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Full Length Research Paper

Efficacy and safety of Artemether-Lumefantrine and Artesunate-Amodiaquine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Northern Côte d'Ivoire

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Abstract

Efficacy and safety of Artemether-Lumefantrine (AL) and Artesunate-Amodiaquine (AS-AQ) used as first line in malaria treatment were assessed in northern Côte d'Ivoire. A non-comparative therapeutic efficacy test of AL and AS-AQ in the treatment of uncomplicated *falciparum* malaria in children and adults was conducted from February to September 2019, in two sentinel sites. The WHO standard therapeutic efficacy test for monitoring antimalarial drug efficacy was used with Adequate Clinical and Parasitological Response (ACPR) corrected by PCR at day 28 as primary outcomes. Secondary endpoints were parasite and fever clearance times. A total of 119 patients were included in the trial with 59 treated with AL and 60 treated with AS-AQ. Per protocol analysis on day 28 showed a PCR-corrected cure rate of 100% (95% CI, 93.4-100.0) and 100% (95%CI, 93.2-100.0) for AL and AS-AQ, respectively. At day 3, three patients in the AL group presented a fever and all patients treated with AS-AQ were apyretic. Delayed parasite clearance was observed in three patients in the AL group and one patient in the AS-AQ group. Both ACTs remain efficacious and well-tolerated for uncomplicated *falciparum* malaria treatment in northern Côte d'Ivoire. However, due to delayed parasite clearance observed, close monitoring of efficacy is essential.

Key words: Malaria, Artemether-Lumefantrine, Artesunate-Amodiaquine, Efficacy, Safety, Côte d'Ivoire.

BACKGROUND

Malaria is an endemic disease that affects several continents around the world. In sub-Saharan countries, malaria remains a major public health problem despite the many strategies developed by WHO and his partners to control and eliminate the disease. In 2018, around 228 million cases of malaria have been recorded worldwide including 213 million (93%) in the African region (WHO, 2019).

Children under five years continue to pay a heavy tribute with 67% of the 405,000 cases of death recorded worldwide (WHO, 2019). In Côte d'Ivoire, malaria is the main reason for hospital consultation, representing 43% of all consultations (MSHP, 2010).

Due to the development and increasing resistance of *P. falciparum* to various antimalarial drugs available, WHO recommend the use of artemisinin-based combination

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therapy (ACTs) for the treatment of uncomplicated malaria (WHO, 2001; MSHP, 2007). Artesunate-amodiaquine (AS-AQ) and Artemether-lumefantrine (AL) are first line recommended drugs for the treatment of uncomplicated falciparum malaria in Côte d'Ivoire since 2005 (MSHP, 2007; MSLS, 2014; MSHP, 2018). More recently, DiHydroArtemisinin-Piperaquine (DHAP) and Pyronaridine-Artesunate have been added to the list of ACTs used in first line treatment by the National Malaria Control Program (NMCP) (MSHP, 2018). The spread of artemisinin resistance to other regions, or its independent emergence in other parts of the world, could trigger an emergency with major consequences for public health (Noedl *et al.,* 2008; Dondorp *et al.,* 2010; Imwong *et al.,* 2017; Fairhust *et al.,* 2012; Woodrow and White, 2017; WHO, 2017).

Previous studies have shown efficacy of ACTs in Côte d'Ivoire (Yavo *et al.,* 2015; Assi *et al.,* 2017a; Toure *et al.,* 2018, 2014).

Routine monitoring of antimalarial drug efficacy is necessary to ensure effective case management and for early detection of resistance. WHO recommends that the efficacy of first-and second-line antimalarial treatments be tested at least once every 24 months at all sentinel sites.

This study was part of the monitoring of the efficacy of the two recommended ACTs in two sentinel sites of the NMCP located in the savannah region in northern Côte d'Ivoire.

The objective was to assess the efficacy and safety of Artesunate-Amodiaquine and Artemether-Lumefantrine in the treatment of uncomplicated falciparum in order to update treatment guidelines.

MATERIAL AND METHODS

Study design

This study was a prospective, non-comparative, non-randomized, open label, therapeutic efficacy test of Artemether-Lumefantrine (AL) and Artesunate-Amodiaquine (AS-AQ). The WHO protocol for evaluating therapeutic efficacy of antimalarial drugs was used (WHO, 2019).

Study sites

The therapeutic efficacy test with the AL was conducted at Odienné and the AS-AQ at Korhogosites between January-September 2019. The two sites were part of the NMCP sentinel sites located in the north of Côte d'Ivoire (Figure 1). *Plasmodium falciparum* transmission was intense and perennial, with recrudescence during the rainy season at every site. In this region *Plasmodium falciparum* was the predominant malaria parasite Henry *et al.,* 2003).

Sample Size

The sample size was calculated using the WHO guidelines on assessment of antimalarial drugs (WHO, 2009). As per the following criteria, the probability for clinical failures with the antimalarial combinations studied should not be higher than 10% (Yavo et al., 2015; Toure et al., 2014; Faye et al., 2012; Menan et al., 2011), for a 95% level of confidence (P) and a precision (p) of 10%, taking into account patients who were excluded or lost to follow-up. Based on these criteria 60 patients were recruited at each site.

Study Population

The study population consisted of outpatients aged 6 months to 65 years who attended health facilities with suspicion of uncomplicated malaria based on symptoms. Patients were referred to the study team for the recruitment. Main inclusion criteria for the study were as follows: body weight ≥5 kg; fever with axillary temperature ≥ 37.5° C or a history of fever in the previous 24 hours; no other cause of fever than suspected malaria and no sign of complicated falciparum malaria (WHO, 2009). Other criteria included ability to take study drugs by oral route, attend a clinic on required days for follow-up and a signed informed consent (by patient or someone in charge of a child).

