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COMPARISON OF NEW DIRECTLY ACTING ANTIVIRALS WITH PEGINTERFERON IN COMBINATION WITH SOFOSBUVIR FOR THE TREATMENT OF CHRONIC HCV INFECTION IN CHRONIC KIDNEY PATIENTS BOTH PRE-DIALYSIS AND ON DIALYSIS

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Abstract:

The HCV infection has a unique association with chronic kidney disease (CKD). The study was conducted from 20 January 2018 to 20 January 2019. The patients from different hospitals of Lahore were included, in which men and women with age range of 18 to 80 years were present. The medication was administered as 400mg/100mg tables once daily for 12 weeks. The assessments were conducted at screening, baseline, weeks 2, 4, 8, and 12 for on treatment and weeks 4 and 12 after treatment. Out of 100 patients, 97 (97%) achieved SVR 12 after 12 weeks of treatment. Majority (80%) of the participants experienced adverse effects; however, these were mild or moderate in severity. The findings of present study recommend use of both types of medications used, that is, peginterferon with sofosbuvir and Declatasvir/Ledipasvir with sofosbuvir for HCV infected patients with CKD. These medications are well tolerated, effective and safe for treatment of 12 weeks.

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INTRODUCTION:

Hepatitis C virus (HCV) infection is responsible for causing mortality and morbidity in various countries. It is an important indicator of liver transplantation also (Fabrizi et al. 2015). Only in United States, its prevalence is estimated to be 2.7 to 3.5 million, which is on further increase. Almost 180 million individuals, making 2.8% of global population, are presently infected with HCV (Beinhardt et al. 2016). HCV infection is manifested with various hepatic complications such as hepatic decompensation, liver cirrhosis, hepatocellular carcinoma (Hundemer et al. 2015). Other manifestations such as renal, metabolic, autoimmune, cardiovascular, central nervous system and lymphoproliferative disorders may also be apparent. The most important extrahepatic manifestation of HCV infection is the kidney disease (Feld et al. 2015).

The HCV infection has a unique association with chronic kidney disease (CKD). Natural history of one disease can result into the other one. HCV may cause CKD through mechanisms such as immune complex–mediated glomerulonephritis, extrahepatic manifestations of cirrhosis and cryoglobulinemic vasculitis with renal involvement (Singer et al. 2016). Recent research works have indicated that viral load of HCV has direct association with development of renal disease. The stage and severity of renal disease depends on amount of HCV viral load (Nazario et al. 2016). The individuals having viral load of more than 167,000 IU/mL are three times more prone towards development of end stage renal disease as compared to patients with low viral loads. On the other hand, HCV infection may occur as a result of CKD treatment (Bhamidimarri et al. 2015). Dialysis, lack of screening of blood transfusion products and inadequate sterilization techniques are important risk factors for HCV infection (Rogal et al. 2016).

The chronic infection with HCV may result in poor outcomes in individuals with CKD (Jacobson et al. 2017). A previous study has indicated that patients suffering from renal disease and HCV had higher mortality, hospitalization rate and poor quality of life scores as compared to individuals with only renal impairment (Park et al. 2015). HCV infection may also result in CKD stage progression, which may result into end stage renal disease (ESRD). A study notified that individuals suffering from HCV infection and CKD has low mean time for progression of CKD as compared to people with only CKD (Fabrizi et al. 2007).

The treatment options of HCV have changed management approach towards HCV infected patients with CKD. One of the important choices of HCV treatment is direct acting antiviral (DAA) agents (Saxena et al. 2016). The safety and efficacy of DAA agents have widely been studied. The old and conventional interferon-based therapy for HCV infection has reported to have poor tolerability and low virologist response rate in CKD patients (Molnar et al. 2015). In treating HCV patients suffering from CKD, which is a difficult to treat population, DAA agents are highly recommended (Lee et al. 2014).

