HHS Public Access

Author manuscript

*Infect Dis (Lond)*. Author manuscript; available in PMC 2016 January 29.

Published in final edited form as:

*Infect Dis (Lond)*. 2015 ; 47(12): 924–929. doi:10.3109/23744235.2015.1078908.

# Use of Sofosbuvir-Based Direct-Acting Antiviral Therapy for Hepatitis C Viral Infection in Patients with Severe Renal Insufficiency

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## Abstract

Sofosbuvir-based direct-acting antiviral therapy revolutionized the treatment of hepatitis C virus (HCV) infection; however, sofosbuvir use is not approved for patients with severe renal insufficiency [estimated glomerular filtration (eGFR) rate below 30 mL/min] or end stage renal disease (ESRD) based on concerns raised during premarket animal testing over hepatobiliary and cardiovascular toxicity in this population. We report the first published data on use of sofosbuvir-based regimens in patients with severe renal insufficiency and ESRD focusing on clinical efficacy and safety. Six patients were treated with full dose sofosbuvir; three received sofosbuvir and simeprevir, two received sofosbuvir and ribavirin and one received sofosbuvir, ribavirin, and interferon. Three of the patients had cirrhosis. On-treatment viral suppression was 100% and sustained virological response (SVR) rate at twelve weeks was 67%. One patient had to discontinue antiviral therapy early due to side effects. No hepatobiliary or cardiovascular toxicity was reported.

### Keywords

Hepatitis C; sofosbuvir; chronic kidney disease; end stage renal disease

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## Introduction

The approval of the first-in-class, pangenotypic, NS5B inhibitor sofosbuvir in 2013 revolutionized the treatment of hepatitis C virus (HCV) infection by leading to high rates of SVR with few side effects [1]. The use of sofosbuvir is restricted to patients with an eGFR of at least 30 mL/min because it has not been studied in patients with an eGFR below 30 mL/min. The active metabolite of sofosbuvir, GS331007, is eliminated by the kidney, and levels of sofosbuvir and GS331007 are substantially higher in patients with severe renal impairment (eGFR < 30 mL/min) or ESRD on hemodialysis [2]. The potential toxicity of these elevated drug and metabolite levels in humans remains unknown; however, premarket animal testing has raised concerns for cardiovascular and hepatobiliary toxicity at higher levels of sofosbuvir dosing [2].

The prevalence of HCV infection is significantly higher in patients with severe renal insufficiency than in those with normal kidney function. The discrepancy is most pronounced in patients on hemodialysis for whom the worldwide prevalence of HCV infection is 13.5%, compared with 3% in the general population [3]. Studies suggest a 34% increase in all-cause mortality in patients with ESRD who are HCV-infected, compared with those who are uninfected, attributable not only to liver-disease related death, but also to increased cardiovascular mortality [4]. According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, the decision to treat HCV infection in patients with severe kidney insufficiency should be done on a case-by-case basis, taking into account the anticipated risks and benefits of HCV therapy and the patient's life expectancy, comorbidities, and candidacy for kidney transplantation [5]. For patients with severe renal insufficiency, approved HCV treatment options are currently limited to standard interferon alone, pegylated interferon alone, or pegylated interferon plus low-dose ribavirin. These regimens have low rates of SVR and unacceptably high side-effect profiles compared with newer antiviral regimens now available to the general population of patients with HCV infection [6,7]. To our knowledge, the only available data on sofosbuvir-based regimens in this population are published in abstract form and report high rates of SVR but increased adverse effects [8,9]. Given how limited the current data are, the purpose of this study is to report the first published data on sofosbuvir-based regimens in patients with an eGFR below 30 mL/min, particularly with regard to clinical efficacy and safety by characterizing our center's experience.

## Methods

This is a retrospective case series that includes patients with HCV infection and an eGFR below 30 mL/min who began sofosbuvir-based antiviral therapy between January 2014 and September 2014 within Partners HealthCare in Boston, MA. Cases were identified using the Research Patient Data Registry at Partners Healthcare. The electronic medical records of the patients were reviewed for demographics, clinical characteristics, and laboratory and pathologic findings. All patients had detectable HCV RNA in serum. Cases were defined as having a baseline eGFR below 30 mL/min or being on hemodialysis at the time of initiation of sofosbuvir therapy. Baseline laboratory values were the most recent values available prior to initiation of antiviral therapy. Post-treatment laboratory values were obtained 12 weeks

