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MAJOR ARTICLE

A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial of Tafenoquine for Weekly Prophylaxis against *Plasmodium falciparum*

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Tafenoquine is a promising new 8-aminoquinoline drug that may be useful for malaria prophylaxis in nonpregnant persons with normal glucose-6-phosphate dehydrogenase (G6PD) function. A randomized, double-blind, placebo-controlled chemoprophylaxis trial was conducted with adult residents of northern Ghana to determine the minimum effective weekly dose of tafenoquine for the prevention of infection by *Plasmodium falciparum*. The primary end point was a positive malaria blood smear result during the 13 weeks of study drug coverage. Relative to the placebo, all 4 tafenoquine dosages demonstrated significant protection against *P. falciparum* infection: for 25 mg/week, protective efficacy was 32% (95% confidence interval [CI], 20%–43%); for 50 mg/week, 84% (95% CI, 75%–91%); for 100 mg/week, 87% (95% CI, 78%–93%); and for 200 mg/week, 86% (95% CI, 76%–92%). The mefloquine dosage of 250 mg/week also demonstrated significant protection against *P. falciparum* infection (protective efficacy, 86%; 95% CI, 72%–93%). There was little difference between study groups in the adverse events reported, and there was no evidence of a relationship between tafenoquine dosage and reports of physical complaints or the occurrence of abnormal laboratory parameters. Tafenoquine dosages of 50, 100, and 200 mg/week were safe, well tolerated, and effective against *P. falciparum* infection in this study population.

Drugs used to prevent malarial infection and disease face the growing threat of resistance in many parts of the world. The armamentarium against malaria must be expanded to counter this threat and to provide new, easily used, and well tolerated chemoprophylactic options to travelers and deployed military personnel. A significant addition would be a long-acting drug that eliminates the early, liver stages of malaria-causing species before they mature into symptom-producing blood-stage forms, which would allow for the early or immediate discontinuation of the drug's use after individuals who received the drug leave a malarious area. Currently, the only drugs near to meeting this criterion are primaquine and atovaquone-proguanil (Malarone; GlaxoSmithKline). Despite impressive prophylactic efficacy against *Plasmodium falciparum* and *Plasmodium*

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vivax infection [1–5], primaquine is not yet approved for this indication. Atovaquone-proguanil is an approved drug combination with both suppressive and causal prophylactic effects against *P. falciparum* infection, and limited data also show its protective efficacy against *P. vivax* infection [6–9]. Atovaquone-proguanil therapy should continue for 7 days following exposure to these parasites.

Tafenoquine (formerly WR 238605) is a new primaquine analogue discovered by the US Army and codeveloped by the US Army Medical Materiel Development Activity and GlaxoSmithKline. Like primaquine, tafenoquine is active against *Plasmodium* liver stages, gametocytes, and sporozoites [10, 11], but unlike primaquine, tafenoquine has pronounced activity against the blood stages, including those of multidrug-resistant malaria-causing species [12, 13]. In addition, tafenoquine is longer-acting and can be administered once weekly [13, 14], in contrast to the daily regimens required for primaquine [1–5, 15] and atovaquone-proguanil [6–8, 16]. Of note, the use of tafenoquine would be limited to persons who are not pregnant and who have normal glucose-6-phosphate dehydrogenase (G6PD) activity. As an 8-aminoquinoline, tafenoquine would cause hemolysis in persons with G6PD deficiency, and must not be used during pregnancy because of its potential effect on the fetus [17–19]. Both primaquine and tafenoquine may induce a generally mild, reversible methemoglobinemia [1, 4, 14, 17, 18].

Tafenoquine has been evaluated in multiple human volunteer trials and shows potent prophylactic activity against *P. falciparum* infection [20, 21]. Tafenoquine prophylaxis in Kenyans was effective at dosages of 200 and 400 mg/week, but the lowest effective dose of the drug has not yet been identified. The aims of this study were to evaluate the protective efficacy, safety, and tolerability of tafenoquine across a broad range of dosages and to assess the relative protection afforded by mefloquine, the current once-weekly standard used by the US military for malaria prevention. Results obtained in this trial would guide dosage selection for phase III studies, in which the target population of users would be largely nonimmune to malaria.

