MAJOR ARTICLE

# A New Primaquine Analogue, Tafenoquine (WR 238605), for Prophylaxis against *Plasmodium falciparum* Malaria

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**We tested tafenoquine (WR 238605), a new long-acting 8-aminoquinoline, for its ability to prevent malaria in an area that is holoendemic for *Plasmodium falciparum*. In a double-blinded, placebo-controlled, randomized clinical trial in western Kenya, adult volunteers received a treatment course of 250 mg halofantrine per day for 3 days, to effect clearance of preexisting parasites. The volunteers were then assigned to 1 of 4 drug regimens: placebo throughout; 3 days of 400 mg (base) of tafenoquine per day, followed by placebo weekly; 3 days of 200 mg of tafenoquine per day, followed by 200 mg per week; and 3 days of 400 mg of tafenoquine per day, followed by 400 mg per week. Prophylaxis was continued for up to 13 weeks. Of the evaluable subjects (223 of 249 randomized subjects), volunteers who received 400 mg tafenoquine for only 3 days had a protective efficacy of 68% (95% confidence interval [CI], 53%–79%), as compared with placebo recipients; those who received 200 mg per day for 3 days followed by 200 mg per week had a protective efficacy of 86% (95% CI, 73%–93%); and those who received 400 mg for 3 days followed by 400 mg per week had a protective efficacy of 89% (95% CI, 77%–95%). A similar number of volunteers in the 4 treatment groups reported adverse events. Prophylactic regimens of 200 mg or 400 mg of tafenoquine, taken weekly for ⩽13 weeks, are highly efficacious in preventing falciparum malaria and are well tolerated.**

Currently recommended chemoprophylactic regimens against malaria have shortcomings. Mefloquine, which an expert group of the Public Health Laboratory Service of the United Kingdom (London) and the United States Centers for Disease Control and Prevention (Atlanta) recommend as chemoprophylaxis for infections with chloroquine-resistant *Plasmodium falciparum*, is associated with neuropsychiatric disturbances that can be severe [1, 2]. Doxycycline must be taken daily, and it has been linked with cases of phototoxicity and gastric upset [3]. Chloroquine taken weekly, combined with proguanil taken daily, which is still recommended in some parts of Europe, has suboptimal efficacy and tolerance [4]. No chemoprophylactic agent is 100% effective in the prevention of falciparum malaria. The rate of resistance to all of the drugs, including mefloquine, is increasing.

New chemoprophylactic agents are needed to address the problems of compliance, tolerance, and efficacy in

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nonimmune populations, such as tourists or soldiers traveling to areas of the tropics where malaria is endemic. A chemoprophylactic drug would, ideally, be taken infrequently to improve compliance, and it would be very well tolerated and highly efficacious against all species of malaria. Primaquine is an 8-aminoquinoline that is related to chloroquine but which is primarily used to treat and eradicate species that cause relapsing malaria, such as *Plasmodium vivax.* Clinical trials in Indonesia have demonstrated the utility of daily doses of primaquine for chemoprophylaxis of both falciparum and vivax malaria [5]. Tafenoquine is a long-acting primaquine analogue that was found during preclinical trials to be more potent and less toxic than primaquine [6]. Initial human trials indicated that ⩾500 mg base of tafenoquine could be tolerated as a single dose and that protection against laboratory mosquito challenge of falciparum malaria was possible [7]. The potential toxicities of concern are the same as those for primaquine: methemoglobinemia or hemolysis in glucose 6 phosphate dehydrogenase (G6PD)–deficient persons [8]. We report the results of a randomized, placebo-controlled field trial that used tafenoquine to prevent malaria in a high-transmission area of Africa.

## PATIENTS AND METHODS

***Subject population.*** The study population included healthy male or female volunteers of 18–55 years of age residing in a highly malarious area of western Kenya near Lake Victoria. Potential study volunteers were excluded from the study if they were pregnant or unwilling to avoid pregnancy, had received drugs with antimalarial activity within the previous 2 weeks, had known hypersensitivity to any study drug, had abnormal baseline hematological or clinical chemistry laboratory values, had G6PD deficiency, had abnormal findings on an electrocardiograph, or had clinically significant concomitant medical problems.

***Study design.*** This comparative clinical trial was double-blinded, placebo-controlled, randomized, and 4-armed in design. The study was conducted near Ndori village in Western Kenya during the main malaria transmission season (May through September 1997). This site was chosen because >95% of malaria cases are caused by *P. falciparum,* there is intense perennial transmission of falciparum malaria, and resistance to chloroquine is widespread.

