NOVEL DIRECT ACTING ANTIVIRAL REGIMENS FOR PATIENTS WITH CHRONIC HEPATITIS C AND CHRONIC KIDNEY DISEASE STAGE 3 TO STAGE 5D

Nauman Kashif, Zahid Farooq Baig, Shahzad Ashraf*

Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan, *Combined Military Hospital Multan/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To assess the safety and efficacy of Sofosbuvir based Antiviral regimens for chronic hepatitis C virus infected patients with chronic kidney disease stage 3 to stage 5D on haemodialysis.
Study Design: Quasi experimental study.
Place and Duration of Study: Nephrology Department, Combined Military Hospital Lahore, from Dec 2018 to Dec 2019.
Methodology: Fifty patients of chronic kidney disease with stage 3 to stage 5D suffering from chronic hepatitis C were selected. Among them 30 patients were stage 3 to stage 5ND pre-dialysis patients while 20 were patients of End Stage Renal Disease (ESRD) on maintenance haemodialysis. Antiviral treatment consisted of Peg Interferon with Sofosbuvir and Ribavirin, Peg Interferon with Sofosbuvir, Ledipasvir with Sofosbuvir, Velpatsvir with Sofosbuvir and Daclatasvir with Sofosbuvir for 12 weeks. The assessments were conducted at baseline, weeks 2, 4, 8 and 12 on treatment and 12 weeks after treatment.
Results: Sustained Virologic Response (SVR) was 96.8% for group treated with Ledipaspavir, Velpatsvir or Declatasvir with Sofosbuvir and 88.9% of patients in Peg IFN/Sofosbuvir/Ribavirin treated group achieved Sustained Virologic Response. Majority (90%) of the participants experienced adverse effects. Two (4%) patient on haemodialysis had treatment discontinuation due to side effects. Dose of Ribavirin was reduced in 4 (8%) patients on haemodialysis during antiviral therapy. Two deaths occurred during the study while on treatment and one death occurred four days after renal transplant.
Conclusion: Sofosbuvir based antiviral regimens i.e. Peg Interferon with and without Ribavirin, Ledipasvir, Velpatsvir and Declatasvir for chronic Hepatitis C infected chronic kidney disease patients including haemodialysis patients, are well tolerated, effective and safe for treatment.

Keywords: Chronic Hepatitis C, Chronic kidney disease, Direct acting antiviral, Sofosbuvir.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is the commonest liver disease in patients with Chronic Kidney Disease (CKD). The infection prevalence varies worldwide, with a higher proportion of infected patients in low income countries. Almost 180 million individuals, making 3% of global population, are presently infected with HCV infection[1]. The prevalence among CKD patients is significantly higher than in general population, from 10% to as high as 59%, depending upon geographic area[2,3]. HCV infection is manifested with various hepatic complications such as hepatic decompensation, liver cirrhosis and hepato-cellular carcinoma. The most important extrahepatic manifestation of HCV infection is the kidney disease[4].

HCV infection may occur as a result of CKD treatment. Haemodialysis, lack of screening of blood transfusion products and inadequate sterilization techniques are important risk factors for HCV infection[5]. The stage and severity of renal disease depends on amount of HCV viral load. The chronic infection with HCV may result in poor outcomes in individuals with CKD and patients suffering from renal disease and HCV have higher mortality, hospitalization rate and poor quality of life scores as compared to individuals with only renal impairment[6].

Correspondence: Dr Nauman Kashif, Classified Medical Specialist & Nephrologist, CMH Lahore Pakistan
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Treatment of HCV infection among the general population has progressed over the last decade. This also pertains to treatment in early CKD patients. Sustained viral response (SVR) has increased progressively from 40–50% with Peg IFN and Ribavirin to >95% with the current direct-acting antiviral agents (DAAs)[7]. Importantly, DAA regimens are for shorter durations and have much improved tolerance. CKD patients with an estimated glomerular filtration rate (eGFR) >30 ml/min/1.73m^2, can be treated with any DAA regimen. In CKD stages 4-5, and especially in dialysis patients, progress in HCV treatment has been much slower. Untill now, treatment options in patients with impaired renal function were limited to Pegylated interferon (dose adjusted with reduced GFR) combined with (low-dose) Ribavirin (RBV). SVR rates with the Peg IFN and ribavirin combinations were around 40%, but side effect with this treatment required frequent early discontinuation and resulted in high failure rates and treatment-related mortality; consequently, only few HCV-infected ESRD patients on maintenance hemodialysis could be offered treatment[8].

