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Artemether-Lumefantrine in the Treatment of Uncomplicated *Plasmodium falciparum* Malaria: Insights from the Clinical Evaluation of Two Generic Drugs: Artefan® and Coartem® in Côte d'Ivoire from 2018 to 2019

Yapo Thomas Aba[1,2], Kalou Dibert Zika[3], Martine Tatiana Yapo[1], Serge Brice Assi[2,4], Offianan Touré[2,5], Jean-Marie Karidioula[1], Tiacoh Landry N'Guessan[5], N'guetta Didier Kanga[5], Emmanuel Bissagnené[2]

[1]Infectious and Tropical Diseases Department, Alassane Ouattara Université, Bouaké, Côte d'Ivoire
[2]Scientific Group Supporting National Malaria Control Program, Abidjan, Côte d'Ivoire
[3]Parasitology and Mycology Department, Alassane Ouattara Université, Bouaké, Côte d'Ivoire
[4]Pierre Richet Institute, Bouake, Côte d'Ivoire
[5]Malaria Department, Pasteur Institute, Abidjan, Côte d'Ivoire
Email: chefaba@yahoo.fr

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Abstract

Introduction: Healthcare practitioners in Côte d'Ivoire have reported low efficacy rates for the Artemether-Lumefantrine (AL) combination in treating uncomplicated malaria. This study aims to compare the therapeutic responses of two generic formulations of this antimalarial agent, Artéfan® and Coartem®, which have been available in Côte d'Ivoire's healthcare facilities since 2008. **Method:** We conducted a comparative analysis of a bi-centric clinical trial in Côte d'Ivoire, evaluating the therapeutic efficacy of Artéfan® in Daloa and Coartem® in Ayamé between 2018 and 2019, following the WHO's 42-day protocol. The primary evaluation metric was the Adequate Clinical and Parasitological Response (ACPR) at day 42 (D42) post-PCR correction. **Results**: A total of sixty-two patients were included at each site. The fever clearance time was 24 hours in both Daloa and Ayamé. Parasitic clearance occurred in 48 hours in Daloa and 72 hours in Ayamé. In the per-protocol analysis at D42, the ACPR was 92% in Daloa and 98% in Ayamé, with no significant difference noted ($p = 0.1$). **Conclusion:** Artéfan® and Coartem® exhibited statistically equivalent therapeutic efficacy. Nonetheless, the Artemether-Lumefantrine combination warrants further surveillance due to notable re-infestation rates.

Keywords

Efficacy Artéfan®/Coartem®, *Plasmodium falciparum* Malaria, Côte d'Ivoire

1. Introduction

Despite significant progress in prevention and case management, malaria continues to pose a major public health challenge in sub-Saharan Africa, characterized by high incidence, mortality, and socioeconomic impact, as reported by the World Health Organization (WHO) [1]-[3]. For many years, due to the resistance of *Plasmodium falciparum*, Artemisinin-based Combination Therapies (ACTs) have been utilized for treating uncomplicated malaria. In response to the growing threat of resistance emerging from Southeast Asia [4]-[8], the WHO initiated a global action plan in 2008. This plan aimed to periodically assess the efficacy of ACTs to refine antimalarial treatment policies and strategies in endemic regions [9].

In Côte d'Ivoire, the National Malaria Control Program (NMCP) has endorsed several ACTs, including Artesunate-Amodiaquine (ASAQ), Artemether-Lumefantrine (AL) since 2008 [10], and more recently, Dihydroartemisinin-Piperaquine (DHA-PPQ) and Pyronaridine-Artesunate (Pyramax®) [11], with financial support from the Global Fund [12]. Among these treatments, Artemether-Lumefantrine remains the most frequently prescribed due to its favorable tolerance profile and various galenic formulations. Nevertheless, healthcare providers in public health facilities have expressed concerns about its suboptimal efficacy in routine clinical practice. This study aims to compare the therapeutic outcomes of two generic formulations of this antimalarial, Artefan® and Coartem®, available to public healthcare facilities in Côte d'Ivoire.

2. Materials and Methods

2.1. Study Design

This study involves a retrospective analysis of data from two clinical trials that assessed the Therapeutic Efficacy (TET) of two generic antimalarial drugs. The trials were conducted between November 2018 and February 2019 following the standard 42-day protocol established by the World Health Organization (WHO) [13]. These trials took place in two distinct health districts in Côte d'Ivoire.