One of the most important direct acting anti-HCV agents (DAA) is sofosbuvir. It is a nucleotide analog and inhibitor of the HCV NS5B polymerase. It prohibits genotype 1-6 HCV-RNA replicons in vitro. It has high genetic hinderance to resistance. Moreover, it has good tolerability and efficacy with limited potentiality towards drug to drug interaction. It is available as a small tablet with high solubility and low permeability. Sometimes, it is available in combination with NS5A inhibitor ledipasvir. After intake of tablet, sofosbuvir is absorbed efficiently with peak plasma concentration formed at about 0.5 to 2 hours after dose. Metabolizes of sofosbuvir takes place in liver resulting in bio-transformation to nucleotide analog uridine triphosphate in hepatocytes. The NS5B is a non-structural protein, which is important for viral RNA replication of Hepatitis C virus, has been found to be a significant target of DAA. The uridine triphosphate analog hinders NS5B polymerase completely, resulting in encumberance of HCV RNA synthesis through RNA chain termination. The catalytic site of enzyme is highly conserved in all the genotypes of HCV, which indicates genotypic efficacy of sofosbuvir. Dephosphorylation results in formation of inactive metabolite of sofosbuvir, which has minimum binding capacity in human plasma. The plasma protein binding of sofosbuvir is approximately 82% in healthy individuals and 85% in people suffering from end stage renal disease (ESRD). The inactive metabolite of sofosbuvir is removed through renal route.

The pharmacokinetic profile results in problems towards managing HCV infected individuals with CKD. Despite the importance of sofosbuvir, meager data has been published regarding sofosbuvir based regimen for such patients. Consequently, there is a lack of proper recommendations for sofosbuvir based regimen for patients on hemodialysis due to non-existenece of efficacy and safety evaluation in this particular population. In many countries, due to lack of international guidelines, direct acting antiviral agents are not completely implemented by healthcare system in patients with hemodialysis. Thus, the present study aimed to assess 2 dosing regimens for HCV infected individuals suffering from CKD and requiring hemodialysis, i.e., sofosbuvir in combination with Peginterferon or Declatasvir/Ledipasvir

METHODOLOGY:

The study was conducted from 20 January 2018 to 20 January 2019. The patients from different hospitals of Lahore were included, in which men and women with age range of 18 to 80 years were present. The participants were suffering from HCV infection and CKD. All the patients were on haemodialysis. The patients with treatment naïve or treatment experienced HCV were included. Previous treatment with any HCV inhibitor was part of exclusion criteria. The informed consents were collected from all the participants.

The participants were divided in two groups. One group was administered with Peginterferon in combination with sofosbuvir, whereas, the other group was given Declatasvir/Ledipasvir in combination with sofosbuvir. The medication was administered as 400mg/100mg tables once daily for 3 months (12 weeks). The assessments were conducted at screening, baseline, weeks 2, 4, 8, and 12 for on treatment and weeks 4 and 12 after treatment.

The plasma concentrations of medications were assessed through high performance liquid chromatography. In order to measure serum HCV RNA, COBAS TaqMan HCV test was used. The genotypes and subtypes of HCV were determined through BLAST analysis of NS5A and NS5B sequences. DDL was used for deep sequencing of NS5A and NS5B regions to identify resistance-associated substitutions (RASs). Physical examinations were conducted on start, week 12 and post treatment visits. Moreover, clinical laboratory tests, monitoring of adverse events and vital sign measurements were performed. The statistical analysis was performed with the help of SPSS v.17.

RESULTS:

In total, 100 patients suffering from HCV infection and CKD were enrolled for the study. The mean age of patients was 62 ± 12 (18-80) years, with 60% male and 40% female patients. 30% patients had cirrhosis. Majority of the patients had genotype 1 (30%) or 3 (25%) HCV infection. The mean HCV RNA level was found to be 4.9 log 10 IU/ml with range of 3.2 to 7.6 log 10 IU/ml. The majority of the patients included in study were suffering from co-morbidities such as hypertension, diabetes, vascular disorders, cardiac issues such as cardiomyopathy, cardiac failure, and coronary artery disease. About 50% of study participants were on calcium channel blockers, 40% were on beta blockers, as shown in the Table 1.

