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## Good Efficacy of Artemether-Lumefantrine for Uncomplicated Falciparum Malaria in Eastern Sumba, East Nusatenggara, Indonesia

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### ABSTRAK

**Tujuan:** untuk menilai keamanan dan efektifitas dari penggunaan kombinasi tetap artemeter-lumefantrine terhadap kegagalan terapi artesunat-amodiaquine lini pertama. **Metode:** studi ini merupakan penelitian terbuka tunggal tanpa kontrol. Kami menilai penggunaan terapi standar artemeter-lumefantrine terhadap 59 subyek dengan malaria tanpa komplikasi yang disebabkan oleh *Plasmodium falciparum* di pulau Sumba, Indonesia Timur. Tidak ada kegagalan terapi hingga hari ke-35. Seorang subjek memiliki parasitemia rekuren pada hari ke-42 yang menunjukkan genotipe konsisten dengan rekrudesensi yang terjadi. Sehingga, efikasi terapi ini diperkirakan sebesar 98,3% (95% CI = 95%-100%). Analisis deskriptif dilakukan dengan menggunakan SPSS versi 12. **Hasil:** dua ratus tiga belas subyek dengan *P. falciparum* yang memenuhi kriteria inklusi dalam studi kemanjuran *in vivo*, 79 subyek diberi artemeter-lumefantrine dan 134 subyek diterapi dengan protokol lain menggunakan artesunat-amodiaquine atau sulfadoksin-pirimetamin. Di antara 79 subyek yang memenuhi kriteria, 59 subyek berhasil menyelesaikan pemeriksaan yang berlangsung selama 42 hari. Seperti yang diharapkan, nilai rerata PCT lebih lama dibandingkan nilai rerata FCT, yaitu masing-masing sebesar  $1,34 \pm 0,67$  (95% CI 1,21-1,47) dan  $1,05 \pm 0,05$  (95% CI 0,95-1,15) hari. Pada hari ke-3 pengobatan, baik demam maupun fase aseksual *P. falciparum* menghilang pada semua subyek. Pengamatan sampai hari ke-35 menunjukkan bahwa 59 subyek yang diobati dengan artemeter-lumefantrine ternyata sembuh. **Kesimpulan:** temuan dari studi tanpa kontrol ini menunjukkan keamanan dan efikasi yang baik artemeter-lumefantrine untuk pengobatan malaria *falciparum* tanpa komplikasi di Pulau Sumba dan Kepulauan Sunda Kecil di Indonesia.

**Kata kunci:** Artemisinin, artemeter-lumefantrin, *Plasmodium falciparum*, Indonesia.

### ABSTRACT

**Aim:** to evaluate the safety and efficacy of a fixed combination of artemether-lumefantrine for likely use against failures of the artesunate-amodiaquine first line therapy. **Methods:** the study was an open label single arm uncontrolled trial. we evaluated the safety and efficacy of standard artemether-lumefantrine therapy in 59 subjects with uncomplicated malaria caused by *Plasmodium falciparum* on the island of Sumba in eastern Indonesia. No treatment failures occurred up to day 35. One subject had recurrent parasitemia on day 42 that

showed a genotype consistent with recrudescence. The efficacy of this therapy was thus estimated to be 98.3% (95% confidence interval=95%-100%). Descriptive analysis was done using the SPSS 12 computer software. **Results:** two hundred and thirteen *P. falciparum* patients met the inclusion criteria for in vivo efficacy study, 79 were given artemether-lumefantrine and 134 were treated under another protocol with artesunate-amodiaquine or sulfadoxine-pyrimethamine. Among 79 eligible subjects, 59 successfully completed the 42-day test. As expected, the mean PCT was longer than the mean FCT, i.e.  $1.34 \pm 0.67$  (95% CI 1.21–1.47) and  $1.05 \pm 0.05$  (95% CI 0.95–1.15) days, respectively. On day 3 of treatment, both fever and asexual stage of *P. falciparum* disappeared in all subjects. Observation until Day 35 showed that all of the 59 subjects treated with artemether-lumefantrine were cured. **Conclusion:** the findings of this uncontrolled study suggest good safety and efficacy of artemether-lumefantrine for treatment of uncomplicated *falciparum* malaria on Sumba Island in the Lesser Sundas archipelago of eastern Indonesia.

