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Randomized Comparison of Artemether-Benflumetol and Artesunate-Mefloquine in Treatment of Multidrug-Resistant Falciparum Malaria

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An open, randomized comparison of artemether-benflumetol (CGP 56 697; Novartis) with artesunate-mefloquine was conducted in 617 patients with acute uncomplicated multidrug-resistant falciparum malaria on the western border of Thailand. Both treatments rapidly and reliably cleared fever and parasitemia, and there was no significant difference in the initial therapeutic response parameters. Parasite genotyping was used to distinguish recrudescences from new infections. The 63-day cure rate for artesunate-mefloquine (94%) was significantly higher than the cure rate for artemether-benflumetol (81%) ($P < 0.001$). Both regimens were well tolerated. Nausea, vomiting, dizziness, sleep disorders, and other neurological side effects were between two and four times more common in the artesunate-mefloquine group than in the artemether-benflumetol group ($P < 0.001$). Artemether-benflumetol is effective and very well tolerated in the treatment of multidrug-resistant falciparum malaria. A higher dose than that used in the present study may improve efficacy.

Despite considerable efforts to eradicate or control malaria, the disease continues to be a major cause of human morbidity and mortality in the tropics. Each year, between 1.5 million and 2.7 million people are thought to die from falciparum malaria (15). No effective malaria vaccine is yet available, and *Plasmodium falciparum* has developed resistance to almost all of the available drugs (19). In Thailand, drug resistance is particularly problematic; in vivo and in vitro resistance has been documented for chloroquine, sulfadoxine-pyrimethamine, quinine, halofantrine, and mefloquine (3, 6, 7, 14, 19).

For centuries, an extract of the wormwood plant (*Artemisia annua*) has been used in China for the treatment of fever. The compound derived from this plant (artemisinin) and its derivatives, artesunate and artemether, are the most potent and rapidly acting antimalarial drugs known, but when used alone, these drugs are associated with high recrudescence rates (2, 4, 21). On the western border of Thailand, where the most drug-resistant parasites in the world occur, the combination of an artemisinin derivative with mefloquine has proved highly effective in the treatment of multidrug-resistant falciparum malaria (4, 8, 12), retaining the benefits of rapidity of action while augmenting cure rates, reducing gametocyte carriage and thus transmission potential, and apparently slowing the development of mefloquine resistance (13). Nevertheless, mefloquine resistance can be anticipated to worsen (20), and alternative drugs are urgently needed.

Benflumetol was synthesized originally by the Academy of Military Medical Sciences in Beijing, People's Republic of China. It is a racemic fluorene derivative with the chemical name 2-dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9*H*-fluoren-4-yl]-ethanol. It conforms structurally, physicochemically, and in mode of action to the aryl amino alcohol group of antimalarials, including quinine, mefloquine, and halofantrine. In preclinical toxicology studies, a 1:6 fixed combination of artemether-benflumetol (AB) proved well tolerated by both rats and dogs receiving doses over 10 times higher than those used subsequently in clinical studies for 1 month (9). The pharmacokinetic properties of benflumetol are reminiscent of those of halofantrine, with variable oral bioavailability (augmented considerably by fats) and a terminal elimination half-life in patients with malaria of approximately 4 to 5 days. Clinical studies in China of AB combinations in several hundred patients concluded that the 1:6 artemether-to-benflumetol ratio was optimal for antimalarial activity. There was no significant toxicity. Thus, these early studies indicated that AB was a safe, well-tolerated, and effective treatment for falciparum malaria.

To study the efficacy and safety of AB against highly multidrug-resistant *P. falciparum* infections, a large randomized prospective trial was conducted with adults and children with uncomplicated falciparum malaria along the western border of Thailand. The current standard therapy of artesunate plus mefloquine (AM) was used as a comparator.

MATERIALS AND METHODS

Patients. The trial was conducted in Mae La, a camp for Karen displaced people. Mae La has a population of approximately 20,000 people and is located 60 km north of Mae Sot in an area with low rates of malaria transmission. The epidemiology of malaria in this area has been described in detail previously (5). The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Bangkok, and the Karen Refugee Committee, Mae Sot, Thailand.

