SciMedCentral

JSM Gastroenterology and Hepatology

Research Article

# Therapeutic Response to Pegylated Interferon α-2a and Ribavirin in Genotype 4 Chronic Hepatitis C in Sub Saharan Africans

Njoya O[1,2,3]*, Ndong Essomba[2], Essi MJ[2], Kowo M[1,3], Luma H[3], Tzeuton C[3], Tagni M[3], Dang I[3], TallaP[3], Kamto D[3], Amadou[3], Eloumou S[3], Leundji H[3], Fondjo M[3], Noah D[3], Malongue A[3], Taku[3], kamdoum M[3] and M Nkam[3]

[1]*Department of Medicine, Faculty of Medicineand Biomedical Sciences University of Yaoundé I, Cameroon*

[2]*Research Laboratory on viral Hepatitis and Health Communication, Cameroon*

[3]*Cameroon Network against viral hepatitis, Cameroon*

***Corresponding author**

Njoya Oudou, Department of Internal Medicine and specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Research Laboratory on Viral Hepatitis and Health Communication, Po. Box 3495 Yaoundé, Cameroon, Tel: 237-699-811-717; Email: oudou_nj@yahoo.fr

**Submitted:** 22 December 2014

**Accepted:** 25 March 2015

**Published:** 27 March 2015



**Keywords**

- Chronic hepatitis C
- Genotype 4
- Black Africans therapeutic response Cameroon

**Abstract**

**Background**

The association of Pegylated interferon (Peg-inf) and Ribavirin (RBV) remains the standard of care for the treatment of genotype 4 Chronic Hepatitis C (CHC4) in sub Saharan Africa. Data on CHC4 in sub Saharan population are scarce.

**Aim:** To investigate the rate of Sustained Virological Response (SVR) in sub-Saharan patients treated with association of Peg-inf alpha 2a and ribavirin.

**Methods:**

- **Patient selection:** We included files of CHC4 Cameroonian patients aged 18 to 70 years, naive to previous interferon therapy. Patients should present with an F2 fibrosis; or F1 with persistent high viral load or elevated ALT.
- **Study design:** It was a multicenter cohort study. All the files were reviewed by a therapeutic committee. Patients were given a weekly 180µg subcutaneous Peg-inf and daily oral ribavirin. The duration of planned therapy was 48 weeks. The primary efficacy endpoint was the SVR. The secondary endpoints were the different Virological Responses (VR) at set points, according to WHO. RNA levels were measured by Real time TaqMan Roche PCR. Data were analyzed using the using $\chi^2$ and Fischer's exact test accordingly.

**Results:** We included 74 female and 128 males patients, aged 42 to 69, for a mean of 53.6±8.2 years. Transmission risk factors were dominated by scarifications piercing and tattoo. The majority of patients (55.4%) had severe fibrosis. The RVR was 16.8%; the EVR, 67.8%; the eRVR, 51.9%; the DVR, 19.2%; the ETR, 48% the partial response, 43.1%; and the SVR, 36.1%.The relapse rate was 24.7%.

**Conclusion:** This first study in sub-Saharan populationsshows that the response to the association of Peg-inf to RBV as standard of care in CHC4 in black African is poor. It confirms what has been observed in Afro Americans. There is a need to shift to new therapeutic protocols and readapt international guide lines, by including the racial component.

## INTRODUCTION

A prevalence of 13% of Chronic Hepatitis C (CHC) as it reported by WHO in Cameroon, is one of the in the world [1]. Genotype 4 Chronic Hepatitis C (CHC4) is very common in Africa and Middle East [1,2,3]. Genotype 4 as well as genotype 1, is a difficult-to-treat genotype. The association of Peg-inf and RBV is so far, the standard of care in the Africa sub Saharan region. Racial differences in the therapeutic response have been reported [4,5]. We had already highlighted poor response in genotype 2 [6]. Though CHC4 in common in Africa most of the publications concerns Egyptian population. We carried out this ever first study in black Africa with the aim to characterize virological response to the actual designed treatment regimen at different time points according to WHO.