SUBJECTS, MATERIALS, AND METHODS

Study site and subjects. The Kassena-Nankana district of northeastern Ghana was selected as the study site on the basis of the logistic capacity and quantified malaria epidemiology of this region. Preliminary study, there, of adults who had completed radical cure treatment had determined the 20-week cumulative incidence of reinfection by *P. falciparum* to be nearly 100% [22].

Study design and sample size estimation. A double-blind, placebo-controlled prospective trial was designed to evaluate the efficacy, tolerability, and safety of 4 different weekly dosages (25, 50, 100, or 200 mg) of tafenoquine (base; GlaxoSmithKline). Once-weekly prophylaxis with mefloquine (salt; Lariam [US formulation]; Hoffmann–La Roche), 250 mg/week, served as a positive reference. A placebo (tafenoquine placebo, GlaxoSmithKline; mefloquine placebo, Hoffmann-La Roche) served as the negative comparator. On the basis of a projected 12-week attack rate of 70% in the placebo group and an anticipated protective efficacy (PE) of 90%–95% for the highest dosage of tafenoquine, an enrollment of 100 subjects per study arm would provide >90% power to maintain the lower 95% confidence limit for the PE at >75%. The size of the mefloquine group was reduced because tafenoquine-placebo comparisons were of primary interest.

Ethical approval, subject selection, and consent. The protocol and consent forms were reviewed and approved by scientific and ethical review boards of the Ghanaian Ministry of Health, US Army, and US Navy. Traditional chiefs, community leaders, and local residents granted local approval of this study. Tribal language consent forms were read by or to every prospective subject. Individual affirmation of informed consent was obtained from those residents wishing to participate.

Screening. Screening was conducted over a period of 2 weeks (13–26 August 1998); informed consent and personal details were obtained, physical examination was performed, and 15 mL of venous blood was obtained for laboratory screening. Inclusion criteria included the following: age of 18–60 years (men) or 50–60 years (women); lack of significant systemic illness as determined by history, physical examination, and clinical laboratory test results (including negative results of a urine pregnancy test for women); and absence of seizures or other neuropsychiatric illness (past or present). The high rate of pregnancy and breast-feeding in women aged 18–49 years precluded their enrollment. For all subjects, the following clinical laboratory tests were done: complete blood count (Coulter Counter; Beckman-Coulter); serum biochemical analysis of levels of alanine aminotransferase (ALT), total bilirubin, and creatinine (Reflotron; Boeringer-Mannheim); dipstick urinalysis; whole-blood screening for G6PD deficiency by means of 2 separate G6PD qualitative assays (visual fluorescence [no. 203-A] and visual color [no. 400K]; Sigma); and microscopy of Giemsa-stained thick and thin blood smears.

Randomization. Subjects were randomly assigned to 1 of 6 study arms. The randomization code was generated in blocks of 11 numbers (2 numbers for each of the 4 tafenoquine groups, 2 for the placebo group, and 1 for the mefloquine group). Code numbers were assigned according to the chronological order of appearance of the subjects at screening. Study drugs were prepackaged and prelabeled with a unique study number according to the randomization code.

Drug administration. Before prophylaxis, subjects received an oral radical cure regimen to eliminate active and latent *Plasmodium* parasites. The regimen was composed of quinine sulfate (salt; Zenith Goldline), 600 mg 3 times daily for 4 days,