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Clinical procedures. Patients who presented to the unit's malaria clinic with symptomatic, microscopically confirmed falciparum malaria were enrolled in the study. The patients or their parents were given written information translated into their language. After written informed consent was obtained, patients were allocated randomly to receive either AB (CGP 56 697; Novartis, Basel, Switzerland) or AM (artesunate from Guilin Pharmaceutical Factory No. 1, Guilin, China, and mefloquine [Lariam] from Hoffman-La Roche, Basel, Switzerland). The drugs were contained in identical, numbered, opaque packets in prerandomized blocks of four. Pregnant and lactating women, children under 5 years of age, and patients with severe or complicated malaria (22) requiring parenteral treatment were excluded from the trial. At enrollment, a medical history was taken, a full physical examination, including a neurological examination, was performed, and blood was collected for quantitative parasite counts and routine hematology. All information was recorded on a standard case record form. All patients were examined once daily until they became asymptomatic and aparasitemic and then seen weekly for 9 weeks. Patients who failed to attend were traced by a home visitor. At each weekly visit, a blood smear was taken and a questionnaire about possible adverse effects was completed. A blood smear was also taken from any patient complaining of fever or symptoms compatible with malaria during the follow-up period. Parasite counts were determined on Giemsa-stained thick and thin blood films. If the count on the thick film exceeded 500 parasites per 500 leukocytes, then the thin film result (expressed as the number of infected erythrocytes per 1,000 erythrocytes) was recorded.

Because of concerns raised by animal studies with intramuscular artemether and arteether which showed an unusual pattern of selective toxicity to certain brain stem nuclei (1), a neurological examination was performed at baseline (upon admission to the study) and on days 3, 7, 28, and 63. The examination included Romberg's test, assessments of gait and balance (walking along a straight line, heel to toe) and fine finger dexterity (ability to pick up a small tablet), tests of auditory and visual acuity, and assessments for nystagmus and behavior abnormality. Blood was taken for full blood counts at baseline and on days 3, 7, 28, and 63.

Drug regimens. AB (Novartis) was dispensed as a fixed-dose combination tablet in an airtight blister pack. Each AB tablet contained 20 mg of artemether and 120 mg of benflumetol. The total dose was 1 to 2 mg of artemether per kg of body weight plus 6 to 12 mg of benflumetol per kg. The minimum dose for patients weighing less than 20 kg was one tablet. For patients weighing between 21 and 30 kg, a dose of two tablets was given; for patients weighing between 31 and 40 kg, a dose of three tablets was given; and for patients weighing more than 40 kg, the usual adult dose of four tablets was given. Each dose was given at 0, 8, 24, and 48 h. AM was given as artesunate (Guilin Pharmaceutical Factory No. 1) in a single daily dose of 4 mg/kg for 3 days plus mefloquine (Hoffman-La Roche) in a split dose, i.e., 15 mg/kg on day 2 and 10 mg/kg on day 3. Drug administration was observed with all patients. If the first dose of AB was vomited, the whole dose was repeated. For patients receiving AM, if any of the drugs in the first dose was vomited within 30 min, the full dose was given again; if vomiting occurred between 30 and 60 min, half the dose was repeated. If vomiting occurred after 60 min or if vomiting of the doses following the first dose occurred in a patient in either one of the two groups, no replacement dose was given.

If a patient was unable to tolerate the medication because of repeated vomiting or the patient's medical condition deteriorated, then rescue parenteral medication was initiated and the patient was excluded from the trial. The rescue medication consisted of intramuscular artemether (3.2 mg/kg; Kunming Pharmaceutical Company, Kunming, People's Republic of China) followed by oral artesunate (a total dose of 12 mg/kg given over 7 days).

Recrudescent infections. Patients with a smear positive for *P. falciparum* or for a mixed infection including *P. falciparum* within 63 days of follow-up were retreated for 7 days with artesunate (total dose, 12 mg/kg). Doxycycline (100 mg/day) for 7 days was also given if the patient was older than 8 years of age.