## PATIENTS AND METHODS

### Patient selection

In Cameroon, to be treated against Chronic Viral Hepatitis C (CVHC) by the combination of Peg-Inf and Ribavirin (RBV), patients undergo a two-step selection. Firstly, each physician

involved in the treatment of viral hepatitis selects his patients for treatment, according to international guidelines, namely the EASL guidelines. Secondly, the files of all patients are reviewed by a Therapeutic Committee (TC).

We included in the study, patients naive to interferon therapy, with a positive RNA by PCR. Patients had to fulfill the following criteria: Be of Cameroonian origin; aged 18 to 70; fibrosis test of at least F2; or F1 with persistent high viral load or elevated ALT, complete at least 12 weeks of treatment, with respect to manufacturer conditions. We used La Roche manufactured Peg-inf and RBV. Initial anemia, high blood sugar level, obesity was corrected before final inclusion.We did not include in this study, patients co infected byhepatitis B virus or HIV; decompensated cirrhosis; chronic alcoholic liver disease; anylong standing co morbidity. We excluded from analysis, lost to follow up patients.

### Fibrosis and necro inflammation evaluation

Base line fibrosis and necro inflammation was evaluated either by histology or indirectly by biological test; patientswere then graded according to Metavir or corresponding classification, from F0 to F4, necro inflammation from A0 to A3 [7,8].

### Study design

Itwas a multicenter cohort study. The final inclusion was decided by the TC which had to ensure that, all the conditions were set for a thorough treatment. The treatment consisted of weekly subcutaneousinjection of 180µg of Peg- Inf, and a daily oral RBV tablets, according to the weight, 1000-1200 mg/day (cut off at 75kg).The duration of planned therapy was 48 weeks. They was a systematic monthly follow-up during outpatient consultations and in between if need was. The primary efficacy end point was the Sustained Virological Response (SVR), defined as undetectable HCV RNA 24 weeks after the end of the 48 weeks of treatment. The secondary endpoints were the different Virological Responses (VR) at set points according to WHO [1]. Baseline evaluation comprised, apart from clinical evaluation, kidney and liver biochemistry profile; fasting blood sugar; full blood count; thyroid hormones level; abdominal ultrasonography; upper digestive endoscopy for patients graded F4 for fibrosis.

We considered as lost to follow-up, any patient who no longer attended the clinical follow-up by the investigators. On the other hand, relapse was any patient who after achieving an End of Treatment Response (ETR) at week 48, showed a positive RNA 24 weeks after.

All the results and follow up were centralized.

### Assessment of efficacy

The different assessment time pointswere 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 Early Virological Response (EVR), defined as more than 2log reduction in HCV RNA level, by quantitative PCR; and the extended Rapid Virological Response (eRVR) defined as undetectable HCV RNA 4weeks and 12 weeks after the start of treatment. At week 24, the Delayed Virological Response (DVR) defined as more than 2 log decline in HCV RNA but detectable HCV RNA at week 12 and undetectable at week 24. At week 48, the End of Treatment Response (ETR) this is the level of HCV RNA at the end of treatment. At week 72, the Sustained Virological Response (SVR), this is defined as undetectable HCV RNA, 24 weeks after the end of full treatment. The SVR was the primary efficacy end point.

The levels of RNA and fibrosis grading (fibro test) were performed by Laboratoire CERBA in Paris, sub contracted by Centre Pasteur du Cameroun. RNA levels were measured by Real time TaqMan Roche PCR.

### 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. The thyroid gland was assessed every 3 monthsuntil the end of treatment, and at week 72.

### Statistical analysis

We used the Statistical Package for Social Science software (SPSS version 18.0Inc.Chicago, II) for statistical analysis. Means ±standard deviation was used for quantitative variables, frequency and proportions for qualitative variables. Bivariate analysis and multivariate logistic regression analysis were 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

Baseline demographic data are summarized in (Table 1). The sex ratio was 1.7. The risk factors of transmission were dominated by scarifications piercing and tattoo; meanwhile, in up to 19.8 % of patients, the risk factor was unknown. The majority of patient aged more than 50 years.

