

EFFICACY OF SIX-DOSE REGIMEN OF ARTEMETHER-LUMEFANTRINE FOR THE TREATMENT OF UNCOMPLICATED *FALCIPARUM* MALARIA, THREE YEARS AFTER ITS INTRODUCTION INTO ÉTHIOPIA

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Summary:

We assessed the clinical and parasitological efficacy of six-dose regimen of artemether-lumefantrine (AL) (Coartem®) for treating uncomplicated *P. falciparum* malaria three years after its introduction into Ethiopia. A total of 102 patients (mean age: 15.7 years; age range: 1-50 years) were enrolled in the study and followed-up for 28 days based on WHO protocol. Treatment with AL resulted in 100 % adequate clinical and parasitological response (ACPR). No severe side-effect of the drug was observed. All patients had rapid clinical and parasitological responses. None of the subject was found to be positive for asexual or sexual stage of the parasite after day 3. A significant increase in the mean of haemoglobin level was observed on day 28 post-treatment (11.4 g/dl on day 0 vs 12.3 g/dl on day 28, $p < 0.05$). Thus, artemisinin-based combination therapies (ACTs) seem to mitigate not only the problem of drug resistance malaria but also the transmission of the disease. Nevertheless, monitoring ACT therapeutic efficacy is crucial in Ethiopia.

KEY WORDS : *P. falciparum*, malaria, artemether-lumefantrine, efficacy, Ethiopia.

Résumé : EFFICACITÉ CLINIQUE ET PARASITOLOGIQUE DE L'ASSOCIATION ARTHÉMÉTHÉTER-LUMÉFANTRINE EN SIX PRISES SUR LE PALUDISME NON COMPLIQUÉ À *P. FALCIPARUM*, TROIS ANS APRÈS SA MISE À DISPOSITION EN ÉTHIOPIE

Nous avons estimé l'efficacité clinique et parasitologique de l'association arthéméther-luméfántrine (AL) (Coartem®) en six prises sur le paludisme non compliqué à *P. falciparum*, trois ans après sa mise à disposition en Éthiopie. 102 patients d'âge moyen de 15,7 ans (1-50 ans) ont été inclus dans l'étude et suivis pendant 28 jours selon le protocole de l'OMS. Une bonne réponse clinique et parasitologique a été observée chez 100 % des sujets traités par AL. Aucun effet secondaire sévère n'a été relevé. Les réponses clinique et parasitologiques ont été rapides chez tous les patients. Après trois jours de traitement, aucun d'entre eux ne présentait de parasite à un stade sexué ou asexué. Une élévation significative de l'hémoglobininémie a été observée au 28^{ème} jour de traitement (11,4 g/dl à J-0 vs 12,3 g/dl à J-28, $p < 0,05$). Si les traitements combinés à base d'artémisinine semblent atténuer les problèmes de résistance de *P. falciparum* aux antipaludéens, ils diminuent aussi la transmission de la maladie. Pour autant, le suivi de l'efficacité de ces traitements combinés est d'une importance capitale en Éthiopie.

MOTS CLÉS : *P. falciparum*, paludisme, arthéméther-luméfántrine, efficacité, Éthiopie.

In Ethiopia, malaria is a major public health problem. *Plasmodium falciparum* is the widely distributed species, which cause the majority of morbidity and mortality especially in malaria epidemic situations (UNICEF Ethiopia). Chloroquine (CQ) was the most common antimalarial drug used to treat *falciparum* malaria for decades in the country. However, the wide spreads of multi-drug resistant *P. falciparum* incapacitated the use of CQ (Taklehaimanot, 1986) and then sulphadoxine-pyrimethamine (SP) (Jima *et al.*, 2005) as in many African countries (Trape, 2001; Korenromp *et al.*, 2003; Winstanley *et al.*, 2004).

