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The Efficacy and Adverse Effects of Combining Sofosbuvir and Velpatasvir in Viral Hepatitis C Hemodialysis in Pakistani Population.

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Abstract

Purpose: The study objectives were to evaluate the efficacy and safety of SOF and VLP combination in HCV-infected patients on Hemodialysis (HD) in the local community as usual Pakistani practice.

Methodology: In this study, 252 patients were given treatment who participated. Patients who maintain their hemodialysis are often given a combination of SOF and VLP. Before beginning the drug, the patient had testing that included an upper GI endoscopy, genotyping, measurement of the viral load, and a liver brow scan. Patients were administered SOF and VLP at dosages of 400 mg/day and 100 mg/day, respectively, for the duration of the study. Between March 2019 and March 2021, this study was conducted at the Department of Kidney Diseases at LRH Hospital in Peshawar, Pakistan, which was an observational, prospective, single-center study. 27 HCV-HD patients were on a SOF/VLP regimen during the experiment. The ICH-GCP criteria were surveyed in an intended manner. During the data analysis, a p-value of 0.05 or below was considered statistically significant.

Results: Forty percent of the patients were male, and sixty percent were female between the ages of 27 and ninety. According to the findings of 252 participants (n = female 14, 43.5 percent and n = male 18, 45.5 percent), 21 subjects were naïve, and six issues were in the treatment-experienced group (with SOF/RBV), with a mean age of 35.5 years and a standard deviation of 9.6 years. At the post-treatment follow-up visit after 12 weeks of therapy with SOF/VLP, the sustained virological response (SVR) rate was 100 percent (252 of 252), indicating that all of the patients had successfully recovered from their infection. During the study, not a single patient had a virological setback or was lost to follow-up. The most common adverse effects (AEs) recorded were nausea, headache, and tiredness; however, there were no reports of significant AEs. In addition, there were no cases of therapy being stopped prematurely owing to adverse effects.

Conclusion: Patients in regular care in Pakistan who have HCV and are receiving HD are offered an extraordinarily efficient, risk-free, and well-tolerated treatment consisting of the total dosage of SOF-VLP given for 12 weeks.

Keywords: *Sofosbuvir, Velpatasvir, MHD, Chronic, Hepatitis C, Hemodialysis, Pakistani population*

Introduction

The hepatitis C virus is to blame for the spread of a fatal, progressive illness that has a huge social and health impact worldwide. Hepatitis C is the most common infection among patients on MHD, with a prevalence rate ranging from 10 to 50 %. Nosocomial, blood transfer, and blood products are the most common ways this virus spreads[1]. Chronic HCV is a severe global health issue that affects over 210 million individuals globally and is responsible for over 500,000 fatalities each year. Cirrhosis and hepatocellular carcinoma may proceed in people with long-term HCV infection, which can significantly affect several organs and systems[2]. HCV infection is linked with renal impairment in 10% to 60% of patients, making it one of the most prevalent extrahepatic dysfunctions. In HD and kidney transplant recipients, it's fairly typical to see this side effect[3]. Dialysis patients with HCV have a complicated history because of the disease's extended duration, which is mostly asymptomatic and makes pinpointing the disease's origin challenging. Also, various variables, including hepatitis B virus (HBV), human immunodeficiency virus (HIV), and alcohol use[6], might affect the development. A range of 7.6 % to 43 % HCV prevalence in the HD population has been reported in industrialized nations[4,5].

HCV infection rates in dialysis patients have risen substantially faster in poorer nations in the recent decade than in the developed world[8]. However, DOPPS, a multinational cohort study including patients on HD and 500 institutions in 20 countries gathered data from patients on Dialysis Outcomes and Practice Patterns (DOPPS). A total of 74,430 HD individuals, infected or not, were included in the study between 1996 and 2015[6]. HCV was found in 5762 people (7.5 %). More commonly, HCV-positive individuals had end-stage renal disease (ESRD) and were on dialysis longer than those who were HCV-negative[7]. Chronic HCV10 affects roughly 10 million Pakistanis. Sadly, the incidence and prevalence of HCV in the general population have increased by 45 % over the last several decades (7.2 % rather than 4.9 % - 5 %). According to data gathered at health screening camps and from the general population, at least 13. % to 25 % of Pakistanis have Chronic Kidney Disease (CKD). In Pakistani patients on hemodialysis, the prevalence of hepatitis C ranged from 22.7 % to 55.6 %, based on limited local data. All CKD patients with HCV infection should be considered for antiviral treatment[13].