2.2. Study Framework and Locations

The studies were conducted in a forested region of Côte d'Ivoire, characterized by intense and year-round malaria transmission. Specifically, they were carried out in the health districts of Daloa and Ayamé. Notably, Daloa, located in the center-west, experiences less rainfall compared to Ayamé in the south-east. Both districts are part of the national malaria surveillance sentinel sites under the coordination of the National Malaria Control Program (PNLP). The designated study sites were

the Garage Urban Health Center in Daloa, situated 435 km from Abidjan, and the general hospital in Ayamé, 134 km from Abidjan.

2.3. Study Populations

The study populations consisted of patients aged between 6 months and 65 years, who consulted for suspected uncomplicated malaria, presenting with fever (axillary temperature ≥ 37.5˚C) or a history of fever within the past 24 hours. Inclusion criteria required that patients be capable of oral medication intake, provide informed consent to participate, and adhere to the study protocol. Participants had a mono-specific infection with *Plasmodium falciparum* confirmed by microscopy (GE/FS), with a parasitic density (Dp) ranging from 2000 to 200,000 trophozoites/µL of blood, and did not meet the WHO criteria for severe malaria [13].

Exclusion criteria included breastfeeding women, pregnant women or those suspected of being pregnant, patients requiring intensive care for severe conditions, particularly severe malaria, those on antibiotics potentially interfering with the studied antimalarials, individuals who had previously taken antimalarials prior to hospital admission, and those with known allergies to the antimalarials under investigation.

Additionally, withdrawal criteria from the study included withdrawal of consent, voluntary or involuntary non-compliance with the study protocol, occurrence of intercurrent diseases, occurrence of serious adverse events, loss to follow-up, and potential death.

The required sample size at each study site was estimated to be at least 60 patients who met the inclusion criteria, accounting for a 10% rate of loss to follow-up and non-inclusion. The sample size calculation was based on WHO recommendations for evaluating antimalarial efficacy [13].

2.4. Survey Procedure

The drug under evaluation was Artemether-Lumefantrine, marketed under the generic names "Artefan®" by Pharma Laboratory at the Daloa site and "Coartem®" by Novartis Laboratory at the Ayamé site. These medications were available in the form of co-formulated tablets containing 20 mg of Artemether and 120 mg of Lumefantrine. The treatment regimen spanned three consecutive days. The dosage was determined based on body weight: 1 tablet every 12 hours for children weighing 5 to 14 kg, 2 tablets every 12 hours for individuals weighing 15 to 24 kg, 3 tablets every 12 hours for individuals weighing 25 to 34 kg, and 4 tablets every 12 hours for individuals over 35 kg. As per the manufacturers' guidelines, these generics must be administered with lipid-rich foods to enhance digestive absorption, a protocol consistently reiterated to patients during evaluations.

Patients received clinical monitoring for 42 days following the schedule "D0, D1, D2, D3, D7, D14, D21, D28, D35, and D42," where D0 denotes the day of enrollment and initiation of antimalarial treatment. During each visit, clinical examinations were conducted to assess the treatment's clinical efficacy (including

symptom progression and fever clearance), patient adherence, and detection of adverse events. Biological follow-up included monitoring hemoglobin concentration (GE/FS), parasitic density, and parasitic clearance. Blood samples were collected on filter paper (confetti) at D0 and between D7 and D42 from patients with a positive thick blood smear, enabling PCR analysis to distinguish between reinfection and recrudescence.

The primary outcome measure was the Adequate Clinical and Parasitological Response (ACPR) on Day 42 following PCR correction. Secondary outcomes included fever clearance and parasitic clearance.

2.5. Ethical and Regulatory Considerations

This study was carried out in accordance with the Helsinki Declarations. Both studies were undertaken following the approval of the National Ethics Committee for Life and Health Sciences (Letter No. 056-18/MSHP/CNER-kp). Written informed consent was obtained from each participant or their legal guardian, and assent was secured from all minor participants aged 10 to 17 prior to enrollment. Insurance was provided to cover civil liability. Confidentiality was maintained through the use of an appropriate coding system.

2.6. Statistical Analysis

The data collected were analyzed using Epi-Info software version 7.1. The Primary Endpoint Response Rate (PERR) was examined using both the Intention to Treat (ITT) approach, which includes all patients who received at least one dose of treatment, and the Per Protocol (PP) approach, which includes only those patients who completed the study in full compliance with the protocol and for whom all required evaluations were performed and data for the primary endpoint were available.

