Hepatitis C treatment of renal transplant and chronic kidney disease patients: efficacy and safety of direct-acting antiviral regimens containing sofosbuvir

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ABSTRACT – Background – Direct-acting antivirals have revolutionized hepatitis C treatment, also for patients with chronic kidney disease (CKD), but some controversy exists regarding the use of sofosbuvir (SOF) in patients with glomerular filtration rate (GFR) <30 mL/min. Objective – To evaluate the efficacy and safety of these regimens for hepatitis C treatment of patients with CKD and after renal transplantation, as well as the impact of SOF on renal function in non-dialysis patients. Methods – All patients with hepatitis C and CKD or renal transplant treated with direct-acting antivirals at a referral center in Brazil between January 2016 and August 2017 were included. Efficacy was evaluated based on viral load (HCV RNA) and a sustained virological response (SVR) consisting of undetectable RNA 12 and/or 24 weeks after the end of treatment (SVR12 and SVR24) was defined as cure. Safety was determined by adverse events and ribavirin, when combined, was administered in escalating doses to all patients with GFR <60 mL/min. The impact of SOF on renal function was determined by the measurement of baseline creatinine during and after the end of treatment and its increase was evaluated using the Acute Kidney Injury Network (AKIN) classification. Results – A total of 241 patients (52.7% females) with a mean age of 60.72±10.47 years were included. The combination of SOF+daclatasvir was the predominant regimen in 75.6% of cases and anemia was present in 28% of patients who used ribavirin (P=0.04). The SVR12 and SVR24 rates were 99.3% and 97.1%, respectively. The treatment was well tolerated and there were no major clinically relevant adverse events, with the most prevalent being asthenia (57.7%), itching (41.1%), headache (40.7%), and irritability (40.2%). Among conservatively treated and renal transplant patients, oscillations of creatinine levels (AKIN I) were observed in 12.5% of cases during treatment and persisted in only 8.5% after the end of treatment. Of these, 2.0% had an initial GFR <30 mL/min and this percentage decreased to 1.1% after SOF use. Only 0.5% and 1.6% of the patients progressed to AKIN II and AKIN III elevation, respectively. Conclusion – The direct-acting antivirals were safe and efficacious in CKD patients treated with SOF-containing regimens, with the observation of high SVR rates, good tolerability and few severe adverse events. The combination with ribavirin increased the risk of anemia and the administration of escalating doses seems to be useful in patients with GFR <60 mL/min. In patients with GFR <30 mL/min, SOF had no significant renal impact, with serum creatinine returning to levels close to baseline after treatment.

INTRODUCTION

Hepatitis C treatment has undergone several changes in recent years, especially after the arrival of direct-acting antivirals (DAAs)\(^1\). Acting at different stages of viral replication, these drugs reach sustained virological response (SVR) levels higher than 90%, resulting in a curable infection not only in the general population, but also in special groups such as transplanted and dialysis patients\(^2\).\(^3\).

With a high prevalence among patients with chronic kidney disease (CKD), hepatitis C is characterized by high morbidity and mortality in this population and early treatment is extremely important in order to prevent complications of the disease\(^4\).

Despite divergences regarding the use of sofosbuvir (SOF) in patients with a glomerular filtration rate (GFR) less than 30 mL/min\(^5\)\(^6\), when DAAs were approved in Brazil in 2015–2016, only regimens including this drug were available and good results have been reported for the general population\(^7\)\(^8\). Inclusive, in a recent real-world data in Brazil, with 3939 patients included and treated with sofosbuvir/daclatasvir or sofosbuvir/simeprevir, SVR rates were higher than 95%\(^9\).

The aim of this study was to evaluate the efficacy and safety of SOF-containing regimens in patients with CKD treated conservatively, patients undergoing dialysis and patients after renal transplantation, as well as the impact of treatment on renal function in non-dialysis patients.
METHODS

This study included all patients with hepatitis C and CKD seen at the Liver-Kidney Outpatient Clinic of Federal University of São Paulo undergoing conservative treatment (characterized by GFR <90 mL/min) or replacement therapy (hemodialysis or peritoneal dialysis) and post-renal transplant patients, who were treated with SOF-containing regimens between January 2016 and August 2017. The informed consent term was explained and obtained from all participants. Except for renal transplant patients, individuals with a GFR >90 mL/min at the beginning of treatment were excluded from the study.