**Key words:** Artemisinin, artemether-lumefantrine, *Plasmodium falciparum*, Indonesia.

## INTRODUCTION

In Indonesia chloroquine treatment failure during *P. falciparum* malaria ranges from 25%–99% in almost every major island of this archipelago nation.<sup>1-3</sup> Biomolecular studies of *P. falciparum* gene mutations linked to chloroquine resistance (pfcrt single nucleotide polymorphisms) tend to corroborate the in vivo findings from the field.<sup>4-5</sup>

The Indonesian Ministry of Health finally replaced chloroquine as the first-line therapy for uncomplicated *falciparum* malaria in 2004, selecting the combination of artesunate-amodiaquine.<sup>6</sup> The principal appeal to artesunate-amodiaquine as the drug of choice for the treatment of *P. falciparum* infection was the fact that amodiaquine was never before used in this country and its lower cost as compared to artemether-lumefantrine. Nevertheless, the high resistance rate of *P. falciparum* to chloroquine in almost all provinces in Indonesia, coupled with the possibility of cross resistance between chloroquine and amodiaquine have cast doubts on the sustainable efficacy of artesunate-amodiaquine.<sup>7-8</sup> Due to low compliance of seven days quinine and doxycycline as the current second line, Indonesia might consider the adoption of artemether-lumefantrine as alternative. Therefore, this study explored the safety and efficacy of a fixed combination of artemether-lumefantrine for likely use against failures of the artesunate-amodiaquine first line therapy.

This study was conducted at the Waingapu Primary Health Center, Eastern Sumba district, Sumba Island in Eastern Nusatenggara province, from February to September 2004. Like other regions of Indonesia, Sumba has dry (May to November) and rainy (December to April)

seasons. At the time of this study chloroquine and sulfadoxine-pyrimethamine were still the first- and the second-line therapies against *falciparum* malaria. However, in 2002, in vivo studies on these drugs in Eastern Nusatenggara, revealed that the failure rates of chloroquine were 65% and 69% on Western Sumba and Alor island, respectively, and 8.5% in Alor for sulfadoxine-pyrimethamine.<sup>9-10</sup>

## METHODS

The study was an open labeled single arm uncontrolled trial. The inclusion criteria were in accordance with those recommended by the WHO.<sup>11</sup> All subjects gave written informed consent. This research protocol was approved by the Committee of Medical Research Ethics of the Faculty of Medicine, University of Indonesia, Jakarta.

The eligible patients were then given Coartem<sup>®</sup> (Novartis) orally, which contains 20 mg artemether and 120 mg lumefantrine in fixed combination, with the following dosage: body weight from 10 to 14 kg: 2 x 1 tablet daily, BW from 15 to 24 kg: 2 x 2 tablets daily, BW from 25 to 34 kg: 2 x 3 tablets daily, BW from 35 kg and above: 2 x 4 tablets daily. The drug was given for a total of 3 days. The morning dose and the evening dose were given in the Waingapu Health Centre under direct supervision.

All subjects were followed up for 42 days and asked to return to the health centre on days 1, 2, 3, 7, 14, 21, 28, 35, and 42. At each visit the axillary temperature was taken using a digital thermometer. Thick and thin blood films and blotting on Whatman filter paper no.1 for parasite genotyping were made by blood samples

obtained by finger prick.

The observation of each patient ended if the treatment failed (becoming parasitemic), succeeded (remaining free of parasitemia up to day 42), or if lost to follow up, withdrawal from the study, or protocol violation.

All adverse event data were collected from the patients in a yes-or-no form during their follow-up visits. If the adverse events started at day 0 and vanished concomitantly with the disappearance of fever and/or parasitemia, a disease-related causality was assumed. If the adverse event persisted despite disappearance of parasite and fever, a drug-related causality was explored.

Parasite clearance time was determined from the first day of drug administration until its disappearance and persisted for 2 days. Fever clearance time was only evaluated in patients having fever on day 0 and measured at the point at which body temperature fell to  $<37.5^{\circ}\text{C}$  and the patient remained afebrile for 2 subsequent days.