3. Results

3.1. Evaluation Conditions

The efficacy of Artéfan® was assessed in Daloa among 62 patients, while Coartem® was evaluated in Ayamé with the same number of patients, all diagnosed with uncomplicated *P. falciparum* malaria. The conditions for evaluation were consistent across both sites, shown by the equal number of patients enrolled ($n = 62$) and similar proportions of patients relative to the total number seen in consultations (19% in Daloa vs. 17% in Ayamé, $p = 0.60$). No informed consent withdrawals were noted post-treatment initiation. Throughout the 42-day follow-up, five violations of the study protocol were observed and excluded from the analysis: two from Daloa and three from Ayamé (3% vs. 5%, $p = 1$).

3.2. Epidemiological, Clinical, and Parasitological Data (Table 1)

Excluding the significantly higher parasite density among patients in Ayamé (20,325 vs. 58,763, $p < 0.05$), the other characteristics were equivalent, including

gender distribution (p = 0.28), average weight (p > 0.05), and fever presence at admission (97% in both sites, p = 1). Although the proportion of children was higher in Ayamé (74% in Daloa vs. 87% in Ayamé, p = 0.11), this difference did not reach statistical significance.

For febrile patients upon admission, temperatures ranged from 39˚C to 37.6˚C at both locations, with averages of 38.7˚C (±11.5˚C) in Daloa and 38.8˚C (±11.5˚C) in Ayamé. Symptoms such as headaches, asthenia, anorexia, and vomiting were recorded with similar overall frequencies at both sites (43% in Daloa vs. 42% in Ayamé, p = 0.89).

Table 1. Characteristics of patients at inclusion on D0.

Features	Daloa N = 62	Ayamé N = 62	OR	IC	P
Male **Female**	35 (56%) 27 (44%)	28 (45%) 34 (54%)	1.57	0.77 - 3.19	0.20
Age ≤ 15 Years **Age > 15 Years**	46 (74%) 16 (26%)	54 (87%) 8 (13%)	0.43	0.16 - 1.08	0.06
Patients with fever **Apyretic patients**	60 (97%) 2 (3%)	60 (97%) 2 (3%)	1.00	0.13 - 7.33	1.00
Average weight (kg)	29 ± 16.9	29 ± 17.1			>0.05
Average Dp (tzp/µL)	20,325 (±26,355)	58,763 (±64,159)			<0.05

3.3. Therapeutic Efficacy

3.3.1. Clinical and Parasitological Efficacy

In Daloa, the thermal clearance was achieved within 24 hours, and parasitic clearance occurred within 48 hours. In contrast, at Ayamé, thermal clearance was similarly achieved within 24 hours, but parasitic clearance was extended to 72 hours since two patients retained parasites 48 hours post-antimalarial treatment. Nonetheless, the delay in parasitological response in Ayamé was not statistically significant compared to the response observed in Daloa (p = 0.292) Table 2.

Table 2. Parasite clearance in 48 hours.

Parasite clearance before 48 hours	Daloa (N = 62)	Ayamé (N = 62)	OR	IC	P-value
Oui	62 (100%)	60 (96.8%)	5.16	0.24 - 109.82	0.292
Non	00 (0%)	02 (3.2%)			

3.3.2. Adequate Clinical and Parasitological Response (ACPR) at Day 42

Instances of late therapeutic failure were observed between days 7 and 42, characterized by fever and positive results in thick and thin blood smear examinations during patient follow-up.

At day 42, on an intention-to-treat basis, the ACPR without PCR adjustment was **75**% in Daloa compared to **81**% in Ayamé. After adjusting with PCR, the rates

were 97% vs 95%, with no significant differences (Table 3).

Table 3. Intent-to-treat therapeutic responses at D42.

Patients at D42	Daloa (N = 60)	Ayamé (N = 59)	OR	IC	P-value
Failure without PCR RCPA without PCR	15 (25%) 45 (75%)	11 (19%) 48 (81%)	1.45	0.6 - 3.49	0.4015
Failure after PCR RCPAafter PCR	2 (3%) 58 (97%)	3 (5%) 56 (95%)	0.87	0.14 - 5.26	0.8783

In the per-protocol analysis, the RCPA without PCR correction was 75% in Daloa compared to 86% in Ayamé (Table 4).

Table 4. Therapeutic responses at D42 in per-protocol analysis.

