

Sofosbuvir-based Treatment for HCV: A Safe Option in Patients Undergoing Hemodialysis

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ABSTRACT

The objective of this study was to ascertain the safety and efficacy of sofosbuvir in patients undergoing hemodialysis. Twenty-three HCV infected patients undergoing hemodialysis were included. Sofosbuvir was administered in combinations with ribavirin, daclatasvir and ledipasvir for 12-24 weeks. Viral response was checked at the end and 12 weeks after completing therapy. Twenty-one (91.3%) were of genotype 3 and two (8.7%) genotype 1. Eight (34.8%) had cirrhosis. Three (13%) were previous relapsers to sofosbuvir and ribavirin, while one (4.3%) was relapser to interferon. Sofosbuvir plus ribavirin was given to four (17.4%), sofosbuvir plus daclatasvir to eleven (47.8%), sofosbuvir plus daclatasvir plus ribavirin to four (17.4%), sofosbuvir plus velpatasvir to three (13%), and sofosbuvir plus ledipasvir to one (4.3%) patient. Twenty-one (91.3%) achieved viral eradication on completion of treatment; two were non-responders. Nineteen (82.6%) had undetectable virus 12 weeks after ending treatment and remaining two (8.7%) relapsed. Adverse effects were not observed. Hence, sofosbuvir can be safely used in patients undergoing hemodialysis.

Key Words: *Sofosbuvir, Hemodialysis, Hepatitis C.*

How to cite this article: Salim A, Farooq MO, Mengal FUA, Malik K. Sofosbuvir-based Treatment for HCV: A Safe Option in Patients Undergoing Hemodialysis. *J Coll Physicians Surg Pak* 2020; **30(11)**:1230-1231.

The prevalence of HCV infection is approximately 2.5% globally and 6-11% in Pakistan.¹ Chronic kidney disease (CKD) is a progressive loss of renal function and most patients progress to end-stage renal disease (ESRD), requiring hemodialysis (HD) and transplant. In Pakistan, incidence of ESRD is estimated to be over 100 new cases per million.² Studies in dialysis centres worldwide revealed HCV prevalence from 1 to 84.6% and a high prevalence of HCV (over 29%) has been described in patients undergoing hemodialysis in Pakistan.³ Treating these patients is an important health challenge. Treatment options with established safety for HCV infected individuals with no cirrhosis, early fibrosis or compensated liver disease, on hemodialysis and no immediate plans for renal transplantation include newer oral direct-acting antiviral agents (DAAs) with limited data about safety and efficacy. Almost all combinations of DAAs use sofosbuvir in combination with ribavirin alone or other agents such as daclatasvir, ledipasvir and velpatasvir. Daclatasvir, ledipasvir and velpatasvir use is safe in patients undergoing hemodialysis. Ribavirin is used in reduced doses in patients on hemodialysis.⁴

However, sofosbuvir, a vital agent with above combination, has been studied in small numbers of patients undergoing hemodialysis; and the data about safety and efficacy is limited. Furthermore, as sofosbuvir is a vital component of all the current oral antiviral treatment regimens available in Pakistan, its use cannot be avoided.

This prospective interventional study was carried out, after obtaining ethical approval, at the Department of Gastroenterology & Hepatology, Shaikh Zayed Hospital, Lahore, from February to November 2018. The working hypothesis was that sofosbuvir is safe to administer in patients undergoing hemodialysis.

ESRD is defined as chronic, irreversible renal failure, also known as CKD Stage 5. This is the stage when renal replacement therapy is needed, either dialysis or transplant. Compensated liver disease was defined as liver pathology with radiological and laboratory features indicating liver cirrhosis such as coarse liver echotexture, splenomegaly, and decreased platelet count; but none of the features described for decompensated cirrhosis. Virological response was defined as undetectable HCV RNA. Sustained virological response was defined as undetectable viral load at 12 weeks (SVR-12). Failure of therapy (or non-responder) was defined as detectable HCV RNA at end of the treatment. Safety was defined as absence of any significant drug-related side effects, causing discontinuation of therapy.