The DAA regimens available for hepatitis C treatment were instituted according to genotype and were conducted following the Clinical Protocol and Therapeutic Guidelines effective in 2015 in Brazil(7). A dose of SOF of 400 mg/day was used.

Three measurements of viral load (HCV RNA) were evaluated to characterize the efficacy of treatment: at the end of drug treatment and at 12 and 24 weeks of follow-up. An SVR with a negative viral load 12 and/or 24 weeks post-treatment (SVR12 and SVR24) was defined as cure.

Ribavirin (RBV) was indicated in cases of previous treatment failure or advanced hepatic fibrosis. When necessary, escalating doses were administered up to the target dose, determined based on GFR and manipulated according to tolerability by the patient, in an attempt to reduce drug-related complications(10,11). This lead-in period was applied to all patients with GFR <60 mL/min with the following targets:

- GFR of 30–59 mL/min, RBV target of 500 mg/day;
- GFR of 15–29 mL/min, RBV target of 250 mg/day;
- GFR <15 mL/min or hemodialysis, RBV target of 250 mg, 3x/week.

Safety was determined based on the main adverse events reported during treatment.

The stage of CKD was evaluated based on the GFR calculated using the CKD-EPI and MDRD equations in all visits.

The impact of SOF on renal function of non-dialysis patients was determined by the measurements of baseline creatinine during and after treatment. Increases in serum creatinine were established in a standardized manner using the Acute Kidney Injury Network (AKIN) classification(12):

- AKIN I: elevation of 0.3 mg/dL or of 1.5 to 1.9 times the baseline creatinine level;
- AKIN II: elevation of 2 to 3 times the baseline creatinine level;
- AKIN III: elevation >3 times the baseline creatinine level or creatinine ≥4.0 mg/dL with an acute increase of at least 0.5 mg/dL.

Ethics approval

The study was approved by the Research Ethics Committee of the São Paulo Federal University – UNIFESP (number 67763717.2.0000.5505), in accordance with Resolution 466/2012 of the National Health Council of the Ministry of Health (Brazil).

RESULTS

A total of 241 patients (52.7% females) with a mean age of 60.72±10.47 years were evaluated. Genotype 1 was the most prevalent and was present in 85.5% of cases. The CKD status was distributed as follows: conservative treatment in 61%, post-renal transplant in 24.9%, and hemodialysis in 14.1%. The general characteristics of the sample are shown in TABLE 1. TABLE 2 shows the treatment regimens used and the number of patients in each group divided according to CKD status.

| TABLE 1. General characteristics of the sample (n=241 patients). |
|-----------------|-------|---|
| Gender          | n     | % |
| Male            | 114   | 47.3 |
| Female          | 127   | 52.7 |
| Age (years)     | Mean (SD) | Range |
|                 | 60.72 ±10.47 | 26–87 |
| Genotype        |        |    |
| Genotype 1      | 206    | 85.5 |
| Genotype 2      | 6      | 2.5 |
| Genotype 3      | 29     | 12.0 |
| Patient group   |        |    |
| Conservative treatment | 147 | 61.0 |
| Hemodialysis    | 32     | 13.3 |
| Peritoneal Dialysis | 2   | 0.8 |
| Renal transplant | 60     | 24.9 |
| Baseline Cr (mg/dL) |        |    |
| Conservative treatment – mean (SD) | 1.13 ±0.55 | 0.68–3.96 |
| Median          | 0.97   |    |
| Renal transplant – mean (SD) | 1.54 ±0.70 | 0.69–4.77 |
| Median          | 1.45   |    |
| Associated comorbidities |        |    |
| Systemic arterial hypertension | 188 | 78.0 |
| Diabetes mellitus | 78    | 32.4 |
| Obesity         | 43     | 17.8 |
| Hepatitis B     | 3      | 1.2 |
| HIV (n=133)     | 6      | 4.5 |
| Alcohol (n=229) |        |    |
| < 40 g/day      | 31     | 13.5 |
| > 40 g/day      | 6      | 2.6 |
| Abstinence      | 31     | 13.5 |
| Cryoglobulin (n=171) |        |    |
| Present         | 50     | 29.2 |
| Fibrosis degree (n=240) |        |    |
| F0/F1           | 45     | 18.8 |
| F2              | 23     | 9.6 |
| F3              | 56     | 23.3 |
| F4              | 116    | 48.3 |
| Child-Pugh (n=116) |        |    |
| A               | 107    | 92.2 |
| B               | 8      | 6.9 |
| C               | 1      | 0.9 |

