

Azithromycin Combination Therapy with Artesunate or Quinine for the Treatment of Uncomplicated *Plasmodium falciparum* Malaria in Adults: A Randomized, Phase 2 Clinical Trial in Thailand

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Background. Because antimalarial drug resistance is spreading, there is an urgent need for new combination treatments for malaria, which kills >1 million people every year. Azithromycin is a macrolide antibiotic that is particularly attractive as an antimalarial because of its safety in children and the extensive experience with its use during pregnancy.

Methods. We undertook a randomized, controlled, 28-day inpatient trial involving patients with acute, uncomplicated *Plasmodium falciparum* malaria. We compared the safety and efficacy of 2 azithromycin-artesunate combinations and 2 azithromycin-quinine regimens in adults with malaria. Treatments were as follows: cohort 1 received 3 days of azithromycin (750 mg twice daily) plus artesunate (100 mg twice daily), cohort 2 received 3 days of azithromycin (1000 mg once daily) plus artesunate (200 mg once daily), cohort 3 received 3 days of azithromycin (750 mg twice daily) plus quinine (10 mg/kg twice daily), and cohort 4 received 3 days of azithromycin (500 mg 3 times daily) plus quinine (10 mg/kg 3 times daily). The enrollment target was 25 evaluable subjects per group.

Results. The 28-day cure rates were similarly high in the artesunate and the standard-dose quinine cohorts: 92.0% (95% confidence interval [CI], 74.0%–99.0%), 88.9% (95% CI, 70.8%–97.6%), and 92.0% (95% CI, 74.0%–99.0%), for cohorts 1, 2, and 4, respectively. Late R1 treatment failures were seen in each of the artesunate and the standard-dose quinine cohorts. The cure rate for cohort 3 was 73.3% (95% CI, 44.9%–92.2%). In this cohort, 3 early treatment failures led to the termination of enrollment after 16 subjects had been enrolled. With mean parasite and fever clearance times (\pm SD) of 34 ± 13 h and 20 ± 20 h, the artesunate combinations were found to have led to a significantly ($P < .001$) faster clinical and parasitological improvement than occurred in the quinine cohorts (74 ± 32 h and 43 ± 37 h, respectively). Treatment-related adverse events were significantly more common in the quinine cohorts ($P < .001$). No deaths or drug-related serious adverse events were observed. In vitro results suggest that the treatment failures—particularly in the low-dose quinine cohort—were associated with decreased susceptibility to quinine, as well as with mefloquine cross-resistance.

Conclusions. These data suggest that azithromycin-artesunate, even when given only once daily for 3 days, and azithromycin-quinine, given 3 times daily, are safe and efficacious combination treatments for uncomplicated falciparum malaria, and they deserve additional study in special patient populations.

The spread of multidrug resistance to malaria and the

absence of new antimalarial compounds led us to investigate currently available agents with a novel mode of action to evaluate their potential use in combination regimens for the treatment of *Plasmodium falciparum* malaria. Azithromycin, a widely-prescribed, advanced-

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generation macrolide antibiotic with a favorable toxicological profile, has shown intrinsic activity against *P. falciparum* both in vitro [1, 2] and for treatment and prophylaxis [3–5]. In combination studies with quinine, azithromycin has demonstrated high efficacy in curing uncomplicated falciparum malaria, and recent prophylaxis trials suggest that azithromycin also has a high efficacy for preventing *Plasmodium vivax* malaria [6, 7].

Azithromycin generally shows a slow parasitological onset of action in treatment of falciparum malaria, and this suggests that its combination with fast-acting substances, such as artesunate, would be beneficial. Combination therapy is widely accepted as the best approach to the management of *P. falciparum* malaria because it produces excellent clinical response and slows the development of antimalarial drug resistance.

Recent data suggest that, in previous studies, treatment failures associated with azithromycin combination therapy were primarily associated with inadequate dosage, because increasing the dosage of azithromycin in combination with quinine leads to high cure rates [6]. Compared with other antibiotics used for malaria treatment (e.g., tetracyclines), azithromycin offers unique advantages because of its safety in children and the extensive experience with its use in pregnant women [8]—the populations most affected by malaria. With an average terminal half-life of almost 3 days (~68 h), azithromycin also has favorable pharmacokinetic properties, which result in practical dosing regimens as short as 3 days. We present results from a randomized clinical trial of artesunate-azithromycin and quinine-azithromycin combinations in Thailand, with the aim of determining the most practical and highly efficacious azithromycin combination therapy for uncomplicated, multidrug-resistant falciparum malaria.

