

Hemodialysis Patients Treated for Hepatitis C Using a Sofosbuvir-based Regimen



Sanjay Kumar Agarwal¹, Soumita Bagchi¹ and Raj Kumar Yadav¹

¹Department of Nephrology, All India Institute of Medical Sciences, New Delhi, India

Introduction: There is paucity of data on sofosbuvir (SOF)-based therapy in patients on maintenance hemodialysis (MHD). The objective of this report is to describe our experience using SOF-based direct antiviral agent (DAA) therapy in MHD patients in India.

Methods: All patients on MHD and treated with SOF-based therapy were included in this study. Before starting treatment, viral load, genotype, liver fibroscan, and upper gastrointestinal endoscopy were performed in all patients. SOF 400 mg/d or on an alternate day, ribavirin 200 mg/d and daclatasvir 60 mg/d were used in different regimens. Hepatitis C virus RNA was assessed at day 10 and at 4 weeks, at end of therapy, and at 12 weeks after stopping therapy.

Results: A total of 62 treatment-naïve patients were included. Mean age was 33.3 ± 10.2 years; 66% were men. Median number of copies were 10^6 /dl. None had clinical evidence of cirrhosis. The most common genotype was genotype 1 in 64.5% of cases, followed by genotype 3 in 29% of cases. Thirty-nine patients were treated with SOF every other day/ribavirin, 2 patients with SOF daily/ribavirin, 6 with SOF every other day/daclatasvir, and 15 patients with SOF daily/daclatasvir. All patients were treated for 12 weeks. Fifty-nine (95.2%) patients had a sustained viral response (SVR). There was no impact of genotype on SVR. Twenty-three patients (37%) had complications while on therapy; 13 (20.3%) had dyspepsia, 4 had tuberculosis, and 3 had bacterial pneumonia. Most of the patients ($n = 23$; 56%) in the ribavirin group required an increase in the erythropoietin dose. No patient discontinued therapy due to complications.

Discussion: SOF-based DAAs were well tolerated and efficacious in this cohort of patients on MHD.

Kidney Int Rep (2017) 2, 831–835; <http://dx.doi.org/10.1016/j.ekir.2017.04.003>

KEYWORDS: DAA; daclatasvir; HCV; hemodialysis; India; sofosbuvir

© 2017 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Hepatitis C virus (HCV) infection is the most common hepatotropic viral infection that affects patients on maintenance hemodialysis (MHD). Its prevalence in patients on MHD ranges from 6% to 60% in different parts of the world. In India, various studies have shown a prevalence of HCV in hemodialysis from 4.3% to 45%.^{1,2} Nosocomial transmission and transmission through blood and blood components are 2 important factors that affect HCV incidence.^{3,4} We have also shown that chronic liver disease is an important cause of mortality in renal transplantation at our center.⁵ HCV also increases the risk of serious infection in renal transplantation patients.⁶ Because HCV infection has been a major issue in many dialysis units in India, these patients are isolated in addition to practicing

universal precautions,⁷ because dialysis personnel have been reported to be noncompliant with universal precautions.⁸

Despite all of these precautions, significant numbers of patients do develop new HCV infection. Kidney Disease Improving Global Outcomes guidelines have suggested treatment with standard interferon (IFN) before transplantation, although the evidence for the recommendation is weak.⁹ We showed a 54% sustained virological response (SVR) in our patients while using pegylated IFN monotherapy with no impact of genotype on SVR, although treatment was limited by significant side effects in these patients.¹⁰ With the development of direct antiviral agents (DAAs), therapy for HCV has been revolutionized. However, there are 2 issues related to DAAs. First, various DAA drugs are not universally available in all countries. Second, doses and safety for all DAAs, particularly sofosbuvir (SOF) in stages IV and V chronic kidney disease (CKD) (glomerular filtration rate <30 ml/min) or during MHD is unclear. In India, only SOF and subsequently

Correspondence: SK Agarwal, Department of Nephrology, All India Institute of Medical Sciences, New Delhi 110029, India. E-mail: skagarwalnephro@gmail.com

Received 25 January 2017; revised 6 April 2017; accepted 11 April 2017; published online 25 April 2017

daclatasvir were available in 2015 to 2016. 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 disease and patients on MHD. We report the first experience of DAA therapy in patients in India who were on MHD and who were awaiting renal transplant.

