Efficacy and Safety of Directly Acting Antivirals in Patients with Hepatitis C Infection on Hemodialysis

Manisha Sahay1*, Priyashree2*, Kiranmai Ismal3, K Anuradha4, Jyoti Lakshmi5

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ABSTRACT

Introduction: The high prevalence of hepatitis C virus (HCV) infection among patients on maintenance hemodialysis (MHD) has been reported in India. Due to the strong association of HCV infection with death and cardiovascular disease, it is important to treat the infection. However, treatment poses a challenge since only a few directly acting antivirals recommended in the guidelines for HCV treatment in the dialysis population are available in India. Pangencode sofosbuvir has concerns about its safety due to its renal elimination.

Materials and methods: This prospective study was undertaken between 2019 and 2020 among patients on hemodialysis with HCV infection. Clinical details, biochemical parameters, viral load, and genotyping were recorded and the outcome of treatment with sofosbuvir in combination with velpatasvir/daclatasvir for 12 weeks was noted. Descriptive and inferential statistical analysis was carried out. The Chi-squared/Fisher exact test was used.

Results: In the present study, 54 hemodialysis patients with HCV were treated with full doses of sofosbuvir and velpatasvir/daclatasvir. Genotype 1 was the most common, seen in 73.5% (n = 41). Around 96.29% (n = 52) of patients achieved sustained virological response (SVR) at the end of the study. None of the patients experienced serious side effects requiring dose reduction or discontinuation of the treatment.

Conclusion: Sofosbuvir combination therapy offers an excellent response in dialysis patients irrespective of the genotype and presence of cirrhosis with minimal monitoring as in non-chronic kidney disease (CKD) patients.

ORIGINAL ARTICLE

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Inclusion and Exclusion Criteria

All patients above 15 years of age with HCV infection with ESRD who were undergoing MHD were included in the study after obtaining informed consent. Patients coinfected with HBV, human immunodeficiency virus were excluded. Patients on antiepileptic drugs, immunosuppressants, chemotherapeutic drugs, and antiarrhythmic drugs were excluded due to drug interactions with DAA. Patients with a previous history of treatment with interferon or DAA, children, and pregnant patients were also excluded from the study. Patients with the presence of antibodies to HCV with no documented HCV RNA were considered as spontaneous clearance and excluded from the study.

Quantitative HCV RNA viral load using commercially available Quantiplus reverse transcription polymerase chain reaction (RT-PCR) kits, and HCV genotype by molecular diagnostics were done for all patients. A cutoff of 15 IU/μL was utilized for detecting the minimal quantity of RNA in the blood.

Baseline data including demographic profile, dialysis vintage, duration of HCV, symptomatology, history of blood transfusions, co-morbidities, details of treatment received, and drugs used was noted. All patients underwent an ultrasound abdomen to assess the presence of fibrosis or cirrhosis.

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1 Professor and Head; 2 Fellow; 3 Professor; 4 Assistant Professor, Department of Nephrology; 5 Professor, Department of Microbiology, Osmania Medical College, Hyderabad, Telangana, India; 6 Corresponding Author


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Liver fibrosis was measured noninvasively by transient elastography (FibroScan) and the liver stiffness measurement was expressed in kilopascals (kPa). A kPa of >11 was considered to be cirrhosis and 7–11 kPa was labeled as fibrosis. Also, fibrosis-4 (FIB-4) and AST to platelet ratio index (APRI) scores were used for assessing fibrosis. APRI score >2 and FIB-4 > 3.25 were considered suggestive of cirrhosis. Assessment for portal hypertension with upper gastrointestinal (GI) endoscopy was performed in indicated cases.

Sofosbuvir 400 mg + velpatasvir 100 mg (fixed drug combination) daily for 12 weeks was administered in patients with fibrosis/cirrhosis and sofosbuvir 400 mg + daclatasvir 60 mg daily for 12 weeks in patients without fibrosis according to assessment by APRI score, FIB-4 score, and FibroScan according to National Viral Hepatitis Control Program by Ministry of Health and Family Welfare, India. Drugs were administered after the dialysis session on the day of MHD.

Postinitiation of DAA, patients on MHD were dialyzed using bridge machines. HCV RNA was performed after 12 weeks after the stoppage of treatment to assess SVR-12.

FibroScan was repeated at 6 months posttreatment to assess the change in liver stiffness. All patients were monitored monthly with complete blood counts, liver function tests and assessed for adherence and side effect profiles.

Statistically Analysis

The data were analyzed descriptively using percentages, means, and standard deviations. Tests of significance were performed using independent student t-tests and χ² analyses as appropriate for the variables used in the comparisons. The level of significance was set at 0.05. All analyses were done with the Statistical Package for the Social Sciences for Windows (version 16; SPSS, Chicago, Illinois).