PATIENTS AND METHODS

Study site and participants. The enrollment target was 100 evaluable patients (those who completed primary study end points). Study participants were adult men and nonpregnant women aged 20–65 years who were recruited at the Hospital for Tropical Diseases (Mahidol University, Bangkok, Thailand), who presented with acute uncomplicated falciparum malaria, who were otherwise healthy, and who had parasite densities of 100–100,000 asexual *P. falciparum* parasites/ μ L. Patients were not admitted to the study if any of the following criteria were present: if they were pregnant or nursing; if they had signs and symptoms of severe malaria; if they had mixed malaria infection at the time of admission to the hospital; if they had received malaria drug therapy or blood transfusions in the preceding 30 days; if there was laboratory evidence or history of significant cardiovascular, liver, or renal functional abnormality; if the patient reported severe vomiting or reported alcohol or drug abuse; if there was any clinically significant illness; or if there

was a likelihood that the patient would require treatment with drugs not permitted by the protocol.

Study design. The study was designed as a single-center, phase II, open-label, randomized study of acute, uncomplicated *P. falciparum* malaria in an inpatient setting. Study participants, who mostly originated from the western border regions of Thailand, were hospitalized for 28 days at the Hospital of Tropical Diseases outside of areas where malaria is endemic, to avoid re-infection with malaria and to ensure prompt treatment of any recrudescence infections or adverse events. The study was approved by the ethics review boards of the Thai Ministry of Public Health (Nonthaburi), the Hospital for Tropical Diseases (Bangkok), and the Human Subjects Research Review Board of the US Army. Written, informed consent was obtained from all study participants.

Sample size. A sample size of 100 subjects in 4 cohorts (a minimum of 25 patients per cohort) was calculated as to provide 95% confidence that a regimen with which all patients are cured is at least 89% efficacious.

Randomization. Patients were randomly assigned to 1 of 4 treatment groups according to a statistical series based on random sampling numbers that had been drawn up for each patient by the study staff. The details of the series were unknown to any of the investigators or to the coordinator and were contained in a set of sealed envelopes.

Study drugs. All subjects received azithromycin in combination with either artesunate or quinine for the treatment of their *P. falciparum* infection. Azithromycin (250-mg tablets; Zithromax; lot ED-O-408-X01) was provided by Pfizer, and quinine (lot 71606C03) was provided by the Walter Reed Army Medical Center (Washington, D.C.). Artesunate (50-mg tablets; Plasmotrim-50 Lactab; Mepha; lot 0351164) was purchased locally. The subjects were randomized to 1 of the following 4 treatment groups: cohort 1 received 3 days of azithromycin (750 mg twice daily) plus artesunate (100 mg twice daily), for a total dose of 4.5 g of azithromycin plus 600 mg of artesunate; cohort 2 received 3 days of azithromycin (1000 mg once daily) plus artesunate (200 mg once daily), for a total dose of 3 g of azithromycin plus 600 mg of artesunate; cohort 3 received 3 days of azithromycin (750 mg twice daily) plus quinine (10 mg/kg twice daily), for a total dose of 4.5 g of azithromycin plus 60 mg/kg quinine; and cohort 4 received 3 days of azithromycin (500 mg 3 times daily) plus quinine (10 mg/kg 3 times daily), for a total dose of 4.5 g of azithromycin plus 90 mg/kg quinine.

All antimalarial medications were administered under supervision with meals or a snack. Acetaminophen and dimenhydrinate were provided, as needed, for symptoms of fever, headache, myalgias, nausea, and/or dizziness, respectively. Other medications or intravenous fluids were provided only as prescribed and were considered to be concomitant medications.

Evaluations. After enrollment, the results of the physical examination, vital signs, adverse events, clinical signs and symptoms, and medication history were recorded daily until day 7, as well as on days 14, 21, and 28 or whenever signs and symptoms consistent with malaria or any other disease or adverse event reappeared. Urine pregnancy testing was performed on the day of enrollment. Complete blood cell counts and blood chemistry analyses were performed on days 0, 3, 7, and 14 and on days 21 and 28 if the previous findings were abnormal. Electrocardiography was performed on days 0, 1, and 3. Urinalysis was done on days 0 and 3 and on day 28 if previous findings were abnormal.

