Original Article

Sofosbuvir Use in the Setting of End-stage Renal Disease: A Single Center Experience

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Abstract

Background and Aims: Patients with chronic hepatitis C (CHC) and end-stage renal disease (ESRD) who are dialysis-dependent form a unique group, in which safety, tolerability and efficacy of sofosbuvir (SOF)-based direct-acting antivirals (DAAs) need further evaluation. ***Methods:*** We performed a retrospective analysis of 14 patients with CHC and ESRD on dialysis who received 15 courses of SOF-based therapy. We evaluated dose escalation to standard-dose SOF in this proof-of-principle experience. ***Results:*** Sustained virological response (defined as undetectable viral load at 12 weeks, SVR-12) was achieved in 13 out of the 15 (86.7%) treatment courses. Seven (46.6%) patients received reduced half dose as conservative proof-of-principal to mitigate potential toxicity. In 13 out of 15 treatment courses, patients completed the designated treatment duration. One patient was treated twice and developed SVR-12 with the retreatment. One patient was lost to follow-up and counted as a non-responder. Premature discontinuations were not due to DAA-related adverse effects. There were no reports of severe adverse effects or drug interactions. ***Conclusion:*** We treated CHC patients with ESRD using dose escalation to standard-dose SOF in this proof-of-principle experience and achieved SVR rates comparable to general population.

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Introduction

The treatment for chronic hepatitis C (CHC) has been revolutionized by the advent of interferon (IFN)-free direct-acting antivirals (DAAs), which show unprecedented safety, tolerability and efficacy profiles. Patients with CHC and end-stage renal disease (ESRD) who are dialysis-dependent form a unique group in which sofosbuvir (SOF)-based DAA regimens need further evaluation. We present our experience with the use of SOF-based regimens in this subpopulation of hepatitis C virus (HCV)-infected patients.

Methods

We studied 14 patients with CHC and ESRD who received 15 courses of SOF-based regimens. One patient was treated twice and developed 12-week sustained virological response (SVR-12) with the retreatment. Patients were predominantly male (86.7% vs. 13.3% females), Caucasian (53.3% vs. 26.7% Hispanic vs. 13.3% African American) and on hemodialysis (93.3% vs. 6.7% on peritoneal dialysis). Most patients were on chronic renal replacement therapy (RRT), the course ranging from 4–132 months, except for 2 patients who started dialysis 4–12 weeks following the initiation of DAA therapy; both these patients had an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 when DAA-based therapy was started. Genotype (GT) distribution was as follows: 8 patients with GT-1 (60%), 1 with GT-2 (7%), 3 with GT-3 (20%) and 2 with GT-4 (13%). Baseline and on-treatment resistance associated variant testing were not performed. The stage of hepatic fibrosis was estimated based on findings from most recent liver biopsy, serum biochemical markers detection, or hepatic elastography performed during abdominal ultrasound and/or magnetic resonance imaging. The results indicated 3 patients (20%) had stage F3–F4 advanced fibrosis or cirrhosis, 3 (20%) had stage F1–F2 fibrosis, 6 (40%) had no fibrosis (F0) and the remaining patients had no data.

Eight patients (57%) had prior IFN failure (2 relapsers and 6 non-responders), while 6 (43%) were treatment-naïve. All treatment regimens included SOF, and 4 out of 15 (26.7%) treatment courses included ribavirin (RBV). Decision to initiate SOF-based treatment, composition of antiviral regimen and length of therapy were influenced by patient preference, viral determinants, severity of liver disease, previous treatment response, antiviral therapy deemed urgent by the nephrologist, drugs available on the market at the time antiviral therapy was initiated, hepatologist experience, and insurance approval process. Similarly, longer therapy duration (12 weeks vs. 24 weeks) was determined based on presence of cirrhosis and previous non-response. Patients with underlying cirrhosis

Keywords: Hepatitis C; End-stage renal disease; Sofosbuvir; Direct-acting antivirals.

Abbreviations: CHC, chronic hepatitis C; IFN, interferon; DAAs, direct-acting antivirals; ESRD, end-stage renal disease; SOF, sofosbuvir; SVR, sustained virological response; RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate; GT, genotype; RBV, ribavirin; LT, liver transplantation; AE, adverse effects.

