



## ORIGINAL ARTICLE

# Efficacy and safety of sofosbuvir-based antiviral therapy to treat hepatitis C virus infection after kidney transplantation

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## Abstract

**Background:** The objectives of this pilot study were to assess the efficacy and safety of an interferon-free sofosbuvir and ribavirin combination regimen to treat chronic hepatitis C virus (HCV) infection in kidney transplant recipients and to study the impact of sofosbuvir on calcineurin inhibitor (CNI) drug levels.

**Methods:** A total of 10 kidney transplant recipients with chronic HCV infection were included in the study. All received sofosbuvir and ribavirin combination therapy. The virological response to therapy and the adverse effects of the drugs were studied. The area under the curve (AUC) and pharmacokinetic data of levels of CNI were compared while the patients were receiving sofosbuvir and ribavirin drugs and when they were no longer on these drugs.

**Results:** In all, 9 of 10 patients (90%) achieved rapid virological response (RVR) with undetectable HCV RNA at 4 weeks and the remaining patient achieved undetectable HCV RNA at 8 weeks. A sustained virological response was seen at 3, 6 and 12 months and was maintained in all 10 patients (100%). The important aspect of the study is the effect of treatment with the sofosbuvir–ribavirin combination regimen on the CNI AUC levels, which resulted in a reduction in the CNI AUC. While used as part of triple-drug immunosuppression, no change in the dose of CNI (tacrolimus and cyclosporine) was required based on measurement of CO levels.

**Conclusions:** The sofosbuvir and ribavirin combination therapy is effective and safe to treat HCV infection in the post-renal transplant setting. There is a need for close CNI level monitoring while these patients are on sofosbuvir therapy. With therapy and viral clearance, there could be reduction in CNI levels due to increased clearance of CNI drugs, which is shown by the AUC measurements. This could be important for patients at high risk for rejection.

**Key words:** CNI drugs, hepatitis C virus, kidney transplant, ribavirin, sofosbuvir

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## Introduction

Hepatitis C virus (HCV) infection is common in chronic kidney disease, mainly in patients with end-stage renal disease (ESRD) undergoing hemodialysis. The persistent HCV infection in kidney transplant recipients, who are already immunosuppressed, has an immunomodulatory effect leading to increased risk of patient mortality and kidney allograft loss [1–3].

The standard of care of HCV treatment, interferon-based therapy, is not safe in the kidney transplant setting due to the immunostimulatory properties of interferons, which can lead to an increased risk of acute rejection [4, 5]. Interferons are relatively contraindicated in kidney transplant settings and can be considered only in cases of severe life- or organ-threatening conditions, like severe cholestatic hepatitis, progressive/advanced fibrosis or mixed cryoglobulinaemia-related vasculitis [6]. Also, interferon-free oral drugs like ribavirin, amantadine (used as monotherapy) or a combination of both do not show encouraging results for HCV load [7–9]. Hence the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment of all HCV RNA-positive patients who are candidates for a kidney transplant while they are still on dialysis [6]. Once sustained virological response (SVR) is achieved pre-transplant, the relapse rate of HCV infection after kidney transplantation is very low [10], but the SVR after interferon therapy in dialysis patients is only 30–50% [11, 12]. The mortality and morbidity with persistent HCV infection in dialysis patients are significantly higher as compared with post-kidney transplant recipients with persistent HCV viremia.

After the introduction of direct antiviral agents (DAAs), there occurred a drastic change in HCV infection treatment in post-transplant settings, especially for liver transplant patients. First-generation DAAs, telaprevir and boceprevir, have not become popular in the transplant setting because they have to be given in combination with interferon therapy. It offered a number of potential benefits, such as high rates of rapid and sustained virologic response, good safety profile, low rates of resistance, pan-genotype efficacy, shortened duration of treatment, usefulness in the treatment of co-infections of HIV and HBV, no need to combine with interferon therapy and, especially, utility in cirrhosis and liver transplantation settings. Various trials of sofosbuvir-based combination therapies with ribavirin or other DAAs such as daclatasvir, simeprevir and ledipasvir in the liver transplant setting have shown very high efficacy, with ~80–95% virological clearance rates [13–17].

With the success and the high viral clearance rates of DAAs in the liver transplant setting, prospects were created for the use these DAAs in the kidney transplant setting as well. There is only one published trial of these DAAs in the kidney transplant setting, but the interactions of these DAAs with immunosuppressants have not been studied using the area under the curve (AUC) and pharmacokinetics of calcineurin inhibitor (CNI) drugs.