Microscopic evaluation. Blood smear specimens were obtained twice daily until the patient was a parasitemic on at least 2 successive smears, then on days 7, 14, 21, and 28 or whenever signs and symptoms consistent with malaria reappeared. One slide was stored for reference, and another was examined by a microscopist at the Hospital for Tropical Diseases laboratory. All slides were transported to the reference laboratory at the Armed Forces Research Institute of Medical Sciences (Bangkok) and were reexamined by an expert microscopist, who was blinded to the findings of the first reader. If the findings of the 2 microscopists were discordant with regard to either the species or the result's positivity, the slides were reexamined by a third reference microscopist, whose reading was accepted as final. Every thick film was screened for 200 oil-immersion fields before declaring a film result to be negative. Asexual parasites and gametocytes were separately counted against 200 WBCs; if the amount was too numerous to count on the thick film, we counted the number of parasites per 1000 RBCs on the thin film.

Efficacy measurements. The primary end points were 28-day cure and safety. Treatment failure was further divided into RI (defined as clearance of asexual parasites within 7 days after the initiation of treatment, followed by early [before day 15]/late [days 15–28] recrudescence until day 28), RII (defined as a decrease in the parasite count to <25% of the baseline value within 48 h but failure to clear parasites by day 7), and RIII (defined as a failure of the parasite count to decrease to <25% of the baseline value within 48 h), in accordance with World Health Organization criteria [9]. Secondary efficacy variables were parasite clearance time (PCT; defined as the time from initiation of treatment until the first time that blood films were negative for asexual parasites of *P. falciparum* and remained negative for the next 48 h), fever clearance time (FCT; defined as the time from initiation of treatment until the oral temperature decreased to <37.5°C and remained at less than this temperature for the next 48 h), and gametocyte clearance time.

In vitro studies. The fresh parasite samples obtained at admission and recrudescence were tested in a histidine-rich protein 2 (HRP2) drug susceptibility assay for susceptibility to

azithromycin, dihydroartemisinin, mefloquine, quinine, and chloroquine, without freezing or preculturing. Cultures and drug susceptibility assays were performed as previously described [10, 11].

Data analysis. Data were entered into electronic case record forms (I*Net; Pfizer). Ninety-five percent CIs for proportions were calculated using the method of Clopper and Pearson [12]. The Mann-Whitney *U* test or the Kruskal-Wallis test was used to compare continuous variables. The χ^2 test was used to compare proportions. Nonlinear regression analysis was used to calculate inhibitory concentrations. QTc intervals were also compared after Bazett and after Fridericia adjustments for heart rate. All tests were 2-sided, with a significance level of .05.

RESULTS

Clinical efficacy. One hundred seventeen subjects were screened, and 97 were randomized to 1 of the 4 treatment groups (figure 1). Five patients were lost to follow-up after returning to their homes or were withdrawn from the study (1 patient was withdrawn because of a serious adverse event [food poisoning] not related to the study drug). Twenty-five patients were evaluable for primary end point in cohorts 1 and 4, twenty-seven were evaluable in cohort 2, and 15 were evaluable in cohort 3. In cohort 3, three early treatment failures (RIII) led to the termination of enrollment after enrollment of 16