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Table 1. Patient profile and baseline characteristics

Patient characteristics	
Age in years, mean (SD)	61 (4.9)
Sex, *n* (%)	
M	13 (86.7)
F	2 (13.3)
Ethnicity, *n* (%)	
Caucasian	8 (53.3)
Hispanic/Latino	4 (26.7)
African American	2 (13.3)
Unknown	1 (6.7)
eGFR in mL/min/1.73 m^2, mean (SD)	11.2 (6.3)
ESRD etiology, *n* (%)	
HTN/DM	5 (33.3)
HRS	4 (26.7)
CNI toxicity	1 (6.7)
MPGN/cryoglobulinemia	3 (20)
Others	2 (13.3)
Type of dialysis	
Hemodialysis	14 (93.3)
Peritoneal	1 (6.7)
Duration of dialysis prior to therapy in months, range (min-max)	128 (4–132)
Genotype, *n* (%)	
GT1	9 (60)
GT2	1 (6.7)
GT3	3 (20)
GT4	2 (13.3)
Most recent fibrosis stage determined by pathology/Fibroscan/Fibrosure, *n* (%)	
F0	6 (40)
F1–F2	3 (20)
F3–F4/cirrhosis	3 (20)
Prior therapy, *n* (%)	
Treatment-naïve	6 (40)
IFN	8 (53.3)
IFN and DAA	1 (6.7)
Ribavirin use, *n* (%)	4 (26.7)
SOF dose reduction, *n* (%)	7 (46.7)
Duration of therapy, *n* (%)	
<12 weeks	2 (13.3)
12 weeks	8 (53.3)
24 weeks	5 (33.3)
Post-liver transplant status, *n* (%)	6 (40)
Pre-therapy laboratory values	
Baseline HCV RNA in IU/mL, mean (SD)	8375588.6 (12523305)
Serum albumin in g/dL, mean (SD)	3.5 (0.6)
INR, mean (SD)	1.2 (0.34)
AST in IU/mL, mean (SD)	45.4 (31.1)
ALT in IU/mL, mean (SD)	43 (26.6)
ALP in IU/mL, mean (SD)	385.3 (593.5)
Total bilirubin in mg/dL, mean (SD)	0.99 (0.6)
Serum creatinine in mg/dL, mean (SD)	5.4 (1.7)
Hemoglobin in g/dL, mean (SD)	11.1 (1.9)
Concomitant tacrolimus, *n* (%)	6 (40)

Abbreviation: SD, standard deviation.

and previous history of treatment failure were treated for 24 weeks with the SOF-based regimen. Six patients (43%) were treated following liver transplantation (LT) in the setting of tacrolimus-based immunosuppression.

Baseline mean (±SD) biochemical laboratory values and characteristics are summarized in Table 1. HCV RNA level was measured by quantitative real-time polymerase chain reaction-based HCV test (COBAS^R AmpliPrep/COBAS^R TaqMan^R HCV Test v2.0). Since no guidelines existed for SOF dosing in ESRD patients, we chose to administer half dose (200 mg) taken orally once daily – by splitting the SOF tablet in half. The first 7 out of 15 (46.6%) treatment courses used the reduced 200 mg per day dose as conservative proof-of-principal to mitigate potential toxicity associated with exposure to free nucleoside derivative of SOF.[1,2] Two patients were switched to full-dose (400 mg once daily) SOF dosing at 4–6 weeks after initiation of the antiviral therapy, irrespective of total length of therapy and based on the hepatologist's preference. These patients were treated by 3 hepatologists at a tertiary care center. Prior to starting the SOF-based treatment, a detailed and comprehensive discussion was conducted with each patient regarding the potential risks of pursuing off-label therapy. Each patient was informed and understood that data regarding the use of SOF in individuals with severe renal impairment were lacking.

Results

In 13 out of 15 treatment courses, patients completed the designated treatment duration, with 2 out of 15 treatments stopped prematurely. One of those 2 patients stopped therapy at week 8, due to prosthetic knee graft infection and related sepsis, but still developed SVR-12. The second patient with premature treatment discontinuation suffered a massive cerebrovascular accident at week 4; he was subsequently lost to follow-up and considered a non-responder in our analysis. None of the treatment discontinuations were deemed therapy-related. In total, 13 out of 14 patients successfully reached SVR-12 (92.8%), representing 13 out of 15 treatment courses (86.6%). Only 1 patient relapsed after completing 12 weeks of antiviral therapy using half dose SOF plus simeprevir. He was successfully retreated for 24 weeks with standard-dose SOF plus ledipasvir co-formulation and developed SVR-12.

