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Virological response of hepatitis Delta infection to treatment with Pegylated Interferon alpha 2a in a high prevalence country

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ABSTRACT

The prevalence of Hepatitis Delta Virus (HDV) infection in Cameroon is 11.01%. Pegylated interferon alpha 2a (PEG-IFN α 2a) is the standard treatment worldwide. This study aimed to describe the virological response to this drug in cameroonians. **Methods:** We carried out a cross-sectional study from 1 January 2012 to 31 December 2018. It took place in eleven (11) health facilities of Yaoundé and Douala. Patients with HDV infection and treated with PEG INF α 2a for at least 48 weeks were included. The primary endpoint was Virologic Response (VR) and secondary endpoints were Rapid Virologic Response (RVR) and Late Virologic Response (LVR). **Results:** We included 133 patients. The mean age was 36.33 ± 10.9 years. The male sex accounted for 65.41% of cases. The VR was 67.67%. Leukopenia, fever, headache, asthenia and abdominal pain were the most common adverse events in 88.72%, 68.42%, 53.38%, 45.11% and 35.34% of cases respectively. Factors associated with VR were the presence of diabetes (aOR= 4.32; CI95% [1.22 - 15.30], p= 0.023), fever (aOR= 5.16, CI95% [1.48 - 18.04], p=0.01) and ALT levels greater than 40 IU/l (aOR= 3.69, IC95% [1.15 - 11.18], p= 0.028). **Conclusion:** VR is high in cameroonians. The presence of diabetes and elevated transaminases are factors associated with this virologic response. We recommend the use of interferon treatment for patients with HDV infection in Cameroon with very strict monitoring of side effects.

Keywords: Hepatitis Delta virus, Virological Response, Pegylated Interferon alpha 2a, Cameroon.

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Introduction

Hepatitis Delta virus (HDV) infection is a public health problem that affects people all-over the world [1]. In 2018, about 15 to 20 million people was concerned according to the Word Health Organization (WHO) [1]. In Cameroon, the prevalence of HDV infection is about 11.01% [2]. B-Delta co-infection causes complications such as cirrhosis and hepatocellular carcinoma (HCC) more rapidly [3]. In France in 2015, a study showed that after one year of follow-up for HDV infection, 28% of patients developed cirrhosis, 15% an episode of cirrhosis decompensation and 2.7% HCC [4].The current treatment for HDV infection is pegylated interferon (PEG IFN) alpha 2a and the dosage is 180 µg per week for at least 48 weeks [5 - 7]. The effectiveness of this treatment is assessed by Virological Response (VR) [8, 9]. VR is defined as the absence of HDV-RNA in the blood 48 weeks after the end of treatment [10, 11]. The mechanism of action of PEG-IFN is not well understood [12] In Cameroon, PEG-IFN alpha 2a is available and subsidized by a government program through Approved Treatment Centers (ATCs) since 2012 at a price of US$84.29 per week. VR to PEG-IFN has several controversies and tolerance to this treatment is uncertain [13]. In 2018, the European Association for the Study of the Liver (EASL) estimated the VR to HDV infection at 25% [14] while the American Association for the Study of Liver Disease (AASLD) found 23 to 57% [15]. A study conducted in Turkey in 2017 showed a VR of 22%[16].The most common side effects include psychiatric disorders, flu-like illness, asthenia, anorexia, weight loss, alopecia, rash and abdominal pain in 30%, 25%, 50%, 30%, 30%, 30%, 10%, 7% and 20% of cases respectively[17,18]. About 40% of cases in Germany in 2016 were also characterized by inflammation at the injection site. In Pakistan in 2011, neutropenia was observed in 30% of patients, which led to a decrease in dose and later on, almost to the discontinuation of treatment [19]. Seeing that the prevalence of HDV infection is high among HBV carriers, the rapid progression to complications, the availability of treatment which is expensive and not always effective, this study aimed to investigate the virological response to HDV treatment with PEG-IFN alpha 2a in cameroonians.

Materials and methods

Study design

This was a cross-sectional study in eleven health facilities of Yaoundé and Douala: four university hospitals, two second-class hospitals and five private health facilities. During 5 month (1st January 2019 up to 30th June 2019), we collected patient's files from 1st January 2012 up to 31th December 2018.

