AN OPEN RANDOMIZED CLINICAL TRIAL OF ARTECOM® *VS* ARTESUNATE-MEFLOQUINE IN THE TREATMENT OF ACUTE UNCOMPLICATED FALCIPARUM MALARIA IN THAILAND

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Abstract. The efficacy and safety of Artecom® were assessed in an open randomized trial in adults presenting with acute, uncomplicated *Plasmodium falciparum* malaria in Thailand. Three hundred and fifty-two patients were randomly enroled at the ratio of 2: 1 into group A:B and received Artecom® (group A) and the standard combination of artesunate and mefloquine (group B) respectively. All patients had rapid initial clinical and parasitological responses. There were no significant differences in fever clearance time and parasite clearance time between the two groups. The 28-day cure rates were high as 97% in both groups. Artecom® was effective and well-tolerated as artesunate-mefloquine, the current treatment in this area of multidrug-resistant *P. falciparum* malaria.

INTRODUCTION

Malaria remains the most important human parasitic disease worldwide causing over 170 million clinical cases per year, and over a million deaths. It is still one of the public health problems in Thailand. Although, data collected in Thailand in the fiscal year 1997 revealed a decline of mortality rate to 1.26 per 100,000 population, the incidence of the disease increased by 25.42% especially *Plasmodium falciparum* infection in the southern part of Thailand (Malaria Division, 1998).

Approximately 1,500-2,200 malaria cases are admitted annually to Bangkok Hospital for Tropical Diseases. These include *P. falciparum* (45%), *P. vivax* (52%), mixed infections of *P. falciparum* and *P. vivax* (2%), a few cases of *P. malariae* and occasional cases of *P. ovale*. Admitted patients are all treated with antimalarial regimens and most of them are enroled for clinical trials.

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In Thailand, treatment of acute uncomplicated falciparum malaria is becoming more difficult because of increasing resistance to all antimalarial drugs, except the artemisinin derivatives (Bunnag and Harinasuta, 1987; Looareesuwan *et al*, 1992a,b,c). The degree of resistance to quinine has gradually increased and recently it is usually administered in combination with tetracycline for seven days (Looareesuwan *et al*, 1992d). Frequent administration due its to short half-lives (6-8 hours), long duration of drug administration (7 days), and side effects of quinine (cinchonism *eg* tinnitus, nausea, vomiting, palpitation, etc) may cause the patient not to complete the whole course of treatment, therefore recrudescence and drug resistance ensue. In contrast, when drug administration is supervised, cure rate of this combination is 90% (Looareesuwan *et al*, 1992d).

The artemisinin derivatives (artesunate and the recently developed dihydroartemisinin which is a short-acting but powerful drug) which have been studied extensively in the treatment of falciparum malaria in Thailand, are well tolerated. Similar to quinine, treatment for at least five days is required when used alone (Bunnag

et al, 1991; Looareesuwan *et al*, 1992; Luxemburger *et al*, 1995; Looareesuwan *et al*, 1997). At present, artesunate has been registered by the Thai FDA for use in the treatment of falciparum malaria.

Mefloquine is another antimalarial drug which is better tolerated than quinine and can be administered during a day, but resistance to mefloquine has developed when used alone. Furthermore, in Thailand where multidrug resistance is encountered, a high dose (25 mg/kg) of mefloquine is recommended for use as a combination with other short acting antimalarial drugs (Nosten *et al*, 1991). Recently, clinical trials of artesunate combination with mefloquine have proved effective and well tolerated (Looareesuwan *et al*, 1992b,c, 1994, 1996; Nosten *et al*, 1994; Price *et al*, 1995; 1997), therefore this regimen has been chosen for treatment of multidrug resistant falciparum malaria in Thailand. However, some patients cannot tolerate adverse effects of mefloquine.

