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Evaluation of the Strategy and Efficacy of Treatment of Chronic Viral Hepatitis C with the Sofosbuvir/Daclatasvir Combination in a Resource-Limited Country

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Abstract

Introduction: The treatment of viral hepatitis C (HCV), a major public health problem, has evolved considerably since the introduction of direct-acting anti-virals (DAAs). The aim of this study was to evaluate the strategy for initiating treatment with Sofosbuvir/Daclatasvir, and also to assess its efficacy. **Patients and Methods:** Included were patients aged at least 15 years, with detectable hepatitis C viremia and treated with a pan-genotypic Sofosbuvir/Daclatasvir regimen at the Centre "Hospitalier Universitaire la Référence Nationale de N'Djamena" between October 2019 and October 2023. The APRI score was used to assess fibrosis. Cure was defined by an undetectable viral load 12 weeks after the end of treatment. **Results:** A total of 835 patients were included (sex ratio 1.55, mean age 50.5 ± 13.73, extremes 20 and 84 years). The 60 - 69 age group was the most represented. The mean APRI score was 0.42 ± 0.29, with extremes of 0.019 and 1.84. The mean viral load was 2,316,193.086 IU/mL. All subjects had good renal function. Cytolysis was absent in 70% of cases. Without genotyping, a pan-genotypic regimen was used in all patients: Sofosbuvir (400 mg)/Daclatasvir (60 mg). The cure rate was 99.4%, with good tolerability. However, four cases of failure were recorded out of the 668 patients who underwent follow-up HCV-PCR testing after 12 weeks of treatment. **Conclusion:** The Sofosbuvir/Daclatasvir regimen is highly effective, with an excellent safety profile. However, the still high cost

of these molecules limits their accessibility to a large proportion of patients.

Keywords

Efficacy, Tolerance, Sofosbuvir/Daclatasvir, HCV, Chad

1. Introduction

Since its discovery in 1989, infection with the hepatitis C virus has been a constant preoccupation of the scientific community. The WHO has recognized it as a major public health problem. According to recent data, there are an estimated 58 million chronic hepatitis C carriers in the world. The disease is estimated to be responsible for 290,000 deaths a year [1].

In sub-Saharan Africa, prevalence varies from 0.6% to 4.1%. The problem is crucial, as 21 million people are thought to be infected with HCV [1]. The problem of viral hepatitis C seems to have long been neglected by that of its "alter ego", viral hepatitis B, certainly due to the greater prevalence of HBV on the one hand, and the inaccessibility of diagnostic and therapeutic means for HCV on the other.

In its chronic form, the infection remains silent for several years. The long-term impact is highly variable, ranging from minimal histological changes to advanced fibrosis and even cirrhosis. One third of chronically infected people will develop cirrhosis or primary liver cancer (PLC) [2] [3].

HCV infection is currently the only chronic viral infection curable by treatment.

The first treatment developed was based on the administration of an immunomodulating protein, interferon alpha. However, the modest cure rates and numerous constraints associated with this treatment stimulated research into its optimization, and led to the development of new HCV-targeting molecules that can be administered orally: direct-acting antivirals. These new treatments, which are effective in over 95% of cases and well tolerated, offer the prospect of large-scale treatment of populations and, according to some authors, even eradication of the virus [4]. The disadvantage of DAAs is their exorbitant cost. However, in countries with limited resources, access to treatment is now possible thanks to generics and the low-cost pan-genotypic treatment strategy. The Sofosbuvir/Daclatasvir-based regimen is being used less and less, but remains easily accessible for resource-limited countries such as Chad.

The aim of this study was to evaluate the strategy and efficacy of the pan-genotypic Sofosbuvir/Daclatasvir combination in the management of chronic viral hepatitis C in N'Djamena, Chad.

2. Methodology

This was a prospective observational study conducted over a 4-year period (Oc-

tober 2019 to October 2023). The study population consisted of patients aged at least 15 years, seen in outpatient hepatology consultations at the Day Hospital Unit and the Internal Medicine/Gastroenterology Department of the "Centre Hospitalier Universitaire la Référence Nationale", which served as settings.

These consultations, specially dedicated to viral hepatitis, were organized as part of the South-South cooperation between the Arab Republic of Egypt and Chad in the fight against viral hepatitis. Patients with a detectable HCV viral load (HCV-RNA > 15 IU/mL) and treated with DAAs, regardless of genotype or severity of liver disease, were included. Sofosbuvir/Daclatasvir was the pan-genotypic regimen used for 12 weeks. Patients with limited life expectancy due to severe extra-hepatic comorbidity (tumor pathology) were not included in the study. Treatment was provided free of charge to all patients included in the study. However, complementary examinations were paid for by the patients themselves.

