Current Efficacy of the First Line Uncomplicated Malaria Treatment in Two Sentinels Sites of Côte d’Ivoire

Offianan Andre Toure1*, N’Guessan Tiacoh Landry1, Ira Bonouman Ama Valerie1, Assi Serge Brice1, Kouame Emmanuel1, Kokora Adonis1, Yao Serge Stephane1, Amata Eric1, Kinifo-Lawson Viviane6, Adjji Eric Gbessi1, Beourou Sylvain1, Tuo Karl1, Ako Ako Aristide Berenger1, Gnonoujui Albert1, Djaman Joseph1,6 and Jambou Ronan1,7

1Unité de Paludologie, Institut Pasteur Côte d’Ivoire, Côte d’Ivoire
2Institut Pierre Richet Bouake/Programme National de lutte contre le Paludisme, Abidjan Côte d’Ivoire, Côte d’Ivoire
3Formation Sanitaire Urbaine à Base Communautaire d’Anonkoua-Kouté Abidjan, Côte d’Ivoire
4Centre de Santé Urbain de Libreville, Man, Côte d’Ivoire
5Département de Biochimie Clinique et Fondamentale, Institut Pasteur Côte d’Ivoire
6Laboratoire de Pharmacodynamie-Biochimique UFR Biosciences, Université Félix Houphouët-Boigny Abidjan, Côte d’Ivoire
7Département de Parasitologie et Insectes vecteurs, Institut Pasteur France, France

Abstract

Background: Artemisinin combination therapies have been wildly used in the treatment of uncomplicated falciparum malaria in most endemic countries. This strategy has been implemented in Côte d’Ivoire since 2005 with Artesunate + Amodiaquine (AS + AQ) and Artemether + lumefantrine (AL). The goal of this study was to assess efficacy and safety of these two drugs in two sentinel’s sites, Man and Abidjan in Côte d’Ivoire.

Methods: An open label, randomized, clinical trial was conducted in Man in the west and Abidjan in the south of Côte d’Ivoire. Patients older than 6 months with uncomplicated falciparum malaria after consent were randomized in AS+AQ and AL group and were followed up for 42 days.

The first endpoint was Adequate Clinical and Parasitological Response adjusted by PCR at day 42. The second endpoints were fever and parasite clearance time, crude cure rate at day 42 and safety of the two ACTs.

Results: A total of 241 patients were randomized in AS+AQ (120) and AL (121) group. The crude cure rate at day 42 in PP analysis was 95.8% and 87.9% in AS+AQ and AL respectively. After correction by PCR ACPR at day 42 was 99.2% in AS+AQ group and 97.4% in AL group. The two ACTs were well tolerated.

Conclusion: AS+AQ and AL remains efficacious in the uncomplicated malaria treatment in the two areas but continue monitoring is needed particularly for AL.

Background

Malaria remains a major public health problem instead of many strategies developed by WHO and his partners to control and eliminate this disease. In malaria endemic Sub-Saharan countries pregnant women and children under-five years are a high risk of malaria and death. Malaria control programs currently comprise integrated interventions, including vector control with use of mosquito nets and spraying with insecticides, Intermittent Preventive Treatment in pregnancy (IPT), early diagnosis and effective treatment of clinical cases [1]. Artemisinin Combination Therapy (ACT) associated with others control and elimination strategies are contributed to reduced malaria morbidity and mortality. But emergence and extension of resistance to artemisinins derivatives in South East Asia could counteract these benefits [1]. Currently, Artemether + Lumefantrine (AL) and Artesunate + Amodiaquine (AS-AQ) are the widely available drugs, which are recommended by most malaria endemic countries in the treatment of uncomplicated falciparum malaria [2]. Monitoring of artemisinin-based combination therapy (ACT) becomes particularly important in the light of emergence of artemisinin resistance in South-East Asia [3,4].

The World Health Organization (WHO) recommends that the efficacy of the first and second-line antimalarial drugs be regularly assessed for early detection and prevention of spread of resistant parasite populations every two years [5].

Surveillance of artemisinin resistance to date has relied on in vivo studies to measure early clearance of peripheral parasitaemia by microscopy and k13 propeller gene mutations [6]. In Côte d’Ivoire, AS + AQ and AL have been recommended in the treatment of uncomplicated malaria since 2005. To detect early artemisinin resistance in the country National Malaria Control Program (NMCP) of Côte d’Ivoire conducted with the help of his Scientific Committee efficacy studies of ACTs recommended for uncomplicated falciparum malaria treatment in the country every two years since 2009. Twelve sentinel sites have been identified around the country and Abidjan and Man are among the first sites since several years. Previous study conducted in these two sites in 2013 demonstrated that both ACT was efficacious and well tolerated [7].

