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Single Center experience with sides effects of "Triomune®" in Mali

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Abstract

Objective: The main objective was to evaluate the sides effects of "Triomune®" among HIV patients followed at Hospital setting.

Methods: Our study concerned 68 patients infected by the HIV under antiretroviral treatment with "Triomune®" in infectious diseases service of Point G hospital center. It was a prospective and observational study with a total duration of six months from January, 1st 2006 to December, 31th 2007. The patients were treated with the generic "Triomune®". Prior to initiation of treatment, the clinical history and biological parameters for each patient were collected including viral load, CD4 cells counts.

Results: The majority of our patients consulted for Candidiasis, fever of long duration, chronic cough and diarrhea. We reported that only 8.2% of patients had symptoms after 24 weeks of treatment. For 37 patients (54.4%) the viral load was undetectable after 24 weeks of treatment. 25.2% of our patients presented clinical side effects between them 17% were serious. The skin rash side effects represented 8.1 % of the cases. They were made of rash and nettle rash. In 8.1% of cases, our patients had stopped their treatment because of dermatological side effects. The peripheral neuropathies and myalgia represented 9.5% of the cases. The adherence to treatment was observed in 74% of the patients. At the end of the 24 weeks of our follow up, 5.8% of our patients died.

Conclusion: This study suggests that "Triomune®" use may lead at sides' effects at any time during the first 24 weeks. These data support the national policy in Mali which is recommending to withdraw this fixe dose combinaison from first line HIV therapy.

Keywords: "Triomune®"; Sides effects; Mali

Introduction

More than 20 years since its discovery, AIDS still remains the primary leading cause of morbidity and mortality in humans. Organizations such as UNAIDS and WHO stated in their 2009 annual reports on the AIDS epidemic, that no less than 33.4 million individuals were seropositive, and 2 million died as a result of HIV infection. In Sub-Saharian Africa, 22.4 million people were HIV carriers and 1.4 million deaths were accounted for by AIDS [1]. In Mali, according to the fourth demographic and health investigation report, the statistics revealed an estimated HIV seroprevalence of 1.3% [2]. Mali began using antiretroviral medications in November 2001 thanks to a national policy named "Initiative Malienne d'accès aux antirétroviraux" (IMAARV). Antiretroviral treatment was proclaimed free on the 14th July 2004 by a presidential order [3]. The national care policies for HIV-infected patients states that Triomune® should be used as the first-line antiretroviral treatment comprising a fixed combination of D4T (stavudine), +3TC (lamivudine), + NVP (nevirapine) presented as a single tablet. This dose combination drug is easy for both patients (adherence improving) and Ministry of Health (more cheaper). But base in Triomune® sides effects (particularly neuropathy and lipodystrophy due to D4T) wich is recommending to do not use this drug. Studies in this topic are rare in low income countries [3-7]. In Mali, there is no data to support this recommendation. The aim of this study was to evaluate sides effects due to Triomune® among patients followed in an hospital setting.

Methods

This study was conducted in the capital city of Mali, Bamako, at the Point G National Hospital, infectious disease department. Using a prospective and observational study design, it was conducted over a 24-month period, from 1st January 2006 to 31st December 2007, and included a 6-month follow-up. The patients were HIV-infected, naive to antiretroviral (ARV) treatment, of both genders. The study's inclusion criteria were: HIV-1 serology positivity, 16 years of age or more, receiving Triomune® treatment, being followed in the infectious disease department, and having given their informed consent. Exclusion criteria were: HIV-2 positivity, less than 16 years of age, not receiving Triomune® treatment, not having given informed consent, or concomitant antituberculosis therapy (rifampicin). For the 68 patients meeting the inclusion criteria, antiretroviral (ARV) therapy was initiated at the center. A patient was considered compliant to treatment if he/she took at least 95% of the total prescribed medication. The adherence was measured by counting the remaining pills prescribed at the past visit [8]. All clinical and biological adverse events which occurred during treatment with Triomune® were collected. Quantitative variables at baseline included age, weight, CD4 cell counts, viral loads, fasting glucose levels, serum creatinine levels, liver enzymes, hemoglobin, and platelet counts. All patients have normal ALT at baseline. These

