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EFFICACY AND SAFETY OF ATOVAQUONE/PROGUANIL COMPARED WITH MEFLOQUINE FOR TREATMENT OF ACUTE *PLASMODIUM FALCIPARUM* MALARIA IN THAILAND

SORNCHAI LOOAREESUWAN, POIRAT WILAIRATANA, KOBSIRI CHALERMARUT, YUPIN RATTANAPONG, CRAIG J. CANFIELD, AND DAVID B. A. HUTCHINSON

Hospital for Tropical Diseases, Mahidol University, Bangkok, Thailand; Pharmaceutical Systems Inc., Talent, Oregon; Glaxo Wellcome, Inc., Research Triangle Park, North Carolina

Abstract. The increasing frequency of therapeutic failures in falciparum malaria underscores the need for novel, rapidly effective antimalarial drugs or drug combinations. Atovaquone and proguanil are blood schizonticides that demonstrate synergistic activity against multi-drug-resistant *Plasmodium falciparum in vitro.* In an open-label, randomized, controlled clinical trial conducted in Thailand, adult patients with acute *P. falciparum* malaria were randomly assigned to treatment with atovaquone and proguanil/hydrochloride (1,000 mg and 400 mg, respectively, administered orally at 24-hr intervals for three doses) or mefloquine (750 mg administered orally, followed 6 hr later by an additional 500-mg dose). Efficacy was assessed by cure rate (the percentage of patients in whom parasitemia was eliminated and did not recur during 28 days of follow-up), parasite clearance time (PCT), and fever clearance time (FCT). Safety was assessed by sequential clinical and laboratory assessments for 28 days. Atovaquone/proguanil was significantly more effective than mefloquine (cure rate 100% [79 of 79] vs. 86% [68 of 79]; $P < 0.002$). The atovaquone/proguanil and mefloquine treatments did not differ with respect to PCT (mean = 65 hr versus 74 hr) or FCT (mean = 59 hr versus 51 hr). Adverse events were generally typical of malaria symptoms and each occurred in < 10% of the patients in either group, with the exception of increased vomiting found in the atovaquone/proguanil group. Transient elevations of liver enzyme levels occurred more frequently in patients treated with atovaquone/proguanil than with mefloquine, but the differences were not significant and values returned to normal by day 28 in most patients. The combination of atovaquone and proguanil was well tolerated and more effective than mefloquine in the treatment of acute uncomplicated multidrug-resistant falciparum malaria in Thailand.

Drug-resistant *Plasmodium falciparum* malaria has been reported in almost all endemic areas, and drug resistance is most severe in Southeast Asia. In Thailand, treatment of acute falciparum malaria is becoming more difficult due to increasing resistance to available antimalarials.[1,2] Chloroquine and pyrimethamine/sulfadoxine are no longer used in Thailand, and quinine is curative in only 90% of patients even when administered in combination with tetracycline for seven days.[3] Mefloquine, which was developed to treat multidrug-resistant falciparum malaria, cures only about 90% of cases when administered as monotherapy,[4] and halofantrine is even less effective.[5] Artesunate, an orally administered artemisinin derivative, is well tolerated but treatment for at least five days is required to achieve cure rates of 88%.[6]

The problem of resistance to currently available antimalarials is compounded by the formidable side effects of some of these drugs. Mefloquine has been associated with neuropsychiatric disturbances,[7,8] halofantrine with prolongation of the QT interval,[9,10] and quinine with tinnitus, central nervous system toxicity, and blood dyscrasias.[11,12] Tetracycline can cause hepatotoxicity in pregnant women and permanent discoloration of teeth and stunting of bone growth in children.[13] Pyrimethamine/sulfadoxine has been linked with severe and sometimes fatal cases of Stevens-Johnson syndrome,[14] epidermal necrolysis,[15] and hepatic necrosis.[16] The unsatisfactory choices among antimalarial drugs has prompted considerable scientific investigation aimed at finding newer, more effective, and better tolerated agents that also demonstrate unique modes of action and a lower propensity to develop resistance.