Data collection

For this study, we used outpatient hepatology department files infected with hepatitis B virus. We included all patients with hepatitis Delta virus treated with pegylated interferon alpha 2a during at least 48 weeks. Patients excluded were all those with decompensated cirrhosis, co-infection with hepatitis C virus (HCV) or human immunodeficiency virus (HIV) and patients with incomplete records. We consecutively included all patient records that met the inclusion criteria. Missing data were obtained from patients or family members through a phone interview. The following data was collected: sociodemographic characteristics such as age, sex, marital status, occupation, place of residence and method of payment, circumstances of discovery of HDV, risk factors and/or modes of transmission of HDV (blood transfusion, IV drug use, scarification, unprotected sex, tattooing, professional activity), family history of liver cancer, HBV/HDV infection); anthropometric parameters (Weight , height , Body Mass Index (BMI) which was calculated using the formula Weight (kg) / Height (meters^2), clinical signs, pre-therapeutic assessment which included viral loads of Hepatitis B Virus (HBV) and HDV which were performed by the TaqMan technique in real time with detection threshold 15 IU/l by the

CERBA laboratory in France; complete blood count (CBC); Transaminases performed by the COBAS e 311 technique, with a normal value of 10 to 40 IU/l. The fibrosis score that was obtained using non-invasive markers was correlated with the METAVIR score. Per-therapeutic assessments (HBV and HDV viral loads, CBC and transaminases at 12, 24 and 48 weeks after the initiation of treatment). Post-therapeutic assessments (HBV viral load and HDV, 48 weeks after the end of treatment). Discontinuation of treatment and reasons were also recorded. The various clinical, biological and management adverse events were well noted.

Definition of operational terms

An incomplete record was a record that did not include one or more in the following: age, sex, CBC, HDV and HBV viral load, fibrosis score, HIV serology and Hepatitis C Virus (HCV) serology.

A responder was a patient whose HDV viral load was undetectable after 48 weeks of treatment [12].

A non-responder was the patient who had a detectable HDV viral load after 48 weeks of treatment [12].

The viral load of the HDV was considered high when it was greater than or equal to 10,000,000 IU/ml and low when it was less than 10,000,000 IU/ml [19].

Virological Response (VR) was the absence of detection of HDV RNA in the blood 24 or 48 weeks after the end of treatment.

Rapid Virological Response (RVR) was the absence of detection of HDV RNA in the blood 24 weeks after treatment initiation.

Late Virologic Response (LVR) was the absence of detection of HDV RNA in the blood 48 weeks after treatment initiation [20, 21].

Fibrosis was correlated with the METAVIR score, which classified hepatic fibrosis in five stages: F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (portal fibrosis with some septa), F3 (portal fibrosis with many septa without cirrhosis), F4 (cirrhosis). We considered as: Significant fibrosis: the fibrosis score ≥ F2 and non-significant fibrosis: the fibrosis score < F2 [22].

Obesity in a patient was defined by a Body Mass Index (BMI) ≥ 30.

Statistical analysis

The data analysis was performed by Statistical Package of Social Sciences (SPSS) software version 25.0. The primary endpoint was Virological Response(VR) and secondary endpoints were Rapid Virological Response(RVR) and Late Virological Response(LVR). Association between the variables was investigated using the Chi-Square test. The significance threshold was set at p value ≤ 0.05. To identify factors associated with VR,we did univariate analysis and multivariate analysis by logistic regression.

Ethical considerations

This work was approved by the Institutional Ethics Committee of the University of Douala under the number 1950 CEI-UD/05/2019/T. We obtained the authorization of all health facilities.