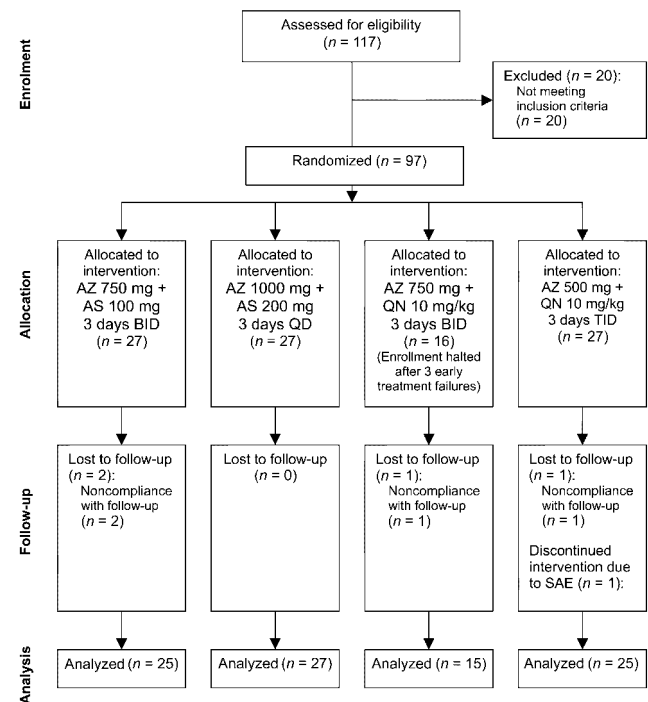


Figure 1. Flow diagram of the progress through the phases of the trial from enrollment until data analysis for the 4 cohorts. AS, artesunate; AZ, azithromycin; BID, twice per day; QD, once per day; QN, quinine; TID, 3 times per day.

subjects. All but 1 subject in group 4 (who was withdrawn because of a serious adverse event) received all medication. The 4 cohorts were well balanced with respect to age, sex, weight, medical history, and severity of disease, the last of which being an entry criterion for this protocol (table 1).

The 28-day cure rates in per protocol analysis were similarly high in the artesunate and the high-dose quinine cohorts (92.0% [95% CI, 74.0%–99.0%], 88.9% [95% CI, 70.8%–97.6%], and 92.0% [95% CI, 74.0%–99.0%]), for cohorts 1, 2, and 4, respectively) (table 2). The cure rate for cohort 3 (low-dose quinine plus azithromycin) was 73.3% (95% CI, 44.9%–92.2%). The corresponding values for the intention-to-treat population in cohorts 1–4 were 92.6%, 88.9%, 75.0%, and 92.6%, respectively, for best-case scenario and 85.2%, 88.9%, 68.7%, and 85.2%, respectively, for worst-case scenario.

Of the 4 treatment failures that occurred in cohort 3, three were considered to be RIII (i.e., treatment was unable to reduce the parasite density to <25% of the baseline value within 48 h). All treatment failures in cohorts 1, 2, and 4 were classified as RI with late recrudescence (i.e., recrudescence after day 14). The total number of failures (RI, RII, and RIII) at the end of treatment was 2 (8.0%), 3 (11.1%), 4 (26.7%), and 2 (8.0%) in cohorts 1–4, respectively.

With a mean PCT and FCT (\pm SD) of 34.49 ± 12.95 h and 19.90 ± 19.55 h, respectively, the artesunate combinations led to significantly faster clinical and parasitological improvement than occurred in the quinine cohorts (74.23 ± 31.71 h and 43.09 ± 36.51 h, respectively; $P = .000$ for PCT and $P = 0.001$ for FCT) (figure 2). There was no significant difference for either PCT or FCT between the 2 artesunate cohorts. In the quinine cohorts, the higher dose of quinine led to a significantly faster parasite clearance than did the lower dose

($P = .005$). There were no significant differences in the mean gametocyte clearance times for cohorts 1–4.

All randomized subjects were analyzed for drug safety. Drug-related adverse events were significantly more common in the quinine cohorts ($P < .001$), mostly related to cinchonism, and electrocardiogram changes (QT intervals) were significantly more pronounced in the quinine groups. One, 3, 8, and 19 drug-related adverse events were seen in groups 1–4, respectively. All but 1 subject in cohort 1 reported at least 1 adverse event. There were 113, 154, 102, and 169 adverse events reported in cohorts 1–4, respectively. Most adverse events were mild or moderate in severity and in the “body-as-a-whole” digestive, hemic, lymphatic, special senses, and urogenital body systems. No drug-related serious adverse events or discontinuations of the study were seen.

Patients receiving quinine had consistent, demonstrable, and statistically significant prolongation of the QT interval. The first dose of quinine significantly prolonged the QT interval, compared with the first dose of artesunate ($P = .000$). The prolongation persisted and may have increased additionally by day 3 ($P = .000$). By day 3, the thrice-daily quinine dosing regimen prolonged QT intervals more than did the twice-daily regimen, but this reached clinical significance only with the Bazett correction ($P = .030$) (table 3).

Plots of vital signs did not reveal discernible, consistent differences across the 4 study cohorts. Plots of the liver size (measured in centimeters below the rib cage) showed that the magnitude of hepatomegaly uniformly decreased across all cohorts in the trial.

