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# EFFECTIVENESS AND SAFETY OF SOFOSBUVIR AND VELPATASVIR IN HEMODIALYSIS PATIENTS SUFFERING WITH HEPATITIS C INFECTION

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**ABSTRACT:**

**BACKGROUND & OBJECTIVE**: There is scantiness of evidence-based knowledge of anti-viral therapy with sofosbuvir (SOF) and velpatasvir (VLP) in patients on maintenance haemodialysis. This report is an attempt to rationalise the safety and effectiveness of SOF and VLP in haemodialysis patients in Pakistan.
**METHODOLOGY**: Twenty treatment-naïve patients were incorporated in this study. Patients on maintenance haemodialysis are being administered SOF and VLP. Before initiation of treatment, all necessary investigations such as viral load, liver fibro scan, genotyping and upper GI endoscopy were made. Patients received 400 mg/day and 100 mg/day dose of SOF and VLP, respectively.
**RESULTS**: Mean age was 25 to 53 years; 30% were male and 70% were female as categorized. No one of these has clinical affirmation of progression of cirrhosis. The most prevalent genotype was genotype 4 that was found in 45% of cases and the second most evident was genotype 1 in 25% of cases and genotype 5 in 30% of cases. Time span of antiviral therapy was 12 weeks.
**CONCLUSION:** SOF and VLP based direct antiviral agents were effectual, puissant and were aptly tolerated in patients on MHD. This drug combination was well tolerated in haemodialysis patients. Not a single patient discontinued this combination therapy due to severe complications.
**KEYWORDS**: Sofosbuvir, Velpatasvir, MHD, Complications, Chronic.

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## INTRODUCTION:

Hepatitis C virus is the culprit of spreading lethal progressive infection and causes enormous social, financial and health burden globally [1,2]. The most frequent infection in patients on MHD is hepatitis C and prevalence rate is almost 6 to 60% [3]. The most usual determinants of the spread of this infection are nosocomial, transference through blood, transference & blood products [4,5].

This elevates the peril to serious infection in patients with renal transplant. HCV being a major issue in Pakistan dialysis centers, isolation of such patients is considered in addition to global safety measures. Regardless of all the precautionary measures taken, notable number of patients fall victim to HCV infections. Guidelines of kidney disease improving global outcomes have recommended the use of Interferon (IFN) before renal transplant to avoid the risk of transplant rejection. Due to evolution of direct antiviral therapy, anti HCV therapy has been altered dramatically. This newly introduced therapy has two major pitfalls; firstly, this is not universally accessible in all countries and secondly, dosage safety has not been established specifically in stage IV and V of chronic kidney disease patients. In Pakistan, the accessibility to SOF and VLP were in 2014 and 2015, since then they are typifying the accuracy of anti HCV therapy in patients on MHD[6]. The initial development of direct antiviral agent (DAA) was focused on genotype 1, and the majority of the available DAA regimens at that time were only effective in patients infected with genotypes 1 and 4. However, they have been approved in terms of safety and efficacy for all recognized genotypes as per the new trial [7]. Nowadays, there are DAAs approved for the treatment of patients on maintenance haemodialysis infected with HCV genotypes 1 and 4, in whom safety and efficacy was confirmed in prospective trials (paritaprevir/ ritonavir, ombitasvir, dasabuvir, or grazoprevir and elbasvir combinations[8-10]. Despite of incomplete particulars about safety and dosage profiles, this treatment should not be halted in this group of patients. Two important facets that supports in prime concern treatment are, high mortality rates in HCV infected patients on MHD [11-13] and secondly reactivation of virus under immunosuppressive drugs have negative influence on prognosis of patients. Given that, there is a lack of knowledge of combined use of SOF and VLP in our community. The subject of discussion here is safety and efficacy profile of treatment with this regimen in patients on MHD, and this is one of first clinical experiment and open label clinical study of Sofosbuvir and velpatasvir**.**

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## METHODOLOGY:

HCV infected patients who had history of renal disease and had undergone the dialysis treatment were being treated with antiviral therapy. Patients who had positive anti HCV antibodies were additionally enquired for qualitative HCV RNA and HCV viral load. Before starting the treatment regimen, their complete blood profile was taken and haemoglobin levels, total leucocyte count, Retic count and alpha fetoprotein were evaluated.

20 patients (6 male and 14 female) with history of renal disease were assessed for treatment with anti HCV agents in OPD from June, 2017 to September, 2018. All of them had to undergo dialysis once a week and there was no history of renal transplant in any of them. Starting range of viral load in blood was 120,000 to 11,000,000 IU/Ml.

Patients had abnormal values of liver enzyme, ALT due to HCV attack that was not exceeding more than 3 times the upper limit during therapy. As response to the treatment dose was safe, we initiated full dose therapy Velpatasvir 100 mg/d and SOF 400 mg/d for all viral genotypes.

Patients were advised to consult their doctor if they encounter any of the adverse effect by the drug. The biochemical tests were repeated after every week for first two weeks and then they were restated as per clinical manifestation. The follow up mode given to patients were weekly for the first month, then fortnightly in the second month and then by the end of 3$^{rd}$ month.