The main purpose of this study was to assess efficacy and safety of AS + AQ and AL the two recommended ACTs in the first line treatment of uncomplicated falciparum malaria in Côte d’Ivoire. Data from this study will help NMCP to update malaria treatment guidelines.

Corresponding Author: Dr. Offianan Andre Toure, Unité de Paludologie, Institut Pasteur Côte d’Ivoire, Côte d’Ivoire, E-mail: andre_offianan@yahoo.fr


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Materials & Method

Study design and sites

This study was an open label, non-inferiority, randomized trial conducted in patients older than 6 months at Man and Abidjan and was carried out according to current WHO protocol [5]. The study was conducted from January to May 2016 in the two sites.

Abidjan located in the south and Man in the west of the country are among the sentinel sites for antimalarial drugs efficacy monitoring since several years.

Malaria transmission is intense with recrudescence during the raining season in the two sites. The main vectors are Anopheles gambiae and Anopheles funestus. Plasmodium falciparum is the predominant malaria parasite, accounting for more than 95% of infections in children under five years of age [7]. The key malaria control interventions in the sites include use of LLNIs, malaria case management with ACTs, Intermittent Preventive Treatment during Pregnancy (IPTp).

Study population

Patients were enrolled in the study according to WHO inclusion and exclusion criteria [5]. Briefly patients older than 6 months with the following inclusion criteria were eligible for the study: mono-infection with P. falciparum detected by microscopy, parasite density between 2,000 and 200,000 asexual parasites/µl, axillary temperature ≥ 37.5 °C or history of fever during the 24 hours before recruitment.

Additional inclusion criteria were minimum body weight of 5 kg, ability to swallow oral medication, informed consent from the patient or from a parent or guardian in the case of children; and ability and willingness to comply with the protocol for the duration of the study and to comply with the study visit schedule.

Exclusion criteria included general danger signs in children under 5 years or signs of severe falciparum malaria according to the definitions of WHO [8]; severe malnutrition according to WHO child growth standards [9]; febrile condition due to diseases other than malaria (e.g. measles, acute lower respiratory tract infection, severe diarrhea with dehydration) or other known underlying chronic or severe diseases (e.g. cardiac, renal or hepatic diseases, HIV/AIDS).

Sample size

The sample size was calculated using the WHO guidelines on assessment of antimalarial drugs [5]. Population size was determined according to the following criteria: the proportion of probable clinical failures with the antimalarial combinations studied should not be higher than 10%, for a level of confidence (P) of 95% and a precision (p) of 10%, taking into account patients who were excluded or lost to follow-up. Using these criteria, a minimum of 50 patients was required in each treatment arm in each site.

Randomization and Drug administration

Patients were randomly assigned to receive either AS+AQ or AL. Both treatments were three-day oral regimens dosed by weight according to the manufacturer's instructions: AS + AQ 5 to <9 kg: one tablet/day of artesunate (AS) 25 mg/amodiaquine (AQ) 67.5 mg; 9 to <18 kg: one tablet/day of AS 50 mg/AQ 135 mg; 18 to <36 kg: 1 tablet/day of AS 100 mg/AQ 270 mg; ≥36 kg: 2 tablets/day of AS 100 mg/AQ 270 mg. AS+AQ was administered once daily under observation by the research team.

AL tablet strength was 20 mg artemether/120 mg lumefantrine: 5 to <15 kg: 1 tablet/dose; 15 to <25 kg: 2 tablets/dose; 25 to <35 kg: 3 tablets/dose; ≥35 kg 4 tablets/dose. AL was administrated twice a day.

The first dose was taken at enrolment, the second dose eight hours later on day 0, and then two doses at 12-hourly intervals for the subsequent two days. The first dose was given at the site by the research team. The second dose was not directly observed and patients were precisely instructed how and when to take this second dose. All tablets were either swallowed whole or crushed with water and Yoghurt.

Patients who vomited during the observation period were retreated with the same dose of medicine and observed for an additional 30 minutes. Patients with repeated vomiting were excluded and were treated according to NMCP treatment guidelines and excluded from the study.

