Research Article

Safety and efficacy of sofosbuvir based regimen in the treatment of hepatitis C virus infection among hemodialysis patients in Morocco

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Abstract

The introduction of a new class of drugs known as direct acting antiviral (DAA) agents represents a revolution in the treatment of hepatitis C virus (HCV) in the general population, as these regimens are associated with higher sustained virological response (SVR) rates and fewer side effects. However, for patients with advanced chronic kidney disease suffering from HVC infection, treatment options including DAA remain limited. The aim of this study is to report our experience on Sofosbuvir (SOF) based regimen in the treatment of HCV in hemodialysis patients.

In this observational study, we included all patients with chronic HCV infection on hemodialysis who were treated with SOF in our Hospital between April 2016 and March 2018. All patients were treated with a combination of 400 mg of SOF three times a week after hemodialysis and of 60 mg of Daclatasvir daily for a total of 12 to 24 weeks.

A total of 20 hemodialysis patients were included in this study. 12 were females and the mean age was 52.1 ± 15.5 years. 11 patients were infected with HCV genotypes 1b. All patients achieved SVR. Clinical and biological tolerance was very good for all patients and none of them had to discontinue treatment because of side effects or developed hepatobiliary and cardiac toxicity. Two patients reported fatigue and another patient reported headaches. However, these symptoms were spontaneously resolved after the end of the treatment.

In Morocco, despite the absence of new DAA combination treatment regimens which are not renally eliminated, our study concludes that SOF based treatment without Ribavirin or Peginterferon was effective and safe with minimal side effects. However, larger studies are still needed in order to validate these results.

Introduction

The prevalence of hepatitis C virus (HCV) in hemodialysis patients is greater than in the general population and contributes to mortality in this population [1].

According to the Moroccan register (MAGREDIAL), the prevalence of HCV in dialysis’s patients was 32%. However, it varies between 11 and 85% in different centers [2].

Until recently, the treatment of HCV infection in end stage renal disease patients and in dialysis patients consisted of the combination of pegylated interferon and ribavirin, which was poorly tolerated and was associated with frequent interruptions and lower sustained virological response (SVR) rates [3]. Therefore, there was a clear need to treat this population with interferon-free regimens.

The introduction of a new class of drugs known as direct acting antiviral agents (DAA) represents a revolution in the treatment of viral HVC in the general population as these
Regimens are associated with higher SVR rates and fewer side effects [4]. However, treatment options with DAA for patients suffering from advanced chronic kidney disease and HVC infection remain limited [5,6].

Among the DAA, Sofosbuvir (SOF) is a nucleotide analog prodrug inhibitor of the HCV NS5B polymerase and constitutes the mainstay of most anti-HCV containing therapies. It inhibits genotype 1-6 HCV-RNA replicons and globally has a good tolerance [7]. The use of SOF is not recommended with creatinine clearance < 30 ml/min/1.73 m² and in dialysis patients as it is eliminated mainly by the renal route [6]. However, some studies with SOF treatment suggest that it is safe and effective when prescribed for hemodialysis patients [8-10]. Thus, the aim of this study is to report our experience on SOF based regimen in the treatment of HCV in hemodialysis patients.

Patients and methods

In this observational study, we included all patients on hemodialysis suffering from chronic HCV infection and who were treated with SOF and Daclatasvir (DAC) in Mohammed V military teaching hospital in Rabat (Morocco) between April 2016 and March 2018. All patients were hemodialyzed thrice a week and were treated with a combination of 400 mg of SOF three times a week after hemodialysis and of 60 mg of DAC daily for a total of 12 to 24 weeks.

Demographic and clinical characteristics were reviewed retrospectively at inclusion and all participants gave their informed consent before treatment, after they received the necessary informations about the data reported in the literature concerning SOF in hemodialysis patients.

All patients had baseline laboratory tests such as liver function tests, blood counts, HBs Ag, HIV serology, the virological status of HCV defined by HCV-polymerase chain reaction (PCR), and HCV genotype. The assessment of fibrosis was performed by noninvasive means (blood tests, pulse elastometry).

In this study, the diagnosis of cirrhosis was made based on clinical, biological and morphological criteria. The assessment of hepatic fibrosis is based on non-invasive scores.

We measured HCV RNA immediately at the end of the treatment and then again 12 weeks after so as to describe the proportion of hemodialysis patients who achieved end of treatment response (ETR) and sustained virological response (SVR) respectively defined by undetectable HCV RNA. We also analyzed results of blood test after 12 weeks post-treatment.

Any event that occurred during the period of treatment was evaluated and reported in this study.