Treatment of falciparum malaria with a combination of atovaquone and proguanil has proved in clinical trials to produce cure rates significantly higher than those of amodiaquine in Gabon,[17] and chloroquine and a chloroquine/pyrimethamine/sulfadoxine triple combination in The Philippines.[18] In one case report,[19] atovaquone/proguanil cured a patient who was infected with *P. falciparum* resistant to quinine/mefloquine, quinine/tetracycline, and quinine/halofantrine combinations. Atovaquone has *in vitro* activity not only against *P. falciparum*, but also against *Pneumocystis carinii, Toxoplasma gondii, Babesia,* and microsporidia spp.. It is currently marketed as monotherapy for the treatment of *Pneumocystis carinii* pneumonia. Proguanil, as monotherapy, is currently marketed outside the United States for prophylaxis against malaria. In antimalarial studies to date, the atovaquone/proguanil combination has been generally well tolerated, with adverse experiences not differing from symptoms commonly seen with malaria itself.[17,18,20–22] Atovaquone, a hydroxynaphthoquinone that inhibits plasmodial mitochondrial electron transport,[23] and proguanil, an isopropylbiguanide that inhibits plasmodial dihydrofolate reductase (primarily via its metabolite cycloguanil),[24] act synergistically as a blood schizonticide.[25] Because atovaquone/proguanil is useful in treating both drug-sensitive and drug-resistant *P. falciparum*,[17–22] it is expected to be curative in almost all cases of falciparum malaria. The objective of the present study was to compare the efficacy, safety, and tolerance of the atovaquone/proguanil combination with mefloquine in adult patients with acute falciparum malaria in Thailand.

PATIENTS AND METHODS

Patient populations. All study participants were patients at the Hospital for Tropical Diseases in Bangkok, Thailand. Patients could be included in the study if they had acute,

uncomplicated falciparum malaria with parasite counts between 1,000 and 200,000/μl of blood, were 16–65 years of age, weighed at least 40 kg, and had no underlying diseases. Patients were excluded from the study if they were pregnant or breastfeeding, or had mixed infections, persistent vomiting, or intercurrent febrile infections. Patients could be withdrawn if their clinical condition deteriorated, their consciousness became impaired, they showed no significant reduction in parasitemia within 48 hr of treatment, they had recrudescent parasitemia, or they experienced a serious adverse event. All patients provided written informed consent.

Study design. This comparative clinical trial was open-label and randomized in design. It was conducted between August 1993 and July 1994. The protocol for this study was reviewed and approved by the institutional review board at the study site. Patients were sequentially admitted to the study. Those patients who had received incomplete antimalarial treatment prior to admission and were not acutely ill were carefully observed until parasitemia began to increase and they developed acute manifestations of falciparum malaria, e.g., fever. All patients were to remain in the same medical ward of the hospital during treatment and a 28-day follow-up period.

Treatment assignment. Patients were randomly assigned to receive either four 250-mg tablets of atovaquone (total = 1,000 mg/day) coadministered with four 100-mg tablets of proguanil hydrochloride (total = 400 mg/day) once a day for three days, or three 250-mg tablets of mefloquine hydrochloride initially plus two tablets 6 hr later. Because pharmacokinetic studies have shown that ingestion of food increases the bioavailability of atovaquone,[26] the atovaquone/proguanil regimen was administered approximately 45 min after ingestion of a liquid meal. Patients who experienced emesis within 1 hr after being dosed received another dose of atovaquone and proguanil. All antimalarial drugs were administered under supervision of the investigators.

Clinical assessment and efficacy endpoints. Clinical examinations were performed at least once a day for the first seven days and on days 14, 21, and 28 after starting treatment. Pulse and body temperature were measured every 4 hr until normal for two days. At each examination, patients were queried from a standard list of 16 symptoms commonly associated with malaria infections and also asked an open-ended question about other symptoms.