MATERIALS AND METHODS

All patients with HCV infection at our hospital with end-stage renal disease who underwent renal replacement therapy (RRT) and who were treated with DAAs were included in the present study. Handling of HCV-infected patients was previously described in detail.¹⁰ Patients with positive anti-HCV antibodies were further investigated for their qualitative HCV RNA, HCV viral load, and HCV genotype as described previously.¹⁰ Because of our previous experience of only 1 patient with histological cirrhosis,¹¹ we clinically assessed the activity of liver disease, and no patient underwent liver biopsy. Before starting treatment, hemoglobin, total leukocyte count, differential leukocyte count, platelets, reticulocyte counts, and alpha fetoprotein were assessed in all patients using standard methods. The timing of HCV infection was considered the time since the alanine aminotransferase levels were high above the normal limit or anti-HCV was positive, whichever was earlier. Diagnosis of HCV, polymerase chain reaction, and genotype testing were described previously.¹⁰ Liver fibrosis was measured non-invasively by transient elastography (Fibroscan, Echosens, Paris, France), and the liver stiffness measurement was expressed in kilopascals. A cutoff value of <6 kPa for the liver stiffness measurement excluded fibrosis, and >9 kPa for the liver stiffness measurement was regarded as significant fibrosis. Hepatic steatosis was measured by controlled attenuation parameters, and a value of ≥ 250 dB/m indicated significant steatosis.

In response to the initial safety and efficacy data using a full dose of SOF in dialysis patients,¹² after the first few patients ($n = 45$), we increased the dose to 400 mg/d for the remainder of the cohort.¹³ After a few months, daclatasvir became available in India, and we started using daclatasvir 60 mg/d with SOF 400 mg/d in all our patients with all genotypes. All patients were asked to contact their primary caregiver (SKA) if they had any adverse symptoms. For the initial 2 weeks, all biochemical tests were repeated weekly; after that, tests were done as per clinical indications. Patients were followed weekly for the first month, biweekly in the second month, and then at the end of third month.

The first quantitative HCV RNA was assessed between the seventh and fifteenth day after the start of treatment. Subsequent HCV RNA was done at the end of first month, at the end of therapy, and 12 weeks after the stoppage of treatment. Initially, we waited for therapy to be completed before renal transplant was done. However, considering the superior safety profile of these drugs in the post-transplantation period, treatment was also continued in the perioperative period.

RESULTS

From June 2015 to September 2016, 62 treatment-naïve patients were treated with various DAA regimens. Table 1 shows baseline characteristics of these patients. Etiology of CKD was unclassified in most ($n = 43$) of the patients, and only 4 patients had underlying diabetic kidney disease. Mean alanine aminotransferase value was 47.8 ± 34.4 IU/dl (range: 7–180 IU/dl), and mean alpha-fetoprotein was 3.3 ± 0.8 IU/dl (range; 2.3–6.3 IU/dl). The most common genotype was genotype 1 in 64.5% of patients (Table 1) followed by genotype 3 in 29% of cases. None of the patients was subjected to liver biopsy, although all had normal upper gastrointestinal endoscopy. None of the patients had thrombocytopenia, increased bilirubin, and/or clinical hepatitis at start of therapy. Other baseline investigations are shown in Table 1. Mean time from the

Table 1. Baseline characteristics of patients on maintenance hemodialysis treated with sofosbuvir-based therapy

Characteristics	Treated patients
No. of patients	62
Mean age (yr)	33.8 ± 10.2 (16–53)
Male	41 (66.1%)
Mean dialysis vintage (mo)	8.2 ± 6.3 (1–15)
Diabetes as native disease	4 (6.4)
Coronary artery disease	Nil
HIV	Nil
Hemoglobin (g/dl)	10.3 ± 2.3
Patients taking EPO	60 (97)
Genotype status	
1	40 (64.5)
2	1 (1.6)
3	18 (29)
4	2 (3.2)
6	1 (1.6)
ALT (IU/dl)	47.8 ± 34.4 (7–180)
Alpha-fetoprotein (mg/dl)	3.35 ± 0.8 (2.3–6.3)
LSM (kPa)	8.4 ± 4.5 (3.1–33.8)
Cap (dB/m)	191.1 ± 81.3 (100–712)
Serum albumin (g/dl)	4.2 ± 0.6 (2.7–6)
Quantitative RNA copies (median and interquartile range)	10^6 (10^4 – 10^8)

Values are n (%) and mean \pm SD (range).

