Sofosbuvir-Velpatasvir Full Dose in Chronic Hepatitis C in End-Stage Renal Disease: An Observational Study from a Himalayan Region

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Full dose Sofosbuvir-Velpatasvir in Chronic Hepatitis C & ESRD

Chronic Kidney Disease

Chronic Hepatitis C

162 patients (114 males, mean age: 43 years)
125 on maintenance hemodialysis
24 with cirrhosis, 4 decompensated

Sofosbuvir + velpatasvir 12 weeks
(24 weeks for decompensated liver disease)

Rapid Virological Response
End of Therapy Response
Sustained Virological Response at 12 weeks

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Abstract

Background  Treatment of chronic hepatitis C (CHC) in the setting of chronic kidney disease and end-stage renal disease (ESRD) is challenging.

Objectives  We planned to evaluate the efficacy and safety of full dose of combination of sofosbuvir-velpatasvir in the treatment of CHC in patients with ESRD or those on maintenance hemodialysis.

Methods  The prospective observational study was conducted in a tertiary care center in North India where all patients with chronic kidney disease (CKD) were assessed. Those with hepatitis C virus (HCV) antibody positivity underwent testing for HCV ribonucleic acid and were treated if eligible. Full dose of sofosbuvir-velpatasvir was administered daily for 12 weeks (or 24 weeks for decompensated liver disease).

Results  Of the 162 patients (mean age: 43.08 ± 12.08 years, 114 males), 125 were on regular hemodialysis. Twenty-four (15%) had evidence of liver cirrhosis, out of which four patients had evidence of decompensation. One hundred forty-two patients (87.6%) had an early virological response. Most patients, 160 (98.7%), obtained end of therapy viral clearance and sustained virological response at 12 weeks after therapy. Two patients died, and rest of the patients completed therapy. The adverse effects noticed were nausea (20%), vomiting (18%), headache (10%), and weakness (7%).

Conclusion  A combination of sofosbuvir and velpatasvir is effective and safe in treating CHC in the setting of CKD.

Keywords

- hepatitis C
- cirrhosis
- chronic kidney disease
- end-stage renal disease
- direct acting antiviral

Introduction

Hepatitis C virus (HCV) infection can also result in extrahepatic manifestations and is associated with a greater chance of developing chronic kidney disease (CKD). HCV infection also increases the likelihood of graft failure following renal transplantation, decreasing renal function and death in patients with CKD. Further, HCV infection is more common in people with CKD, especially those who are on maintenance dialysis, with rates as high as 80% in underdeveloped nations. This could be related to increased need for blood transfusions for anemia and the need for hemodialysis. Therapy for HCV infection has significantly changed in recent years, with direct-acting antiviral drugs (DAAs) taking the place of pegylated interferon and ribavirin combination. Large clinical studies and real-world experience have demonstrated that DAA-based regimens have much greater effectiveness rates. These regimens also provide the benefits of fewer side effects, improved tolerance (which suggests greater rates of treatment completion), shorter treatment duration, oral delivery, and a reduced pill load. Several patient populations previously thought to be challenging to treat, such as individuals with hemophilia, human immunodeficiency virus infection, or who take immunosuppressive medications as a result of past organ donation, have effectively benefited from DAA regimens.

DAAs have, however, mostly been used in CKD patients with estimated glomerular filtration rates (GFR) > 30 mL/min. Sofosbuvir has a predominance in renal excretion, and there is emerging evidence of its safety in individuals with GFR < 30 mL/min. In this study, we planned to evaluate the effectiveness, safety, and side effect profile of sofosbuvir-velpatasvir at full dosage in end-stage renal disease (ESRD) patients and also in patients who are on hemodialysis.

Methods

Setting
The present study was conducted at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, India, between September 1, 2018 and February 20, 2021. The institutional ethics committee (IEC-SKIMS) cleared the study with reference number RP 86/2020. After fully describing the study’s design to each patient in the local language, their informed consent was obtained.

Patients
The patients were identified as having CKD using the CKD-EPI equation and were divided into several CKD groups following the most recent Kidney Disease Improving Global Outcomes recommendations. Hepatitis C antibody was assessed in all CKD patients using the enzyme-linked immunosorbent assay technique. We included all ESRD patients and those on hemodialysis with detectable HCV ribonucleic acid (RNA) levels. We excluded patients if they were unwilling to participate or if they had already been exposed to a DAA (irrespective of duration).

Treatment Regimen
All of the patients received therapy in accordance with the current standards for CKD patients with hepatitis C infection. The patients were given a once-daily pill containing the full dose of sofosbuvir and velpatasvir (400 mg/100 mg) for 12 weeks, or for 24 weeks in the case of decompensated
liver disease. Patients were instructed to take the pill the evening after their dialysis treatment on the day of their appointment.