In vitro findings. A total of 73 samples obtained on the day of study enrollment were successfully tested for their in vitro drug susceptibility to azithromycin, dihydroartemisinin,

Table 1. Demographic and baseline characteristics of study subjects.

Characteristic	Cohort			
	1 ^a	2 ^b	3 ^c	4 ^d
Sex, no. of patients				
Male	23	23	15	25
Female	4	4	1	2
Age, mean years \pm SD	28 \pm 7.1	28.8 \pm 6.9	26.4 \pm 6.0	27.7 \pm 7.6
Weight, mean kg \pm SD	52.7 \pm 6.1	52.3 \pm 5.1	54.8 \pm 7.4	52.9 \pm 5.9
Height, mean cm \pm SD	162.2 \pm 6.9	162.8 \pm 6.3	165.0 \pm 6.2	161.9 \pm 4.5
Enrollment parasite density, GM/ μ L	2120	6761	7018	5431

NOTE. GM, geometric mean.

^a Three days of azithromycin (750 mg twice daily) plus artesunate (100 mg twice daily), for a total dose of 4.5 g of azithromycin plus 600 mg of artesunate.

^b Three days of azithromycin (1000 mg once daily) plus artesunate (200 mg once daily), for a total dose of 3 g of azithromycin plus 600 mg of artesunate.

^c Three days of azithromycin (750 mg twice daily) plus quinine (10 mg/kg twice daily), for a total dose of 4.5 g of azithromycin plus 60 mg/kg quinine.

^d Three days of azithromycin (500 mg 3 times daily) plus quinine (10 mg/kg 3 times daily), for a total dose of 4.5 g of azithromycin plus 90 mg/kg quinine.

Table 2. Primary (cure rates) and secondary (parasite and fever clearance) efficacy measures for all 4 treatment groups (efficacy evaluable population).

Characteristic	Cohort			
	1 ^a	2 ^b	3 ^c	4 ^d
No. of patients evaluable on day 28	25	27	15	25
Cure				
No. of patients	23	24	11	23
Percentage of patients (95% CI)	92.0 (74.0–99.0)	88.9 (70.8–97.6)	73.3 (44.9–92.2)	92.0 (74.0–99.0)
Treatment failure, no. of patients				
RI	2	3	1	2
RII	0	0	0	0
RIII	0	0	3	0
PCT, h				
Mean ± SD	33.14 ± 15.27	35.74 ± 10.49	93.06 ± 32.0	62.94 ± 26.11
Range	8.8–79.1	18.2–55.6	37.0–149.1	14.5–115.5
FCT, h				
Mean ± SD	23.35 ± 22.49	16.71 ± 16.16	51.37 ± 32.81	38.13 ± 38.34
Range	0.0–76.2	0.0–61.3	0.0–114.0	0.0–140.0

NOTE. FCT, fever clearance time; PCT, parasite clearance time; RI, clearance of asexual parasites within 7 days after the initiation of treatment, followed by early [before day 15]/late [days 15–28] recrudescence until day 28; RII, decrease in the parasite count to <25% of the baseline value within 48 h but failure to clear parasites by day 7; RIII, failure of the parasite count to decrease to <25% of the baseline value within 48 h.

^a Three days of azithromycin (750 mg twice daily) plus artesunate (100 mg twice daily), for a total dose of 4.5 g of azithromycin plus 600 mg of artesunate.

^b Three days of azithromycin (1000 mg once daily) plus artesunate (200 mg once daily), for a total dose of 3 g of azithromycin plus 600 mg of artesunate.

^c Three days of azithromycin (750 mg twice daily) plus quinine (10 mg/kg twice daily), for a total dose of 4.5 g of azithromycin plus 60 mg/kg quinine.

^d Three days of azithromycin (500 mg 3 times daily) plus quinine (10 mg/kg 3 times daily), for a total dose of 4.5 g of azithromycin plus 90 mg/kg quinine.

mefloquine, quinine, and chloroquine. Samples from patients with the 3 RIII treatment failures in the twice-daily quinine cohort had quinine IC₅₀s (116.4, 103.3, and 93.2 ng/mL) that were considerably greater than the geometric mean (64.4 ng/mL; 95% CI, 55.9–74.09 ng/mL), and 2 of them were classified as highly resistant to mefloquine (i.e., they had an IC₅₀ of >30 ng/mL), a drug that is widely used in Thailand and that is known for its cross-resistance with quinine. Quinine IC₅₀s were almost twice as high (114.8 ng/mL) for patients who later experienced treatment failures (RI and RIII) than in the overall mean.