Ethical approval for this study was approved by the Institutional Ethical Committee of Hospital. Statistical analysis was performed using SPSS 19 (IBM Corp., Armonk, NY, USA). Numerical data were expressed as mean ± standard deviation and categorical data in percentage and numerical values.

Matched pairs t test was using to calculate the difference between means of quantitative variables. \( p < 0.05 \) was considered to be statistically significant.

Results

A total of twenty hemodialysis patients were treated in this study. Twelve were females and eight were males. The mean age of the patients was 52.1 (± 15.5) (range: 45–62) years. Duration of hemodialysis was 42.3 ± 3 months. The etiology of end stage renal disease was diabetic nephropathy in twelve patients, glomerulonephritis in four patients and unknown in the others.

The mean of pre-treatment HCV RNA level was 507000 IU/ml. Eleven patients were infected with HCV genotypes 1b, whereas four and five patients were infected with genotypes 1a and 2, respectively.

Fibrosis stage was F0 F1, F2, F3 and F4 in 40%, 30%, 15%, 10%, 5% respectively.

Three of the twenty patients had cirrhosis which was well compensated. The Child Turcotte Pugh score was A for two patients and B for one patient.

None of the patients had HIV infection or HBV co-infection.

Regarding the pre-therapeutic assessment, the average hemoglobin level was 9.4 g/dl, the average leukocyte level is 5600/mm and the average ALT level is 32 ui/l. all patients had normal TSH and phosphorus levels.

Eighteen patients were treatment naïve and two patients had previously received HVC treatment with combination of pegylated interferon and ribavirin but with no response to treatment in one patient and relapser in the other patient.

No one of our hemodialysis patients has received treatments that would have interacted with SOF or DAC such as amiodarone, antiarrhythmic treatment, anticonvulsants or antimicrobial agents.

Treatment duration was 12 weeks for seventeen patients and 24 weeks for three patients who also suffered from compensated cirrhosis.

Treatment with SOF and DAC for a duration of 12 to 24 weeks resulted in an EVR and SVR in all of the patients and no patient had a virologic relapse after the end of treatment during the study period.

Clinical and biological tolerance was very good and no patient had to discontinue treatment because of side effects or developed hepatobiliary or cardiac toxicity secondary to SOF (manifesting with arrhythmia or myocardial infarction).
Two patients reported fatigue and another patient reported headaches. However, these symptoms were spontaneously resolved after the end of treatment.

We also observed a significant reduction in the mean of aspartate aminotransferase and alanine aminotransferase values between the baseline and 12 weeks after the end of treatment ($p = 0.04, p = 0.02$), respectively (Table 1).

All patients took erythropoietin before treatment and none of them received a blood transfusion nor needed an increased erythropoietin dose during the treatment period. Of note, the pre-existent anaemia has improved 12 weeks after the end of treatment, comparing to baseline values of haemoglobin. However, this result was statistically no significant ($p = 0.1$) (Table 1).

**Discussion**

Although the current guidelines do not recommend in first line a SOF containing regimen in patients with advanced chronic kidney disease or requiring hemodialysis, several small studies reported an encouraging experience with this anti-viral agent in these populations and conclude that SOF treatment was effective and safe with minimal side effects [6,10-14]. On the basis of several studies published in the literature (but with a small numbers of patients), we opted for a protocol based on a combination of 400 mg of SOF three times a week after hemodialysis and of 60 mg of DAC daily for a total of 12 to 24 weeks [15,16].

In this observational study we achieved 100% of SVR with the combination of SOF and DAC in 20 hemodialysis patients with minimal side effect profile. Table 2 describes our results comparing to several studies that analyzed the use of SOF in advanced chronic kidney disease. We observed a high efficacy of SOF regimen with mild adverse events except for hematological side effects when used ribavirin or peginterferon [10-14].

In Morocco, among DAA only SOF and DAC are available. Therefore, there is no other choice except SOF-based regimen for treating HCV infection in our country. However, the metabolites of SOF are eliminated by the kidneys, hence SOF is restricted to patients with advanced chronic kidney disease and in hemodialysis.

