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Full Length Research Paper

Therapeutic effectiveness assessment of antiviral drugs used in chronic hepatitis treatment in three Ivorian university hospitals

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This work aims to evaluate the effectiveness of drugs used for the management of chronic viral hepatitis in the three major university hospitals in Abidjan. This is a retrospective cross-sectional descriptive study of 203 patients investigated for treatment protocols, patient parameters before and after treatment. It emerged that treatment with pegylated Interferon alpha 2a resulted in a significant decrease in viremia for an average treatment duration of 48 weeks in patients with chronic viral hepatitis B; on the one hand, the combination of Ribavirin + pegylated Interferon alpha 2a, Ribavirin + Sofosbuvir and Daclatasvir + Sofosbuvir provided cure in patients with chronic viral hepatitis C for an average duration of treatment of 12 to 24 weeks. However, the cure of patients with chronic viral hepatitis C was mostly clinical. The examinations that could attest to the healing were not performed by most of the patients, due to the high costs of virologic and enzymatic ones. These results constitute an important database for the therapeutic survey of people with chronic viral hepatitis in Côte d'Ivoire and an additional argument to accelerate the general subvention for the management of these viral diseases.

Key words: Viral hepatitis B-C-D, antiviral drugs, virologic markers, enzymatic markers.

INTRODUCTION

Chronic viral hepatitis remains a major global public health issue (Hutin et al., 2018). These infections due to hepatitis B (HBV) and hepatitis C (HCV) viruses mainly affect Africa: the prevalence of HCV in Central Africa is estimated at 10%, and that of HBV in WestAfrica is estimated at 8% overall (Feray, 2015). Also,in Côte d'Ivoire,despite a prevalence of about 12% of HBV and 5% of HCV, detection and management of

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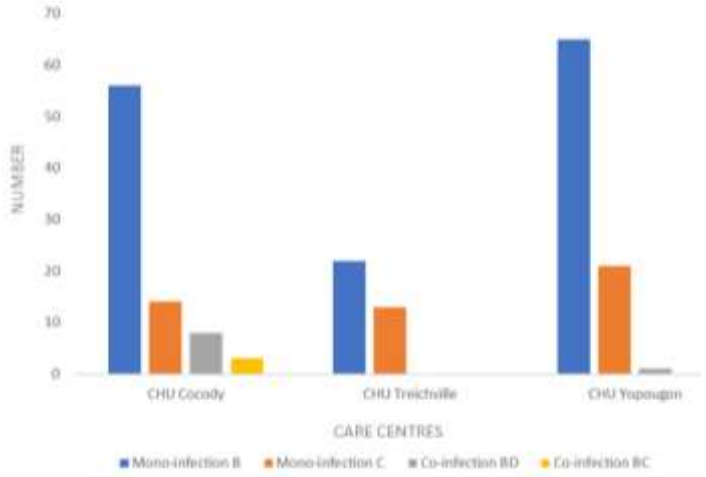

Figure 1. Distribution of study subjects according to viral type.

viral hepatitis B and C are still very limited (Enel et al., 2015) due to the costs of not only biological examinations but also of drugs. Indeed, the vial of pegylated Interferon alpha 2a, sufficient just for one week of treatment costs 300 US dollars, while treatment lasts for 24 to 48 weeks. In response to the threat posed by this scourge, Côte d'Ivoire has adopted, since 2015, a strategy to reduce mortality due to hepatitis B, C and delta (D) viruses by subsidizing some drugs, especially pegylated Interferon alpha 2a (Pegasys®) and Ribavirin (Copegus® and Ribavir®), indicated in the treatment of these viral infections in approved centers, namely three University Hospitals (CHU) in Abidjan; Bouaké in province and the Regional Hospital (CHR) in Yamoussoukro (PNLHV, 2017). The consequences of this strategy have not been assessed yet in terms of therapeutic service. Three years after the establishment of this national programme for the subsidized management of drugs for chronic viral hepatitis in Côte d'Ivoire, what is the therapeutic outcome? This is the research question that prompted the present investigations in the three main university hospitals in Abidjan, also the most frequented by patients receiving chronic viral hepatitis drugs. Thus, the objective of this study is to describe the treatment protocols established in Abidjan university hospitals, as well as the virologic and enzymatic parameters of patients before and after treatment.

MATERIALS AND METHODS

This study, not a clinical trial, but a retrospective, descriptive and cross-sectional study, was carried out on the basis of custom survey sheets for the patients' records, semi-direct interviews with physicians in charge of chronic viral hepatitis and telephone interviews with patients to collect some information missing from clinical records. It focused on patients with chronic viral hepatitis, registered in the databases of hospital pharmacies of the University Hospitals of Cocody, Treichville and Yopougon in Abidjan for the dispensing of medicines, and managed in hepato-gastroenterology units of the same hospitals from August 2015 to July 2018.

