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Original Article

Response of Sofosbuvir and Daclatasvir combination in Chronic Hepatitis C with Hemodialysis Pakistani Patients: A Single Centre Study

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Abstract

Background: Globally, Hepatitis C is the primary causes of acute and chronic hepatitis in end-stage renal disease patients and highly prevalent in hemodialysis patients. In Asia, Hepatitis C Virus (HCV) infection has become a serious public health problem, whereas, in Pakistan, 26.02% hemodialysis patients are infected with HCV infection. The advent of direct-acting antivirals (DAAs) has brought HCV treatment into a revolutionized era. Among the approved DAAs, sofosbuvir (SOF) is the only one that has a significant renal elimination whereas daclatasvir (DAC) is not eliminated by the kidneys. The aims of the study were to assess the effectiveness and safety of SOF and DAC combination in HCV infected patients on Hemodialysis (HD) in the local population as per routine Pakistani practice.

Methodology: An observational, prospective, single-centre study was conducted from December 2017 till September 2018 at the Nawaz Sharif Kidney Hospital, Swat, Pakistan. Total 27 HCV- HD subjects on SOF/DAC regime for 12 weeks, were enrolled in the study. The study was conducted as per the ICH-GCP Guidelines. The collected data was analyzed using SPSS Software version 19 and p-value < 0.05 was considered significant.

Results: As per the results of 27 subjects', (n= female 12, 44.5% and n = male 15, 55.5 %), 21 subjects were naive and 6 were the treatment experienced group (with SOF/RBV) with mean age of 35.5±9.6 years. On SOF/DAC treatment for 12 weeks, the sustained virological response (SVR) rate was 100% (27 of 27) at the post treatment follow-up visit after 12 weeks. No patients had a virological failure or lost to follow-up during the study. The reported adverse events (AE's) were mainly nausea, headache and fatigue, no serious AE reported. Moreover, no treatment discontinuation due to side effects was observed.

Conclusion: The combination of the full dose of SOF-DAC for 12 weeks provides a highly effective, safe and well-tolerated therapy for Pakistani patients with HCV on HD in routine Pakistani practice.

Keywords

Hepatitis C, Hemodialysis, Sofosbuvir Daclatasvir Combination, Pakistani Population

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Introduction

The Chronic HCV is the major global health problem affecting around 170 million people worldwide and causing 500,000 deaths annually[1]. The patients with long standing HCV infection are at risk for progression of cirrhosis and hepatocellular carcinoma with other serious consequences for several organs and systems[2]. The kidney disorder is one of the most common extra-hepatic dysfunctions associated with HCV infection affecting 10% to 60% of patients[3]. It is very common among HD and kidney transplant patient[4]. The history in dialysis patients with HCV is unclear and remains difficult for several reasons, including the very long duration of disease, mainly asymptomatic and difficult to determining the disease onset[5]. Also, the multiple factors can alter the progression including coinfection with hepatitis B virus (HBV), human immunodeficiency virus (HIV), and alcohol use[6].

The HCV seroprevalence in the HD population has ranged from 7.8% to 44% in developed countries[7]. However, over the last one-decade, the incidence and prevalence of HCV infection in the dialysis patients has advanced much higher in developing countries than for the developed world[8]. The Dialysis Outcomes and Practice Patterns Study (DOPPS), an international, cohort study recruited patients on HD, conducted at 500 facilities and involved 21 countries[9]. From the period between 1996 and 2015, 76,689 HD adults enrolled with or without HCV infection. The prevalence of HCV was 5762 (7.5%). In comparison with the HCV negative group, the HCV positive patients were more frequently effected with end-stage renal disease (ESRD) and were on dialysis for longer period of time[9].

In Pakistan, approximately 10 million people are affected with Chronic HCV[10]. Unfortunately, 40% rise in the incidence and prevalence of HCV in the general population as compared to previous estimates (6.8% rather than 4.7%-5%)[10]. Chronic Kidney Disease (CKD) is becoming prevalent in Pakistani population, the data from the health screening camps and from the community has been found to be around 12.5%-25%[11&12]. For the prevalence of hepatitis C in Pakistani patients on hemodialysis, limited local data explored the prevalence around 23.7%-56.6%[12].

