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Research Article

Therapeutic Response of Black Africans in the Treatment of Genotype 2 Chronic Viral Hepatitis c by Pegylated Interferon-ribavirin

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Abstract

Background: Although genotype 2chronic hepatitis C (CHC2) is usually credited with very good responses, data from sub Saharan Africans are poorly documented.

Aim: To characterize the response to Pegylated interferon alpha 2a, and ribavirin in the sub-Sahara.

Methods:

Patient Selection: We consecutively included consented CHC2 treatment-naïve adults from all treatment centers in Cameroon. Eligible patients, free from any other chronic liver disease or HIV infection, were required to have a serum viral load of at least 2000 copies HCV RNA/mL, and a level of fibrosis of F2 or higher.

Study design: The medical records of patients who sought treatment were systematically reviewed by a committee. Efficacy was assessed by rapid virological response (RVR); early virological response (EVR); end of treatment response (ETR); and sustained virological response (SVR). Adverse events were recorded monthly. Data were analyzed using $\chi 2$ and Fisher's exact tests as appropriate.

Results: We included 102 patients aged 42 to 71 years. Risk factors of transmission were dominated by past history of invasive surgery, RVR was achieved by47% of patients; EVR by 88.2%; and ETR by 74.5%. Twenty seven patients relapsed; we ended with a SVR in 48% of patients. The viral kinetic showed a slow reaction to treatment.

Conclusion: The therapeutic response to Pegylated interferon ribavirin combination of blacks from the sub-Sahara, with CHC2 is by far lower than in Caucasians, Black Africans seem to react more slowly to therapy. Pending the arrival of new drugs, therapeutic protocols need to be reconsidered.

Keywords: Chronic hepatitis C; Genotype2; Sub-Sahara; Therapeutic response

Introduction

Even though genotype2 chronic hepatitis C (CHC2) is usually credited of very good response, empirically, we noticed occurrence of relapses. By the way the results of some studies have highlighted racial differences in therapeutic response; meanwhile the response to therapy in sub Saharan Africans is still poorly documented. According to WHO, Cameroon has one of the highest prevalence of infection by hepatitis C virus (HCV) in the world and the highest prevalence in sub-Sahara. The treatment of CHC so far available in this part of the world, is the combination of Pegylated interferon and ribavirin, even though not affordable by the majority of patients suffering from CHC. Racial differences have been reported in some countries but data from sub Saharan countries, where most of the patients in the world are found, are still not that available. We carried out this study with the aim to determine the therapeutic response to the classical treatment of CHC2 in a sub Saharan country with high prevalence of HCV infection.

Methods

Patient selection

We consecutively included in the study, adult Cameroonian patients, naïve of any treatment against CHC. CHC2 patients were selected from all the centers of treatment of CHC in Cameroon. We included in this study, CHC2 patients who did have neither any other chronic liver disease, nor HIV infection. The patients should have a viral load of at least 2000 copies HCV ARN/mL of serum. The level of fibrosis should be F2 and above. By the way patients should full filed all the conditions of a treatment by Pegylated interferon alpha 2a (peg-inf) and Ribavirin according to manufacturer. We used Roche manufactured peg-inf and Ribavirin. Patients should have completed 24 weeks of treatment.

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Study design

The medical records of patients who sought treatment were systematically reviewed by a committee. After eligibility, inclusion required informed consent. Data collected from the different treatment centers were centralized for analysis. Data from patients treated for 24 weeks with weekly 180 µg peg-inf interferon alpha 2 (peg inf) Subcutaneous plus daily oral ribavirin at a dose of 1000 mg for patients weighing up to 75 kg, and 1200 mg per day for those weighing more than 75 kg were included in the analysis. Patients were followed up during external consultation, through analysis of biological records and adverse events analysis. Medical and psychological assistance were given as appropriate.

Assessment of efficacy

Efficacy was assessed by measurement of serum HCV RNA at Weeks 4, 12 and 24 of treatment and 24weeks after the end of treatment, to assess rapid virologic response (RVR), early virologic response (EVR), end of treatment response (ETR) and sustained virologic response (SVR), respectively. The primary efficacy endpoint was SVR, defined as the absence of detectable HCV RNA in the serum. The serum HCV RNA was measured using a real time Taq Man Roche reverse-transcription–polymerase chain reaction assay. The sensitivity was 15 IU (1.2 log IU) per mL.