Patients with signs or evidence of severe malaria or malnutrition, febrile condition due to illnesses other than malaria (e.g. measles, acute lower respiratory infection, severe diarrheal illness with dehydration), history of serious side effects to Artesunate-Amodiaquine and those pregnant or breastfeeding were excluded.

Baseline evaluation and treatment

Screening

Patients symptoms were assessed at enrolment. Axillary or rectal temperature, body weight measurement and physical examination were performed. A thick and thin blood smear for parasitemia and blood sample on filters paper (Whatman 3MM) for molecular analysis were collected before treatment.

Treatment

Three formulations of AS-AQ produced by Guilin Pharmaceutical Co., Ltd. were received: 25mg AS/67.5mg AQ, 50mg AS/135mg AQ, 100mg AS/270mg AQ. For the AL only one formulation (20mg Artemether /120mg Lumefantrine) was received from Novartis Co, Ltd. Patients received AL and AS-AQ at Odienné and Korhogosites respectively. Both treatments were three-day oral regimens dosed by weight according to instructions from the manufacturer.

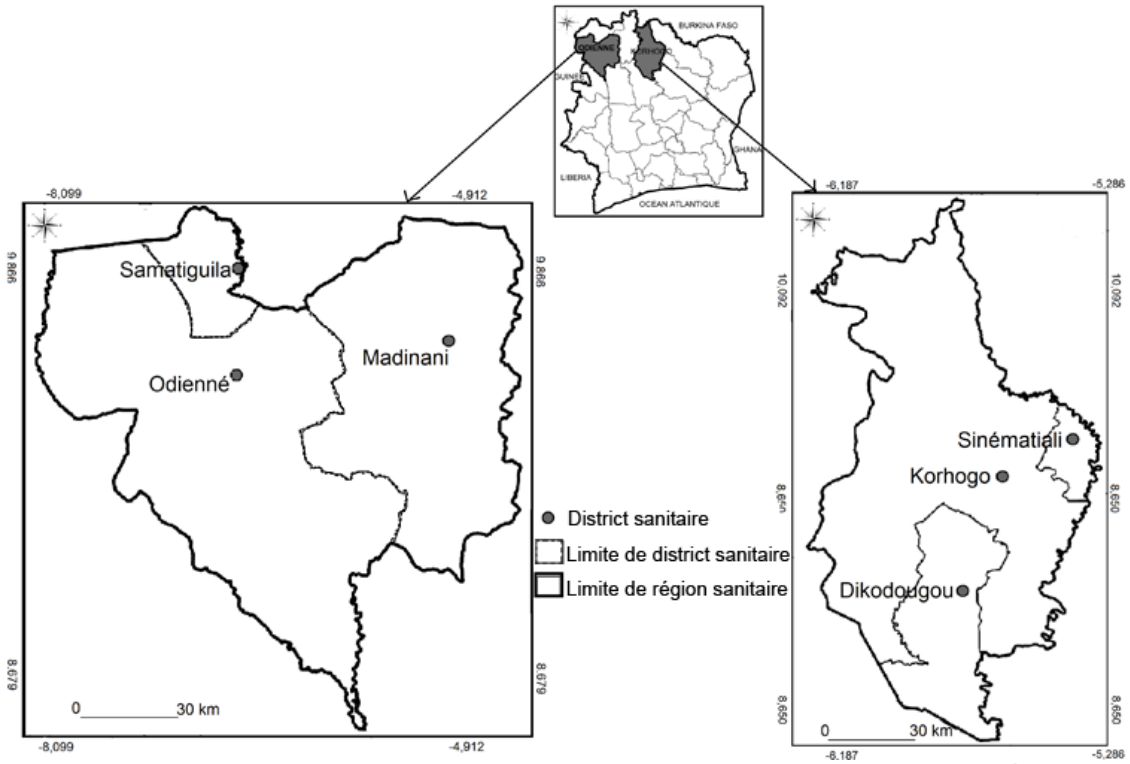

Figure 1. A map showing the two sanitary districts where the two studies were performed. **Odienné:** Artemether-Lumefantrine, **Korhogo:** Artesunate-Amodiaquine.

Different doses of AS-AQ were administered as follows: 5 to <9 kg: one tablet per day of artesunate (AS) 25 mg/amodiaquine(AQ) 67.5 mg; 9 to <18 kg: one tablet per day of AS50 mg/AQ 135 mg; 18 to <36 kg: 1 tablet a day of AS100 mg/AQ 270 mg and ≥36 kg: 2 tablets a day of AS 100 mg/AQ 270 mg. Patients received tablets of AS-AQ that they swallowed under direct supervision by study team on study day 0, 1 and 2. Administration for the Artemether-Lumefantrine was as follows:between 5 to <15 kg: 1 tablet per dose; 15 to <25 kg: 2tablets per dose; 25 to <35 kg: 3 tablets per dose and ≥35 kg 4 tablets per dose. Each AL dose was administrated twice a day on day 0, 1 and 2. The first dose was swallowed at enrollment under direct supervision by the study team. The second dose was administered eight hours later on day 0, and then one dose at 12hourly intervals on the remaining two days from home under family supervision, mainly for children.

To check the intake of the second doses of AL, patients had to return the next day with empty blisters. For children, mothers were trained by the team on how to administer the drug. If a child vomited <30 min after his oral intake, a full dose was given. If vomiting persisted, the patient was dropped off the study. Any participant withdrawn because of vomiting received a rescue medication (injectable artesunate or injectable quinine) as per the National Malaria Control Program guidelines.