According to the management strategy provided by the Kidney Disease: Improving Global Outcomes (KDIGO) work group, all CKD patients with HCV infection should be evaluated for antiviral treatment[13]. Before the initiation of the treatment, the decision should be based on the potential benefits and risks of therapy, including life expectancy, candidacy for kidney transplantation, and comorbidities[13]. Also, the risks and benefits of antiviral therapy must be discussed with the patients and the patients should participate in the decision-making process[13]. Major advancement has been made over the last 2 eras for the management of HCV in the general population[14]. Initially with the monotherapy treatment of interferon (IFN), increased progress of SVR rates from 7 to 10%, by adding ribavirin (RBV) it further increases to 25% and with peginterferon and ribavirin, it elevates to 40–50%. However, it is challenging to treat patients due to the associated toxicities of IFN[15&16]. The toxicity of IFN also aggravated by the concomitant use of RBV that is minimally eliminated with HD; thus combination regime associated with substantial hematologic toxicity and risk for anemia[15-17]. Also, both are eliminated by the kidneys and

require significant dose reduction in patients with impaired kidney function[17].

IFN-based therapies have poor efficacy and a high AE rate in patients on dialysis, as reflected in the DOPPS study reported results, where patients on regular dialysis with HCV-positive and on IFN-based therapies were extremely low (5%) efficacy response[18]. In addition, IFN-based therapies are associated with greater rates of allograft rejection after kidney transplant[18].

The emergence of DAAs revised the strategies for HCV management and revolutionized by target specific nonstructural proteins of the virus, resulting in the disruption of viral replication and infection[19&20]. Currently, there are four classes of DAAs according to their mechanisms of action and therapeutic target, the nonstructural proteins 3/4A (NS3/4A) protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B non-nucleoside polymerase inhibitors, and NS5A inhibitors[19&20]. With the induction of DAAs, the rate of SVR reaches over 90–95% of the normal renal function subjects. Importantly, the treatment with DAA regimens shorten the treatment duration (mostly 12 weeks), is interferon free and tolerable adverse events[19&20]. Overall, the choice of the regimen should be based on genotype (and subtype), viral load, concomitant medications, kidney function, transplant candidacy, and comorbidities[19&20].

According to the records much studies had been published, addressing the burden and prevalence of HCV infection in hemodialysis patients[21&22]. However, DAA regimens with properties of high efficacy, lesser side effects and increased tolerance, have not been extensively studied in the HD patients with HCV in the local population. Previously the authors investigated the safety and efficacy of SOF and RBV in HCV patients with stage 4 or 5 CKD and on HD[23]. This prospective study was conducted to investigate the response to the combination of SOF and DAC in stage 4 or 5 CKD Pakistani patients, affected by HCV in routine Pakistani practice.

Methodology

This observational, prospective, single-centre study was conducted at the Nawaz Sharif Kidney Hospital, Swat, Pakistan as per ICH-GCP guidelines. The study was approved by an Institutional Ethics Committee and continued from December 2017 to September 2018. As per study inclusion and exclusion criteria, 27 subjects with 18 years of age or above were enrolled. The selected patients had HCV genotype 3 infection and were dialysis dependent. The patients included both naive (n=21) and treatment experienced/relapse (n=6) on SOF/RBV regime treatment for HCV infection. The study was completed with no dropouts and proper follow-up visits were conducted during the study duration. All the subjects received the study drug, SOF (400mg) /DAC (60mg) treatment for 12 weeks with 4 follow-up visits (Baseline visit, at time of enrolment and start of treatment, after 4 weeks of treatment, 12 weeks, end of treatment (ETR) and SVR (HCV RNA level below the threshold of quantification, sustained for 12 weeks after treatment ends, is considered predictive of cure[24]), after 12weeks of ETR. The safety was monitored from the day when the first dose of the study drug was given till the cessation. SPSS version 19 was used for analysis. All variables were summarized using the number of observations, mean, standard deviation (SD) or standard error, median, minimum and maximum. ± 95 % confidence intervals were provided in the inference tables where applicable. All hypothesis tests were two-sided and conducted using a 0.05 significance level unless otherwise stated.

Results

Out of the total 27 Chronic HCV patients on HD (ESRD) receiving SOF-DAC regime, there were 15 males (55.5%) and 12 (44.5%) females, with a mean age of 36±9 years (age range 18–60). All patients were on HD for last 2-3 years, 2 times per week.