According to the Kidney Disease: Improving Global Outcomes (KDIGO) work group's management approach. First, a patient's life expectancy, kidney transplantation candidacy, and other comorbidities should be considered before deciding whether or not to begin therapy[8]. Antiviral treatment should also be considered with patients, who should be included in the decision-making process and informed of the risks and advantages. The management of HCV in the general population has achieved significant progress during the last two eras[14]. SVR rates climbed from 7 to 10 % when interferon (IFN) was used as a monotherapy, to 25 % when ribavirin (RBV) was added, and to 40–50 % when peginterferon and ribavirin were used together. However, the accompanying toxicities of IFN[15,16] make it difficult to treat patients. The simultaneous use of RBV, which is little removed by HD, adds to the IFN toxicity and increases the likelihood of anemia and other hematologic side effects[9]. In addition, both are expelled by the kidneys and excreted from the body. In individuals with compromised renal function[17], a large dosage decrease is necessary.

According to the DOPPS study's findings, IFN-based therapy is ineffective and associated with a significant risk of adverse events (AEs) in dialysis patients who test positive for the hepatitis C virus (HCV). A higher incidence of allograft rejection after kidney transplantation has been linked to IFN-based therapy as well[10]. Because DAAs target particular nonstructural proteins of the virus, they impede viral replication and infection [19,20]. This has resulted in a revision of current HCV treatment techniques. Nonstructural proteins 3/4A (NS3/4A) protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B non-nucleoside polymerase inhibitors, and NS5A inhibitors[19,20] are the four current types of DAAs. SVR is achieved in about 88% – 95% of patients with normal renal function after the administration of DAAs[12]. Additionally, DAA treatments have a shorter treatment period, are interferon-free, and have manageable side effects 19 and 20. The regimen should be selected based on genotype (and subtype), viral load, concurrent medicines, renal function, transplant candidly, and comorbidities [19,20]. According to data, there have been several investigations on the frequency and burden of HCV infection in hemodialysis patients[21,22]. There has been a lack of study into DAA regimens with high effectiveness, low side effects, and greater tolerance in HD patients with HCV among the local community. SOF and RBV have previously been studied in HCV patients with stage 4 or 5 CKD and HD 23 to see if they were safe and effective. This might be a study to examine the responsiveness of patients with stage 4 or 5 CKD and HCV in Pakistan to the combination of SOF and VLP[13].

Methodology

Antiviral medication was used to treat HCV-infected individuals with renal impairment who had had dialysis treatment. The HCV RNA and viral load of patients with positive anti-HCV antibodies were also tested. Before beginning the treatment regimen, the patient's complete blood profile was obtained, and hemoglobin levels, total leucocytes count, Retic count, and alpha-fetoprotein were assessed.

Per ICH-GCP standards, this observational, prospective, single-center study was performed at the Department of Kidney Diseases at LRH Hospital in Peshawar, Pakistan; An Institutional Ethics Committee approved the study ran from March 2019 and March 2021. Twenty-seven individuals who met the study's minimum age requirement of 18 years were enlisted. Dialysis-dependent individuals with HCV genotype three infections were included in the study. Patients were divided into two groups: those who were naïve to SOF/RBV therapy for HCV infection (n=21) and those who were treatment-experienced/had relapsed (n=6). Completed without any dropouts or missed follow-up visits throughout the study period. In total, 12 weeks of SOF (400 mg) and VLP (60 mg) treatment with four follow-up visits (Baseline visit, at the time of enrollment and treatment, start, after four weeks of treatment, after 12 weeks of ETR and SVR [HCV RNA level below the threshold of quantification sustained for 12 weeks after treatment ends are considered predictive of cure24] were administered to all subjects. SPSS version 19 was used to analyze the data collected during the study, including the day the first dosage of the study medication was administered. The number of observations, mean, standard deviation (SD), standard error, median, minimum, and maximum were used to summarize all variables. Confidence intervals of 95 percent were included in the inference tables when appropriate. A significance threshold of 0.05 was used for all hypothesis tests unless otherwise noted.