after completion of therapy. The eGFR was calculated based on the serum creatinine measurement prior to the initiation of treatment using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Patients were considered to have cirrhosis by liver biopsy (Ishak stage five or six) or if the treating physician determined that cirrhosis was likely based on clinical findings, imaging, and/or non-invasive fibrosis score (FibroSure [LabCorp; Burlington, NC] or FibroScan [Echosens; Paris, France]). The cause of renal disease was determined based on a renal biopsy specimen or on documentation by the treating physician. Adverse events were determined through review of clinical notes and laboratory values throughout the treatment period. Cardiovascular toxicity was defined as any documentation of myocardial infarction, angina, congestive heart failure, stroke, or arrhythmia during or after antiviral treatment. Hepatobiliary toxicity was defined as aminotransferase or alkaline phosphatase level elevation during or after antiviral treatment to 1.5-fold pre-antiviral treatment therapy levels. The indication for HCV treatment was determined by chart review. The Institutional Review Board of Partners Healthcare approved this study.

## Results

Six HCV infected patients with an eGFR < 30 mL/min or on hemodialysis were treated with a sofosbuvir-based regimen. The patients had a mean age of 60±14 years. Five were male, five were white, and one was black (Table 1). The average duration of HCV infection prior to initiation of sofosbuvir was 30±4 years. Three patients were treatment naïve, two patients had a relapse following prior treatment, and one was intolerant to ribavirin because of anemia. Three of the patients had cirrhosis, and one had undergone orthotopic liver transplantation due to hepatocellular carcinoma. All patients were infected with HCV genotype 1. The median pretreatment serum viral level was 2,990,000 IU/mL (interquartile range 330,000 to 4,770,000). Two of the patients had ESRD and were on hemodialysis; the mean eGFR in the remaining four patients was 27±2 mL/min. The mean baseline hemoglobin level was 11.5±1.3 g/dL (Table 1).

### Treatment Safety and Efficacy

All patients received an antiviral regimen that included sofosbuvir at a dose of 400 mg once daily. Three patients received sofsobuvir and simeprevir, two patients received sofosbuvir and ribavirin, and one patient received sofosbuvir, ribavirin, and pegylated interferon. Four patients were treated for 12 weeks and two patients were treated for 24 weeks (Table 1). The patient treated with sofosbuvir, ribavirin, and pegylated interferon (Patient 2) discontinued therapy four days prematurely due to anemia and leukopenia. Prior to discontinuation, this patient’s ribavirin dosing had been reduced from 600 mg twice daily to 600 mg in the morning and 400 mg in the evening at week 6 of antiviral therapy and then further reduced to 400 mg twice daily at week 8 of antiviral therapy due to profound anemia requiring multiple red blood cell transfusions. Indications for treatment included anticipation of renal transplantation, advanced cirrhosis with prior hepatocellular carcinoma, recurrent HCV infection in a transplanted liver, and cryoglobulinemic membranoproliferative glomerulonephritis.

HCV RNA was undetectable in serum by week 4 and remained undetectable during treatment in all patients. There were no on-treatment viral breakthroughs. The SVR at 12 weeks post-treatment (SVR12) was 67%. Two relapses occurred after discontinuation of treatment. The first patient (Patient 3) was treatment experienced with HCV genotype 1b infection and cirrhosis; she received 24 weeks of sofosbuvir and ribavirin. The second patient (Patient 4) was treatment naïve, had unsubtypeable genotype 1 infection and cirrhosis; he relapsed after a 12-week course of sofosbuvir and simeprevir.

The mean on-treatment nadir eGFR was 25±6 mL/min for the four non-hemodialysis patients. At 12 weeks post-treatment their average eGFR was 37±13 mL/min. The mean on-treatment nadir hemoglobin and post-treatment hemoglobin levels for five of the patients (these data were unavailable for one patient) were 9.7±2.5g/dL and 11.4±1.7g/dL respectively. Anemia developed in all three patients treated with ribavirin, all of whom were taking erythropoietin-stimulating agents (ESA) prior to the start of antiviral therapy. In two cases, the anemia was mild and did not necessitate blood transfusions or a change in ESA dosing; the other patient developed significant anemia requiring biweekly blood transfusions and an increase in the frequency of ESA dosing from monthly to weekly. The only patient who received pegylated interferon also developed leukopenia, which was treated with filgrastim. In one patient (Patient 3) treated with sofosbuvir and ribavirin, the eGFR worsened during antiviral treatment and a renal biopsy performed two weeks after completion of sofosobuvir and ribavirin revealed lupus-like immune complex glomerular disease with tubulointerstitial nephritis; positive antinuclear, anti-histone, anti-double-stranded DNA, and anticardiolipin antibodies and hypocomplementemia were detected in the patient's serum. In retrospect, she had a high antinuclear antibody titer (1:640) prior to initiation of antiviral therapy, however during therapy was the first time she manifested symptoms of lupus (joint pain, nephritis). She was treated with prednisone and mycophenolate mofitil with improvement in renal function to a value significantly above her pretreatment level, but experienced a relapse in HCV infection 4 weeks after sofosbuvir and ribavirin were discontinued.