As a response to increasing levels of resistance to anti-malarial drugs, WHO (2001) recommends that all countries experiencing resistance to conventional mono-

therapies, such as CQ, AQ or sulfadoxine-pyrimethamine (SP), should use combination therapies, preferably those containing artemisinin derivatives (ACTs – artemisinin-based combination therapies) for treatment of uncomplicated *falciparum* malaria. In line with this WHO guideline, Ethiopia has also decided to use artemether-lumefantrine (AL) as the first-line drug for the treatment of uncomplicated *falciparum* malaria since July 2004 (FMOH, 2004). The safety and therapeutic efficacy of six-dose regimen of AL against *P. falciparum* was studied at its introduction in limited malaria endemic sites and reported to be 99.1 % efficacious (Jima *et al.*, 2005b). Nevertheless, experience from previous unexpected resistance development of *falciparum* malaria parasite to effective antimalarial drugs necessitates substantial re-assessment of the efficacy of AL against *P. falciparum* to monitor efficacy on regular basis for possible emergence of resistance and ensuring a continued coverage of effective treatment (Hasting *et al.*, 2007). In this study, the current clinical and parasitological efficacy of six-dose regimen of AL

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was assessed for the treatment of uncomplicated *falciparum* malaria three years after its introduction into Ethiopia.

PATIENTS AND METHODS

STUDY SITE AND PERIOD

The study was conducted at Alaba Kulito Health Center, Southern Ethiopia between October and December 2007. Alaba Kulito Health Center is found in a rural town about 313 km to the south of Addis Ababa. Most of the inhabitants were belonged to Alaba ethnic group and earn their living as farmers practicing settled mixed agriculture, mainly cultivation of maize and rearing of cattle. Alaba area experiences dry winter and rainy summer seasons. It's annual temperature and rainfall ranges between 18-23°C and 857-1,085 mm, respectively. The area is located at an altitude ranges from 1,700 to 2,200 meter above sea level. The area is endemic for malaria and the transmission is seasonal. Malaria transmission occurs from August to December following the major rainy season while minor transmission occurs in April and May. *P. falciparum* and *P. vivax* are prevalent in the area. The area is characterized by low to moderate malaria transmission intensity. The study site was purposely selected; because it is an area where a treatment failure rate of SP to *P. falciparum* was recorded in 2003 (Jima *et al.*, 2005a), and AL has been used as the first-line drug for the treatment of uncomplicated *falciparum* malaria since its implementation in the country (FMOH, 2004).

PATIENT ENROLMENT

All self presented patients age over one year and suspected for malaria were eligible to be screened for recruitment in the study. WHO guideline for the *in vivo* assessment of the therapeutic efficacy of anti-malarial drugs in the treatment of uncomplicated *falciparum* malaria was used to estimate sample size and enrolled the patients (WHO, 2003). Accordingly, the inclusion criteria were mono-infection with *P. falciparum*, parasitaemia between 1,000 and 100,000/µl of blood, axillary temperature ≥ 37.5 °C or a history of fever during the last 24 hours, body weight > 10 kg, absence of severe malnutrition, absence of febrile conditions caused by diseases other than malaria, absence of signs of severe malaria, haemoglobin (Hb) ≥ 5 g/dl, able to come during the stipulated schedule and informed consent of parents/guardians.

TREATMENT AND FOLLOW-UP

Patients were treated with six-dose regimen of AL (Coartem®; Novartis Pharma AG, Basel, Switzerland)

according to body weight as per the national malaria diagnosis and treatment guideline (FMOH, 2004). The patients were directly observed for at least 30 minutes following the first dose administration. For those who vomited within 30 minutes of treatment, the full treatment dose was repeated. All patients took the morning doses under direct supervision for the three consecutive days, while the evening doses were given to the patients or their guardians to be taken at home with adequate instruction. Next morning, the patients or their guardians were interviewed for proper use of the drug and absence of vomiting. Paracetamol tablets were given to some of the patients who were complaining for high fever.

