HSPC The Open Access Publisher

J C N JOURNAL OF CLINICAL NEPHROLOGY
ISSN 2576-9529

Research Article

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

Mouna Tamzaourte[1]*, Yassir Zajjari[2], Sanae Berrag[1], Tarik Adioui[1], Aziz Aourarh[1] and Driss El Kabbaj[2]

[1]Department of Gastroenterology I, Military Hospital Mohammed V, Hay Ryad BP 10100, Rabat, Morocco

[2]Department of Nephrology-Dialysis, Military Hospital Mohammed V, Hay Ryad BP 10100, Rabat, Morocco

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.

More Information

***Address for Correspondence:**
Dr. Mouna Tamzaourte, Department of Gastroenterology 1, Military Hospital Mohammed V, Hay Ryad BP 10100 Rabat, Morocco. Tel: 00212661490807; Email: mouna.tamzaourte@gmail.com

Submitted: April 27, 2021
Approved: August 25, 2021
Published: August 26, 2021

How to cite this article: Tamzaourte M, Zajjari Y, Berrag S, Adioui T, Aourarh A, et al. Practice patterns and outcomes of repository corticotropin injection (Acthar® Gel) use in childhood nephrotic syndrome: A study of the North American Pediatric Renal Trials and collaborative studies and the Pediatric Nephrology Research Consortium. J Clini Nephrol. 2021; 5: 077-080.

DOI: 10.29328/journal.jcn.1001078

Keywords: Sofosbuvir; Hepatitis C; Hemodialysis

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 m^2 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 litterature 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 reponse 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 (U/l)	26.2 +/- 2.2	14 +/- 1.2	0.04
ALT (U/l)	32.3 +/- 4.5	13 +/- 1.1	0.02
ALP (U/l)	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
Hundemer, 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 a 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 (1 p was lost to follow up	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	G1a (*n* = 13) 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

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 sub-therapeutic 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 profil 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 aand reported mild side effects.

Furthermore, a prospective observational study reported by Desnoyer, et al, compared two treament 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). However, 2 patients with compensated cirrhosis relapsed in the half dose group [8]. In our study, all cirrhotic patients (three) were treated for 24 weeks with SOF three times a week and DAC daily, we achieved 100% of SVR without virologic relapse after the end of treatment during the study period, the tolerance was good for all patients. Therefore, we suggest treating hemodialysis patients with a compensated cirrhosis for at least 24 weeks in order to achieve optimal efficacy, as well as a good tolerance without relapse. However, this hypothesis still requires larger studies for confirmation.

Although the findings of the current study SOF are encouraging, our experience had several limitations. Firstly, it had a small sample size. Secondly Lack of measurement of SOF and its inactive metabolite levels were another limitation. Therefore, Larger prospective studies are needed in order to determine the proper SOF regimen in hemodialysis patients, tataking into consideration both efficacy and safety.

Conclusion

In Morocco even though there are no new DAA combination treatment regimens that 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.

References

1. Fabrizi F, Lunghi G, Ganeshan SV, Martin P, Messa P. Hepatitis C virus infection and the dialysis patient. Semin Dial. 2007; 20: 416-422. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/17897248/
2. Sekkat S, Kamal N, Benali B, Fellah H, Amazian K, et al. Prevalence of anti-HCV antibodies and seroconversion incidence in five haemodialysis units in Morocco. Nephrol Ther. 2008; 4: 105-110. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/18272446/
3. Duseja A, Choudhary NS, Gupta S, Dhiman RK, Chawla Y, et al. Treatment of chronic hepatitis C in end stage renal disease: experience at a tertiary care centre. Tro Gastroenterol. 2012; 33: 189–192.
4. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. J Hepatol. 2017; 66: 153-194. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/27667367/
5. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients 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/
6. Gane E, Lawitz E, Pugatch D, Papatheodoridis G, Bräu N, et al. Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment. N Engl J Med. 2017; 377: 1448-1455. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29020583/
7. Kirby BJ, Symonds WT, Kearney BP, Mathias AA. Pharmacokinetic, Pharmacodynamic, and Drug-Interaction Profile of the Hepatitis C Virus NS5B Polymerase Inhibitor Sofosbuvir. Clin Pharmacokinet. 2015; 54: 677-690. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/25822283/
8. Desnoyer A, Pospai D, Le MP, Gervais A, Heurgué-Berlot A, et al. Sofosbuvir containing regimen for HCV infection in hemodialysis patients: 400 mg daily or only on the day of hemodialysis. J Hepatol. 2016; 65: 40-47. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/26952005/
9. Saxena V, Koraishy FM, Sise ME, Lim JK, Schmidt M, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. Liver Int. 2016; 36: 807–816. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/26923436/
10. Singh T, Guirguis J, Anthony S, Rivas J, Hanouneh IA, et al. Sofosbuvir-based treatment is safe and effective in patients with chronic hepatitis C infection and end stage renal disease: a case series. Liver Int. 2016; 36: 802–806. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/26824848/
11. Hundemer GL, Sise ME, Wisocky J, Ufere N, Friedman LS, et al. Use of sofosbuvir-based direct-acting antiviral therapy for hepatitis C viral infection in patients with severe renal insufficiency. Infect Dis (Lond). 2015; 47: 924-929. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/26365684/
12. Gevers TJG, Burger D, Schipper-Reintjes E, Kooistra MP, Richter C. Full-dose sofosbuvir and daclatasvir for chronic hepatitis C infection in haemodialysis patients. Neth J Med. 2016; 74: 225-227. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/27323683/
13. Choudhary NS, Kumar A, Bodh V, Bansal SB, Sharma R, et al. Efficacy and safety of sofosbuvir-based regimens in chronic hepatitis C patients on dialysis. Indian J Gastroenterol. 2017; 36: 113-116. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/28281085/
14. Nazario HE, Ndungu M, Modi AA. Sofosbuvir and Simeprevir in Hepatitis C genotype 1- patients with End-Stage Renal Disease on hemodialysis or GFR <30mL/min. Liver Int. 2016; 36: 798-801. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/26583882/
15. Dumortier J, Bailly F, Pageaux GP, Vallet-Pichard A, Radenne S, et al. Sofosbuvir-based antiviral therapy in hepatitis C virus patients with severe renal failure. Nephrol Dial Transplant. 2017; 32: 2065-2071. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/27760839/
16. Agarwal SK, Bagchi S, Yadav RK. Hemodialysis patients trated for hepatits C using a sofosbuvir containing regimen/ Kidney International Reports. 2017; 2: 831–835. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29270489/
17. Cornpropst MT, Denning JM, Clemons D, Marbury T. The effect of renal impairment and end stage renal disease on the single-dose pharmacokinetics of PSI-7977. J Hepatol. 2012; 56: S433.