in biochemical parameters in half-dose Sofosbuvir and Daclatasvir group

Investigations	Pre-treatment	Post-treatment	P-value
Hemoglobin (g/dl), (M ± SD)	9.82±1.5	9.68±1.3	0.546
Bilirubin (mg/dl), Me (Q25-Q75)	0.79(0.55-1.2)	0.81(0.3-1.02)	0.876
AST (U/L), Me (Q25-Q75)	53.23(19-288)	48.87(25-178)	0.768
ALT (U/L), Me (Q25-Q75)	55.45(22-345)	49.23(27-195)	0.653
Albumin (mg/dl), (M ± SD)	3.78±0.38	3.92±0.43	0.850

Table 2

Pre- and post-treatment changes in biochemical parameters in full-dose Sofosbuvir and Velpatasvir group

Investigations	Pre-treatment	Post-treatment	P-value
Hemoglobin (g/dl), (M ± SD)	9.66±1.2	9.32±1.0	0.435
Bilirubin (mg/dl), Me (Q25-Q75)	0.88(0.34-1.7)	0.79(0.45-1.5)	0.786
AST (U/L), Me (Q25-Q75)	58.11(17-322)	42.70(22-192)	0.879
ALT (U/L), Me (Q25-Q75)	56.47(24-387)	49.23(27-195)	0.884
Albumin (mg/dl), (M ± SD)	3.24±0.23	3.89±0.43	0.782

In this series, 100% of both groups patients achieved sustained virological response with undetectable HCV RNA in 12 weeks (Fig. 1).

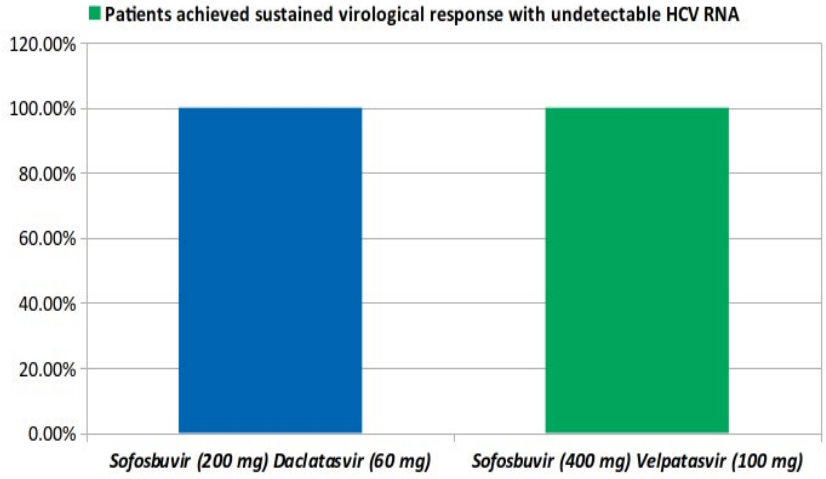

Fig. 1. Virological response in studied HD patients after 12 weeks of the antiviral treatment.

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. There were non-significant gastrointestinal side effects (nausea in 8.2% patients) in the full-dose Sofosbuvir group.

In the half-dose Sofosbuvir group, the patient had to expend 500 BDT (588 USD) daily and in the full-dose Sofosbuvir group, the daily treatment cost was 845 BDT (9.94 USD) ($p = 0.213$).

At the end of 12 weeks, the cost of antiviral treatment was significantly low in the half-dose Sofosbuvir group compared to the full-dose Sofosbuvir group: 42000 BDT (494 USD) vs 70980 BDT (835 USD), $p = 0.5$ (Fig. 2).

