

## Original Research Article

# Efficacy and safety of sofosbuvir based antiviral therapy for chronic hepatitis C infection in patients with advanced chronic kidney disease

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### ABSTRACT

**Background:** Screening studies for hepatitis C have proved that it is more prevalent in patients with renal diseases. Chronic hepatitis C infection in patients with kidney disease not only accelerates renal deterioration but also adversely affects morbidity and mortality. Availability of direct acting antiviral drugs has revolutionized treatment of hepatitis C even in difficult patients. In advanced kidney diseases, selection of treatment is difficult. Aim of this study was to evaluate the efficacy and safety of Sofosbuvir based DAAs in patients with advanced CKD.

**Methods:** In this Quasi experimental study, CHC patients with or without cirrhosis having advanced CKD (eGFR <30 ml/min per 1.73 m<sup>2</sup>) and/or on dialysis were enrolled. End points of the study were documentation of SVR 12 or discontinuation of therapy. Different regimens of oral DAAs with or without Ribavirin were used.

**Results:** 86 patients with a median age of 53 years were enrolled. 37 patients were on maintenance dialysis and 49 were not on dialysis with eGFR <30 ml/min per 1.73 m<sup>2</sup>. Virological response was 92.68% at the end of treatment and SVR was achieved by 90.2% twelve weeks after therapy. Insomnia 14%, headache 11% and anemia 7% were main adverse effects. Mean eGFR and creatinine before and after treatment remained the same. Only 2 patients relapsed, both were on dialysis thrice weekly.

**Conclusions:** All Sofosbuvir based regimens used for the treatment of CHC in patients with end stage renal disease are effective and well tolerated. Close follow up is advised to monitor side effects.

**Keywords:** Chronic renal failure, Hepatitis C, Sofosbuvir

### INTRODUCTION

Since its discovery in 1989, hepatitis C virus is a serious global health issue resulting in significant morbidity and mortality.<sup>1</sup> Global prevalence of hepatitis C is 2.8%, affecting more than 180 million people worldwide and it was rising up till recently when very effective antiviral drugs were developed.<sup>2,3</sup> Chronic hepatitis C (CHC) infection is more common in Pakistan with a prevalence of 6.8% in general population.<sup>4</sup> Evidence supports that

hepatitis C infection is a systemic disorder affecting many organ systems.<sup>5</sup> Extra-hepatic manifestations of hepatitis C infection are also important contributors to the morbidity including rheumatological, metabolic, renal, cardiovascular, neurological and lymphoproliferative disorders.<sup>6,7</sup>

Screening for hepatitis C among different population groups made it evident that it is more prevalent in patients with renal diseases as compared to general

population.<sup>8</sup> There are certain possible explanations for this higher prevalence such as, chronic kidney disease patients are immunocompromised which makes them more prone to infection, repeated blood transfusion to treat anemia and repeated hemodialysis increases the risk of exposure to the virus.<sup>9,10</sup> Dialysis Outcomes and Practice Patterns Study (DOPPS), a study published in 2004 showed that prevalence of hepatitis C virus is 13.5 % in patients on hemodialysis.<sup>5</sup> But this varies a great deal among different areas of the world, such as 1% in United Kingdom to 48.9% in Pakistan.<sup>11,12</sup>

Pathological factors of hepatitis C inducing renal damage include, immune complex deposition, insulin resistance leading to accelerated atherosclerosis, idiopathic membranoproliferative glomerulonephritis and essential mixed cryoglobulinemia.<sup>9,10</sup> Chronic hepatitis C infection in patients with chronic kidney disease not only accelerates the renal deterioration but also adversely effects morbidity and mortality in patients on hemodialysis and renal transplant.<sup>13,14</sup> Combination of pegylated interferon and ribavirin was the standard treatment of CHC in past but in patients on maintenance dialysis they have lower success rates and high adverse effects. In renal transplant patients they were also associated with higher rates of graft rejection.<sup>15</sup> Introduction of Direct Acting Antivirals (DAAs) agents for the treatment of CHC has significantly improved outcome even in patients with Chronic Kidney Disease (CKD). Treatment recommendations are based on CKD GFR category. For patients with eGFR >30 ml/min per 1.73 m<sup>2</sup>, selection of DAAs is not affected by deranged renal functions. In advanced CKD i.e G4-G5 and G5D (on dialysis), selection of DAAs depends upon degree of renal damage and genotype of HCV infection.<sup>16</sup> Recommended DAA for patients with eGFR <30 ml/min per 1.73 m<sup>2</sup> include, Grazoprevir/Elbasvir, Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir and Glecaprevir/Pibrentasvir.<sup>17,18</sup> These drugs are either costly or not available in most of the countries including Pakistan. Drugs like Velpatasvir, Daclatasvir or Ledipasvir have non-renal excretion so these are considered safe in advanced CKD, but most of the regimens with these drugs include Sofosbuvir which has renal excretion and there is limited clinical data on its usage in this patient population.<sup>17,18</sup>

The purpose of this study was to evaluate the efficacy and adverse effect profile of different Sofosbuvir based DAA regimens in patients with advanced CKD.

