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Direct-Acting Antiviral Hepatitis C Therapy in Patients with Chronic Renal Failure

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Abstract: ***The prevalence of hepatitis C virus (HCV) infection is estimated at 3% in the global population, it is higher in patients on hemodialysis, the treatment of viral hepatitis C has increased with appearance of new antiviral molecules specifically targeting the virus that has revolutionized the therapeutic response. Materials and methods: This is a retrospective study from 2015 to February 2018 in the service of hepato-gastroenterology, University Hospital Mohamed VI, Marrakech including 33 hemodialysis patients or follow-up for renal insufficiency not dialyzed and put on treatment by sofosbuvir400mg / day in association with daclatasvir 60mg / d including 2 patients with severe renal insufficiency (creatinine clearance <30 ml / min / 1.73 m2) we opted for sofosbuvir 400 mg once every 48 hours and always in combination with daclatasvir 60 mg / d . HCV viral load, liver function and renal function Clinical and biological tolerance were assessed. Results: Genotype 1 is predominant representing 44% of cases. The average viral load is 5.31 Log UI / l. The results of our study are very satisfactory. The SVR of 12 weeks after discontinuation of treatment was obtained in all cases. The renal tolerance was very good. There was no impairment of renal function, only one patient had deep asthenia .In the non-availability of other molecules in Morocco, our study supports the use of the combination of sofosbuvir400mg / d and daclatasvir 60mg / d, which is effective and well tolerated. Our study supports the use of the combination of sofosbuvir400mg / d and daclatasvir 60mg / d, which is effective and well tolerated.***

Keywords: viral hepatitis C, hemodialysis, renal failure, direct antivirals, response, adverse effects

1. Introduction

Viral infections, especially those caused by hepatitis C virus (HCV) and hepatitis B, are common in patients undergoing chronic hemodialysis. Viral hepatitis C (HCV) remains the main viral infection in hemodialysis patients. The severity of this infection is its high risk of progression to chronicity and the development of cirrhosis or hepatocarcinoma. Despite a high prevalence of HCV infection in hemodialysis patients; existing studies on the treatment of this population considered "difficult to treat" are rare. The main objective of this work is to describe our experience in the management of patients with viral hepatitis C hemodialysis and direct anti viral.

Objective: To analyze the efficacy and safety of these antivirals in patients with chronic renal failure and hemodialysis.

2. Patients and Methods

This is a retrospective study on HVC patients' files followed from 2015 to February 2018 in the gastroenterology department at the University Hospital Center Mohamed VI of Marrakech. All patients with chronic renal insufficiency and hemodialysis with chronic viral hepatitis C who were naive, relapsed or non-responders, all genotypes combined, cirrhotic or not, put on treatment with direct antivirals alone (sofosbuvir, daclatasvir) We excluded of our study: Patients with chronic viral hepatitis with GFR ≥ 60ml / min / 1.73m and patients who were lost to follow-up. Patients eligible for treatment have all benefited from a pretreatment assessment, which once normal, started treatment with direct anti-viral. A consultation every 04 weeks until the end of treatment S12 or S24 then 03months after stopping treatment except in case of major adverse effects with as a balance sheet: a viral load, NFS, urea creatinine, liver test. The purpose of this consultation is to ensure adherence, evaluate potential adverse effects and identify potential drug interactions. The duration of the treatment is established according to the genotype of the virus, the degree of the fibrosis and according to the therapeutic status (naive or in failure). The data were entered, coded and analyzed on an Excel file. The analysis was carried out by the description of the sample studied according to Sociodemographic, epidemiological, paraclinical and therapeutic clinical characteristics.

3. Results

Of a total of 453 cases of viral hepatitis C, 33 patients undergoing hemodialysis and follow-up for non-dialysis renal insufficiency were placed on direct anti-viral drugs (sofosbuvir 400 mg and dactaslavir 60 mg). The mean age of our patients was 37 years with extremes ranging from 21 to 71 years old. A female predominance was noted in 53.86% of patients with a sex ratio F / H of 1.16. 12 patients had a history of chronic hypertension (hypertension) under treatment (30.77% of cases), three patients were followed for dysthyroidism, 6 patients were diabetic type I and 12 patients with type II diabetes. Patients had been on dialysis for an average of 10 years with extremes ranging from 1 to 27 years, with 2 sessions per week (in 76.94% of cases). Viral infection was found on average 5.4 years after the start of hemodialysis in 6 patients most often during an etiological assessment of asthenia Only 11 patients received systematic screening for HCV before hemodialysis having made the diagnosis. The pre-therapeutic median viral load was 4351611.84 IU / ml. 6 patients had a viral load less than 800000 IU / ml. In Fibroscan, 22 patients had moderate to severe fibrosis (F2-F4). Transaminases were ≥ 2 times normal in patients 12 In this series, genotype (G) 1b was found in 16 cases genotype 4 in 6 cases, genotype 2 in 5 cases.

