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Effectiveness of Treatment of Chronic Viral Hepatitis C by Direct-Acting Antivirals in Togo

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Abstract

Background: Viral hepatitis C is the second leading cause of hepatocellular carcinoma after hepatitis B in Africa and Togo in particular. The advent of direct acting antivirals has revolutionized the care and prognosis of patients infected with hepatitis C virus (HCV). **Objective:** To evaluate the sustained virological response (SVR) 12 weeks after oral treatment without interferon in HCV infected patients with genotypes 1 and 2. **Patients and Method:** Descriptive and analytical study based on the retrospective collection of data in the hepatogastroenterology unit of the University Hospital Campus of Lome (Togo) from July 11, 2016 to April 22, 2018. All patients who had a chronic viral hepatitis C with viral replication, naive, regardless of the genotype, regardless of the degree of liver fibrosis, and who had completed their treatment with direct-acting antivirals were included. **Results:** We recruited 84 patients, 60 of whom were infected with HCV genotype 2 (71.43%) and 24 with HCV genotype 1 (28.57%). There were 58 men and 26 women (sex ratio: 0.45). In HCV genotype 1 patients, the median age was 54.29 years and Sofosbuvir/Ledipasvir was the most used combination (62.50%). In HCV genotype 2 patients, the median age was 54.5 years and Sofosbuvir associated with Ribavirin was the most used treatment (81.66%). The virological response at the end of treatment was 100% (genotype 1) and 93.30% (genotype 2). The SVR 12 was 100% (genotype 1) and 91.70% (genotype 2). Five patients were in treatment failure (genotype 2). **Conclusion:** Direct-acting antivirals were effective in our patients. The rate of sustained virological response was above 90%.

Keywords

Viral Hepatitis C, Direct-Acting Antivirals, Sustained Virological Response, Togo

1. Introduction

The World Health Organization (WHO) estimates that 170 to 180 million people are infected with the hepatitis C virus (HCV) [1]. The epidemic mainly concerns countries with limited resources where access to screening and treatment remains very inadequate. While America and Europe have 31.5 million infected people, Africa and Asia have 111 million. In Africa, the prevalence is estimated at 3% [2]. Nevertheless, the figures vary considerably between the different mainland regions, with Central Africa having the highest prevalence estimated at 6% compared to 1.6% in South and East Africa and 2.4% in West Africa. [2] [3]. Egypt has the highest prevalence of HCV in the world estimated at 14.5% in the 15 - 59 age group [4]. In Togo, the seroprevalence of HCV is estimated at 6.5% [5]. HCV infection is the second leading cause of hepatocellular carcinoma (HCC) after hepatitis B in Africa and Togo in particular [6]. The advent of new antiviral agents has revolutionized the care and prognosis of patients infected with HCV. Thanks to the excellent efficacy and the very good tolerance of direct antivirals, the care of patients infected with HCV in Africa is easier. To date, there are no data available on the effectiveness of new direct-acting antivirals (DAAs) in Togo. The aim of our study was to evaluate the sustained virological response (SVR) 12 weeks after oral treatment without interferon in HCV infected patients with genotypes 1 and 2.

2. Patients and Method

It was a descriptive study based on the retrospective collection of data in the hepatogastroenterology unit of the University Hospital Campus of Lome (Togo) from July 1, 2016 to May 31, 2018. The study population consisted of all patients who had a chronic viral C infection with viral replication, naive, regardless of the genotype, regardless of the degree of liver fibrosis, and having been placed under direct-acting antivirals. Were included, patients who had completed their treatment with DAAs.

3. Definition of Virological Responses

Virological responses to treatment were defined as follows:

- RVR (rapid virological response): Undetectable HCV-RNA after 4 weeks of treatment.
- Virologic response at the end of treatment: Undetectable HCV-RNA after 12 weeks of treatment.
- SVR12 (Sustained Virologic Response): HCV-RNA undetectable at 12 weeks after stopping treatment.

4. Parameters Studied

Have been studied in our study:

1) **Patient's characteristics at inclusion**

- **Epidemiological characteristics:** age and gender.