***Treatment assignment.*** To clear any preexisting cases of parasitemia, all volunteers initially received a curative treatment regimen of 250 mg of halofantrine (Halfan; SmithKline Beecham), which was administered once per day for 3 days. Subjects were randomized to receive 1 of 4 weekly suppressive prophylactic regimens: placebo throughout; 400 mg of tafenoquine per day for 3 days, followed by weekly doses of placebo; 200 mg of tafenoquine per day for 3 days, followed by 200 mg per week; and 400 mg of tafenoquine per day for 3 days, followed by 400 mg per week. Each regimen was administered for a period of up to 13 weeks. All tafenoquine doses are in mg of the base. Because results from early phase I studies suggest that ingestion of food increases the gastrointestinal tolerance and bioavailability of tafenoquine, all treatment regimens were administered with a small meal. Trained field workers under physician supervision directly observed dosing, and compliance was additionally confirmed by tablet count.

***Clinical assessment and efficacy end points.*** The efficacy end point was the proportion of subjects who developed patent parasitemia during tafenoquine chemoprophylaxis, as compared with the placebo control group. The first confirmed instance (2 consecutive positive smears) of malaria parasitemia that occurred after administration of the first dose of study drug and within 7 days of the last dose of study drug was considered to be a "failure of prophylaxis." At the screening visit, subjects provided a medical history and underwent physical examination, evaluation of vital signs and hematology and biochemistry values, and a malaria blood smear (thick blood films); in addition, female subjects underwent a blood pregnancy test. Thick blood films were stained with Giemsa stain, and malaria parasite counts were determined by counting the number of asexual parasites per 200 WBCs. A blood slide was not considered negative until an examination of 200 oil-immersion fields (1000×) showed no parasites. Blood smears were assessed by 2 independent observers. Hematology values that were monitored included hemoglobin, hematocrit, platelets, total WBC count, and lymphocyte count. Biochemistry values monitored included creatinine and alanine transaminase. After their screening visit, eligible volunteers began the 3-day halofantrine treatment regimen, followed 4 days later by the loading dose regimen of their assigned treatment group. On a weekly basis (done when the subjects received their medication), volunteers were questioned regarding adverse events, a malarial blood smear was performed, and a review of concomitant medication was performed. Subjects who had symptomatic prophylaxis failures were treated with pyrimethamine-sulfadoxine and appropriate supportive care. During a 4-week follow-up period after the end of study drug administration, thick blood films and assessment of adverse events continued.

***Statistical analysis.*** The efficacy analysis was carried out on a modified intent-to-treat population, including all subjects who completed the clearance and loading regimens, who took ⩾1 weekly dose of study drug, and who had ⩾1 efficacy assessment in which a blood smear was assessed. Failure of prophylaxis rates were compared by calculating point estimates and 95% CIs for the protective efficacy of each dose of tafenoquine relative to placebo. Protective efficacy (*PE*) is defined as $PE\ (\%) = [(I_{\text{placebo}} - I_{\text{drug}})/I_{\text{placebo}}] \times 100$, where $I_{\text{placebo}}$ is the number of subjects with parasitemia in the placebo group divided by the number of subjects at risk in the placebo group,