CKD: chronic kidney disease; Cr: creatinine.
Among the 150 patients using RBV, 28% had anemia with hemoglobin (Hb) <10.0 g/dL: 19.4% of conservatively treated patients, 5.3% of renal transplant patients, and 3.3% of dialysis patients. Due to the drop in Hb levels, the RBV dose was readjusted in 42% of cases and the drug was discontinued in only 15.3%. Five patients have presented Hb <7.0 g/dL (three using RBV) and exhibited clinical stabilization after blood transfusion.

Anemia was associated with RBV use (P=0.04), but there was no significant association between its use and blood transfusion (P=1.00) or between anemia and CKD status (P=0.739). The SVR, defined as a negative viral load, was 99.3% after 12 weeks (SVR12) and 97.1% after 24 weeks (SVR24).

Three recurrences occurred, defined as positive HCV RNA in patients with previously negative viral load after treatment: two in renal transplant patients and one in dialysis patient. Both transplant patients carried genotype 1a (one with Child A cirrhosis and the other without advanced fibrosis), while the dialysis patient carried genotype 1b and also had Child A cirrhosis. All three used SOF + DCV + RBV.

Three patients presented without a response, persisting detected viral load 12 or 24 weeks after treatment: two patients with CKD treated conservatively that realized irregular treatment and one dialysis patient who developed atrial flutter in the first month of DAA use and had drugs discontinued after this episode.

There was no case of dropout and the treatment was well tolerated by the patients, with no major clinically relevant adverse events in most cases. Adverse reactions were more prevalent among conservatively treated patients and the most commonly reported were asthenia (57.7%), itching (41.1%), headache (40.7%), and irritability (40.2%). Other adverse events included flu-like symptoms, dizziness, insomnia, and nausea, as shown in TABLE 3. In addition, no significant association was observed between adverse events and CKD status (P=0.351), gender (P=0.871), or age (P=0.351).

Evaluation of the renal impact of SOF use among conservatively treated and renal transplant patients showed discrete oscillation (AKIN I) in creatinine levels in 12.5% of cases during treatment, which persisted in only 8.5% of the sample 12 weeks after the end of treatment. Among these patients, only 2.0% had an initial GFR <30 mL/min and this percentage decreased to 1.1% after medication use. Although evident, these were mild alterations without clinical repercussions that did not persist in 1/3 of this subgroup.

Serum creatinine elevations were observed in only two (AKIN II) and three (AKIN III) cases; however, among the latter, baseline creatinine was higher than 3.0 mg/dL in all patients.

There was no significant difference between baseline creatinine levels and those obtained at the end of treatment in patients with CKD treated conservatively (P=0.973) or renal transplant group (P=0.60), nor at 12 weeks of follow-up in either group (P=0.622 and P=0.694, respectively). Likewise, no significant difference in GFR was observed when baseline levels were compared to the values at the end of treatment and those obtained after 12 and 24 weeks of follow-up in conservatively treated (P=0.485) varying from 63.9 mL/min to 61.9 mL/min in this group and from 51.4 mL/min to 50.0 mL/min in renal transplant patients (P=0.550). Specifically for CKD stages 3 and 4, this variation was from 45.90 mL/min to 45.89 mL/min in stage 3 and from 24.41 mL/min to 24.11 mL/min in stage 4.

**DISCUSSION**

The treatment of hepatitis C in patients with CKD has been a challenge over the years; however, the arrival of DAAs has substantially increased the likelihood of cure in this group, with SVR rates similar to those observed in the general population (13-15). Regarding the use of SOF, rates ranging from 67% to 87% have been reported for dialysis patients, which can reach 89.4% in stage 4 and 5 CKD but with some patients using half the recommended dose (200 mg/day), a fact that could lead to a decrease in the response. Among renal transplant patients, the response rates reach 100% at the dose of 400 mg/day, representing a good treatment option in this population (16-19).