Patients were regularly re-assessed on days 1, 2, 3, 7, 14, 21 and 28 and any other day when he/she reported unwell. Blood was obtained by finger prick on days 0, 3, 7, 14, 21 and 28. Thick and thin blood films were prepared, stained with 10 % Giemsa for 10 minutes and microscopically examined for malaria parasites. Parasite count was performed by counting the number of asexual parasites per 200 white blood cells, and parasite density was calculated per micro liter of blood assuming total leucocytes of 8,000/µl (WHO, 2003). Blood films were considered negative if no asexual forms of *P. falciparum* were observed thick in 100 film fields. Species were confirmed on the fixed thin smear. Gametocytes were also scanned and counted during the follow-up period.

Blood samples were also collected on day 0 on to filter paper for molecular analysis in case of parasite reappearance during the follow-up period. Haemoglobin was measured on day 0 and day 28 using a HemoCue portable photometer. Relevant clinical signs and symptoms as well as body temperature of all the study subjects were assessed and recorded by experienced health officers on day 0 and during the follow up periods.

ASSESSMENT OF TREATMENT OUTCOME

Early Treatment Failure (ETF), Late Clinical Failure (LCF), Late Parasitological Failure (LPF) and Adequate Clinical and Parasitological Response (ACPR) were assessed as outcomes using WHO guideline for the *in vivo* assessment of the therapeutic efficacy of anti-malarial drugs in the treatment of uncomplicated *falciparum* malaria (WHO, 2003).

STATISTICAL ANALYSIS

Data were entered and analyzed using a software designed by WHO for therapeutic efficacy assessment (<http://www.who.int/malaria/toolsformonitoring.html>). Efficacy data was analyzed for patients who completed the follow-up. Variables ETF, LCF, LPF, ACPR, asexual and sexual stages, average body temperature, haemoglobin level and clinical sign and symptoms

were summarized using tables and figures when appropriate. Changes in average parasitaemia and gametocyte levels between day 0 and day 3, and changes in average haemoglobin level between day 0 and day 28 were compared using paired t-test and χ^2 test was used to compare proportion. *P* value less than 0.05 was considered statistically significant.

ETHICAL CONSIDERATIONS

The study protocol was reviewed and approved by the Ethics Committee of the Aklilu Lemma Institute of Pathobiology, Addis Ababa University as well as by the National Ethical Clearance Committee. Written informed consent was obtained from participants or guardians. Blood samples were collected under aseptic conditions. Patients who were not included in the study, but found positive either for *P. falciparum* or *P. vivax malaria* were treated according to the national policy for malaria treatment in Ethiopia (FMOH, 2004).

RESULTS

Of 2,000 self presenting febrile patients screened for malaria, 190 (9.5 %), 1,048 (52.4 %) and 7 (0.35 %) were infected with *P. falciparum*,

Characteristic	Value
No. of patients	
< 5 years	15 (14.7 %)
5-15 years	38 (37.3 %)
> 15 years	49 (48.0 %)
Mean age (years)	15.7 (range : 1-50)
Mean body weight (kg)	35.8 (range : 9.7-78.5)
Average body temperature (°C)	37.5 (range : 35.5-40)
Mean haemoglobin (g/dL)	11.4 (range : 5-17.1)
Mean parasitaemia (count/ μ l of blood)	8,264.3 (range : 1,000-88,000)
Mean gametocytaemia (count/ μ l of blood)	0.3 (range 0-14) ^c

Table I. – Baseline characteristics on day 0 of the 102 patients who completed the follow-up.

Description	Day 0 Mean (SD)	Day 3 Mean (SD)	Day 7 Mean (SD)	Day 14 Mean (SD)	Day 21 Mean (SD)	Day 28 Mean (SD)
Trophozoites/ μ l of blood	8,264.3 (12,620.6)	8.6 (54.8)	0	0	0	0
Gametocytes/ μ l of blood	0.3 (1.6)	0.1 (0.8)	0	0	0	0
Haemoglobin (g/dL)	11.4 (2.8)	NM	NM	NM	NM	12.3 (2.3)
Average body Tem (°C).	37.5 (0.8)	36.8 (0.6)	36.6 (0.6)	36.4 (0.7)	36.6 (0.5)	36.7 (0.5)

NM = not measured.

