Original Article

Safety of SOF for Chronic Hepatitis C in CKD

Efficacy and Safety of Sofosbuvir (SOF) - Based Regimen for Chronic Hepatitis C Infection in Chronic Kidney Disease (CKD) Patients

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ABSTRACT

Objective: Sofosbuvir (SOF) is mostly eliminated via the kidneys. Patients with varied pretreatment estimated glomerular filtration rates (eGFR) were studied to determine the effectiveness and safety of SOF-containing regimens in chronic Hepatitis C patients.

Study Design: Cohort study

Place and Duration of Study: This study was conducted at the AJKMC, Muzaffarabad from 01.01.2020 to 30.06.2020.

Materials and Methods: Patients over the age of 18 in Pakistan who have been diagnosed with chronic HCV and whose eGFR is below 60 mL/min/1.73 m^2 are included. Between 01/01/2020 to 30/06/2020, they were treated at hospital for chronic hepatitis C with SOF-based antiviral medication. Laboratory tests, an abdominal sonogram, and a clinical evaluation were performed on every patient. For the latter, CBC, transaminases, bilirubin, albumin, HCV viral load, HBsAg, creatinine, fasting plasma glucose, alpha-fetoprotein, pregnancy tests, and hemoglobin A1c were measured.

Results: An initial eGFR was calculated in 100 subjects (3a genotype): The eGFR levels of 75 patients were below 30 while those of 25 patients were over 30. SVR was achieved in 90% of patients with SOF-based regimen. In 7% of the patient's adverse effect after SOF-based regimen was observed mainly due to worsened renal functionalities.

Conclusion: Treatment based on SOF proved effective and safe, causing very mild adverse effects. Larger research is still required to confirm these findings, however.

Key Words: Hepatitis C, Chronic Kidney Disease, Antiviral, Sofosbovir

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INTRODUCTION

Sofosbuvir (SOF) is the cornerstone of various FDA-approved oral hepatitis C regimens. Extremely large amounts of SOF are converted to active component GS-461203 and then dephosphorylated to the inactive component GS331007[1].

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In patients with an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73 m^2, the systemic exposure to SOF was 170% greater and the systemic exposure to GS-331007 was 450% higher than in those with normal renal function[2,3]. Therefore, individuals undergoing hemodialysis or those with an eGFR of 30 ml/min/1.73 m^2 or less should not take SOF. Patients with renal failure, such as those on dialysis, have a high unmet need for hepatitis C virus (HCV) therapy alternatives. Currently, glecaprevir, pibrentasvir, elbasvir, grazoprevir and ritonavir with or without dasabuvir are the only all-oral regimens authorized by the FDA for treatment in individuals with severe renal impairment. The risk of developing CKD and progressing to end-stage renal disease (ESDR) is higher in people with HCV infection, according to large-scale population observational studies[4,5]. This is due to the fact that HCV infection can cause renal dysfunction either directly, through cryoglobulinemic vasculitis and glomerulonephritis, or indirectly, through hepatic cirrhosis and related problems of portal hypertension. It is reasonable to anticipate an increase in the usage of SOF in patients with mild to severe renal impairment

because to the high demand and lack of viable alternatives[6]. In light of the aforementioned literature, the purpose of the present research was to assess the effectiveness and safety of SOF-based DAAs in CKD patients with chronic HCV infection.

MATERIALS AND METHODS

This is a cohort study. Patients over the age of 18 in Pakistan who have been diagnosed with chronic HCV and whose eGFR is below 60 mL/min/1.73 m^2 are included. Between 01/01/2020 to 30/06/2020, they were treated at hospital for hepatitis C infection with SOF-based antiviral medication. The potential for harm was outlined in detail, and patients signed a document giving their consent to publish their anonymous data in scientific journals. Laboratory tests, an abdominal sonogram, and a clinical evaluation were performed on every patient. For the latter, CBC, transaminases, bilirubin, albumin, HCV viral load, HBsAg, creatinine, fasting plasma glucose, alpha-fetoprotein, pregnancy tests, and hemoglobin A1c were measured. If a patient's serum creatinine was greater than 1.2 mg/dL, their eGFR was determined using the CKD-EPI equation. The fibrosis severity was determined by calculating a value of FIB-4. When other diagnostic options were unavailable or inconclusive, cirrhosis was diagnosed based on a FIB4 >3.25 value, an ultrasound image suggestive of cirrhosis, or a fibroscan result of 12.5 kPa. According to the established protocol, patients with hepatitis C infection were given SOF-based treatments. Those with an eGFR between 30-60 mL/min/1.73 m^2 (Stage III renal disease) and those with an eGFR of 30 mL/min/1.73 m^2 or less were considered to have stage IV or V renal disease. Both groups took 400 milligrams of SOF, but the first took it once daily and the second took it every other day. Dialysis patients received 400 mg of SOF an hour before their dialysis session. The following methods were used to track the efficacy and safety of SOF-based treatment plans: The patients were kept under observation (a) clinically for side effects, hepatic decompensation signs, and revaluation of possible medication interactions; and (b) laboratory-wise at weeks 12, and 24. (to test for SVR). In the lab, complete blood count, creatinine, eGFR, and a biochemical profile of the liver were measured. There was a follow-up assessment of viral load 12 weeks after therapy had ended. When HCV RNA levels dropped below the cutoff for detection (15 IU/mL), SVR was regarded to have been achieved. SPSS version 26 was used for the statistical analysis. Calculations were presented as means and standard deviations for numerical data, while percentages and raw numbers were used to represent categorical information. The means of quantitative variables were compared using a matched pairs t test. A value of p 0.05 was deemed as statistically significant.

