Sofosbuvir Based Regimen in Management of Hepatitis C for Patients With End Stage Renal Disease on Hemodialysis: A Single Center Experience from India

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Background: Hepatitis C infection is known to increase the morbidity in patients with end stage renal disease (ESRD). Interferon based treatment is poorly tolerated and has limited cure rates in these patients. In limited available data, sofosbuvir based regimens have been shown to have favorable outcomes in these patients. **Methods:** We treated 7 patients with ESRD on hemodialysis, 6 with chronic hepatitis C and one with acute hepatitis C. Two of them were cirrhotic of which one was decompensated. All patients were treated with sofosbuvir 200 mg with daclatasvir 60 mg or ribavirin 200 mg once daily. Patients with evidence of cirrhosis were treated for 24 weeks, others were treated for 12 weeks. HCV RNA quantitative PCR was monitored at weeks 2, 4, 12, end of therapy and after 12 weeks of end of treatment (SVR12). **Results:** The study cohort included five males and two females, aged (48.4 ± 14.5 years). Four patients had genotype 1 and three had genotype 3. One patient was treated with sofosbuvir and ribavirin while others were treated with sofosbuvir and daclatasvir. One patient died of unrelated cause during the therapy. One patient who received sofosbuvir and daclatasvir, could not complete the therapy beyond 20 weeks because she developed recurrent hypoglycemia, which improved after stopping the therapy, all the other patients had SVR 12. There was no change in Hb levels or erythropoietin requirement in the patients receiving sofosbuvir and daclatasvir. **Conclusion:** Our data suggest that sofosbuvir based therapy is effective in patients with ESRD and hepatitis C, including those with liver cirrhosis. Its use may be recommended especially in countries where other drugs are not available. Due to limited experience however, patients should be closely monitored for adverse effects. Hypoglycemia may be a potential adverse effect of sofosbuvir and daclatasvir therapy. (J CLIN EXP HEPATOL 2018;8:116-120)

Hepatitis C virus (HCV) infection is common in patients with end stage renal disease (ESRD).¹ Chronic hepatitis C (CHC) infection is known to increase the morbidity and mortality in these patients.²

Direct-acting antivirals (DAA) have revolutionized the treatment of CHC, with increased rates of sustained virologic response (SVR) and minimal side effects. Hepatitis C in ESRD continues to be labeled as 'difficult to treat population', however there have been studies showing positive response of various DAA combinations in this population.³

Keywords: hepatitis C, direct-antiviral agents, end-stage renal disease, liver cirrhosis

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Abbreviations: CHC: chronic hepatitis C; DAA: direct-acting antivirals; ESRD: end stage renal disease; HCV: hepatitis C virus; SVR: sustained virologic response

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There is limited evidence of treatment with DAAs in these patients. Another important aspect is the availability of limited drugs in several countries. In India, available DAAs at the time of completion of this study include, sofosbuvir, daclatasvir and sofosbuvir, ledipasvir combination.

Peginterferon based treatment is successful in achieving SVR in only about half of the patients receiving the treatment and is associated with significant side effects, which can prohibit the treatment completion.⁴ Goel et al. showed 58% response when ribavirin was used with peginterferon.⁵ The major limitation of treating patients on dialysis with sofosbuvir based regimens is limited safety data. The concentrations of sofosbuvir have shown to be significantly higher in these patients as compared to normal population and it was not recommended routinely in patients with eGFR <30 ml/min.

Based on the currently available drugs in India and few studies, recent guidelines on the basis of studies have suggested treatment with sofosbuvir in half of its usual dose and daclatasvir, irrespective of genotype.⁶ We describe our experience of sofosbuvir based regimens

in treatment of chronic hepatitis C population on dialysis.

METHODS

Consecutive patients with ESRD and Hepatitis C, who agreed to be treated were enrolled in the study from October 2015 to October 2016.

Patients were offered the best therapeutic combination available at the time of start of therapy. They were told in detail about the limitation of safety and efficacy data of available DAAs in ESRD population and an informed consent was taken to this effect. Patients were allowed to drop out in case an unexplained side effect or if they wished to discontinue treatment during the therapy. All patients who started the treatment were included for analysis.

As a part of initial evaluation patients were evaluated with HCV RNA quantitative PCR, genotype, LFT, USG abdomen. Fibroscan was done for all patients. Upper gastrointestinal endoscopy was done in patients with liver cirrhosis for assessment of varices.

Irrespective of genotype, patients were treated with half of standard dose of sofosbuvir (200 mg daily) and ribavirin 200 mg as tolerated for 24 weeks in the earlier phase (when sofosbuvir was the only DAA available in India), and then with sofosbuvir (200 mg daily) with daily daclatasvir 60 mg, for 12 weeks in patients without liver cirrhosis and 24 weeks for those with compensated or decompensated cirrhosis. None of these patients were on medications that have interactions with sofosbuvir or daclatasvir.