Table 1: Baseline characteristics of HCV patients on hemodialysis treated with SOF-DAC therapy (12 weeks treatment)

Characteristics	Treated patients (n=27)
	Mean±SD
Age (years)	36±9
Mean dialysis (year)	2±1
Study groups	n(%)
Naive	21 (77.8)
Treatment Experienced	6 (22.2)
Gender	
Male	15 (55.5)
Female	12 (44.5)
HCV- Genotype 3 status	27 (100)
Comorbid	
Diabetes with Hypertension	11 (44.7)
Hypertension	16 (59.2)

*HCV= Hepatitis C Virus; SOF= Sofosbuvir; DAC= Daclatasvir; n= Frequency

Virological response

As shown in Table 2a, all the enrolled patients had not detectable HCV RNA, post treatment after week 12 (SVR-12). The high rate SVR12 was achieved in 27 patients (27/27, 100%) in both naive and treatment experienced group (table: 2-A). In the study, the HCV RNA assessed by "HCV quantitative test" at baseline and SVR12 visits and "HCV qualitative test" at week 4 and ETR visits.

Table 2a: Virological Response (Treatment efficacy characteristics)

	n(%)
End-treatment response	27 (100)
Sustained virological response (SVR)-12 weeks	27 (100)
Early treatment discontinuation	Nil (0)
Relapse	Nil (0)

Safety of antiviral therapy

After completion of the treatment, the mean haemoglobin (Hb) showed about 10.2 g/dl (±1.2), no rise in serum total bilirubin (0.8±0.2 mg/dl). The Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were in the upper normal limit from the week 4 therapy and follow-up visits, and overall improvement in liver enzymes (Table 2b). There were no significant differences in laboratory parameters before and after treatment, except for normalization of liver enzymes in patients with SVR-12. Out of 27, 10 patients (37%) received Erythropoietin at a weekly dose whereas as 17

(63%) were dependent on blood transfusion. In the study, no serious AEs was reported, however mild headache, fatigue and nausea were reported by few patients only. No treatment discontinuation was observed due to these side effects.

Table 2b: Characteristics indicating safety of antiviral therapy

	Mean±SD
Total bilirubin (mg/dl)	0.8±0.2
Hemoglobin (Hb) (g/dl)	10.2±2.2
Mild Adverse Events (AEs)	n(%)
Headache	15 (55)
Fatigue	10 (37)
Nausea	7 (26)
Treatment interruptions due to AE	None
Hospitalizations due to AE	None
Death/lost to follow-up	None
Complications with dialysis	None
	Mean±SD
ALT	29.98 ± 8.02
AST	34.58 ± 7.02

*Hb= Hemoglobin; ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase

*Standard Range for ALT=17-81; Standard Range for AST=20-90

Discussion

The kidney is an important component of the HCV clinical syndrome, besides the liver and other systems and organs[24]. This notorious viral infection is very common among HD patients, associated with higher risk of death, hospitalization, and anaemic complications, and with a variety of undesirable quality-of-life (QoL) scores, including depression, anorexia, pruritus, greater pain, and worse vitality[9, 25&26]. Fortunately, with the discovery of DAAs, well tolerated oral regimens for HCV has expanded treatment options in patients with severe CKD and HD and now the patients are recommended to consider for an antiviral therapy[27-29]. The present study is the first attempt to provide a local population data on the efficacy and safety of SOF-DAC regimen for the treatment of HCV patients on HD. The results indicated that the rate of SVR-12 was very high, (100% SVR in the study sample), when SOF-DAC regimen was administered to HCV-infected patients (Table 2a). Before DAAs, over the last two spans, standard Interferon (IFN) and Ribavirin (RBV) regimen were the initial choice to treat the HCV patients with ESRD (on HD) with all pros and cons[30&31].

In 2013, the advent of second-generation DAAs e.g.: SOF, DAC and Simeprvia, approved the guidelines for the IFN and RBV-free combination regimen in HCV[16]. Multiple trials and meta-analysis of all genotypes of HCV proved the high outcomes of SVR with DAAs and SOF and consider it as the backbone of new antiviral regimens[32]. The resulting outcome with SVR ranged between 70% and 98.3%[26&27]. Initially, the developed DAAs has shown quite high rates of SVR, however, there were still some patients for whom it is unclear whether the therapy is appropriate

or likely to be effective due to co-existing clinical conditions, such as patients with renal failure, especially ESRD, on dialysis or decompensated liver cirrhosis, and organ transplant recipients[15&24]. Fortunately, with the evidence from the trials result, the SVR rates may exceed 95%, even in patients on renal replacement therapy[26&27].