At the clinical point of view, asthenia appeared to be the most frequent symptom. Biological data revealed a variety of sub types, and most of the patients presented with severe fibrosis and high viral load (Table 2).

### Virological response

At week 24, 91 patients still had positive RNA, and 73 of them showed more than 2 log decline. Out of these, 14 presented with undetectable RNA at week 24, giving a DVR rate of 19.2%. At the end of treatment, among the patients who did not achieve an STR, 87 showed more than 2 log decline for a partial response of 43.1%. After achieving an ETR of 48% patient ended up with an SVR of 36.1% with a relapse rate of 24.7% (Table 3) (Figure 1).

Considering demographic and biological data, the SVR rate was not significantly different with respect to gender age and viral sub types, but we noticed a significant difference according to fibrosis grade (Table 4).

### Tolerability and adherence

The most frequent clinical adverse effect reported by patients was asthenia. It was nearly 2 times more frequent than the second, which was made of flu like symptoms. None of the adverse effects

**Table 1:** Baseline demographic data of patients N=202.

| Characteristics | n (%) |
|---|---|
| **Gender** | |
| Male | 128(63.3%) |
| Female | 74(36.7%) |
| **Age groups** | |
| [40-45] | 8(4%) |
| [45-50] | 34(16.8%) |
| [50-55] | 58(28.7%) |
| [55-60] | 56(27.7%) |
| [60-65] | 38(18.8%) |
| [65-70] | 8(4%) |
| **Mean age** | 53.6±8.2 years |
| **Social level** | |
| Senior executive | 61(30.2%) |
| Middle manager | 95(47%) |
| Working class | 27(13.4%) |
| House wife | 19(9.4%) |
| **Risk factors for HCV infection** | |
| S/ P/ T* | 105(51.9%) |
| Dental care | 97(48%) |
| Invasive surgery | 65(32.1%) |
| Unknown | 40(19.8%) |
| Blood transfusion | 38(18.8%) |
| VHC in entourage | 4(2.1%) |
| **Co morbidities** | |
| High Blood Pressure | 86(42.5%) |
| Mild obesity | 61(30%) |
| Diabetes | 27(13%) |
| At risk Alcohol intake | 15(7%) |

**Table 2:** Clinical and biological baseline data N=202.

| Characteristics | n (%) |
|---|---|
| **Clinical presentation at diagnosis**** | |
| Asthenia | 109(53.9%) |
| Arthralgia | 58(28.7%) |
| Myalgia | 44(21.7%) |
| Hepatomegaly | 25(12.3%) |
| **Sub types** | |
| 4 unclassified | 93(46%) |
| 4f | 74(36.6%) |
| 4a/c/d | 15(7.4%) |
| 4c/d | 6(3%) |
| 4a/c+ 4d+ 4e+ 4o | 14(7%) |
| **Viral load** | |
| High | 114(56.4%) |
| Low | 88(43.6% |
| **ALT level** | |
| Normal (N) | 63(31.2%) |
| 1-2N | 80(39.6%) |
| 2-3N | 21(10.4%) |
| >3 N | 38(18.8%) |
| **Necro inflammation** | |
| A1or A2 | 154(76.2%) |
| A3 | 48(23.8%) |
| **Fibrosis** | |
| F1or F2 | 90/202(44.6%) |
| F3 or F4 | 112(55.4%) |

**Table 3:** Virological response.

| Assessment time points | Types of virological response |
|---|---|
| Week 4 | RVR: 34/202(16.8%) |
| Week 12 | EVR: 137/202(67.8%)<br>eRVR:105/202(51.9%) |
| Week 24 | Negative RNA: 111/202(55%)<br>DVR 14/73(19.2%) |
| Week 48 | ETR: 97/202(48%)<br>Partial response: 87/202(43.1%) |
| Week 72 | SVR: 73/202 (36.1%)<br>Relapse: 24/97(24.7%) |