Method and Technique

HCV serology was performed using a 3rd-generation ELISA method (Abbott). The detection and quantification of HCV RNA were performed by real-time PCR with a quantification threshold of 15 IU/mL. The APRI score was used to assess liver fibrosis. Viremia was monitored 12 weeks after the end of treatment by the same PCR test. Cure was defined by an undetectable viral load (HCV-PCR < 15 IU/mL) 12 weeks after the end of treatment

While treatment failure was defined by detectable viremia 12 weeks after the end of treatment, as recommended by the WHO [1]. Patients who had received the 3 boxes of treatment indicated but who failed to attend the appointment for the viral load check 12 weeks after the end of treatment were considered lost to follow-up. Data were entered and analyzed using SPSS 18.0 software. Chi-square test was used with significance level of $p < 0.05$.

3. Results

The study included 835 patients with chronic hepatitis C and detectable viral load. The mean age was 50.5 ± 13.73 (extremes: 20 - 84 years), with the 50 - 69 age group (42.2%) the most represented. A male predominance was found: 60.78% of men, with a sex ratio of 1.59.

As shown in **Table 1**, the mean hepatitis C viral load was 2316193.086 ± 7486260.714 IU/mL. Most patients had normal Alanine Amine Transferase (ALAT) levels (69.6%). Mean ALT was 36.74 ± 25.72 with extremes of 3.4 and 99 IU/L. All patients had normal creatinine levels. Hematologically, the mean platelet count was 216.109 /L.

The APRI score used to assess fibrosis was below 1 in most cases, with a mean of 0.42 ± 0.29 and extremes of 0.019 and 1.84. In 2.69% of cases, it was above 1. Morphological studies of the liver by ultrasound were normal in 97% of cases. Only 3 patients had compensated cirrhosis and 1 had decompensated cirrhosis.

The latter, with decompensated cirrhosis, was also diabetic. Imaging also revealed two cases of hepatic steatosis. Bivariate analysis showed a statistically significant relationship between hepatitis C carriage and male sex (p = 0.03). There was also a highly significant statistical relationship between APRI score above 1 and male sex (p = 0.00). On the other hand, being male had no influence on the elevation of hepatitis C viral load.

With regard to treatment efficacy and tolerability, after 12 weeks of treatment, 668 patients underwent viral load monitoring. Of these, 664 had an HCV PCR result of less than 15 IU/mL, *i.e.* negative, for a cure rate of 99.4%. No cases of intolerance were reported.

Table 1. Epidemiological, biological and therapeutic characteristics of patients.

Number	**835 patients**
Average age	50.5 ± 13.73 (extremes: 20 - 84 years)
Age range 50 - 60	42.2%
Sex-ratio (H/F)	1.55
Average viral load	2316193.086 UI/mL
Les transaminases (ALAT)	Normal in 70% of cases
APRI score	0.42 ± 0.29 (extremes: 0.019 and 1.84)
Therapeutic regimen	Sofosbuvir (400 mg)/Daclatasvir (60 mg)
Sustained virological response (SVR)	99.4%
Failure	4/668
Tolerance	good

4. Discussion

This study, the first of its kind in our context, assessed the therapeutic strategy and choice of regimen for Sofosbuvir/Daclatasvir-based HCV treatment introduced through South-South cooperation with the Arab Republic of Egypt, and included 835 patients. Treatment efficacy was assessed in 664 patients. The mean age in this study was 50.5 ± 13.73, with extremes of 20 and 84 years. A mean and/or median age of around 50 or 60 was reported by several African authors: Diarra in Mali reported a mean age of 49.5 ± 17.6 years [5].

A median age of 55 and 60 was also found in Côte d'Ivoire and Cameroon respectively [6] [7]. In France, the median age was 53 ± 12 years, according to Dijoux [8]. The age range most represented in this series was 50 to 69 years. The age distribution of patients shows an increasing proportion with age. The same observation was made in Meda's general population study in Burkina Faso [9]. This phenomenon is well known and has been reported in numerous studies, including meta-analyses [10]-[14]. It is due to the accumulation of risk exposure with age. We might also suspect that the incidence of infection decreases over time, as a result of improvements in the safety of care procedures and, above all, transfusion safety.

Thus, older subjects would have a theoretically higher risk of infection. According to Léa Duchesne *al.* in a study entitled Afrique sub-saharienne et hépatite C, people aged over 50 accounted for over 50% of all HCV infections and over 90% of cases of advanced liver disease and HCV-related mortality [15]. In this series, the 50 - 69 age group represented over 40% of the study population, corroborating this model. In this study, 60.78% of patients were male, giving a sex ratio of 1.6. This male predominance was also found in several studies in Burkina Faso and Egypt [16] [17]. A statistically significant relationship was found between male sex and hepatitis C virus infection in our series. In Burkina Faso, on the other hand, Meda et al. found no significant difference between the sexes [9].