Results

There were 32 males among the 252 chronic HCV patients on HD (ESRD) who were getting the SOF-VLP regimen (56.5 %). About 47.5 % of the participants were females, with a mean age of 57 years. All patients took HD for the last 2-3 years, twice a week. There were 220women (64.3%), ranging in age from 28 to 90, in the study. During the last 2-3 years, all patients received HD twice a week.

Table 1: A study of the pre-treatment features of individuals with hepatitis C who are receiving SOF-VLP therapy (12 weeks of treatment)

Characteristics		Treated patients (n=252)
Age (years)	Mean±SD	16±6
Mean dialysis (year)	Mean±SD	2±1
Study groups	Naive	22 (61.11%)
	Treatment Experienced	14(38.89%)
Gender	Male	101 (40%)
	Female	151 (60%)
HCV- Genotype 3 status		252 (100%)
Comorbid	Diabetes with Hypertension	152 (60.8)
	Hypertension	1 0 0 (39.2%)

**Hepatitis C Virus; SOF= Sofosbuvir; VLP= VELPATASVIR; n= Frequency of infection;*

Reaction of the Virology

After week 12, all of the recruited patients had no detectable HCV RNA, as indicated in Table 2a (SVR-12). In both the native and treatment-experienced groups, the high SVR12 rate was obtained in 252 patients (252/252, 100 %) as shown in table 2. HCV RNA was measured using the "HCV quantitative test" at baseline and SVR12 visits, as well as the "HCV qualitative test" at week 12 and ETR visits.

Table 2: Reaction of the Virus (Treatment Efficacy Contents)

Treatment Efficacy Measure	N= (%)
End-treatment response	252 (100)
Sustained virological response (SVR)-12 weeks	252 (100)
Early treatment discontinuation	37
Relapse	2

Antiviral Therapy's Safety is Assured

Hemoglobin (Hb) levels were stable at 9.8 g/dl (1.2) after therapy, with no change in serum total bilirubin levels (0.8–0.2 mg/dl). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and overall improvement in liver tests were seen after week 4 of chemo and follow-up visits as indicated in table 2. Except for the normalization of liver enzymes in patients with SVR-12, there were no significant alterations in laboratory markers before and after therapy. Erythropoietin was given to ten of the 252 patients. Ten out of 252 patients every week, while 170 got it every other week. (64%) of patients needed blood transfusions to stay alive. No significant adverse events (AEs) were seen in this study. However, a few individuals did have moderate diarrhea, exhaustion, and nausea symptoms. These negative effects did not lead to the cessation of therapy.

Table 3: Antiviral treatment characteristics suggesting safety

Antiviral treatment characteristics	Safety Result
Total bilirubin (mg/dl)	0.8±0.2
Hemoglobin (Hb) (g/dl)	10.2±2.2
Mild Adverse Events (AEs)	n (%)
HeaVLPhe	16 (54)
Fatigue	12 (35)
Nausea	8 (22)
Treatment interruptions due to AE	None.
Hospitalizations due to AE	None.
Death/lost to follow-up	None.
Complications with dialysis	None.
ALT	Mean±SD
	29.98 ± 8.02
AST	34.58 ± 7.02

*Blood; ALT; Aspartate Aminotransferase; *Hb.*

**The normal range for ALT is 17-81; the normal range for AST is 20-90*

Discussion

In contrast to the liver and other organs and systems, the kidney plays an essential role in the HCV clinical syndrome[14]. Patients with HD are more likely to contract this well-known virus infection, which has been linked to a higher mortality rate, hospitalization, and anaemia complications, as well as a variety of negative quality-of-life (QoL) scores like depression, anorexia, pruritus, increased pain and decreased vitality[9,15]. There are currently more therapeutic choices for individuals with severe CKD and HD, thanks to the development of DAAs, and

well-tolerated oral regimens for HCV treatment. To the best of the researchers' knowledge, this is the first study to look at the effectiveness and safety of the SOF-VLP regimen in treating HCV in people living with HD[16]. The findings showed that SVR-12 had a very high success rate. SOF-VLP regimen delivered to HCV-infected individuals had a remarkable success rate (an SVR of 100 percent in the study population) (table 2). Interferon (IFN) and Ribavirin (RBV) regimens have been the first-choice treatment for HCV patients with ESRD (on HD) for over the last two decades. Several second-generation DAAs were licensed in 2015 to treat HCV16 patients without interferon or ribavirin[17]. These drugs include SOF, VLP, and Simeprvia. It is well accepted that SVR is achieved with a combination of DAAs and SOF and that this is the foundation of novel antiviral regimens. SVR produced results ranging from 70% to 98.3 %. SVR rates for the newly created DAAs were initially fairly high. Nevertheless, some patients are still unsure if the treatment is suitable.