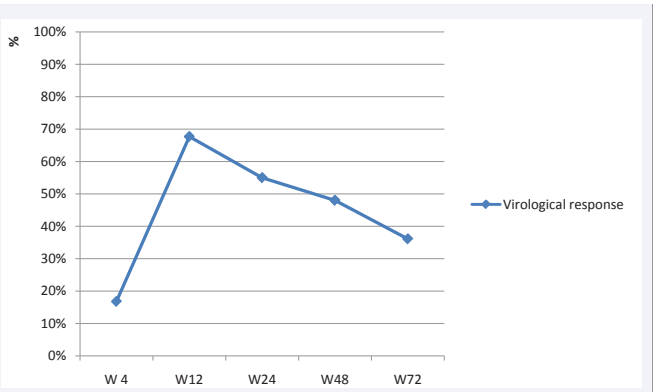


**Figure 1** Evolution curve of the virological response at different time points.
W: week.

indicated interruption of treatment. Hematological side effects were successfully managed (Table 5).

All the patients followed their treatment completely, giving an adherence rate of 100%.

## DISCUSSION

Many publications have reported that HCV genotype 4 which is a difficult-to-treat genotype, and is common in Middle East and Africa [1,4,5]. The standard of care in Africa is still the association of Peg-inf and ribavirin. Early report on the treatment of CHC4 had shown that the rate of SVR varied from 61.1% (9) to 73% [10] in Egypt, whereas in black Africans leaving in the western countries poor response rate as low as 26.5%,has been reported [5,11].

We herein report a 48% ETR anda 36.1% SVR rate in a cohort of 205 black African originated from Central Africa.These results show a poor therapeutic response of black Africans chronically infected by CHC4, to the association of Peg- inf and RBV, as it is actually designed. Previous studies reported remarkable racial

**Table 4:** SVR according to demographic and biological parameters

| Parameters | n | SVR | P value |
|---|---|---|---|
| **Gender** | | | |
| Male | 128 | 45/128(35.2%) | 0.70 |
| Female | 74 | 28/74(37.8%) | |
| Age | | | |
| ≤50 years | 42 | 18/42(42.8%) | 0.31 |
| >50 years | 160 | 55/160(34.4%) | |
| **Major Sub types** | | | |
| 4 unclassified | 93 | 38/93(40.8%) | |
| 4f | 74 | 29/74(39.1%) | |
| 4a/c/d | 15 | 3/15(20%) | |
| 4c/d | 6 | 0/6(0%) | |
| 4a/c+ 4d+ 4e+ 4o | 14 | 3/14(21.4%) | 0.11 |
| **Fibrosis** | | | |
| F1or F2 | 90 | 44/90(48.9%) | |
| F3or F4 | 112 | 29/112(25.9%) | 0.00 |
| **Necro inflammation** | | | |
| A1or A2 | 154 | 55/154(35.7%) | |
| A3 | 48 | 18/48(37.5%) | 0.82 |
| **Viral load** | | | |
| High | 114 | 45/114(39.4%) | |
| Low | 88 | 28/88(31.8%) | 0.26 |

**Table 5:** Main recorded clinical and biological adverse events*.

| Clinical adverse events | |
|---|---|
| Asthenia | 171/202(84.6%) |
| Flu like symptoms | 90/202(44.5%) |
| Anorexia | 53/202(26.2%) |
| Irritability | 46/202(22.8%) |
| Weight loss | 40/202(19.8%) |
| Cough | 36/202(18.8%) |
| Skin hyper pigmentation | 32/202(15.8%) |
| Diarrhea | 18/202(8.9%) |
| Alopecia | 2/202(0.9%) |
| Depression | 2/202(0.9%) |
| **Biological adverse events** | |
| Anemia | 99/202(49%) |
| Neutropenia | 86/202(42.6%) |
| Thrombocytopenia | 76/202(37.6%) |