ALT, alanine aminotransferase; Cap, controlled attenuation parameter; EPO, erythropoietin; LSM, liver stiffness measurement.

Table 2. Treatment groups in the study

Treatment drugs	No. of patients	SVR n (%)
SOF 400 mg A/D + Rib 200 mg/d	39	37 (94.8)
SOF 400 mg/d + Rib 200 mg/d	2	2 (100)
SOF 400 mg A/D + DAC 60 mg/d	6	6 (100)
SOF 400 mg/d + DAC 60 mg/d	15	14 (93.3)
Total	62	59 (95.2)

A/D, alternate day; DAC, daclatasvir; Rib, ribavirin; SOF, sofosbuvir; SVR, sustained virological response.

diagnosis of HCV infection to the initiation of treatment was 43.2 ± 18.8 months (range: 5–140 months). The treatment regimens used and number of patients in each regimen are shown in Table 2. All patients were treated for 12 weeks. Sixty (96.8%) patients had an undetectable viral load by the 14th day, whereas all patients (100%) had an undetectable viral load by week 4, and there was no virologic breakthroughs on therapy. SVR, defined as a negative viral load at 12 weeks after therapy, was achieved by 59 (95.2%) patients. There was no difference in response rates in relation to genotype. Three patients who relapsed had 1 each of the 1, 3a, and 4 genotypes.

Twenty-three patients (37%) had complications while on therapy. Thirteen (20.3%) patients had dyspepsia after start of treatment. Most of the patients (23 of 41; 56%) in the ribavirin group required an increase in mean weekly erythropoietin doses of $12,000 \pm 1873$ U (range: 10,000–16,000 U), with or without injectable iron therapy. Three patients required blood transfusion. Patients who were not on ribavirin did not require an increase in erythropoietin doses.

The maximum dose of erythropoietin given was 16,000 U/week in 5 patients. None of the patients had any other biochemical abnormality attributed to drug treatment. Four patients developed tuberculosis, and 3 experienced bacterial pneumonias; all of these patients were treated appropriately. None of the patients discontinued therapy due to side effects. Of the treated patients, 22 had undergone renal transplant at the time of writing this paper.

DISCUSSION

This is the first report on the experience of DAAs in patients on MHD from India and the largest single-center experience on SOF-based therapy in hemodialysis patients. Considering the efficacy and safety of these drugs in these patients, management of HCV-infected patients in hemodialysis is going to change dramatically. This is much more relevant in a country like India, where in some dialysis units, HCV infection prevalence is still >50% (unpublished data).

A recently published meta-analysis showed that there were 11 studies on the efficacy of DAAs in 264 patients on MHD, including 1 multicenter study that enrolled 122 patients (Table 3).^{14–20} The SVR in all these studies^{13,15–23} ranged between 66.7% and 98.3%, with a pooled SVR of 93.2%. For several subgroup populations, SVR in SOF-based therapy was 89.4%. For genotype 1 patients, the pooled SVR rate at 12 weeks was 93.1%. Nineteen patients in 2 studies were treated with a half-dose of SOF, and 4 of them failed to reach SVR rate at 12 weeks, suggesting that the SOF dose may be an important variable for SVR. In addition, in our patient group, all 3 patients who relapsed after

Table 3. Details of studies on direct antiviral agents in patients on hemodialysis