A recent pilot study in kidney transplant patients using various combinations of sofosbuvir with other DAAs with or without ribavirin showed good virological clearance rates. There was a reduction in the levels of CNI drugs while these patients were on sofosbuvir; which was in a group of patients on triple immunosuppression (CNI, CellCept and steroids) [18]. A combination of sofosbuvir and ledipasvir was successfully used to treat a kidney transplant recipient with HCV infection [19].

The objectives of this pilot study were to assess the efficacy and safety of an interferon-free, sofosbuvir-based regimen to

treat HCV RNA-positive kidney transplant recipients and the impact of these drugs on CNI levels.

## Materials and methods

### Patients

Patients with chronic HCV infection (all genotypes) after kidney transplantation who received a kidney from a deceased or living donor were selected for the study. The patients included those with relapses of HCV infection who received interferon and ribavirin therapy in the pre-transplant period as well as those with newly acquired HCV infection in the post-transplant period and those who were transplanted without receiving any therapy in the pre-transplant period even though high HCV RNA titers were present at the time of kidney transplantation. Patients with any estimated glomerular filtration rate (eGFR)—even those with ESRD in the post-kidney transplant period, with any induction therapy and with any maintenance immunosuppression therapy—were included in the study.

Patients with any of the following conditions or characteristics were excluded from the study: decompensated liver disease; any other organ transplant recipient (liver, heart, lung, etc); concurrent HIV infection; or hemoglobin (Hb) <8 g/dL, serum bilirubin  $\geq 4\times$  the upper limit of normal (ULN) and serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT)  $\geq 10\times$  ULN.

All patients provided written informed consent before starting the therapy and before undertaking any study-related procedures.

### Treatment details

All patients received sofosbuvir and ribavirin combination therapy. The total planned duration of treatment was 6 months for genotypes 1 and 4 and 3 months for genotypes 2 and 3.

The sofosbuvir dose was 400 mg/day if eGFR was  $>30$  mL/min/1.73 m<sup>2</sup> and 200 mg/day if eGFR was  $<30$  mL/min/1.73 m<sup>2</sup>. Sofosbuvir was stopped if any serious untoward effect occurred, that is, if serum bilirubin increased to  $>10$  mg/dL or  $>3$  times the baseline, and if SGOT or SGPT increased  $>5$  times baseline or  $>10$  times the ULN.

The ribavirin dose was adjusted according to the Hb and eGFR levels. The starting dose was 400 mg/day if Hb was  $>10$  g/dL and 200 mg/day if Hb was 8–10 g/dL. It was not given if Hb was  $<8$  g/dL. The dose of ribavirin was adjusted if Hb decreased to 8–10 g/dL. Also, the dose was decreased to 200 mg/day and erythropoietin injection was added according to the response. If Hb was  $<8$  g/dL even after erythropoietin injection was added, then ribavirin was stopped. The ribavirin dose was also adjusted according to the eGFR.

### HCV viral load quantification

We quantified HCV viral load using the COBAS TaqMan Analyzer.

#### CNI drug pharmacokinetics and level monitoring

We conducted pharmacokinetic studies in each of the transplant recipients. Six of the patients were on tacrolimus- and four on cyclosporine-based immunosuppression. Pharmacokinetic studies were done twice, with calculation of the AUC, first before starting the drug sofosbuvir for HCV viremia and repeated after starting the sofosbuvir. Pharmacokinetic parameters were calculated from eight blood samples (0–12 h post-dose) by chemiluminescent

microparticle immunoassay (CMIA) (Architect i-1000; Abbott, Abbott Park, IL, USA).

The AUC of the CNI drug (either cyclosporine or tacrolimus) was calculated both while the patients were receiving sofosbuvir and ribavirin drugs and while not on these drugs. The receiver operating curve (ROC) was drawn and both ROCs (while with and without sofosbuvir) were compared to assess the true impact of the sofosbuvir and ribavirin combination regimen on CNI levels. For calculating the AUC of the CNI drug (either cyclosporine or tacrolimus), blood samples were collected at 0, 1, 2, 3, 4, 6, 8 and 12 h after receiving the morning dose of the drug. The AUC was calculated twice, while patients were taking sofosbuvir and while they were not on sofosbuvir.