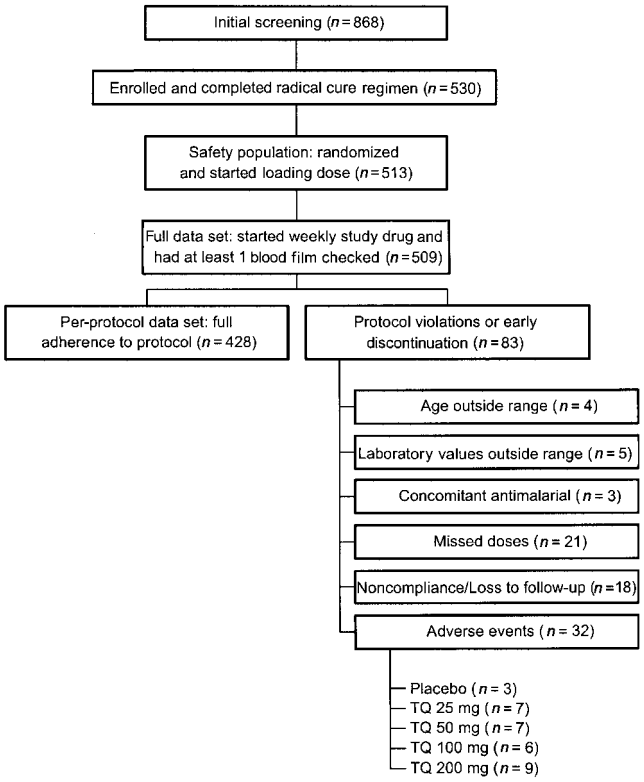

Figure 1. Design of randomized, double-blind, placebo-controlled chemoprophylaxis trial to determine the minimum effective weekly dose of tafenoquine for the prevention of infection by *Plasmodium falciparum*. TQ, tafenoquine.

followed by a 7-day course of doxycycline (Vibramycin; Pfizer), 100 mg twice daily, and primaquine phosphate (base; Sanofi-Winthrop), 30 mg once daily, followed by a 7-day course of primaquine phosphate, 30 mg once daily, for a total treatment course of 18 days. After the 18-day radical cure phase and a 5-day drug-free break (to permit recovery from primaquine-induced methemoglobinemia), each subject received a supervised 3-day loading dose of the study drug or placebo which they had been randomized to receive. The first dose of the weekly regimen of study drug or placebo was given 7 days after completion of the loading dose. All medications were given after a meal and witnessed by a member of the study team. A "double-dummy" design allowed double-blind administration of tafenoquine and mefloquine active drugs and their corresponding placebos.

Surveillance. Study subjects were visited daily in their homes during the radical cure and loading dose phases of this study to check the safety of and subjects' compliance with the drug regimens. During the prophylaxis and follow-up phases, health workers visited the subjects 3 times weekly; 1 visit coincided with drug administration and blood smear preparation. Health workers checked the subjects' health at each visit and reported complaints or symptoms to the study-team physicians. Subjects with physical complaints were examined by a study physician the next day or on an emergent basis, as needed. Hematologic analysis was done on days 4 and 10 after starting the loading dose phase and during weeks 4, 8, 12, and 15. Biochemical analysis was done during weeks 4, 8, 12, and 15.

Parasitologic and clinical assessment and efficacy end points. Thick and thin blood films were Giemsa stained and read for the presence of malaria-causing parasites by qualified microscopists. All slides positive for the presence of malaria-causing parasites, and an equal number of randomly selected slides with negative results were reevaluated by a second (blinded) microscopist. Two hundred thick-film fields were examined at $\times 1000$ magnification before assigning a negative result. For primary efficacy, subjects were considered to have experienced prophylaxis failure if they had a single blood film with a positive result at any time between the first loading dose and 7 days after the last dose of study drug or placebo. Unless terminated earlier, study drug or placebo administration ended when subjects became symptomatic and had positive blood smear results, when they had 2 consecutive positive blood smear results, or when they completed 12 weeks of prophylaxis. Symptomatic malaria was defined as a positive blood smear result in conjunction with any 2 of the following symptoms: fever (axillary temperature of $\geqslant 37.5$°C), chills, myalgia or arthralgia, headache, nausea, vomiting, dizziness, or abdominal pain. Symptomatic subjects were treated with oral chloroquine according to the local standard of care and assessed for their response to therapy. Subjects were monitored for an additional 4 weeks beyond the final, week 12 dose of the study drug or placebo to assess the duration of the prophylactic effect.

Statistical analysis. Data were double-entered and verified, and data files were locked before analysis. Data analysis for efficacy used 2 data sets: the "full, intent-to-treat" data set ($n = 509$), comprising all subjects who took at least 1 dose of the weekly study drug or placebo, and the "per-protocol" data set ($n = 428$), comprising those subjects who strictly fulfilled the protocol criteria. The safety and tolerability analyses included data for all subjects who received at least 1 dose of the study drug or placebo ($n = 513$).

Calculation of the PE for each active treatment compared with placebo was based on the crude attack rate (defined as the number of cases of prophylaxis failure/the number of subjects), with 95% CIs derived using the method described by Koopman [23]. Additionally, the incidence density of infection (defined as the number of prophylaxis failures/person-years of treatment) was calculated by life-table analysis [24]. The effects of weight and age on prophylaxis outcome were assessed by logistic regression, initially for individual tafenoquine groups and then for all of the tafenoquine groups.