Results

A total of 54 patients with chronic kidney disease (CKD) on MHD with HCV were studied in this period of 2 years. The mean age of the study population was 45.1 ± 10.7 years with males contributing up to 75.9%. The etiological profile for CKD was 35.2% (n = 9) of patients had chronic interstitial nephritis (CIN), 42.6% (n = 23) had chronic glomerulonephritis (CGN), 22.2% (n = 12) had diabetic kidney disease with a mean duration of diabetes being 10.8 ± 2.2 years.

The mean duration of MHD was 3.4 ± 1.6 years with a range of 6 months to 9 years. A total of 37 patients of 54 (68.5%) had a past history of blood transfusion either before or after the initiation of Hemodialysis. None of the patients had a history of intravascular drug abuse or high risk behavior.

Hypertension was present in 83.3% (n = 45) patients and a history of coronary artery disease was present in 7.4% (n = 4). The duration between diagnosis and treatment initiation was 4 ± 2 months. The baseline biochemical parameters are depicted in Table 1.

Hepatitis C virus (HCV) genotyping was studied in all patients. HCV genotype 1 was the most common, seen in 75.9% (n = 41) followed by genotype 3–24.07% (n = 13) of the patients.

The median HCV RNA load (performed by Quantiplex HCV RT-PCR kit) was 2,83,894.5 IU/mL with a range of 18.7–7834124 IU/mL. Ultrasound abdomen showed fatty liver in 13% (n = 07) patients and altered echotexture in 18.5% (n = 10) patients.

Fibrosis of liver assessment with FibroScan showed 55.5% (n = 30) had fibrosis and 16.6% (n = 09) patients had cirrhosis. The mean value on FibroScan was 8.5 ± 1.4 kPa. Upper GI endoscopy was done in patients with FibroScan values of >11 kPa and none of the patients had features suggestive of portal hypertension (varices or portal hypertensive gastropathy).

The mean APRI score was 0.71 ± 0.55 with 9.2% (n = 5) patients having scores >2 (cirrhosis). The mean FIB-4 score was 1.5 ± 0.89; 7.4% (n = 4) of patients had a score >3.25 (cirrhosis).

The presence of diabetes was associated with higher fibrosis as assessed with FibroScan as shown in Table 2. Duration of HCV did not show a similar influence on fibrosis.

Patients with the presence of fibrosis or cirrhosis 72.2% (n = 39) were treated with FDC of sofosbuvir and velpatasvir. The remaining 27.7% (n = 15) of patients received sofosbuvir and daclatasvir.

Among this, all patients who received sofosbuvir + velpatasvir achieved SVR-12. Two patients (4.1%) in the sofosbuvir + daclatasvir group did not achieve SVR-12. Six patients succumbed in the study period before the measurement of SVR-12. All deaths were related to severe COVID-19 infection with multiorgan dysfunction.

Among patients who did not achieve SVR-12, both were males and had CIN as their native kidney disease. Both the patients had HCV genotype 1 infection with a mean MHD duration of 3.5 ± 0.7 years.

Fibrosis was assessed with noninvasive methods before treatment and after achieving SVR-12 as shown in Table 3. A significant reduction in fibrosis values was noted posttreatment when measured with FibroScan. However, a similar significant reduction was not recognized when assessed with APRI or FIB-4 score. Biochemical parameters did not show significant change with the completion of treatment as shown in Table 4. Clinical and biochemical parameters between patients who achieved SVR-12 and who did not are shown in Table 5.
None of the patients experienced serious side effects requiring dose reduction or discontinuation of the DAAs. Minor side effects include—vomiting in 11.1% (n = 6), headache in 5.5% (n = 3), and myalgia in 1.8% (n = 1) patients.

Table 3: Changes in fibrosis before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Before DAA (in kPa)</th>
<th>After DAA (in kPa)</th>
<th>Significance (student t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroscan</td>
<td>10.5 ± 6.3</td>
<td>7.4 ± 2.6</td>
<td>0.008</td>
</tr>
<tr>
<td>APRI score</td>
<td>0.71 ± 0.55</td>
<td>0.5 ± 0.62</td>
<td>0.329</td>
</tr>
<tr>
<td>Fib-4 score</td>
<td>1.5 ± 0.89</td>
<td>1.4 ± 0.72</td>
<td>0.423</td>
</tr>
</tbody>
</table>