## Results

### Virological response

At baseline, the median HCV RNA concentration was 3.65 million IU/mL (range 0.2–16.4). Among the 10 patients, 9 achieved rapid virological response (RVR) with undetectable HCV RNA at 4 weeks regardless of the pretreatment viral load. The remaining patient achieved undetectable HCV RNA at 8 weeks. Even this patient had an HCV RNA level of 50 IU/mL at 4 weeks. So the RVR rate was 90% (9/10) in this study. The two patients who had ESRD on maintenance hemodialysis also attained an RVR with undetectable HCV RNA at 4 weeks while they received sofosbuvir 200 mg once a day and ribavirin at a dose of 200 mg thrice per week.

In this study, the virological response had no relation with the pretreatment viral load, whether induction with anti-thymocyte globulin (ATG) or basiliximab was received or not or the type of induction received, the maintenance immunosuppression received, the pretreatment serum creatinine or eGFR value and the time gap between transplantation and the start of treatment.

All 10 patients completed 12 months of follow-up after the end of treatment. An SVR at 3 months (SVR3) and at 12 months (SVR12) was seen in all 10 patients (100%).

### Liver enzyme parameters

Liver enzyme levels were significantly decreased during and after anti-HCV therapy. SGPT decreased from 120.5 IU/L (range 25–234) at baseline to 27 IU/L (range 25–68) at the completion of therapy ( $P \leq 0.5$ ). SGOT decreased from 91.0 IU/L (range 21–129) to 24 IU/L (range 14–54) at end of therapy ( $P \leq 0.5$ ). Serum bilirubin was normal in all the patients before the start of treatment and there was no significant change during or after the treatment.

### Kidney allograft function

At the start of the therapy, four patients had an eGFR  $>60$  mL/min/1.73 m<sup>2</sup>, two patients had an eGFR between 30 and 60 mL/min/1.73 m<sup>2</sup>, two patients had an eGFR between 15 and 30 mL/min/1.73 m<sup>2</sup> and two patients had an eGFR  $<15$  mL/min/1.73 m<sup>2</sup> and were on maintenance hemodialysis. In all eight patients with an eGFR  $>15$  mL/min/1.73 m<sup>2</sup>, no significant change was observed in kidney graft function with eGFR and serum creatinine being stable during the treatment (Table 1).

Among the eight patients who had an eGFR  $>15$  mL/min/1.73 m<sup>2</sup>, only one patient had a mild increase in serum creatinine from baseline (from 2.26 mg/dL to 2.72 mg/dL) due to acute gastroenteritis after 1 month of treatment, but serum creatinine

Table 1. Patient characteristics at baseline

Characteristics	Value
Age (years), median (range)	38.5 (21–56)
Male (n):female (n)	7:3
Induction	
No induction	3
ATG	1
Basiliximab	6
Maintenance immunosuppression, n	
Cyclosporine	4
Tacrolimus	6
Mycophenolate mofetil	10
Prednisolone	10
Genotype, n	
1	7
2	1
3	1
4	1
GFR range (mL/min/1.73 m <sup>2</sup> ), n	
$>60$	4
30–60	2
15–30	2
$<15$	2
HCV RNA, million IU/mL, median (range)	3.65 (0.2–16.4)
Hemoglobin, g/dL, mean $\pm$ SD	13.3 $\pm$ 1.2
SGOT, IU/L (n = 5–40), median (range)	91.0 (23–256)
SGPT, IU/L (n = 5–40), median (range)	120.5 (25–234)

decreased to the baseline value within 5 days after gastroenteritis was controlled.

No acute rejection episode or graft loss was observed during therapy. However, no protocol biopsies were performed to detect subclinical rejection.

### Hematological parameters

At the baseline, three patients required erythropoietin; all three had an eGFR  $<30$  mL/min/1.73 m<sup>2</sup>. Among these three patients, one developed severe anemia, received four units of packed red blood cells, had an increase in erythropoietin requirement and the ribavirin was stopped. Another patient with an eGFR  $>60$  mL/min/1.73 m<sup>2</sup> had a decrease in Hb from 14.2 g/dL at baseline to 10.0 g/dL after 1 month of treatment and thus required a dose reduction of ribavirin from 200 mg twice a day to 200 mg once a day, after which the Hb level increased again to 12.4 mg/dL.

Overall there was a mild decrease in the mean Hb level during therapy: 13.2  $\pm$  1.2 g/dL at baseline, 12.16  $\pm$  1.09 at Week 4 and 11.04  $\pm$  1.82 at the completion of therapy. Except the two patients mentioned above, the remaining eight patients tolerated the treatment well and did not require any dose reduction of ribavirin.