The primary efficacy endpoint was the 28-day cure rate; only patients whose outcome at day 28 was known could be evaluated for 28-day cure rates. The response to treatment was based on the World Health Organization classification system.[27] A sensitive response (S) is indicated by parasite clearance within seven days without recrudescence during the 28-day follow-up period. Resistant responses were subdivided into R1 responses (parasite clearance within seven days, followed by recrudescence within 28 days), R2 responses (marked reduction of parasitemia, but without clearance over a seven-day period), and R3 responses (no significant reduction of parasitemia during the first 48 hr). Patients were classified as unevaluable and excluded from analysis of 28-day cure rates if they were withdrawn from the study, or not followed for at least 28 days (even if they were aparasitemic and clinically well when last seen). Cure rates were calculated from the ratio of S responses/total of S + R1 + R2 + R3.

Parasite clearance times (PCTs) and fever clearance times (FCTs) were considered corroborative evidence of efficacy. The PCTs were calculated from initiation of antimalarial treatment until the first time that peripheral blood films were negative for asexual parasites. The FCTs were similarly calculated from initiation of treatment until the body temperature had decreased to 37.2°C, and remained no higher than 37.2°C for at least 24 hr.

Laboratory assessments. Thick and thin blood films were prepared every 6 hr for determination of parasite counts until three films were negative. Thereafter, blood films were prepared daily until day 7 and weekly until day 28. The films were stained with Giemsa stain and parasite counts were determined by counting the number of asexual parasites per 1,000 red blood cells on a thin film or per 200 white blood cells on a thick film and expressing the results in counts per microliter of peripheral blood. A blood slide was not considered negative until an examination of 200 oil-immersion fields on a thick film showed no parasites.

Blood was obtained for routine hematology and clinical chemistry studies prior to treatment and on study days 3, 7, 14, and 28. Hematologic parameters tested were hematocrit, hemoglobin, red blood cell count, white blood cell count, and differential and platelet counts. Clinical chemistry tests included glucose, blood urea nitrogen, creatinine, total bilirubin, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), and albumin. Blood was also obtained prior to treatment for assay of glucose 6-phosphate dehydrogenase (G6PD) status. Routine urinalyses were performed prior to treatment and on day 7. Stool specimens were examined for ova and parasites.

Safety analysis. Data from all study participants were used in the safety analysis. Adverse experiences, defined as any clinical finding that first occurred or increased in intensity within 10 days of treatment initiation, were derived from the signs and symptoms recorded at clinical assessments, plus additional information regarding duration of the experience, its intensity, seriousness, and attributability to the study drug (as determined by the investigator), and any action taken. Laboratory abnormalities that first occurred or increased in intensity were also evaluated.

Statistical analysis. For each treatment group, descriptive statistics (means, standard deviations, medians, and ranges) were calculated for continuous demographic variables and initial physical findings. For discontinuous variables, the rate or percentage abnormal were determined. Geometric means were calculated for initial parasite counts. Differences in baseline characteristics were compared by analysis of variance (ANOVA). The Yates' corrected chi-square analysis[28] was used to compare differences between treatment groups in cure rates and to calculate 95% confidence intervals. The Mann-Whitney U test was used to calculate differences in medians, with 95% confidence intervals, for the FCT and PCT, and differences in median hematology and biochemistry test results at each time period. A difference between medians was considered statistically significant if P was < 0.05.

TABLE 1
Demographic characteristics and pretreatment signs and symptoms of patients in each study group

Parameter*	Atovaquone/ proguanil (n = 91)	Mefloquine (n = 91)
Male : female	71:20	74:17
Age (years)		
Mean (SD)	27.9 (10.3)	23.7 (7.4)
Range	16–63	15–54
Height (cm), mean (SD)	161.2 (7.0)	161.8 (6.9)
Weight (kg), mean (SD)	52.9 (8.5)	51.5 (6.7)
Fever (°C)		
Mean (SD)	38.0 (0.7)	38.1 (0.8)
Highest before treatment	40.1	40.2
Parasite count (/μl)		
Geometric mean	38,270	46,108
Range	570–198,800	1,134–416,000
G6PD-deficient, no. of patients (%)	8 (9)	8 (9)

* G6PD = glucose 6-phosphate dehydrogenase.