Artecom® (compound dihydroartemisinin) a combination of dihydroartemisinin 32 mg, piperaquine 320 mg and trimethroprim 90 mg per tablet (Lot 010701 supplied free of charge by Tonghe Pharmaceutical Co, Ltd. Chongqing, China, lot 010701, Approval no. GYSZ X20010001) is claimed to be highly effective. In addition, this combination is well tolerated and convenient for use (given at hour 0, 6, 24, 32). This compound has been used in clinical trials and proved safe and well tolerated in China, Vietnam, Lao PDR, Cambodia and elsewhere. We report here a clinical trial of Artecom® *vs* artesunate and mefloquine (a standard regimen for treatment of multidrug resistant falciparum malaria in Thailand) at the Bangkok Hospital for Tropical Diseases to determine the safety, tolerability, and efficacy.

MATERIALS AND METHODS

All patients who fulfilled inclusion criteria were enroled (acute uncomplicated falciparum malaria, either male or female; if female, pregnancy test has to be negative before enrolment to the study, positive asexual forms of *P. falciparum* in blood smear, weight more than 40 kg and age more than 14 years, ability to take oral medication, agreement to stay in the hospital for at least 28 days). Informed consent to the study was obtained. The patients were admitted to the Bangkok Hospital for Tropical Diseases for 28 days to exclude reinfection and to assess the safety and efficacy of Artecom® and artesunate plus mefloquine. We excluded severe malaria according to WHO criteria (Warrell *et al*, 1990), severe vomiting not allowing oral medication, pregnancy or lactating females, significant concomitant systemic diseases (for example systemic bacterial infections, liver and/or kidney insufficiencies, chronic disease or severe malnutrition), diseases requiring therapy except malaria, ingestion of other antimalarials in the past 14 days or presence in urine of sulphonamides or 4-aminoquinolones. Clinical evaluation including neurological examination focused on brain stem, cerebellar function, muscle strength in all limbs, extraocular and facial muscle strength, deep tendon reflexes, finger-to-nose tests, and also parasite count were performed 12 hourly until negative then daily for 28 days. Malaria parasite count per microliter was obtained by calculation against the white blood cell count on a thick film. Geometric mean parasite count was used as a standard method. Blood films were considered negative if no parasites were seen in 200 oil-immersion microscopic fields. Fever clearance time was taken as the period from the start of treatment until the oral temperature decreased to 37.5ºC and remained below this temperature for the next 48 hours. Side effects were defined as signs and symptoms that occurred or became more severe after treatment started. Cure rate at day 28 (cured patients/evaluable patients x 100%) was defined as the absence of parasite recrudescence during 28 days of follow-up. If there was RI, RII, or RIII failure (World Health Organization, 1973), standard antimalarial drugs of the hospital were given. Adverse events were also treated by standard procedures at the Bangkok Hospital for Tropical Diseases. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol

University, Bangkok, Thailand.

Upon admission to the ward, patients were randomly allocated for treatment at a ratio of 2:1 into groups A:B as follows:

Group A: Artecom® for adult over 14 years (or weight ≥ 40 kg), day 0 of admission : 2 tablets were given orally at 0, 6, 24, 32 hours (1 tablet contains: dihydroartemisinin 32 mg, piperaquine 320 mg, trimethoprim 90 mg) (total dose = 8 tablets). At time 0 hour, an additional 1 tablet of 26.4 mg primaquine (for adult) was also given.

Group B: Artesunate (4 mg/kg/day) was given once a day for 3 day together with mefloquine 8 mg/kg/day for 3 days.

All patients were treated symptomatically as indicated (*eg* intravenous fluid and antipyretics) according to the standard practice in the hospital. In cases of RI, RII, or RIII responses (Warrell *et al*, 1990), other antimalarial drugs (*eg* quinine plus tetracycline for falciparum malaria and chloroquine followed by primaquine for vivax malaria) were used as indicated.

