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BRIEF REPORT

Atovaquone/Proguanil Therapy for *Plasmodium falciparum* and *Plasmodium vivax* Malaria in Indonesians Who Lack Clinical Immunity

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Thirty-eight of 295 subjects participating in a randomized, double-blind, placebo-controlled trial of the efficacy of daily administration of atovaquone/proguanil for malaria prevention developed malaria at some time during the 20-week prophylaxis period. These subjects (3 atovaquone/proguanil recipients and 35 placebo recipients) were treated with 4 tablets of atovaquone/proguanil per day for 3 days. Atovaquone/proguanil provided safe, well-tolerated, and effective therapy for uncomplicated malaria in nonimmune Indonesians.

Malaria is the most common life-threatening infectious disease among travelers. Chemoprophylaxis effectively reduces the risk of acquiring disease, but many people who could benefit from chemoprophylaxis do not use it as directed [1]. Each year, >10,000 North American and European people acquire malaria while traveling abroad, and several hundred of these people die [2, 3]. Deterioration of the global malaria situation during the past 30 years, which has been caused predominantly by resistance to antimalarial drugs and the deterioration of vector-control programs in poorer countries [4, 5], along with the increasing number of travelers, makes malaria an important health risk for visitors to tropical areas where malaria is endemic.

Susceptibility to antimalarial drugs often follows distinct geographical patterns. Confidence in chemotherapy by the physician who treats patients with malaria may hinge on the published record of therapeutic outcomes in regions where infections are endemic. We describe our clinical experience with a new antimalarial drug that contains a fixed combination of atovaquone and proguanil hydrochloride (Malarone; GlaxoSmithKline) for the treatment of uncomplicated malaria due to *Plasmodium falciparum* and *Plasmodium vivax* in nonimmune adults infected in Papua, the easternmost province of Indonesia, which occupies the western half of the island of New Guinea. Four other reports have described the efficacy of atovaquone/proguanil against *P. falciparum* malaria in Southeast Asia [6–9], an area notorious for the presence of drug-resistant malaria. This study also adds to 2 published reports about the therapeutic efficacy of atovaquone/proguanil against *P. vivax* malaria in Southeast Asia [6, 10]. We conducted the study in an area where most *P. vivax* strains are resistant to chloroquine [11, 12].

Subjects and methods. Subjects were treated during the period of April 1999 through June 2000 in 3 villages (SP4, SP5, and SP6) that are within a few kilometers of the Pacific Ocean, along the northeastern coast of Papua (formerly Irian Jaya), Indonesia. Subjects had participated in a randomized, placebo-controlled trial of atovaquone/proguanil that is reported elsewhere [13]. In brief, we enrolled Javanese adults who were considered to lack clinical immunity to malaria on the basis of life-long residence in nonmalarious areas before migration to Papua. Before they started receiving prophylaxis, all subjects received directly observed curative therapy with 1 g of atovaquone and 400 mg of proguanil hydrochloride per day for 3 days, followed by 2 tablets of primaquine phosphate (Sanofi Winthrop; 15 mg base per tablet) daily for 14 days. After they received curative therapy, subjects immediately began taking daily doses of either prophylactic medication (atovaquone, 250 mg, and proguanil hydrochloride, 100 mg) or matching placebo (1:1 randomization) for up to 20 weeks. During the prophylaxis period, microscopic examination of Giemsa-stained thick blood films was performed weekly or any time a subject complained of experiencing symptoms

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consistent with malaria. Subjects with slide-confirmed malaria during the prophylaxis period constituted the treatment population reported here.

Confirmation of asexual parasitemia by 2 expert microscopists prompted the administration of directly observed therapy with atovaquone/proguanil (atovaquone, 1 g, and proguanil, 400 mg, q.d. for 3 days) ⩽24 h after the initial diagnosis. Posttherapy follow-up consisted of monitoring the subject's temperature (via the ear canal) and examining blood films on days 1–7, 14, 21, and 28 after the initiation of therapy. Subjects infected with *P. vivax* also received 30 mg of primaquine per day for 14 days immediately after they completed atovaquone/proguanil therapy.