Conditions reported at nonroutine clinic visits and routine home visits were summarized as the number of subjects who

Table 1. Sex, age, and weight composition of groups in a randomized, double-blind, placebo-controlled chemoprophylaxis trial to determine the minimum effective weekly dose of tafenoquine for the prevention of infection by *Plasmodium falciparum*.

Characteristic	Placebo group (n = 94)	Tafenoquine groups, by dosage				Mef group, 250 mg/week (n = 46)	All groups (n = 509)
		25 mg/week (n = 93)	50 mg/week (n = 91)	100 mg/week (n = 94)	200 mg/week (n = 91)		
Women, no. (%)	32 (34)	38 (41)	34 (37)	27 (29)	32 (35)	13 (28)	176 (35)
Age, years							
Mean	53	53	53	53	54	52	53
Median	53	54	54	54	54	53	54
Range	46–60	45–59	38–59	46–60	46–69	45–59	38–69
Weight, kg							
Mean (SD)	48.0 (6.8)	46.0 (4.6)	49.9 (7.3)	47.3 (7.1)	44.9 (4.3)	49.1 (5.0)	47.3 (6.2)
Median	47	46	50	47	45	50	47
Range	35–65	35–54	40–71	35–62	35–55	40–57	35–71
Men, no. (%)	62 (66)	55 (59)	57 (63)	67 (71)	59 (65)	33 (72)	333 (65)
Age, years							
Mean	39	40	36	38	39	37	38
Median	40	40	36	38	38	35	39
Range	17–60	14–63	18–58	18–60	18–63	19–58	14–90
Weight, kg							
Mean (SD)	54.8 (6.3)	56.3 (9.0)	55.4 (7.9)	55.4 (6.8)	54.1 (6.6)	56.3 (6.4)	55.3 (7.2)
Median	55	55	56	56	54	57	55
Range	35–73	37–90	33–77	36–68	36–72	42–72	33–90

NOTE. Mef, mefloquine.

reported each condition. Laboratory data were also summarized. Statistical analyses of safety and laboratory data were limited, because the study was not powered to make these comparisons.

RESULTS

Subject population. The flow chart (figure 1) shows that 338 of the 868 candidates screened were not enrolled in the study. G6PD deficiency accounted for 179 of 338 exclusions and was present in 20.6% of this adult population. As a result of inclusion criteria limiting their enrollment, women comprised 35% of the enrollees, were older, and weighed less than did their male counterparts (table 1). Forty-seven percent of the screened population was parasitemic at the enrollment screening. The radical cure phase of treatment was completed by 530 subjects, and 509 went on to receive the 3-day loading dose and first dose of the weekly regimen of the study drug or placebo, which marked the full, intent-to-treat data set and start of the 12-week prophylaxis period. Blood smear findings were negative for all subjects at the start of administration of the loading dose.

Efficacy. Outcome measurements for the incidence of *P. falciparum* infection and PE of drug groups relative to the placebo group are presented in table 2 for the full, intent-to-treat data set. Comparable levels of protection, ranging from 84.4% to 87.2%, were demonstrated in the tafenoquine groups receiving dosages of 50, 100, and 200 mg/week and in the reference group receiving mefloquine, 250 mg/week. Measurements of PE, based on the incidence density of infection, ranged from 92.8% to 94.3% for these groups. The cumulative proportion of subjects who remained uninfected over time is shown by group in a Kaplan-Meier plot (figure 2). Comparable measurements of crude incidence, incidence density, cumulative incidence, and PE were obtained for both the full, intent-to-treat data set (n = 509) and the per-protocol data set (n = 428) with use of the first occurrence of parasitemia as the primary outcome variable. Mild malaria symptoms coincident with parasitemia were reported in the placebo group (11 of 86 subjects) and in the groups receiving tafenoquine dosages of 25 mg/week (5 of 58), 50 mg/week (1 of 13), and 200 mg/week (1 of 12). Follow-up after chloroquine therapy revealed no cases of treatment failure.