### Nonhematological adverse events

Among the 10 patients, 7 had no significant adverse events. One patient had easy fatigability, muscle cramps, anorexia and headache during treatment. Another patient had noninfectious acute gastroenteritis and recovered after 5 days. One patient had hyperuricemia with gout and required febuxostat to decrease uric acid, but its relationship to treatment with sofosbuvir is not definite. All 10 patients completed the course of

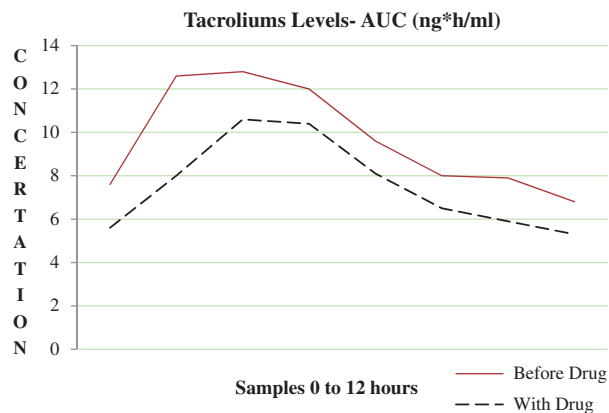


Fig. 1. Tacrolimus levels—AUC (ng \*h/mL).

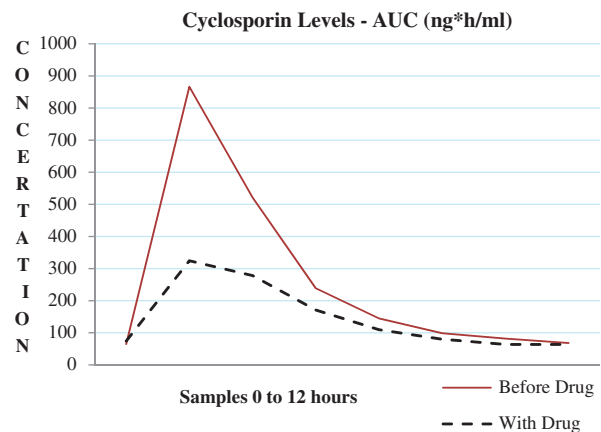


Fig. 2. Cyclosporine levels—AUC (ng\*h/mL).

sofosbuvir therapy and none of the patients discontinued the sofosbuvir due to adverse effects.

### Effect of antiviral therapy on immunosuppressive therapy

The important aspect of this study was that we compared the AUC of CNIs for these 10 patients, wherein 4 patients received cyclosporine and 6 patients were on tacrolimus-based immunosuppression. This was done twice (i.e. the AUC of CNIs before starting sofosbuvir therapy and after starting therapy). There was a significant reduction in the AUC of both cyclosporine and tacrolimus with the use of sofosbuvir. Patients also required a dose adjustment of CNI with the use of sofosbuvir. The AUC for tacrolimus (Figure 1) was  $108.83 \pm 24.29$  ng\*h/mL before starting sofosbuvir, which decreased to  $85.51 \pm 18.25$  ng\*h/mL after 7 days of antiviral treatment with sofosbuvir ( $P=0.001$ ). The AUC for cyclosporine (Figure 2) was  $2584.2 \pm 141.7$  ng\*h/mL before starting sofosbuvir, which decreased to  $1409.6 \pm 130.5$  ng\*h/mL after 7 days of antiviral treatment with sofosbuvir ( $P=0.084$ ). After stopping sofosbuvir and ribavirin, both tacrolimus and cyclosporine showed a trend toward an increase in C0 levels, but it was not statistically significant (C0 tacrolimus:  $7.2 \pm 0.51$  ng/mL before stopping sofosbuvir,  $5.6 \pm 1.16$  ng/mL on stopping sofosbuvir,  $7.6 \pm 3.5$  ng/mL after stopping sofosbuvir; C0 cyclosporine:  $83.6 \pm 24.18$  ng/mL before stopping sofosbuvir,  $67.8 \pm 30.4$  ng/mL on stopping sofosbuvir,  $75.6 \pm 43.4$  ng/mL after stopping sofosbuvir).

### Discussion

The interferons are relatively contraindicated in kidney transplant recipients, as they can lead to an increased risk of acute rejection and graft kidney loss [4, 5], except in cases of severe life or organ-threatening conditions such as severe cholestatic hepatitis, progressive/advanced fibrosis or mixed cryoglobulinemia-related vasculitis [6]. Before the introduction of DAAs, there was no safe and effective therapy for HCV infection in post-renal transplant recipients.