Results

Figure 1 describes the process that resulted in the inclusion of 133 patients. Table 1 describes the general characteristics of the population. The mean age was 36.33 ± 10.9 years. Males accounted for 65.41% of cases (n=87). Among the risk factors, unprotected sexual intercourse was found in 85.71% of cases (n=114), followed by scarification and dental care, which accounted for 62.41% of cases (n=83) and 32.1% of cases (n=42) respectively. Alcohol consumption accounted for 82.41%cases (n=83), diabetic and hypertensive patients had proportions of 12.03% (n=16) and 16.54% (n=22) respectively. Moreover, 45.11% (n=60) and 36.82% (n=49) of cases had asthenia and jaundice as clinical symptoms respectively, while 16.92% (n=22) had obesity. Prior to treatment, ALT levels were high in 48.06% (n=60) of patients and AST levels were high in 45.79% (n=60) of patients. A high HDV viral load

Table I : General characteristics of the study population

Variables	Values
Age (mean ± standard deviation)	36,33 ± 10,9
Gender (Male)	N= 87 (65,41%)
Risk factors	
Unprotected sex	N= 114(50,6%)
Scarification	N= 81(62,41%)
Dental care	N= 42(32,31%)
Tatoo	N= 14(10,53%)
Professional activity	N= 8(6,02%)
Blood transfusion	N= 6(4,51%)
Comorbidities	
Alcohol	N= 83 (82,41%)
Diabetes	N= 16 (12,03%)
Obesity	N= 22 (16,92%)
Clinical symptoms	
Asthenia	N= 60 (41,11)
Jaundice	N= 49 (36,02)
Abdominal pain	N= 20 (15,04)
Hépatomegaly	N= 1 (2,26)
Biology	
White blood cells (cell/mm3)	3,61 ± 2,69
Hemoglobin (g/dl)	12,86 ± 1,64
Neutrophils (cell/mm3)	5,82 ± 2,29
Platelets <150 (cell/mm3)	151,72 ± 67,75
AST ≥ 40 (UI/L)	38,15 ± 24,35
ALT ≥ 40 (UI/L)	43,85 ± 26,74
HDV viral load	
≤10000000 UI	N= 86 (64,66%)
>10000000 UI	N= 47 (35,33%)
HBV viral load	
<2000 UI/l	N= 112 (91,72%)
≥2000 UI/l	N= 21 (15,78%)
Fibrosis score	
Significant fibrosis (≥F2)	N= 45(36,29)
Insignificant fibrosis (<F2)	N= 79 (63,71)

Table 2 : Virological response of HDV depending on the duration of treatment

Variable	RVR n(%)	LVR n(%)
HDV RNA	31(23,1%)	82(61,2%)

RVR= Rapid Virologic Response (S24) LVR= Late Virologic Response (S48)

Tableau 3 : Frequency of clinical and biological side effects encountered during treatment

Variable	Effective (n)	Percentage (%)
Fever	91	68,42
Headaches	71	53,38
Asthenia	60	45,11
Abdominal pain	47	35,34
Chills	43	32,33
Arthralgia	37	28,03
Irritability	33	24,81
Nausea	31	23,31
Myalgia	30	22,56
Insomnia	20	15,04
Anorexia	11	8,27
Depression	7	1,23
Injection reaction site	2	1,50
Leucopenia	118	88,72
Anemia	29	22,14
Thrombopenia	20	15,03

Table 4 : Factors associated with virological response to treatment

Factors	Adjusted OR	CI for adjusted OR 95%		p-value
		Inferior	Superior	
Age : [35-47]	1,37	0,45	4,09	0,573
High HDV viral load	2,69	0,94	7,66	0,064
Diabetes	**4,32**	**1,22**	**15,30**	**0,023**
Fever	**5,16**	**1,48**	**18,04**	**0,01**
Irritability	2,17	0,72	6,52	0,167
Arthralgia	2,28	0,78	6,64	0,131
ALT : > 40	**3,69**	**1,15**	**11,86**	**0,028**
AST : > 40	1,15	0,31	4,28	0,83