TABLE 2
Pretreatment laboratory results

Parameter*	Atovaquone/ proguanil (n = 91)		Mefloquine (n = 91)	
	Mean	Abnormal†	Mean	Abnormal†
Hemoglobin (g/dl)	11.3	68 (75) L	11.1	66 (73) L
Hematocrit (%)	34.1	65 (71) L	33.4	63 (69) L
Red blood cell count ($\times 10^{12}$/L)	4.1	56 (62) L	4.1	53 (58) L
White blood cell count ($\times 10^{9}$/L)	6.4	18 (20) L	6.4	12 (13) L
		4 (4) H		3 (3) H
Platelets ($\times 10^{9}$/L)	130	57 (63) L	135	57 (63) L
BUN (mg/dl)	16.6	21 (23) H	18.8	27 (30) H
Creatinine (mg/dl)	1.1	7 (8) H	1.2	10 (11) H
Glucose (mg/dl)	116	45 (50) H	112	41 (45) H
Albumin (g/dl)	4.0	15 (17) L	3.9	15 (17) L
Bilirubin (mg/dl)	1.6	45 (50) H	1.5	37 (41) H
AST (U/L)	47.2	31 (34) H	42.0	32 (35) H
ALT (U/L)	67.4	30 (33) H	36.0	26 (29) H

* BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
† L = value below normal; H = value greater than normal. Values in parentheses are percentages of patients.

RESULTS

Patient characteristics. A total of 182 Thai patients with acute uncomplicated falciparum malaria were randomized to treatment with atovaquone/proguanil (n = 91) or mefloquine (n = 91), of whom 158 (87%) (79 in each treatment group) completed the study and were evaluable. Of the 24 unevaluable patients, 22 (11 in each treatment group) had resolution of parasitemia and were well enough to go home due to social reasons but were lost to follow-up between day 7 and day 24. One patient in the atovaquone/proguanil group was withdrawn from the study for concurrent shigellosis and tuberculosis noted after admission to the study, and one in the mefloquine group was withdrawn because of a deteriorating clinical condition during the first 12 hr after treatment. No patients died during the study. Ten patients were excluded from the analyses of FCTs because they had no fever when treatment was initiated (or within 24 hr thereafter), a concurrent febrile illness, or were withdrawn prior to fever clearance. Two patients were excluded from the analysis of PCT because they were withdrawn prior to parasite clearance, as described above.

The two treatment groups were similar with respect to all demographic characteristics, except age (Table 1). Patients in the atovaquone/proguanil group were approximately four years older (mean = 27.9 versus 23.7 years) than patients in the mefloquine group ($P = 0.004$, by ANOVA). The two treatment groups were also similar with respect to baseline signs and symptoms and pretreatment laboratory test values (Table 2). The pre-malaria health status of all patients was considered good. No patient had severe or cerebral malaria. One hundred patients (55%) had a history of vomiting at admission; in no case was the vomiting considered to be severe enough to prevent oral therapy. Laboratory test results were typical of those commonly seen in patients with acute malaria. They showed a modest degree of anemia, with more than two-thirds of the patients having low hemoglobin and hematocrit values and more than half having a low red blood cell count. The types of medications taken concomitantly by patients during the study did not differ between the atovaquone/proguanil and mefloquine treatment groups. The most commonly used concomitant medications in the two treatment groups were the antipyretic/analgesic acetaminophen (94.5% and 87.9% of the patients, respectively) and the anti-emetic dimenhydrinate (85.7% and 75.8% of the patients, respectively).