- **Virological markers:** viral genotype C, viremia in UI/ml and Log UI. Viremia was performed in the CERBA laboratory in Paris, France. The detection threshold for viremia was 15 IU/ml, *i.e.* 1.2 Log, HIV status, total HBsAg and Ac anti-HBc.
- **Hepatopathy information:** hepatic ultrasound, Transaminases (AST and ALT in UI/l: hepatic cytolysis was defined by AST or ALT > 1.5 times the upper limit of normal (ULN), hemogram, prothrombin rate, APRI score (a score > 2 at the start of treatment was considered a hepatopathy marker at cirrhosis stage [7]), FIB-4 score (a score > 3.25 at the beginning of treatment was considered a marker of severe fibrosis [8]), Actitest-Fibrotest. The METAVIR score was based on a blood test (Fibrotest). No liver biopsy was performed in our patients.
- **Treatment with DAAs:** the drugs used were: Sofosbuvir 400 mg (SFV) combined with Ribavirin (1000 mg if the patient's weight < 75 kg and 1200 mg if the patient's weight ≥ 75 kg) (RBV) or Sofosbuvir 400 mg combined with Ledipasvir 90 mg (LDV) in fixed combination with or without Ribavirin (1000 mg if the patient's weight < 75 kg and 1200 mg if the patient's weight ≥ 75 kg) or Sofosbuvir 400 mg combined with Daclatasvir 60 mg (LDV) with or without Ribavirin (1000 mg if the patient's weight < 75 kg and 1200 mg if the patient's weight ≥ 75 kg).

2) Follow-up for evaluation of the effectiveness of treatment

- During treatment, monitoring of transaminases and viral load C at inclusion, S4 and at the end of treatment (in case of detectable viral load at S4, monthly monitoring could be done until viro-suppression). We specified the RVR rate and the virological response rate at the end of treatment.
- After the end of treatment, monitoring of transaminases and viral load C 12 weeks after the end of treatment. We have specified the rate of SVR 12.

5. Data Entry and Clearance

At the end of the collection, the cards were entered into a database designed under the Epidata software version 3.1.

6. Statistical Analysis

Statistical analysis was performed with the R Studio software version 3.4.2. It included a descriptive analysis of the population and a comparative analysis. In the descriptive analysis for the characteristics collected (socio-demographic characteristics, biological and clinical characteristics), the results were expressed in terms of size and percentage for the qualitative variables or mean and standard deviation for the quantitative variables (or median and interquartile range depending on the choice which was made). In terms of comparative analysis, the statistical tests used were the Pearson Chi-square test or the Fisher exact test for qualitative variables and the Student's test for quantitative variables or the Wilcoxon non-parametric series test. In the comparative analysis we looked at each genotype (genotypes 1 and 2), a relationship between all the variables collected

according to the detectability.

Ethical Considerations

Data collection was retrospective. However, at the initiation of this study, patients were informed on the objectives of the study and gave their consent. Anonymity was respected when collecting data.

7. Results

7.1. General Characteristics of Patients

We recruited 84 patients, 60 of whom were infected with HCV genotype 2 (71.43%) and 24 with HCV genotype 1 (28.57%). There were 58 men and 26 women (sex ratio: 0.45). All patients were naive to any previous antiviral C treatment. HIV retroviral serology and the search for HBsAg were negative in all patients.

7.2. Characteristics of Patients Infected with HCV Genotype 1

Of the 24 patients, there were 16 men and 8 women (Table 1). The median age was 54.29 with an interquartile range (IQR) of 46.25 years to 64 years. SFV/LDV was the most used combination (62.50%). The mean value of HCV-RNA at inclusion in the study was 3,111,701 IU/ml with extremes of 4210 IU/ml to 15,600,000 IU/ml. Three patients had F4 fibrosis Fibrotest. Hepatic cytolysis was noted in 13 patients. Thrombocytopenia was found in 8 patients.

7.3. Characteristics of Patients Infected with HCV Genotype 2

Of the 60 patients, there were 42 men and 18 women (Table 1). The median age was 54.5 years with an interquartile range (IQR) of 45.75 to 61 years. SFV associated with RBV was the most used antiviral treatment (81.66%). The mean value of HCV-RNA at inclusion in the study was 27,910,000 IU/ml with extremes of 4210 to 1,480,000,000 IU/ml. Eleven patients had F4 fibrosis at Fibrotest. Hepatic cytolysis was noted in 35 patients. Thrombocytopenia was found in 19 patients.

7.4. Therapeutic Effectiveness

For patients infected with HCV genotype 1, the RVR was 100% and the virological response at the end of treatment was 100%; the SVR 12 was 100% (Figure 1). For patients infected with HCV genotype 2, the RVR was 100% and the virological response at the end of treatment was 93.30%; SVR 12 was 91.70% (Figure 1). In these genotype 2 HCV-infected patients, the median age ($p = 0.883$), gender ($p = 0.61$), median viral load C at inclusion ($p = 0.097$), presence of significant fibrosis at Fibrotest ($p = 0.341$), FIB-4 ($p = 0.380$), APRI score ($p = 0.528$) were not significantly associated with SVR12.

7.5. Treatment Failure

Five patients were in treatment failure (Table 2); these were genotype 2 patients

who were all on SFV/RBV (8.33%). These 5 patients who failed treatment had a viral load > 5 log on inclusion; among them, one had an undetectable viral load at the end of treatment and it was at 3 months after the end of treatment that the viral load became detectable at 6.08 log. No patient infected with HCV genotype 1 failed treatment.