Patients, aged 18 years and above, of either sex with HCV infection and having no liver fibrosis, early fibrosis or compensated cirrhosis on hemodialysis for ESRD were included. Drug associated risks were explained and written informed consent taken

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Received: July 12, 2019; Revised: March 18, 2020;

Accepted: May 10, 2019

DOI: <https://doi.org/10.29271/jcpsp.2020.11.1230>

from all recruited patients. All patients received sofosbuvir, in different combinations with either daclatasvir, velpatasvir or ledipasvir, with or without ribavirin. Ribavirin 400 mg was given on alternate days in all combinations that included ribavirin. Duration of therapy was based on type of regime used, prior treatment history and severity of hepatic fibrosis. Clinical parameters including hemoglobin, INR, albumin, total bilirubin, ALT, LDH quantitative PCR for HCV RNA, HCV genotype and abdominal ultrasound were checked. Patients were called two weeks after start of the treatment with fresh hemoglobin and LFTs to check for ribavirin induced anemia or derangement of liver functions from baseline. Following this, patients were then called at the end of 4th week of treatment and LFTs, RFTs, CBC and HCV RNA levels were analysed. Patients with worsening of anemia had dose of erythropoietin increased to 10,000 U (as all were already receiving erythropoietin 4000 U once weekly) with or without reducing dosage of ribavirin (if on a ribavirin inclusive regime). After four weeks, patients were followed up monthly till completing treatment. Viral response was checked again on completion of treatment and at 12 weeks after completion. SPSS version 21 was used to analyse the data.

A total of 23 patients were recruited, 18 (78.3%) males and 5 (21.7%) females with an average age of 41.5 ± 14.5 years. Genotype 3 was predominant, affecting 21 (91.3%) patients, while two (8.7%) had genotype 1. Almost a third of the patients (8: 34.8%) had liver cirrhosis. Most patients (19: 82.6%) had no past history of treatment for HCV. Sofosbuvir, 400mg daily, was given to all patients in the following combinations: sofosbuvir and ribavirin in four (17.4%) patients; sofosbuvir and daclatasvir in eleven (47.8%); sofosbuvir, daclatasvir and ribavirin in four (17.4%); sofosbuvir, velpatasvir and ribavirin in three (13%); sofosbuvir and ledipasvir in one (4.3%) patient. Treatment duration was 24 weeks in 4 treatment-experienced patients and four patients receiving sofosbuvir plus ribavirin. Duration was 12 weeks in the remaining 15 patients.

Twenty-one (91.3%) patients achieved HCV clearance on completion of therapy, while two were non-responders. Nineteen (82.6%) patients maintained viral clearance at 12 weeks after end of therapy. Two patients experienced viral relapse, seen by detectable HCV RNA, within 12 weeks after ending therapy. No significant adverse effects attributable to antiviral therapy were noted.

Sofosbuvir-based anti-HCV therapy seems safe for use in patients with HCV undergoing hemodialysis. This study has one of the larger genotype 3 HCV (predominant in Pakistan) populations compared to recent studies.^{5,6} It showed favourable responses in cirrhotic patients as well as treatment-experienced patients. Importantly, sofosbuvir was used with a wide variety of other DAAs, in addition to ribavirin. All combinations were well tolerated, using both patented and lower cost generic DAAs. Duration of therapy in our study was same as per guidelines that govern treatment for patients not undergoing hemodialysis. Encouraging responses were observed, *albeit* slightly less than those observed

in comparable patients not undergoing hemodialysis. Factors specific to ESRD may directly affect viral response to DAAs and these need further exploration. Only two patients reported side effects, which were mild occasional headache and weakness. These were deemed non-specific and could be related to renal disease or co-morbidities that contributed to ESRD.

Sofosbuvir can be safely used for treating HCV in patients undergoing maintenance hemodialysis for ESRD, in all recommended combinations with ribavirin or other DAAs. Its use yields excellent viral response without any noticeable adverse effects.

PATIENTS' CONSENT:

All patients were explained all relevant drug associated side effects and written and informed consents were obtained prior to recruitment in study.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

AS: Original study concept and design, data analysis and interpretation, drafting of paper. Gave final approval of study for submission for publication. Agreed for accountability for all aspects of study.

MOF: Acquisition, analysis and interpretation of data.

FUAM: Acquisition, analysis and interpretation of data.

KM: Critical revision of study. Final approval of study for submission for publication.

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