Efficacy. At 28 days follow-up, 100% of the evaluable patients in the atovaquone/proguanil group were cured, compared with 86% in the mefloquine group (Table 3). The difference in cure rates was 14% (95% confidence interval = 6–21.8%, $P < 0.002$). The patients not cured after treatment with mefloquine had an R1 pattern of resistance. No significant differences were observed between treatment groups with respect to PCT or FCT (Table 3). Patients who were cured were generally free of malarial symptoms within 48 hr of treatment initiation in both groups. The change in *P. falciparum* parasite counts followed a similar pattern in the two treatment groups, except that the counts in patients receiving mefloquine increased above baseline during the first

TABLE 3
Therapeutic response at day 28 evaluation

	Atovaquone/ proguanil (n = 91)	Mefloquine (n = 91)
No. of patients with 28 days follow-up	79	79
No. (%) of patients cured	79 (100)	68 (86)
Fever clearance time (hr)*		
Median	53.5	50.0
Mean (SD)	58.9 (36.1)	50.9 (31.2)
Range	3–152	4–147
Parasite clearance time (hr)†		
Median	66.5	65.0
Mean (SD)	65.2 (17.6)	73.8 (29.0)
Range	24–127	24–167

* Fever clearance time was analyzed in 84 patients in the atovaquone/proguanil group and in 88 patients in the mefloquine group.
† Parasite clearance time was analyzed in 90 patients in each treatment group.

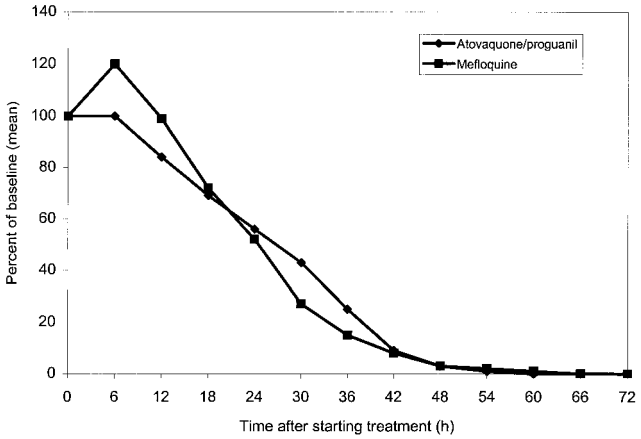

FIGURE 1. Effect of atovaquone/proguanil and mefloquine on the rate of *Plasmodium falciparum* parasite disappearance. h = hours.

few hours after treatment initiation (maximum mean increase = 19% at 6-hr postdose, Figure 1). Quantitative parasite counts were not always available before treatment was initiated. When results were obtained, it was found that a few patients had initial *P. falciparum* parasite counts outside the 1,000–200,000/μl range. Five patients in the mefloquine group had parasite counts > 200,000/μl and one patient in the atovaquone/proguanil group had a count < 1,000/μl. The responses to treatment in these patients were indistinguishable from the responses in other patients.

Eight patients developed delayed primary attacks of *P. vivax* malaria during days 21–28 of follow-up. These patients, all of whom had received atovaquone/proguanil, were treated with small (450-mg) doses of chloroquine to eliminate erythrocytic forms of *P. vivax* until their follow-up period for *P. falciparum* was completed. At completion of the follow-up period, these patients were treated with primaquine to eliminate exoerythrocytic forms (hypnozoites).

Safety. The adverse experiences that were reported were typical of malaria symptoms and were reported in 36% (33 of 91) and 35% (32 of 91) of patients treated with atovaquone/proguanil and mefloquine, respectively. The most frequent adverse experiences in the atovaquone/proguanil group were vomiting (10%), sore throat (8%), diarrhea (5%), and abdominal pain (2%). Eight of the nine patients who experienced vomiting for the first time after initiation of atovaquone/proguanil and five who had this symptom at baseline and continued to vomit during treatment required re-administration of one dose of therapy. The investigator attributed vomiting in these patients to the large number of tablets (eight) required for each dose of atovaquone/proguanil. Only one adverse experience (one case of nausea) was considered to be possibly related to treatment with atovaquone/proguanil.