RESULTS

Three hundred and fifty-two patients were enroled. Demographic clinical data and pretreatment laboratory characteristics are shown in Table 1. Four patients were excluded due to appearance of urinary sulphonamides and 4-aminoquinolones. Seventy-two patients did not complete the 28-days follow up due to social reasons not related to adverse effects. Thus, 276 patients out of 352 patients (78%) completed the 28-day study. All patients were parasitologically negative at the time they were discharged from our hospital. No patients were deteriorated in clinical or biochemical changes after treatment in both groups. Parasitologic and clinical responses are shown in Table 2. Fig 1 shows changes in parasitemia after treatment. The cure rates at 28 days of follow-up were 97% for both treated groups. There were no significant differences in fever clearance time and parasite clearance time between the two

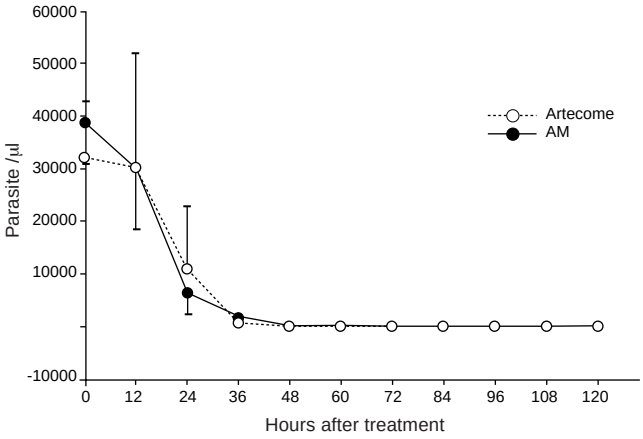

Fig 1- Malaria parasite reduction ± standard deviation of the mean (%) after treatment.
Artecom®=Artecom treatment group; AM = artesunate-mefloquine treatment group.

groups. No patients had RII or RIII failures.

No deaths occurred. No patients had vomiting related to the drugs. There were no major adverse effects, and no neurologic or neuropsychiatric manifestations during treatment or during the 28-day follow-up period. Some minor symptoms such as nausea, headache, dizziness occurred in group A (8, 9, 11 patients) and in group B (10, 8, 12 patients) respectively. However, these signs and symptoms could not be differentiated from malaria symptoms as they disappeared between 2-5 days after treatment while fever subsided. The results of serial parasitological tests revealed that 2 patients treated with Artecom® had positive asexual forms in blood smears of *P. vivax* on days 23 and 26 of treatment and were successfully treated with chloroquine followed by primaquine as the standard treatment at the hospital.

DISCUSSION

Artemisinin derivatives are potent, rapidly acting antimalarial that can reduce parasitemias by more than 90% within 24 hours in uncomplicated malaria cases. However, the rate of recrudescence within 28 days when used alone can be as high as 10-100% depending upon dosage, duration of treatment, and severity of

Table 1
Clinical and laboratory characteristics of study groups before treatment.

	Artecom® (n = 234)	AM (n = 118)
Male/Female	153 / 81	82 / 36
Age (yr)		
Mean (SD)	24.8 (13.3)	26.7 (12.4)
Range	12 - 53	14 - 70
Mean (SD) height in cm	154.0 (16.5)	159.2 (10.7)
Mean (SD) weight in kg	47.3 (14.7)	49.4 (10.7)
Fever (SD)		
Duration before admission (days)	4.4 (6.8)	4.3 (3.2)
Highest fever before treatment (ºC)	37.7 (0.7)	37.7 (0.9)
No. of patients with:		
Splenomegaly	27	12
Hepatomegaly	36	35
Urine positive for drugs[a]	3	1
First malaria attack	116	50
Geometric mean parasites count (per μl)	25,846	18,486
Range : High	268,640	182,400
Low	13	14
Laboratory data (SD)		
Packed cell volume (%)	35.5 (6.4)	36.1 (6.5)
WBC count (per μl)	5,504 (1,935)	5,583 (1,826)
Blood urea (mmol/l)	14.9 (8.0)	16.4 (8.6)
Serum creatinine (μmol/l)	0.9 (0.4)	1.0 (0.2)
Total bilirubin (μmol/l)	1.2 (1.1)	1.6 (1.0)
Serum AST	43.8 (39.2)	49.6 (40.4)
Serum AAT	40.5 (44.4)	46.1 (44.8)
Albumin (g/dl)	3.9 (0.6)	3.7 (0.5)
Alk PO_4	119.8 (61.8)	116.1 (57.7)