Due to the non-availability of all direct viral anti-viral drugs in Morocco without renal resonance that can be administered in combination, the only available sofosbuvir has been prescribed in combination with the 400 mg dose in all patients monitored for renal insufficiency or on hemodialysis. andsofosbuvir 400 mg once daily in combination with daclatasvir in 2 patients with creatinine clearance <30 ml / min / 1.73 m2 with regular monitoring of creatinine clearance according to AFEF recommendations. 20 patients were naive of any therapy, 13 patients were interferon failure or failed interferon ribavirin combination, or adverse effects increased by the erythropoietin disease in 80% of cases, the duration of treatment was determined according to the genotype, the degree of fibrosis and according to the therapeutic status of the patient (in failure or naive) it was 3 months in 18 patients and 6 months in 15 patients. The results of our study are very satisfactory; the SVR 12 week after discontinuation of treatment was obtained in 100% of cases. Tolerance was very good; only one patient presented a deep asthenia that is 3.2% of cases. In our series, no patient presented with severe bradycardia. The impact of these direct antivirals on certain biological parameters (ASAT, ALAT, GGT, Bilirubin, platelet count, GFR) was also evaluated by comparing the values before starting the treatment with those obtained at the end of the treatment did not notice a biological disturbance during the follow-up.

4. Discussion

It has been estimated that around 170 million people worldwide are living with the hepatitis C virus (HCV) and 500,000 people died from HCV-related liver disease in 2010. Hepatitis C is closely related to bind related to renal function. Thus, the prevalence of hepatitis C in patients on hemodialysis (HD) is higher than that found in the general population. A study published in 2013 by Dialysis Outcomes and Practice with data from more than 49,000 patients from different countries around the world showed that the prevalence of HCV infection in HD patients was 9.5%, varying between 3.3 and 16.8% [1].
In Morocco, this seroprevalence is 32% according to the Moroccan Magredial register. However, this is an overall average because the seroprevalence varies, in the same country, according to the dialysis units. In a recent retrospective study of 141 chronic hemodialysis patients between April 2010 and September 2012 at HMIMV, the prevalence of hepatitis C virus in chronic treated hemodialysis patients was 12.1% [2].

Nosocomial blood (transfusion) and nosocomial HCV modes (in hemodialysis centers) [3] explain the frequency of HCV infection among dialysis patients. The presence of HCV infection in these populations has a significant impact on the indication of renal transplantation in these patients because of the increased mortality after transplantation [4].

The natural history of viral hepatitis C in hemodialysis is, however, characterized by a low-noise evolution. Indeed, and as demonstrated by Fabrizi et al for 10 years, the level of transaminases is low during chronic renal failure (CKD) [5]. This decrease was attributed to vitamin B6 deficiency and the presence of uremic toxins in the blood, which could alter the detection of transaminases [6] [7]. Gouveia et al compared ALT in 202 hemodialysis patients including 15 anti-HCV positive [8]. In our study, transaminases were ≥2 times normal in 5 patients (61.54%). The authors found that the ratio of ALTs to the upper limit of normal was 0.7 in patients infected with the virus. They concluded that a rate exceeding 70% of the laboratory's normal upper limit is highly predictive of viral hepatitis C with a sensitivity of 67% and a specificity of 75%, liver fibrosis often moderate. [9] [10] with 80% of patients F0 / 1 according to METAVIR, 20% of patients F2.6% F3, and only 4% F4. [11-12]

Virologically, viral load is low in hemodialysis patients; the capacity for antibody synthesis is reduced in patients with renal insufficiency, accounting for a relatively high percentage of false negatives in ELISA or RIBA [13]. In renal transplant patients infected with HCV, the rate of progression of hepatic fibrosis is accelerated. Hepatitis C is associated with an increase in all-cause mortality and increased liver-related mortality, although cardiovascular disease remains the leading cause of death in these patients