Table 1: Characteristics of patients

Characteristics	Frequency
Age (years)	62 ± 12 (18-80)
Gender	
Male	60 (60%)
Female	40 (40%)
Cirrhosis	30 (30%)
Genotypes	
1	30 (30%)
2	10 (10%)
3	25 (25%)
4	20 (20%)
5	5 (5%)
6	10 (10%)
HCV RNA level	4.9 (3.2-7.6) log 10 IU/ml

Out of 100 patients, 97 (97%) achieved SVR 12 after 12 weeks of treatment, as shown in the Table 2. All the patients who achieved SVR 12, showed study drug adherence rates of more than 90%, which was measured by pill counts. The patients who did not achieved SVR 12 showed virologic relapse at week 4, after treatment as shown in the Table 2. On treatment virologic failure was not evident and plasma levels for HCV RNA were observed to decline massively during treatment.

Table 2: Treatment response

	Frequency	Percentage
SVR 12	97	97%
Virologic failure	3	3%

All the patients were included in the resistance analysis population. It was observed that 60% patients had NS5A and 40% had NS5B nucleotide inhibitor RAS at baseline. Majority (96%) of patients for both categories achieved SVR12.

The adverse events experienced by participants are shown in the Table 3. Majority (80%) of the participants experienced adverse effects; however, these were mild or moderate in severity. The most common adverse effect was observed to be nausea (15%), followed by headache 913%), vomiting (12%), insomnia (10%) and fatigue (10%). Although 2 patients (2%) were observed with serious adverse effects, they were not related to study treatment. No patient discontinued treatment due to adverse effects. No adverse effects took place due to renal dysfunction and no deaths occurred during the study.

Table 3: Adverse effects

	Frequency	Percentage
Adverse effects	82	82%
Headache	13	13%
Fatigue	10	10%
Nausea	15	15%
Vomiting	12	12%
Insomnia	10	10%

DISCUSSION:

The present study is an effort towards comparing two important regimens of sofosbuvir for HCV infected patients, suffering from CKD and on hemodialysis. This study is important as only few research works have been published that study this particular population for sofosbuvir containing regimen.

The use of sofosbuvir in individuals on or requiring hemodialysis can result in sofosbuvir accumulation and adverse side effects due to its renal route of elimination. Previous research works have shown that in patients with ESRD, and taking in sofosbuvir, the plasma concentration of sofosbuvir 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. Most of the research works have not pointed out towards pharmacokinetics relation in HCV genotypes. However, some studies performed on HCV genotype 3, have indicated low SVR rates and pharmacokinetics to be linked especiall in hemodialysis, non-responding and relapse patients.
In the present study, sofosbuvir plasma concentrations were not detectable before or after the treatment. As the patients received multiple doses of the medication during hemodialysis, no accumulation of sofosbuvir occurred for both the comparative regimens during the treatment period. These findings suggest higher intake of sofosbuvir with high efficacy of hemodialysis in removing the inactive form of sofsbuvir, which is in accordance with the previous research works. The plasma concentration of inactive form of sofosbuvir is higher than the normal renal patients due to renal route being the major way of eliminating it.

The SVR12 rate was found to be achieved by 97% patients. Three patients had virologic failure and relapsed with NS5A resistance. All of them had cirrhosis and belonged to group of sofosbuvir in combination with peginterferon. No serious adverse effects were observed in participants and consequently no treatment related discontinuation occurred during the study. In order to avoid risk of bradycardia or heart attack, patients receiving amiodarone were not included. Resultantly, no cardiac adverse event occurred in both the groups.
Overall the treatments of sofosbuvir with either with Peginterferon or Declatasvir/Ledipasvir were safe and well tolerated. However, in terms of efficiency, treatment with sofosbuvir in combination with Declatasvir/Ledipasvir was better. This is in accordance with the previous research works 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 (Dumortier et al. 2017).

It can be said that sofosbuvir can act as an alternative option for HCV infected patients with hemodialysis and CKD. 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 works needs to be conducted to explore this area of research.

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

CONCLUSION:

The findings of present study recommend use of both types of medications used, that is, sofosbuvir with peginterferon and sofosbuvir with Declatasvir/Ledipasvir for HCV infected patients with CKD. These medications are well tolerated, effective and safe for treatment of 12 weeks.