Clinical procedures

Physical examination, vital signs, body temperature, and clinical assessment were done at day 0 (screening), and at all follow-up visits (days 1, 2, 3, 7, 14, 21, 28, 35 and 42).

Medical history, demographic information and contact details were collected at screening. We recorded body weight at date 0 and Axillary, or rectal temperature was performed at baseline (day 0 before dosing) and on days 1, 2, 3, 7, 14, 21, 28, 35 and 42 or at any unscheduled visit.

Laboratory Procedures

Microscopy

Thick/thin blood smears were collected at the time of screening to confirm adherence to the inclusion and exclusion criteria. Thick blood films were also done at days 2, 3, 7, 14, 21, 28, (35 and 42) or on any other day if the patient returns spontaneously and parasitological reassessment is required. Blood smears were stained with Giemsa 10% and were examined at magnification 100X (oil immersion). Parasitemia was measured by counting the number of asexual parasites against a number of leukocytes in the thick blood film, based on a putative count of 8000 leukocytes per microliter of blood.

The number of asexual parasites was counted against 200 leukocytes using a hand tally counter. If P. falciparum gametocytes were seen, a gametocyte count was performed against 1000 leukocytes. Counts were performed by two independent microscopists; discrepant readings were resolved by a third reader.

Parasite genotyping

Blood spots on Whatman® 3MM filter paper were prepared for PCR genotyping on screening and in the event of re-appearance of parasites, confirmed by microscopy, or on any other day if a patient returned with fever. Multiplicity of infection was assessed using three polymorphic loci (merozoite surface proteins 1 and 2 and glutamate-rich protein). Briefly, filter paper blood samples collected
The study was conducted according to the Declaration of Helsinki and national legal and regulatory requirements. Protocol, CRF and consent form were approved by the “Comité National d’Ethique de la Recherche” of Côte d’Ivoire.

Results

Study trial profile and baseline characteristics

A total of 1,188 patients have been screened for eligibility criteria in the two sites among them 120 and 121 were randomized respectively in AS+AQ and AL group.

A total of 118 and 116 patients had available data for PP analysis at day 42 respectively in AS+AQ and AL group (Figure 1). The patient population had 56 (46.7%) male and 64 (53.3%) female patients in AS+AQ group. In AL group patient population had 62 (51.2%) and 59 (48.8%) males and females respectively. The mean age was 8.7 and 11.1 years respectively in AS+AQ and AL group. Overall, both groups of patients were comparable at the inclusion regarding baseline characteristics (Table 1).

Statistical analysis

Data generated were recorded in individual participants Case Record form (CRF). Data were entered and analyzed with EPI-Info™ software (v 7.1; Centers for Disease Control and Prevention, Atlanta, GA). Analysis of treatment outcome was intention-to-treat (ITT) and per protocol. Per-protocol analysis included all patients who matched all inclusion criteria, were properly randomized, had received the study drugs according to the protocol, and for whom data were available on the study endpoint without protocol violation during the follow-up time. ITT analysis comprised all randomized patients fulfilling the inclusion criteria without repeated vomiting after the first study drug administration. Frequencies were compared by either chi-squared or Fisher's exact tests, as appropriate, and continuous variables by Student's t-tests when the data are normally distributed.

Table 1: Participant’s baseline characteristics at day 0.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AS-AQ (N=120)</th>
<th>AL (N=121)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>56 (46.7)</td>
<td>62 (51.2)</td>
<td>0.60a</td>
</tr>
<tr>
<td>Female (%)</td>
<td>64 (53.3)</td>
<td>59 (48.8)</td>
<td>0.60a</td>
</tr>
<tr>
<td>Mean Age (years) (±SD)</td>
<td>8.7 (9.92)</td>
<td>11.1 (12.48)</td>
<td>0.11b</td>
</tr>
<tr>
<td>&lt; 5 years (%)</td>
<td>49 (40.8)</td>
<td>52 (43)</td>
<td>0.89a</td>
</tr>
<tr>
<td>5 - &lt; 15 years (%)</td>
<td>51 (42.5)</td>
<td>41 (33.9)</td>
<td>0.23a</td>
</tr>
<tr>
<td>≥ 15 years (%)</td>
<td>20 (16.7)</td>
<td>28 (23.1)</td>
<td>0.25a</td>
</tr>
<tr>
<td>Mean Temperature (°C) (±SD)</td>
<td>38.3 (0.74)</td>
<td>38.1 (0.61)</td>
<td>0.09b</td>
</tr>
<tr>
<td>Mean Weight (Kg) (±SD)</td>
<td>25 (20.12)</td>
<td>29.2 (23.09)</td>
<td>0.13b</td>
</tr>
<tr>
<td>Mean Parasitemia ( asexual parasites/µl) (±SD)</td>
<td>40112 (49235)</td>
<td>31479 (40541)</td>
<td>0.13b</td>
</tr>
</tbody>
</table>