The study end point was the time of incidence of recrudescent infections in the two treatment groups. However, because the patients in the trial continued to live in the area of transmission, reinfection during the 9 weeks of follow-up was also possible. Recrudescences were distinguished from reinfections by parasite genotyping by use of PCR. Blood samples were taken at baseline and on the day of reappearance of parasites. Since the majority of infections in this area are with isolates with only one or two genotypes per infection (11), typing of three polymorphic loci (MSP1, MSP2, and GLURP) with allele frequencies which we have previously characterized in this population allows discrimination between a new infection and a recrudescence. Population allele frequencies of these loci were calculated, thereby providing the baseline information to calculate the probability of incidence of a new infection with a different or the same genotype. No allele combination occurs with a frequency exceeding 5% in this population, and therefore, patients with the same parasite PCR profiles in the first and second infections were considered to have a recrudescent infection (1a).

In vitro sensitivity tests. In vitro antimalarial sensitivity tests were done on admission with fresh isolates from a subgroup of 20 patients presenting with primary infections and from an additional 20 patients on the day of reappearance of parasites. For another 5 patients, paired primary and recrudescent cryopreserved isolates were analyzed. Inhibitory concentrations were determined by the radiolabelled hypoxanthine uptake inhibition method (18).

Adverse experiences. Adverse experiences were checked daily for 4 days and then recorded weekly during the 63 days of follow-up. For each possible side effect, the investigator had to determine whether it could be drug related. Symptoms present at baseline (i.e., disease-attributable symptoms) were summarized separately from those that started or worsened after admission. Adverse experiences which developed after drug treatment but before reappearance of parasites were considered by the investigator as possibly related to the given drug. Serious adverse experiences would have been reported separately, and the trial monitor would have been notified immediately of them.

Monitoring. This trial was part of the phase III evaluation of CGP 56 697, the AB combination made by Novartis. Both the clinical conduct and the laboratory procedures were reviewed at regular intervals by independent monitors.

Statistical analysis. The trial was designed to show equivalence in efficacy between AB and AM in terms of 28- and 63-day cure rates and parasite reductions. The 63-day cure rate for the AM combination was assumed to be 85%, and that for the AB combination was assumed to be 80%. If the upper boundary of the 95% one-sided confidence limit for the difference did not exceed 15%, the two proportions were regarded as equivalent. With a power of 90% and allowance for a 20% dropout rate, the sample size required was 308 patients for each treatment group. This sample size also had more than 80% statistical power to detect a difference in cure rates of 85 and 75% with 95% confidence. Statistical analysis of the data was performed with SPSS for Windows (SPSS Software, Gorinchem, The Netherlands) and Epi Info (Centers for Disease Control and Prevention). Continuous data were compared by Student's *t* test or the Mann-Whitney U test where appropriate. Categorical data were analyzed by the chi-square test with Mantel-Haenszel stratified analysis.

Parasite and fever clearance times, the times to resolution of other signs, including anemia (hematocrit, <30%), hepatomegaly, splenomegaly, and the risks of treatment failure were all evaluated by survival analysis. Survival data were compared by use of Kaplan-Meier plots and the Mantel-Haenszel log rank test. The analysis of cure rates was performed both for all recurrent infections and for the final PCR genotyping-adjusted failure rates on an intention-to-treat and evaluable basis.

RESULTS

Between December 1995 and September 1996, a total of 617 patients were recruited: 309 patients in the AB group and 308 in the AM group. There were 128 (20.7%) children under 13 years of age. In total, 139 patients (61 AB and 78 AM patients) could not be included in the final evaluation for the following reasons: incomplete follow-up to 9 weeks (101 patients), failure to complete trial treatment course (3 patients), administrative problems (11 patients), failure to meet protocol criteria (5 patients), noncompliance (3 patients), concomitant use of trimethoprim-sulfamethoxazole (13 patients), self treatment with quinine (3 patients), adverse experience (2 patients), and death (1 patient). Overall compliance was good: 87% of the patients completed 28 days of follow-up, and 80% completed 63 days of follow-up. The baseline characteristics were similar for both treatment groups (Table 1). Hepatomegaly was more common in children than in adults, occurring in 26 and 9%, respectively ($P < 0.001$). The corresponding figures for incidence of splenomegaly were 41 and 18%, respectively ($P < 0.001$).

