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Clinical Efficacy of Artemether-Lumefantrine Artesunate-Amodiaquine of Children from Three Chadian Provinces with Acute of Uncomplicated *Falciparum malariae* from 6 Months to 5 Years

Issa Ramat Adam[1,2], Nack Jacques[2], Hamit Mahamat Alio[1,3*], Akono Ntonga Patrick[2], Abakar Idriss Lawane[1], Mahamat Ali Bolti[1,3]

[1]Laboratory of Medical Parasitology and Mycology, Faculty of Health and Human Sciences, University of N'Djamena, N'Djamena, Chad
[2]Laboratory of Animal Biology, University of Douala, Douala, Cameroon
[3]Renaissance University Teaching Hospital, N'Djamena, Chad
Email: *hamitalio@yahoo.fr, *hamitalio@gmail.com

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Abstract

Introduction: Artemisinin-based combination therapies are the first-line antimalarial drugs used to treat uncomplicated *Plasmodium falciparum* malaria in many endemic countries worldwide. In Chad, since the adoption of artemisinin-based combination therapy (ACTs) in its first-line treatment policy for uncomplicated malaria in 2005, Artemether-Lumefantrine and Artesunate-Amodiaquine have been used in many hospitals and health centers. The main objective of this study was to provide the baseline data of Artemether-Lumefantrine and Artesunate-Amodiaquine efficacy in three regions where many people suffered from malaria disease. **Material and Methods:** The baseline efficacy of two combination therapies was evaluated between January and April 2020 in Mosoro, Mondou and Dourbali Provinces in Chad. A two-arm single cohort study was conducted to assess the clinical efficacy of artesunate-amodiaquine and artemether-lumefantrine for the treatment of 1113 children aged from 6 to 59 months with uncomplicated *Falciparum malariae* diagnosed by thick blood smear examination, using the World Health Organization validated protocol. **Results:** On day 3, all patients in both groups had cleared parasitemia, after treatment, the patients presented a higher hemoglobin level in both groups artemether-lumefantrine (10.97 ± 1.39) and artesunate-amodiaquine (11.87 ± 1.81), respectively. On day 28, all patients had adequate clinical and parasitological responses with 99.82% of

artesunate-amodiaquine and 99.10% of artemether-lumefantrine. Overall, both drugs were well tolerated at the clinical and biological level, no late parasitological failures have been recorded in artemether-lumefantrine and artesunate-amodiaquine groups, also both forms of Artemisinin-based combination therapy were still effective and safe in the treatment of uncomplicated *P. falciparum* malaria in Chad.

Keywords

Plasmodium falciparum, Artemeter-Lumefantrine, Artesunate-Amodiaquine, Efficacy, Parasitological Density, Hemoglobin Levels

1. Introduction

Malaria is widespread in tropical areas worldwide and causes high morbidity. The emergence of parasite resistance to antimalarial medicines constitutes a challenge impeding countries' abilities to advance towards elimination; these include lack of sustainable funding, risks posed by conflict in malaria endemic zones, and mosquito resistance to insecticides [1]. It is estimated that there were 229 million clinical cases of malaria and around 409,000 deaths in 2019, of which nearly 67% were children aged from 0 to 59 months [2]. Almost 85% of malaria deaths worldwide in 2018 were concentrated in 20 countries in Africa region and India. Nigeria alone accounted for nearly 24% of these deaths, followed by the Democratic Republic of Congo (11%), the United Republic of Tanzania (5%), as well as Angola, Mozambique and Niger (4%) each. It is estimated that nearly 24 million children in sub-Saharan Africa suffered from *P. falciparum* malaria infections in 2018. In Chad, malaria causes a serious health problem that represents 42% of first consultation cases in different health centers, 39% of hospitalization and 32% of death cases [3].

To reduce malaria-related morbidity and mortality, Artemisinin Combination Therapies (ACTs) have been integrated into the recent success of global malaria control, and protecting their efficacy for the treatment of *P. falciparum* malaria is a global health priority. In Chad, antimalarial treatment for uncomplicated *falciparum malaria* is based on ACTs in accordance with the World Health Organization recommendation for regions with resistance to antimalarials. The majority of the studies analyzing efficacy of this antimalarial regimen are conducted in high transmission regions, and selection of mutations that could possibly confer *P. falciparum* resistance to ACT has been reported both in vivo and ex-vivo by [4] [5]. The advice for government health programs is to closely monitor parasite genotypic, phenotypic and clinical dynamics of *P. falciparum* infections in response to ACTs, despite its continued efficacy.