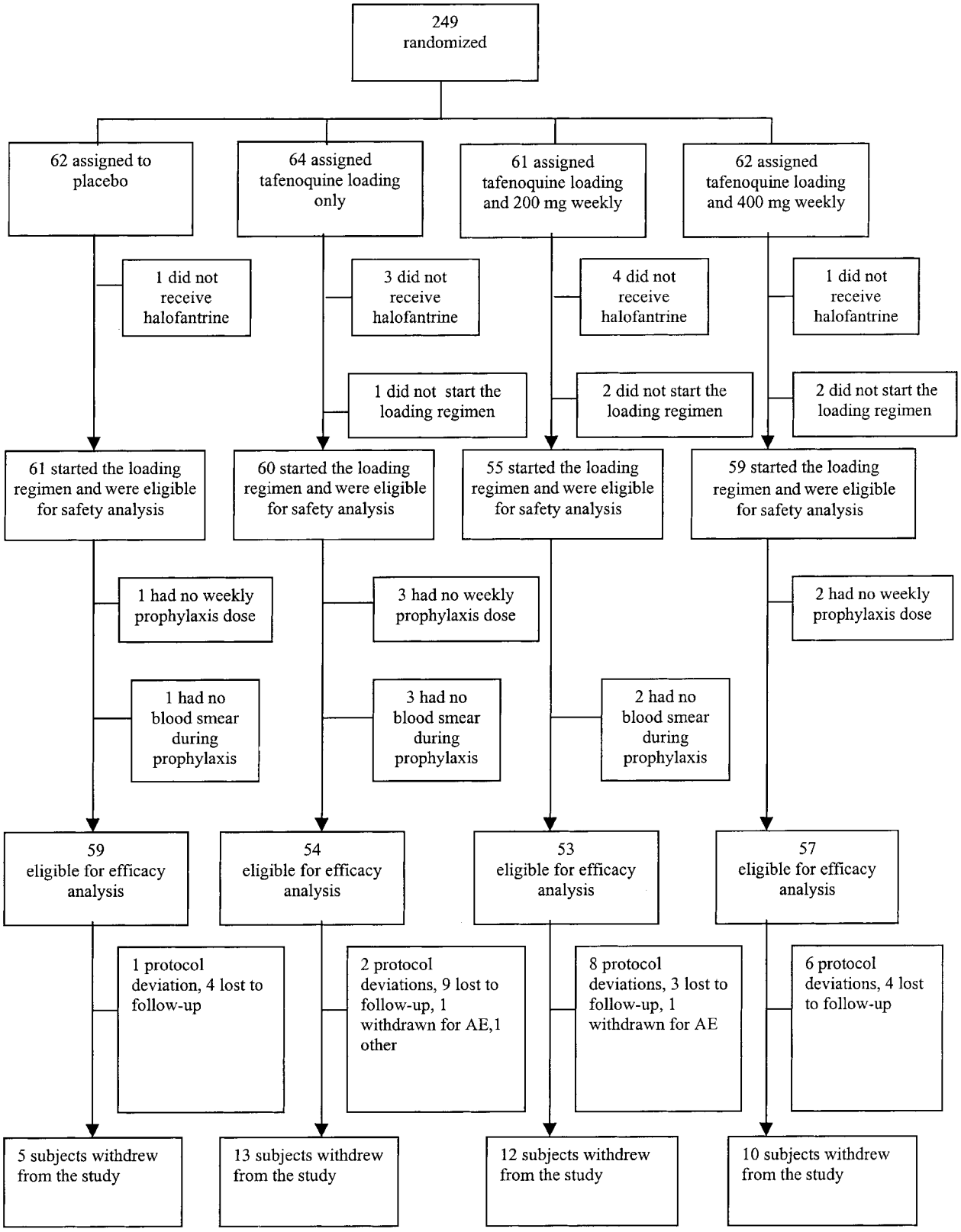


**Figure 1.** Profile of tafenoquine chemoprophylaxis trial conducted in western Kenya, 1997. AE, adverse event.

**Table 1. Demographic characteristics of 235 subjects enrolled in a chemoprophylaxis study who took ⩾1 dose of treatment.**

| Characteristic | Placebo group ($n$ = 61) | Tafenoquine group: Loading dose only ($n$ = 60) | Tafenoquine group: Loading dose and 200 mg per week ($n$ = 55) | Tafenoquine group: Loading dose and 400 mg per week ($n$ = 59) |
|---|---|---|---|---|
| No. male/no. female | 34/27 | 36/24 | 38/17 | 35/24 |
| Age, years | | | | |
| Mean ± SD | 32.3 ± 11.6 | 32.3 ± 12.0 | 33.4 ± 12.4 | 32.1 ± 10.1 |
| Range | 18–55 | 17–55 | 18–54 | 18–50 |
| Weight, kg | | | | |
| Mean ± SD | 61.8 ± 9.7 | 59.9 ± 8.8 | 61.5 ± 8.2 | 61.5 ± 7.3 |
| Range | 39–83 | 45–84 | 45–79 | 42–76 |
| Height, cm | | | | |
| Mean ± SD | 169 ± 9.0 | 169 ± 8.0 | 170 ± 8.3 | 169 ± 8.1 |
| Range | 146–192 | 154–188 | 148–194 | 145–190 |

and $I_{drug}$ is the number of subjects with parasitemia in the drug group divided by the number of subjects at risk in the drug group. The study was designed to conclude superior efficacy of tafenoquine over placebo if the lower limit of the 95% CI for protective efficacy was ⩾60%.