In the mefloquine group, the most frequent adverse experiences reported were sore throat (8%), nausea (5%), insomnia (3%), and vomiting, diarrhea, anorexia, dizziness, and headache (2% each). Neither of the two patients with vomiting required re-administration of mefloquine. Four adverse experiences were considered possibly related to mefloquine (two cases of nausea, one of anorexia, and one of headache).

In most patients, laboratory abnormalities improved after starting treatment, and by day 28 clinically significant laboratory abnormalities other than eosinophilia were present in no more than three patients in either group (Table 4). New or more profound abnormalities in laboratory values emerged after starting treatment in a few patients. Marked anemia (hematocrit < 25%, hemoglobin level < 7.5 g/dl, or red blood cell count < 3×10^{12}/L) occurred in 8% of the patients in the atovaquone/proguanil group and 14% of the patients in the mefloquine group. Only two of the 26 patients who developed marked anemia were deficient in red blood cell G6PD (one patient in each treatment group). Elevated liver enzyme levels (ALT or AST > 100 U/L) occurred in 13–16% of the patients in the atovaquone/proguanil treatment group and 7% of the patients in the mefloquine group. Although elevated liver enzyme levels can be seen in patients with evolving malaria infections,[29] a greater degree of changes on days 3 and 7 after dosing and a greater frequency of high levels in the atovaquone/proguanil group suggested a possible relationship with atovaquone/proguanil treatment, although not statistically significant. In no case did ALT or AST elevations prevent patients from completing their course of treatment. By day 28 of follow-up, AST values had normalized in nine of the 12 atovaquone/proguanil patients and in all six of the mefloquine patients in whom significant elevations developed during treatment. Similarly, by day 28, ALT values were nor-

TABLE 4
Number (%) of patients developing clinically significant laboratory abnormalities during the study

		Atovaquone/proguanil (n = 91)		Mefloquine (n = 91)	
Parameter*	Criteria	Developing abnormality	Abnormal at day 28	Developing abnormality	Abnormal at day 28
Hematocrit	<25%	6 (7)	0	8 (9)	1 (1)
Hemoglobin	<7.5 g/dl	4 (4)	0	7 (8)	2 (2)
Red blood cell count	$<3 \times 10^{12}$/L	8 (9)	0	14 (15)	1 (1)
White blood cell count	$<3 \times 10^{9}$/L	3 (3)	0	3 (3)	0
Neutrophil blood count	$<1 \times 10^{9}$/L	4 (4)	0	2 (2)	0
Eosinophil count	>1,000/μl	38 (42)	32 (35)	54 (59)	37 (41)
Platelet count	$<50 \times 10^{9}$/L	3 (3)	0	3 (3)	0
Creatinine	>2.0 mg/dl	0	0	1 (1)	0
Albumin	<3.0 g/dl	6 (7)	0	4 (4)	0
Bilirubin	>2.0 mg/dl	6 (7)	0	1 (1)	0
ALT	>100 U/liter	15 (16)	2 (2)	6 (7)	1 (1)
AST	>100 U/liter	12 (13)	3 (3)	6 (7)	0

* ALT = alanine aminotransferase; AST = aspartate aminotransferase.

mal in 13 of 15 patients treated with atovaquone/proguanil and in five of six patients treated with mefloquine in whom significant elevations had occurred.

The incidence of eosinophilia, which was present at baseline in 4% of the atovaquone/proguanil group and 7% of the mefloquine group, increased dramatically during both treatment regimens (to 42% and 59% of the patients receiving atovaquone/proguanil and mefloquine, respectively). Abnormally high eosinophil counts continued to be present at almost as high a level by the end of follow-up; this correlated with the presence of one or more intestinal parasites found in stool examinations in approximately 74% of the patients. Parasites most often encountered were hookworm (46%), *Trichiura* (34%), *Ascaris* (22%), *Strongyloides* (14%), and *Opisthorchis* (7%). Treatment for intestinal parasitism was delayed until follow-up of the affected patients' malaria infection was complete at 28 days.