Table II. – Levels of parasitaemia, sexual stage and average body temperature of the participants on admission and during the follow up period.

P. vivax and with *P. falciparum* plus *P. vivax* respectively. Among falciparum malaria cases, 108 (56.8 %) fulfilled the inclusion criteria and enrolled in the study. Six patients (5.6 %) were excluded from the analysis (five cases were lost to follow-up and one individual took additional anti-malarial medication from private pharmacy during the follow-up period). Of the 102 patients who completed the follow-up, 97 (95.1 %) had asexual stage and 5 (4.9 %) had both asexual and sexual (gametocytes) stages. The baseline characteristics of participants are shown in Table I.

Table II shows level of parasitaemia, gametocytes and body temperature during the follow up period. High parasitaemia reduction rate was observed on day 3 compared to day 0 (8,264.3 vs 8.6, $p < 0.000$). None of the subject was found positive for asexual parasitaemia or gametocytes after day 3 and thereafter. Haemoglobin level also showed progressive increment from an average of 11.4 g/dL on day 0 to 12.3 g/dL on day 28 ($p < 0.05$).

Of 102 patients who completed the follow-up, 100 % were assessed as ACPR, and there was no treatment failure (Table III).

Treatment outcomes	Number of patients	Percentage
ETF	0	0 % (95 % CI: 0-3.5 %)
LCF	0	0 % (95 % CI: 0-3.5 %)
LPF	0	0 % (95 % CI: 0-3.5 %)
ACPR	102	100 % (95 % CI: 96.5-100 %)
Total	102	

Table III. – Parasitological and clinical responses of patients with uncomplicated *P. falciparum* malaria following treatment with Coartem[®].

On day of admission, 96 (94.1 %), 82 (80.4 %), 74 (72.5 %), 78 (76.5 %), 34 (33.3 %), 21 (20.6 %), 19 (18.6 %) and 4 (3.9 %) subjects had complained fever, weakness, muscle pain, headache, anorexia, cough, vomiting and diarrhea respectively. Most of these cli-

Symptoms	Follow-up days and number of complaints (%)							
	Day 0	Day 1	Day 2	Day 3	Day 7	Day 14	Day 21	Day 28
Fever	96 (94.1 %)	57 (55.9 %)	18 (17.6 %)	7 (6.9 %)	2 (2.0 %)	0 (0 %)	0 (0 %)	1 (0.98 %)
Weakness	82 (80.4 %)	61 (59.8 %)	21 (20.6 %)	11 (10.8 %)	7 (6.9 %)	6 (5.9 %)	1 (0.98 %)	0 (0 %)
Headache	78 (76.5 %)	35 (34.3 %)	10 (9.8 %)	6 (5.9 %)	4 (3.9 %)	6 (5.9 %)	0 (0 %)	1 (0.98 %)
Muscle pain	74 (72.5 %)	44 (43.1 %)	11 (10.8 %)	6 (5.9 %)	2 (2.0 %)	5 (4.9 %)	2 (2.0 %)	1 (0.98 %)
Anorexia	34 (33.3 %)	11 (10.8 %)	3 (2.9 %)	0 (0 %)	1 (0.98 %)	0 (0 %)	0 (0 %)	0 (0 %)
Cough	21 (20.6 %)	14 (13.7 %)	10 (9.8 %)	4 (3.9 %)	2 (2.0 %)	2 (2.0 %)	2 (2.0 %)	0 (0 %)
Vomiting	19 (18.6 %)	1 (0.98 %)	0 (0%)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Diarrhea	4 (3.9 %)	2 (2.0 %)	2 (2.0 %)	0 (0 %)	1 (0.98 %)	0 (0 %)	1 (0.98 %)	0 (0 %)

Table IV. – Patients clinical complain on admission and during the follow up period.

nical symptoms were resolved by day 3 ($p < 0.05$), and few patients complained up to day 28 (Table IV). Any severe adverse effect of the drug was not reported/observed during the follow-up.