REFERENCES:

1. Beinhardt, S, AlZoairy, R, Ferenci, P, Kozbial, K, Freissmuth, C & Stern, R 2016, 'DAA-based antiviral treatment of patients with chronic hepatitis C in the pre- andpostkidney transplantationsetting', *Transpl Int*, vol 29, pp. 999–1007.
2. Bhamidimarri, K, Czul, F, Peyton, A, Levy, C, Hernandez, M & Jeffers, L 2015, 'Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of hepatitis C in patients with end stage renal disease', *J Hepatol*, vol 63, pp. 763–765.
3. Dumortier, J, Bailly, F, Pageaux, G, Vallet-Pichard, A, Radenne, S & Habersetzer, F 2017, 'Sofosbuvir-based antiviral therapy in hepatitis C virus patients with severe renal failure', *Nephrol Dial Transplant*, vol 32, no. 12, pp. 2065–2071.

4. Fabrizi, F, Takkouche, B, Lunghi, G, Dixit, V, Messa, P & Martin, P 2007, 'The impact of hepatitis C virus infection on survival in dialysis patients: metaanalysis of observational studies', *J Viral Hepat*, vol 14, no. 10, pp. 697–703.
5. Fabrizi, F, Verdesca, S, Messa, P & Martin, P 2015, 'Hepatitis C virus infection increases the risk of developing chronic kidney disease: a systematic review and meta-analysis', *Dig Dis Sci*, vol 60, no. 12, pp. 3801–3813.
6. Feld, J, Jacobson, I, Hezode, C, Asselah, T, Ruane, P & Gruener, N 2015, 'Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection', *N Engl J Med*, vol 373, pp. 2599–2607.
7. Foster, G, Afdhal, N, Roberts, S, Brau, N, Gane, E & Pianko, S 2015, 'Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection', *New Engl J Med*, vol 373, no. 27, pp. 2608–2617.
8. Hundemer, G, Sise, M, Wisocky, J, Ufere, N, Friedman, L & Corey, K 2015, 'Use of sofosbuvir-based direct-acting antiviral therapy for hepatitis C viral infection in patients with severe renal insufficiency', *Infect Dis*, vol 47, pp. 924–929.
9. Jacobson, I, Lawitz, E, Gane, E, Willems, B, Ruane, P & Nahass, R 2017, 'Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials', *Gastroneterology* , vol 153, pp. 113–122.
10. Lee, J, Lin, M, Chang, J, Hung, C, Chang, J & Chen, H 2014, 'Hepatitis C virus infection increases risk of developing end-stage renal disease using competing risk analysis', *PLoS ONE*, vol 9, no. 6, p. e100790.
11. Molnar, M, Alhourani, H, Wall, B, Lu, J, Streja, E & Kalantar-Zadeh, K 2015, 'Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans', *Hepatology*, vol 61, no. 5, pp. 1495–1502.
12. Nazario, H, Modi, A, Ndungu, M, Ramirez, R, Tujague, L & Weinstein, J 2016, 'Sofosbuvir-based, ribavirin-free regimens in patients with chronic hepatitis C and end-stage renal disease: a look at safety, tolerability and efficacy', in *European Association for the Study of the Liver (EASL)*, Barcelona, Spain.
13. Park, H, Adeyemi, A, Henry, L, Stepanova, M & Younossi, Z 2015, 'A meta-analytic assessment of the risk of chronic kidney disease in patients with chronic hepatitis C virus infection', *J Viral Hepat*, vol 22, no. 11, pp. 897–905.
14. Rogal, S, Yan, P, Rimland, D, Lo, RA-RH & Fried, L 2016, 'Incidence and progression of chronic kidney disease after hepatitis C seroconversion: results from ERCHIVES', *Dig Dis Sci*, vol 61, no. 3, pp. 930–936.
15. Saxena, V, Koraishy, F, Sise, M, Lim, J, Schmidt, M & Chung, R 2016, 'Safety and efficacy of sofosbuvir-containing regimens in hepatitis C infected patients with impaired renal function', *Liver Int*, vol 36, pp. 807–816.
16. Singer AW, MB, Osinusi, A, Brainard, D, Littman, M & Troostendburg, V 2016, 'Direct-acting antiviral treatment patterns among hepatitis C patients with advanced chronic kidney disease: a retrospective cohort study', *Hepatology*, vol 62, no. 396A.