**Definitions and Outcomes**
We recorded the clinical presentation, previous severe medical or surgical conditions, and the performance status of all patients. All patients underwent standard tests, including hemogram, liver, and kidney function tests, and other workup as clinically directed. Liver cirrhosis was determined if the patient showed esophageal or gastric varices during endoscopy or ascites with a serum-ascites albumin gradient greater than 1.1 g/dL. The liver transient elastography was used to evaluate patients for fibrosis. The liver stiffness test had threshold values of >7.1 kPa F2 for severe fibrosis and >12.5 kPa F4 for cirrhosis.16 The patients were followed up through the completion of treatment followed by 12 weeks of follow-up, or till the maximal follow-up or any outcome in form of death or loss to follow-up occurring either during treatment or during the posttreatment follow-up period.

**Follow-Up and Assessment**
Patients were checked on clinically every 2 weeks, and kidney function tests were performed every month while they were receiving therapy. Following that, they were checked every 4 weeks until 12 weeks after the end of the treatment. Those with cirrhosis underwent more regular follow-ups or when the doctor deemed it essential. Any adverse effects were carefully noted, paying particular attention to any impact on the hepatic, cardiac, and renal systems. Measurements of blood HCV RNA concentration were used to determine the virological response after 4 weeks of therapy (rapid virological response), after the prescribed 12 or 24 weeks of treatment (end-of-treatment response, or ETR), and 12 weeks after treatment had ended (sustained virological response [SVR12]).

**Results**

**Patients**
We included 162 patients with mean age of 43.08 ± 12.08 years. The study group consisted of 48 females and 114 males. Thirty-seven (22.8%) of the 162 patients were not receiving dialysis, leaving 125 (77.2%) of them on regular dialysis. Before starting dialysis, 106 (84.8%) of the patients receiving dialysis had a test for hepatitis C antibodies. None of the patients had their anti-HCV antibody levels checked at regular intervals. Only seven patients had an HCV diagnosis before initiating regular dialysis sessions, whereas 118 individuals received an HCV diagnosis while receiving dialysis, with 98% of these patients being dialysed from private dialysis facilities. The mean creatinine concentration was 7.01 ± 2.61 mg/dL. The mean hemoglobin, bilirubin, alanine transaminase (ALT), albumin, and international normalized ratio (INR) were 9.2 ± 2.9 g/dL, 1.25 ± 1.1 mg/dL, 77.51 ± 99.7, 3.19 ± 0.44 g/dL, and 1.06 ± 0.11, respectively. Of this studied group, 24 (15%) had evidence of liver cirrhosis, out of which 4 patients had evidence of decompensation. Among the patients with liver disease, mean Model for End-Stage Liver Disease (MELD) score in the group was 13.88, while the mean liver stiffness was 23.4 kPa.

**Treatment and Posttreatment Evaluation**
At 4 weeks of treatment, 142 patients (87.6%) had viral clearance Early Virological Response (EVR). The majority of patients, 160 (98.7%), obtained end of therapy viral clearance (ETR), and the same number of patients continued to have viral clearance 12 weeks following the end of the treatment (SVR12). Two study participants died during the treatment (see below). During the period of the study, one patient had kidney transplantation; his RNA levels were undetectable after 12 weeks of therapy (ETR), and he maintained them at 12 weeks after treatment.

All relevant baseline measures, including the change in mean values for albumin, creatinine, bilirubin, ALT, and the INR, were determined before and after the intervention (12 weeks after treatment). The change in mean MELD score and liver stiffness among the patients with liver disease was computed. The mean blood bilirubin and ALT levels significantly improved, with p-values of 0.003 and 0.0001, respectively. The changes in serum creatinine, albumin, and MELD score were not statistically significant. During the course of the trial, there was no discernible decrease in hemoglobin (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>12 wk</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.25 ± 1.1</td>
<td>0.97 ± 0.09</td>
<td>0.003</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>77.51 ± 99.7</td>
<td>37.4 ± 5.77</td>
<td>≤ 0.0001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>7.01 ± 2.61</td>
<td>6.9 ± 2.9</td>
<td>1.51</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>3.19 ± 0.44</td>
<td>3.32 ± 0.37</td>
<td>0.72</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.2 ± 2.9</td>
<td>9.1 ± 1.9</td>
<td>0.71</td>
</tr>
<tr>
<td>Platelet count (×10^9/L)</td>
<td>112.12 ± 52.32</td>
<td>115 ± 63.7</td>
<td>0.65</td>
</tr>
<tr>
<td>MELD</td>
<td>13.88 ± 3.66</td>
<td>12.93 ± 4.46</td>
<td>0.39</td>
</tr>
<tr>
<td>LSM (kPa)</td>
<td>23.4 ± 2.02</td>
<td>21.9 ± 0.47</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine transaminase; HCV, hepatitis C virus; LSM, liver stiffness measurement; MELD, Model for End-Stage Liver Disease. P-Value: change in pre and post treatment in different clinical parameters.
**Adverse Effects**
Headaches (16, 10%), nausea (32, 20%), vomiting (29, 18%), and generalized weakness (11, 10%) were the most frequent side effects. Seven patients were brought for treatment because of their disturbed blood sugar levels; one of them had diabetic ketoacidosis, although they were all known diabetics using insulin. One patient, a 65-year-old male, died of a large anterior wall myocardial infarction 10 weeks after initiation of anti-HCV therapy, while the other, a 59-year-old male, passed away from bilateral pneumonia with multiorgan failure 1 week after treatment ended. Endoscopy revealed the existence of low-grade esophageal varices and nodular gastric antral vascular ectasia in one patient who had underlying decompensated liver disease and required endotherapy in the form of argon plasma coagulation. None of the patients stopped taking their medicine.