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measurements were reported separately and considered high or low depending on the normal ranges set of our laboratory. The side effects of the treatment were evaluated using the WHO toxicity scale [9] and evaluated according to the WHO method of causality [10]. The HIV blood test was only performed after discussion with the patient. In order to confirm a positive HIV blood test, the mean of two different methods in use in Mali was taken. In our investigation, the HIV serostatus of each patient was confirmed using ImmunoComb II (Organics, Strasbourg, France) and Genie II (Sanofi Diagnostics Pasteur, France). Biological examinations included a HIV-RNA assay for viral load (Amplicor cobas HIV-1, Monitor Kit; Roche, Branchburg, NJ) and CD4 cell counts (Facs-Count Immunocytochemistry systems; Becton-Dickinson, Miami, FL). Immunological efficacy was defined as an increased CD4 cell count during antiretroviral treatment.

Virological efficacy was defined as blood viral load becoming undetectable during the antiretroviral treatment (<50 copies/ml). HBV or HCV examinations were not routinely made at the time. This study was approved by the ethical committee of the leading clinical center for this study (**Faculté de Médecine, de Pharmacie et d'odontostomatologie de Bamako, Mali**). Statistical analysis: Statistical analysis was performed using SPSS 12.0 for Windows. Values obtained at baseline and after 24 weeks were compared using Fisher's exact test.

Results

Clinical and biological characteristics of the 68 patients at baseline are shown in Table 1. After 24 weeks of treatment, there was a statistically significant reduction in oral candidiasis (IO) (p <0.001), fever (p <0.001), chronic cough (p <0.001), and chronic diarrhea (p <0.001) occurrences (Table 2) as well as a statistically significant improvement of biological parameters including anemia (p=0.036) and hypoglycemia (p=0.004) (Table 3). Body weight increased during treatment, with a mean increase of 7.6 kg per patient. Furthermore, CD4 cell counts increased, with a mean increase of 162 cells/mm³. For 37 patients (54.4%), the viral load was undetectable after 24 weeks of treatment. Skin rashes were observed in 8.1% (5/61) of cases and four (6.5%) occurred during the first month of treatment. For these five patients, the severity (WHO grade 3) warranted the discontinuation

Characteristic	Patients (n=68)
Demography	
Sex	24(35.3)
Female	44(64.7)
Age	
Mean years (range)	35[17-66]
Biological	
CD4 cell count rate mean (range)	139.3 [10-416]
HIV-1 RNA (copies/mL)	
Mean (range)	500460.3[1200-1100000]
Clinical	
CDC stage	
A	1
B	11
C	56
Weight (kg)	
Average Weight (range)	57.2 [29-82]
Others treatments	
Cotrimoxazole	51(75)
Fluconazole	34(50)

Table 1: Demographic, clinical and biological characteristic of the 68 patients.

Clinicals signs	% at inclusion n=68	% at 12 weeks n=61	% at 24 weeks n=50	p value (Fisher test)
Oral candidosis (OI)*	34	0	0	p<0.001
Fever	28	1	0	p<0.001
Chronic cough	25	2	1	p<0.001
Chronic diarrhea	21	2	1	p<0.001
Vomiting	4	0	1	NS (p=0.125)
Prurigo	3	0	0	NS (p=0.249)
Lymph Nodes	3	0	0	NS (p=0.249)

OI opportunistic infections

Table 2: clinicals signs at inclusion and after 24 weeks of treatment.

Sides effects	% at 4 Weeks n=68	% at 12 weeks n=61	%at 24 weeks n=50	p value (Fisher test)
Clinical				
Cutaneos	5	2	0	NS (p=0.21)
Neurological	2	4	4	NS (p=0.41)
Nausea/vomiting	1	1	0	NS (p=1)
Biogical				
Transimasemia	18	22	0	(p=0.000)
Creatinine	7	4	0	NS (p=0.051)
Aneamia	61	29	10	p=0.000
Metabolic	24	6	1	NS (p=0.36)

Table 3: Clinicals and biological sides effects at inclusion and after 24 weeks of treatment.