Due to the high levels of clinical resistance to chloroquine, amodiaquine, and sulphadoxine-pyrimethamine, the Chadian Ministry of Public Health changed the national antimalarial drug policy in 2005. Two Artemisinin-based Combina-

tion Therapies (ACTs) were adopted: Artesunate-Amodiaquine and Artemether-Lumefantrine for the first-line and second-line treatment of uncomplicated malaria. The criteria used to select subjects for an antimalarial drug efficacy trial define the study population and can impact treatment outcomes and study results. For example, in endemic areas, increasing age is associated with greater antimalarial immunity and improved therapeutic response [4] [6] and a higher parasite burden at the time of treatment may be associated with less favourable outcomes [7]. The WHO recommended that patient selection criteria are restrictive, and do not cover the full range of patients with uncomplicated malaria. In practice, the criteria used to enroll patients into antimalarial drug efficacy studies often vary with respect to age, parasite density, and baseline [8].

2. Material and Method

2.1. Study Area

The present study took place from January to April 2020 in three provinces of Chad; the main objective of this study was to provide the baseline data of Artemether-Lumefantrine (AL) and Artesunate-Amodiaquine (ASAQ) efficacy in three regions where much people suffered from malaria disease. Febrile children aged between 6 months and 5 years were enrolled after a written informed consent was obtained from the parents or the legal guardian.

2.2. Study Procedures

Patients with malaria-like symptoms were received at selected hospitals. Meticulous clinical examinations of the patients and laboratory investigations were conducted immediately after inclusion. Patients who met baseline inclusion criteria were randomly assigned to one of the two treatment groups. Drug administration was supervised by a member of the research team and patients were kept under observation. After the initial dose, patients had a follow-up within 28 days. Each patient was scheduled for follow-up examinations on day 0, 1, 2, 3, 7, 14, 21, 28, any other time the participant felt unwell during the study period will be treated. During the visit day, the following information was collected: 1) clinical data, 2) biological data (diagnosis of malaria and determination of parasitemia), 3) any details about drug adverse events. In case of treatment failure, the placement therapy was offered according to the national treatment guidelines.

2.3. Procedures during Inclusion and Follow-Up

After obtaining the informed written consent, a complete medical history (symptoms, current medications and previous use of anti-malarial drugs), biographic and contact details were noted. A complete physical examination was performed and a case record form was filled in for each patient. Body weight was recorded at day 0; temperature was recorded using a thermometer with a precision of 0.1˚C at baseline and on follow-up days, and additionally measured as

clinically indicated. On each follow-up, clinical signs and symptoms were registered, including symptoms such as fever, headache and abdominal pain; blood have been drowned from vain and conserved put it in EDTA tube for hemoglobin test, blood smears were also performed to detect malaria parasites. During the study period, all male and female patients aged 6 to 59 months inclusive, with fever (axillary temperature ≥ 37.5˚C) or history of fever in the last 24 h, visiting the peripheral health centers of Massakory, Dourbali or Mondo health districts. Children weighing less than 5 kg or more, with a confirmed *P. falciparum* (parasitaemia ≥ 4000/µL to 200,000/µL) mono-infection, hemoglobin level above 5.0 g/dl, and agreed to participate whenever applicable by giving their assent and if their parents or guardian provided written informed consent. Patients were not included if they were not willing to participate or had participated to any drug trial within the last 30 days, or had known hypersensitivity to the study drug, or were severely malnourished (defined as weight for height < 70% of the median NCHS/WHO reference), or had severe malaria.

2.4. Laboratory Analysis

Microscopic blood examination and quality control. Thick and thin blood films were prepared and stained with Giemsa for screening and subsequent species diagnosis and parasitemia calculation on days 0, 1, 2, 3, 7, 14, 21 and 28 or if reassessment was required. Parasite counts were done on thick films and the number of parasites per 200 white blood cells (WBCs) were counted by light microscopy. Parasite density, expressed as the number of asexual parasites per µL of blood, was calculated by dividing the number of asexual parasites by the number of WBCs counted, and then multiplying it by an assumed WBC density of typically 8000 per µL. A blood-slide sample was considered negative when examination of 200 fields containing at least ten WBCs per field revealed no asexual parasites. The presence of gametocytes on the day the patient was enrolled or on the day of follow up was also recorded.

2.5. Hemoglobin and Antimalarial Drug Blood Concentration

Hemoglobin was determined on days 0 and 28 in 10 µL of capillary blood sample with the HemoCue blood Hemoglobin system. Specimens were be labeled anonymously (study number, day of follow-up, date).

2.6. Follow-Up and Loss

Follow-up visits and procedures were scheduled per protocol on days 1, 2, 3, 7, 14, 21, and 28. Patients were allowed to return to hospital at any time if they had fever or any general danger signs as described under exclusion criteria. The study team made home visits as follow-ups for study participants that were late for their scheduled visits. Patients who failed to return on days 1 or 2 and missed one dose of the treatment or enrolled patients who could not attend scheduled visits were considered lost to follow-up and excluded from study.