The results of this study show that, although there is a tendency towards male predominance, this remains variable.

Biologically, all patients included in this study had a detectable hepatitis C viral load, *i.e.* greater than 15 IU/mL. The mean hepatitis C viral load was 2,316,193.086 ± 7,486,260, 714 IU/mL. Sombié et al. in Burkina Faso reported viremia > 800,000 IU/mL (5.9 log) in 54.3% of patients [18]. This series gives an order of magnitude for the viral load of infected patients. Indeed, during interferon therapy, a low initial viral load is significantly correlated with the achievement of a sustained virological response (SVR), and the kinetics of viral load decay are predictive of therapeutic response [19] [20]. It should be remembered that the latter theory has lost its prognostic value since the advent of powerful direct antiviral therapies.

Regarding hepatic cytolysis, most patients had normal Alanine Amine Transferase (ALAT) levels (69.6%). The mean ALAT level was 36.74 ± 25.72, with extremes of 3.4 and 99 IU/L. The prevalence of these "chronic hepatitis with normal transaminases" varies in the literature from 7.5% to 53%. The absence of cytolysis is thought to be linked to a weak host immune response to the virus. Histological lesions are usually moderate, and significantly less severe than in patients with elevated amino transferase activity. Factors associated with these forms appear to be female gender, HLA alleles DRB1*1302, DRB1*1101, DQB1*0604, and genotype 1 [21].

Liver fibrosis was assessed using a WHO-validated non-invasive liver fibrosis test (APRI). This test has the advantage of being free and downloaded onto the smartphone. The APRI score used was below 1 in 87.31% of cases, with a mean of 0.42 ± 0.29 and extremes of 0.019 and 1.84. In 2.69% of cases, it was greater than 1. Patients with an APRI score below 1 all responded well to treatment. A statistically significant relationship between APRI score and good therapeutic response was found in this study ($p = 0.00$). This result shows that patients were recruited largely before the onset of fibrosis, which spoils a good prognosis. Patients with significant cytolysis and an APRI score greater than 1 were followed up for variable periods prior to the start of treatment. Treatment was introduced after improvement in transaminases.

The treatment of hepatitis C has undergone considerable evolution since the use of interferon alpha, a physiological molecule combining antiviral and immunomodulatory properties, through to its pegylated counterpart (INF-Peg) associated with Ribavirin [22]. This growing evolution, which has improved the management of this condition, has been revolutionized by the advent of new treatments constituting the second generation of pan-genotypic DAAs.

In the present study, pan-genotypic treatment with the combination of Sofosbuvir 400mg and Daclatasvir 60mg after 12 weeks of treatment resulted in a cure rate of 99.4% (664/668). This result is consistent with the literature [23]. This rate is higher than the 93% found in Cameroon [7]. It is also higher than those of Outidi et *al*. in Gabon [24]. The Sofosbuvir/Daclatasvir combination is suboptimal in certain genotypes, such as 2. We note that previous studies, albeit preliminary, have demonstrated the high prevalence of genotype 4 in chronic HCV carriers This justifies the high cure rate in this work, which contradicts the version according to which sub-Saharan African origin was associated with a poorer therapeutic response [8].

With regard to tolerability, no cases of treatment interruption were reported, and there was no recourse to hospitalization due to treatment side effects. Patients enrolled in the study reported no major adverse events. Cheinquer also reported no treatment-related adverse events [25]. The Sofosbuvir/Daclatasvir combination is therefore extremely well tolerated.

In this study, 4 cases of failure were recorded out of 668 patients with a control viral load. As factors influencing therapeutic failure, cirrhosis was incriminated in this series. The 4 cases of failure were cirrhotic patients with an APRI score > 1. In addition to cirrhosis, one of these patients was a type 2 diabetic who had been followed for ten years. Dijoux and Eloumou Bagnaka also highlighted severe fibrosis, cirrhosis and/or its complications (ascites, encephalopathy, esophageal varices, HCC) as factors associated with therapeutic failure [7] [8].

5. Conclusion

The introduction of DAAs in the treatment of hepatitis C has revolutionized the management of this condition. Although the cost of the molecules and complementary tests has often been an obstacle, generics and above all the pan-genotypic treatment strategy based on Sofosbuvir/Daclatasvir, thanks to South-South cooperation, have contributed considerably to facilitating management in our context. In addition to their efficacy, this regimen offers the advantage of good tolerability. Factors associated with treatment failure are dominated by cirrhosis and its complications.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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