Laboratory evaluations

Parasitological assessments

Plasmodium falciparum parasite was identified by examining thick and thin blood smear. Each slide was air-dried and stained with 10% Giemsa for 30 minutes.

Thick and thin blood films for parasite counts were obtained and screened on day 0 to confirm adherence to the inclusion criteria and on days 1, 2, 3, 4, 7, 14, 21 and 28 or at any unscheduled visit, if needed.

Parasitemia was determined by counting the number of asexual parasites and number of leucocytes in 200 high-powered fields based on a putative count of 8,000 leucocytes/µL of blood (Assi et al., 2017a, b). Two qualified independent microscopists read all slides. Slides were considered negative if no parasite was detected after reading 200 fields. Presence of gametocytes was also recorded. Readings with discordant results (difference in species diagnosis, difference in parasite density of $\geq$25%, or any difference that affected recruitment or study outcome) were re-examined by a third microscopist; the parasite density was calculated by averaging the two closest densities while the final parasite species was determined by the two concordant reads. Blood samples were drawn for hematocrit to estimate the level of anemia at inclusion on day 0 and any other days in case of adverse event.

Parasite genotyping

Dried Blood Spots (DBS) on Whatman® 3MM filter paper (three spots per card) were prepared for polymerase chain reaction (PCR) genotyping for all subjects at day 0 and at the relevant follow-up visit in the case of treatment failure.
Parasite DNA was extracted from DBS using QIAamp DNA blood mini kits (QIAgen GmbH, Hilden, Germany) according to the manufacturer's instructions. Paired DNA samples (day 0 and day of parasites recurrence) were genotyped by analyzing the polymorphic loci of merozoite surface proteins 1 and 2 (msp1 and msp2), and glutamate rich protein (glurp) genes to discriminate re-infection from recrudescence as described previously (Toure et al., 2014. WHO, 2009, 2007). A "new infection" was a subsequent occurring parasitemia in which all the alleles in parasites from the post-treatment sample were different from those in the admission sample, for one or more loci tested. In a "recrudescence," at least one allele at each locus should be in common for both paired samples.

Safety assessment

Safety of both ACTs was monitored by passive and active methods through interviews with participants and clinical assessments (and biological assessments if necessary) during the 28 days of follow-up. The reported/captured events were recorded in respective case report forms for each follow-up visit. Any clinical or biological sign not present at inclusion and which appeared during follow-up time or any sign present at day 1 but worsening after was considered as adverse event.

Outcomes

Treatment outcomes were classified according to the WHO criteria (WHO, 2009) as adequate clinical and parasitological response (ACPR), early or late clinical failure and early or late parasitological failure at Day 28 confirmed by PCR (WHO, 2009, 2007). Safety outcomes were the incidence of adverse events. Adequate clinical and parasitological response is defined as absence of parasitemia on day 28, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure (WHO, 2009).
The first endpoint was ACPR at day 28 and the secondary endpoints were parasite and fever clearance times and safety.

Statistical analysis

Generated data were recorded in a log book and an individual participant's case recording files. Data were entered and analyzed with SPSS Version 17 (SPSS Inc., Chicago, IL, USA). Intention to treat (ITT) and per protocol (PP) analysis were done.

Ethical issues

The protocol of this study was reviewed and approved (Approval Number 056/MSHP/CNER-kp) by the national ethic committee "Comité National d'Ethique et de la Recherche of Côte d'Ivoire (CNER)". The study was carried out in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice.

RESULTS

Baseline characteristics

Of 350 patients screened, 119 met the inclusion criteria and were enrolled. 60 received AL and 59 received AS-AQ. Of these, 05 lost to follow up in the AL group and 01 in the AS-AQ group (Figure 2). Baseline characteristics of the study participants are summarized in Table 1. More than half of the participants were between 5 and 25 years old (53.8%). Patients under 5 years of age represented 24.4% of participants. The mean age of the study population was 11.0 (range 0.5-50 years) and the mean temperature at inclusion was 38.2°C. The geometric mean parasitemia at baseline was 21014 (range 2040-198981) parasite/µL among all study participants.

Efficacy Outcomes

The results of treatment efficacy are presented by treatment group, unadjusted and adjusted by genotyping (Table 2). Of the 55 patients completing the entire follow up period in the AS-AQ groups, 54 achieved adequate Clinical and Parasitological Response (ACPR) and one was a Late Clinical Failure (LCF).
The uncorrected-PCR cure rates at day 28 was 89.7% (95%CI, 78.8-96.1) in the AL group and 98.2 % (95%CI, 90.3-100) in the AS-AQ group. The PCR-corrected ACPR on day 28 in the per-protocol analysis was 100% (95%CI,93.2-100) in the AL group and 100% (95%CI, 93.4-100) in AS-AQ group (Table 2).

Fever clearance

The proportion of participants with fever at the screening was 83% and 95% in AL and AS-AQ groups respectively. Three patients in the AL group presented fever and all patients treated with AS-AQ were apyretic at day 3 (Figure 3).