Table 1. Patients characteristics at inclusion.

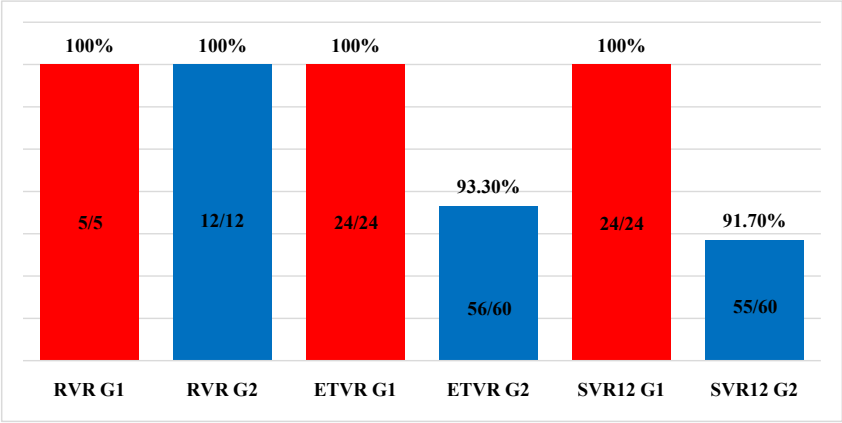
	Genotype 1 (n = 24)	Genotype 2 (n = 60)
Epidemiological parameters		
Gender		
Male	16 (66.67)	42 (70)
Female	8 (33.33)	18 (30)
Age in years: median (IQR)	54.29 (46.25 - 64)	54.5 (45.75 - 61)
Direct-acting antivirals used		
SFV/LDV n (%)	15 (62.50)	0 (0)
SFV/DCV n (%)	8 (33.33)	10 (16.67)
SFV/RBV n (%)	0 (0)	49 (81.66)
SFV/DCV/RBV n (%)	1 (4.17)	1 (1.67)
Virological markers		
HCV RNA in UI/ml: median (IQR)	813,221 (281,561 - 3,111,701)	688,600 (233,000 - 4,792,000)
HCV RNA in log: median (IQR)	5.895 (5.450 - 6.423)	5.830 (5.265 - 6.680)
Hepatopathy information		
Cirrhosis (Fibrosis F4): n (%)	3 (12.50)	11 (18.33)
Methods for assessing fibrosis		
FIB-4: n (%)	24 (100)	57 (95)
FIB-4: median (IQR)	2.625 (1.360 - 3.5530)	2.370 (1.260 - 4.590)
APRI: n (%)	24 (100)	57 (95)
APRI: median (IQR)	0.855 (0.4475 - 1.4125)	0.99 (0.61 - 2.260)
Fibrotest: n (%)	20 (83.33)	50 (83.33)
AST (UI/l): median (IQR)	52 (34 - 83)	56 (40 - 104.8)
ALT (UI/l): median (IQR)	66 (33.75 - 85.25)	66.5 (40 - 104.8)
Biological parameters: median (IQR)		
Platelets (/mm^3)	172.5 (131.8 - 213.5)	168 (133 - 200)
Neutrophil (/mm^3)	1650 (1245 - 2612)	1894 (1462 - 2294)
Haemoglobin (g/dl)	12.7 (11.22 - 13.55)	13.3 (12.05 - 14.80)

IQR: Interquartile range, SFV: Sofosbuvir; LDV: Ledipasvir; RBV: Ribavirin; DCV: Daclatasvir.

Table 2. Characteristics of patients in treatment failure.

Genotype	Gender	Age (years)	Cirrhosis	HCV RNA (log UI)	Drugs used	Time of treatment failure
2	2	62	NO	5.27	SFV/RBV	End of treatment
2	1	66	NO	7.35	SFV/RBV	End of treatment
2	1	48	NO	6.87	SFV/RBV	End of treatment
2	1	38	NO	7.24	SFV/RBV	End of treatment
2	1	55	NO	6	SFV/RBV	12 weeks after the end of treatment

SFV: Sofosbuvir; RBV: Ribavirin.



RVR: Rapid virological response ETVR: End of treatment virological response
SVR: Sustained virological response G1: Genotype 1 (red) G2: Genotype 2 (blue)

Figure 1. Virological responses in patients infected by hepatitis C virus genotypes 1 and 2.