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

and ethnic differences in the response to the treatment of CHC by this same treatment regimen. As a matter of fact, in 2004, difference between white; Hispanic; and Afro Americanswas reported In USA [10]. In 2013, a 26.5% SVR rate was reported in Belgium, among the black Africans, with CHC4, and originates from some countries in Central Africa [5]. Even though the cohort in the present study is less than the one done in Belgium; this study is probably to date, the first one in a relatively homogenous population of the Blacks in sub Saharan Africa. It concerns a country, namely Cameroon, where HCV touches more than 13% of the general population. All patients enrolled, underwent the same protocol and there was no drug dose reduction all along the treatment. We noticed that the eRVR was nearly similar to response at mid term. What we refer to as midterm virological response could have predicted the ETR, then the SVR; but we rather noticed a progressive regression. The curve of virological response is peculiar in the sense that, a poor RVR was followed by a strong, improvement towards the 12$^{th}$ week. This is similar to what has been observed in genotype 2 Chronic Hepatitis (CHC2), in the same population [6], and different from the biphasic reduction in virus load, that was already demonstrated in late nineties [11]. The poor responsiveness to antiviral therapy in the blacks is still to have thorough explanation. A part from poor intracellular action of Peg-inf; [12,13] the concept of iron load has been stated [14].

It is worth pointing out, the high rate of partial response, which is related to DVR; and the relapse. This suggests that probably, if the treatment could be extended, they might be chances to have better SVR rate.

In line with some previous studies [9,10,13], we found a significant better SVR in patients with mild fibrosis than in those with more severe fibrosis. Patient aged no more than 50 tend to have better virological response rate even though statistically not significant. Contrary to some Egyptian [10.15] and European studies [16], we found no significant difference in the SVR rate among the subtypes.

Scarifications are of common practice in traditional medical care in Africa [18]. Piercing is nearly systematic in female. Added to tattoo of lesser practice, these factors appeared to be leading risk factors of transmission of HCV in our cohort, in line with what we reported concerning CHC2 [6] and differently to northern countries,were intravenous drug use is often the leading mean of transmission [18].

Even though we reported many adverse effects, they were mild in general. The treatment protocol was therefore well tolerated. Hematology related adverse effect was the most clinically harmful but well managed, and did not lead to an interruption of the treatment. In the present study just like in Egyptians patients fever appears to be less common than in Caucasians [14,15,19].

Adherence is a predictive factor to SVR [20]. In the current study, all patients followed their treatment fully. The reasons of this 100% rate of adherence are the fact that practically all the injection are done in hospital, the close follow up by physicians and experience exchange in between patients. By the way, the fact that most of the patients pay for their treatment could explain their adherence.

## CONCLUSION

The response to the association of Peg-inf to RBV as standard of care in genotype 4 chronic hepatitis C in black Africans is still poor and cannot permit to control this epidemic situation in some part of the world. The results of this study, which are in line with what was reported in Afro Americans, strongly suggest that the current international guidelines should integrate the ethnic or racial component, whatever the molecules in use.

## ACKNOWLEDGMENTS

We would like to thank the following: MbopiKeou FX and

Karima Njoya for contributing in edition, all the nursesin Douala and Yaoundé, especially at the medicine ward of the Yaoundé University Hospital Centre, for their collaboration in the follow up and drug administration.