Parasite clearance

At day 3, parasite clearance rate was 91.5% in the AL group and 98.3% in the AS-AQ group. Three patients

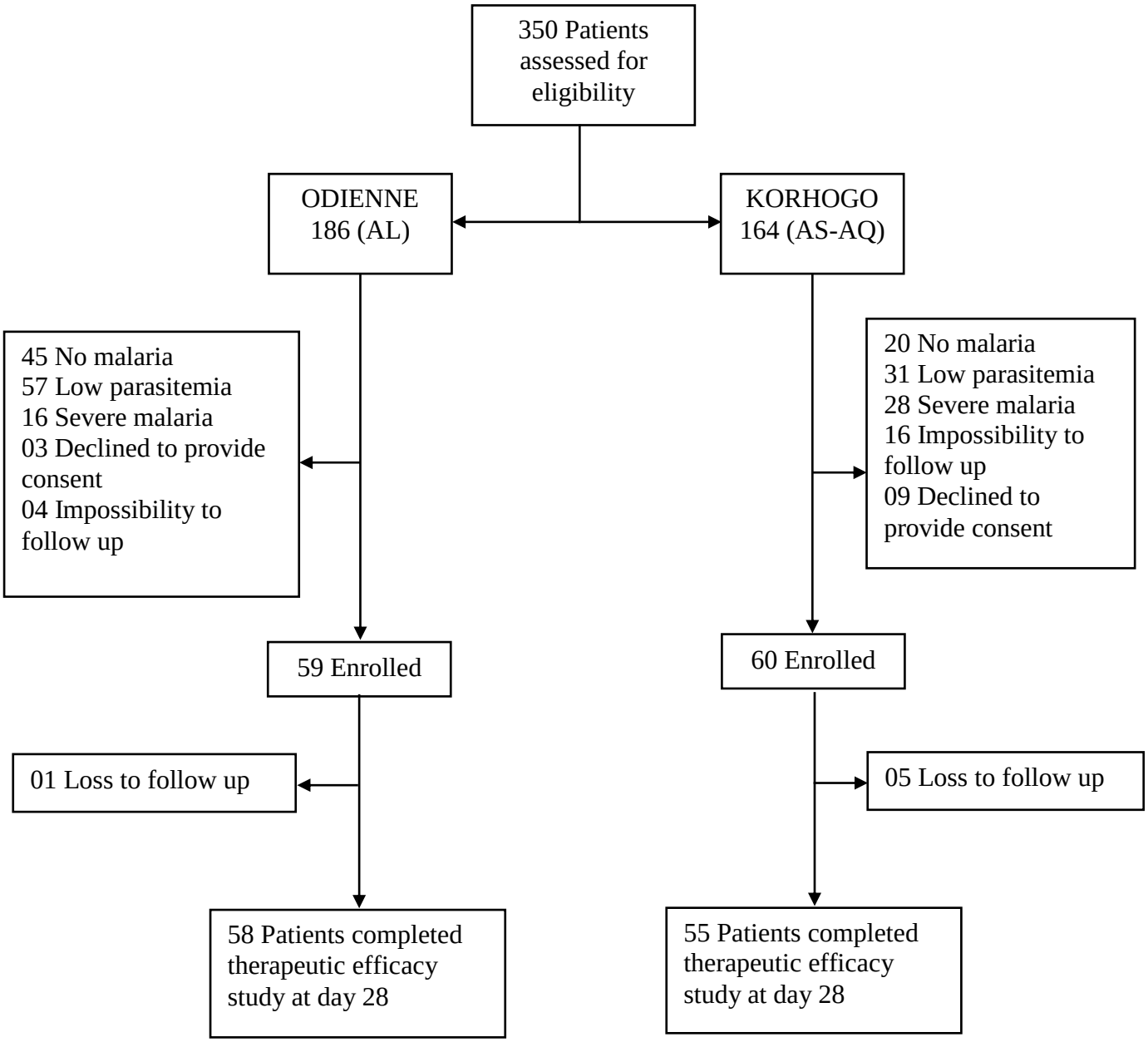

Figure 2. Trial profile

presented delayed parasite clearance at day 3 in the AL group and 1 patient in AS-AQ group. The geometric mean of parasites at day 3 was 106 parasites/µL in the AL group and 28 parasites/µL in the AS-AQ group.

Safety

Table 4 showed the distribution of clinical adverse events (AEs) recorded during the study. No severe adverse events that necessitated withdrawal from the study or referral to hospital was observed in both groups. Most of the recorded adverse events were minor. However, we noted many AEs in the AS-AQ group compared to the AL groups. With AS-AQ treatment we scored 10 AEs, with the most frequent being drowsiness (22), vomiting (06), abdominal pain (4) and cough (4). In the AL group we noticed three AEs, ranging from abdominal pain (2), coughing (2) to headache (1).

DISCUSSION

As part of a monitoring plan for the efficacy of antimalarials, WHO recommends that national malaria control programmes (NMCP) regularly assess the efficacy