The patients' questionnaire focused on the type of chronic hepatitis, the molecules of the treatment protocol, the duration of treatment and the results of biological examinations (Appendix).

The dispensing of the medicines was done exclusively in the pharmacies of approved centers outside tenofovir 300 mg tablets (Gentovir®) which was delivered in private pharmacies. In the pharmacy units of the university hospitals, medicines were the same, that is, Peginterferon 180 µg/mL vial (Pegasys®), Ribavirin 200 mg tablets (Copegus®) or 200 mg capsules (Ribavir®), Sofosbuvir 400 mg tablets (SSB®) and Daclatasvir 60 mg tablets (Dakasvir®).

Biological examinations were performed mainly at three centers, namely Pasteur Institute of Cocody, CIRBA (Integrated Bio-clinical Research Centre in Abidjan) and Longchamp laboratories as private center. The determination of viral load used molecular biology based on the principle of a nucleic acid amplification test for the quantitation of Hepatitis B Virus DNA and Hepatitis C Virus RNA genotypes 1 through 6 in human plasma and serum. For the other markers (HBsAg, anti-HBc, HBeAg, anti-HBe, anti-HCV), methods used were either enzyme immunoassay principle with formation of a sandwich complex. The results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration. This is either an enzyme-linked fluorescent immunoassay (ELFA) that is performed in the automated VIDAS system, or a combination of an enzyme immunoassay sandwich method with a final fluorescent detection, that is ELFA.

RESULTS

Viral types

During the study period, 203 patient records were found, the majority of which were mono-infection with viral hepatitis B (Figure 1).

Treatment regimens

Treatment protocols were essentially based on the combination therapy, in particular the bi-therapy

Table 1. Treatment regimens of chronic viral hepatitis in Abidjan University Hospitals.

Viral type	Molecules	Presentation	Dosage	Treatment duration
Mono-infection B	Peginterferon + Tenofovir	180 µg/mL vial 300 mg tablets	1 vial subcutaneous per week 1 tablet in the morning	48 weeks Seroconversion
Mono-infection C	Peginterferon + Ribavirin	180 µg/mL vial 200 mg tablets/capsules	1 vial subcutaneous per week ≥ 75 kg: 1200 mg in two taken daily ; <75 kg: 1000 mg in two taken daily	12 to 24 weeks
	Sofosbuvir + Daclatasvir	400 mg tablets 60 mg tablets	1 tablet in the morning 60 mg in the morning	12 weeks
	Ribavirin + Sofosbuvir	200 mg tablets/capsules 400 mg tablets	≥ 75 kg: 1200 mg in two taken daily ; <75 kg: 1000 mg in two taken daily 1 tablet in the morning	12 to 24 weeks
Co-infection BD	Peginterferon	180 µg/mL vial	1 vial subcutaneous per week	48 weeks
Co-infection BC	Sofosbuvir + Ribavirin + Peginterferon	400 mg tablets 200 mg tablets/capsules Ampoule 180 µg/ml	1 tablet in the morning ≥ 75 kg: 1200 mg in two taken daily ; <75 kg: 1000 mg in two taken daily 1 vial subcutaneous per week	12 weeks

including almost totally pegylated Interferon alpha 2a (Table 1).

Virologic markers prior to treatments

The diagnosis of viral hepatitis B was made mainly by the determination of the HBs antigen (Table 2). HCV testing was conducted by detecting the antibody directed against HCV antigen. If positive, viral RNA was tested at a rate greater than 15 IU/L for chronic viral hepatitis C. HCV antigen determination was not necessary (Table 3).

Post treatments virologic markers

The HBs antigen and viral DNA were the most determined markers for evaluating the efficacy of viral hepatitis B treatment (Table 4).

As with the diagnosis, testing for antibodies directed against HCV antigen and/or viral RNA were the markers for assessing the cure of viral hepatitis C (Table 5).

Enzymatic markers

Most of the subjects in our study series had enzymatic activities Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) varying between 30 and 60 IU/L prior to treatment (Table 6), to decrease from 10 to 30 IU/L after treatment (Table 7).