The calculations of primary interest are those based on numbers of treatment failures per group, but calculations based on incidence density of failure (taking into account the duration of follow-up for each subject) are also presented. "Incidence density" is defined as the number of subjects with parasitemia in the treatment group divided by the number of subject-years of exposure in that treatment group.

## RESULTS

***Patient characteristics and disposition.*** A total of 249 volunteers qualified for inclusion in the study, of whom 235 completed the clearance and loading regimens (9 did not begin halofantrine therapy, and 5 did not begin the loading dose) and were considered evaluable for safety. An additional 12 subjects either had no weekly dose of study drug (6 subjects) or no blood smear performed after they began receiving the study drug (6 subjects). The remaining 223 volunteers were considered evaluable for efficacy (figure 1). Other withdrawals during the course of the study we caused by occurrence of adverse events (1 subject who had hemolytic reaction and 1 who had acute ethanol intoxication) and pregnancy (1 subject; figure 1).

The 4 treatment groups at screening were similar with respect to demographic characteristics (table 1). A total of 94 volunteers (40%) had positive malaria smears at screening, all of whom were negative at the first visit after receiving the halofantrine. The modified halofantrine regimen (750 mg given over 48 h, instead of 12 h) was effective for the purpose of eliminating preexisting cases of parasitemia and was very well tolerated. The types of medications taken concomitantly by the subjects during the study (data not shown) did not differ among the treatment groups.

***Prophylactic efficacy.*** Volunteers randomized to any of the

**Table 2. Malaria status of 223 subjects by the end of the 13-week prophylaxis period, according to chemoprophylaxis group.**

| Characteristic | Placebo group ($n$ = 59) | Tafenoquine group: Loading dose only ($n$ = 54) | Tafenoquine group: Loading dose and 200 mg per week ($n$ = 53) | Tafenoquine group: Loading dose and 400 mg per week ($n$ = 57) |
|---|---|---|---|---|
| Malaria during chemoprophylaxis, no. (%) | 54 (92) | 16 (30) | 7 (13) | 6 (11) |
| Protective efficacy, % (95% CI) | — | 68 (53–79) | 86 (73–93)[a] | 89 (77–95)[a] |
| Incidence density per human-year (95% CI) | 6.49 (4.97–8.47) | 1.33 (0.82–2.17) | 0.58 (0.27–1.21) | 0.44 (0.20–0.98) |
| Protective efficacy based on incidence density, % (95% CI) | — | 80 (64–88) | 91 (81–96) | 93 (84–97) |

[a] This concludes that there was superiority over placebo.

regimens containing tafenoquine were protected from malaria infection (table 2). Volunteers who received 400 mg of tafenoquine per day for only 3 days had a protective efficacy of 68% (95% CI, 53%–79%) at the end of the prophylaxis period, when compared with subjects who received placebo; they also demonstrated efficacy similar to those who received weekly medication until study day 70 (figure 2). Protective efficacy of the 3-day tafenoquine regimen, when calculated at 7 weeks, was 82% (95% CI, 59%–92%). Protective efficacies at the end of the prophylaxis period showed that volunteers who received 200 mg per day for 3 days followed by 200 mg per week had a protective efficacy of 86% (95% CI, 73%–93%), and those who received 400 mg per day for 3 days followed by 400 mg weekly had a protective efficacy of 89% (95% CI, 77%–95%). Incidence density calculations gave higher estimates of protective efficacy (loading only, 80%; 200 mg per week, 91%; 400 mg per week, 93%) by accounting for the length of time each volunteer stayed in the study (table 2). Ninety-two percent of the subjects in the placebo group developed parasitemia during the study period, which is consistent with previous chemoprophylaxis trials in this area [9]. The few treatment failures that occurred in the subjects who received tafenoquine does weekly did not result in persistent parasitemia or symptomatic malaria.