## METHODS

### Study Design

Quasi Experimental study

### Duration of study

January 2016 to June 2018

### Setting of the study

Gastroenterology & Hepatology department, Madina Teaching Hospital, Faisalabad.

### Inclusion criteria

- Patients of either gender
- Age more than 18 years
- Chronic hepatitis C (Detectable HCV RNA in serum more than 6 months)
- All genotypes of HCV
- Advance CKD (eGFR <30 ml/min per 1.73 m<sup>2</sup>) calculated by CKD-EPI equation<sup>19</sup>
- Patients with or without cirrhosis
- Patients with prior exposure to non-DAA hepatitis C treatment.

### Exclusion criteria

- Patient with CKD and eGFR >30ml/min per 1.73 m<sup>2</sup>
- Prior treatment with DAAs
- Patients having hepatocellular carcinoma
- Patients with portal vein thrombosis
- Patients having HIV co- infection

### End points of the study

- 12 weeks of follow up after completion of treatment
- Discontinuation of therapy due to adverse effects.
- Death or loss of follow up either during treatment or during post treatment follow up period

**Sampling Technique:** Consecutive non-probability sampling

### Treatment:

**Duration:** Duration of therapy was planned according to latest recommendation from AASLD guidelines.<sup>17</sup>

**Drugs:** DAAs available in our country were used including, Velpatasvir, Daclatasvir, Sofosbuvir with or without Ribavirin.

**Dose:** All patients received drugs on daily bases in following dose.

Sofosbuvir 400 mg, Daclatasvir 60 mg, Velpatasvir 100 mg, all once daily and Ribavirin 400 mg twice daily (titrated according to renal impairment and tolerance).

**Consent:** At the start of study all patients were informed that Sofosbuvir containing regimens are not approved in patients with severe renal dysfunction (eGFR <30 ml/min per 1.73m<sup>2</sup>). All patients understood that data regarding the use of these medications in this patient population is limited and they consented to the off label use of these medications.

**Cirrhosis:**

Cirrhosis is defined on combination of laboratory, imaging characteristics or clinical parameters.<sup>20</sup>

Combination of any 2 of the following; platelets count <140000/µl, presence of oesophageal varices, evidence of cirrhosis and/or portal hypertension and/or ascites by imaging studies, Fibrosure or equivalent test, elastography or equivalent compatible with stage 4 fibrosis.

**Follow-up of patients:**

Clinical and laboratory follow-up of patients was done 2 weekly during the course of treatment and then 4 weekly till 12 weeks after completion of therapy.

Virological response was assessed by measuring HCV RNA at following intervals;

- 4 weeks after starting therapy
- At the end of therapy (12 or 24 weeks)
- 12 weeks after completion of therapy to document SVR 12.

HCV RNA was measured using COBAS® AmpliPrep/COBAS® TaqMan® HCV quantitative Test, v2.0 (Roche, Branchburg, NJ, USA), with the lower limit of detection of 15 IU/mL.

**Statistical Analysis:**

Categorical and numeric data were summarized using proportions/ratios and median (range) respectively and compared between groups using chi-square and Mann-Whitney U tests respectively. p values below 0.05 were considered significant. All analyses were performed using SPSS software, version 13.0 (IBM, Armonk, NY, USA).The study was approved by the Ethics Committee of our university.

**RESULTS**

A total of 86 patients fulfilling the inclusion criteria were enrolled in the study with baseline characteristics as mentioned in table 1.

Median age of the study cohort was 53 years, 37 patients were on maintenance dialysis twice or thrice weekly and 49 were not on dialysis with eGFR <30 ml/min per 1.73m<sup>2</sup>. Two major etiologies were found for chronic renal failure, diabetic nephropathy (36) and hypertension (43), 7 patients had no identifiable cause for the renal failure. 60 patients had no evidence of cirrhosis of liver, 21 had compensated cirrhosis and 5 patients had decompensated cirrhosis, with 3 having prior episodes of variceal bleed and 2 had hepatic encephalopathy in the past. In the study group 82 patients were treatment naïve while 4 patients were non-responders to Peg-INF and Ribavirin in the past.