Patients at D42	Daloa (N = 60)	Ayamé (N = 59)	OR	IC	P-value
Failure without PCR RCPA without PCR	15 (25%) 45 (75%)	8 (14%) 51 (86%)	2.13	0.82 - 5.47	0.1140
Failure after PCR RCPA after PCR	5 (8%) 55 (92%)	1 (2%) 58 (98%)	5.27	0.59 - 46.57	0.0980

Overall, concerning the primary outcome measure, the ACPR was 92% in Daloa and 98% in Ayamé following PCR correction, with no statistically significant difference: this demonstrates that the efficacy of the two compounds is identical at both sites (Table 4).

4. Discussion

The study juxtaposed the assessments of two generics of Artemether-Lumefantrine across two distinct geographical locations, adhering to WHO recommendations [13] and PNLP directives [11]. Within this framework of ACT efficacy monitoring, open-label trials without comparators, small sample sizes, and the WHO 28 or 42-day protocol were permitted [13]. This analysis aimed to determine whether the clinical, parasitological, and molecular deficiencies attributed to the Artemether-Lumefantrine available to health practitioners in public health facilities were genuine, and if they were associated with either of the commercial brands (Artefan® vs Coartem®) of this molecule.

Epidemiologically and clinically, the evaluation conditions for AL were consistent across both sites, including the number of patients enrolled, follow-up loss rates, the number of patients assessed up to day 42, as well as patient distributions by gender, age, body weight, and clinical symptoms. In both Daloa and Ayamé, holoendemic *P. falciparum* malaria predominates among individuals under 15 years of age, with elevated parasitic densities during the rainy seasons and a high prevalence among children under five years old [14].

The clinical efficacy of the two AL generics is comparable with respect to the

estimated thermal clearance at 24 hours in both locations. However, the parasitic clearance rates differ, being 48 hours in Daloa and 72 hours in Ayamé. Although this difference in the time required for parasite elimination is not statistically significant, it may suggest the slower action of Coartem® when faced with a higher parasitic density than that noted in Daloa. This could potentially indicate treatment failures, but this is not the case since Coartem® is associated with a lower failure rate (13%) compared to its competitor (25%). Additionally, in the per-protocol analysis at day 42, the primary efficacy endpoint (RCPA post-PCR) is 92% in Daloa and 98% in Ayamé.

The parasitological efficacy of the two AL formulations remains strong in Côte d'Ivoire. The emergence of resistance to artemisinin derivatives, first described in Southeast Asia in 2008, was identified through PCR, which distinguishes between reinfections and recrudescences [5] [7]-[9]. While PCR is not commonly used in routine malaria diagnosis in Africa, it is valuable in clinical studies like ours as it precisely differentiates these occurrences [15]. Resistance to antimalarial drugs significantly impacts public health, increasing the risk of patient mortality through therapeutic failures. Moreover, it raises the financial burden of medical consultations by escalating disease transmission rates and the incidence of malaria attacks [11] [12] [15] [16].

Resistance to artemisinin derivatives has been identified in several regions of Asia. By the end of 2013, researchers had pinpointed a molecular marker, the k-13 propeller, associated with delayed parasite clearance both in vitro and in vivo [5] [7] [17]-[21]. Studies by Dondorp *et al.* [18]-[20] demonstrated that ACT resistance manifests through slow parasite clearance, despite adequate plasma levels of artemisinin. Parasites bearing this k-13 propeller gene have been detected globally, including in Africa, where the R562H mutation has been documented in Rwanda, and the 5622I mutation in Eritrea, Ethiopia, and Sudan [22] [23]. However, the emergence and increase of these mutations in Africa have not been linked to reduced ACT efficacy [2]. Like previous studies in Côte d'Ivoire on the therapeutic efficacy of antimalarials [15] [24]-[26], this study did not include resistance gene screening in its methodology. The 8% failure rate reported after PCR correction in Daloa warrants further investigation into resistance genes among patients experiencing treatment failure in Daloa.

5. Conclusion

Artéfan® and Coartem®, two widely prescribed generic formulations of the Artemether-Lumefantrine combination in the health districts of Côte d'Ivoire, exhibit comparable therapeutic efficacy. Therefore, their use remains justified in the management of uncomplicated malaria. Nonetheless, ongoing surveillance is crucial due to their significant reinfestation rates. Additionally, Coartem® warrants closer monitoring owing to its parasitological clearance being at the lower limit of acceptable values. In Daloa, further studies are needed to investigate potential resistance genes that may threaten the future efficacy of ACTs.

Conflicts of Interest

The authors declare no conflicts of interest.

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