The SOF-based regimens included SOF and simeprevir (n = 6, 40%), SOF and ledipasvir co-formulation (n = 4, 27%), SOF and RBV (n = 2, 13%), SOF and ledipasvir co-formulation plus RBV (n = 1, 6.3%), SOF, RBV and PEGylated-IFN (n = 1,

6.3%), and SOF and daclatasvir (*n* = 1, 6.3%). RBV dose was restricted to no more than 200 mg per day. There were no significant changes in hemoglobin levels associated with low-dose RBV. None of the patients experienced hepatic decompensation or complications related to RRT during SOF exposure.

Minor adverse effects (AEs) observed were headache in 1 (0.06%), acid reflux in 1 (0.06%), and fatigue in 3 (20%), of which 2 had chronic fatigue at baseline prior to starting SOF-based therapy. Two patients (13.3%) developed anemia, only 1 of whom being transfusion-dependent in the setting of critical sepsis and concomitant RBV use. The other patient with anemia was not taking RBV, but was recently placed on hemodialysis with worsening of ESRD, making anemia of chronic disease as a likely etiology. None of the patients developed severe AEs or drug-drug interactions with their concomitant tacrolimus-based immunosuppression.

Laboratory data following completion of the antiviral therapy showed mean hemoglobin of 11.6 g/dL (±2.2), no rise in serum total bilirubin (0.7 ± 0.2 mg/dL), and overall improvement in liver enzymes (Table 2). Cryoglobulinemia in 3 patients did not resolve at 6 months, despite a favorable response. As expected, none of the dialysis-dependent patients demonstrated improvement in renal function at 3- and 6-month follow-up visits, except for 1 patient who was lost to follow-up. There were no significant differences in laboratory parameters before and after antiviral therapy, except for normalization of liver enzymes in patients with SVR-12.

Table 2. Therapy efficacy and safety characteristics

Therapy efficacy characteristics	
Early treatment discontinuation, *n* (total, %)	2 (15, 13.3)
End-treatment response, *n*, (%)	14 (100)
Sustained virological response-12 weeks, *n* (%)	13 (92.8)
Relapse, *n* (%)	1 (0.06)
Therapy safety characteristics	
Post-therapy laboratory values	**Mean (SD)**
Serum albumin in g/dL	3.6 (0.9)
INR*	1.2 (0.2)
AST in IU/mL	21.5 (7)
ALT in IU/mL	20 (14.6)
ALP in IU/mL	119.7 (86.3)
Total bilirubin in mg/dL	0.7 (0.2)
Serum creatinine in mg/dL	5.5 (1.9)
Hemoglobin in g/dL	11.6 (2.2)
Mild AE, related/unrelated, on therapy	***n*, (%)**
Headache	1 (0.06)
Fatigue	3 (20)
Acid reflux	1 (0.06)
Anemia as ≥2 g/dL decrease in hemoglobin	2 (13.3)
Treatment interruptions due to AE	None
Hospitalizations due to AE	None
Death/lost to follow-up	1 (0.06)
Complications with dialysis	None
Any interaction with tacrolimus, if applicable	None

*Post-therapy INR not available for 2 patients.
Abbreviation: AE, adverse effects.

Discussion

Compared to the general population, there is a higher prevalence of CHC in patients with ESRD (defined as eGFR <30 mL/min/1.73 m^2),[3,4] especially in those undergoing hemodialysis who have an approximately 5-fold higher seroprevalence (7.8% vs. 1.6% in general population).[5,6] CHC has a significant negative impact on mortality and morbidity in dialysis-dependent patients, not only from liver-related complications,[7–10] but also from increased extra-hepatic comorbidities.[11] Historically, IFN-based regimens had suboptimal cure rates and poor tolerability, leading to treatment discontinuation. Only a few case reports and case series have explored the use of first generation protease inhibitors in combination with IFN and RBV in ESRD patients on RRT;[12,13] these analyses consistently reported poor tolerance leading to higher dropout rates and lack of response.[14]

Withholding CHC therapy in patients on maintenance dialysis wait-listed for renal transplantation can lead to progression of liver disease,[15] particularly in those with early-stage fibrosis and potential need for simultaneous liver-kidney transplantation. SOF was first among its class of nonstructural protein 5B polymerase inhibitors to be introduced and revolutionized CHC treatment. SOF is mainly cleared renally, and studies have shown 456% higher levels of its major systemic metabolite (GS-331007) in individuals with severe renal dysfunction as compared with those with normal renal function.[16] Future studies are needed to evaluate the safety and efficacy of SOF-based regimens in individuals with ESRD, especially those on RRT.