RESULTS

Treatment effectiveness in relation to pre-treatment patient characteristics 90% of the study population showed a SVR (90 out of 100 participants). Viral responses were analyzed in light of demographic characteristics. A number of factors were found to be significantly associated with non-response, including dialysis use, treatment history, albumin levels, hemoglobin levels, and other parameters (Table 1).
Decompensated cirrhosis (Child B) was found in 19 patients, or 19%, and SVR was achieved in 16 patients, or 84.25%. Fortunately, nobody experienced any major side effects. 35 patients (35%) were on dialysis. thirty of them achieved SVR (85.7%), and 3 patients (8.5%) withdrawn treatment due to worsened renal function.
Patients' clinical features during treatment and relation with renal impairment.

Table No.1: Treatment success according to patient features and treatment protocol at the outset

Parameters	Sample size (n=100)	Treatment outcomes		
		SVR	Non-SVR	P value
Gender				
Male	65	59	6	
Female	35	31	4	
Age (Mean)	57.43	57.08	48.9	0.04
Age (Median)	55	55	45	
BMI	27.13	27.09	25.32	0.17
Viral Load (Mean)	4.56	4.43	0.56	0.01
Creatinine	1.7	1.7	1.7	-
eGFR	50.12	50.12	39.17	0.19
Dialysis	35	30 (85.7%)	2(6%)	-
Bilirubin	0.76	0.8	0.26	-
Albumin	4.5	5	3	0.49
ALT	36.4	33.8	22.7	0.009
Hemoglobin	13.2	13.8	11.1	0.37
AFP	6	5	19	.755
FIB-4	2.3	2..5	2.7	.231
Liver stiffness (kPa)	17.1	17.4	20	0.22
Cirrhosis by sonograph	1043	977	45	0.00
Previous decompensation				
Ascites	35	33 (94%)	2 (6%)	
Hepatic encephalopathy	6	5 (83%)	1 (17%)	
Oesophageal varices	15	14 (93%)	1 (7%)	
Treatment regime				
SOF+DAC	55	51 (92.7%)	4 (7.3%)	
SOF+VEL	45	39 (86.7%)	6(13.3 %)	

According to the KDIGO criteria, the patients were split into two groups. Patients have renal disease of stage IV or V were categorized into group with eGFR <30 mL/min/1.73 m^2, while the patients with stage III renal disease were categorized into eGFR ≥30 mL/min/1.73 m^2. A statistical variation was in the SVR was observed in both groups. About 68% participants achieved SVR in eGFR <30 mL/min/1.73 m^2. While 97% participants in eGFR ≥30 mL/min/1.73 m^2 achieved SVR.

SVR and Treatment regimens. In terms of the employed regimens, In Table 1. 92.7% SVR was achieved in the participants with SOF+DAC. 96.7%, SVR was achieved in regimen cohort of SOF+VEL.

Treatment failure and adverse effect In the 10 patients who had treatment failure, 2 patients (2%) did not attain a negative viraemia at the conclusion of the course of therapy, 1 patient (1%) relapsed, and 7 patients (7%) stopped the course of therapy due to side effects. The primary adverse event that required therapy cessation in individuals with renal impairment were worsening of kidney's functioning (7 patients).