***Safety.*** Two hemolytic events occurred during the study in volunteers who received tafenoquine and whose G6PD status had been incorrectly determined during screening. One woman, who was later found to be heterozygous for the (A-) (202, 376G) G6PD variant, developed intravascular hemolysis and required a 2-unit blood transfusion. Hemolysis did not continue after the acute event, no renal compromise was seen in spite of blackwater urine, and she restored and maintained normal hematologic parameters for 6 months after the event. Another woman, who was later found to be homozygous for the (A-) G6PD variant, remained asymptomatic despite an acute 3-g decrease in hemoglobin, which was noticed only because of routine blood tests. She restored her hemoglobin level without intervention. Both women had received 400 mg of tafenoquine per day for 3 days prior to the hemolytic events. Among volunteers who received weekly doses of tafenoquine, mean plateau concentrations of methemaglobin (±SD) were 2.5% ± 1.6%, for subjects who received 200 mg per week, and 4.5% ± 2.5%, for those who received 400 mg per week. Gastrointestinal upset was more common in volunteers who received 400 mg per week, and adverse dermatological events were more common across the tafenoquine groups when compared with the placebo group (although skin rash was uncommon). Other adverse events that could not be directly attributed to the study drug were reported in a similar number of volunteers in the 4 treatment groups (table 3).

## DISCUSSION

The new primaquine analogue, tafenoquine, appears to be an effective form of chemoprophylaxis in an area of intense, chlo-

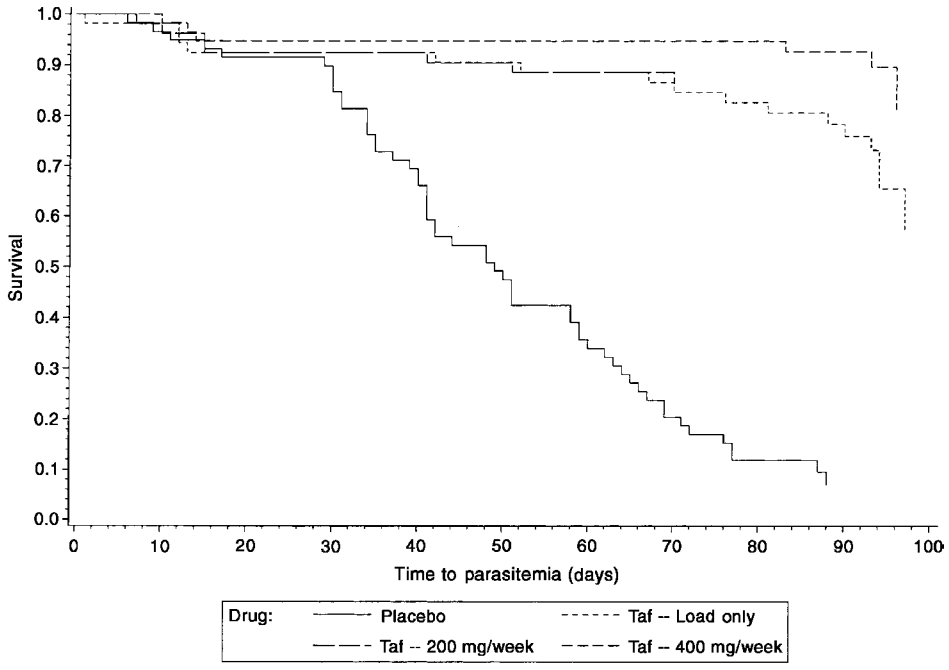


**Figure 2.** Kaplan Meier plot of all volunteers remaining aparasitemic starting from the initial dose of study medication. Cumulative survival shows the percentage of volunteers in each drug arm remaining after dropouts are censored. Survival rate is the fraction of total group remaining uninfected. Taf, tafenoquine.

**Table 3. Adverse events reported by 235 subjects while they were receiving study medication, reported as number (%) of volunteers with such an event, according to body system, and as individual events that occurred in >5% of the subjects in any treatment group.**