DISCUSSION

In this study, we carried out efficacy study on AL three years after its implementation in an area where a treatment failure of SP to *P. falciparum* was previously documented (Jima *et al.*, 2005a). Series evidences have shown high efficacy of ACTs against *P. falciparum* even in multidrug-resistant strains of the parasite (Lefevre *et al.*, 2001; Makanga *et al.*, 2006; Adama *et al.*, 2007; Menard *et al.*, 2008; Kaddouri *et al.*, 2008). Nevertheless, substantial re-assessment of the efficacy of this combination therapy against *P. falciparum* is crucial to monitor possible emergence of resistance and ensuring a continued coverage of effective treatment.

Our results showed 100 % ACPR to AL. This is comparable with the previous study that showed a high treatment success rate (99.1 %) in the country (Jima *et al.*, 2005b). The finding of this study is also in agreement with other studies in children and adults elsewhere using ACTs (Van Vugt *et al.*, 1999, 2000; Lefevre *et al.*, 2001; Flade *et al.*, 2005; Jima *et al.*, 2005b; Piola *et al.*, 2005; Piola *et al.*, 2005; Guthmann *et al.*, 2006; Van den Broek *et al.*, 2006; Adama *et al.*, 2007).

In a study conducted in Senegal, the efficacy of AL was found to be 100 % when given as six doses, while it was found to be reduced by 3.6 % when given as four doses (Faye *et al.*, 2007). Study by Lefevre *et al.* (2001) showed a high efficacy and safety of six-dose of AL when administrated as four tablets twice daily for three consecutive days. Moreover, a pooled analysis

of individual patient data confirmed higher efficacy of six-dose regimen of AL compared to four-dose regimen in children (Makanga *et al.*, 2006). The present result also indicated the importance of maintaining the six-dose regimen for the treatment of uncomplicated *falciparum* malaria with regularly monitoring for its effectiveness especially in areas where multi-drug resistance *falciparum* malaria is common (Hastings *et al.*, 2007). In this study, treatment with AL was also found to induce rapid clearance of malaria symptoms which is in agreement with previously conducted study in Ethiopia and clinical studies conducted elsewhere using ACTs (Bakshi *et al.*, 2000; Lefevre *et al.*, 2001; Jima *et al.*, 2005b; Mulenga *et al.*, 2006; Menard *et al.*, 2008). In addition to its rapid parasitological and malaria symptoms clearance, AL showed high gametocyte reduction during the follow-up. This observation supports the implication that artemisinin-based combination therapy could have additional benefit to the community by reducing *falciparum* malaria transmission if the drug is widely deployed in endemic areas (Targett *et al.*, 2001; Guthmann *et al.*, 2006; Van den Broek *et al.*, 2006; Mulenga *et al.*, 2006; Hatz *et al.*, 2008). Compared to baseline data, a significant increase in the mean of haemoglobin level was observed on day 28 post-treatment, which also indicates the added benefit of treating patients with this combination therapy as anemia could be aggravated by resistant parasite (Guthmann *et al.*, 2006; Van den Broek *et al.*, 2006; Mulenga *et al.*, 2006).

CONCLUSION

AL was found to be highly efficacious for the treatment of *falciparum* malaria three years after its introduction in Ethiopia without serious

adverse events. In addition, the drug has shown a gametocytocidal effect. Thus, ACTs seem to mitigate not only the problem of drug resistance malaria but also the transmission of the disease. Nevertheless, there is a need to assess periodically the therapeutic efficacy of AL in Ethiopia, as part of the activities for the surveillance of the emergence of resistant parasite against this valuable drugs.

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