An American study showed that nearly half (41%) of patients newly on the waiting list for a liver transplant were diagnosed with HCV infection [6]. biomedicine show that the shortage of grafts has worsened in 2013 with an increase in the total number of applicants (+ 10%), more important than the increase in the number of transplants with needs that remain higher than the transplant possibilities. (2.4 candidates for a graft usable in the year against 1.8 in 2007). It may be thought that the eradication of the virus would thus make it possible to reduce the demand for grafts during periods of scarcity. During the 2013-2022 period, well managed AVDs are expected to save 4425 (4183-4684) liver transplants (40%) with a 88% reduction in non-transplanted patients for HCC and 42% for decompensated cirrhosis [14]

The KDIGO Good Practice Guideline recommends treating all patients with chronic kidney disease (CKD) stage 5D who are HCV-positive when they are candidates for renal transplantation. In addition, eradication of HCV before RT seems to improve survival and decrease the frequency of chronic allograft nephropathy [15]. In the last decade, interferon-based (IFN) without ribavirin (RBV), were the only treatment options available to HD HCV-infected patients. The advent of direct-acting antivirals (AAD) has revolutionized the management of HCV infection in the general population, [16] but few data are available on their prescription in HD patients. [17, 18]

Most approved DAAs are metabolized by the liver so renal clearance is minimal. However, sofosbuvir (SOF), the backbone of a majority of antiviral regimens, after oral administration of 400 mg of SOF, the peak plasma is reached approximately between 0.5 and 2 hours in the subject, 80% of the product are eliminated in the urine (78% inactive form and 3.5% in unchanged form). It is a prodrug that is phosphorylated into an active metabolite (GS461203) and then phosphorylated into its inactive metabolite (GS331007) [19]. SOF and metabolite GS331007 are eliminated by the kidney and therefore accumulate in patients with a GFR <30 ml / min. Given the lack of clinical

trials assessing safety and efficacy in patients with TIR, the label does not recommend its use in these patients. However, a recent study by Desnoyer et al. , compared the plasma concentration of SOF and its inactive metabolite (GS331007) in patients receiving SOF therapy with a standard dose of SOF (400 mg / day, n = 7) or SOF administered 3 times / week (n = 5). The authors found that neither SOF nor its metabolite GS331007 accumulates between HD sessions or during the study period. In addition, the extraction rate of GS331007 was 52%, which was similar to historical data. There was no side effects related to the treatment. More information is needed to confirm these findings, but it seems plausible to allow the use of SOF-based therapies [18], in patients with IRT and no other treatment options with very careful follow-up. It is not necessary to adjust the dosage of SOF in patients with glomerular filtration rate (GFR) greater than 30 ml / min / 1.73 m2. In contrast, there is currently no dose adjustment guideline for SOF in renally impaired patients with GFR <30 ml / min / 1.73 m2, Saxena et al. [20], with data from HCV-TARGET, compared results in terms of efficacy and safety in patients with GFR <45 ml / min (n = 82, of which 5 on HD) or> 45 ml / min (n = 1811) receiving SOF therapy. The authors found similar results in terms of efficacy (SVR of 83 vs. 82%, respectively) but a significantly higher number of adverse events, particularly anemia (22 vs. 6%, p <0.001) and worsening renal function (15 vs. 1%, p <0.001) in the group of patients with GFR <45 ml / min. However, there is no follow-up data to assess whether renal function is restored after stopping treatment. A 4-hour HD session eliminates about 18% of the administered dose [21], so it is advisable to take SOF after the HD session. In the dialysis patient, the SOF was given at the usual dosage (400 mg / day) or at a reduced dosage (200 mg / day or 400 mg every other day or three times a week after each dialysis) in several studies. It is associated with RBV or simeprevir, with SVR rates at 12S, ranging from 40 to 88% depending on the treatment regimen and whether or not there is cirrhosis. Thus, according to the latest AFEF recommendations, March 2018, patients with severe renal insufficiency (stage 4 or 5) or dialysis can be treated with direct antivirals, but non-Sofosbuvir regimens should be preferred. Otherwise, the use of Sofosbuvir regimens should be evaluated, close monitoring of renal function is required and antiviral therapy should be discontinued if renal function worsens.

