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Original Article

Promising Direct Acting Antivirals in Cameroon

Introduction des antiviraux d'action directe dans le traitement de l'hépatite C au Cameroon : des avancées significatives

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RÉSUMÉ

But. L'introduction récente du sofosbuvir au Cameroun représente une étape importante dans le traitement des génotypes 1, 2 et 4 de l'hépatite C chronique (CHC). Les données sur l'efficacité de cette association au Cameroun sont rares. Le but de cette étude était de caractériser la réponse à l'association sofosbuvir ribavirine avec ou sans interféron pégylé au Cameroun. **Méthodes**. Nous avons inclus de manière consécutive des CHC 1,2 et 4 adultes de deux centres de traitement publics et d'un centre de traitement privé au Cameroun. Les patients admissibles devaient avoir toutes les réponses virologiques documentées. Les dossiers médicaux des patients qui ont demandé un traitement ont été systématiquement examinés par un comité. L'efficacité a été évaluée par réponse virologique rapide (RVR), réponse de fin de traitement (ETR); et réponse virologique soutenue (RVS). Les événements indésirables ont été enregistrés. Les données ont été analysées en utilisant le test de Chi-deux de Pearson ou le test exact de Fisher, selon le cas. **Résultats**: Nous avons inclus 72 patients âgés de 31 à 82 ans. Une charge virale élevée était présente dans 65,2% des cas. Les génotypes 1,2 et 4 représentaient respectivement 29,2%, 51,4% et 19,4%. Nous avons eu 33,3% de patients cirrhotiques et 84,7% de patients naïfs. 83,3% (60/72) des patients ont atteint la réponse virologique rapide. La réponse en fin de traitement était présente chez 91,6% (66/72) et la réponse virale soutenue chez 91,6%. **Conclusion**. Les ADD constituent une avancée significative dans la prise en charge de l'hépatite C virale chronique au Cameroun.

ABSTRACT

Background: The recent introduction of sofosbuvir in Cameroon represent an important step in the treatment of genotypes 1, 2 and 4 Chronic Hepatitis C (CHC). Data on efficacy of this combination in Cameroon are scarce. The aim of this study was to characterize the response to sofosbuvir ribavirin combination with or without pegylated interferon in Cameroon. **Methods:** We consecutively included consented CHC 1,2 and 4 adults from two publics and one private treatment centers in Cameroon. Eligible patients were required to have all virological response documented. The medical records of patients who sought treatment were systematically reviewed by a committee. Efficacy was assessed by Rapid Virological Response (RVR), End of Treatment Response (ETR); and Sustained Virological Response (SVR). Adverse events were recorded. Data were analysed using Pearson's Chi-square test or Fisher's exact test as appropriate. **Results:** We included 72 patients aged 31 to 82 years. A high viral load was present in 65.2%. Genotypes 1,2 and 4 accounted respectively for 29.2%,51.4% and 19.4%. We had 33.3% cirrhotic and 84.7% naïve patients. RVR was achieved by 83.3% (60/72) of patients; ETR by 91.6% (66/72) and SVR by 91.6% (66/72). The formal protocol was pegylated interferon plus ribavirin and we added sofosbuvir. The therapeutic response is by far better than the one without Direct Acting Antiviral (DAA). **Conclusion.** DDAs constitute a significant advance in the management of chronic viral hepatitis C in Cameroon.

INTRODUCTION

Hepatitis C virus infection (HCV) leads to chronic hepatitis C (CHC). It is a major global health concern. In 2005, WHO estimates the global prevalence of anti-HCV antibody to 2.8%, approximately 185 million people of whom 350 000 die per year [1,2]. In sub-Saharan Africa, it ranges from 2% and 2.8% for East and West Africa to 13.8% in Cameroon [2,3].The pegylated interferon (Peg Inf) based protocol used up to 2015, in for the treatment of CHC. resulted in a sustained virological response (SVR) of no more than 48% and 36.1% for genotypes 2 and 4 respectively. This rate was quite different from the one observed in Caucasians. [6]. As new molecules, the Direct Acting Antivirals (DAAs), recently introduced in Cameroon were known to give better SVR, we systematically added Sofosbuvir (Sof) to the Peg Inf based protocol. The aim of this study was to characterize the response to sofosbuvir ribavirin combination with or without pegylated interferon in Cameroon.

METHODS

Patients selection

Pre-treatment work up. The viral load (by real-time PCR TaqMan Roche®) with a detection threshold of 12-15 IU / ml (1.0 to 1.2 logIU / mL); the level of fibrosis, and the necrotic inflammatory activity (by indirect methods, Fibrotest® and Actitest®), were performed by the Laboratoire Cerba in France, subcontracted by the Centre Pasteur du Cameroun.

We consecutively included in the study, adult Cameroonian patients treated for CHC with a protocol including a Sofosbuvir. Patients were selected from three centers of treatment of CHC in Cameroon: The Yaoundé Hospital, The Yaoundé Central Hospital of and « Centre Médical la Cathédrale ». We included in this study all CHC patients eligible for treatment of CHC by the association of Sof/ribavirin (RBV) or Sof/RBV/Peg Inf..