Table 4: Changes in biochemical parameters with treatment

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.6 ± 1.2</td>
<td>8.8 ± 1.2</td>
<td>0.054</td>
</tr>
<tr>
<td>Platelet count (lakh cells/mm³)</td>
<td>2.02 ± 0.66</td>
<td>2.11 ± 0.59</td>
<td>0.421</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.82 ± 0.35</td>
<td>0.75 ± 0.23</td>
<td>0.268</td>
</tr>
<tr>
<td>Serum albumin (gm/dL)</td>
<td>3.08 ± 0.5</td>
<td>3.05 ± 0.5</td>
<td>0.892</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>36.7 ± 20.1</td>
<td>31.9 ± 14.3</td>
<td>0.610</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>35.5 ± 23.2</td>
<td>31.3 ± 16.7</td>
<td>0.521</td>
</tr>
</tbody>
</table>

Table 5: Comparison of clinical and biochemical parameters between patients who achieved and failed SVR-12

<table>
<thead>
<tr>
<th></th>
<th>SVR attained (n = 46)</th>
<th>SVR not attained (n = 2)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.3 ± 10.6</td>
<td>33.5 ± 16.2</td>
<td>0.10</td>
</tr>
<tr>
<td>Disease CKD/CGN/DKD</td>
<td>19/17/10</td>
<td>0/2/0</td>
<td>0.23</td>
</tr>
<tr>
<td>Genotype: 1/3</td>
<td>28/9</td>
<td>2/0</td>
<td>0.57</td>
</tr>
<tr>
<td>HCV duration</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.39</td>
</tr>
<tr>
<td>MHD duration</td>
<td>3.4 ± 0.7</td>
<td>3.5 ± 0.7</td>
<td>0.96</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>8.7 ± 1.2</td>
<td>7.6 ± 0.1</td>
<td>0.19</td>
</tr>
<tr>
<td>Platelet</td>
<td>2.0 ± 0.6</td>
<td>1.7 ± 0.4</td>
<td>0.55</td>
</tr>
<tr>
<td>Serum creat</td>
<td>6.7 ± 1.8</td>
<td>6.1 ± 0.7</td>
<td>0.65</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>3.5 ± 0.4</td>
<td>3.07 ± 0.5</td>
<td>0.27</td>
</tr>
<tr>
<td>APRI</td>
<td>0.6 ± 0.4</td>
<td>0.2 ± 0.07</td>
<td>0.24</td>
</tr>
<tr>
<td>Fib-4</td>
<td>1.5 ± 0.8</td>
<td>0.8 ± 0.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Fibroscan</td>
<td>8.5 ± 2.9</td>
<td>5.4 ± 0.2</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Table 6: Comparison of various studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients(N)</td>
<td>62</td>
<td>59</td>
<td>51</td>
<td>54</td>
</tr>
<tr>
<td>Genotype</td>
<td>64.9%</td>
<td>46%</td>
<td>79%</td>
<td>77%</td>
</tr>
<tr>
<td>1</td>
<td>29%</td>
<td>32%</td>
<td>15%</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median HCV RNA (IU/MI)</td>
<td>10⁶</td>
<td>5.8 Log₁₀</td>
<td>2 × 10⁶</td>
<td>283894.5</td>
</tr>
<tr>
<td>Treatment regime</td>
<td>Sofosbuvir (daily)+</td>
<td>Sofosbuvir (400 mg) +</td>
<td>Sofosbuvir (400 mg) +</td>
<td>Sofosbuvir (400 mg) +</td>
</tr>
<tr>
<td></td>
<td>ribavirin/daclatasvir</td>
<td>velpatasvir (100 mg) daily</td>
<td>velpatasvir (100 mg) daily</td>
<td>velpatasvir (100 mg) daily</td>
</tr>
<tr>
<td>SVR₁₂</td>
<td>95.2%</td>
<td>95%</td>
<td>96%</td>
<td>95.6%</td>
</tr>
<tr>
<td>Side effects</td>
<td>Dyspepsia</td>
<td>Headache</td>
<td>Nausea</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td></td>
<td>Headache</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Myalgia</td>
</tr>
</tbody>
</table>

DISCUSSION

Despite the lack of dosing recommendations for sofosbuvir-containing regimens for HCV in ESRD patients, it is commonly used as an off-label in clinical practice. Moreover, some of the real-world case series have shown negligible safety concerns with full-dose sofosbuvir-based regimes.11–15 Although HCV infection is curable in the general population, there is still hesitancy in treating patients with MHD in this part of the world due to the nonavailability of recommended drugs and the fear of renal adverse events.2,4

In this study, we followed National hepatitis C guidelines in the management of HCV infection in ESRD patients on MHD.16 Patients were treated with pangenotypic regimes of full-dose sofosbuvir with velpatasvir or daclatasvir based on the presence of fibrosis/cirrhosis.