Artecom®=Artecom treatment group.
AM=artesunate-mefloquine treatment group.
SD = standard diviation of the mean.
WBC = white blood count.
AST, ALT = aspartate and alanine aminotransferases (U/l).
Alk PO_4 = alkaline phosphatase (U/l).
[a]Sulphonamides and 4-aminoquinolones

disease (Bunnag *et al*, 1991; Arnold *et al*, 1990; Hien *et al*, 1991; Li *et al*, 1994). These drugs are often combined with other long acting antimalarials such as mefloquine, (in this study combined with piperaquine and trimethoprim, to improve efficacy and compliance). The rationale of using of the combination is the same as standard treatment of multidrug treatment for tuberculosis, patients with HIV and most cases of cancer. The rapid killing of parasitemia by artemisinin derivatives is used to accelerate the therapeutic response, prevent dangerous early treatment failures in case of high grade resistance, reduce the parasite biomass and reduce gametocyte transmission (Looareesuwan *et al*, 1999). The benefit of adding appropriate and suitable long acting drugs is to prevent recrudescence by killing residual parasites, reduce the chance of resistant mutants surviving, and in addition, the long acting antimalarial might

Table 2
Therapeutic responses.

	Artecom® (n = 234)	AM (n = 118)
No. of patients with 28 days follow-up	194	82
No. (%) cured at 28 days (cured/evaluable patients)	189 (97%)	80 (97%)
Recrudescence on days : (median)	22	20
(range)	(13-28)	(19-22)
Fever clearance time (h)		
Mean (SD)	30.7 (28.3)	34.7 (28.3)
Range	4-160	4-98
Parasite clearance time (h)		
Mean (SD)	42.7 (14.6)	47.2 (17.6)
Range	16-72	20-81
No. of patients with *P. vivax*	2	0
days of appearance	23, 26	0

Artecom®=Artecom treatment group; AM=artesunate-mefloquine treatment group.

protect the efficacy of artemisinin derivatives in low transmission areas. Combined administration of artemisinin derivatives and mefloquine in different dosages and duration has been studied in uncomplicated malaria in many countries. This combination is now a standard treatment for multidrug resistant falciparum malaria in Thailand. However, some disadvantages of using artesunate-mefloquine might be seen (*eg* some patients could not tolerate mefloquine, the combinations of artesunate-mefloquine might not be available in some areas, and at present there is no fixed combination of artesunate and mefloquine available in the market). Artecom® has more advantage in this respect and more importantly, since the drug is produced as a fixed combination, less duration of treatment and possibly lower cost than artesunate-mefloquine. Other long acting drugs combined with artemisinin derivatives are under development.

In this study, all patients responded satisfactorily to the two treatment regimens. The present study shows a high total cure rate (97%) in both groups. Artecom® showed a similar cure rate to the standard treatment (artesunate-mefloquine). However at present, it remains unclear whether the improved cure rate is due to synergistic effect of the combination of dihydroartemisinin, piperaquine and trimetroprim. There was no case fatality in the study. Comparing with 3-day combination of artesunate-mefloquine treatment, Artecom® is given only for 2 days with 4 doses. The shorter period of administrating drugs is better; it has a higher chance of treatment course completion and thus improved compliance.

The results of this study indicate that Artecom® is effective and well-tolerated. Artecom® may be an alternative treatment to the standard combination of artesunate-mefloquine in treatment of multidrug resistant uncomplicated falciparum malaria such as is prevalent in Thailand. However, additional studies in special groups (in children, pregnant women, field trials) are needed in order to get more information of Artecom® in general practice.

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