2.7. Ethical Considerations

The study protocol was reviewed and approved by the National Malaria Control Program (NMCP) in Chad. Written consent was obtained from the children's parents before entering the study. The study was conducted according to the WHO good clinical practices guidelines and according to the Chadian ministry of health regulations.

2.8. Statistical Analysis

All data were recorded using IBM SPSS Statistics, version 25, comparisons of different parameters in both arms were done using, Fisher's exact test. The level of significance for statistical tests was set at 0.05.

3. Results

3.1. Baseline Characteristics of Participants

During the study period, 1113 patients were screened and treated with either AL or ASAQ for twenty eight days. About 50.31% of the participants treated with AL and 51.21% treated with ASAQ. The mean of parasitemia was 11720.24 with the interval of 2000.200000 and 17834.84 with the interval of 2000.200000 respectively in AL and ASAQ groups. Other characteristics were described in (Table 1).

3.2. Efficacy Results

On day 0, parasitemia was identified in 28 patients in AL groups, with a mean of parasite load of 11,720 parasites/µl and 27 patients in ASAQ groups with a mean of parasite load of 9534 parasites/µl; eleven patients were positive on day 1, with a mean of 3063.38 parasites in AL groups and 144 patients with a mean of 1782.02 in ASAQ groups (Table 2). On day 3, all patients in both two groups had cleared parasitemia. An adequate clinical and parasitological response, defined by a negative thick blood smear on day 28, was found in ASAQ and AL treatments were 99.82% and 99.10% on day 28 respectively, and no late parasitological failures were detected in two groups of treatments and no serious adverse events were registered, on other hand 2 (0.36) and 1(0.17) of patients had en earlier treatment failure in both groups AL and **ASAQ** (Table 2).

The study showed that Patients presented a lower hemoglobin level in AL groups (7.64 ± 1.89) and (8.11 ± 1.77) in ASAQ groups in day 0, (8.88 ± 1.91) and 9.38 ± 1.11 in day 7, but in day 28 after treatment the patients presented a higher hemoglobin level in both groups AL (10.97 ± 1.39) and ASAQ (11.87 ± 1.81) respectively (Table 3).

4. Discussion

Clinical response to antimalarial therapy involves a complex interaction between the parasites, drugs and the host response; *In vivo* tests are considered the gold standard method of measuring antimalarial drug resistance [9]. Host immunity

Table 1. Demographic and clinical characteristics of patients.

Characteristics	AL	ASAQ
Sexe	**n (%)**	**n (%)**
Masculin	320 (57.15)	320 (56.14)
Feminin	240 (42.85)	250 (43.85)
Total	**560 (100)**	**570 (100)**
Age (months)		
mean	4.33	3.70
interval	0.5	0.4
Weight		
mean	15.26	13.13
interval	7.55	6.42
Temperature ˚C		
mean	38.66	38.55
interval	37.50 - 40.50	35.60 - 40.80
Parasitemia		
mean	11720.24	17834.84
Interval	2000.20000	2000.200000
Symptoms	**n (%)**	**n (%)**
Anorexia	70 (12.5)	75 (13.5%)
Asthenia	41 (7.32%)	61 (10.70%)
Vomiting	62 (11.07%)	80 (14.03%)
Cephalea	105 (18.75%)	114 (20%)
Cough	80 (14.28%)	90 (15.78%)
Abdominal pain	202 (36.07%)	150 (26.31%)
Total	**560**	**570**

Legend: AL = Arthemether lumefantrine; ASAQ = Artesunate-Amodiaquine; n = Number of population examinated; (%) = Parcentage.

Table 2. Treatment outcomes at 28 days in 1113 patients.

Treatment out comes	Thick blood film	
	AL n (%)	ASAQ n (%)
	n (%)	n (%)
ETF	2 (0.36)	1 (0.17)
ECF	1 (0.17)	0 (0.00)
LPF	2 (0.35)	0 (0.00)
ACPR	**555 (99.10)**	**569 (99.82)**
Total	560 (100.00)	570 (100.00)

Legend: ETF = Earlier treatment failure; ECF = Earlier clinical failure, LPF: Late parasitological failure; ACPR = Adequate clinical and parasitological responses; n = Number of population ex-aminated; (%) = Parcentage

Table 3. Patients distribution according to hemoglobin rate variations.