**Discussion**
The present study adds to the growing evidence of the efficacy of DAA for HCV in the setting of renal disease. The study also elucidates that the standard dose of sofosbuvir-velpatasvir combination is associated with excellent SVR rates. The study also shows that most adverse effects of this therapy are mild and easily manageable. Achievement of SVR is typically linked to improvements in liver function, normalization of liver enzymes (as shown in our study), and may be associated with improvement or regression of hepatic necroinflammation and fibrosis (which remains to be documented in setting of CKD).

Hepatitis C is quite common in people with CKD. Jasuja et al found that hemodialysis patients had a prevalence of hepatitis C of 27.7%. In a cohort of 459 patients on hemodialysis attending four dialysis centers in Kashmir, India, Masoodi et al at SKIMS reported a 10% (n = 46) seroconversion rate for HCV in their prospective research from Kashmir. Patients who received dialysis at multiple hemodialysis centers and for a longer period of time experienced a higher seroconversion.

Many of the drugs recommended for treatment of HCV in CKD (like combination of glecaprevir and pibrentasvir for individuals with HCV-1, and grazoprevir and elbasvir fixed doses for those with ESRD) are not available in India. Therefore, we evaluated the pan-genotypic combination of sofosbuvir-velpatasvir. The European Association for Study of Liver advises treating individuals with GFR 30 mL/min/1.73 m² for 12 or 24 weeks in the case of patients with decompensated liver disease with a fixed dosage combination of sofosbuvir and velpatasvir. It is unclear if patients with ESRD and those receiving hemodialysis can tolerate this fixed dosage combination. Many recent studies have shown good and effective results with use of full-dose combination of sofosbuvir and velpatasvir in ESRD patients and patients on hemodialysis.

A meta-analysis of seven studies showed the overall pooled SVR rate of sofosbuvir and velpatasvir in patients with HCV on renal replacement therapy was 97.69% (95% confidence interval [CI]: 95.71–98.92). There was no significant heterogeneity ($I^2$: 39.3%, p-value of Cochran’s $Q = 0.13$) among the studies. The pooled estimate of efficacy of sofosbuvir-velpasvir combination among patients with cirrhosis was 91.94% (95% CI: 77.03–98.52). No serious adverse event attributable to sofosbuvir and velpatasvir was reported in the included studies.

Our study had certain limitations, including the absence of viral resistance profile and lack of pharmacokinetic data. Further, the findings cannot be generalized to certain subgroups because of small patient populations in some subgroups, such as renal transplantation and decompensated liver disease. However, the study adds to the growing evidence of benefit of this combination in CKD and first such report from the Kashmir region.

To conclude, in the absence of the recommendations for drugs available in India in most guidelines, the outcomes of this one tablet fixed dose combination (sofosbuvir-velpasvir) are promising and can aid in the treatment of chronic hepatitis C in this difficult population.

**Ethical Statement**
The institutional ethics committee (IEC-SKIMS) cleared the study with reference number RP 86/2020. Informed written consent was obtained before inclusion.

**Authors’ Contributions**
Conceptualization: A.A., A.S., M.W. Methodology, investigation, and original draft: A.A. Project administration and supervision: A.S. Data curation, visualization, and software: M.K., G.M.G. Initial draft: S.P. Resources: J.S. Data curation: H.D. Validation: N.A. All authors approved the final version.

**Data Availability Statement**
The data associated can be obtained from the corresponding author on a reasonable request.

**Funding**
None.

**Conflict of Interest**
None declared.

**Acknowledgments**
None.

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