Treatment protocol

The treatment was to last 12 weeks. Genotype 1 and 4 patients were given triple therapy sofosbuvir 400mg daily, ribavirin at the dosage of 1000mg / 24 hours if weight <75Kg and 1200mg / 24hrs if weight ≥75Kg orally a weekly 180µg Peg Inf subcutaneous injection. Genotype 2 patients were given sofosbuvir ribavirin. The sofosbuvir was Gilead brand whereas PegInf and

Study design

The medical record of patients who sought treatment were systematically reviewed by a committee. After eligibility, data was recorded from medical records and were centralized for analysis. The duration of planned therapy was 12 weeks. The primary efficacy end point was the sustained virological response (SVR), defined as undetectable HCV RNA 12 weeks after the end of 12 weeks of treatment. The secondary endpoints were the different virological response at set point according to World Health Organization (WHO) [1]. We considered as lost to follow-up, any patient who no longer attended the clinical follow-up by the investigators.

Assessment of efficacy

The different assessment time points were designed according to WHO guidelines [1]: At week 4, the rapid virological response (RVR), defined as undetectable HCV RNA by qualitative PCR. At week 12, the end of treatment response (ETR) defined as undetectable HCV RNA by qualitative PCR. Twelve weeks after the end of the treatment, the sustained virological response (SVR).

Assessment of safety

The safety was assessed during follow up, by physical examination; adverse effect recording and analysis; laboratory reports. Monthly laboratory tests, included: biochemistry of liver functions; full blood count.

Statistical analysis

Data were entered using Census and Survey Processing system (CSPro 6.0). We used the Statistical Package for Social Science software (SPSS version 21.0) for statistical analysis. Means ±standard deviation was used for quantitative variables, frequency and proportions for qualitative variables. Bivariate analysis was performed, using $\chi 2$and Fischer's exact test wherever appropriate. A p value of less than 0.05 was considered statistically significant.

RESULTS

Patients characteristics

We included 72 patients. Baseline demographic data are summarized in (Table 1). The sex-ratio was 0.8. The risk factors of transmission were dominated by invasive surgery and blood transfusion. The majority of patient aged more than 50 years.

Table 1: Baseline demographic data of patients N=72

Characteristics	n (%)
Gender	
Male	33 (45.8%)
Female	39 (54.2%)
Age groups	
[30-39[	1 (1.3%)
[39-49[	9 (12.5%)
[49-59[	28 (38.8%)
[59-69[	26 (36.1%)
≥ 69	8 (11.1)
Mean age	57.7+/-8.8 years
Risk factors for HCV infection	
S/P/T*	2 (2.7%)
Dental care	5 (6.9%)
Invasive surgery	10 (13.8%)
Blood transfusion	6 (8.3%)
No risk factor	49 (68%)
Co morbidities	
High blood pressure	23 (31.9%)
Diabetes	9 (12.5%)
At risk alcohol intake	3 (4.1%)
HBV coinfection	1 (1.3%)
Dyslipidaemia	1 (1.3%)
No comorbidity	35 (48.6%)
*: S/P/T: Scarification/Piercing/Tatoo	

Genotype 2 was the most frequent, and most of the patient presented with high viral load and severe fibrosis (Table 2).

Table 2: Clinical and biological baseline data N=72.

Characteristics	n (%)
Genotypes	
1	21 (29.2%)
2	37 (51.4%)
4	14 (19.4%)
Viral load	
High	47 (65.2%)
Low	25 (34.7%)
ALAT level	
Normal	44 (61.1%)
High	26 (36.1%)
Fibrosis	
F0	7 (9.7%)
F1 or F2	27 (37.5%)
F3 or F4	38 (52.7%)
Necroinflammation	
A0	17 (23.6%)
A1 or A2	36 (50%)
A3	19 (26.3%)
Therapeutic status	
Naïve	61 (87.7%)
Relapse	7 (9.7%)
Non responders	4 (5.5%)

Virological response

At week 4, 12 patients still had a positive RNA but with a more than 2 log decline. At the end of treatment, 64 patients had a negative RNA giving an ETR of 91.6%. We ended with a SVR of 91.6% with no relapse (Tab 3).

Table 3: Virological response and genotype

	Type 1 (n=21)	Type 2 (n=37)	Type 4 (n=14)	Total (n=72)
RVR	20 (95.2%)	30(81%)	10(71.4%)	60(83.3%)
ETR	20 (95.2%)	32(86.4%)	14(100%)	66(91.6%)
SVR12	20(95.2%)	32(86.4%)	14(100%)	66(91.6%)

Considering demographic and biological data, the SVR rate was not significantly different with respect to gender, age, genotype, viral load, fibrosis and therapeutic status (Table 4).