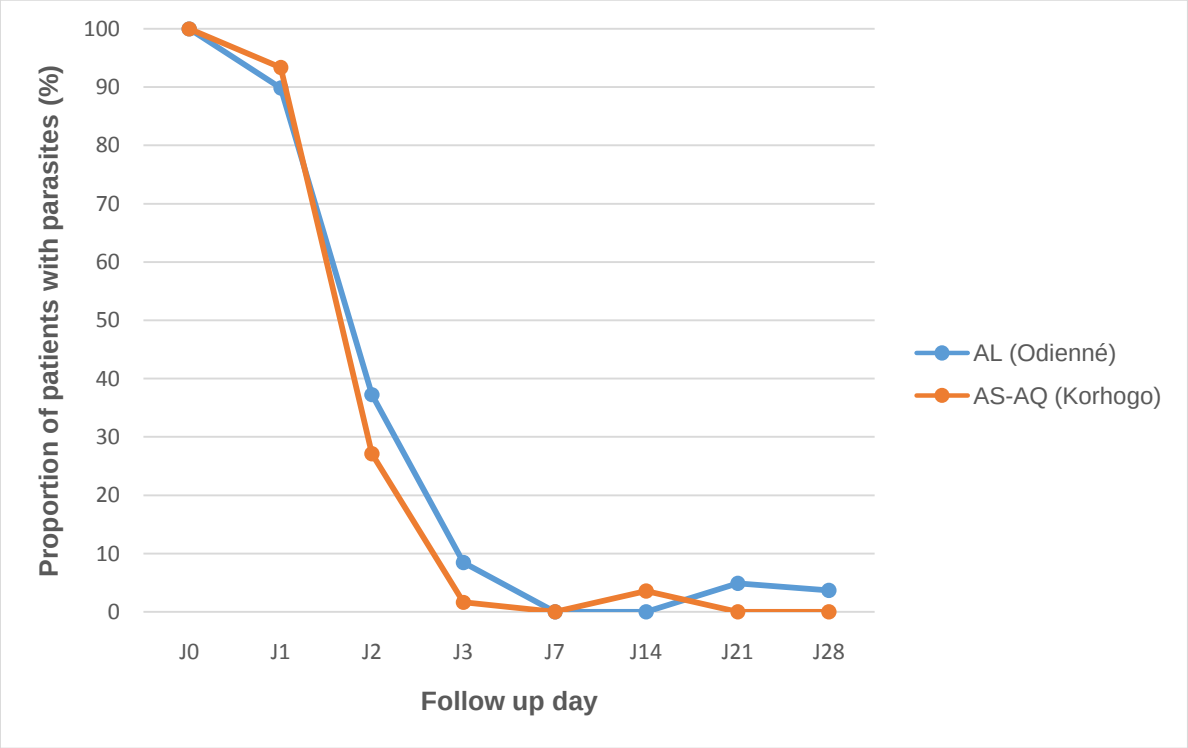

Figure 3. Proportion of patients with parasites during follow-up.

Table 1. Baseline characteristics in the ITT cohort.

Patients characteristics at day 0	AL (59)	AS-AQ (60)	Total (119)
Sex			
M, n (%)	35 (59.3)	43 (72.7)	78 (65.5)
F, n (%)	24 (40.7)	17 (28.3)	41 (34.5)
Mean Age (SD) years	10.5 (±11.5)	11.5 (±6.5)	11.0 (±6,6)
Min - Max	0.5-50	2-30	0.5-50
[0-5[, n (%)	23 (39.0)	6 (10.0)	29 (24.4)
[5-15[, n (%)	25 (42.4)	39 (65.0)	64 (53.8)
[>=15[, n (%)	11 (18.6)	15 (25.0)	26 (21.8)
Meanweight, kg (SD)	27.7 (±20.5)	33.7 (±19.6)	30.7 (±16.5)
Min - max	7-86	8-87	7-87
Meantemperature, °C (SD)	38.1 (±0.8)	38.4 (±0.7)	38,2 (±0.6)
GM parasite count, µL	19462	22661	21014
Min-Max	2109-197791	2040-198981	2040-198981

Abbreviations: AL, Artemether-LumefantrineAS-AQ, Artesunate-Amodiaquine; GM, geometric mean; ITT, intention to treat; SD, standard deviation; M, Male; F, Female.

of ACTs deployed as their first line treatment of malaria (WHO, 2009). In Côte d'Ivoire, Artesunate-amodiaquine (AS-AQ) and Artemether-lumefantrine (AL) are used for treatment of uncomplicated malaria since 2005. The therapeutic efficacy tests (TET) enabled evaluation of efficacy and tolerability of these two ACTs at two sentinel sites of NMCP in northern Côte d'Ivoire.

The current study based on in vivo efficacy of the ACTs using 28-follow up day's protocol was conducted in

Table 2. Treatment outcomes for AL and AS-AQ before and after PCR adjusted in PP analysis.

Outcomes	Odienné(AL) n=59		Korhogo (AS-AQ) N=60	
	n	% (95%CI)	n	% (95%CI)
PP patients seen at day 28	58	-	55	-
PP crude failure rate at day 28	06	10.3 (4.8-20.8)	01	1.8 (0.0-9.7)
PP crude cure rate at day 28	52	89.7 (78.8-96.1)	54	98.2 (90.3-100)
PCR adjusted failure rate at day 28	0	0	0	0
PCR adjusted cure rate at day 28	52	100 (93.2-100)	54	100 (93.4-100)

Abbreviations: AL, Artemether-Lumefantrine;AS-AQ, Artesunate -Amodiaquine; PP, Per protocol.

Table 3. Clinical adverse events in the ITT population.

Adverse events	Odienné (AL) N=59			Korhogo (AS-AQ) N= 60		
	n	%	95%CI	n	%	95%CI
Drowsiness	0	-	-	22	36.7	25.7-49.4
Vomiting	2	3.4	10.9-11.6	6	10.1	4.7-20.1
Abdominal pain	2	3.4	0.9-11.6	4	6.7	2.6-16.0
Cough	0	-	-	4	6.7	2.6-16.0
Diarrhea	0	-	-	2	3.3	0.9-11.3
Itching	0	-	-	2	3.3	0.9-11.3
Headache	1	1.7	0.3-9.0	1	1.7	0.3-8.9
Insomnia	0	-	-	1	1.7	0.3-8.9
Dizziness	0	-	-	1	1.7	0.3-8.9
Asthenia	0	-	-	1	1.7	0.3-8.9

Abbreviations: AL, Artemether-Lumefantrine; AS-AQ, Artesunate-Amodiaquine.

patients older than 6 months with uncomplicated *P. falciparum* malaria.