Clinical and parasitological responses. The initial responses to the two treatments were very similar. Four patients received rescue medication. Treatment of two patients on AM was discontinued because of repeated vomiting of mefloquine, and two patients on AB were hyperparasitemic at baseline and their parasitemia increased further immediately following treatment. On admission, 322 (52%) of the patients had fever (oral temperature of >37.5°C). Of these, 163 (53%) in the AB group and 159 (52%) in the AM group defervesced in the first 24 h after admission, and more than 90% of the patients in both groups were afebrile within 72 h. There was no difference in fever clearance times between the two treatment groups; median (range) fever and parasite clearance times in both groups were 1 (1 to 4) and 2 (1 to 3) days, respectively. All patients had cleared their parasitemias by day 3. Overall, 58 (9%) of the patients had gametocytes detected in their peripheral blood smears in the first 72 h after admission, 34 (11%) that were on AB and 24 (7.8%) that were on AM ($P = 0.17$). Six of the 559 patients without gametocytes on admission sub-

TABLE 1. Clinical and laboratory variables upon patient admission

Patient type and variable	Value[a] for:			*P* value
	AB group	AM group	All patients	
All patients				
Total no.	309	308	617	
Age (yr)	20 (5–66)	20 (5–65)	20 (5–66)	NS
No. of males	210 [68]	211 [68.5]	421 [68.2]	NS
Wt (kg)	46 (12–68)	46 (12–72)	46 (12–72)	NS
No. with hepatomegaly	37 [12]	41 [13]	78 [13]	NS
No. with splenomegaly	67 [22]	73 [24]	140 [23]	NS
No. with previous malaria infection within last 3 mo	30 [10]	33 [11]	63 [10]	NS
Temp (°C)	37.8 (35.4–40.5)	37.6 (36–40.5)	37.7 (35.4–40.5)	NS
Geometric mean parasite count/μl	4,336 (10–512,297)	4,581 (13–235,688)	4,456 (10–512,297)	NS
Hematocrit	38.3 (18–53)	37.7 (19–52)	38.1 (18–53)	NS
Leukocyte count (10^9/liter)	7.1 (1.3–19.6)	7.3 (2.6–23.5)	7.2 (1.3–23.5)	NS
% Lymphocytes	39 (13–82)	40 (9–89)	40 (9–89)	NS
% Neutrophils	61 (18–87)	60 (11–91)	60 (11–91)	NS
No. of platelets (10^9/liter)	129 (36–379)	131 (40–385)	120 (36–385)	NS
Children of <13 yr				
Total no.	64	64	128	
Age (yr)	9.5 (5–12)	8.5 (5–12)	9.0 (5–12)	NS
Wt (kg)	21 (12–34)	20.5 (12–37)	21 (12–37)	NS
No. with hepatomegaly	14 [22]	19 [30]	33 [26]	NS
No. with splenomegaly	28 [44]	25 [39]	53 [41]	NS
Temp (°C)	37.9 (36.3–40)	38 (36.1–40.3)	38 (36.1–40.3)	NS
Geometric mean parasite count/μl	3,905 (49–512,297)	7,270 (15–177,988)	5,315 (15–512,297)	NS

[a] Unless otherwise indicated, values shown are medians. All values in parentheses are ranges, whereas all values in brackets are percentages.

sequently developed gametocytemia. *Plasmodium vivax* parasitemia occurred in 83 (26.5%) of the patients in the AB group and 57 (18.5%) of the patients in the AM group during the 63-day follow-up (relative risk [RR] = 1.45; 95% confidence interval [CI] = 1.08 to 1.96, $P = 0.016$).