Table 4: SVR and demographic / biological parameters

Characteristics	n	SVR	p value
Gender			
Male	33	30/33 (90.9%)	
Female	39	36/39 (92.3%)	1.00
Age groups			
<50 years	10	5/10 (50%)	
≥50 years	62	61/62 (98.3%)	1.00
Genotypes			
1	21	20/21 (95.2%)	1.00
2	37	32/37 (86.4%)	0.19
4	14	14/14 (100%)	0.29
Viral load			
High	47	42/47 (89.3%)	
Low	25	24/25 (96%)	0.19
Fibrosis			
F4	24	23/24 (95.8%)	
F0, F1, F2 or F3	48	43/48 (89.5%)	0.64
Therapeutic status			
Non Naïve	11	9/11 (81.8%)	
Naïve	61	57/61 (93.4%)	0.59

Tolerability and adherence

The most frequent clinical adverse effect reported by patients was asthenia (Table 5). None of the adverse effect indicated interruption of treatment. All the patients followed their treatment completely, giving an adherence rate of 100 %.

Table 5a: Main recorded clinical adverse events*

Clinical adverse events	n (%)
Asthenia	10/72 (13.8%)
Anorexia	3/72 (4.1%)
Itching	3/72 (4.1%)
Constipation	2/72 (2.7%)
Cervicalgia	1/72 (1.3%)
Lombalgia	1/72 (1.3%)
Dyspepsia	1/72 (1.3%)
Cough	1/72 (1.3%)
Insomnia	1/72 (1.3%)
Drowsiness	1/72 (1.3%)
Vertigo	1/72 (1.3%)
Thirst	1/72 (1.3%)
Rash	1/72 (1.3%)
Dry skin	1/72 (1.3%)
No clinical adverse event	57/72 (79.1%)

Table 5b: Main recorded biological adverse events*

Anemia	14/72 (19.4%)
Neutropenia	19/72 (26.3%)
Thrombocytopenia	13/72 (18%)

*:one patient could present with more than one side effect

DISCUSSION

This study was aimed to characterize the therapeutic response of Cameroonians after introduction of sofosbuvir to formal pegylated interferon plus ribavirin in the management of chronic hepatitis C. It was a multicentric cohort study including 72 patients followed in the different centers of chronic viral hepatitis C treatment. Direct acting antiviral drugs against CHC have been recently introduced in Cameroon, thus the results of our study should be useful appreciating the contribution of these drugs in therapeutic response and tolerance. Caucasians-based experience showed better virological response and treatment tolerance [9,10]. In the present study, we found a high rate of virological response compare to the previous interferon based regimens. The incidence and severity of side effects was negligible and no patient discontinued the treatment.

Early reports on the treatment of CHC with INF-PEG ribavirine had shown low rate of SVR as 48% for genotype 2 [4] and 36.1% for genotype 4 [5]. Higher rates have been reported with the sofosbuvir PEG-INF ribavirine or sofosbuvir ribavirine regimens. Thus in Egypt, whereas in black Africans leaving in western countries SVR up to 90% have been described [9,11].

We report 91.6% ETR and 91.6% SVR in our study. Previous studies reported remarkable racial and ethnic difference in the response to the treatment of CHC with protocols not including DAA [6,12].

From the fourth week of treatment we had a 83.3% rate of RVR substantially increasing through the end and the twelve week after treatment contrasting with the biphasic evolution with previous regimens [13]. The direct action of sofosbuvir on NS5B HCV protein represent the plinth of the rapid and strong response described [8].

Within genotypes, genotype 2 showed the worse virological response with 86.4% ETR and 86.4% SVR without significant statistical association. Besides, no factor as fibrosis, age, high baseline viral load nor therapeutic status was associated with absence of virologic response. S282T variants associated with sofosbuvir resistance have not been sought in this study [14]. Except from this, the difference in virologic response observed remains actually unexplained.

With regard to transmission risk, a past history invasive surgery, were the highest risk factors for transmission in our patients. Nevertheless, in 68% of our patients, we did not find any obvious risk factor for transmission. In the sub-Saharan region, these are similar to what is found in the northern countries. However, while intravenous drug addiction is less common in Africa than in Europe and the United States [15], in African countries, the practice of traditional medicine often involves the use of sharp instruments for blood-letting or for direct application into

the blood of substances with supposed curative properties [16].

With regard to the safety of treatment; little patients presented clinical and biological adverse events compared to the population on previous regimens [17]. Asthenia is reported as the main clinical adverse effect in black and Caucasians [9,17], but is well tolerated. Biological adverse events include anemia, decrease neutrophil count and thrombopenia with variable representation whatever less than with previous regimens [17]. The short term of treatment is a great advantage offered by these new regimens permitting better tolerance and good adherence since no patient discontinue the treatment.

CONCLUSION

The virological response rate of blacks from the sub Saharan region infected by HCV had a great amelioration similar than in Caucasians, with the adjunction of sofosbuvir in previous regimens according to current recommendations. This direct acting antiviral also permit us to conduct short term treatment with better tolerance and adherence.

Authorship contributions and disclosure of conflicts of interest

The authors declare no conflicts of interest.

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