Daclatasvir is an inhibitor of NS5a. It obtained a European marketing authorization (AMM) in August 2014. It is indicated in combination with SOF in patients with a viral C infection. It is particularly interesting for the treatment of patients infected with a genotype virus. 3. After administration, 88% of the DCV dose is eliminated in the stool and only 6.6% in the urine [20]. Thus, no dosage adjustment is necessary in severe chronic renal failure. The most commonly reported adverse events (frequency 10%) associated with the combination of SOF and DCV are fatigue, headache and nausea. In our series, only one patient presented with deep asthenia Due to the risk of severe bradycardia and conduction disorders, the National Agency for the Safety of Medicines and Health Products (ANSM) advises against associating SOF with amiodarone.

Other treatment regimens are proposed in the latest recommendations in March 2018 of the French Society of Hepatology (AFEF) according to the level of DFG. Thus, for patients with GFR> 30 ml / min / 1.73 m2, no dose adjustment is required for DAAs. If GFR is <30 ml / min / 1.73 m2, the following treatment options are recommended: Glecaprevir + Pibrentasvir for 12 weeks For HCV genotype 1 infections: Grazoprevir + Elbasvir for 12 weeks Patients with severe stage renal impairment 4 (estimated glomerular filtration rate 15-29 mL / min / 1.73m2) or 5 (estimated glomerular filtration rate <15 ml / min / 1.73 m2 or dialysis) can be treated with direct antiviral agents but schemas without Sofosbuvir should be privileged. In dialysis patients undergoing renal transplantation, initiation of pre- or post-transplantation therapy should be discussed on a case-by-case basis.

In the EXPEDITION IV study, 104 patients (19% of patients with compensated cirrhosis) with severe renal insufficiency, including 82% of hemodialysis patients, were treated with Glecaprevir + Pibrentasvir for 12 weeks. SVR was 98% (one treatment stop and one patient lost to follow-up) (29). The Grazoprevir + Elbasvir combination for 12 weeks was evaluated in genotype 1 patients with end-stage renal disease. SVR was 99% [21].

Our study was able to show a very good efficacy in the 33 patients followed for chronic renal insufficiency or in the hemodialysis stage put under the combination of sofosbuvir 400mg / day and daclatavir 60mg / day for a treatment of 12 weeks with a SVR obtained in 100 % of patients and especially good tolerance with very rare adverse effects, profound asthenia in a single patient, without any worsening of renal function in any of the patients. The other international studies combining sofosbuvir and daclatasvir were reassuring, with good results in terms of efficacy and tolerance. Waiting for the entry of Grazoprevir and elbasvir at the Moroccan market. Treatment of HCV in patients with chronic renal failure and hemodialysis by the combination regimen of sofosbuvir400mg / d and daclatasvir 60mg / d may be proposed with close monitoring of renal function and antiviral therapy should be discontinued if aggravated.

5. Conclusion

Viral hepatitis C is a major public health problem, both because of its frequency and because of its complications with the risk of progression to cirrhosis and hepatocellular carcinoma. It is more common and more severe in chronic hemodialysis patients and renal transplant patients than in the general population. Recently, the treatment of hepatitis C has progressed significantly with the appearance of new antiviral molecules specifically targeting viral proteins: direct acting antivirals (DAAs). The pharmacokinetic profile of Sofosbuvir, which has about 80% renal elimination, poses challenges for the management of patients with chronic kidney disease. Thus, the new recommendations for the treatment of HCV in chronic renal failure and chronic hemodialysis favor treatment regimens without sofosbuvir. Our study aimed to evaluate the efficacy and the tolerance of the generics association available in Morocco for Sofosbuvir 400mg / d and daclatasvir 60mg / day in 18 chronic hemodialysis patients, the results were astonishing and

reassuring with a negativity of the viral load at 4 weeks in all patients and a sustained virological response (SVR) 12 weeks after stopping treatment in 100% of patients, the tolerance was also very good and only one patient had a profound asthenia, without any aggravation of the renal function in any of the patients, our study supports the use of this treatment with close monitoring of renal function in order to stop it in the event of worsening of renal function, therapeutic projects must aim more and more hemodialysis is a population where the prevalence of HCV is high and a source of transmission of the virus, studies in this population have not shown great difficulties including ours, which can consolidate the dream of a world where the virus viral hepatitis C will be a history.

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