Treatment efficacy. In this trial, *P. falciparum* parasites reappeared in 61 (24.6%) of the 248 evaluable patients treated with AB and in 28 (12.2%) of the 230 evaluable patients treated with AM (RR = 2.0; 95% CI = 1.34 to 3.03, $P < 0.001$). PCR genotyping indicated that 36 (59%) of the patients treated with AB and 9 (32%) of the patients in the AM group had a true recrudescence of their initial infections (RR = 1.84; 95% CI = 1.03 to 3.27, $P = 0.02$), and 15 and 12 patients in the respective groups had new infections. Paired PCR results were not available for the remaining 17 (10 AB and 7 AM) patients. Therefore, on an evaluability basis, the cure rates in the two groups were 83.9 and 95.7%, respectively ($P < 0.001$), excluding patients with new infections and patients with reappearance of parasites but no PCR results. However, if the proportion of recrudescent and new infections in the latter group without PCR results is the same as that in the patients with PCR results, then the adjusted failure rates become 43 of 230 patients (18.7%) in the AB group and 12 of 214 patients (5.6%) in the AM group. The unadjusted 28-day cure rates were 82.1% (224 of 273) for AB and 97.3% (257 of 264) for AM. After PCR adjustment for new infections, these cure rates became 85.2% for AB and 97.7% for AM. By a univariate analysis, two factors were found to be associated with an increased risk of overall treatment failure in the AB group, a baseline parasite count of >50,000/μl (RR = 2.08; 95% CI = 1.1 to 3.9, $P = 0.022$) and an admission temperature of ≥39°C (RR = 2.23; 95% CI = 1.2 to 4.2, $P = 0.016$). High baseline parasitemia was not a significant risk factor for failure independent of temperature (by Mantel-Haenszel stratified analysis, RR = 1.79; 95% CI = 0.8 to 3.3, $P = 0.062$). The mean (± standard deviation) time to true recrudescence was shorter in the AB group than in the AM group, 23 (±7) versus 33 (±14) days ($P = 0.003$).

In vitro sensitivity. The results of the in vitro testing are summarized in Table 2. There were no significant differences

TABLE 2. In vitro responses to five drugs of fresh unpaired isolates of *P. falciparum* before and after AB treatment and of five paired cryopreserved isolates

Drug	Fresh unpaired isolates				Cryopreserved paired isolates			
	Primary infection		Recrudescent infection		Primary infection		Recrudescent infection	
	Median IC_{50} (25–75%ile)	*n*	Median IC_{50} (25–75%ile)	*n*	Median IC_{50} (25–75%ile)	*n*	Median IC_{50} (25–75%ile)	*n*
Mefloquine	40 (11–59)	24	32 (20–74)	26	35 (20–46)	5	40 (14.7–48.8)	5
Artesunate	2 (1.4–4.0)	26	2.2 (1.5–3.7)	26	2.1 (1.2–2.2)	5	1.8 (1.3–3.1)	5
Artemether	7.4 (4.3–10.9)	22	7.4 (5.2–8.5)	16	2.4 (1.8–3.9)	5	3.3 (1.0–4.1)	5
Benflumetol	54 (34–67)	18	42 (24–74)	14	47 (25–62)	5	45 (26–68)	5
Quinine	333 (209–568)	25	385 (213–679)	25	185 (145–442)	5	104 (81–284)	5

between the drug susceptibilities of the primary isolates and those of the recrudescent ones.

Retreatment. Of the 89 patients in whom parasites reappeared during the follow-up period, 60 were treated with artesunate, 21 were treated with a combination of artesunate plus doxycycline, and 7 were treated with artemether; for one patient, the treatment details were not recorded. Artesunate and artemether were given in 7-day regimens. Of the patients who received artesunate or artemether, 33 (50%) could be monitored for 63 days; two patients (6%) treated with artesunate experienced recrudescence during this follow-up period and were retreated again with artesunate in a 7-day regimen.