Assessment of safety

During follow up, safety was assessed by laboratory tests. There was a monthly (4weeks) recording and evaluation of adverse events. If required, this period of time could be shortened.

Statistical analysis

Bivariate and multivariate analyses were performed, using χ^2 and Fisher's exact tests as appropriate. A P value of less than 0.05 was used to indicate statistical significance.

Results

Patient's characteristics

We included a total of 102 patients, of whom 68 were males and 34 females. Their age ranged from 42 to 71 years, with a mean of 58.1±8.6 years. The most-represented age group was that of 55–65 years.

Based on self-reporting, the dominant assumed risk factor of transmission was past history of invasive surgery, followed by scarifications, tattoo and piercing; 20% of patients had no apparent risk factor. Diabetes and obesity were common comorbidities. Fifty two percent of patients had severe fibrosis, assessed by biological indirect method or liver biopsy; with regard to virology, 71% of patients presented with a high baseline viral load. ALT was normal in one third of patients (Table 1).

Virologic response

At the end of follow up, 48% of patients achieved an SVR. The viral kinetics showed a peculiarity between Week4 and Week 12, as it moved from 47% to 88, 2% of patients showing undetectable RNA, which subsequently regressed progressively (Table 2).

Factors associated with a sustained virologic response

Bivariate analysis showed no association between epidemiological characteristics and virologic response or between clinical signs and virologic response. However, baseline body mass index (BMI), high ALT level and dyslipidemia were all significantly associated with virologic response (p values of 0.024, 0.04 and 0.01, respectively).

Table 1: Demographic characteristics of the Patients, prior to treatment. N=102

Characteristic	n (%)
Gender	
Male	68(67%)
Female	34 (33%)
Age groups	
35-45	6 (6%)
45-55	23(23%)
55-65	46 (45%)
65-75	27 (26%)
Mean age(yr)	58.1±8.6
Social level	
Senior executive	57 (56%)
Middle manager	19 (19%)
Working class	26 (25%)
Risk factors	
Invasive surgery	32 (31%)
S T P*	17(17%)
Dental care	15(14.7%)
Blood transfusion	14(13.5%)
VHC in entourage	4(4.3%)
No risk factor	20(19.6%)
Functional signs	
Asthenia	16(16%)
R H P**	4(4%)
Co morbidities	
Diabetes	19(18%)
At risk Alcohol intake	5(5%)
Mild obesity	34(33%)
Virology	
Base line viral load	
High	72(70.6%)
Low	30(29.4%)
Sub types	
Biochemistry & fibrosis	
Normal Alt	34(33%)
2 x normal	38(37%)
3 x normal	30(30%)
F2	49 (48%)
F3	45 (44%)
F4	8 (8%)

*Scarifications tattoo and piercing
**Right hypochondria pain

Table 2: Virologic response.
N=102

Response	n (%)
RVR	
ARN negative	48 (47%)
ARN positive	54 (53%)
ERV	
ARN negative	90 (88.2%)
ARN positive	12 (11.8%)
ETR	
ARN negative	76(74.5%)
ARN positive	26(25.5%)
SVR	49/102(48%)
Relapse	27/76 (35.5%)

In addition, low baseline viral load and achievement of an RVR correlated with achieving an SVR (p=0.031 and p=0.11, respectively).

Multivariate analysis suggested that achieving an SVR was associated with normal baseline BMI and that low baseline viral load appeared to be a predictor of achieving an SVR.

Of the 54 patients who still had positive RNA at Week 4 (RVR assessment), 64% achieved an ETR; and 33% of these achieved an SVR (Table 3). Of those who achieved EVR, 65% subsequently had an SVR.

Adverse events

Most adverse events were those commonly associated with peg-inf-based treatment. Hematologic-related adverse events were most common. The most common clinical adverse event was asthenia (Table 4).

Discussion

We present the results of a cohort of 102 cases of CVHC G2 in black Africans treated with peg inf combined with ribavirin according to international recommendations. SVR, which signals treatment success, was 48%. On Multiple component analysis, the SVR was significantly associated with achieving RVR and normal baseline BMI. Viral kinetics during treatment was better between Week4 and Week12. The majority of adverse events were of hematologic origin.