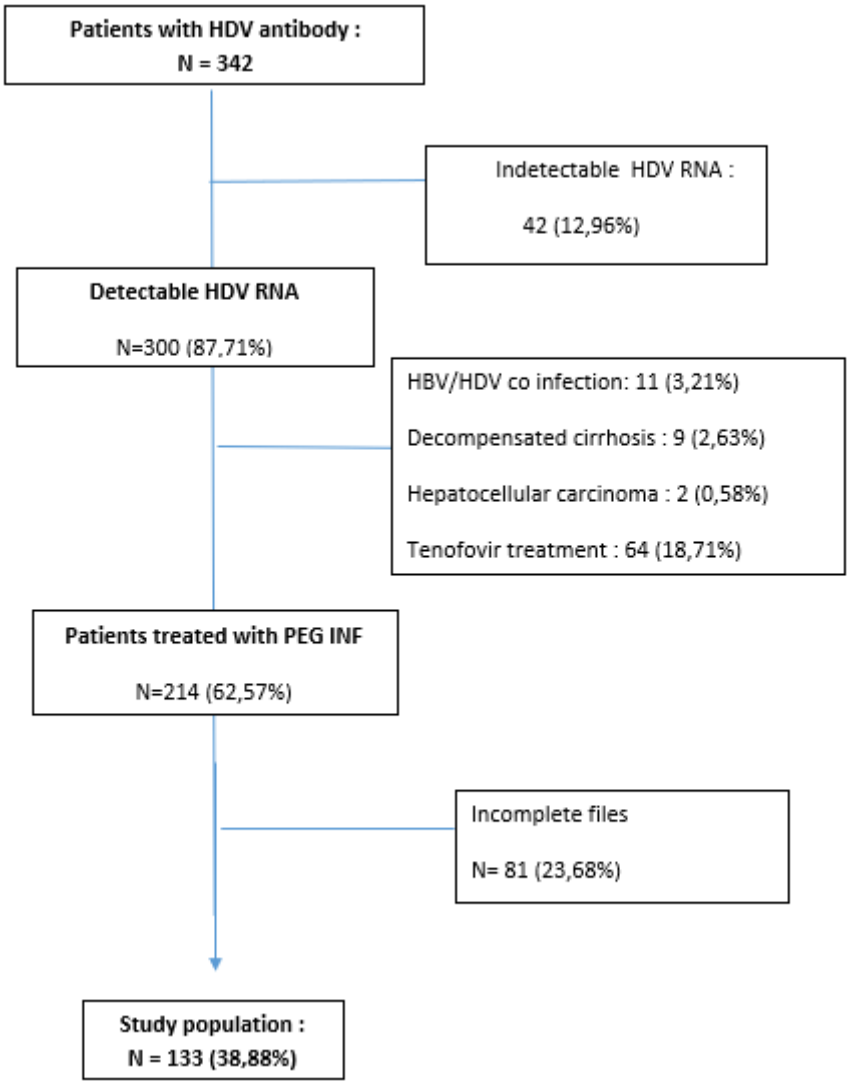

Figure 1 Flow chart describing patients' selection

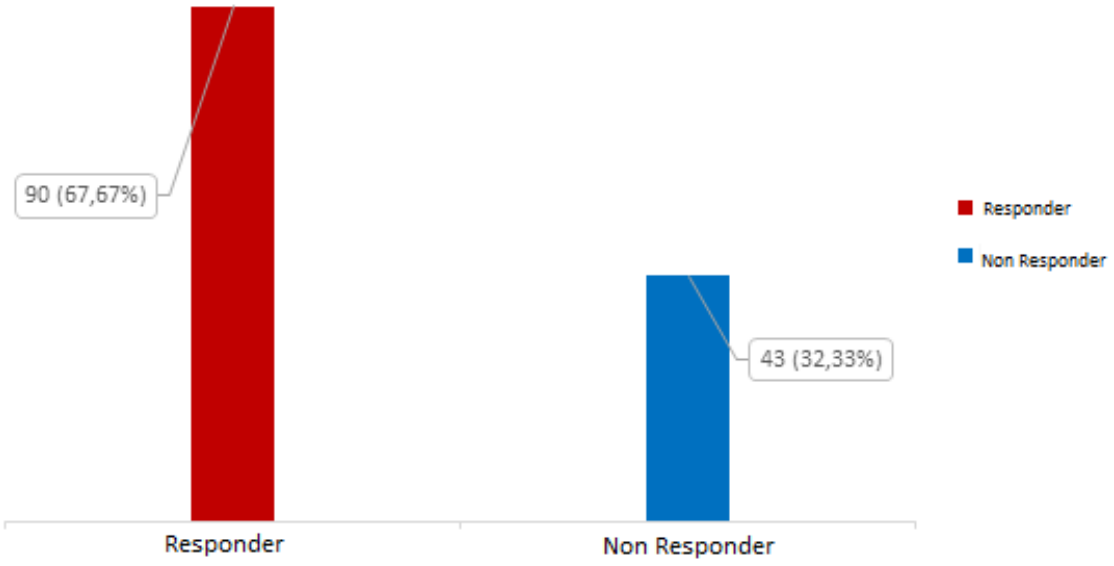

Figure 2 Global Virological response of the study population

was found in 35.33% of patients (n=47). Non-significant fibrosis was found in 63.71% of cases (n=79). At 48 weeks after the end of treatment, the virological response was 67.67% (Figure 2). An early virological response was found in 23.1% (n=31) of cases whereas 61.2% (n=82) of cases were late (Table 2). The adverse events observed during treatment is shown in Table 3; the presence of fever in 68.42% of cases (n=91), followed by headache in 53.38% of cases (n=71), asthenia in 45.11% of cases (n=60) and finally abdominal pain in 35.34% of cases (n=47). In the study population, 118 patients had leukopenia which represented a frequency of 88.72% and 29 patients had anemia with a frequency of 22.14% (Table 3). Factors associated with VR after adjustment were the presence of diabetes (aOR= 4.32; CI95% [1.22 - 15.30], p= 0.023), presence of fever (aOR= 5.16, CI95% [1.48 - 18.04], p=0.01) and an ALT rate greater than 40 IU/l (aOR= 3.69, CI95% [1.15 - 11.18], p= 0.028) as shown in Table 4.

Discussion

We conducted a cross-sectional study in 11 health facilities in the cities of Yaoundé and Douala in Cameroon. We found a virological response of 67.67%. Given that the data was collected from patients files, our main limitation was missing data.

The mean age in our study was 36.33 ± 10.9 years. It is similar to that found by Butler et al in 2018[2] and Luma et al in 2017[23]; this average age is the same as that found in HBV patients in Cameroon [24]. The male predominance found in this work is the same as that found by Stockdale et al in 2017[25] in London and Luma et al in Cameroon in 2017[23]. The risk factors found in delta virus infection are mainly male homosexuality, intravenous drug use, human immunodeficiency virus (HIV), hepatitis C virus infection and sexual intercourse with multiple partners[26, 27]. The VR was 67.67% in this work. This response was high compared to that found in most Western studies [11 - 13, 17, 