ADR	Number	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous	7	1	1	5	0
Neurological	10	2	0	8	0
Nausea/vomiting	2	1	1	0	0
Transimasemia	40	17	20	3*	0
Creatinine	11	7	4	0	0
Aneamia	61	25	28	8	0
Metabolic	31	21	5	0	0

* hepatitis biological

Table 4: Severity of adverse drug reactions (ADR).

ADR	Certain	Probable	Possible	Unlikely	Conditional/ unclassifiable	Non assessable /Unclassifiable
Cutaneous	5	1	1	0	0	0
Neurological	7	1	1	1	0	0
Nausea/vomiting	0	1	1	0	0	0
Transimasemia	3	5	7	13	6	4
Creatinine	0	2	2	4	3	0
Aneamia	8	17	11	13	7	5
Metabolic	0	5	4	8	7	2

Table 5: Causality assessment of ADR.

of NVP. NVP was substituted by Efavirenz. In 6.6% (4/61) of cases, peripheral neurological pathologies associated with muscle pain were noted at baseline and continued through the duration of the study. In nine patients the intensity (WHO grade 3) was severe and the use of D4T was interrupted (Table 4). Liver toxicity including an increase in ALT levels was observed in 40.98% (25/61) of cases; it was of moderate intensity (WHO grade 2) in 36.06% (22/61) and severe (WHO grade 3) in 4.91%(3/61) patients. Renal toxicity, reflected by an increase in serum creatinine levels occurred in 6.6% (4/61) of patients (WHO grade 1) (Table 5). These latter side effects were often transient and not serious enough to interrupt treatment. Four patients died (5.8%) (4/68) in the study. Treatment adherence was 74% (37/50), with compliance problems due to either side effects, or postponing or missing medical appointments, observed in only 14 patients.

Discussion

Treatment Efficacy

Clinical symptoms, morbidity and mortality: The introduction of combination ART has led to significant reductions in morbidity and mortality associated with HIV infections [11]. Clinical symptoms, including diarrhea, cough, and fever have been reduced dramatically. Hammer et al. [12] reported a progressive reduction of clinical symptoms within 6 months of ART. Their results are in line witch our data .Another interesting parameters is weight gain (improvement of general health status).In our study we noted an average weight gain of 7.6 kg per patients. In the Nigeria study, Idigbe *et al.* also noted an average patient weight gain of 4.8kg after 12 weeks of ART [5]. Mortality is another big problem. The higher mortality in low-income countries during the first months of ART (6.4%) compared with those in Europe and North America was only partly explained by the lower CD4 cell counts and more advanced clinical stage. Co-morbidities that are present in many patients starting HAART in resource-poor settings, including tuberculosis and invasive bacterial and fungal infections, might have increased mortality, [13] considering that access to prophylaxis, diagnostic facilities, and effective treatment for opportunistic infections is often limited. Immune responses might also be a problem, particularly for tuberculosis [14]. During our study, four deaths (5.8% of patients) occurred within the first month of treatment. Both patients' general health had deteriorated and their CD4 cell counts had dropped dramatically. It's important to note that in our cohort, patient with tuberculosis was excluded.

This mortality was acceptable compared to others similar studies. For example Laurent et al. reported five deaths at the beginning of treatment, amounting to 8% of the overall patient population [15]. The explanation of an acceptable mortality in our study is the fact that the treatment was introduced in an infectious diseases department, as prophylaxis against opportunist infection was also made.

Biological parameters and Viro-immunological efficacy: Several studies from North America and Europe [16-20], showed that anaemia in HIV-infected patients is associated with higher rates of disease progression and death, independently of the CD4 cell count and other prognostic factors. Studies from Ethiopia [20] and Asia [21] have also confirmed this association. In our study anaemia was present in 59.2% and statistically improved after treatment.

Chêne et al. in their study observed that adjusted hazard ratios for AIDS or death were high in patients with low CD4 cells count and high viral load compared to patient with high CD4 cells count and low viral load after six months of treatment (0.55 and 0.59 versus 0.18 and 0.29). Baseline CD4 and HIV-1 RNA were not associated with progression after controlling for 6-month concentrations [22]. These results showed the importance of improving CD4 cells count and reducing viral load despite low initial parameters. After 24 weeks of treatment in our cohort, the viro-immunlogical status of our patient was improved. These results are encouraging and in line with those of Laurent et al. in their study performed in Cameroon with a gain of 83 CD4 at 24 weeks [23].