Study no.	Author/yr	Region	No	Treatment strategy	Mean age (yr)	Men (%)	Cirrhosis (%)	Mean baseline HCV RNA (log ₁₀ IU/ml)	Previous treatment (%)	Genotype (%)	No. of patients with SAE (%)	SVR (%)
1	Brahmidimari 2015 ²¹	USA	15	SOF + SMV	60	73	60	Mean 6.99	60	1 (100)	0	86.7
2	Roth 2015 ²²	Multicentric	122	Non-SOF based	58	100	5.7	≥ 5.9 (56.6%)	17.2	1 (100)	13	94.3
3	Hundemer 2015 ¹⁵	USA	6	SOF, SMV, RBV, PR	60	83	50	6.48	50	1 (100)	33	66.7
4	Beinhardt 2016 ¹⁶	Austria	10	SOF, PR, SMW, DCV, RBV	51	NR	40	6.1	40	1 (60) 3 (20) 4 (20)	50	95.5
5	Miyazaki 2016 ¹⁷	Japan	10	DCV, Asunaprevir	68	70	0	7.46–7.79	NR	NR	20	95.5
6	Nazario 2016 ⁴	USA	17	SOF monotherapy	57	82	47	>5.9 (76.5%)	18	1 (100)	0	97.2
7	Pockros 2016 ¹⁸	USA	20	OBV, PTV, Ritonavir, DSV	60	85	0	6.6	NR	1 (100)	20	90
8	Saxena 2016 ¹⁹	USA & Europe	18	SOF, SMV, RBV, PR	65	22	38.9	6.11	55.6	1 (78) 2 (17) 3 (6)	16	88.2
9	Singh 2016 ²⁰	USA	8	SOF, SWV, LDV	56	25	37.5	6.62	12.5	1 (75) 3 (12.5) 4 (12.5)	12.5	87.5
11	Desnoyer 2016 ¹³	France	10	SOF, SMW, DCV, LDV, RBV	52	80	80	6.59	60	1 (90) 2 (10)	0	80
12	Present study 2016	India	62	SOF, RBV, DCV	34	66	Nil	7	Nil	1 (6) 3 (29)	11.2	95.2

DCV, daclatasvir; DSV, dasabuvir; LDV, ledipasvir; OBV, ombitasvir; PR, pegylated interferon combined with ribavirin; PTV, paritaprevir; RBV, ribavirin; SM, simeprevir; SOF, sofosbuvir.

completion of therapy were on 400 mg alternate day SOF treatment. Desnoyer *et al.*¹³ showed that SOF and its active metabolites did not accumulate in patients on hemodialysis and suggested use of 400 mg/d SOF with close monitoring. Available literature and our own experience showed excellent efficacy of various DAAs, including SOF-based therapy in HCV patients on hemodialysis, with a SVR close to 90% in most studies. In many studies, the most common genotype was genotype 1. Genotype 1 was also seen in 64.5% of patients, followed by genotype 3 in 29% of cases in the present study. Genotypes 2 and 6 were seen in 2 patients, respectively, and genotype 4 was found in 2 patients.

With such excellent efficacy, the next issue of concern is safety. The present study also showed excellent safety, with an increase in dyspepsia being the only frequent side effect. In patients on hemodialysis, dyspepsia might not always be attributed to drug therapy. There was no difference in dyspepsia whether patients were on SOF 400 mg alternate day or daily therapy. Patients who were on ribavirin therapy did require an increase in erythropoietin dose, which was not unexpected. We were forced to use ribavirin because other DAAs were not available initially. Once daclatasvir became available, we substituted this medication in combination with SOF and stopped using ribavirin. Previous studies showed serious adverse events ranging from 0% to 50% of patients. There are many issues to be taken into account when interpreting side effects in these studies. First, the number of patients in many of these studies were few, which could distort interpretation of the percentage of side effects. Second, except for 2 studies,^{17,18} all others had patients with cirrhosis (range: 40%–80%). In the present study, no patient had clinical cirrhosis (normal endoscopy in all), although we did not perform liver biopsies in any of the patients. Third, in many of these studies, previous treatment had failed in patients with HCV. Fourth, almost all studies had used treatment with DAAs in addition to SOF, making it difficult to interpret which drug was responsible for the side effects.

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. Patients with ESRD usually do not have cirrhosis because most of the time this is a contraindication for an isolated renal transplantation, which nephrologists supervise. This makes handling of DAAs in this clinical setting easy because some of the DAAs (e.g., protease inhibitors) are not recommended in decompensated cirrhosis. 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. Considering this ambiguity about SOF use in MHD patients, we are sharing our large single-center experience of the excellent safety and efficacy of SOF in these patients.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGEMENTS

We acknowledge the contribution made by department of gastroenterology in performing liver fibroscan and upper gastrointestinal endoscopy in all patients.