DISCUSSION

In carrying out our retrospective and cross-sectional descriptive study on the evaluation of the effectiveness of pharmacological treatment, we noted that for the management of patients with chronic viral hepatitis B, the molecules used were pegylated Interferon alpha 2a associated with Tenofovir. Since Tenofovir is not included in the grant, patients purchased it from private pharmacies. Thus 143 patients with chronic viral hepatitis B were placed under this protocol, of which 46 patients were able to complete their treatments with pegylated Interferon alpha 2a, and only 6 patients were able to perform virologic examinations after treatment. Results of virologic examinations performed after the use of pegylated Interferon alpha 2a showed a significant decrease in viral level (undetectable viral load less than or equal to 20 IU/L) for 5 patients. Indeed, according to the World Health Organization (WHO), which recommends the treatment of viral hepatitis B

Table 2. virologic characteristics of patients with HBV prior to treatment.

Number	HBsAg	Anti-HBc	Anti-HBe	HBeAg	Viral DNA
26	+	+	ND	ND	ND
02	+	+	+	-	ND
14	+	+	-	-	ND
08	+	+	ND	ND	+
01	+	+	-	+	+
06	+	+	+	-	+
86	+	ND	ND	ND	ND
Total: 143					

+, Positive marker; -, negative marker; ND, not determined

Table 3. Virologic characteristics of patients with HCV prior to treatment.

Number	Anti-VHC	VHCAg	Viral RNA
16	+	ND	ND
32	+	ND	+
Total	48		

+, Positive marker; -, negative marker; ND, not determined.

Table 4. Post treatment virologic markers of patients with HBV.

Patients	HBsAg	Anti-HBc	Anti HBe	HBeAg	Viral DNA (UI/L)	Treatment duration
Patient 1	+	ND	ND	ND	-	48 weeks
Patient 2	+	ND	ND	-	+ (≥ 56,64)	24 weeks
Patient 3	+	ND	ND	ND	-(≤ 10)	144 weeks
Patient 4	+	ND	ND	ND	-(≤ 10)	48 weeks
Patient 5	+	ND	ND	ND	-(≤ 20)	20 weeks
Patient 6	+	ND	ND	ND	-(≤ 20)	48 weeks

+, Positive marker; -, negative marker; ND, not determined.

Table 5. virologic markers of patients with HCV declared cured after treatment.

Number	Anti-VHC	VHCAg	Viral RNA	Treatment duration
3	-	ND	Undetectable	12 and 24 weeks
14	ND	ND	ND	ND
Total 17				

-, Negative marker; ND, not determined.

Table 6. AST and ALT activities of subjects prior to treatment.

Activity (UI/L)	AST	ALT
10-30	15 patients	12 patients
30-60	17 patients	19 patients
60-90	01 patient	04 patients
> 90	01 patient	01 patient
Total	36 patients	36 patients

Table 7. Post-treatment AST and ALT activities.

Activity (UI/L)	AST	ALT
10-30	9 Patients	8 Patients
30-60	6 Patients	5 Patients
60-90	0 Patient	2 Patients
> 90	0 Patient	0 Patient
Total	15 Patients	15 Patients

with Tenofovir or Entecavir, powerful molecules to significantly decrease viral load and rarely leading to the emergence of a pharmaco-resistance; the objective of the treatment is to achieve a profound suppression of viral multiplication reflected by circulating viral DNA (WHO, 2016). The French National Society of Gastro-Enterology (SNFGE), for its part, recommends two therapeutic strategies: the first, based on Interferon, aiming to obtain a prolonged virologic response after the cessation of treatment and the second, based on long-lasting nucleoside or nucleotide analogues (Entecavir, Tenofovir), usually lifetime, for a stable viro-suppresion over time (SNFGE, 2015). In practice, the objective is the seroconversion of the HBe antigen (HBeAg) to anti-HBe antibodies in patients who are HBeAg positive, while in patients with chronic HBeAg negative hepatitis, the objective is to obtain a lasting viremia of less than 105 copies/ml (WHO, 2016). Thus, pegylated Interferon alpha 2a inhibits viral replication and promotes decreased viremia (Perrillo, 2006). Pegylated Interferon alpha 2a therefore remains effective in the management of patients with chronic viral hepatitis B (Fried et al., 2002). However, for a better evaluation of the effectiveness of treatments, it is important to introduce generic forms of Tenofovir systematically in hospital pharmacies of Abidjan university hospitals.