The meta-analysis approach and by systematic review to investigate the outcomes of DAA therapies in Asian patients with HCV GT3, the overall results were found of 92.7% of SVR-12 in 4230 patients from 15 studies, higher SVR than old therapy of Peg-IFN+RBV[34]. Importantly, non-cirrhotic patients experienced a very high SVR-12 of 98.9%, whereas only 88.6% of the cirrhotic patients, treated with either SOF+RBV for 24 weeks (n=2340) or SOF+Peg+RBV for 12 weeks (n=1417)[35].

The present study of the local Pakistani population treated with the SOF and DAC regimen as per the European Association for the Study of the Liver Disease (EASL) 2014 guidelines[35], an IFN-RBV free regimen in HD patients. However, the recommended dose of 400 mg SOF is not approved for patients on HD, as concerns of accumulating SOF's metabolites with potential cardiovascular and hepatobiliary toxicity. Importantly, it is also reported that by lowering the dose will potentially lead to lower levels of the active metabolite (GS461203) and lower efficacy[36]. Therefore, in the present study, the SOF complete dose (400mg) was maintained. In the study, with SOF, the combination of DAC was used as the treatment therapy. DAC is a nonstructural protein 5A (NS5A) inhibitor metabolize by liver, therefore no dosing adjustments are required in patients with CKD and mostly used in combination with SOF for patients with genotype 3 infection[37]. In past studies, patients with CKD and ESRD, were effective and well tolerated with Daclatasvir[38]. A previous meta-analysis showed DAAs-based antiviral therapies were effective and well tolerated in stage-4–5 CKD patients and 11 studies reported an effective treatment with DAAs for advanced-CKD patients, with SVR 12 reaching 93%[26&39].

With the high rate SVR (100%) response, the next issue of concern was safety. The present study also showed an excellent safety response, by replacing RVB with DAC (Table 2b). The frequent side effect of RBV was anaemia and the usually elimination observed via renal pathway. In the study, no major change in the level of Haemoglobin (Hb), apart from the consequences of CKD (Table 2b). The previous studies showed that with RBV combination, serious AE's ranging from 0% to 50% of patients[9]. In the present study, no serious adverse event was reported and the reported AEs were mild in the nature (Table 2b). In the previous studies, serum transaminase concentrations were not markedly elevated among HCV+ patients[9]. In our study, at the baseline visit, the serum transaminase was in the normal range and throughout the study treatment and final SVR12 visit, the enzymes was not elevated among all the recruited patients (Table 2b).

To summarize, with the emergence of new DAAs, the HCV treatment in ESRD with dialysis has changed drastically and now curable in most cases. Ultimately, it helps to reduce the prevalence of HCV in HD and eradication of HCV from HD units. However, in many developing countries, the

availability of DAAs and costs of drugs is the major issue. Therefore, even in the presence of clear-cut HCV management guidelines, many clinicians compromise the use of emerging DAAs in HCV treatment with CKD. Fortunately, the current study treatment designed as per the latest ASLD and EASL guidelines and local population infected with HCV and ESRD had experience of the excellent response in terms of safety, tolerability and efficacy.

Despite promising and comprehensive results, we assume that our study had several limitations. It was a Single-Centre study including hospitalized CKD patients with limited sample size. Due to non-affordable subjects, fibro scan was not done for liver status staging. Lastly, very recently, velpatasvir, a second-wave antiNS5a agent with potent efficacy against GT3, should be available as in combination with SOF for 12 weeks[21].

Conclusion

As per study results, the DAC- SOF combination was safe, well tolerated and highly effective (shown high SVR rates) for HD patients with genotype 3 HCV infection. However, the treatment effects on renal function progression require more investigations especially the safety analysis as increased risk of renal function deterioration and anemia events in advanced-CKD subjects, though these might be due to the natural disease progression in these patients. Also, the effectiveness and safety needs to be confirmed by larger series and with the new generation DAAs as per the availability in the local population.

Conflicts of Interest

None.

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