Duodecimal HCV RNA was assessed between 7th and 15th day after treatment was started, followed by repetition at end of the month, at termination of therapy and 12 weeks post therapy

The regimen consisted of 1 tablet each of 400mg SOF and 100mg VLP, administered daily in morning independent of dialysis session for duration of 12 weeks via non-probability consecutive sampling technique

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) Version 22 (IBM Corporation, Washington DC, United States). Categorical variables were reported as frequencies (percent-ages) and continuous variables as median (range). Categorical variables were compared using the $x^2$ or the Fisher's exact tests; continuous variables were compared using the Student's t test, the Mann-Whitney U test or the Kruskall-Wallis test, when appropriate. $p<0.05$ was considered statistically significant. All hypothesis tests were two-sided and conducted using a 0.05 significance level unless otherwise stated.

## RESULTS:

Statistically, 20 patients were treated with antiviral therapy from June 2017 to September 2018. Genotype 4, which is the most common genotype as compared to its variants in HCV positive patients, was evident in 45% of patients followed by the next commonly found genotype 1 and 5 in 25% and 30% patients, respectively. None of the patient had undergone liver biopsy and they had normal upper GI endoscopy. No one of them had elevated platelets level, elevated bilirubin levels, or clinically evident hepatitis at the start of treatment.

All patients were given this antiviral therapy for the duration of 12 weeks and 100% of patients' viral load was unnoticeable by 14th day. No significant difference was seen in response rates with respect to all mentioned genotypes. Patients who complained of relapse had one each of genotype 1 and genotype 4. All patients complained of fatigue and tiredness after initiation of treatment. Five percent patients required high dosage of erythropoietin (12,000U/week) with or without iron therapy parenterally. Maximum dose injected of erythropoietin was 16,000U/week in 5 (25%) of the patients. The biochemical profiles of other patients remained normal.

Laboratory findings after completion of the therapy gave this data; Mean haemoglobin of 11.6 g/dL, no elevation in serum bilirubin (0.7 mg/dL), overall improvement in liver enzymes; ALT, AST, ALP. None of the patients validated improvement in renal function at 3rd and 6th week except for 1 patient who lost his access to follow up. No remarkable difference in laboratory parameters was found, values are shown in tables-II and II.

**Table-I: Patient profile and baseline characteristics.**

| Characteristic | n (%) |
|---|---|
| **Age in years (Average)** | |
| **Mean ±SD** | **39±3.1** |
| **Range** | **25-53** |
| **Gender** | |
| Male | 6 (30) |
| Female | 14 (70) |
| **Body Mass index** | |
| Mean ±SD | 25± 2.3 |
| **Range** | **18-51** |
| **HCV Geno type** | |
| 1 | 5 (25) |
| 4 | 9 (45) |
| 5 | 6 (30) |
| Diabetes as native disease | 0 |
| HIV | 0 |
| Coronary artery disease | 0 |
| | **Mean (±SD)** |
| Serum Albumin in g/dL Mean (±SD) | 3.9± 0.03 |
| AST IU/Ml Mean ±SD | 41±0.01 |
| ALT IU/Ml Mean ±SD | 33±0.01 |
| Serum Creatinine mg/dl Mean ±SD | 5.4±0.03 |
| Hemoglobin in g/dLMean ±SD | 11.9±0.05 |
| Total bilirubin in mg/dl Mean ±SD | 0.8±0.03 |

**Table-II: Adverse events reported during the study period.**

| Variable | N | % |
|---|---|---|
| Discontinuation of treatment due to adverse effect | 0 | 0 |
| **Adverse Events** | | |
| Fatigue | 20 | 100 |
| Nausea | 18 | 90 |
| Headache | 17 | 85 |
| Insomnia | 4 | 20 |
| Pruritus | 2 | 10 |
| Anemia | 19 | 95 |
| Cough | 6 | 30 |
| Arthralgia | 9 | 45 |