The results showed that, AS-AQ appeared to be a better treatment option on the basis of uncorrected-PCR responses, based on the lower percentage of recurrent parasitemia with uncorrected Adequate Clinical and Parasitological Response (ACPR) observed for 90.3-100% patients with AS-AQ and 78.8-96.1 % with AL. After correction for PCR, both AL and AS-AQ were still efficacious against uncomplicated *falciparum* malaria. Previous studies conducted in Côte d'Ivoire have demonstrated similar PCR-corrected cure rate with AL and AS-AQ for uncomplicated *P.falciparum* malaria treatment (Yavo et al., 2015; Toure et al., 2018, 2014). These results are also consistent with the high cure rates reported for ACTs elsewhere in several sub-Saharan African countries (Mandara et al., 2018; Roth et al., 2018; Dama et al., 2018; Raobela et al., 2018; Davlantes et al. 2018; Abuaka et al., 2017).

In addition, molecular studies in Côte d'Ivoire and other countries in Africa have shown the absence of mutation points in the kelcher 13 (k-13) gene associated with artemisinin resistance (Menard et al., 2016, Taylor et al., 2015; Kamau et al., 2015; Ogouyèmi-Hounto et al., 2016), further suggesting that artemisinin is still effective.

Fever clearance was fast in the two groups, confirming previous data (Van Den Broek et al., 2006; Bharti et al., 2016). At day 2, all patients treated with AS-AQ were nonfebrile while 3.4 % were febrile in the AL group at day 3.

Prompt parasite clearance times with both AL and AS-AQ groups were in agreement with findings from southern Nigeria (Gbotosho et al., 2011). Overall, three patients (8.5%) had parasitemia at day 3 in the AL group. Treatment with AL was given in two doses per day. After the first daily dose administered in the day by the study team, patients have had to take the other doses in the evening at home without supervision. A non-compliance with treatment at home could explain this high rate of parasitemia at day 3, which could be a major limitation of the study.

But, this finding is far below the WHO threshold of 10% (WHO, 2010), and therefore suggests that artemisinin (partial) resistance following ACT treatment against uncomplicated *P. falciparum* malaria is not a concern in Côte d'Ivoire.

This study also reports that both drugs were well tolerated with minor Adverse Events (AEs) and no any severe cases were found. The good safety profile of AL was demonstrated, compared to previous studies and was well tolerated with minimal AEs compared to AS-AQ (Yavo et al., 2015; Toure et al., 2018, 2014). In most health facilities in Côte d'Ivoire, AL is prescribed more often than AS-AQ because of patients' complaints following the use of AS-AQ (NMCP, unpublished data). Most of the AEs were minor and mainly reported in all

study sites. This good tolerance of both ACTs has also been observed in other studies in Côte d'Ivoire and elsewhere in Africa (Yavo et al., 2015; Toure et al., 2018, 2014; Mandara et al., 2018; Roth et al., 2018; Dama et al., 2018; Raobela et al., 2018; Davlantes et al., 2018; Abuaka et al., 2017).

CONCLUSION

This study showed that both AL and AS-AQ are safe, with high efficacy for the treatment of uncomplicated falciparum malaria supporting recommendation of the two ACTs as first line malaria treatment in the country. Nevertheless, delayed parasite clearance time and high rates of treatment failures before PCR correction observed support the need for regular monitoring of efficacy and gene mutation for resistance during NMCP treatment programme.

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Bibliography

Abuaku BK, Mensah BA, Ofori MF, Myers-Hansen J, Derkyi-Kwarteng AB, Essilfie F, Dokurugu M, Amoakoh E, Koram KA, Gansah A (2017). Efficacy of artesunate/amodiaquine in the treatment of uncomplicated malaria among children in Ghana. Am. J. Trop. Med. Hyg. 97 (3):690-695.

Assi S, Aba Y, Yavo J, Nguessan A, Tchiekoi N, San N, Bissagnene E, Duparc S, Lameyre V, Tanoh M (2017a). Safety of a fixed-dose combination of artesunate and amodiaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in real-life conditions of use in Côte d'Ivoire. Malar. J. 3; 16(1):8.

Assi SB, Nguessan AF, Aba YT, Toure AO, Menan H, Yavo JC, San KM, Bissagnéné E, Duparc S, Lameyre V, Tanoh MA (2017b). Sustained Effectiveness of a Fixed-Dose Combination of Artesunate and Amodiaquine in 480 Patients with Uncomplicated *Plasmodium falciparum* Malaria in Côte d'Ivoire. Malar. Res. Treat. 3958765. Published online 2017 Dec 7. doi: 10.1155/2017/3958765.

Bharti PK, Shukla MM, Ringwald P, Krishna S, Singh PP, Yadav A, Mishra S, Gahlot U, Malaiya JP, Kumar A, Prasad S, Baghel P, Singh M, Vadadi J, Singh MP, Bustos MDG, Ortega LI, Christophel EM, Kashyotia SS, Sonal GS, Singh N (2016).Therapeutic efficacy of artemether–lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria from three highly malarious states in India. Malar. J. 15:498.

Dama S, Niangaly H, Djimde M, Sagara I, Guindo CO, Zeguime A, Dara A, Djimde AA, Doumbo OK. A randomized trial of dihydroartemisinin–piperaquine versus artemether- lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria in Mali. Malar. J. 2018; 17:347.

Davlantes E, Dimbu PR, Ferreira CM, Joao MF, Pode D, Félix J, Sanhangala E, Andrade BN, Souza SDS, Talundzic E, Udhayakumar V, Owens C, Mbounga E, Wiesner L, Halsey ES, Martins JF, Fortes F, Plucinski MM (2018). Efficacy and safety of artemether-lumefantrine, artesunate–amodiaquine and dihydroartemisinin-piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in three provinces in Angola, 2017. Malar. J. 17:144. 28.