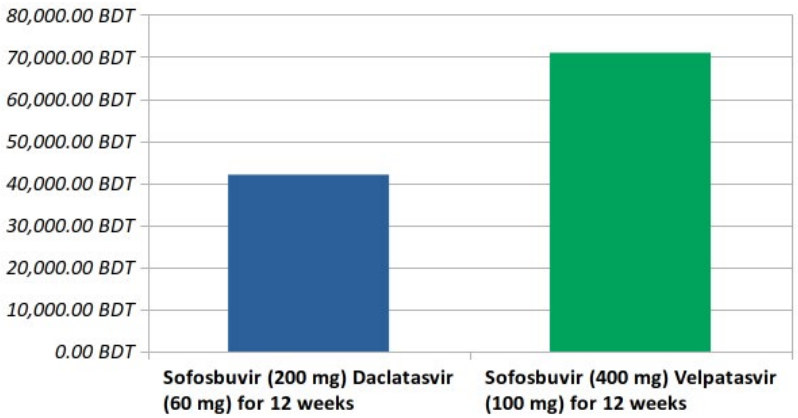

Fig. 2. Medical expenditure after 12 weeks of HCV antiviral treatment in HD patients.

Discussions. Sofosbuvir is an NS5B polymerase inhibitor that is metabolized intracellular and forms the active metabolite GS-461203, followed by de-phosphorylation resulting in the inactive compound GS-331007. GS-331007 is primarily excreted by the kidney (78 % of the administered dose) [14-16]. Therefore, increased metabolite levels, safety, and efficacy of Sofosbuvir treatment in HD patients remain an issue.

There are few studies devoted to Sofosbuvir use in ESRD patients. Nevertheless, there is no specific recommendation on this topic yet.

Daclatasvir is an NS5A inhibitor that is administered at a dosage of 60 mg/day. This medicine is highly bound to plasma proteins (99 %). It is hepatically metabolized (CYP3A4) and is a substrate of P-group. Biliary excretion is the major route of elimination [15]. Studies have demonstrated that no dose adjustments of Daclatasvir are necessary for CKD patients [20, 21].

In our study, 26 HD patients were treated with low-dose (200 mg) Sofosbuvir and full-dose (60mg) Daclatasvir for 12 weeks irrespectively of HCV genotype. All the patients achieved sustained virological response in 12 weeks. Besides, in our study, there were no significant differences in pre- and post-treatment levels of hemoglobin and liver function tests. Similar to our experience Taneja et al. [22] showed sustained virological response in 65 CKD patients with eGFR<30ml/min/1.73m^2 received low-dose Sofosbuvir and full-dose Daclatasvir. Chowdhury et al. [23] demonstrated the sustained virological response in patients who were

treated in an alternate days regime for 12 weeks. In their study, low-dose Sofosbuvir and full-dose Daclatasvir were well tolerated by ESRD patients and there were no major side effects and no treatment discontinuation. A similar result has been obtained in Taneja et al. study [22]. Several small studies and case reports have shown that both low-dose (200 mg) and full-dose (400 mg) of Sofosbuvir treatment were well-tolerated [17, 24]. Several case series have also described a good safety profile of half-dose Sofosbuvir treatment [23, 25-28].

Velpatasvir is a novel NS5A inhibitor that is licensed in a fixed-dose tablet with Sofosbuvir (100 mg/ 400 mg). Velpatasvir is primarily metabolized by the liver and excreted through the biliary system [29-31]. In the present study, 44 HD patients were treated with full-dose Sofosbuvir 400mg and Velpatasvir (100 mg), given daily for 12 weeks. All the patients achieved sustained virological response with undetectable HCV RNA after 12 weeks of the treatment. A similar study has been done by Borgia et al. [32] where 95% of patients achieved sustained virological response.

The main limitation of our study is a small sample size. However, the study might be the basis for future large-scale research.

Conclusions. In this study, the spontaneous seroconversion of HCV was 14%. The low-dose of Sofosbuvir with Daclatasvir treatment is safe, well-tolerated and as effective as full-dose Sofosbuvir and Velpatasvir in HD patients with chronic hepatitis C. The cost of low-dose Sofosbuvir antiviral treatment is significantly chipper compared to the full-dose regime and can be recommended in the treatment of HCV in ESRD patients in the developing countries.

Disclosure. Nothing to declare

Authors contribution. ***M. Mostafi*** conceived the original idea and supervised the project. ***M. Mostafi*** and ***M. Jabin*** was a major contributor in writing the manuscript. ***M. Mostafi*** and ***M. Jabin*** also developed the theory and performed the investigation with the help of ***Z. Chowdhury***, ***M.U. Khondoker***, ***S.M. Ali***, ***R. Tamanna***, ***R. Rezwan*** and ***S.B. Alomgir***.

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