## Discussion

To our knowledge, this is the first published series of patients with severe renal insufficiency or ESRD treated with sofosbuvir-based antiviral therapy for chronic HCV infection. We report 100% on-treatment viral suppression and an SVR12 rate of 67% with sofosbuvir-based therapy. These results compare favorably to SVR rates with standard or pegylated interferon monotherapy (SVR rates below 50%) [6,10] and pegylated interferon combined with low-dose ribavirin (SVR rates approximate 60%) [7,11]. Sofosbuvir was prescribed at full dose in all patients. Reported adverse effects included anemia and leukopenia, which were seen only in patients treated with ribavirin and interferon-containing regimens, respectively. Of the three patients treated with ribavirin, all developed anemia and one (Patient 2) required multiple red blood cell transfusions and increased ESA dosing. However, this patient's ribavirin dosing was above that recommended for an eGFR below 30mL/min based on AASLD guidelines [12]. Notably, this same patient, who was treated with sofosbuvir, ribavirin, and pegylated interferon, dropped out prior to completion of antiviral therapy due to anemia and leukopenia. However, the dropout occurred with just 4

days of antiviral therapy remaining and an SVR12 was still achieved. We recommend a ribavirin dose of 200 mg daily in patients with eGFR < 30mL/min, as also recommended by AASLD guidelines [12]. Also, one patient developed lupus-like immune-complex renal injury with tubulointerstitial nephritis during the course of treatment that improved with immunosuppression; however, positive lupus serologies predated antiviral therapy. It remains unclear whether antiviral therapy contributed to the development of lupus nephritis. No evidence of cardiovascular or hepatobiliary toxicity was noted in this study population, although this series is too small to draw conclusions about safety.

Our study demonstrates that sofsbuvir-based antiviral therapy may be effective for individuals with HCV infection and severe renal insufficiency both with and without cirrhosis. This data is particularly valuable for renal transplant candidates, as HCV eradication pre-transplant would lead to lower rates of post-transplantation liver disease [13] and may prolong patient and graft survivals [14]. Of note, newer direct-acting antiviral combination treatment regimens are becoming available, including ombitasvir/paritaprevir/ritonavir/dasabuvir and grazoprevir/elbasvir, which are not renally cleared and have been shown to be safe and efficacious in small study populations of patients with HCV genotype 1 and severe renal insufficiency or ESRD [15,16]. Despite their enhanced efficacy and safety, a major limitation of direct-acting antiviral therapy is cost; this may be prohibitive for patients with HCV infection and severe renal insufficiency in low-income countries. In these cases, HCV treatment options may remain limited to standard interferon alone, pegylated interferon alone, or pegylated interferon plus low-dose ribavirin. Further larger-scale prospective studies are needed to explore the pharmacokinetics (including optimal dosing, safety, and efficacy) and cost-effectiveness of the various regimens containing direct-acting antiviral agents in patients with severe renal insufficiency and ESRD to determine the optimal combination and duration of direct-acting antiviral therapy.

## Acknowledgments

Funding: NIH K24 DK078772 (RTC), ASN Foundation for Kidney Research Fellows Award (MES)

Disclosure Statement: MES discloses receiving research grant from Gilead Sciences. LSF discloses royalties from Elsevier, UpToDate, McGraw-Hill, and Wiley. KEC discloses prior history on advisory boards for Gilead Sciences. RTC discloses research grants from Gilead Sciences, Bristol Myers Squibb, Abbvie Pharmaceuticals, Janssen and Merck.

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*Infect Dis (Lond)*. Author manuscript; available in PMC 2016 January 29.