DISCUSSION

The results of this study indicate that a regimen of atovaquone in combination with proguanil once a day for three days is significantly more effective than a two-dose regimen of mefloquine for treatment of falciparum malaria in an area where multiple drug resistance is common. In view of the 100% cure rate observed with atovaquone/proguanil, this combination constitutes an important therapeutic advance not only in Thailand, but also in other parts of the world where mefloquine resistance continues to increase.[30] The efficacy of atovaquone/proguanil is particularly groundbreaking for Southeast Asia, where an effective and well tolerated antimalarial with a novel mechanism of action has been sought for more than a decade in the face of widespread resistance of *P. falciparum* to the single antimalarials chloroquine, quinine, and halofantrine, and to the combination of pyrimethamine and sulfadoxine.[1,2]

The atovaquone/proguanil regimen evaluated in the present study has also resulted in 100% cure rates of falciparum malaria in a clinical trial conducted in the Philippines, in which it proved significantly more effective than recommended regimens of chloroquine (cure rate = 30%; $P < 0.001$) and chloroquine/pyrimethamine/sulfadoxine (cure rate = 88%; $P < 0.05$).[18] In Gabon, the atovaquone/proguanil regimen was associated with a significantly higher cure rate than amodiaquine (98% versus 81%; $P < 0.005$).[17] Although the cure rate with atovaquone/proguanil did not differ from that of pyrimethamine/sulfadoxine in a comparative clinical trial in Zambia (100% versus 99%),[22] this would not be expected to be the case in Southeast Asia, where resistance to pyrimethamine/sulfadoxine is common.[31]

Atovaquone/proguanil did not differ from mefloquine with respect to PCT or FCT, parameters considered suggestive of the rate of drug effect. The PCT and FCT were classified as secondary efficacy endpoints in this study because of their variability, with the respective times being influenced by differences in patients' prior experience with malaria (immunity), level of infection (as reflected by initial parasite counts), and use of antipyretics (for FCT). The PCT observed in the atovaquone/proguanil group in the present study (65.2 hr) was within the range noted for atovaquone/proguanil in other clinical trials (47–72 hr),[32] although the FCT (58.9 hr) was considerably longer (27–39 hr).[32] Examination of *P. falciparum* counts over time revealed that mefloquine, unlike atovaquone/proguanil, was associated with a substantial increase in the number of *P. falciparum*-infected erythrocytes in the peripheral blood during the first few hours following treatment initiation. A similar increase in parasite count over the first 16 hr following treatment initiation was also observed with mefloquine in a study by Jiang and others,[33] but not in a study by Li and others.[34]

Atovaquone/proguanil exemplifies how synergism rather than just additive activity can be achieved via a combination of antimalarial agents. *In vitro,* the concentration of drug that inhibits parasite growth by 50% (IC_{50}) of atovaquone against various *P. falciparum* strains is 0.7–4.3 nM, making it consistently more potent than chloroquine, which has an IC_{50} of 74–633 nM against the same strains.[35] The active metabolite of proguanil, cycloguanil, has an IC_{50} against various sensitive strains of *P. falciparum* of 17.6–78.7 nM.[36] However, the combination of atovaquone and proguanil consistently demonstrates synergy against sensitive strains of *P. falciparum.*[25] This *in vitro* synergy appears to be reflected in the superior clinical efficacy demonstrated by the combination compared with its individual components. In Thailand, atovaquone given alone cured only about two-thirds of patients with acute, uncomplicated falciparum malaria, even when relatively large doses were administered for seven days, and proguanil, given alone at doses of 400–1,000 mg/day for three days, cured less than 10% of patients.[20,32] However, the regimen of atovaquone/proguanil evaluated in the present study achieved a 100% cure rate.