One of the most important direct acting antiviral agents (DAA) is Sofosbuvir (SOF). It is a potent inhibitor of the HCV NS5b polymerase, which has pan-genotypic activity with decreased development of resistance, and is the backbone of most of treatment regimens. Moreover, it has good tolerability and efficacy with limited potential towards drug - drug interaction. Metabolism of Sofosbuvir takes place in liver resulting in biotransformation to nucleotide analog uridine triphosphate. The NS5B is a non-structural protein, which is important for viral RNA replication of Hepatitis C virus, the target of DAA. The uridine triphosphate analog hinders NS5B polymerase completely, resulting in encumberance of HCV RNA synthesis through RNA chain termination. Dephosphorylation results in formation of inactive metabolite of Sofosbuvir, which has minimum binding capacity in human plasma. The inactive metabolite of Sofosbuvir is removed through renal route[9].

The pharmacokinetic profile results in problems towards managing HCV infected individuals with CKD. Since Sofosbuvir has renal route of excretion, up to now little data has been reported regarding its antiviral efficacy and safety in HCV-infected patients with GFR <30 ml/min. Other antivirals are eliminated mainly from the gastrointestinal system, and dose reduction is not required[7]. The metabolite of Sofosbuvir, GS-331007, accumulates in patients with severe renal impairment or ESRD, which was the reason in the exclusion of these patients in previous studies and lack of dosing recommendations. However, new clinical trials in patients with ESRD on maintenance haemodialysis demonstrate frequent use of Sofosbuvir based regimens in these patients, with no safety concerns established[10]. In many countries, due to lack of international guidelines, direct acting antiviral agents are not completely implemented by healthcare system in patients on hemodialysis.

The present study aimed to assess 2 dosing regimens for HCV infected individuals suffering from CKD stage 3 to stage 5 and requiring hemodialysis, i.e., sofosbuvir in combination with PegIterferon or Declatasvir, Ledipasvir and Velpatsvir.

METHODOLOGY

This quasi experimental study was conducted from December 2018 to December 2019. Fifty patients of chronic kidney disease with stage 3 to stage 5D (on hemodialysis) suffering from chronic hepatitis C reporting to Nephrology department Combined Military Hospital Lahore were enrolled over a period of one year, in which men and women with age range of 18 to 70 years were enlisted via non-randomized convenience sampling. The CKD patients suffering from chronic HCV infection with genotypes 1 to 6, treatment naïve or previously treated chronic HCV infection, without or with compensated cirrhosis were included. Previous treatment with any DAA drug was part of exclusion criteria. The informed consents were collected from all the participants. Study design was approved from

hospital ethics review board vide certificate no. 148/2020.

The participants were suffering from HCV infection and CKD stage 3 to 5 including haemodialysis patients using Cockroft Gault eGFR formula. Among them 30 patients were stage 3 to stage 5 predialysis patients while 20 were patients of End Stage Renal Disease (ESRD) on maintenance haemodialysis. They were started with various treatment regimens as shown in table-II. One group received recommended Peg Interferon 135 ug subcutaneously once a week along with Tab Sofosbuvir 400 mg daily and Tab Ribavirin 400 mg daily for CKD stage 3 to stage 5ND predialysis patients and Tab Ribavirin 200 mg daily for CKD 5D haemodialysis patients for 12 weeks. A sub group of this cohort was offered Peg IFN 135 ug subcutaneously weekly with Sofosbuvir 400 mg daily without Ribavrin. The others received Tab Ledipasvir 90 mg or Tab Velpatsvir 100 mg or Tab Daclatasvir 60 mg along with Tab Sofosbuvir 400 mg daily as single pill combination for 12 weeks. Baseline complete blood counts, liver functions, renal functions, Anti-HCV antibodies, Ultrasound abdomen and quantitative PCR for HCV RNA and genotype were carried out. The assessments were conducted at baseline, weeks 2, 4, 8 and 12 on treatment and 12 weeks after treatment. The patients were not randomized in different treatment groups which did not allow comparisons bet-ween treatment regimens.