Adverse effects. Both regimens were well tolerated. Nine patients (five on AB and four on AM) vomited within 1 h of their first dose, and this dose was replaced. Three patients on AB vomited dose 2, and one patient on AB vomited dose 3. In the AM group, five patients vomited dose 2 and five patients vomited dose 3. Of these, two patients on AM required rescue medication because of repeated vomiting of mefloquine. AB was generally better tolerated than AM, although there were no serious drug-related adverse reactions recorded for either group. Overall, 177 (57%) of the patients receiving AB and 232 (75%) of the patients receiving AM had minor adverse effects which could have been related to trial medications. AM-treated patients had significantly higher rates than AB patients of dizziness (35 versus 15%; RR = 2.3; 95% CI = 1.7 to 3.2, $P < 0.001$), sleep disorders (25 versus 12%; RR = 2.1; 95% CI = 1.4 to 2.9, $P < 0.001$), vomiting (13 versus 3.1%; RR = 5.1; 95% CI = 2.5 to 10.8, $P < 0.001$), nausea (17 versus 6%; RR = 2.6; 95% CI = 1.6 to 4.2, $P < 0.001$), and palpitations (19 versus 10%; RR = 1.9; 95% CI = 1.2 to 2.8, $P = 0.002$). Neurological side effects (abnormal gait, paresthesia, tremor, nystagmus, abnormal coordination, and ataxia) were significantly more common in the AM group than in the AB group (10 versus 3%; RR = 3.1; 95% CI = 1.6 to 6.2, $P < 0.001$). There were no serious neuropsychiatric reactions or other evidence of serious central nervous system toxicity in this study. Twelve (4%) of the patients in the AB group and nine (3%) in the AM group experienced pruritus and/or a rash (RR = 1.3; 95% CI = 0.6 to 3.1, $P = 0.50$) which could have been attributed to the drug. There was no difference between the two treatment groups in any of the hematological parameters measured during the follow-up. Anemia was defined as hematocrits below 30% for patients of <15 years, below 34% for women, and below 35% for men. In the AB group, the numbers of patients with anemia were 63 of 303 (21%) on admission, 79 of 248 (32%) on day 3, 82 of 276 (30%) on day 7, and 40 of 215 (19%) on day 28. In the AM group, the corresponding numbers were 65 of 297 (22%) on admission, 79 of 249 (32%) on day 3, 102 of 277 (37%) on day 7, and 29 of 230 (13%) on day 28. No differences were observed between the two treatment groups. The single fatality in the study was a patient killed in a family fight.

DISCUSSION

Both AM and AB proved to be effective treatments for acute, uncomplicated falciparum malaria in the area of multidrug resistance studied. Benflumetol has been evaluated only recently outside China, where it was discovered, and it clearly contributes significantly to the efficacy of the combination preparation with artemether. Treatment for 3 days with artemether alone at doses higher than those used in this study is associated with nearly a 100% recrudescence rate (2, 4), yet the combination of AB was effective in 81% of the patients in the present study. These in vivo and in vitro studies indicate significant activity against the multidrug-resistant *P. falciparum* parasites prevalent in this area of Thailand. However, overall cure rates with AB were not as good as those with the combination of AM. These cure rates were based on PCR genotyping of the primary and recurrent parasites. This approach can underestimate the true recrudescence rate when mixed-parasite populations are present in the original isolate and the drug-resistant genotype is present at numbers too low to amplify. This is more likely in areas of high transmission, where multiple-genotype infections are common. In the area of the present study, the majority of infections are caused by one or two genotypes per infection, and thus, differentiation between new and recrudescent infections is less vulnerable to errors of interpretation (11). Recrudescences following AB treatment occurred earlier than those following AM treatment. The differences in both antimalarial efficacies and the times to recrudescence probably reflect the more rapid elimination of benflumetol (half-life = 4 to 6 days) (9) than of mefloquine (half-life = 14 to 21 days) (10) and thus the shorter time for which suppressive concentrations are present in the blood. Antimalarial efficacy for slowly eliminated drugs is a function of the time for which blood levels exceed inhibitory concentrations for the infecting parasites (20). Obviously, if a larger dose or longer course of treatment was given, then the time for which blood levels exceeded the inhibitory level would be prolonged and efficacy should improve. As in studies with mefloquine, recrudescences following benflumetol treatment were more likely to occur in patients with high parasitemias (16, 20). The time to eradicate the parasite biomass in such patients is longer because the initial burden is higher, and blood concentrations of the antimalarial drug may fall below inhibitory levels before all the infecting parasites are killed (20).