Treatment groups	D0	D7	D14	D28
AL	7.64 ± 1.89	8.88 ± 1.91	8.39 ± 3.56	10.97 ± 1.39
ASAQ	8.11 ± 1.77	9.38 ± 1.11	9.47 ± 2.56	11.87 ± 1.81
P	0.101	0.043	0.0033	0.774

Legend: AL = Arthemether lumefantrine; ASAQ = Artesunate-Amodiaquine,; P = p value; D0 = day 0; D7 = seven days; D14 = fourteen days; D28 = twenty eight days.

plays a critical role in the clearance of malarial parasites. For example, the ability of monocytes to kill intracellular parasites is a function of antibody-dependent mechanisms [10]. The production of specific antibodies has been associated with protection against clinical attacks of malaria. Acquired antimalarial immunity develops following repeated exposure to infecting parasites [11]. The objective of this study was to provide the baseline data of Artemether-Lumefantrine and Artesunate-Amodiaquine efficacy in three regions where much people suffered from malaria disease. The AL and ASAQ appeared to be a better treatment option on the basis of non-PCR-corrected responses, based on the lower percentage of recurrent parasitaemia observed. The results showed a high cure rate for both regimens after a standard 28-day follow-up with an ACPR rate adjusted by 99.82% in ASAQ and 99.10% in AL. This is consistent with efficacy results reported from several studies of [12], in Cameroon and [13] in Ghana, the fact that there was more reinfection than recrudescence shows that malaria transmission is high in all three study sites, indeed in Chad, malaria is perennial with a peak during rainy seasons in three sites. Our study found that the cure treatment rate of ASAQ was superior to AL during 28 days of observation, same results reported by [14] in Bourkina faso who noted the higher rate of ACPR in ASAQ group. Also this result is different from the result of [15] [16] [17] who compared ASAQ with AL over a follow-up duration of 28 days and demonstrated a lower reinfection rate for AL, and found that AL was superior to ASAQ in preventing new infections. In the present study on day 3, all patients in two groups had cleared parasitemia with an adequate clinical and parasitological response defined by a negative thick blood smear on day 28, no late parasitological failures were detected in two groups of treatments and no serious adverse events were registered. This finding is consistent with the study of [18] [19] in which no serious adverse effects were reported, and that could be explained by the higher efficacy of combination treatment for decreasing the gametocyte rate during the treatment with ACTs and therefore leads to a significant reduction in the spread of resistance. The clinical tolerance was good with minor adverse events in both treatment groups confirming previous studies such as [12]. In this study, a progressive haematological improvement was observed from baseline to day 28 between the two treatment groups; however, patients from ASAQ group had relatively higher Hb at enrolment which was maintained throughout the follow-up.

Higher mean Hb in ASAQ than AL might be attributed to differences in nutritional status and other conditions associated with anaemia such as concurrent infections [20]. It could also be due to differences in age, since patients enrolled in ASAQ had significantly higher mean age compared to AL (4.33 vs 3.77 years for ASAQ and AL, respectively). Improvements in Hb during follow-up could suggest that malaria might be a major contributing factor to the low haemoglobin levels and anaemia at recruitment as reported in other studies done in Tanzania by [21], and elsewhere in sub-Saharan Africa by [22] [23]. On the other hand, this result was confirmed by [24] in Ivory Coast who noted in his study that the patients of two groups of treatment had a higher average of hemoglobin level on day 28 after treatment, and that could be explained by the efficacy of the combination treatment in two groups. This study was limited by the lack of PCR correction to distinguish true recrudescence with new infection and the limited follow up period of 28 days for these ACTs; nonetheless, the results obtained are of great relevance since it described the real time behavior of the drugs in term of efficacy and tolerability and the late occurrence of the failures were in line with clinical trial previously reports; the time limit of follow up to 28 days may have contributed to underestimate the failures but has the advantage to reduce the risk of new infection. More generally, these ACTs (AL and ASAQ) retained a certain efficacy in the treatment of uncomplicated malaria; however, some studies such as [25] [26] reported an efficacy level of AL during 28 days follow up below the threshold set for the ACTs adopted; for all these studies, PCR corrected outcomes were above 90% success. More than scientific interest or intrinsic efficacy of the drugs, it is questionable to whether ACTs real life efficacy should be based on the PCR corrected results or the uncorrected one or a combination of the two approaches. It may be time to initiate the discussion on current first line drugs replacement and investigate to which extend retrieved drugs (non ACT drugs like chloroquine) could be given a new life for the treatment of malaria [27].

5. Conclusion

During this study, ASAQ and AL were effective and well-tolerated in the treatment of uncomplicated *falciparum* malaria. Therefore, this result supports the continued use of these ACTs in the management of malaria with added advantage provided in public health facilities in slowing the spread of malaria drug resistance and of global reduction or elimination of malaria in Chad.

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Author's Contribution

All authors contributed to the conduct of this work and to the drafting of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

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