26, 27]. On the other hand, it is close to those found by Rizzeto et al in 2016 and Ormerci et al in Spain in 2011[28,29]. Studies carried out in the West have always been carried out on a small sample and some have associated analogues. There is also the significant role of interferon side effects, which have sometimes led to early discontinuation of treatment. Interferon treatment at the right doses is essential. It has been shown that in addition to the effect on virological response, it also has a significant effect on transaminase normalization, fibrosis regression and even survival [26]. The use of a combination of interferon and analogues in the treatment of HDV has not demonstrated its effect [26, 27]. The persistence of Delta viral replication is a predictive factor of mortality [27]. It is therefore imperative to treat patients with the available molecules by strictly monitoring adverse reactions. Normalization of transaminases under interferon is observed in 40 to 70% of patients under treatment with a risk of escape in nearly 97% of cases [26, 27].

Conclusion

At the end of this work, we can conclude that the virological response is good in cameroonians. Considering the poor prognosis associated with viral replication, we recommend the use of pegylated interferon alpha 2a in HDV patients who do not present contraindications. It is also important that this treatment is made accessible to all.

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Conflict of Interest

This work was not funded. The authors do not declare any conflict of interest.

Abbreviations

AASLD: American Association for the Study of Liver Diseases

HCC: Hepatocellular carcinoma

ATCs: Approved Treatment Centers

EASL: European Association for the Study of Liver

PEG-IFN: Pegylated interferon

WHO: World Health Organization

VR: Virological response

RVR: Rapid Virological Response

LVR: Late Virological Response

SPPS: Stastistical Package for Social Science

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HDV: Hepatitis Delta Virus

HIV: Human Immunodeficiency Virus

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