Dondorp AM, Yeung S, White L, Nguon C, Day NP, Socheat D, Von Seidlein L (2010). Artemisinin resistance: current status and scenarios for containment. Nat. Rev. Microbiol. 8: 272-280.

Fairhurst RM, Nayyar MLN, Breman JG, Hallett R, Vennerstom JL, Duong S, Ringwald P, Wellems TE, Plowe CV, Dondorp AM (2012). Artemisinin-resistant malaria: research challenges, opportunities, and public health implications. Am. J. Trop. M. Hyg. 87: 231-241.

Faye B, Kuété T, Kiki-Barro CP Roger CT, Thérèse N, Jean-Louis AN, Claude AK, Khadime S, Hervé EIM, Oumar G, Oumar F, Albert SE, Koné M (2012). Multicentre study evaluating the non-inferiority of the new paediatric formulation of artesunate/amodiaquine versus artemether/lumefantrine for the management of uncomplicated *Plasmodium falciparum* malaria in children in Cameroon, Ivory Coast and Senegal, Malar. J. vol. 11, article 433.

Gbotosho. GO, Sowunmi A, Okuboyejo TM Happi CT, Folarin OA, Micheal OS, Adewoye EO (2011). Therapeutic efficacy and effects of artemether-lumefantrine and artesunate-amodiaquine coformulated or copackaged on malaria-associated anemia in children with uncomplicated *Plasmodium falciparum* malaria in Southwest Nigeria. Am. J. Trop. M. Hyg.84(5): 813-819.

Henry MC, Rogier C, Nzeyimana I, AssiSB,Dossou-Yovo J, Audibert M, J. Mathonnat J, Keundjian A, Akodo E, Teuscher T, Carnevale P (2003). Inland Valley rice production systems and malaria infection and disease in the Savannah of Côte d'Ivoire. Trop. Med. Int. Health.8 (3): 449-558.

Imwong M, Suwannasin K, Kunasol C, Sutawong K, Mayxay M, Rekol H, Smithuis FM, Hlaing TM, Tun KM, Van der Pliijm R, Tripura R, Miotto O, Menard D, Dhorda M, Day PJ N, Whit NJ, Dondorp AM (2017). The spread of artemisinin-resistant *Plasmodium*

falciparum in the Greater Mekong subregion: a molecular epidemiology observational study. Lancet Infect. Dis. 17:491-497.

Kamau E, Campino S, Amenga-Etego L, Drury E, Ishengoma D, Johnson K, Mumba D, Kekre M, Yavo W, Mead D, Bouyou-Akotet M, Apinjoh T, Golassa L, Randrianarivelojosia M, Andagalu B, Maiga-Ascofare O, Amambua-NgwaA,Tindana P, Ghansah A, MacInnis B, Kwiatkowski D, Djimde AA (2015). K13-propeller polymorphisms in *Plasmodium falciparum* parasites from sub-Saharan Africa. J. Infect. Dis. 211 (8):1352-1355.

Mandara CI, Kavishe RA, Gesase S, Mghamba J, Ngadaya E, Mmbuji P, Mkude S, Mandike R, Njau R, Mohamed A, Lemnge MM, Warsame M, Ishengoma DS (2018). High efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated *falciparum* malaria in Muheza and Kigoma Districts, Tanzania. Malar. J. 17:261.

Menan H, Faye O, Same-Ekobo A, Oga ASS, Faye B, Kiki-Barro CP, Kuete T, N'diaye JL, Vicky AM, Tine R, Yavo W, Kane D, Kassi KF, Kone M (2011). Comparative study of the efficacy and tolerability of dihydroartemisinin piperaquine-trimethoprim versus artemether-Lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Cameroon, Ivory Coast and Senegal, Malar. J. vol. 10, article 185.

Ménard D, Khim N, Beghain J, Adegnika AA, Shafiul-Alam M, Amodu O, Rahim-Awab G, Barnadas C, Berry A, Boum Y, Bustos MD, Cao J, Chen JH, Collet L, Cui L, Thakur GD, Dieye A, Djallé D, Dorkenoo MA, Eboumbou-Moukoko CE, Espino FECJ, Fandeur T, Ferreira-da-Cruz MF, Fola AA, Fuehrer HP, Hassan AM, Herrera S, Hongvanthong B, Houzé S, Ibrahim, ML, Jahirul-Karim M, Jiang L, Kano S, Ali-Khan W, Khanthavong M, Kremsner PG, Lacerda M, Leang R, Leelawong M, Li M, Lin K, Mazarati JB, Ménard S, Morlais I, Muhindo-Mavoko H, Musset L, Na-Bangchang K, Nambozi M, Niaré K, Noedl H, Ouédraogo JB, Pillai DR, Pradines B, Quang-Phuc B, Ramharter M, Randrianarivelojosia M, Sattabongkot J, Sheikh-Omar A, Silué KD, Sirima SB, Sutherland C, Syafruddin D, Tahar R, Tang LH, Touré, OA Tshibangu-wa-Tshibangu P, Vigan-Womas I, Warsame M, Wini L, Zakeri S, Kim S, Eam R, Berne L, Khean C, Chy S, Ken M, Loch K, Canier L, Duru V, Legrand E, Barale JP, Stokes B, Straimer J, Witkowski B, David A. Fidock DA, Christophe Rogier C, Pascal Ringwald P, Frederic Ariey F, Odile Mercereau-Puijalon O, for the KARMA Consortium (2016). A worldwide map of *Plasmodium falciparum* K13-propeller polymorphisms. N. Engl. J. Med. 374:2453-2464.

MSHP (2007). Ministère de la Santé et de l'Hygiène Publique. Arrêté N°024/CAB/MSHP du 02 janvier 2007 portant institution d'un schéma thérapeutique pour le traitement du paludisme en Côte d'Ivoire. Abidjan: Journal officiel.