Notes: achi-squared test; bStudent's t-test.
Abbreviations: AS-AQ, artesunate-amodiaquine; AL, artemether-lumefantrine; GM, geometric mean, ITT, intention to treat.
The most commonly reported and possibly drug-related adverse events to both combination therapies were effects of malaria infection. None of the patients presented with serious adverse events. Adverse effects such as anorexia (42.5% vs 28.1%), drowsiness (28% vs 0%), dizziness (30% vs 2.5%), Headache (77.7% vs 48.8%) were more frequent in the AS+AQ group compared to the AL group (p < 0.05). All of these events were described as mild or moderate (Table 3).

**Discussion**

Malaria is still associated with high morbidity and mortality especially in children under five years of age in Sub-Saharan endemic countries.

Artemisinin-based combination therapies (ACTs) are recommended by most of National malaria control programs as the first-line treatment for uncomplicated *P. falciparum* malaria. This strategy has produced a notable decrease in the mortality and in reducing the global malaria burden.
burden. However, Resistance of Plasmodium to artemisinins reported in several countries in South-East Asia, therefore, of great concern [11,12,13]. The spread or independent emergence of artemisinin resistance in other parts of the world could pose a major public health problem as no alternative antimalarial medicine is available at present with the same level of efficacy and tolerability as ACTs.

The present study based on the in vivo efficacy using 42-follow up days protocol was conducted to provide supporting evidence for the clinical efficacy of AS + AQ and AL in the country. The two ACTs were adopted and implemented as anti-malarial drug policy in Côte d’Ivoire since 2005. Results from this study demonstrated high efficacy of the two ACTs as PCR adjusted ACPR for each ACT remains above the 95% efficacy threshold recommended by the WHO [5]. Both treatments proved to be efficacious but delayed parasite clearance time observed in AL group in Abidjan site raise concerns. In this study more than 3 trade name of artemether + lumefantrine have been used at Abidjan site. All these drugs have been provided by the NMCP. Among 10 patients with clinical failure 9 have received the AL drug from the same pharmaceutical lab. Administration of artemether-lumefantrine with food is important to achieve sufficient exposure to lumefantrine up to day 7, which is required for a high cure rate [14, 15]. In this study only first doses of AL were observed. As absorption is fat dependent, patients were precisely instructed to give the second dose with fatty food at home. However, intake of this second dose was not directly controlled. Food is known to increase the bioavailability (BA) of lumefantrine by up to 16-fold and that of artemether by up to 3-fold.

General inter-individual variability for drug absorption and pharmacokinetic may be associated with changes in the bioavailability of a drug and consequently may affect the therapeutic efficacy.