The results with AM were better than anticipated from the previous rate of decline in mefloquine sensitivity. This study differs from our previous ones in that a higher proportion of patients (80%) were adults; in the past, approximately 50% have been children, and children have a greater risk of treatment failure than adults (16). Nevertheless, with this taken into account, the treatment response to AM has not changed significantly over a period of 60 months. This suggests that the progression of mefloquine resistance has slowed since the widespread introduction of artesunate in this area in 1994 (13). Both drug combinations in this study gave rapid initial responses, attributed to the artemisinin derivatives. These ensured rapid recovery and prevented the risk of deterioration to severe malaria that sometimes occurs when mefloquine or other slow-acting antimalarials are used alone. The artemisinin derivatives also reduced gametocytemia, which prevents transmission of the infection (13). In areas of low transmission, this may have a significant impact on malaria incidence.

AB was better tolerated than AM. Although the majority of patients had complaints that could have been drug related, in most instances, these were also features of malaria itself. However, the study was not blind, and a bias in the evaluation of drug-related side effects was possible. Nevertheless, there was no adverse effect that could be clearly related to AB, whereas AM was associated with a significantly increased incidence of adverse central nervous system effects, presumably related to the mefloquine component, an incidence two to four times higher than that associated with AB. Dizziness, sleep disorder, nausea, and vomiting were all significantly more common in the AM group. The difference between the two groups probably represents the true incidence of mefloquine-attributable neurological effects (17). All were reversible, and there was also no evidence of any hearing or balance abnormality attributable to the artemisinin derivatives.

This large trial confirms the safety and continued efficacy of AM in the treatment of multidrug-resistant falciparum malaria. The new AB combination (CGP 56 697) was also effective, but less so than AM, and was better tolerated than AM. In general, artemether and artesunate are considered equivalent in terms of antimalarial activity. The dose of artemether used in this study was half that of artesunate. Both a larger dose and a longer course of AB are now being evaluated in the treatment of multidrug-resistant falciparum malaria, and preliminary results are encouraging.

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REFERENCES

1. **Brewer, T. G., S. J. Grate, J. O. Peggins, P. J. Weina, J. M. Petras, B. S. Levine, M. H. Heiffer, and B. G. Schuster.** 1994. Fatal neurotoxicity of arteether and artemether. Am. J. Trop. Med. Hyg. **51:**251–259.

1a. **Brockman, A.** Unpublished observations.

2. **Bunnag, D., C. Viravan, S. Looareesuwan, J. Karbwang, and T. Harinasuta.** 1991. Clinical trial of artesunate and artemether on multidrug resistant falciparum malaria in Thailand: a preliminary report. Southeast Asian J. Trop. Med. Public Health **22:**380–385.

3. **Looareesuwan, S., T. Harinasuta, and T. Chongsuphajaisiddhi.** 1992. Drug resistant malaria with special reference to Thailand. Southeast Asian J. Trop. Med. Public Health **23:**621–634.

4. **Looareesuwan, S.** 1994. Overview of clinical studies on artemisinin derivatives in Thailand. Trans. R. Soc. Trop. Med. Hyg. **88**(Suppl. 1)**:**9–11.

5. **Luxemburger, C., K. L. Thwai, N. J. White, H. K. Webster, D. E. Kyle, L. Maelankirri, T. Chongsuphajaisiddhi, and F. Nosten.** 1996. The epidemiology of malaria in a Karen population on the western border of Thailand. Trans. R. Soc. Trop. Med. Hyg. **90:**105–111.

6. **Mockenhaupt, F. P.** 1995. Mefloquine resistance in *Plasmodium falciparum*. Parasitol. Today **11:**248–253.