MSHP (2010). Ministère de la Santé et de l'Hygiène Publique. Programme National de Lutte contre le Paludisme, Rapport de l'analyse situationnelle. PNLP, Abidjan, Côte d'Ivoire.

MSHP (2018). Ministère de la Santé et de l'Hygiène Publique. Arrêté N°190/CAB/MSHP du 27 novembre 2018 portant actualisation du schéma thérapeutique et préventif du paludisme en Côte d'Ivoire. Abidjan: Journal officiel.

MSLS (2014). Ministère de la Santé et de la Lutte contre le Sida. Arrêté N°109/CAB/MSLS du 14 juillet 2014 portant institution d'un schéma thérapeutique pour le traitement du paludisme en Côte d'Ivoire. Abidjan: Journal officiel.

Noed H, Schaecher YSK, Smith BL, Socheat D and Fukuda MM (2008). Evidence of artemisinin-resistant malaria in western Cambodia. N. Engl. J. Med. 359: 2619-2620.

Ogouyèmi-Hounto A, Damien G, Deme AB, Ndam NT, Assohou C, Tchonlin D, Mama A, Hounkpe VO, Moutouama JD, Remoué F, Ndiaye D, Gazard DK (2016). Lack of artemisinin resistance in*Plasmodium falciparum*in northwest Benin after 10 years of use of artemisinin-based combination therapy. Parasite. 23, 28.

Raobela O, Andriantsoanirina V, Rajaonera DG, Rakotomanga TA, Rabearimanana S, Ralinoro F, Ménard D, Ratsimbasoa A (2018). Efficacy of artesunate–amodiaquine in the treatment of *falciparum* uncomplicated malaria in Madagascar. Malar. J. 17:284.

Roth JM, Sawa P, Makio N, Omweri G, Osoti V, Okach S, Choy F, Schallig HDFH, MensP(2018). Pyronaridine-artesunate and artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Kenyan children: a randomized controlled non- inferiority trial. Malar. J. 17:199. 29.

Talisuna AO, Karema C, Ogutu B, Juma E, Logedi J, Nyandigisi A, Mulenga M, Mbacham WF, Roger C, Guerin PJ, D'Alessandro U, Snow RW (2012). Mitigating the threat of artemisinin resistance in Africa: improvement of drug-resistance surveillance and response systems. Lancet Infect. Dis. 12(11): 888-896.

Taylor SM, Parobek CM, DeConti DK, Kayentao K, Coulibaly SO, Greenwood BM, Tagbor H, Williams J, BojangK,Njie F, Desai M, Kariuki S, Gutman J, Mathanga DP, Martensson A, Ngasala B, Conrad MD, Rosenthal PJ, Tshefu AK, Moormann AM, Vulule JM, Doumbo OK, Kuile FOT, Meshnick SR, Bailey JA, Juliano JJ (2015). Absence of putative artemisinin resistance mutations among *Plasmodium falciparum* in Sub-Saharan Africa: a molecular epidemiologic study. J. Infect. Dis. 211(5):680-688.

Toure OA, Assi SB, N'Guessan TL, Adji GE, Ako AB, Brou MJ, Ehouman MF, Gnamien LA, Coulibaly MAA,

Coulibaly B, Beourou S, Bassinka I, Soumahoro A, Kadjo F and Tanoh MA (2014). Open-label, randomized, non-inferiority clinical trial of artesunate-amodiaquine versus artemether-lumefantrine fixed-dose combinations in children and adults with uncomplicated falciparum malaria in Côte d'Ivoire. Malar. J. 13:439.

Toure OA, Landry TN, Assi SB, Kone AA, Gbessi EA, Ako BA, Coulibaly B, Kone B, Ouattara O, Beourou S, Koffi A, Remoue F, Rogier C (2018). Malaria parasite clearance from patients following artemisinin-based combination therapy in Côte d'Ivoire. Infect. Drug Resist. 11: 2031-2038.

Van Den Broek I, Kitz C, Al Attas S, Libama F, Balasegaram M, and Guthmann JP (2006). Efficacy of three artemisinin combination therapies for the treatmentof uncomplicated *Plasmodium falciparum* malaria in the Republic of Congo. Malar.J, vol. 5, article 113.

WHO (2001). World Health Organization. Antimalarial Drug Combination Therapy: Report of a Technical Consultation, World Health Organization, Geneva, Switzerland.

WHO (2007). Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite population. Edited by Informal consultation organized by the Medicines for Malaria Venture and cosponsored by the World Health Organization. Amsterdam: Medicine for Malaria Venture and the World Health Organization.

WHO (2009). Methods for Surveillance of Antimalarial Drug Efficacy. Geneva: World Health Organization.

WHO (2010). Global report on antimalarial drug efficacy and drug resistance: 2000-2010.

WHO (2017). Artemisinin and artemisinin-based combination resistance. Geneva: World Health Organization.

WHO (2019). World malaria report 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

Woodrow CJ, White NJ (2017). The clinical impact of artemisinin resistance in Southeast Asia and the potential for future spread. FEMS Microbiol. Rev. 41(1):34-48.

Yavo W, Konaté A, Kassi FK, Djohan V, Angora EK, Kiki-Barro PC, Vanga-Bosson H, Menan EIH (2015). Efficacy and Safety of Artesunate-Amodiaquine versus Artemether-Lumefantrine in the Treatment of Uncomplicated *Plasmodium falciparum* Malaria in Sentinel Sites across Côte d'Ivoire. Malar. Res. Treat. 878132, 8pages.