The use of antimalarial drug combinations is based in part on the belief that simultaneous exposure to drugs with diverse modes of action reduces the probability that the parasite will develop resistance to each constituent drug, because the probability of multiple mutations at independent loci will be low.[37] From a pharmacokinetic standpoint, proguanil, whose active metabolite, cycloguanil, has an elimination half-life of about 16 hr,[38] is cleared from the body faster than atovaquone, which has an elimination half-life of about 70 hr when administered once a day.[35] Although it is theoretically possible that such a difference in pharmacokinetics might encourage resistance to the longer-acting component,[37] this has not surfaced as a problem to date.

The atovaquone/proguanil regimen was generally well tolerated. The most common adverse event, an increase in vomiting over baseline, was noted in fewer than 10% of the patients. Vomiting was also the most frequent adverse event reported by Radloff and others in their clinical trial evaluating the same regimen of atovaquone/proguanil in patients with falciparum malaria in Gabon.[17] These investigators believed that the increased incidence of vomiting was most likely attributable to the large number of tablets (eight) that had to be taken per atovaquone/proguanil dose. If this is the case, then the incidence of vomiting may be expected to decrease when atovaquone/proguanil is made available as a formulation combining both drugs in one tablet.

The elevations in ALT and AST levels observed in 16% and 13%, respectively, of patients in the atovaquone/proguanil group in the present study were also seen in an earlier, uncontrolled, dose-ranging study conducted at the same institution in Thailand.[20] In the latter study, ALT levels in-

creased to abnormally high concentrations in 12% of patients and AST levels increased in 6% of the patients. Seven of these patients had persistent elevations at 28 days, five of whom had hepatitis B surface antigenemia. The investigators speculated that hepatitis, which is present in a high proportion of patients in Thailand, could have played a role in the observed elevations of liver enzyme levels. Although hepatitis B surface antigen testing was not performed in the present study, the presence of subclinical hepatitis in the patient population cannot be ruled out. Approximately one-third of all patients had abnormally high ALT and AST levels pretreatment, the cause of which was assumed to be malaria but could have been complicated by other factors. Most of the patients treated with atovaquone/proguanil in whom elevations of ALT or AST levels were seen had normal enzyme values by day 28 of follow-up, indicating that any liver effects were generally short-lived. Significant elevations of ALT and AST levels in patients in Gabon treated with atovaquone/proguanil were not observed in the study of Radloff and others,[17] nor were the mean serum transaminase levels for the group elevated at baseline. The possibility of mild hepatotoxicity due to atovaquone/proguanil cannot be excluded, although acute toxicology studies in rats and dogs that received high doses of the combination did not show significant adverse effects on the liver.[39]

Following initiation of treatment in this study, the incidence of eosinophilia increased from 4% at baseline to 42% in the atovaquone/proguanil group, and from 7% at baseline to 59% in the mefloquine group. The elevated eosinophil counts were likely related to helminth infections detected among approximately three-fourths of the patients during the study, with transient suppression of pre-existing eosinophilia by *P. falciparum* parasitemia.[40]

In conclusion, the combination of atovaquone and proguanil is more effective than mefloquine in the treatment of acute uncomplicated multi-drug resistant falciparum malaria. Atovaquone/proguanil is generally well tolerated, although a few patients experience increased vomiting and elevated ALT and AST values. The availability of a highly effective, well-tolerated combination product with a novel mechanism of action will help to address a critical need in antimalarial therapy.

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Authors' addresses: Sornchai Looareesuwan, Poirat Wilairatana, Kobsiri Chalermarut, and Yupin Rattanapong, Hospital for Tropical Diseases, Mahidol University, Bangkok 10400, Thailand. Craig J. Canfield, Pharmaceutical Systems Inc., 677 Valley View Road, Talent, OR 97540. David B. A. Hutchinson, Betsoms Farmhouse, Pilgrims Way, Westerham, Kent TN16 2DR, United Kingdom.

Reprint requests: Malarone Publication Coordinator, Room 50-3308B, Glaxo Wellcome, Inc., 5 Moore Drive, Research Triangle Park, NC 27709, or email to: malarone@glaxowellcome.com.

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