Continued weekly administration of the study drug or placebo after the first positive blood smear result for asymptomatic subjects revealed that the tafenoquine regimens of 100 and 200 mg/week suppressed any further reappearance of parasites during the remaining period of prophylaxis. Monitoring of subjects 4 weeks beyond the week 12 prophylaxis end point showed new and recurrent cases of parasitemia in the groups receiving

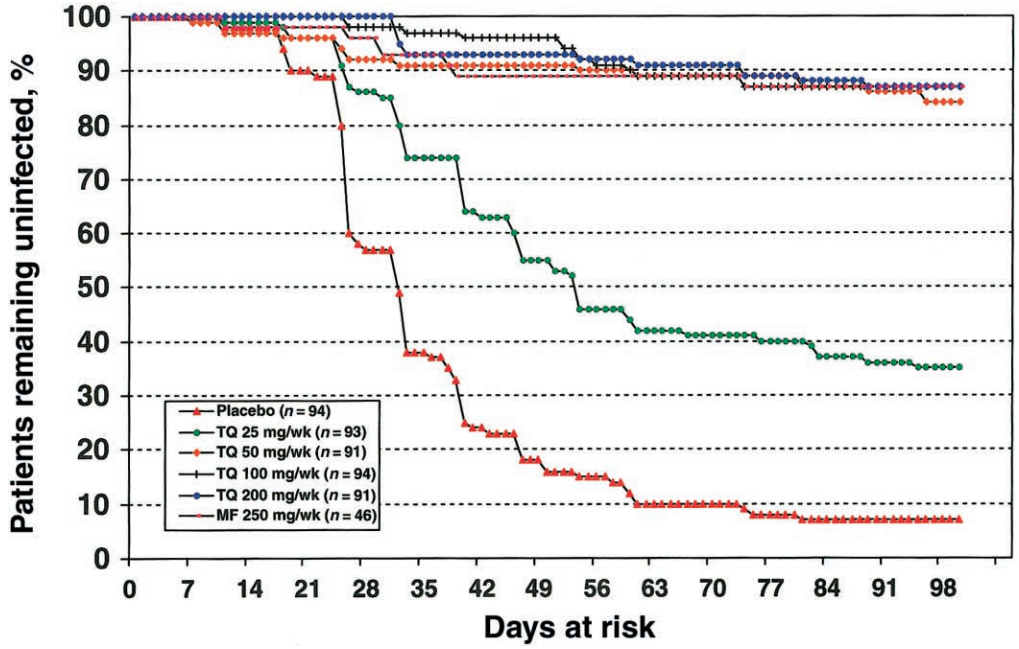

Figure 2. Cumulative proportions of subjects in the study groups who remained malaria-free. The days at risk comprised the time between the first loading dose and 7 days after the last dose of study drug or placebo. MF, mefloquine; TQ, tafenoquine; wk, week.

tafenoquine dosages of 25 mg/week (4 new and 12 recurrent cases of parasitemia) or 50 mg/week (7 new and 1 recurrent case), or mefloquine dosages of 250 mg/week (1 new and 2 recurrent cases), but no new infections were seen in the groups receiving tafenoquine dosages of 100 or 200 mg/week.

The analysis of dose response (in the tafenoquine arms only) indicated a significant interaction between treatment efficacy and body weight ($P < .001$), primarily because of a higher incidence of positive blood smear results among heavier subjects in the tafenoquine group receiving the lowest dosage (25 mg/week). Relative to the placebo cohorts, the PE in the group receiving tafenoquine, 25 mg/week, for those with a body weight lower than median was 56%, compared with a PE of 7% for those with a weight greater than the median.