| | No. (%) of subjects who received | | | |
|---|---|---|---|---|
| | | Tafenoquine | | |
| Adverse event | Placebo ($n$ = 61) | Loading dose only ($n$ = 60) | Loading dose and 200 mg per week ($n$ = 55) | Loading dose and 400 mg per week ($n$ = 59) |
| Dermatologic | 5 (8) | 12 (20) | 12 (22) | 13 (22) |
| Furunculosis | 0 (0) | 3 (5) | 3 (6) | 1 (2) |
| Rash | 1 (2) | 1 (2) | 2 (4) | 3 (5) |
| Skin disorder | 4 (7) | 5 (8) | 6 (11) | 4 (7) |
| Musculoskeletal | 12 (20) | 11 (18) | 11 (20) | 12 (20) |
| Myalgia | 12 (20) | 11 (18) | 10 (18) | 11 (19) |
| Respiratory | 16 (26) | 21 (35) | 30 (55) | 23 (39) |
| Pharyngitis | 1 (2) | 1 (2) | 5 (9) | 5 (9) |
| Upper respiratory tract infection | 15 (25) | 21 (35) | 23 (42) | 20 (34) |
| Neurologic | 11 (18) | 11 (18) | 14 (26) | 15 (25) |
| Headache | 11 (18) | 10 (17) | 13 (24) | 14 (24) |
| Gastrointestinal | 17 (28) | 20 (33) | 16 (29) | 27 (46) |
| Abdominal pain | 2 (3) | 1 (2) | 2 (4) | 6 (10) |
| Constipation | 3 (5) | 7 (12) | 4 (7) | 7 (12) |
| Diarrhea | 2 (3) | 4 (7) | 4 (7) | 6 (10) |
| Gastritis | 4 (7) | 4 (7) | 2 (4) | 5 (9) |
| Gastroenteritis | 5 (8) | 7 (12) | 3 (6) | 6 (10) |
| Any adverse event | 41 (67) | 46 (77) | 47 (86) | 50 (85) |

roquine-resistant falciparum malaria. Although other studies have suggested that tafenoquine may be a promising replacement for primaquine in the treatment and eradication of vivax malaria [10], this is the first field trial for malaria prevention that has been performed, having been completed in 1997. A subsequent trial done in 1999 that involved persons 12–20 years of age in Gabon further evaluated the 3-day regimen for use as a convenient, short-term prophylactic, and showed that 50-mg, 100-mg, and 200-mg tafenoquine base given during a 3-day period had high prophylactic efficacy during a 10-week period [11]. The successful use of a 3-day tafenoquine regimen both in East and West Africa raises the future possibility that short-term travelers to highly endemic areas could be protected from malaria by medication taken just prior to travel. Prior to any widespread use of tafenoquine, further studies need to be conducted, particularly in persons with lower intrinsic immunity to malaria and in other areas of the world where drug-resistance patterns may differ from those in East Africa. This initial trial does, however, suggest that tafenoquine could become a welcome addition to the antimalarial drug armamentarium in the future.

Giving drugs to healthy persons to prevent a potentially lethal infection requires both a high level of efficacy and safety, particularly in the light of recent reports that have linked antimalarial prophylaxis with many states of ill health, real or imagined. The 2 hemolytic events in G6PD-deficient persons provide evidence that, just as with primaquine, G6PD-deficient persons should not be prescribed tafenoquine. Same-day testing of G6PD status can readily be determined using well-established laboratory methods. The other anticipated toxicity of 8-aminoquinolines is methemaglobinemia, and, despite monitoring for it during this trial, no worrisome methaglobin concentrations were found. Only adverse dermatological events were found to be more common in subjects who received tafenoquine than they were in those who received placebo, although the incidence of skin rash was low. To date, ~2000 persons have received this new compound, and no clear comment can be made on the possibility of unusual or rare adverse events at this point.

Should tafenoquine successfully complete its remaining clinical trials, there are several potentially useful applications that may be possible, besides the most obvious one—protecting the short-term traveler going to an area where malaria is endemic.

The ability of tafenoquine to kill all forms of the parasite and its very long (2-week) half-life suggest it may have a public health role during malaria epidemics when mass drug administration might be appropriate [12, 13]. Protection of vulnerable indigenous groups, such as plantation workers, pregnant women, or preschool children, remains a speculative possibility pending further studies.

Even before the introduction of a new anti-infective compound, one must assess the potential for eventual evolution of drug resistance. The long half-life of tafenoquine implies that some parasites will be exposed to low concentrations of the drug during its long elimination phase. Such a situation encourages the selection of drug-resistant strains, but it may be ameliorated by the drug's antitransmission potential because of its killing of sporozoites and, possibly, gametocytes [14]. Certainly, some of the best groups for the eventual use of a long-acting 8-aminoquinoline would be short-term travelers who leave the endemic area with therapeutic drug concentrations and persons who live in an area of seasonal transmission where drug administration could be timed to the transmission season. Strategies that expose persons to malaria infection while drug concentrations become subtherapeutic are effectively producing drug-resistant parasites. Rational development of new antimalarial compounds requires not only careful clinical trials but also a clear determination of what the best potential uses of the drug will be given the increasing need to deal with multiple drug-resistant parasites.

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