**Table 1: Baseline characteristics of the study population.**

Demographics	All patients (n=86)
Median age, y (Range)	53 (45-64)
Gender, male	51 (59.3%)
Patients on dialysis	37 (43.02%)
Patients GFR <30, no dialysis	49 (56.97%)
Patients without cirrhosis	60 (69.76%)
Patient with cirrhosis	26 (30.23%)
Treatment naïve	82 (95.34%)
Treatment experienced	
Peg-INF + RBV	4 (4.65%)
Mean baseline Haemoglobin (Range)	10.4 (9.2-12.9)
Patients on erythropoietin replacement	30 (34.88 %)
Mean baseline ALT	27
Mean baseline AST	31
Mean baseline Total Bilirubin	0.7
Mean baseline INR	1.0

We used different Sofosbuvir based drug regimens for the treatment of CHC, details in table 2.

**Table 2: Different Drug Regimens.**

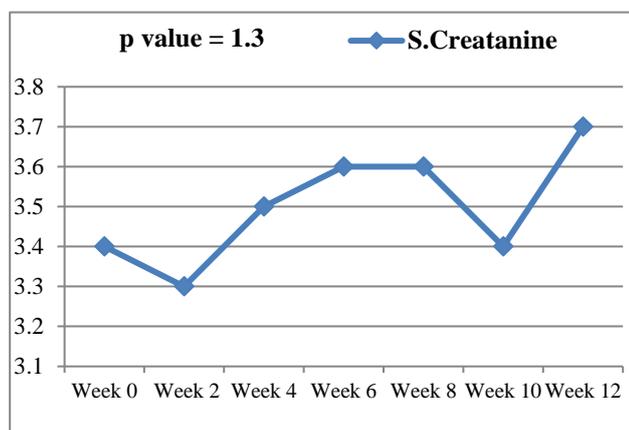
Drug Regimen	No. of Patients
Sofosbuvir + Velpatasvir	32
Sofosbuvir + Daclatasvir	28
Sofosbuvir + Velpatasvir + Ribavirin	17
Sofosbuvir + Daclatasvir + Ribavirin	9

Four patients died during the course of study. Two patients on maintenance dialysis died, one with bacterial infection leading to sepsis and other after severe pulmonary edema. They had completed their course of antiviral therapy uneventfully and SVR was yet to be done. Two patients had massive variceal bleed, one was having compensated cirrhosis (completed antiviral therapy with Sofosbuvir, Daclatasvir and Ribavirin) and other was having decompensated cirrhosis (received 2 months of therapy with Sofosbuvir, Daclatasvir and Ribavirin), at the start of therapy and both were not on dialysis.

Eighty five patients completed course of antiviral therapy 12 or 24 weeks based on the baseline status of liver. Virological response was checked at 4 weeks after starting the therapy, at the completion of therapy and 12 weeks after completion of therapy. One patient died during the therapy, he had negative PCR at 4 weeks of therapy. 3 other patients died before documenting SVR 12 but all of them had PCR negative at 4 weeks of therapy and at the end of therapy. In the remaining 82 patients, 76(92.68%) patients achieved end of treatment response and of these 74(90.24%) patients succeeded to

sustain the virological response 12 weeks after completion of therapy. Only 2 patients relapsed, both of these patients were having compensated cirrhosis with genotype 3 and were on dialysis 3 times a week.

Regarding tolerability of the drugs, 70% patients reported no adverse effects while on treatment. Most common adverse effects noted in the study population at some point during the course of treatment, in decreasing order of frequencies were insomnia 14%, headache 11% and anemia 7%. Anemia was mild which was managed by Ribavirin dose reduction and erythropoietin stimulating factors. During the treatment there were no missed doses of the drugs; dose adjustment was not done for Velpatasvir, Daclatasvir and Sofosbuvir, while the dose of Ribavirin was adjusted according to parameters such as patient's weight, anemia and tolerability of the drug. In patients not receiving dialysis, the mean eGFR and creatinine levels before treatment (21.3 ml/min/1.73m<sup>2</sup> & 3.4 mg/dl) were not much different (p value 1.3) than the mean values after treatment (19.1 ml/min/1.73m<sup>2</sup> & 3.7 mg/dl).