Patients were closely observed through the study duration. HCV RNA quantitative PCR was monitored at 2 weeks, 4 weeks, 12 weeks for all patients and 24 weeks, for patients needing treatment for 24 weeks. Sustained virological response at was checked after 12 weeks of end of treatment (SVR 12).

Caregiver information was stored in database and they were provided with a helpline number to inform and report any untoward event.

RESULTS

Seven patients consented to begin the therapy. The study cohort included five males and two females with mean age of 48.4 ± 14.5 years.

Characteristics and outcomes of individual patients is summarized in Table 1.

Genotype 1 predominated in the study population (5/7; 71.4%). One (14.3%) was having acute hepatitis C, two (28.6%) had liver cirrhosis of which one was decompensated and two (28.6%) were treatment experienced with Peg Interferon based therapy with no response. One of the

patients with liver cirrhosis had chronic hepatitis B co-infection and was being treated with Entecavir 0.5 mg once weekly before initiating hepatitis C therapy.

After two weeks of treatment, six (85.7%) patients had non-detectable viral load. One patient died in third week of therapy. At week four of therapy all the patients had non-detectable virus levels (6/6; 100%), and continued to do so during the therapy. All patients developed SVR 12.

Patient 1, was 37-year-male, developed icteric illness. Bilirubin was 4.4 mg/dl, SGPT: 1025 IU/L and SGOT: 637 IU/L. HCV antibody which was negative in past investigations, was now positive. Other causes of acute hepatitis were ruled out. HCV RNA Quantitative RNA was $6 \log_{10}$. Features of viral hepatitis improved. He continued to have same viral load after 3 months of follow up and was offered treatment with the available therapy during the time. He was treated for 24 weeks with sofosbuvir 200 mg daily with ribavirin 200 mg daily, but dose adjustment was needed for anemia and the average daily dose of ribavirin was 104.76 mg/day. After 2 weeks of therapy HCV RNA decreased to 239 IU/ml. No blood transfusions or adjustment of erythropoietin dose change was required.

Patient 3, died suddenly at home in week 3 of therapy. There was no previous history of cardiac disease or intake of drug known to be interacting with antiviral therapy.

Patient 5, a 62-year-female developed recurrent hypoglycemia in week 18th of the therapy. There was no history of diabetes mellitus. Insulinoma was excluded with investigations including endosonography. She discontinued the therapy in week 20th, after 12 weeks of stopping the therapy she had non-detectable viral load. No further episodes of hypoglycemia occurred till the last follow up.

Other patients had unremarkable course during the treatment and follow up.

DISCUSSION

Experience with Interferon free, DAA therapy is growing in patients with ESRD with HCV infection. A recent meta-analysis showed SVR 12 with DAAs in 93.2% patients with stage 4 and stage 5 ESRD.⁷ In a recently published large trial it was shown that though sofosbuvir based regimens are useful, they have potential for serious adverse events.⁸ There is evidence of use of elbasvir-grazoprevir, simeprevir and combination of ombitasvir, paritaprevir, ritonavir and dasabuvir in these group of patients, however these DAAs are currently not available in India and several other countries.⁹

All except one patient (with acute hepatitis C; one who received ribavirin with sofosbuvir), had non-detectable viral load in second week of therapy, suggesting the potency of Sofobuvir based regimen in patients with ESRD. Negative viral load in second week of therapy or vRVR (very rapid virologic response), is suggestive of

Table 1 Characteristics and Outcome of Treated Patients.

Patient No.	Illness	Age	Sex	Baseline RNA (IU/ml)	Genotype	Cirrhosis	Treatment experienced	Treatment	Duration planned (weeks)	Duration taken (weeks)	Less than detectable viral load after starting treatment				SVR 12	Side effects
											2 weeks	4 weeks	12 weeks	24 weeks		
1	AHC	37	M	1,000,000	1	No	No	Sof + riba	24	24	No	Yes	Yes	NA	Yes	Anemia, responsive to ribavirin dose adjustment
2	CHC	54	F	350,000	1	No	No	Sof + dacla	12	12	Yes	Yes	Yes	NA	Yes	None
3	CHC	31	M	5,722,737	1	Yes With chronic hepatitis B on entecavir	No	Sof + dacla	24	24	Yes	Yes	Yes	Yes	Yes	None
4	CHC	32	M	400,000	3	No	Yes	Sof + dacla	12	3	Yes	NA	NA	NA	NA	Died in week 3 of therapy
5	CHC	62	F	35,460	1	Yes, decompensated	No	Sof + dacla	24	20	Yes	Yes	Yes	NA	Yes ^a	Hypoglycemia, persisting after stopping treatment
6	CHC	61	M	78,976	3	No	No	Sof + dacla	12	12	Yes	Yes	Yes	NA	Yes	None
7	CHC	62	M	79,000	3	No	Yes	Sof + dacla	12	12	Yes	Yes	Yes	NA	Yes	None

^a12 weeks from when the treatment was stopped at 20 weeks.