Table No.2: Characteristics at baseline and the rate of SVR in relation to the degree of renal impairment

	eGFR ≥30 mL/min (n = 75)	eGFR <30 mL/min (n = 25)	P Value
Gender			
Male	50	15	
Female	25	10	
Age			
Mean	58.75	51.23	0.30
Median	59	54	
BMI			
Mean	28.23	27.12	0.105
Median	27	26	
Viral Load (Mean)	$0.51x10^6$	$0.38x10^6$	0.15
Creatinine	1.5	6.32	0.23
Dialysis	23	7	-
Bilirubin	0.88	0.85	0.205
Albumin	3.21	4.1	0.119
ALT	39	43	
Hemoglobin	12.91	13.2	0.45
AFP	6	6	0.50
FIB-4	2.89	1.76	0.022
Liver stiffness (kPa)	13	19.02	0.001
Cirrhosis by sonograph	920	132	0.001
Previous decompensation			
Ascites	29	6	
Hepatic encephalopathy	1	5	
Oesophageal varices	2	13	
Treatment regime			
SOF+DAC	36 (48%)	14 (56%)	
SOF+VEL	39 (52%)	11 (44%)	
Treatment response			
SVR	73 (97%)	17 (68%)	
Non-SVR	2(3%)	8(32%)	

DISCUSSION

Contrary to the widespread global practice of SOF limitation, several recent studies have shown the safety and effectiveness of SOF-based regimens in renal impairment participants. This trial observed at the effectiveness and safety of treating patients with chronic HCV who also had mild to severe chronic kidney disease. Twenty-five percent of patients with severe renal impairment and seventy-five percent of individuals with less severe renal illness obtained SVR. Finding that SOF generates about the same amount of active intracellular metabolites regardless of renal function may explain the high SVR rate.[7] High rates of SVR were also seen in a study of the safety and effectiveness of full dosage SOF in 29 patients with severe renal failure conducted by Cox-North et al[8]. In their phase II research of 59 patients with chronic HCV and ESRD on hemodialysis dialysis, Borgia et al. similarly showed an SVR rate of 95% after treatment with open-label full dosage sofosbuvir/velpatasvir for 12 weeks[9]. Among 28 patients with HCV G1 and stage 3 CKD, Shin et al. observed an SVR rate of 85.7% after evaluating the effectiveness and safety of full-dose SOF. Maybe that's because their research included more participants who already had cirrhosis and were on treatment than ours did[10]. A comparable SVR rate of 83% was seen by Saxena et al. in patients with an eGFR of 45 mL/min when using full-dose SOF-based regimens. The relatively high rate of treatment discontinuation owing mostly to adverse effects may account for their lower SVR[11].

Only 10% of patients in our study had treatment failure (non-response plus discontinuation), and no baseline factors were found to be associated with treatment failure in the subgroup of patients with severe renal impairment. According to the trials, patients who had never received treatment before enrolling in the DAA study did slightly better than those who had previously failed on Peg-IFNRBV medicine. SVR rates in cirrhotic patients range from 33% to 100%, and are heavily determined by the level of severe fibrosis[10].

7 people in this research (7%) dropped out of therapy due to adverse side events. Treatment termination was most common due to worsening renal functions in the subgroup of individuals with severe renal impairment. The frequency with which studies document unwanted outcomes varies widely. All patients getting RBV in Cox-North et al. study reported increased anemia, but no treatment dropouts (8). However, 79/1789 (4%) of participants in the well-known TARGET research by Saxena et al., reported stopping treatment due to adverse effects; 6% of these were considered to be "severe."[11] Paradoxically, the treatment completion rate

of SOF-based therapy in our study was higher than that observed with the use of renal disease-specific regimens, such as paritaprevir/ ritonavir/ ombitasvir+ dasabuvir ribavirin in the ERCHIVES study[12], in which only 69% (38/55) of patients with stage 4 0r 5 CKD completed therapy; or grazoprevir/elbasvir in the C-SURFER study. The latter included things like patients passing away, being lost to follow-up, refusing treatment, doctors dropping them, and patients leaving because of doctors' aggressive behaviours[13].

A total of 56 patients (56%) in our research had decompensated cirrhosis (Child B), and 93% of them achieved SVR. There were no severe adverse effects recorded. Seven patients (14.9%) with decompensated cirrhosis and ascites were included in Singh et al studies on the effects of full dosage SOF in patients with severe renal impairment. At the completion of therapy, 100% of their patients were responding well, and SVR was attained in 95.7%. In the pre-dialysis group, therapy did not improve hemoglobin or estimated glomerular filtration rate[14].

Hemodialysis patients in this trial had an SVR of 85.7%, with 5% dropping out due to anemia. This figure is much lower than that found by Agarwal et al., who evaluated the effectiveness and safety of SOF-based treatment in a group of 62 patients on maintenance hemodialysis. He found an SVR of 95.2% in his research[15]. There were no treatment discontinuations due to adverse events, however the majority of patients in the RBV group (n = 23; 56%) needed an increase in the erythropoietin dosage. Present study hemodialysis cohort was small, and the discrepancy IN SOF dose may explain the decreased SVR rate. Patients in the earlier trial were given RBV and SOF every day, but our hemodialysis patients only got medication every other day before their hemodialysis sessions. Several recent studies confirmed that the effectiveness of SOF decreases with decreasing dosage[16,17].