Blood samples for genetic analysis from patients were taken prior to treatment and at the time of treatment failure. This technique was applied to discriminate whether reappearance of parasitemia during follow up period originally from new infection or a recrudescence of old infection. Microscopic examination was not able to differentiate these two conditions, but merozoite surface protein-2 genotyping discriminated recrudescence from re-infection. Real-time quantitative PCR, using LightCycler system (Roche Applied Science), was performed with fluorescent SYBR Green 1 dye binding specifically to double-stranded DNA.<sup>12</sup> PCR product identity was assessed by the specific melting temperature obtained for each genotype and confirmed by gel electrophoresis migration.

Descriptive analysis was done using the SPSS 12 computer software. Only patients having taken 6 doses of drug and classified as “failed” or “successful” were included in the per-protocol analysis.

## RESULTS

Blood examination was done on 2,278 patients who came to the Waingapu Primary Health Center suspected of having malaria. A total of 23% (525) had slide-proven malaria with *P. falciparum* (356) the dominant species followed by *P. vivax* (119), mixed infection of the

two species (47), and *P. malariae* (3), respectively.

Two hundred and thirteen *P. falciparum* patients met the inclusion criteria for in vivo efficacy study, 79 were given artemether-lumefantrine and 134 were treated under another protocol with artesunate-amodiaquine or sulfadoxine-pyrimethamine (Sutanto et al, unpublished). Twenty out of 79 patients were then not included in per-protocol analysis for several reasons. Three were hospitalized on the first day of artemether-lumefantrine treatment. The reason of hospitalization of the 3 patients were vomiting, diarrhea and high fever ( $\geq 39^{\circ}\text{C}$ ). These symptoms were due to malaria disease, but were not related to the treatment. They were then given intravenous quinine and all were discharged from the hospital after 3 days. The other 12 were found to have *P. vivax* infection during the 42-day follow-up period. Four patients were lost to follow-up on day 28 (1 subject) or day 42 (3 subjects). One subject was excluded with evidence of *P. falciparum* reinfection as indicated by the PCR test showed 3D7-type at admission and FC27-type on day 42, was therefore classified as having been reinfected. In summary, among 79 eligible subjects, 59 successfully completed the 42-day test.

As expected, the mean PCT was longer than the mean FCT, i.e.  $1.34 \pm 0.67$  (95% CI 1.21 – 1.47) and  $1.05 \pm 0.05$  (95% CI 0.95 – 1.15) days, respectively. On Day 3 of treatment, both fever and asexual stage of *P. falciparum* disappeared in all subjects.

Observation until Day 35 showed that all of the 59 subjects treated with artemether-lumefantrine were cured. On day 42, however, parasitemia had reappeared in 1 subject. Genotyping analysis showed that one had identical 3D7-type alleles at admission and failure (d42), confirming recrudescence. Therefore, the corrected cure rate on day 42 was 98.3% (58/59). The summary of recruitment patients until the outcomes of in vivo study is showed in **Figure 1**.

Gametocytemia occurred in 18 (30.5%) subjects in this study. In 8 (13.6%) cases gametocytemia was identified prior to treatment, while in 10 (16.9%) it was found during the treatment period (six, three and one persons on days 1, 2 and 3, respectively). Thereafter, a consistent disappearance of gametocyte till day 42 was observed in all cases. The mean length of the gametocytemia was 2.5 days (95% CI 1.59 – 3.41, range 1 – 6 days).

The most frequent of physical complaints on day of recruitment were headache and nausea, which were 86.2% and 67.8%, respectively. Other complaints were far less common (**Figure 2**). Complaint of headache became 16.9% on day-7 and persisted to day 42 in 5% of these subjects.