DISCUSSION

Recent data suggest that there are high failure rates for even the most advanced combination therapies in Southeast Asia [13]. Drugs with novel modes of action are, therefore, urgently needed to be able to treat these infections in the future. Azithromycin is a drug registered worldwide and approved for use in children. Data on safety of use during pregnancy exist from a study demonstrating improved birth outcomes when mothers were treated for presumptive sexually transmitted diseases during pregnancy [8]. When azithromycin is used in combination with either artesunate or quinine, it has demonstrated efficacy

for treatment of uncomplicated falciparum malaria, with cure rates of ~90%. However, the study region has intermittent and unstable transmission patterns, which are a true test of drug efficacy when compared with the results of studies involving older children and adults in constant-transmission regions [14]. Artesunate used as 7-day monotherapy had efficacy rates of 95% and 85% at 28 and 42 days, respectively; thus, the combination regimen allowed for a 3-day treatment course with similar efficacy [15].

When used in combination, artesunate or quinine have the role of quickly reducing the initial parasite biomass, whereas azithromycin, with its longer half-life, has to reliably eliminate the remaining parasites. Artesunate and quinine are relatively fast-acting drugs that are rapidly eliminated from circulation. With its longer half-life and slow onset of action, azithromycin is a complimentary combination partner for these drugs, because it allows for covering ~3 parasite life cycles with only a 3-day drug administration. Azithromycin's intracellular location may allow for slower development of resistance for respiratory pathogens, and careful studies in the developing world have not documented widespread resistance of pneumococci [16, 17]. Potential limitations to azithromycin efficacy may be the dependence on inflammation [18] to deliver the drug to a

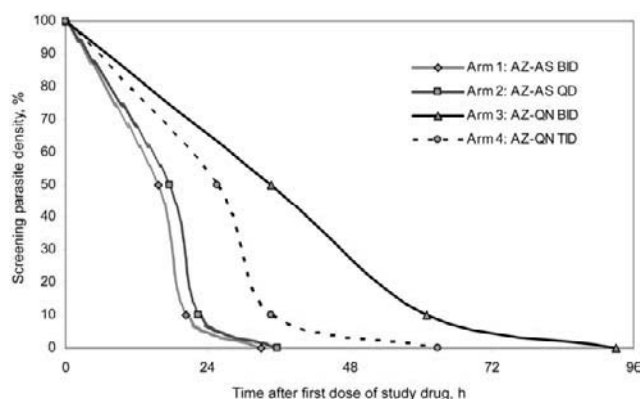


Figure 2. Parasite reduction curves with 50% and 90% parasite reduction times. Mean 50% parasite reduction times (\pm SD) were 15.6 ± 7.8 , 17.6 ± 11.0 , 34.8 ± 24.1 , and 25.6 ± 16.4 h for cohorts 1–4, respectively. The corresponding mean 90% parasite reduction times (\pm SD) were 20.2 ± 9.0 , 22.4 ± 9.8 , 61.0 ± 29.4 , and 34.8 ± 17.8 h. AS, artesunate; AZ, azithromycin; BID, twice per day; QD, once per day; QN, quinine; TID, 3 times per day.

site of infection and less accumulation in RBCs than in WBCs [19]; thus, there is a need to maximize pharmacodynamic parameters when treating patients with malaria.

The azithromycin combinations were generally well tolerated. Relatively poor efficacy in the treatment of falciparum malaria with standard doses of azithromycin (1500 mg total over 3 days) [20] and recent good results with higher doses used in combination with quinine [6] led us to investigate 3–4.5-g total doses of azithromycin. Even with these high doses of azithromycin (750–1000 mg per dose), and even though

there were acutely ill patients throughout the entire study, only 3 doses had to be readministered after patients vomited, and no patient discontinued therapy as a result of treatment-related adverse events. Patients in all cohorts were seriously ill with falciparum malaria and could be expected to have varying degrees of laboratory abnormalities and other adverse events. The rate of all-cause adverse events was comparable among cohorts, except for symptoms consistent with cinchonism, a symptom complex typically associated with the use of therapeutic doses of quinine. Quinine also prolonged the QT interval in a dose-related fashion, as described elsewhere [21].