8. Discussion

The main limitation of our study is the relatively small size of our sample, which could be explained by the financial difficulty of patients in paying direct acting antivirals. However, our study has noted the effectiveness of these drugs in the treatment of patients with chronic viral hepatitis C in Togo. In our study, the rapid virological response (RVR) was 100% for all genotypes 1 and 2 patients in whom the viral load has been achieved; the virological response at the end of treatment was 100% (genotype 1) and 93.3% (genotype 2); SVR 12 was 100% (genotype 1) and 91.7% (genotype 2). Five patients were in treatment failure either at the end of treatment (4 non-responders) or 12 weeks after the end of treatment (1 responder-relapser patient). These 5 patients were all genotype 2. In the Reddy *et al.* [9] study, 513 patients infected with HCV genotype 1 (161 naïve and cirrhotic patients) were treated for 12 or 24 weeks with Sofosbuvir/Ledipasvir with or without ribavirin. The SVR rate was 96%, without influence of duration of treatment or combination with ribavirin. In the American cohort [10], 1014 non-cirrhotic naïve patients with low viral load were treated with Sofosbuvir/Ledipasvir for 8 weeks; SVR was 93% comparable to that

seen in 808 patients treated for 12 weeks (96%). In the TARGET study [11], 674 naive patients (38% cirrhotic patients) were treated with Sofosbuvir/Ledipasvir for 8 to 24 weeks (40 patients had received ribavirin additionally); SVR was 96%. In 323 non-cirrhotic naïve patients with a viral load < 6,000,000 IU/ml, 131 patients and 192 patients were treated for 8 and 12 weeks respectively; SVR was 97% in both groups. These results favored treatment with Sofosbuvir/Ledipasvir for 8 weeks in naïve patients without cirrhosis with a viremia < 6,000,000 IU/ml and for 12 weeks in other patients. The current recommended treatment for genotype 1 HCV is Sofosbuvir/Velpatasvir or Sofosbuvir/Ledipasvir. At the time of inclusion of patients in this study, the treatments available in Togo for HCV genotype 1 were Sofosbuvir/Ledipasvir and Sofosbuvir/Daclatasvir. In our study, 63% of patients infected with HCV genotype 1 were put under Sofosbuvir/Ledipasvir and 37% were put under Sofosbuvir/Daclatasvir. The cure rate was 100%. This reflects the effectiveness of direct acting antivirals. In the case of genotype 2 HCV, the current recommended treatment is Sofosbuvir/Velpatasvir. At the time of recruitment of patients in our present study, the molecules available in Togo in case of genotype 2 viral C infection were Sofosbuvir/Ribavirin or Sofosbuvir/Daclatasvir. In our study, 81.6% of patients infected with HCV genotype 2 were treated with Sofosbuvir/Ribavirin and 16.7% with Sofosbuvir/Daclatasvir. In the VALENCE trial [12], SVR after 12 weeks of treatment with Sofosbuvir/Ribavirin was 93% (68/73); SVR was 94% (59/63) in non-cirrhotic patients and 82% in patients with cirrhosis; SVR was 97% (29/30) in non-cirrhotic naïve patients, 100% (2/2) in cirrhotic naïfs, 94% (30/32) in non-cirrhotic pretreated and 78% (7/9) in cirrhotic pretreated. In the Omata *et al.* [13] study in Japan, 90 naïve patients and 63 pre-treated patients infected with HCV genotype 2 were treated with Sofosbuvir/Ribavirin for 12 weeks. Of the 90 naïve patients, the SVR was 98%. Of the 63 pretreated patients, SVR was 95%. The SVR rate was 94% in cirrhotic patients. In the literature, irrespective of genotype, elevated viremia, cirrhosis, and failure of previous antiviral C treatment were the main failure factors in responder-relapse patients [14] [15]. In our study, no virological or biological factors were associated with SVR 12; the small size of our sample could explain it. In the event of failure of DAA therapy, it is recommended to document poor treatment adherence, drug interactions and intercurrent pathologies that may interfere with the absorption of DAAs. A non-optimal therapeutic scheme or premature discontinuation of treatment should be sought.Viral re-infection must also be ruled out [16]. If none of the above-mentioned causes of treatment failure are found in case of failure of direct antiviral agent treatment, it is recommended to evaluate the resistance mutations before deciding on the new therapeutic line [16]. In our study, we believe that poor observation of treatment may explain this failure. It is true that ribavirin is no longer in the forefront of current recommendations for the treatment of chronic viral C infection [16] [17] [18]. However, in resource-limited countries like Togo, where availability and accessibility of DAAs are difficult given their high cost, Sofosbuvir/Ribavirin (less expensive) could be used if there is no con-

traindication to the use of ribavirin. However it is necessary to prioritize treatment protocol without ribavirin.

9. Conclusion

Direct-acting antivirals have revolutionized the management of viral hepatitis C in the world and in Togo in particular. These drugs offer the possibility of oral therapy without interferon. This study could be extended to include a large number of patients to look for clinical, virological, and biological factors associated with SVR 12.

Conflicts of Interest

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

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