Treatment safety

Recently, reports have linked the use of NNRTIs, such as NVP and efavirenz, with the development of skin rash and hepatotoxicity [24]. There is particular concern about infected patients co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV), because the progression of liver disease is accelerated in these patients [25].

Skin rash: In their study Kumarasamy et al found that skin rash represented 66% of side effects and side effects was the most common reason for modifying therapy [26]. In our study, this side effect was presents in 7.35% (5/68) of our patients. Of note is that five patients discontinued their treatment due to NVP-related dermatological side effects (WHO grade 3). In an efficacy and tolerance study of Triomune® conducted in Thailand, Anekthananon et al. observed skin rashes in 12% of patients after 24 weeks of treatment [27]. Mouhari-Toure et al. noted that 9% of patients presented dermatological side effects in Togo [28].

Neurological involment: Peripheral neuropathy is the most common HIV-related neurologic disorder in the HAART and Pre-HAART era and has been studied as an important complication of HIV since the onset of the AIDS epidemic [29]. Kumarasamy et al, found that D4T was significantly associated with developing peripheral neuropathy [26]. Some factors can be contribute to the aggravation of toxicities (alcohol, others substance abuse). Peripheral neurological pathologies represented in our study 18% (9/50) at after 24 weeks. They are responsible for many stopping over 10% during the treatment. These safety results are comparable to those obtained by Montessori et al. [30] and Mouhari-Toure et al. [28].

Liver toxicity: Clinical studies have indicated that grade 3 (ALT and/or AST levels >5 times the ULN) and grade 4 (ALT and/or AST levels >10 times the ULN) hepatotoxicity is observed in 5 % –10% of HIV-positive patients treated with combination ART for >6 months [24]. Although abnormal laboratory transaminase levels are common in these patients, there is a perception that serious clinical hepatic events are more frequent during treatment with NNRTI-based regimens than NRTI- or PI-based regimes. Reisler et al. [31] in a meta-analysis of laboratory data and mortality from 21 clinical studies conducted between 1991 and 2000,observed that the overall incidence of severe hepatotoxicity, defined as increases in ALT or AST levels to >5 times the ULN, was 6.2% (95% CI, 5.7–6.7%). This was not the case in our study where 4.91% of our patients presented an severe increased ALT level (WHO grade 3). Anekthananon et al. reported hepatic toxicity of grade 3 or 4 in 7% of patients after 24 weeks of treatment with Triomune® [28].

Adherence: Crucial among determinants of effective therapy, is a patient's level of adherence to the antiretroviral regimen. Factors that have an impact on adherence include characteristics of the treatment regimen, of patients and clinicians, and of the clinical setting. The simplification of current antiviral regimens, without the loss of potency, is essential to achieving the goal of complete adherence. In our study, treatment adherence was not enough (74%). These results are similar to those obtained by (Nachega et al. (13% -73%) and Mahy et al. (80%) [32,33] and those obtained by Sylla et al. in paediatric patients at Bamako, Sylla et al. [34] 71,2% at six months and 79,6% at 12 months).

Study limitations were technical problems, such non-attendance, and limit time of investigation (24 weeks, financial limitations). Despite these limitations, the study allowed us to gain insights into the efficacy, safety and pharmacovigilance of the first-line HIV medication used in Mali.

Conclusion

This study suggests that "Triomune®", use may lead to many sides effects at any time during the first 24 weeks. Despite the efficacy of Triomune, our data support the national policy in Mali which is recommending withdrawing this fixe dose combination from first line HIV therapy.

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Authors' Contributions

OAA, DS, DA wrote the proposal, secured the funding and organized the data collection. MA and MAI investigated the study. FS supervised the study. YJC analyzed and interpreted the data. OAA, DS, DA and YJC developed the manuscript. All of the authors read and approved the final manuscript.

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