The combination of azithromycin with artesunate, even when given only once daily for 3 days, has been shown to be a safe and efficacious drug combination for the treatment of falciparum malaria, even in areas with a high prevalence of multidrug resistance [22]. The obvious advantages of this regimen lie in the possibility of administering only a single dose per day, as well as the short duration of treatment thereby raising hopes of better compliance with treatment and faster clinical and parasitological improvement. This faster improvement is largely attributable to the fast action of artemisinin compounds, which reduce the parasite burden by the factor 10,000 in each cycle [23].

For the combination of azithromycin with quinine, the in vivo and in vitro data reflect the fact that the combination partner has to take the full burden of quickly reducing the initial parasitemia. In areas of compromised quinine and mefloquine susceptibility, such as Thailand, the lower dosage of quinine used in the twice-daily cohort will, therefore, not always provide enough initial impact to adequately reduce the parasite

Table 3. Uncorrected and corrected QT interval data with Fridericia's and Bazett's adjustments.

Comparison	Change from baseline QT interval, mean milliseconds \pm SE				P ^e
	Cohort 1 ^a	Cohort 2 ^b	Cohort 3 ^c	Cohort 4 ^d	
Day 1 vs. baseline					
Unadjusted	4 \pm 5.2	19 \pm 6.1	27 \pm 6.4	32 \pm 6.5	.002
Fridericia adjusted	–3 \pm 3.5	7 \pm 4.6	21 \pm 4.4	25 \pm 4.2	.000
Bazett adjusted	–7 \pm 3.6	0 \pm 3.9	17 \pm 4.4	20 \pm 3.6	.000
Day 3 vs. baseline					
Unadjusted	22 \pm 6.6	33 \pm 6.6	49 \pm 11.7	61 \pm 7.6	.000
Fridericia adjusted	4 \pm 4.6	14 \pm 4.4	28 \pm 5.9	43 \pm 5.6	.000
Bazett adjusted	–6 \pm 4.7	3 \pm 3.8	17 \pm 4.5	33 \pm 4.9	.000

^a Three days of azithromycin (750 mg twice daily) plus artesunate (100 mg twice daily), for a total dose of 4.5 g of azithromycin plus 600 mg of artesunate.

^b Three days of azithromycin (1000 mg once daily) plus artesunate (200 mg once daily), for a total dose of 3 g of azithromycin plus 600 mg of artesunate.

^c Three days of azithromycin (750 mg twice daily) plus quinine (10 mg/kg twice daily), for a total dose of 4.5 g of azithromycin plus 60 mg/kg quinine.

^d Three days of azithromycin (500 mg 3 times daily) plus quinine (10 mg/kg 3 times daily), for a total dose of 4.5 g of azithromycin plus 90 mg/kg quinine.

^e For comparison of cohorts 1 and 2 vs. cohorts 3 and 4.

burden. At least 2 of the 3 RIII treatment failures in this cohort appear to have been the result of reduced quinine susceptibility and cross-resistance with mefloquine.

In view of similarly high cure rates obtained with these combinations, the obvious advantage of artesunate as a combination partner is that it leads to a significantly faster clinical and parasitological improvement. It also allows for very convenient dosing regimens and is particularly well tolerated. The advantages of quinine, on the other hand, are its safety record during pregnancy and the fact that quinine is licensed in many western countries; also, it is the only currently available rapid-acting antimalarial available for treatment of patients who experience artemisinin treatment failure if resistance to artemisinin should emerge. The 3-day regimen evaluated is also a marked improvement over the standard 7–10-day regimens currently in use for quinine monotherapy.

Future studies of azithromycin with artesunate would be appropriate with a 30 mg/kg daily dose for children. This regimen may prove to be an alternative to empirical treatment of children with fever in geographic areas where diagnosis is difficult, as well as for patients with typhoid, pneumococcal sepsis, and malaria cases presenting with fever [24, 25].

In conclusion, these data suggest that azithromycin-artesunate, even when given only once daily for 3 days, and azithromycin-quinine, given 3 times daily, are safe and efficacious combination treatments for uncomplicated falciparum malaria. They warrant additional testing in larger studies.

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