## REFERENCES

1. World Health Organization. Guidelines for the screening and treatment of persons with hepatitis C infection. Guidelines, Geneva. 2014; 121.
2. Khattab MA, Ferenci P, Hadziyannis SJ, Colombo M, Manns MP, Almasio PL, et al. Management of hepatitis C virus genotype 4: recommendations of an international expert panel. J Hepatol. 2011; 54: 1250-1262.
3. Xu LZ, Larzul D, Delaporte E, Bréchot C, Kremsdorf D. Hepatitis C virus genotype 4 is highly prevalent in central Africa (Gabon). J Gen Virol. 1994; 75: 2393-2398.
4. Gaglio PJ, Rodriguez-Torrres M, Herring R, Anand B, Box T, Rabinovitz M et al. Racial differences in response Rates to Consensus Interferon in HCV infected patients Naïve to Previous Therapy. J Clin Gastroenterol 2004; 38: 599-604.
5. Nkuize M, Mulkay JP, Adler M, Lasser L, Michielsen P, de Galocsy C, et al. Response of Black African patients with hepatitis C virus genotype 4 to treatment with peg-interferon and ribavirin. Acta Gastroenterol Belg. 2013; 76: 291-299.
6. Njoya O, Ntsama L, Essi MJ, Kowo M, Luma H, Tzeuton C, et. al. Therapeutic Response of Black Africans in the Treatment of Genotype 2 Chronic Viral Hepatitis C by Pegylated Interferon-ribavirin. Austin J Gastroenterol. 2014; 1: 4.
7. [No authors listed]. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. the French METAVIR Cooperative study Group. Hepatology. 1994; 20: 15-20.
8. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996; 24: 289-293.
9. EI Makhzangy H, Esmat G, Said M, Elraziky M, Shouman S, Refai R, et al. Response to pegylated interferon alfa-2a and ribavirin in chronic hepatitis C genotype 4. J Med Virol. 2009; 81: 1576-1583.
10. EI Khayat HR, Fouad YM, EI Amin H, Rizk A. A randomized trial of 24 versus 48 weeks of peginterferon alpha-2a plus ribavirin in Egyptian patients with hepatitis C virus genotype 4 and rapid viral response. Trop Gastroenterol. 2012; 33: 112-117.
11. Yasui K, Okanoue T, Murakami Y, Itoh Y, Minami M, Sakamoto S, et al. Dynamics of hepatitis C viremia following interferon-alpha administration. J Infect Dis. 1998; 177: 1475-1479.
12. Hoofnagle JH, Wahed AS, Brown RS Jr, Howell CD, Belle SH; Virahep-C Study Group. Early changes in hepatitis C virus (HCV) levels in response to peginterferon and ribavirin treatment in patients with chronic HCV genotype 1 infection. J Infect Dis. 2009; 199: 1112-1120.
13. De Maria N, Colantoni A, Idilman R, Friedlander L, Harig J, Van Thiel DH. Impaired response to high-dose interferon treatment in African-Americans with chronic hepatitis C. Hepatogastroenterology. 2002; 49: 788-792.
14. Bräu N, Bini EJ, Currie S, Shen H, Schmidt WN, King PD, et al. Black patients with chronic hepatitis c have a lower sustained viral response rate than non-blacks with genotype 1 but same with genotypes 2/3, and this is not explained by more frequent dose reductions of interferon and ribavirin. J Viral Hepat. 2006; 13: 242-249.
15. Kamal SM, E Kamary SS, Shardell MD, Hashem M, Ahmed IN, Muhammadi M, et al. Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: The role of rapid and early virologic response. Hepatology. 2007; 46: 1732-1740.
16. Roulot D, Bourcier V, Grando V, Deny P, Baazia Y, Fontaine H, et al. Epidemiological characteristics and response to peg interferon plus ribavirin treatment of hepatitis C virus genotype 4 infection. J Viral Hepat. 2007; 14: 460-467.
17. Njoya O. Voies de transmission et mode de contamination des hépatites virales. In: Hépatites virales en mots simples. Paris Harmattan 2013; 89: 37-40.
18. Wiley TE, Brown J, Chan J. Hepatitis C infection in African Americans: its natural history and histological progression. Am J Gastroenterol. 2002; 97: 700-706.
19. Ford N, Kirby C, Singh K, Mills EJ, Cooke G, Kamarulzaman A, et al. Chronic hepatitis C treatment outcomes in low- and middle-income countries: a systematic review and meta-analysis. Bull World Health Organ. 2012; 90: 540-550.
20. McHutchison JG, Patel K, Poynard T, Lindsay KL, Trepo C, Dienstag J et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology. 2002; 123: 1061-1069.

**Cite this article**

*Njoya O, Essomba N, Essi MJ, Kowo M, Luma H, et al. (2015) Therapeutic Response to Pegylated Interferon α-2a and Ribavirin in Genotype 4 Chronic Hepatitis C in Sub Saharan Africans. JSM Gastroenterol Hepatol 3(2): 1041.*