AHC = acute hepatitis C; CHC = chronic hepatitis C; SVR = sustained virologic response; Sof = sofosbuvir 200 mg; Riba = ribavirin 200 mg alternate day; Dacla = daclatasvir 60 mg.

efficacy of treatment regimen and may be considered as a useful measure in viral kinetics.¹⁰ Although we have done vRVR, it is not recommended.

To best of our understanding, our patient with acute hepatitis C, is the first report of successful treatment of acute hepatitis C in ESRD, we used sofosbuvir with ribavirin in this patient since sofosbuvir was the only DAA available in India at that time. Treatment was given for 24 weeks according to the prevalent recommendations at that time for genotype 1 patients who are interferon ineligible.¹¹ Naggie et al. had reported a high relapse in patients with acute hepatitis C with HIV coinfection when treated with sofosbuvir and ribavirin for 12 weeks.¹² Previous data had suggested that patients with acute hepatitis C be observed for 12 weeks before beginning the therapy to give an interval for spontaneous resolution of virus.¹³ However, with availability of DAAs these recommendations may change in future.¹⁴

One of the patients with ESRD and CHC had sudden death while he was in third week of treatment. Sudden death may occur in patients with ESRD and is usually thought to have cardiac cause.^{15,16} This patient did not have any known cardiac illness, there was no known interacting drug that this patient was receiving.

We noted recurrent episodes of hypoglycemia, requiring hospitalization in one of the patients with decompensated liver disease treated with sofosbuvir and daclatasvir in 18th week of therapy discontinuation of DAAs was done after week 20th with no further similar episodes till date. Although ESRD and liver cirrhosis are known to be independent risk factors for hypoglycemia,^{17,18} in POSITRON study hypoglycemia was reported as a treatment emergent side effect in one patient.¹⁹ This patient had achieved SVR 12 (12 weeks from when the treatment was discontinued). Hypoglycemia episodes were most likely caused by DAA therapy given its temporal association, improvement on discontinuation of the drugs and its known association, even though rare. Using Naranjo causality scale hypoglycemia in this patient qualified as a possible adverse drug reaction to DAAs.²⁰

Desnoyer et al. treated eight patients with sofosbuvir and daclatasvir with four patients on daily full dose sofosbuvir and four on thrice weekly sofosbuvir for 12 or 24 weeks. Interestingly, seven of these patients had cirrhosis. They reported relapse in two patients who had cirrhosis and were treated for 12 weeks with thrice weekly regimen. Based on their data, authors recommended daily full dose sofosbuvir in patients who are treatment experienced or have liver cirrhosis. However, it is possible that the relapse in these two patients was due to the shorter duration of treatment rather than thrice weekly regimen, since another patient with cirrhosis, treated for 24 weeks, achieved SVR with thrice weekly regimen.²¹ We achieved SVR 12 in all the patients with cirrhosis (two; one of whom was decompensated) and

those who were interferon experienced (two). A recent study from India showed good SVR 12 with 400 mg alternate day sofosbuvir.²² We therefore suggest half-dose sofosbuvir daily (200 mg) with daclatasvir 60 mg daily for 12 weeks and 24 weeks for patients without and with liver cirrhosis respectively. Issue of full dose versus half dose sofosbuvir needs further evaluation in terms of efficacy and safety, as full dose sofosbuvir has been shown to be well tolerated.⁷

Another important aspect of treating patients who have compromised renal function, with sofosbuvir based therapy, irrespective of use of ribavirin, is further deterioration in the renal functions, this aspect was evident from the HCV-TARGET cohort and further highlights the importance of close monitoring of these patients.²³

To conclude, with our limited database of HCV infection in patients with ESRD, which had heterogeneous patient population, including a patient with acute hepatitis C and two patients with liver cirrhosis one of whom was HBV co-infected while the other was decompensated, we archived a high rate of SVR in difficult to treat population with half the usual dose of sofosbuvir and full dose daclatasvir. However, it is important to monitor these patients closely for adverse events. Randomized controlled trials with larger number of patients may be suggested based on our results to define the best dose and duration of treatment in patients with ESRD in regions where sofosbuvir based regimens are mainstay of treatment.

CONFLICTS OF INTEREST

The authors have none to declare.

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