The last 2 years have witnessed significant changes in HCV management with the introduction of a new generation of DAAs, especially sofosbuvir-based combination therapies with ribavirin, and other DAAs such as daclatasvir, simeprevir and ledipasvir. Various trials of DAAs in the liver transplant setting have shown very high efficacy, with ~80–100% virological clearance rates and good safety profiles [13–17].

Based on various trials of DAAs for HCV infection in the liver transplant setting, some important guidelines have been released. The American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) published joint guidelines for the management of chronic HCV infection. As per these guidelines, after liver transplantation, sofosbuvir combined with simeprevir or daclatasvir with or without ribavirin for 24 weeks is recommended for the initial therapy of HCV genotype 1 infection. For genotypes 2 and 3, sofosbuvir and ribavirin for 24 weeks is recommended [20].

The European Association for the Study of the Liver (EASL) recommends on treatment of HCV with a combination of sofosbuvir and ribavirin for 12 weeks (genotypes 2 and 3), with a fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6) or with a combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes). No dose adjustment is required for tacrolimus or cyclosporine with sofosbuvir–ribavirin, sofosbuvir–ledipasvir or sofosbuvir–daclatasvir [21].

With the success and safety of DAAs in the liver transplant setting, renewed interest in the use of these DAAs in the post-kidney transplantation setting has prompted trials on the success and safety of these DAAs in kidney transplant recipients.

In our study, we selected 10 kidney transplant recipients with high HCV RNA titers with different eGFR ranges, including 2 patients who were on dialysis. The RVR was 90% (9/10) and 100% of patients went into remission by 8 weeks. Liver enzymes also normalized within 4 weeks. In our study, the virological response was not related to pretreatment viral load, receipt of induction, type of induction received, maintenance immunosuppression received, pretreatment serum creatinine or eGFR value or the time gap between transplantation and the start of treatment.

No acute rejection episode or graft loss was observed during therapy. All 10 patients completed 12 weeks of treatment and at the end of treatment, all of them showed an SVR at 3 months with undetectable HCV RNA levels and all the 10 patients completed 12 months of follow-up after the end of therapy; all of them maintained an SVR at 6 and 12 months. Although some patients had minor side effects, as mentioned already, none of the patients required discontinuation of sofosbuvir due to adverse effects. In our study, ribavirin was also well tolerated, with only one patient requiring blood transfusions and discontinuation of ribavirin and another patient requiring a ribavirin dose reduction. Overall, there was a mild decrease in the mean hemoglobin level during therapy.

Our study results are in accordance with another published study by Kamar *et al.* [18] on the use of DAAs in post-renal transplant recipients, which showed an 88% RVR rate, minor adverse events and no need for significant modification of immunosuppressive medication while on antiviral treatment. Our study showed an excellent RVR and good safety profile. But as indicated by the AUC measurement, there was a significant reduction in the AUC of CNIs while on sofosbuvir treatment. This may be related to increased clearance of CNIs while on treatment with sofosbuvir, which was associated with viral clearance.

The major strength of our study is comparison of the AUC of CNIs before starting sofosbuvir therapy and 1 week after the start of therapy with sofosbuvir among the patients receiving cyclosporine ( $n = 4$ ) or tacrolimus ( $n = 6$ ). The study showed a decrease in the AUC of CNIs with the use of sofosbuvir, which was more significant in patients on tacrolimus as compared with cyclosporine A. None of the patients required dose adjustments of CNI drugs. There appears to be underexposure to CNIs with sofosbuvir use as indicated by measurement of the AUC. While on sofosbuvir, patients should be closely monitored for CNI levels, preferably by AUC measurement at least once before starting therapy with sofosbuvir and repeat AUC measurements 1 week after starting therapy. This could be important for high immunological risk patients.

The major limitations of this study are the sample size was small, liver histology was not studied, the fibrosis state of the liver was not taken into account and sofosbuvir levels were not monitored.

The study results are encouraging, indicating a good safety profile and efficacy of the sofosbuvir-ribavirin combination after transplantation, even in patients with compromised graft function. This combination was mainly used in genotype 1 HCV infection but was also effective in other HCV genotypes (genotypes 2–4).

## Conclusion

Sofosbuvir and ribavirin combination therapy is useful and safe to treat HCV infection in the post-renal transplant setting at any level of kidney function. There was a reduction in CNI drug exposure with the use of sofosbuvir therapy, as shown by the AUC. None of the patients required any significant dose modification of CNIs while these patients were being monitored by C0 levels of CNIs.

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