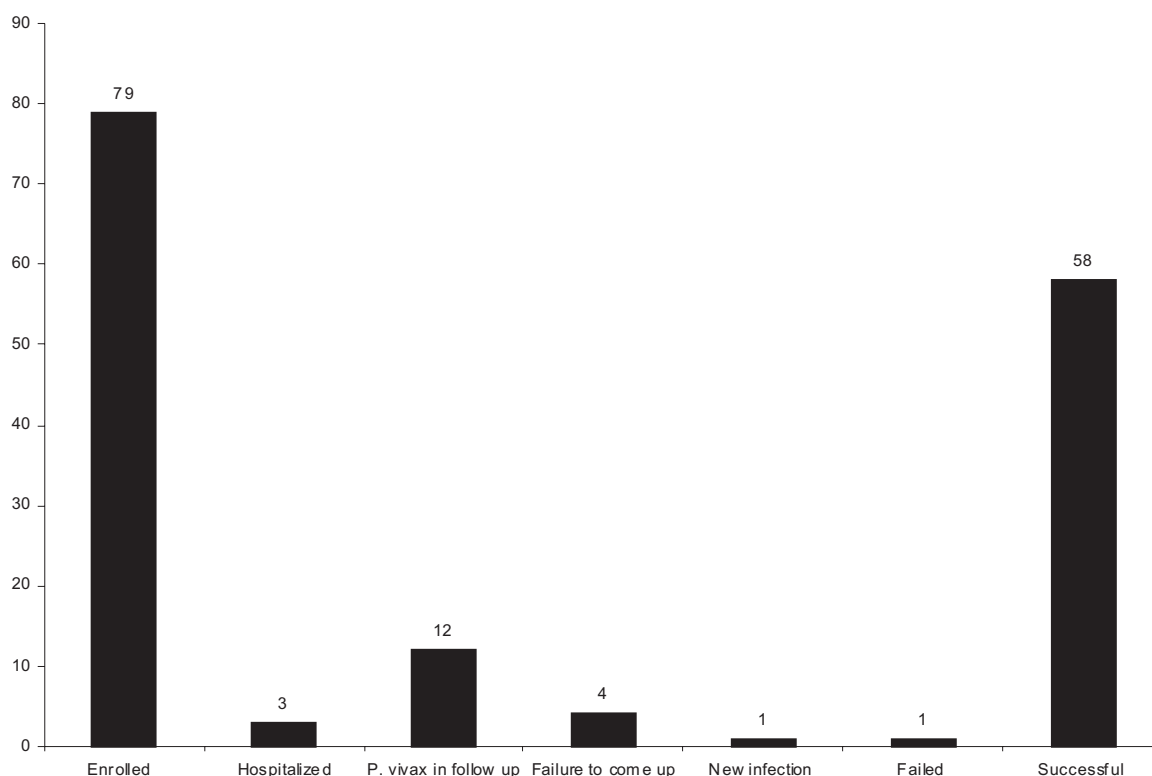
## DISCUSSION

In the present study artemether-lumefantrine proved safe and highly efficacious in 59 residents of eastern Sumba Island presenting with uncomplicated falciparum malaria. Another study in southern Papua of Indonesia, an area with multidrug resistant *P. falciparum* also showed high cure rate (95.3%) of artemether-lumefantrine after PCR correction.<sup>13</sup> The intensity of malaria transmission over the Indonesian archipelago varies widely among endemic areas, and pattern of drug resistance shift over both geographic area and time. Therefore, decision for treatment policy is more complex here than in other malaria countries. However, these two studies

(Sumba and Papua) demonstrated good efficacy of the artemether-lumefantrine consistently. Other studies outside Indonesia also had shown that artemether-lumefantrine effective for *P. falciparum* in areas of low to high level of malaria transmission, in non immune or semi immune infected children, in addition to the multidrug resistant parasite, with efficacy of 93.6%, 93%, 95%, 93.3% and 95.5%, respectively.<sup>14-17</sup>

Serious adverse events of the three hospitalized patients in this study could not only be attributed to the drug reactions itself, considering that headache and gastrointestinal disturbances were documented as major symptoms of patients on admission. All these patients were discharged from hospital without any sequelae. Therefore tolerance to artemether-lumefantrine in this study was deliberately good.