The therapeutic response of HCV G2, like that of G 3, has been reported to be better than that of G1 and G4 [1-3]. The outcomes have been so good in some cases that new protocols were proposed, with shorter length of treatment or lower dosage [4]. Some racial differences in therapeutic response have been reported [5-8] with these positive outcomes for G2 treatment largely reported from Caucasian populations; however, detailed studies from sub Saharan Africa are still not available.

Table 3: Viral kinetic in patients who were still RNA+ at Week 4.
N=54

ETR	
Responder	35 (64.8%)
Non responder	19 (35.2%)
SVR	
Effective SVR	14/35 (40%)
Relapse	21/35 (60%)
Over all response	
Success	14 (26%)
Failure	40 (74%)

Table 4: Adverse events.

Adverse events	n(%)
Biological	
Neutropenia	84 (82%)
Anemia	61 (60%)
Thrombocytopenia	61 (60%)
Hyperthyroidism	4 (4%)
Clinical	
Asthenia	41 (40%)
Weight loss	35 (34%)
Fever	14 (14%)
Anorexia	10 (10%)
Skin change	9 (9%)
Cough	6 (6%)
Myalgia	6 (6%)

Cameroon has a very high prevalence of hepatitis C, with a broad genotypic variability [9]. Our study shows significantly poorer outcomes of treating G2 than those previously published in series of Caucasian patients. [2,10]. The first study published on Cameroonian populations, reported were very good response [11]. Empirical observation beyond the end of treatment, however, showed frequent relapses [12]. The first controlled trials laid emphasis on genotypes as the most important variable which could influence treatment outcome [13]. The viral kinetics appeared as another concept that could also explain the differences in the therapeutic response [14]. The kinetic curve of virologic responses has a characteristic not often reported in the series of Caucasian patients. Indeed, we found that, in our cohort, a low RVR was followed by a strong, improvement towards the 12th week of treatment. The biphasic reduction in virus load during treatment with peg IFN interferon was already demonstrated in late nineties, as authors reported an initial rapid decrease in serum HCV level followed by slower one [15]. Later on, other studies suggested that racial differences in the response to antiviral therapy were due to greater unresponsiveness to intracellular action of peg-IFN, precisely in black's patients [16]. In our cohort, we have noticed instead, an initial slow decrease followed by a more rapid decrease of serum HCV RNA levels. Thus, it appears that, black Africans may have a slow reaction to peg IFN and ribavirin treatment, with a slower virologic response. They have been several attempts to explain this characteristic in the blacks. The concept of iron overload was mentioned as was the production of cytokines In addition. Then came the concept of impaired ability to inhibit viral production [17]. Between the 12th and the 24th week, we observed a decline in the rate of good response, explaining the poorer overall treatment outcomes compared with those observed in Caucasians. By not discontinuing treatment at week 8 for patients who had not achieved a good RVR, we enabled a number of them to achieve an SVR.

With regard to transmission risk, 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 or the United States [18], 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 [19]. A past history of these practices or invasive surgery, were the highest risk factors for transmission in our patients. Nevertheless, in 20% of our patients, we did not find any obvious risk factor for transmission, similar to rates previously reported in a Study on African-Americans [12].

With regard to the safety of treatment, adverse events were for the most part of hematologic origin, including neutropenia and anemia. They are often found consistently in black and Caucasian patients [18]. Although asthenia and fever are reported in most studies [2,8,18], fever seems to be less common among black and Egyptian patients [8,20,21]. Asthenia and weight loss often have an impact on the quality of life of patients, but this is not specific to any racial group, as reported in several studies in different populations [22].

Conclusion

The therapeutic response of blacks from the sub Saharan region with CHCV G2 to peg-inf combined with ribavirin is lower than in Caucasians, using the current international treatment recommendations. Black Africans seem to react more slowly to therapy. Genetic differences between black Africans and Caucasian populations should be considered when designing therapeutic trials and consensus recommendations for treatment. Pending the arrival and the affordability of new treatment molecules, therapeutic protocols may need to be reconsidered.

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