The classical recommended dose of 400 mg SOF in general population is not clearly approved for populations with end stage renal disease on hemodialysis due to accumulating metabolites with potential hepatobiliary and cardiovascular toxicity. Indeed, SOF is a prodrug metabolized by liver to the active metabolite (GS461203) and subsequently to the inactive metabolite (GS331007) [10]. Since the inactive

### Table 1: The comparison of biological parameters before treatment and 12 weeks after treatment.

| Biological parameters | Before treatment | 12 weeks after treatment | p value |
|-----------------------|------------------|-------------------------|---------|
| Haemoglobin (g/dl)    | 9.46 +/- 1.1     | 10.1 +/- 0.5            | 0.1     |
| Leucocyte count (k/µl)| 5.6 +/- 0.5      | 5.7 +/- 0.3             | 0.15    |
| Platelet count (k/µl)| 222 +/- 10       | 247 +/- 5               | 0.2     |
| AST (UI)              | 26.2 +/- 2.2     | 14 +/- 1.2              | 0.04    |
| ALT (UI)              | 32.3 +/- 4.5     | 13 +/- 1.1              | 0.02    |
| ALP (UI)              | 84.1 +/- 3.2     | 77.5 +/- 2.3            | 0.09    |
| Total bilirubin (mg/dl)| 6.03 +/- 0.5    | 5.3 +/- 0.6             | 0.3     |

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase

### Table 2: Comparison between our results and several studies used Sofosbuvir in advanced chronic kidney disease.

| Series / year of publication | Number of patients | Number of cirrhosis patients | Antiviral regimen | Genotypes and treatment duration (weeks) | % of SVR | Side effects observed |
|------------------------------|--------------------|-------------------------------|-------------------|-----------------------------------------|----------|----------------------|
| Hunderer, et al. [11]        | -eGFR< 30 ml/min/1.73 m² (n = 4) - hemodialysis (n = 2) | 3                              | - SOF-SIM (n = 3) - SOF-RIB (n = 2) - SOF-RIB-peginterferon (n = 1) | G1 (6p)/12-24 | 67 | -Anemia in 3 p treated with RIB - Leukopenia in 1 p treated with peginterferon - worsened of eGFR in 1 p treated with SOF and RIB |
| Gevers, et al. [12]          | - hemodialysis (n = 2) | 2                              | -SOF-LED-rib (n = 1) - SOF-DAc (n = 1) | G1a (n = 2)/12 | 100 | Anemia in 1 p treated with RIB |
| Singh, et al. [10]           | -hemodialysis (n = 8) | 3                              | -SOF-SIM (n = 4) - SOF-LEP (n = 4) | G1 (n = 6) G3 (n = 1) G4 (n = 1)/12 | 87.5 | Headache-Nausea—Vomiting (n = 1) Anaemia (n = 6) |
| Choudhary [13]               | hemodialysis who completed the period of treatment (n = 10) | 2                              | -SOF-RIB-peginterferon (n = 8) -SOF-DAc (n = 2) | G1 (n = 7) G3 (n = 2) G4 (n = 1)/12-24 | 80 | Anaemia (n = 7) Thrombocytopénia (1 p treated with peginterferon) Fatigue (n = 4) |
| Nazario, et al. [14]         | eGFR< 30 ml/min/1.73 m² (n = 2) hemodialysis (n = 15) | 8                              | -SOF-SIM | Not available (n = 4)/12 | 100 | Anaemia (n = 1) Insomnia (n = 2) Headache (n = 1) Nausea (n = 1) |
| Our study/2019               | hemodialysis (n = 20) | 3                              | -SOF-DAc | G1 (n = 15) G2 (n = 5)/12-24 | 100 | Fatigue (n = 2) Headache (n = 1) |

eGFR: estimated Glomerular Filtration; p: patient; Genotypes: G; SVR: Sustained Virologic Response; SOF: Sofosbuvir; SIM: Simeprevir; RIB: Ribavirine; LED: Ledipasvir

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metabolite is eliminated by the kidney, concern was raised that this metabolite would accumulate in patients with advanced chronic kidney disease, potentially leading to toxicity [17]. However, a reduced dose might also be subtherapeutic and is associated to a risk of low efficacy [8]. Therefore, some authors suggest that prescribing standard doses of SOF is mandatory in order to achieve SVR in hemodialysis patients, but this course of treatment’s safety profile is unknown [10,17]. In our study, all patients achieved SVR with a combination of 400 mg of SOF three times a week and 60 mg of DAC daily and reported mild side effects.

Furthermore, a prospective observational study reported by Desnoyer, et al, compared two treatment regimen, one using SOF 400 mg once daily (7 patients) and the other one three times a week (5 patients). Its conclusion suggested that during the period of treatment, SOF and its inactive metabolite did not accumulate with either regimen between hemodialysis sessions, and SOF was well tolerated by all hemodialysis patients in this study. Among the twelve patients, ten achieved SVR (All of the patients receiving SOF daily, and 3 out of 5 patients receiving SOF three times a week (5 patients). Its conclusion suggested by Desnoyer, et al, compared two regimen, one with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase study. Lancet. 2015; 386: 1537–1545. PubMed: https://pubmed.ncbi.nlm.nih.gov/26456905/

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