REFERENCES

1. Agarwal SK, Dash SC, Gupta S, et al. HCV infection in hemodialysis: "NO isolation" policy should not be generalized. *Nephron Clin Practice*. 2009;111:c133–c140.
2. Agarwal SK, Dash SC, Irshad M. Hepatitis C infection during haemodialysis in India. *J Assoc Physicians India*. 1999;47:1139–1143.
3. Pereira BJ, Levey AS. Hepatitis C virus infection in dialysis and renal transplantation. *Kidney Int*. 1997;51:981–999.
4. Le Pogam S, Le Chapiro D, Christen R, et al. A hepatitis C in a haemodialysis unit: molecular evidence for nosocomial transmission. *J Clin Microbiol*. 1998;36:3040–3043.
5. Agarwal SK, Dash SC, Mehta SN, et al. Results of renal transplantation on conventional immunosuppression in second decade in India: a single centre experience. *J Assoc Physicians India*. 2001;50:532–536.
6. Agarwal SK, Dash SC, Irshad M, et al. Impact of hepatitis C viral infection on renal transplant outcome in India—a single center study. *J Assoc Physicians India*. 2000;48:1155–1159.
7. Agarwal SK, Irshad M, Dash SC. HCV infection during renal replacement therapy: should we dialyze all hepatitis C positive patients on dedicated machines? *Nephron*. 1998;79:479–480.
8. Agarwal SK, Mohan MP, Varghese M. Assessment of awareness regarding universal precaution among the nursing staff of AIIMS in 1997. *J Assoc Physicians India*. 1998;46:1061.
9. KDIGO Work Group. Guideline 4: Management of HCV-infected patients before and after kidney transplantation. *Kidney Int*. 2008;73(Suppl 109):S53–S68.
10. Agarwal SK, Bhowmik D, Mahajan S, et al. Pegylated interferon monotherapy for hepatitis C virus infection in patients on hemodialysis: a single center study. *Indian J Nephrol*. 2016;26:244–251.
11. Agarwal SK, Dattagupta S. Liver biopsy in patients on hemodialysis with hepatitis C virus infection: an important tool. *Indian J Nephrol*. 2015;25:152–157.
12. ClinicalTrials.gov. Sofosbuvir plus ribavirin, or ledipasvir/sofosbuvir in adults with HCV infection and renal insufficiency. Available at: <https://clinicaltrials.gov/ct2/show/NCT01958281>. Accessed January 14, 2017.

13. Desnoyer A, Pospai D, Patrick Lê M, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. *J Hepatol*. 2016;65:40–47.
14. Li T, Qu Y, Guo Y, et al. Efficacy and safety of direct-acting antivirals-based antiviral therapies for hepatitis C virus patients with stage 4-5 chronic kidney disease: a meta-analysis. *Liver Int*. 2016;1–8.
15. Hundemer GL, Sise ME, Wisocky J, et al. Use of sofosbuvir-based direct-acting antiviral therapy for hepatitis C viral infection in patients with severe renal insufficiency. *Infect Dis (Lond)*. 2015;47:924–929.
16. Beinhardt S, Al Zoairy R, Ferenci P, et al. DAA based antiviral treatment of patients with chronic hepatitis C in the pre-and post kidney transplantation setting. *Transpl Int*. 2016;29:999–1007.
17. Miyazaki R, Miyagi K. Effect and safety of daclatasvir-asunaprevir combination therapy for chronic hepatitis C virus genotype 1b-infected patients on hemodialysis. *Ther Apher Dial*. 2016;20:462–467.
18. Pockros PJ, Reddy KR, Mantry PS, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. *Gastroenterology*. 2016;150:1590–1598.
19. Saxena V, Korashy FM, Sise ME, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int*. 2016;36:807–816.
20. Singh T, Guirguis J, Anthony S, et al. Sofosbuvir-based treatment is safe and effective in patients with chronic hepatitis C infection and end stage renal disease: a case series. *Liver Int*. 2016;36:802–806.
21. Bhamidimarri KR, Czul F, Peyton A, et al. Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of hepatitis C in patients with end stage renal disease. *J Hepatol*. 2015;63:763–765.
22. Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet*. 2015;386:1537–1545.
23. Nazario HE, Ndungu M, Modi AA. Sofosbuvir and simeprevir in hepatitis C genotype 1-patients with end-stage renal disease on haemodialysis or GFR <30 ml/min. *Liver Int*. 2016;36:798–801.