Results. During the prophylaxis period, 40 subjects developed malaria (37 while receiving placebo and 3 while receiving atovaquone/proguanil) 20–140 days after they started receiving prophylaxis [13]. Two subjects from the placebo group were excluded from the analysis of therapy (one because of vomiting that required intravenous quinine therapy, and the other because of a breach of treatment protocol). Atovaquone/proguanil therapy was administered to 19, 16, and 3 patients with *P. falciparum, P. vivax,* or mixed infections, respectively. The geometric mean parasite counts at the time of diagnosis were 3238 parasites/μL (range, 80–32,360 parasites/μL) for subjects with *P. falciparum* malaria and 451 parasites/μL (range, 40–10,400 parasites/μL) for subjects with *P. vivax* malaria.

Table 1 summarizes the demographic and clinical characteristics of treated subjects. Subjects were predominantly young adult men, which reflects the demographic characteristics of the population recruited for the prophylaxis study [13]. One or more of the following symptoms was considered to be consistent with clinical disease caused by malaria: fever, chills, headache, nausea, abdominal pain, arthralgias, myalgias, and malaise. Clinical disease was more common for *P. falciparum* infection than for *P. vivax* infection. Fever occurred in 18 (82%) of 22 subjects infected with *P. falciparum* (including 3 mixed-species infections) and in 7 (44%) of 16 subjects infected with *P. vivax* (excluding mixed infections). At least 1 symptom of malaria occurred in 21 (96%) of 22 subjects infected with *P. falciparum* and in 12 (75%) of 16 subjects infected with *P. vivax.*

All subjects completed therapy without interruption. Only 1 subject had an adverse event that was possibly attributable to therapy. A 37-year-old man with *P. falciparum* malaria developed abdominal pain ⩽24 h after he completed therapy. No specific cause was identified, and he recovered fully after 1 day without requiring medical intervention.

All subjects had a prompt clinical and parasitological response to treatment with atovaquone/proguanil. Fever resolved after a mean of 1.5 days (range, 0–3 days) among subjects with *P. falciparum* malaria and 0.8 days (range, 0–4 days) among subjects with *P. vivax* malaria (figure 1, *bottom*). Parasitemia resolved after a mean of 2.7 days (range, 1–4 days) among subjects with *P. falciparum* malaria and 2.5 days (range, 1–3 days) among subjects with *P. vivax* malaria (figure 1, *top*). For the 3 subjects who developed parasitemia while taking atovaquone/proguanil prophylaxis (2 had *P. vivax* infection and 1 had a mixed infection), parasitemia did not recur during the 4-week follow-up period. Among the 35 subjects who developed parasitemia while taking placebo, 1 subject had recurrent *P. falciparum* parasitemia on day 21. A second subject treated for *P. falciparum* malaria developed *P. vivax* parasitemia on day 28.

Discussion. We evaluated atovaquone/proguanil therapy in 38 subjects with acute, uncomplicated malaria caused by *P. falciparum* and/or *P. vivax* in Papua, Indonesia. Atovaquone/proguanil therapy was safe, effective, and well tolerated in these subjects. All subjects completed the regimen, and only 1 subject experienced an adverse event (moderate abdominal pain) that may have been related to therapy.

All subjects had prompt clearance of fever and parasitemia, and 21 (96%) of the 22 subjects with *P. falciparum* malaria did not have recurrent parasitemia during the 28-day follow-up

Table 1. Demographic and clinical characteristics of subjects receiving atovaquone/proguanil therapy for uncomplicated malaria in Papua, Indonesia.

Characteristic	*Plasmodium falciparum*–infected subjects (n = 19)	*Plasmodium vivax*–infected subjects (n = 16)	Subjects with mixed infection (n = 3)
Sex, no. male/no. female	16/3	13/3	3/0
Weight, mean kg	54.5	50.9	50.8
Age, mean years (range)	37.1 (15–60)	32.8 (15–48)	25.7 (20–33)
Febrile subjects, %	79[a]	44	100
Symptomatic subjects, %	96	75	100
Asexual parasitemia, mean no. of parasites/μL (range)	3238 (80–32,360)	451 (40–10,400)	3460 (2480–5880) for *P. falciparum;* 404 (80–1720) for *P. vivax*

[a] When the *P. falciparum*–infected group and the mixed-infection group were combined, 82% of the subjects were febrile.