For chronic viral hepatitis C, 48 patients were recorded. The molecules used were pegylated Interferon alpha 2a associated with Ribavirin in 35 patients, Sofosbuvir associated with Ribavirin in 4 patients and Daclatasvir associated with Sofosbuvir in nine patients, with average treatment duration of 12 weeks to 24 weeks. The protocols were therefore based more on indirect-acting antivirals than on direct-acting antivirals, contrary to WHO recommendations. WHO and SNFGE recommend direct-acting antiviral treatment (Daclatasvir, Ledipasvir, Velpatasvir, Sofosbuvir, Simeprevir, etc.), all with combining, for some genotypes, pegylated Interferon alpha 2a and/or Ribavirin (SNFGE, 2015; WHO, 2014). At the end of these treatments, 17 patients were declared cured and only 3 patients were able to perform the paraclinical examinations. Biological evidence of healing has not often been established. However, it is apparent that treatment protocols for the management of patients with chronic C viral hepatitis are effective and provide healing, at least clinically. These results are consistent with studies that have shown an effectiveness of bi-therapy «pegylated Interferon alpha 2a + Ribavirin» with 55% of the sustained virologic response rate (Fried et al., 2001). Our results are also consistent with those studies that have shown an effectiveness of bi-therapy «Sofosbuvir + Daclatasvir» with a sustained virology response greater than 80% (Hézode et al., 2015). Authors have also reported good results with other therapeutic combinations. For example, in patients treated with "Ledipasvir + Sofosbuvir" or "Ledipasvir + Sofosbuvir + Ribavirin", 90 to 100% achieved a sustained virologic response 12 weeks after discontinuation (Afdhal et al., 2014; Kowdley et al., 2014; Lawitz et al., 2014; Gane et al., 2014).

For BD and BC co-infections, only 12 patients were recorded, including 9 patients for HBDV and 3 patients for HBCV. Pegylated Interferon alpha 2a was the only molecule used to manage BD co-infection for an average treatment duration of 48 weeks, in accordance with WHO and SNFGE recommendations for the management of delta virus infection (WHO, 2016; SNFGE, 2015). The molecules used were Sofosbuvir, pegylated Interferon alpha 2a and Ribavirin for the management of co-infection BC for an average treatment duration of 12 to 24 weeks.

Virologic examinations were not performed by these patients for the maximum duration of treatment. Exchanges with them revealed a continuation of treatments with Tenofovir and pegylated Interferon alpha 2a.

Clinically, if the subsidized molecules (pegylated Interferon alpha 2a and Ribavirin) have been shown to be effective in the management of chronic viral hepatitis, the completion of paraclinical examinations remains a real problem for these patients, who find the costs very high. For example, some patients were forced to discontinue treatment, increasing the number of treatment failures due to lack of financial means, and others to the failure to perform their examinations, making it difficult to survey therapy. In this context, the effectiveness of treatments becomes clinical, and there are often cases of relapse since the paraclinical examinations; in this case the virologic examinations are the only ones that attest to the effectiveness of the treatments.

Conclusion

A descriptive retrospective study to assess the

effectiveness of the treatment of chronic viral hepatitis in Côte d'Ivoire was done. In six patients with a high viral load at the beginning of treatment, five had an undetectable viral load at the end of the treatment period with pegylated Interferon alpha 2a. As for the treatment protocols for the management of patients with chronic C viral hepatitis, they provided clinical healing, since biological evidence was established only for three patients. Faced with the barriers to effective treatment of viral hepatitis in our country, it is wise to focus action on awareness, prevention and early detection. Another means of control would be the systematic screening of pregnant women because they are the gateway to the screening of their entourage in case of positivity, and subsequent early management of detected-positive people and vaccination for detected-negative people. In addition, the extension of the grant to biological monitoring and other molecules becomes necessary.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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APPENDIX

Fact sheet

1) Patient identification

Record number _____

Patient name _____

Age: ☐ 0-14 years ☐ 15-24 years ☐ 25-50 years ☐ 51 years and older

Gender: ☐ male ☐ female

Care start: _____

Viral type: B☐ C☐ D☐

Co-infection ☐ BC ☐ BD

2) Treatment protocol

☐ Peginterferon

☐ Peginterferon + Tenofovir

☐ Peginterferon + Ribavirin

☐ Peginterferon + Sofosbuvir + Ribavirin

☐ Ribavirin + Sofosbuvir

☐ Sofosbuvir + Daclatasvir

3) Treatment duration

☐ 12 weeks

☐ 24 weeks

☐ 48 weeks

☐ Other to be specified _____

4) Biological examinations results

Serology: (+) positive (-) negative

Laboratory: _____

Viral load before treatment.

Sampling date	HBsAg	Anti-HBs	Viral DNA	Anti-HBe	HBeAg	anti-HBC	Viral RNA

Viral load after treatment.

Sampling date	HBsAg	Anti-HBs	Viral DNA	Anti-HBe	HBeAg	anti-HBC	Viral RNA

5) Enzymatic activities

AST or ALT before treatment: yes ☐ no ☐ unknown ☐

- **AST** _____ **U/l**
- **ALT** _____ **U/l**

AST or ALT after treatment: yes ☐ no ☐ unknown ☐

- **AST** _____ **U/l**
- **ALT** _____ **U/l**