A study conducted in Nigeria indicated an increase in parasite clearance time and high frequency of crude late parasitological burden.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASAQ (%)</th>
<th>AL (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIT Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolled patients</td>
<td>120</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Patients seen</td>
<td>118/120 (98.3)</td>
<td>116/121 (95.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Missing</td>
<td>0/2/120 (1.7)</td>
<td>0/5/121 (4.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Crude failure rate</td>
<td>07/120 (5.8)</td>
<td>19/121 (15.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Crude cure rate</td>
<td>113/120 (94.2)</td>
<td>102/121 (84.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>PCR adjusted failure rate</td>
<td>03/120 (2.5)</td>
<td>8/121 (6.6)</td>
<td>0.22</td>
</tr>
<tr>
<td>PCR adjusted ACPR</td>
<td>115/120 (97.5)</td>
<td>113/121 (93.4)</td>
<td>0.57</td>
</tr>
<tr>
<td>PP Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients seen</td>
<td>118</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>Crude failure rate</td>
<td>05/118 (4.20)</td>
<td>14/116 (12.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Crude cure rate</td>
<td>113/118 (95.8)</td>
<td>102/116 (87.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>PCR adjusted failure rate</td>
<td>01/118 (0.8)</td>
<td>03/116 (2.6)</td>
<td>0.60</td>
</tr>
<tr>
<td>PCR adjusted ACPR</td>
<td>117/118 (99.2)</td>
<td>113/116 (97.4)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Table 2: Therapeutic response in the two groups at day 42. AS + AQ, artesunate + amodiaquine; AL, artemether–lumefantrine. P values were obtained by Fisher’s exact test.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASAQ (N=120)</th>
<th>AL (N=121)</th>
<th>Fisher’s Exact Test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>51 42.5 28.0 57.0</td>
<td>34 28.1 11.5 44.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Asthenia</td>
<td>43 35.8 20.3 51.3</td>
<td>35 28.9 12.5 45.4</td>
<td>0.33</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 11.8 -8.7 32.1</td>
<td>8 6.6 -16.9 30.1</td>
<td>0.26</td>
</tr>
<tr>
<td>drowsiness</td>
<td>33 27.5 10.8 44.2</td>
<td>0 0 - -</td>
<td>-</td>
</tr>
<tr>
<td>Cough</td>
<td>2 0.17 -41.1 44.4</td>
<td>12 9.9 -11.2 31.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Dizziness</td>
<td>36 30.0 13.6 46.4</td>
<td>3 2.5 -31.8 36.7</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25 20.8 2.9 38.8</td>
<td>16 13.2 -6.5 32.9</td>
<td>0.17</td>
</tr>
<tr>
<td>Headache</td>
<td>86 71.7 61.6 81.8</td>
<td>59 48.8 35.2 62.4</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Myalgia</td>
<td>24 20.0 1.9 38.1</td>
<td>22 18.2 -0.2 36.6</td>
<td>0.86</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>34 28.3 11.7 45.0</td>
<td>34 28.3 11.5 44.7</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>a 04.2 -23.3 31.7</td>
<td>5 4.1 -23.3 31.6</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 05.0 -20.8 30.8</td>
<td>3 2.5 -31.8 36.7</td>
<td>0.49</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 08.3 -13.8 30.5</td>
<td>5 4.1 -23.3 3.6</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Table 3: Clinical adverse events.
failures among the patients, indicating reduction in the therapeutic
efficacy of Artemether + lumefantrine [16].

In the same site (Abidjan) in 2013, three years ago ACPR after
adjustment by PCR of AS + AQ and AL was 100% for each drug at day
42. The same result was obtained with the two ACTs in Man site in 2013
[7]. Others studies conducted in the country have demonstrated also
good efficacy of AS+AQ and AL in the treatment of uncomplicated
c africanum malaria [17, 15, 19-22].

Although most studies carried out in malaria endemic countries in
Africa [23-26] had shown good efficacy and safety of ACTs for the
 treatment of uncomplicated malaria, the conditions of clinical trials
do not fully reflect real field situation. Results from studies conducted
with unsupervised malaria treatment showed low cure rate after
adjustment by PCR at day 28 [27,28].

Some studies demonstrated that unsupervised intake of AL
was highly efficacious despite the lumefantrine plasma levels
concentrations being significantly lower than in patients whose
 treatment had been supervised [29-32].

Both treatments were generally well tolerated; the overall incidences
of AEs were more frequent in the AS + AQ than AL treatment groups.
The most commonly occurring AEs included anorexia, drowsiness,
dizziness and Headache.

Our study has several limitations. The lack of sufficient sampling
times for fever and parasite clearance time. We were not able to
determine the levels of drugs concentration which may have been of
interest for its contribution to the therapeutic efficacy of ACTs.

Conclusion

Although results from this study proved good efficacy of AS+AQ ad
AL in the treatment of uncomplicated falciparum malaria in the two
sites, constant monitoring of these two ACTs is needed.

Competing Interests

The authors declare that they have no competing interests.

Author’s Contributions

All authors participated in the design, implementation, and
analysis or data interpretation of the study. Offianan AT was involved
in all phases of the study, N’guessan Tiacho L, Kouame E, Kokora A.,
Amata Eric, Kinifo-Lawson V were responsible for conducting field
studies and coordination of study procedures. Ira Bonouma, Djanam
Josefn Assi Serge B and Ronan jambou supervised the study. Data
analysis was done by Adji Eric Gbessi. Coulibaly Baba and Ako Ako
Aristide B performed PCR analysis. Yao Serge S and Albert Gondjui
undertook lab procedures. The manuscript was drafted by Offianan
Andre Toure. All authors critically reviewed the report and approved
the final version of the report for submission.

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of uncomplicated Plasmodium falciparum in Ankonoua kouto,
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