

Original Article

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Effectiveness of Sofosbuvir regime in Hepatitis C virus infection in hemodialysis Pakistani patients: Single Centre Study

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Abstract

Background: Chronic Hepatitis C (CHC) infection is the most common chronic liver disease in patients with end-stage renal disease (ESRD) and highly prevalent on hemodialysis patients. The DOPPS data reported an overall prevalence of 13.5 percent among adult hemodialysis patients. The reported data in Pakistan reflected 26.02% hemodialysis patients with HCV infection. Over the last few years, the direct-acting antivirals have been revolutionary in the treatment of hepatitis C, and sofosbuvir (SOF) is the backbone of most modern treatment strategies with better prognosis of the infection and tolerability. The aim of the study was to assess the effectiveness and safety of Sofosbuvir regime on HCV infected patients on hemodialysis (HD) in the local population as per routine practice.

Method: This was an observational, prospective; single-center study enrolled 30 HCV HD subjects on sofosbuvir ribavirin regime for 12 weeks.

Results: As per results of 30 subjects' (n= female 13, 44% and n = male 17, 56 %) with mean age \pm standard deviation 60.5 ± 7.5 years. On SOF/ribavirin (RBV) treatment for 12 weeks, the sustained virological response rate was 100% (27 of 27) at 12 weeks. 95% confidence interval, (95 to 100). No patients had virologic failure during treatment. No patient had treatment discontinuation due to side effects. Adverse events were reported in at least 10% of the patients were mainly pruritus, fatigue, and nausea. No serious adverse event reported.

Conclusion: The Sofosbuvir based antiviral therapy is safe and effective in the treatment of HCV with ESRD, including HD patients with a high rate of SVR in patients.

Keywords

Hepatitis C, Hemodialysis patients, Sofosbuvir, Pakistani population

Introduction

HCV infection is a global health concern with an estimated disease burden affecting 2.35% of the total world population¹. The HCV patients with chronic kidney disease (CKD) have a high risk for the progression to ESRD as compared to non-infected HCV patients^{2,3}. The prevalence of HCV infection in the dialysis patients has advanced affectedly over the last one-decade with the incidence and prevalence is much higher in

developing countries than to the developed world⁴. A more recent analysis from 2012 to 2015 of DOPPS - 5 study (500 facilities, 17,000 patients and 21 countries) showed that HCV prevalence among hemodialysis patients remains higher than in the general population with a prevalence of 9.5% (in 11,394 patients)⁵.

In Pakistan, approximately 10 million people are suffering from HCV, the 6% of

the overall population. The recent published data (2009-2015) on HCV prevalence suggests that the infection is on the rise in Pakistan and almost 40% increase among the general population as compared to previous estimates (6.8% rather than 4.7%-5%)⁶. For the HCV percent in HD patients, as per the published literature and small sample size (ranging from 28-190) studies (n=6) results showed that the 26.02% of the haemodialysis patients is HCV infected and the rate of Prevalence become high in the past as compared to recent studies⁷.

For the management of HCV with HD patients, previously, it was challenging to treat patients due to the associated toxicities of interferon (IFN) therapy⁸. With the safety concerns, the effectiveness of Interferon regime was also not promising with Low sustained virologic response (SVR) rates (33%–37%) and discontinuation rates (17%–30%) that further limit its applicability^{8, 9}. The toxicity of IFN also aggravated by the concomitant use of RBV that is minimally eliminated by HD; thus combination regime associated with substantial hematologic toxicity and risk for anemia^{8, 9, 10}. Although RBV can be used with dosage modifications in patients with impaired renal function¹¹.

With the development of direct antiviral agents (DAAs), therapy for HCV has been revolutionized. However, the issue related to DAAs that various DAA drugs are not universally available in all countries¹². Like in Pakistan, only SOF and subsequently Daclatasvir were available in 2015 to 2017. Because of suboptimal SVR, higher cost, and the moderate degree of adverse effects of IFN-based therapy, there was an intense interest in using DAAs in patients with end-stage renal disease¹².

The previous studies data supporting the prevalence of rationale of HCV infection in hemodialysis Pakistani patients and the study key objectives were to evaluate the effectiveness and safety of Sofosbuvir regime (Ribavirin) in HCV patients on HD in routine practice.

Methodology

This was an observational, prospective, single-center study conducted at the Nawaz Sharif Kidney Hospital, Swat, Pakistan as per ICH-GCP guideline. The study was approved by an Independent Ethics Committee. The study period was from Jan 2017 to October 2017. As per study inclusion and exclusion criteria, 30 subjects with age of 18 years and above and patients selected had HCV genotype 3 infection and dependence on dialysis. The patients previously not taken any treatment for HCV infection. Whereas 3 subjects were dropped out due to lost to follow-up in the study. All the subjects received the study drug, SOF/RBV treatment for 12 weeks for follow up and evaluate effectiveness and safety in HCV patients on hemodialysis. Spss Software version 19 was used to summarize all variables using number of observations for analysis of the results. p value < 0.05 was considered significant. All variables were summarized using the number of observations, mean, standard deviation or standard error, median, minimum and maximum. \pm 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

In this study, 30 patients with Chronic Hepatitis C (HCV) on hemodialysis (ESRD) received a SOF-RBV regime from Jan 2017 to October 2017 at the Nawaz Sharif Kidney

Hospital, Swat. No patient had decompensated cirrhosis. There were 14 men (46%) and 16 (53%) women, of mean age 33 ± 7 years (range 20–55). All patients had detectable HCV RNA, and all are (30/100%) had genotype (GT) 3. All 30 patients (100%) were naive of antiviral treatment. Treatment duration was 12 weeks, according to the regimen. A dose of SOF (400 mg), once daily and RBV (200mg) alternate day given in all HD patients.