Physical examinations was conducted on each visit to clinic. Clinical examination, laboratory tests and monitoring of adverse events was performed more frequently for patients on haemodialysis. The statistical analysis was performed with the help of SPSS v.17.

RESULTS

In total, 50 patients suffering from chronic HCV infection and CKD were enrolled for the study. The mean age of patients was 45 yrs ± 13 SD; males were 32 (64%) and females 18 (36%). Majority of the patients had genotype 3 (36%) or 2 (30%) as shown in table-I. The mean HCV RNA level was found to be 4.9 log 10 IU/ml ± 2.6 SD. The majority of the patients included in study were suffering from co-morbidities such as hypertension, diabetes mellitus, ischemic heart disease such as coronary artery disease, cardiomyopathy, cardiac failure, and peripheral vascular disease. About 70% of study participants were on calcium channel blockers, 40% were on beta blockers, 45% on nitrates, statins and aspirin.

Table-I: Characteristics of patients.

Characteristics	Frequency
Age (years)	45 ± 13 SD
Gender	
Male	32 (64%)
Female	18 (36%)
CKD Stage	
CKD 3 (eGFR 30-60 ml/min)	12 (24%)
CKD 4/5 ND (eGFR<30 ml/min)	18 (36%)
CKD 5D/ESRD (dialysis)	20 (40%)
Cirrhosis (compensated)	12 (24%)
Genotypes	
1a, 1b	11 (22%)
2a, 2b	15 (30%)
3a, 3b	18 (36%)
4	3 (6%)
5	-
6	3 (6%)
HCV RNA level	4.9 log 10 IU/ml + 2.6 SD
Treatment Naive	34 (68%)
Previous Treatment	16 (32%)

Table-II: Treatment regimens.

Antiviral Regimens	Frequency
PEG-Interferon/ Sofosbuvir/Ribavirin	12 (24%)
PEG-Interferon/Sofosbuvir	6 (12%)
Velpatsvir/Sofosbuvir	14 (28%)
Ledipasvir/Sofosbuvir	12 (24%)
Daclatasvir/Sofosbuvir	6 (12%)

Out of 50 patients, 47 (94%) achieved Sustained Virologic Response (SVR) after 12 weeks of treatment and 3 (6%) patients had virologic failure as shown in table III. SVR was 96.8% for group treated with Ledipaspavir, Velpatsvir or Declatasvir with Sofosbuvir and 88.9% of patients in Peg IFN/Sofosbuvir/RBV treated group achieved SVR. Majority (90%) of the participants

experienced adverse effectsas shown in table-IV. The mild common adverse effects were observed to be nausea 15 (30%), headache 12 (24%), vomiting 08 (16%), insomnia 20 (40%) and fatigue 16 (32%). Anaemia was a prominent finding occurring in 32 (64%) during treatment particularly in Peg IFN/Ribavirin treated group requiring escalation of dose of recombinant erythropoietin, particularly in CKD patients on haemodialysis.

Table-III: Treatment response.

	Sustained Virologic Response	n	%
Overall	47	50	94
Virologic failure	3	50	6
Peg-Interferon/ Sofosbuvir +/- Ribavirin	16/18	50	88.9
Velpatsvir/Ledipasvir/Daclatasvir + Sofosbuvir	31/32	50	96.8

Table-IV: Adverse effects.

	Frequency	Percentage
Adverse effects	45	90
Anaemia	32	64
Thrombocytopenia	28	56
Leucopenia	18	36
Headache	12	24
Fatigue	16	32
Fever	10	20
Myalgia	15	30
Arthralgia	14	28
Nausea	15	30
Vomiting	08	16
Insomnia	20	40
Blood Transfusion	15	30
Depression	13	26
Treatment Discontinuation	02	4
Death	03	6

Two patients had to discontinue Peg IFN/SOF/ RBV because of severe anaemia whose baseline Hb was 8 mg/dl before start of treatment and was suffering from multiple comorbidities and extreme of age. There was no treatment discontinuation in other group. Blood transfusion in form of Red Cell Concentrate was required in 15 (30%) patients, all were on maintenance haemodialysis. The dose of RBV was required to be reduced in 2 patients undergoing haemodialysis to 200 mg three times a week and required discontinuation of RBV in 2 patients on account of Anaemia. Two deaths occurred during the study because of complications of vascular access and Ischemic heart disease while on treatment and one death occurred after achieving End of Treatment Response (ETR) on DAC/SOF regime, four days after renal transplant.