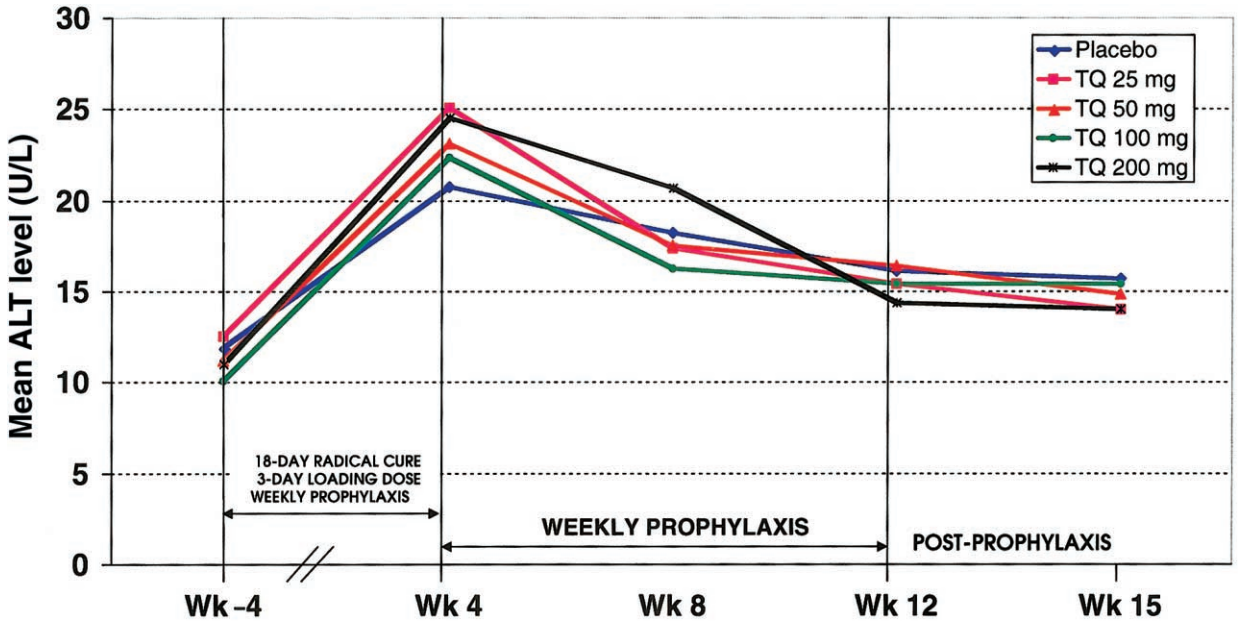

Figure 3. Mean alanine aminotransferase (ALT) profiles over time for the study groups. TQ, tafenoquine; wk, week.

Table 2. Primary outcomes in randomized, double-blind, placebo-controlled chemoprophylaxis trial to determine the minimum effective weekly dose of tafenoquine for the prevention of infection by *Plasmodium falciparum:* incidence of infection and protective efficacy of study drug regimens relative to placebo.

Variable	Placebo group (n = 94)	Tafenoquine groups, by dosage				Mef group, 250 mg/week (n = 46)
		25 mg/week (n = 93)	50 mg/week (n = 91)	100 mg/week (n = 94)	200 mg/week (n = 91)	
Positive blood-smear result, no. of subjects	86	58	13	11	12	6
Incidence (attack rate), %	91.5	62.4	14.3	11.7	13.2	13.0
Protective efficacy, %	NA	31.8[a]	84.4[a]	87.2[a]	85.6[a]	85.7[a]
Lower 95% confidence limit	NA	20.2	74.8	78.3	76.2	71.9
Upper 95% confidence limit	NA	43.4	90.7	92.7	91.6	93.3
Total person-weeks[b]	504	799	1079	1148	1110	564
Incidence density per subject-year	8.9	3.8	0.6	0.5	0.6	0.6

NOTE. Protective efficacy (%) = $\{[I_{placebo} - I_{drug}]/I_{placebo}\} \times 100$, where $I_{placebo}$ = number of subjects with prophylaxis failure in the placebo group/number of subjects at risk in the placebo group, and I_{drug} = number of subjects with prophylaxis failure in the drug group/number of subjects at risk in the drug group. Mef, mefloquine; NA, not applicable.

[a] Significantly different ($P < .05$) from the value for placebo group.

[b] Person-time from the start of the loading dose to 7 days after the final administration of study drug or placebo or the time of discontinuation from the study.

Tolerability. Table 3 summarizes adverse events in the study groups during drug or placebo administration, which are separated into those reported by subjects during visits to the health clinic and those reported by subjects during home-visits by study personnel. The tafenoquine groups demonstrated adverse-event rates comparable to those of the placebo group and showed no evidence of a dose-related effect; rates of clinic or home visits and of enumerated adverse events were comparable among the 4 tafenoquine groups. Physical complaints involving the musculoskeletal, gastrointestinal, and respiratory systems collectively accounted for 52%–70% of the total adverse events that prompted health clinic visits in each group (table 4). There were 9 serious adverse events in the study. Six of these occurred during the period of study drug or placebo administration, only 1 of which resulted in premature discontinuation of therapy. No serious adverse events were considered by study physicians to be related to the study drug, and no deaths occurred.