CONCLUSION

This study suggests that SOF-containing regimens are effective and safe for the treatment of those with chronic HCV who have moderate to severe renal impairment, as well as those who have hepatic decompensation. Patients with an eGFR 30 mL/min/1.73 m2 have been shown to benefit from taking sofosbuvir every other day. To underline safety issues and alter the prevailing thinking, however, prospective studies are required.

Author's Contribution:

Concept & Design of Study:	Noman Kareem Qureshi
Drafting:	Farooq Ahmed, Munazza Nazir
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Revisiting Critically:	Noman Kareem Qureshi, Farooq Ahmed
Final Approval of version:	Noman Kareem Qureshi

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REFERENCES

1. Farnik H, El-Duweik J, Welsch C, Sarrazin C, Lötsch J, Zeuzem S, et al. Highly sensitive determination of HCV protease inhibitors boceprevir (SCH 503034) and telaprevir (VX 950) in human plasma by LC–MS/MS. J Chromatography B 2009;877(31):4001-6.
2. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterol 2005;128(2):343-50.
3. Baid-Agrawal S, Schindler R, Reinke P, Staedtler A, Rimpler S, Malik B, et al. Prevalence of occult hepatitis C infection in chronic hemodialysis and kidney transplant patients. J Hepatol 2014;60(5): 928-33.
4. Ladino M, Pedraza F, Roth D. Hepatitis C virus infection in chronic kidney disease. J Am Society Nephrol 2016;27(8):2238-46.
5. Marinaki S, Boletis JN, Sakellariou S, Delladetsima IK. Hepatitis C in hemodialysis patients. World J Hepatol 2015;7(3):548.
6. Kirby BJ, Symonds WT, Kearney BP, Mathias AA. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of the hepatitis C virus NS5B polymerase inhibitor sofosbuvir. Clin Pharmacokinetics 2015;54(7):677-90.
7. Desnoyer A, Pospai D, Lê MP, Gervais A, Heurgué-Berlot A, Laradi A, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. J Hepatol 2016;65(1):40-7.
8. Cox-North P, Hawkins KL, Rossiter ST, Hawley MN, Bhattacharya R, Landis CS. Sofosbuvir-based regimens for the treatment of chronic hepatitis C in severe renal dysfunction. Hepatol Communications 2017;1(3):248-55.
9. Borgia SM, Dearden J, Yoshida EM, Shafran SD, Brown A, Ben-Ari Z, et al. Sofosbuvir/velpatasvir for 12 weeks in hepatitis C virus-infected patients with end-stage renal disease undergoing dialysis. J Hepatol 2019;71(4):660-5.
10. Shin HP, Park JA, Burman B, Kozarek RA, Siddique A. Efficacy and safety of sofosbuvir-based regimens for treatment in chronic hepatitis C

genotype 1 patients with moderately impaired renal function. Clin Molecular Hepatol 2017;23(4):316.

11. Saxena V, Koraishy FM, Sise ME, Lim JK, Schmidt M, Chung RT, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. Liver Int 2016;36(6):807-16.
12. Butt A, Ren Y, Puenpatom A, Arduino J, Kumar R, Abou-Samra AB. Effectiveness, treatment completion and safety of sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir+ dasabuvir in patients with chronic kidney disease: an ERCHIVES study. Alimentary Pharmacol Therapeutics 2018;48(1):35-43.
13. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour Jr H, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet 2015;386(10003):1537-45.
14. Singh A, Kumari S, Kumar P, De A, Singh V. Sofosbuvir with NS 5A inhibitors in hepatitis C virus infection with severe renal insufficiency. J Viral Hepatitis 2018;25(12):1501-6.
15. Agarwal SK, Bagchi S, Yadav RK. Hemodialysis patients treated for hepatitis C using a sofosbuvir-based regimen. Kidney International Reports 2017; 2(5):831-5.
16. Choudhary NS, Kumar A, Bodh V, Bansal SB, Sharma R, Jain M, et al. Efficacy and safety of sofosbuvir-based regimens in chronic hepatitis C patients on dialysis. Ind J Gastroenterol 2017; 36(2):113-6.
17. Perumpail R, Wong R, Ha L, Pham E, Wang U, Luong H, et al. Sofosbuvir and simeprevir combination therapy in the setting of liver transplantation and hemodialysis. Transplant Infectious Disease 2015;17(2):275-8.