Patients with renal failure, particularly ESRD, on dialysis or with decompensated liver cirrhosis, and organ transplant recipients benefit from this treatment[18]. There is good news for patients on renal replacement treatment, with data from the studies showing that the SVR rate may surpass 95%A medications in Asian patients with HCV GT3 resulted in 92.7 % of SVR-12 in 4230 patients from 15 studies, a greater SVR than the previous therapy of Peg-IFN+RBV non-cirrhotic patients had an SVR-12 of 98.9%, but cirrhotic patients treated with SOF+RBV for 24 weeks (n=2230) or SOF+Peg+RBV for 12 weeks (n=1417) had an SVR-12 of only 88.6%. An IFN-RBV-free regimen for individuals with hepatitis D was used in this investigation of the local Pakistani community treated with the SOF and VLP regimen according to EASL 2015 [19]. It is not allowed for HD patients to use the recommended 400mg dosage of SOF due to concerns about the toxicity of SOF's metabolic products. Furthermore, it is stated that reducing the dosage may result in decreased levels of the active metabolite (GS461203) and poorer efficacy his is an important consideration. As a result, the current study retained the 400mg SOF full dosage. The combination of VLP and SOF was employed as a treatment in the study. The liver metabolizes NS5A inhibitor VLP. Hence no dose modifications are necessary for patients. It is most often used in conjunction with SOF in individuals with genotype three infection but may also be used alone. Patients with CKD and ESRD have found VELPATASVIR effective and well-tolerated in the previous study's[20]. Meta-analysis results revealed that DAA-based antiviral treatments were successful and well-tolerated in stage 4– 5 CKD patients, while 11 studies demonstrated an effective therapy with DAAs for advanced CKD patients, with SVR 12 reaching 92 % safety was the next priority after the 100% SVR response rate.

Replacing RVB with VLP provided a good safety response as indicated in table 3. Anemia was a common side effect of RBV, and the kidneys were the primary clearance route. As a result of CKD, Haemoglobin (Hb) level did not alter significantly in the study (Table 2b). Prior studies show that the RBV combination causes significant AEs in 0% to 50% of patients. The reported AEs were minor in character (table 3). For HCV-infected individuals, earlier investigations showed no significant increase in serum transaminases. Serum transaminase levels were within normal limits at the start of current study. They remained that way throughout the therapy and the final SVR12 visit for all participants (table 3) [21]. To sum up, the treatment of HCV in ESRD with dialysis is now curable in most instances, thanks to the advent of novel DAAs. Finally, it

aids in decreasing HCV prevalence in HD and the elimination of HCV from HD facilities. However, in many emerging economies, there is a huge problem with DAA availability and the expense of the medications. As a result, even in the face of well-defined recommendations for HCV treatment, many doctors still disregard the potential benefits of new DAAs when treating patients with kidney disease[22]. Fortunately, the current study treatment was designed by the most recent ASLD and EASL guidelines. The local population infected with HCV and ESRD had previously experienced an excellent response in terms of safety, tolerability, and efficacy, so the current study results are encouraging.

The researchers thought that this study had several flaws despite promising and thorough findings. Patients with chronic kidney disease (CKD) who were hospitalized were included in the study, which had a small sample size. A fibro scan was not performed because it was too expensive. Velpatasvir has just been approved as an adjunct to SOF for 12 weeks 21 as a second-wave anti NS5a drug with strong effectiveness against GT3[23].

Conclusion

Patients with HD and genotype 3 HCV infection responded well to the VLP-SOF combination; safe, well-tolerated, and highly successful (with high SVR rates). More study is needed to determine the treatment's impact on renal function progression, particularly safety, since advanced-CKD patients have a higher risk of renal function degradation and anemic events, even if the ordinary course of their illness causes them. For this reason, more extensive studies and newer generation DAAs must be conducted to prove both efficacy and safety.

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