Safety. Thirty-three abnormal clinical laboratory test results were considered possibly or probably related to the study drug and led to the premature discontinuation of treatment for these subjects. Among these were 23 cases of abnormally elevated ALT levels, ranging from 61.9 to 193 U/L (placebo group, 2 cases; tafenoquine, 25 mg/week, 4 cases; tafenoquine, 50 mg/week, 4 cases; tafenoquine, 100 mg/week, 7 cases; and tafenoquine, 200 mg/week, 6 cases), 8 cases of low hemoglobin levels, <8.0 g/dL (placebo group, 1 case; tafenoquine, 25 mg/week, 2 cases; tafenoquine, 50 mg/week, 2 cases; and tafenoquine, 200 mg/week, 3 cases), and 2 cases of thrombocytopenia, which were subsequently found to be spurious and due to platelet clumping. The majority of abnormal ALT values were

Table 3. Adverse events among subjects during the period of study drug or placebo administration.

Variable	Placebo group	Tafenoquine groups, by dosage				Mef group, 250 mg/week
		25 mg/week	50 mg/week	100 mg/week	200 mg/week	
No. of subjects (safety population)	94	93	93	94	93	46
No. (%) of subjects with AEs at clinic presentation	52 (55)	47 (50)	50 (54)	59 (63)	53 (57)	21 (46)
No. of clinic visits	74	74	85	100	91	29
Total no. of AEs reported at clinic visits	91	92	107	129	102	34
No. (%) of subjects who reported AEs from home	60 (64)	60 (64)	58 (62)	62 (66)	54 (58)	25 (54)
Total no. of home visits at which AEs were reported	102	109	112	119	90	41

NOTE. AE, adverse event; Mef, mefloquine.

Table 4. Adverse events that occurred at a frequency of >5.0% in each study group.

Adverse event	Placebo group (n = 94)	Tafenoquine groups, by dosage				Mef group, 250 mg/week (n = 46)
		25 mg/week (n = 93)	50 mg/week (n = 93)	100 mg/week (n = 94)	200 mg/week (n = 93)	
Dysentery/diarrhea	15 (17.0)	14 (16.9)	14 (13.5)	20 (17.5)	12 (12.4)	4 (12.5)
Abdominal pain	6 (6.8)	3 (3.6)	3 (2.9)	9 (7.9)	2 (2.1)	3 (9.4)
Gastritis	2 (2.3)	2 (2.4)	1 (1.0)	2 (1.7)	5 (5.1)	1 (3.1)
Back pain	10 (11.4)	5 (6.0)	4 (3.8)	6 (5.3)	6 (6.2)	0
Myalgia	4 (4.5)	9 (10.8)	5 (4.8)	12 (10.5)	13 (13.4)	3 (9.4)
Polyarthralgia/arthralgia	3 (3.4)	4 (4.8)	9 (8.6)	7 (6.1)	5 (5.1)	0
Respiratory tract infection	7 (7.9)	9 (10.8)	14 (13.5)	18 (15.8)	14 (14.4)	9 (28.1)
Sore throat	6 (6.8)	3 (3.6)	7 (6.7)	6 (5.3)	4 (4.1)	1 (3.1)
Rash	7 (7.9)	0	2 (1.9)	3 (2.6)	1 (1.0)	1 (3.1)
Headache	6 (6.8)	5 (6.0)	7 (6.7)	15 (13.2)	4 (4.1)	1 (3.1)
Clinical malaria	4 (4.5)	7 (8.4)	0	0	4 (4.1)	0
Other	18 (20.4)	22 (26.5)	38 (36.5)	16 (14.0)	27 (27.8)	9 (28.1)
>1	88	83	104	114	97	32

NOTE. Data are no. (%) of subjects unless otherwise indicated. Mef, mefloquine.

detected at the routine week 4 blood test (18 cases of abnormal ALT values in week 4, 3 cases in week 8, and 2 cases in week 15). Nearly every subject, irrespective of study arm, experienced a notable, predominantly mild elevation in ALT level from baseline to week 4 that progressively diminished through the period of weekly study drug or placebo administration to the end point (figure 3). There were no dose-related differences between tafenoquine groups in either the frequency or magnitude of elevated ALT values. No association was observed between ALT levels and weight cohorts in either of the high-dosage tafenoquine groups. Subjects with abnormally elevated ALT levels improved and/or their ALT levels normalized after cessation of tafenoquine therapy.