7. **Nosten, F., F. O. ter Kuile, T. Chongsuphajaisiddhi, C. Luxemburger, H. K. Webster, M. Edstein, L. Phaipun, K. L. Thwai, and N. J. White.** 1991. Mefloquine resistant falciparum malaria on the Thai-Burmese border. Lancet **337:**1140–1143.

8. **Nosten, F., C. Luxemburger, F. O. ter Kuile, C. Woodrow, T. Chongsuphajaisiddhi, and N. J. White.** 1994. Treatment of multi drug resistant *Plasmodium falciparum* malaria with 3 day artesunate-mefloquine combination. J. Infect. Dis. **170:**971–977.

9. **Novartis.** Novartis database. Novartis, International Clinical Research, Basel, Switzerland.

10. **Palmer, K. J., S. M. Holliday, and R. N. Brogden.** 1993. Mefloquine: a review of its antmalarial activity, pharmacokinetic properties and therapeutic efficacy. Drugs **45:**430–475.

11. **Paul, R., I. Hackford, A. Brockman, C. Muller-Graf, R. N. Price, C. Luxemburger, N. J. White, F. Nosten, and K. P. Day.** Transmission intensity and *Plasmodium falciparum* diversity in Shoklo camp on the Thai-Burmese border. Am. J. Trop. Med. Hyg., in press.

12. **Price, R. N., F. Nosten, C. Luxemburger, A. Kham, A. Brockman, T. Chongsuphajaisiddhi, and N. J. White.** 1995. Artesunate versus artemether in combination with mefloquine for the treatment of multidrug resistant falciparum malaria. Trans. R. Soc. Trop. Med. Hyg. **89:**523–527.

13. **Price, R. N., F. Nosten, C. Luxemburger, F. O. ter Kuile, L. Phaipun, T. Chongsuphajaisiddhi, and N. J. White.** 1996. Effects of artemisinin derivatives on malaria transmissibility. Lancet **347:**1654–1658.

14. **Pukrittayakamee, S., W. Supanaranond, S. Looareesuwan, S. Vanijanonta, and N. J. White.** 1994. Quinine in severe falciparum malaria: evidence of declining efficacy in Thailand. Trans. R. Soc. Trop. Med. Hyg. **88:**488–491.

15. **Sturchler, D.** 1989. How much malaria is there worldwide? Parasitol. Today **5:**39–40.

16. **ter Kuile, F. O., C. Luxemburger, F. Nosten, L. Phaipun, and N. J. White.** 1995. Predictors of mefloquine treatment failure: a prospective study in 1,590 patients with uncomplicated falciparum malaria. Trans. R. Soc. Trop. Med. Hyg. **89:**660–664.

17. **ter Kuile, F. O., F. Nosten, C. Luxemburger, D. Kyle, P. Teja-Isavatharm, L. Phaipun, R. N. Price, T. Chongsuphajaisiddhi, and N. J. White.** 1995. Mefloquine treatment of acute falciparum malaria: a prospective study of adverse effects in 3673 patients. Bull. W. H. O. **73:**631–642.

18. **Webster, K. H., E. F. Boudreau, K. Pavanand, K. Yongvanitchit, and L. W. Pang.** 1985. Antimalarial drug susceptibility testing of Plasmodium falciparum in Thailand using a microdilution radioisotope method. Am. J. Trop. Med. Hyg. **34:**228–235.

19. **White, N. J.** 1992. Antimalarial drug resistance: the pace quickens. J. Antimicrob. Chemother. **30:**571–585.

20. **White, N. J.** 1997. Assessment of the pharmacodynamic properties of antimalarial drugs in vivo. Antimicrob. Agents Chemother. **41:**1413–1422.

21. **World Health Organization.** 1993. The role of artemisinin and its derivatives in the current treatment of malaria. Report on an informal consultation convened in Geneva, 27–29 September 1993. Mimeograph document WHO/MAL 94, 1067. World Health Organization, Geneva, Switzerland.

22. **World Health Organization, Division of Control of Tropical Diseases.** 1990. Severe and complicated malaria. Trans. R. Soc. Trop. Med. Hyg. **84**(Suppl. 2)**:**1–65.