DISCUSSION

In CKD patients, acute HCV infections may remain asymptomatic with mild alanine aminotrnsferase (ALT) eleavation which is followed by seroconversion in 90% of cases, one to six months later[11]. Usually less than 5% of patients on haemodialysis clear HCV infection without treatment therefore, acute infections may need to be treated as soon as the diagnosis is established[11,12]. Importantly, HCV infection is characterized by intermittent HCV viremia in hemodialysis patients. This may result in false negative results in HCV RNA assays and also contributes to transmission of HCV infection in dialysis units[13].

The present study is an effort towards comparing two important regimens of Sofosbuvir for HCV infected patients suffering from moderate to advanced CKD including hemodialysis patients. This study is important as only few research works have been published that evaluate this particular population for sofosbuvir containing regimen. The SVR rate was found to be achieved by 94% patients. Three patients had virologic failure and relapsed; two of them had cirrhosis and belonged to peg-interferon group and one with daclatasvir and sofosbuvir group.

Anaemia and increased requirement of blood transfusion could not be attributed entirely to adverse reaction to drugs as the blood transfusion was mostly required for CKD patients on maintenance haemodialysis whose anaemia depends on multiple factors e.g. adequacy and frequency of dialysis, nutritional status and comorbidities. Overall the treatment of Sofosbuvir with either Peginterferon or Declatasvir/ Ledi-

pasvir/Velpatsvir was safe and well tolerated. However, in terms of efficiency, treatment with sofosbuvir in combination with Declatasvir/ Ledipasvir/velpatsvir was better. This is in accordance with the previous research work by Dumortier *et al* that documents high SVR rates with good overall tolerance, safety and efficacy. The real world uses of these medications are also devoid of any safety concerns[14].

Bhamidimarri *et al* has shown that the plasma concentration of Sofosbuvir in patients with ESRD is more as compared to individuals with normal renal function. It has also been noted that reduced and adjusted dose of Sofosbuvir can result in treatment failure[15]. The results of this study were comparable to Beinhardt *et al* who achieved SVR of 96% in patients with ESRD on maintenance hemodialysis with majority of patients tolerating full dose of Sofosbuvir well, without much safety concerns[8].

The results of present study were better than study conducted by Saxena *et al* who achieved a SVR of 83% in patients of CKD with eGFR <45 ml/min treated with Sofosbuvir containing regimens and with higher rate of anaemia and worsening of renal function[16].

A high rate of SVR was achieved in a large multicenter Polaris 2 and Polaris 3 trials and showed good safety and efficacy of DAA in chronic HCV infection without and with compensated cirrhosis in advanced CKD patients[17]. The result of this study were comparable to Borgia *et al* in which, treatment with full dose sofosbuvir in patients with ESRD on maintenance haemodialysis resulted in a SVR rate of 95%[18].

It can be said that sofosbuvir can act as an alternative option for HCV infected patients with CKD and on hemodialysis. However, close monitoring of patients is required along with cardiac, biological and clinical surveys. Drug monitoring is also essential for safety of treatment. As use of Sofosbuvir in HCV patients with hemodialysis and CKD is not clearly recommended, further clinical trials with prospective research work needs to be conducted to explore this area of research.

The present study was limited in terms of number of patients and patients with decompensated liver disease were excluded from the study, which restricted generalizability of findings of present study.

CONCLUSION

Sofosbuvir based antiviral regimens i.e. Peg Interferon with and without Ribavirin, Ledipasvir, Velpatsvir and Declatasvir for chronic Hepatitis C infected chronic kidney disease patients including haemodialysis patients, are well tolerated, effective and safe for treatment.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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