Hematologic profiles for the 6 study arms followed virtually identical trends over the 6 time points at which samples were obtained. In each arm, the radical cure phase, from baseline (−4 weeks) to the start of study drug or placebo administration (time 0), was characterized by generally minor elevations in hemoglobin levels, minor increases in leukocyte counts, and minor decreases in platelet counts. During the period from the initiation of the loading-dose phase through the 12-week course of weekly prophylaxis, these levels demonstrated recovery toward mean baseline values for all subject groups.

DISCUSSION

The purpose of this trial was to study the dose-related protective efficacy, tolerability, and safety of 4 different weekly dosing regimens of tafenoquine, ranging from 25 to 200 mg/week. The trial was designed to permit analysis of the relationship between tafenoquine dosage and PE, relative to placebo, but the trial was not powered to allow for more than a descriptive comparison of the efficacy and safety of the tafenoquine dosages, relative to the mefloquine dosage. This trial was the next logical step from the recent phase II trials in Africa of tafenoquine prophylaxis with dosages of 200 mg/week and 400 mg/week [20] and with a 400-mg daily, 3-day loading-dose-only regimen [20, 21]. As is the case with other 8-aminoquinoline compounds, administration of tafenoquine to G6PD-deficient persons runs the risk of inducing the significant side effect of intravascular hemolysis [13, 14, 18, 21]. Careful preliminary screening of subjects for G6PD deficiency and confirmatory retesting was necessary to ensure the safe conduct of our trial.

Despite the range of lower concentrations studied, we saw no dose-dependent continuum in our results. We found comparably high levels of efficacy and comparably infrequent reports of adverse events for the tafenoquine dosages of 50, 100, and 200 mg/week. Similar PEs and CIs were calculated in a 13-week trial of tafenoquine in which Kenyan adults received dosages of 200 mg/week [21]. However, in contrast to the gastrointestinal and dermatologic complaints associated with the 200 and 400 mg/week tafenoquine dosage regimens in Kenyans [21], no clear adverse event trends were seen in our Ghanaian treatment groups.

Intermediate protection (PE, 32%) significantly greater than that afforded by placebo but less than that afforded by tafenoquine, 50 mg/week, was observed in the arm receiving tafenoquine, 25 mg/week. Within-group cohort comparison based on division of the group receiving tafenoquine, 25 mg/week, at the group's median body weight (51 kg) showed that this lowest tafenoquine dosage offered significantly better protection to subjects who weighed <51 kg (PE, 56%; 95% CI,

37%–69%), whereas those who weighed >51 kg derived no better protection (PE, 7%; 95% CI, −9% to 21%) than did subjects who received placebo.

Laboratory test results yielded no indication of dose-related or cumulative toxicity associated with tafenoquine loading doses and weekly prophylaxis. Of note, early changes from baseline (elevated hemoglobin levels, WBC counts, and ALT levels, and decreased platelet counts and bilirubin levels) were seen in the placebo, tafenoquine, and mefloquine study arms; these changes were possibly a result of the radical cure regimen. Elevations in hemoglobin levels and leukocyte counts may reflect a reversal of malaria's effects on bone marrow and erythropoiesis [25–27] and/or drug-induced stimulation or disturbance [17, 28].

Abnormal elevation of the ALT level to >60 U/L was the main reason for the premature discontinuation of treatment for subjects in our study and was an effect largely confined to the tafenoquine groups. No abnormal ALT findings were reported in 4 previous trials in humans, 3 of which administered tafenoquine at higher doses and at more frequent (daily) intervals [14, 20, 21, 29].

In summary, this large trial demonstrates the minimum effective weekly dose of tafenoquine in semi-immune subjects and provides key information about dosage selection for phase III studies, in which the target population for the ultimate use of the drug would be largely nonimmune. Tafenoquine has the potential to be used in a variety of situations beyond that of chemoprophylaxis. The compound is effective as part of a radical cure regimen for *P. vivax* infection [29]. There could be a role for this drug in outbreak management and long-term malaria suppression because of its extended half-life and potential transmission-blocking qualities [10, 13]. In any of these roles, sensitive screening for G6PD deficiency and for pregnancy are required to ensure the safe use of this potent and promising new antimalarial drug.

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