A recent meta-analysis in patients with CKD on MHD had shown a pooled SVR of 93.2% with a minor difference in terms of genotype.17 Our study showed an SVR of 95.6% with only two patients not attaining SVR. Both patients had genotype 1 with no fibrosis and were treated with daclatasvir. In a similar study from India, SVR with daclatasvir was achieved at 95.2% (Table 6).18

Desnoyer et al. had shown that sofosbuvir or its inactive metabolite did not accumulate with both full or half-dose sofosbuvir between hemodialysis sessions or throughout the treatment course.19 Importantly, SVR rates were similar in both doses of sofosbuvir. Also, pharmacokinetic properties with different dosing regimes of sofosbuvir were determined, suggesting that the low sofosbuvir dose might be suboptimal in these patients. The adverse events were not related to an elevated toxic metabolite which was
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exceeded only in the full-dose sofosbuvir group. The available limited studies with full-dose sofosbuvir-based regimes show similar efficacy across all genotypes and regions.\(^1\)

Another important concern after efficacy is the safety of different doses of these regimes. Initial studies have shown the worsening of renal function with sofosbuvir-based regimes in patients with moderate renal insufficiency.\(^2\) However, it is difficult to attribute it to drug per se and may be related to the natural dynamic course of CKD itself. There are more recent data suggesting excellent safety with full-dose sofosbuvir regime. Meta-analysis of 11 studies has shown a pooled adverse events rate of 8–11%, with negligible serious events in most of the studies.\(^2\) It is important to note that the adverse events were more common in patients with advanced liver disease and patients with prior treatment failure who may require a longer duration of treatment or the addition of ribavirin. Ribavirin is known to cause anemia and increase the need for erythropoietin in CKD patients.\(^3\)

Our study showed minor adverse events in 10 (18.5%) patients, which were self-limiting and did not require modification or discontinuation of dose. There was no difference in hemoglobin, creatinine, or liver biochemistry posttherapy. These results are comparable to two papers from North India, where rates of adverse effects were 10% with no difference between the predialysis and dialysis groups.\(^2\)

With the newer available DAA, the major determinants of poor response are fibrosis/cirrhosis, prior failure with interferon or earlier DAA therapy, and genotype 3. This population requires 6 months of DAA therapy and resistance testing before initiation of DAA.\(^4\)

In our study, cirrhosis was present in nine (16.6%) patients. None of them had decompensated liver disease. Fortunately, all of them achieved SVR with no major adverse effects. A study by Taneya et al.\(^5\) in patients with ESRD, found 19.6% of patients with cirrhosis (FibroScan values of >12.5 kPa) among which one patient had decompensated cirrhosis, and another study by Manoj et al.\(^6\) had 23.9% patients with compensated cirrhosis.\(^2\)

FibroScan-based assessment of fibrosis needs costly equipment which may not be available in all centers. We assessed fibrosis with novel biomarkers like APRI, and Fib-4 scoring which showed only four–five patients with cirrhosis. This shows a lower prevalence of patients with significant fibrosis in our cohort. Fibrosis was also assessed pre and posttreatment and showed a significant reduction in fibrosis. This determines the reduction in ongoing inflammation with treatment. A similar reduction has been shown in other studies as well.\(^2,3\) Also, diabetes was determined as an important confounding factor for the presence of fibrosis. In a study by Hajjani et al., mean liver stiffness scores in the diabetic group were significantly higher than in nondiabetics.\(^4\) Diabetes is one of the common causes of nonalcoholic fatty liver disease and may have an additive effect on overall fibrosis.\(^5\)

Due to the lower number of patients in DAA failed cases (n = 2), a multivariate analysis could not be performed to find predictors for nonattainment of SVR. On univariate analysis, none of the parameters were predictive. Hence, DAA were effective in achieving SVR regardless of age, sex, genotype, duration of disease, or degree of fibrosis.

The small sample size, single-center study, and nonestimation of sofosbuvir and its metabolites to correlate side effects were a few of the limitations of the study. Also, comparison with ESRD patients, not on MHD would have given more insight on the adverse effects profile in this difficult-to-treat population. The 6 months courses of full-dose sofosbuvir in patients with concomitant CKD and decompensated liver disease or prior DAA failure cases would further validate the safety profile in these cases. Nevertheless, we had a comparatively larger cohort from a single center with different CKD profiles and a sufficient follow-up period. Also, fibrosis assessment and correlation were done in all patients.

To conclude, data from this study support the use of full-dose sofosbuvir with velpatasvir or daclatasvir with excellent efficacy and safety in patients with ESRD on MHD.

References