Several centers have reported their experiences. Nazario *et al.*[17] treated 17 (2 out of the 17 following liver transplantation) genotype-1a hemodialysis-dependent patients with 12 weeks of SOF and simeprevir therapy and reported 100% SVR-12 without any therapy-related AE. Another case series by Kalyan *et al.*[18] showed that 12 out of 15 patients with GT1 on RRT and treated with half-dose SOF developed SVR-12 (87%). Interestingly, lower SVR rates were almost always related to underlying cirrhosis. None of the patients in this series were transplant recipients. The longitudinal "real world" multicenter HCV-TARGET study included a large pan-genotypic patient cohort with renal insufficiency, including liver transplant recipients, treating them with full-dose SOF-containing therapy and achieving comparable SVR rates to overall SVR (88%); although higher frequency of anemia was noted irrespective of RBV use, worsening renal function and higher rates of AE were noted in groups with advanced renal impairment.[19] Beinhardt *et al.*[20] also recently reported a 96% rate of SVR-12 on SOF-based regimens in a study of 24 patients, 10 of whom were on RRT, 8 of whom were kidney transplant recipients, and 7 of whom were liver-kidney transplant recipients.

Use of new DAAs in the post-transplant setting requires knowledge of drug-drug interactions with common immunosuppressive agents, mainly calcineurin inhibitors. Our study consisted of 40% post-transplant patients who were treated

in a real world clinical practice setting with SOF-based DAAs. There were also no drug-drug interactions or need for immunosuppression dose adjustments to maintain therapeutic peak/trough levels in our study patients. A recent study reported acceptable efficacy, with SVR rate of 70% (90%, CI 56–82%), and good tolerability without interactions of SOF and RBV-based therapy with tacrolimus, mycophenolate, prednisone, cyclosporine or azathioprine in LT recipients.[20] As newer agents continue to emerge in the DAA category, promising data is surfacing from studies like C-SURFER and RUBY-1 that show high cure rates and favorable safety profiles for these drugs in this particular patient population.[21,22] Therefore, it is important to recognize that other agents have been licensed in the USA and Europe with excellent safety profiles in the setting of ESRD. Based on our experience, the SOF-based regimen is a safe and effective alternative if other agents are not available.

Conclusions

SOF, a prodrug efficiently extracted by first-pass hepatic uptake, avoids significant renal excretion. In the liver, SOF is metabolized to the uridine monophosphate that can either be further phosphorylated to the active triphosphate form (GS-461203), a uridine triphosphate analog of the HCV NS5B polymerase,[3] or be dephosphorylated to the free nucleoside. The free nucleoside enters the circulation and is excreted primarily in the urine. Current guidelines recommend avoiding SOF therapy in patients with severe renal dysfunction. However, we treated our patients with dose escalation to standard-dose SOF in this proof-of-principle experience because the active triphosphate levels in the liver should be equivalent in patients with or without renal disease.

Our experience provides meaningful insight into applying the remarkable efficacy data reported in registration trials for SOF in a real-life practice setting not addressed in those trials. As with most retrospective studies, prospective studies are warranted to further validate our observations. We await the results of ongoing studies using SOF in patients on hemodialysis with different dosing schedules.

Conflict of interest

Aijaz Ahmed is a consultant and advisory board member for AbbVie Pharmaceuticals, Gilead Sciences, and Janssen Pharmaceutical, and has research funding/grant from Gilead Sciences. The other authors have nothing to disclose.

Author contributions

Study concept and design (AA, ERY, RBP, GC, RK, TJD, ASL, AA), acquisition of data (AA, ERY, RBP, GC, AA), analysis and interpretation of data (AA, ERY, RBP, GC, RK, TJD, ASL, AA), drafting of the initial and final manuscript (AA, ERY, RBP, GC, AA), critical revision of the manuscript (AA, ERY, RBP, GC, RK, TJD, ASL, AA), and study supervision (AA).

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