**Figure 1:Mean S.Creatinine.**

## DISCUSSION

Treatment of CHC in patients with advanced CKD was controversial in the past in spite the proven fact that it increases mortality and morbidity. Treating CHC in patients with renal disease has always been a difficult task. Historically these patients were treated with Peg- INF and Ribavirin, but this regimen had high rates of adverse effects, dropouts and low success rates.<sup>21</sup> Introduction of DAAs for the treatment of hepatitis C revolutionized the treatment but initially they were used in combination with Peg- INF and Ribavirin, and in patients with renal failure these drugs had low tolerability. As the DAAs kept on evolving, interferon free regimens became possible, but the issue was renal excretion of most of these drugs especially Sofosbuvir which is the integral part of all the regimens. In the recent guidelines some of the drugs have been proposed to treat hepatitis C in patients with severe renal compromise but most of these drugs are either very costly or not available

in most of the countries of the world including Pakistan.<sup>17,18</sup>

C-SURFER study is a phase III multicenter trial conducted to see the efficacy and tolerability of DAAs in CKD patients. In this trail they used Grazoprevir 100 mg/day (HCV NS3/4A inhibitor) and Elbasvir 50 mg/day (HCV NS5A inhibitor), SVR rate noted was 99.1%.<sup>22</sup> As these drugs are not available, we are presenting real life data of different regimens consisting of commonly available DAAs to treat hepatitis C in this difficult to treat patient population and we have found very encouraging results. SVR in our study population was 90.24% with relapse in just 2 patients. If GFR is above 30ml/min/1.73m<sup>2</sup> Sofosbuvir is used at a dose of 400mg per day. However in many research trails Sofosbuvir is tested at full or half dose in CKD stage 4 or 5 patients and their results showed good results and no significant adverse events, but most of these studies were conducted on small group of patients.<sup>23,24</sup> The SVR 12 rate from a recently published study ranged from (58-100% ) in patients with advanced CKD with Sofosbuvir based regimen.<sup>25</sup> In a multicenter experience of Sofosbuvir based regimens in end stage renal disease, the researchers measured plasma levels of Sofosbuvir and its active metabolite and confirmed the accumulation of active metabolite in plasma but it didn't led to any clinically significant adverse effects. The success rate in this trail was 88%.<sup>26</sup>

Due to multiple co-morbidities in CKD patients, conducting safety trail is a challenging job.<sup>27</sup> Adverse effects profile of Sofosbuvir based regimen was good in our study population including minor side effects like insomnia headache and anemia. Anemia is a serious side effect especially in the context of renal failure, but it was observed in only 7% and it didn't lead to any drop out from the study or skip dose. Nazario et al stated results of 17 patients with CKD using full dose Sofosbuvir and Simeprevir in genotype 1 hepatitis C. All patients achieved SVR 12 and adverse effects were minor with just one patient receiving blood transfusion for anemia.<sup>24</sup> Anemia was noticed to be associated with the use of Ribavirin despite being used at lower doses.<sup>25</sup> Mostly the studies have used reduced dose (half or alternate day) of Sofosbuvir in these patients. In a multicenter observational prospective study, authors compared daily full dose of Sofosbuvir with thrice weekly dose and it was noticed that Sofosbuvir itself or its inactive metabolite didn't accumulate in plasma with either regimen in between the dialysis session and drug was well tolerated by the study population. However, it was noticed that in thrice weekly dose group 2 patients relapsed as compared to none in the daily dose group.<sup>28</sup> Cox-NP and colleagues in a retrospective study using Sofosbuvir and Ribavirin in patients with severe renal dysfunction including on dialysis patients reported SVR 12 rates of 97%. Out of all 29 patients, only 4 developed anemia which in 3 patients responded to dose reduction of Ribavirin and erythropoietin stimulating factors, while in 1 patient they had to discontinue the drug. They also

reported that patients who were not on dialysis showed no significant difference in pre-treatment and post-treatment levels of eGFR and creatinine as seen in our study.<sup>29</sup> Results from a French study published in 2016 showed Sofosbuvir based regimen in CKD patients are well tolerated. Other than anemia, the adverse effects noted were headache (32%), asthenia (28%), digestive discomfort (20%) and insomnia (16%).<sup>26</sup>

## CONCLUSION

In conclusion, we state that all Sofosbuvir based regimens used for the treatment of chronic hepatitis C in patients with end stage renal disease are effective and well tolerated. A close follow up in such patients is advised especially to monitor hemoglobin levels and renal functions.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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