In addition to being efficacious, DAAs are also considered safe in CKD, with few adverse events similar to patients without CKD stage V on hemodialysis. Attention must only be paid to the higher risk of anemia in cases receiving the combination with RBV (20-23). Anemia, which usually affects 40%–50% of patients using RBV in the therapeutic regimen (24-25), manifested in 28% of the sample. Administration of escalating doses of the drug, with the dose established according to the GFR, improved tolerability and reduced the rates of anemia when compared to those reported in the literature and can therefore be considered a highly effective preventive measure (26).

Regarding the renal impact of SOF in non-dialysis patients, we noted slight elevations in a small portion of the population studied.

**TABLE 2. Treatment regimens (n=241 patients).**

| Treatment regimen | Conservative | CKD status | Renal transplant |
|-------------------|--------------|------------|------------------|
|                   | n  | %     | n  | %     | n  | %     |
| Sofosbuvir + Daclatasvir | 99 | 41.1 | 25 | 10.4 | 58 | 24.1 |
| Sofosbuvir + Simeprevir | 44 | 18.3 | 8  | 3.3  | 0  | 0     |
| Sofosbuvir + Ribavirin | 2  | 0.8  | 1  | 0.4  | 2  | 0.8  |
| Sofosbuvir + peg- INF + Ribavirin | 2  | 0.8  | 0  | 0    | 0  | 0     |

CKD: chronic kidney disease; peg-INF: pegylated interferon.

**TABLE 3. Adverse events during treatment with DAAs (n=241).**

| Adverse event | n  | %     |
|---------------|----|-------|
| Asthenia      | 139| 57.7  |
| Itching       | 99 | 41.1  |
| Headache      | 98 | 40.7  |
| Irritability  | 97 | 40.2  |
| Flu-like symptoms | 91 | 37.8  |
| Dizziness     | 90 | 37.3  |
| Insomnia      | 83 | 34.4  |
| ↓ Visual acuity | 78 | 32.4  |
| Nausea        | 73 | 30.3  |
| Anorexia      | 63 | 26.1  |
| Dysgeusia     | 62 | 25.7  |
| Depression    | 56 | 23.2  |
| Alopecia      | 53 | 22.0  |
| Diarrhea      | 48 | 19.9  |
| Exanthema     | 4  | 1.7   |

↓, decline.
which did not exceed values above AKIN I in most of them. These increases were reversible in a significant percentage, similar to the finding of Maan et al. for the general population30).

In dialysis patients, reliable assessment of renal function was not possible because of the constant variation in creatinine levels in this group. However, the use of SOF had no significant renal impact and treatment showed good efficacy and safety in this population. This fact was also observed in patients with stage 4 and 5 CKD, with slight improvement of GFR 12 weeks after the end of treatment in some cases27,28. Within this context, Desnoyer et al. found no significant accumulation of the inactive metabolite of SOF (GS-331007) in dialysis patients, with the drug being a good option for the treatment of this population39).

Although this increase in creatinine levels is most feared in the population with GFR <30 mL/min, worsening of renal function during treatment was mainly observed among patients with GFR >30 mL/min, which was nonsignificant and reversible in most cases31,32. Taken together, the present findings are similar to those reported in the literature but higher SVR rates were observed when compared to the already reported rates.

This study has some limitations. The patients were not randomized to receive different regimens of treatment, but it reflects real life choices among doctors. Furthermore, the number of hemodialysis patients was relatively small. However, the number of hemodialysis patients was relatively small. Considering that SOF could worsen renal function in CKD patients, the information regarding treatment in conservative patients is probably more useful than that in hemodialysis patients.

CONCLUSION

The data of this study permit to conclude that DAAs are efficacious drugs for the treatment of patients with CKD, including conservatively treated, dialysis and post-renal transplant patients. These drugs have no significant impact on renal function and can be used safely in this population.

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Authors’ contribution

Michels FBL: data collection, literature review and writing of text. Amaral ACC, Carvalho-Filho RJ, Vieira GA, Souza ALS: data collection and discussion of the results. Ferraz MLG: orientation, revising and approval of the final manuscript.

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