Although this study showed good efficacy and tolerance of artemether-lumefantrine for *P. falciparum* cases, the high cost of the drug and its ineffectiveness to *P. vivax* as the other



**Figure 1.** *P. falciparum* enrolled cases in Eastern Sumba and its analyses to outcomes of in vivo artemether-lumefantrine efficacy study

dominant species in Indonesia, limits artemether-lumefantrine utilization as second line therapy to *P. falciparum*. The current second line for *P. falciparum* cases in Indonesia is seven days combination of quinine and doxycycline or tetracycline. The low compliance of this combination due to chinchonism makes it as unfavorable choice both for doctors and patients. Therefore, this study is important as preliminary data for searching a better second line therapy.

## CONCLUSION

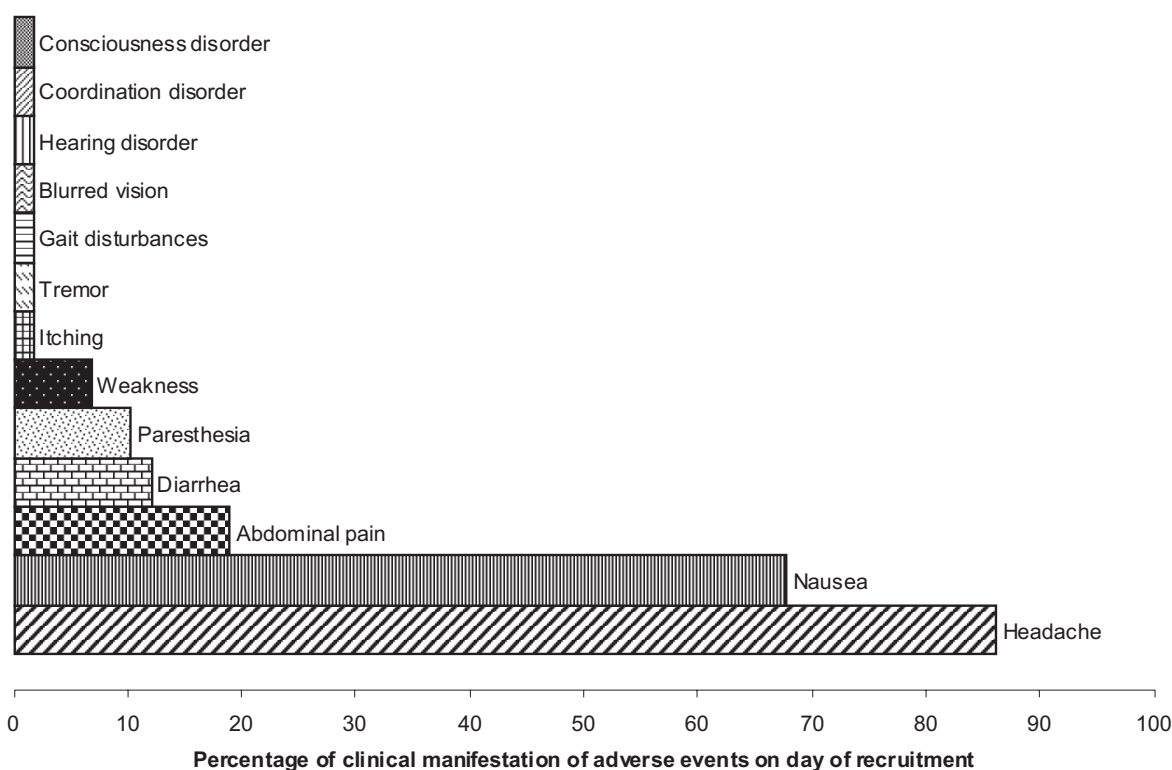
The findings of this uncontrolled study suggest good safety and efficacy of artemether-lumefantrine for treatment of uncomplicated falciparum malaria on Sumba Island in the Lesser Sundas archipelago of eastern Indonesia. A clinical trial of this combination against parasites that manage to survive treatment with artesunate-amodiaquine is required to fully assess its value as a second line therapy for uncomplicated falciparum malaria.

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**Figure 2.** Various clinical symptoms on admission of in vivo artemether-lumefantrine study in Eastern Sumba. Headache, nausea, abdominal pain, and diarrhea were the major symptoms

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