**Table 1**

Demographics, clinical characteristics and follow-up of patients with severe renal insufficiency or ESRD treated with sofosbuvir-based regimens

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Age/gender | 78 M | 61 M | 56 F | 69 M | 58 M | 37 M |
| Race | White | White | White | White | Black | White |
| Pre-treatment serum HCV Viral load (IU/mL) | 3200000 | 9640000 | 2780000 | 330000 | 4770000 | 79600 |
| HCV genotype | 1a | 1a | 1b | 1 non-subtypeable | 1a | 1 non-subtypeable |
| Duration of HCV infection (years) | 30 | 28 | 30 | 35 | 25 | 35 |
| Cirrhosis | Yes | No | Yes | Yes | No | No |
| Prior transplantation | No | No | Liver for HCC | No | Kidney, failed | No |
| Prior antiviral therapy | None | Peg-IFN/RBV discontinued early due to anemia | Peg-IFN/RBV relapse | None | Standard IFN monotherapy relapse | None |
| Baseline seum Cr (mg/dL) | 2.34 | 2.3 | 1.8 | 2.47 | HD | HD |
| Baseline eGFR (mL/min) | 27 | 29 | 29 | 26 | HD | HD |
| Baseline Hgb (g/dL) | 12.9 | 11.4 | 9.5 | 12.1 | 10.8 | 12.5 |
| Cause of renal disease | Unknown | Diabetes | Unknown | Cryoglobulinemic MPGN | Diabetes s/p transplant with graft failure | Autosomal Recessive Polycystic Kidney Disease |
| Antiviral regimen | Sofosbuvir 400 mg daily + Simeprevir 150 mg daily | Sofosbuvir 400 mg daily + Ribavirin 600 mg twice daily + PEG-IFN 180 mcg SC weekly | Sofosbuvir 400 mg daily + Ribavirin 200 mg twice daily | Sofosbuvir 400 mg daily + Simeprevir 150 mg daily | Sofosbuvir 400 mg daily + Simeprevir 150 mg daily | Sofosbuvir 400 mg daily + Ribavirin 200 mg twice daily |
| Ribavirin dose reduction during treatment | N/A | Yes, to 400 mg twice daily | Yes, to 200 mg daily | N/A | N/A | No |
| Treatment duration (weeks) | 12 | 12, stopped 4 days early due to anemia and leukopenia | 24 | 12 | 12 | 24 |
| Treatment Indication | Advanced cirrhosis with prior HCC | Potential future renal transplant | HCV recurrence in transplanted liver | Cryoglobulinemic MPGN | Listing for renal transplant | Listing for renal transplant |
| SVR12 | Yes | Yes | No | No | Yes | Yes |
| Nadir serum Cr on treatment (mg/dL) | 2.22 | 2.4 | 3.09 | 2.53 | HD | HD |
| Nadir eGFR on treatment (mL/min) | 31 | 28 | 16 | 25 | HD | HD |

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Serum Cr at SVR12 (mg/dL) | 1.78 | 2.3 | 1.05 | 2.50 | HD | HD |
| eGFR at SVR12 (mL/min) | 39 | 29 | 54 | 26 | HD | HD |
| Nadir Hgb on treatment (g/dL) | 13.1 | 6.7 | 8.4 | 11.1 | Unknown | 9.3 |
| Hgb at SVR12 (g/dL) | 13.5 | 10.2 | 9.2 | 12.1 | Unknown | 11.9 |
| Use of ESAs | None | Epoetin increased from monthly pre-treatment to weekly during antiviral treatment | Stable weekly epoetin dose before and during antiviral treatment | None | None | Stable epoetin dose before and during antiviral treatment |
| Adverse effects | None | 1. Anemia (requiring epoetin and RBC transfusions)<br>2. Leukopenia (requiring filgrastim) | 1. AKI: lupus-like immune complex disease and tubulointerstitial nephritis on renal biopsy specimen. Treated with prednisone and MMF with improvement.<br>2. Anemia (mild) | None | None | Anemia |

Legend: AKI = acute kidney injury, Cr = creatinine, eGFR = estimated glomerular filtration rate, ESA = erythropoietin stimulating agent, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HD = hemodialysis, Hgb = hemoglobin, IFN = interferon, IU = international units, MMF = mycophenolate mofitil, MPGN = membranoproliferative glomerulonephritis, N/A = not applicable, Peg-IFN = pegylated interferon, PO = by mouth, RBC = red blood cell, s/p = status post, SVR12 = sustained virologic response at 12 weeks post-treatment