Virological response

The response rates (HCV RNA below the limit of detection) at week 12, SVR (12 week) was achieved in 27 patients (27/30, 90%), three (3) patients were lost to follow-up. The Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels significantly improved over the treatment period from 45 IU/ml (14–147) and 48 IU/ml (13–127) at baseline to 20 IU/ml (10–45) and 21 IU/ml (10–69) at the end of treatment ($P < 0.05$), respectively.

Safety of antiviral therapy

At the beginning of antiviral therapy, the average hemoglobin level was 9 mg/L (anemia) and 17 patients (56%) were receiving Erythropoietin at weekly dose. The significant increase in Erythropoietin dose was observed in patients treated with RBV. Three patients (10%) presented with severe anemia (hemoglobin level < 6 g/L) received a blood transfusion and 1 (3%) patient during blood transfusion required to stop Ribavirin without association with HD. Apart from anemia, frequent side effects included headache (22%), asthenia (18%), digestive discomfort (i.e. diarrhea or nausea, 24%) or insomnia (12%). No patient had treatment discontinuation due to side effects.

Discussion

HCV infection in ESRD patients is associated with an increased risk of all-cause and liver-related mortality, particularly in those who are on Hemodialysis (HD) and recommended the patients to consider for an antiviral therapy^{13, 14}. The present study of the local population reflected the updated knowledge of the HCV patients on hemodialysis (ESRD) treated with SOF-Ribavirin, antiviral therapy. Over the last two decades, standard IFNa (2a or 2b) and RBV regime was the initial choice to treat the HCV patients with ESRD¹⁵. The First-generation (DAA) telaprevir and boceprevir became available in 2011 as added the triple therapy of PEG-IFN and RBV. However, such triple therapy associated with the major concerns about the tolerability and the risk of anemia. Second-generation DAA became available in 2013, initially including SOF, Daclatasvir and Simeprevir¹⁶. Until now, SOF has been the backbone of 'new' antiviral regimens and has been used as part of combination therapy with IFN and/or RBV, or in IFN/RBV-free regimens¹⁷. The 11 studies, meta-analysis on the efficacy of DAAs in hemodialysis (11 studies) and the resulting outcome with SVR ranged between 66.7% and 98.3%. For several subgroup populations, SVR in SOF-based therapy was 89.4%^{18, 19}. The available literature and our own study results showed excellent efficacy of SOF-based therapy in HCV patients on hemodialysis, with an SVR close to 90% as in most studies.

With such excellent efficacy, the next issue of concern is safety. The present study also showed excellent safety, with an increase in anemia mainly due to RBV, the only frequent side effect. The Patients who were on ribavirin therapy did require an increase in erythropoietin dose, which was not unexpected. Earlier the use ribavirin mainly

due to the availability of other DAAs. As the recent introduction of daclatasvir and became available for the local population, we substituted this medication in combination with SOF and stopped using ribavirin. Previous studies showed serious adverse events ranging from 0% to 50% of patients²⁰.

Despite promising and comprehensive results, we assume that our study had several limitations. The first one is that the sample size that was not sufficient to allow precise evaluation of patient. Sub-groups according to fibrosis stage, HCV GT or level of renal failure. Additional data from larger series will probably become available in the near future, in order to optimize antiviral treatment in patients with ESRD. Lastly, new second-generation DAA will become available, without significant renal elimination, and could eventually replace SOF in new multidrug regimens. Very recently, velpatasvir, a second-wave antiNS5a agent with potent efficacy against GT2 and GT3, should be available as in combination with SOF for 12 weeks²¹. Thus, till update as per delayed in the DAAs registration from the regulatory authority, the therapeutic options are still limited to SOF-based regimens.

Currently, in many countries, HCV during dialysis is a major problem; in many of these countries, availability of DAAs and costs of drugs are also an issue. Furthermore, SOF not only can be used in the presence of cirrhosis, but it is also a pan-genotype DAA and is the most important DAA for treatment of HCV patients in any setting. In the absence of clear-cut guidelines for the use of SOF in dialysis patients, many clinicians hesitate to use SOF-based therapy. The local single-center experience of the

excellent safety and efficacy of SOF in these patients.

Conclusion

In conclusion, our study supports the use of Sofosbuvir and Ribavirin based regimen for the treatment of HCV patients with ESRD, as it is for patients without severe renal failure. This needs to be confirmed by larger series with the replaced of Ribavirin to the new second-generation DAA as per the availability in the local population.

Conflicts of interests

None.

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