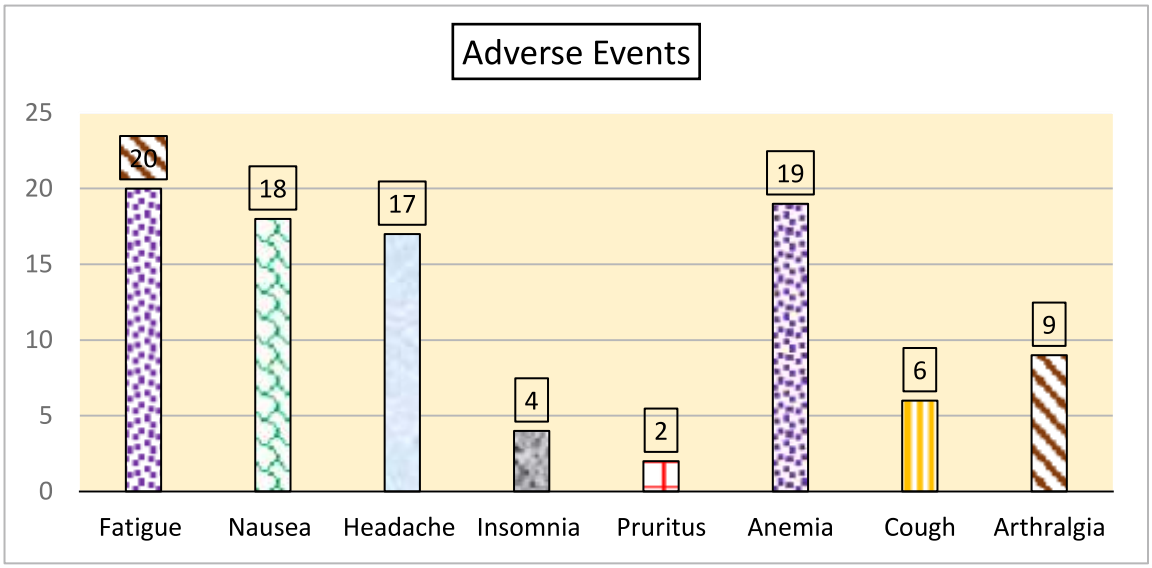


**Figure-I: Adverse events after drug use**

**Table-III: Showing treatment status of the patients.**

| Treatment status n (%) | | |
|---|---|---|
| Total Treatment | 20 | |
| Relapse | 3 (15) | ± 0.02 |
| Non responder | 0 | ± 0.00 |
| Partial Responder | 0 | ± 0.00 |

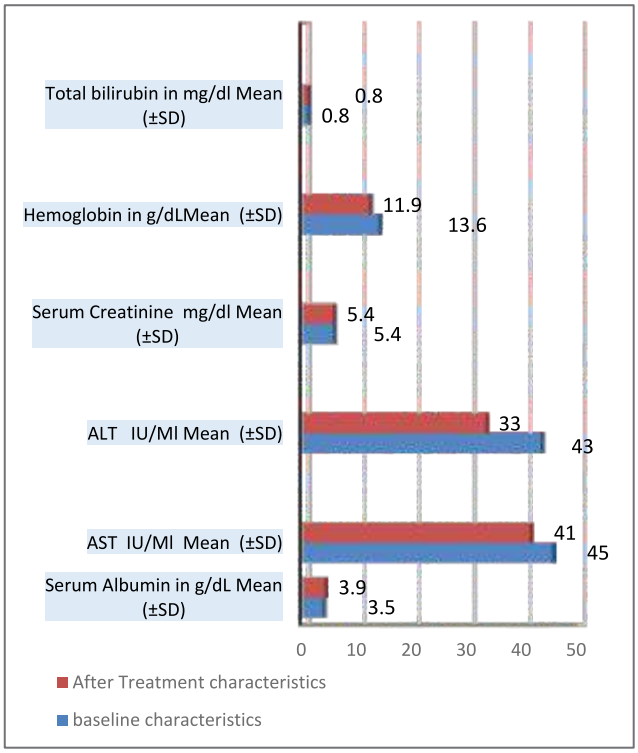


**Figure-II: Therapy efficacy before and after drug use**

## DISCUSSION:

This is first experimental study conducted in Pakistani (Lahore) population in which DAA drugs effect was notice in haemodialysis patients. This is more relevant in Pakistan, where most of the dialysis centre is treating patients with HCV infection. Considering the safety and efficacy of DAA drugs in haemodialysis patients with HCV infection is getting better

Most common adverse effects observed during the treatment regimen was fatigue, headache and nausea as reported in other studies of SOF therapy [14]. None of the patients put halt to treatment due to any side effect. Overall, this newly introduced combination was very well tolerated and was efficient in patients with chronic HCV infection. We studied recently published data in which Khan RA et al [15] treated 17 cases of haemodialysis dependent patients with 12 weeks of treatment with SOF and simeprevir regimen and showed effective response without any therapy related adverse effect. Another case study by Kalyan et al demonstrated 12 out of 15 cases with GT 1 on RRT and were given half dose SOF developed systemic vascular resistance (87%). Low systemic vascular resistance rates were almost every time related to underlying cirrhosis pathology.

Insignificant side effects that were complained by patients during therapy; headache in 17(85%), nausea in 18 (100%), insomnia in 4 (20%), arthralgia in 9(45%), cough in 6 (20%) of which 2 had history of chronic cough at treatment institution. 19 patients developed anaemia. No patient developed any serious adverse effect or any drug interaction with immunosuppressive agent. Our results were similar to some other studies conducted in Hepatitis C patients [8,13]. Hepatitis affects liver & alter various glycoproteins levels which can result in different pathophysiological process harmful for the body [1, 16]. It is very important to treat Hepatitis C virus infection with effective treatment without causing serious health problem.

## CONCLUSION:

According to our study use of DAA drugs especially SOF and VLP during haemodialysis is safe. It will boost the confidence of doctors in using this combination in clinical practice. A further study with large sample size is required to come to a definitive conclusion.

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**Author's Contribution:**

**Yasir Mehmood**: Conception, Design the study & reference collection.
**Muhammad Imran Ashraf:** Data collection & Analysis.
**Khadija Mastoor:** Drafting & Editing.
**Adnan Afzal:** Manuscript Writing.
**Zafar latif Awan:** Reference Collection.

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