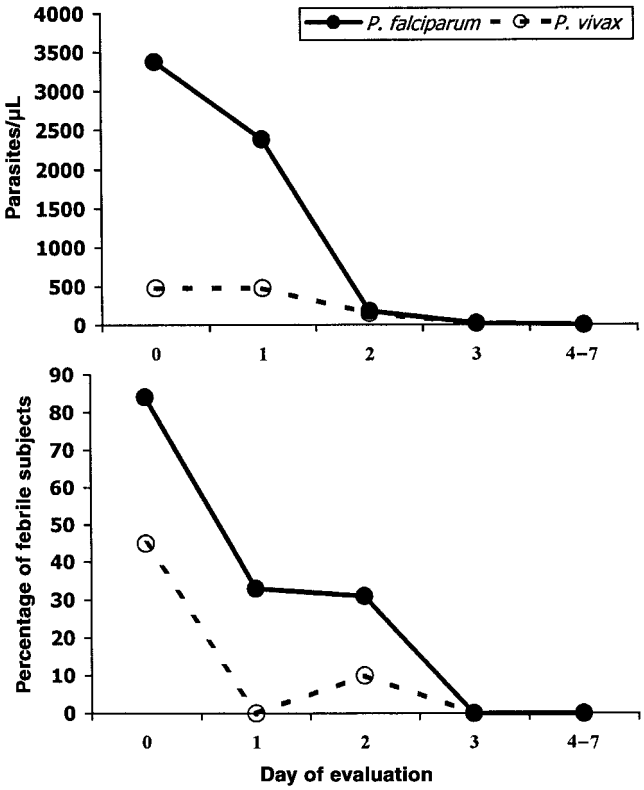

Figure 1. Parasitological and clinical response to treatment with atovaquone/proguanil for uncomplicated malaria in Papua, Indonesia. *Top,* Geometric mean parasite count for *Plasmodium falciparum* and *Plasmodium vivax* during the week after the start of therapy. *Bottom,* Percentage of subjects infected with *P. falciparum* or *P. vivax* who had documented fever during the week after the start of therapy.

period. In 1 subject, recurrent *P. falciparum* parasitemia on day 21 could have been due to recrudescence (RI response [14]) or reinfection. Attempts to distinguish between these possibilities by genotyping of PCR-amplified parasite DNA from samples obtained before treatment and at the time of recurrence were not successful.

No evidence of clinical resistance to atovaquone/proguanil therapy appeared among the 3 subjects for whom atovaquone/proguanil prophylaxis failed. This suggests that these prophylaxis failures were related to factors other than drug-resistant parasites. The high efficacy of atovaquone/proguanil for the treatment of uncomplicated malaria caused by *P. falciparum* in this study corroborates the findings of other reports from Southeast Asia [6–9].

The 19 subjects with parasitemia due only to *P. falciparum* did not receive primaquine, and 1 of these subjects developed *P. vivax* parasitemia on day 28 after initiating treatment with atovaquone/proguanil. Because subjects in this study were continually exposed to malaria-infected mosquitoes, the parasitemia could have been a delayed primary episode resulting from an infection that occurred shortly before rescue treatment was initiated, or it could have been a posttreatment episode resulting from an infection that occurred shortly after the rescue treatment regimen was finished.

On the basis of previous studies that have indicated that atovaquone/proguanil has little or no effect on hypnozoites of *P. vivax* (the latent liver-stage parasites responsible for relapse), in our study, therapy for *P. vivax* malaria included a 30-mg primaquine base given daily for 14 days after the completion of atovaquone/proguanil treatment. One previous study of atovaquone/proguanil for the treatment of *P. vivax* malaria that did not include primaquine reported that 14 (74%) of 19 subjects had recurrent *P. vivax* infection 16–26 days after initiating therapy [6]. In another study, 30 mg of primaquine was given daily for 14 days after the completion of atovaquone/proguanil therapy; all 42 subjects who were still being observed at day 28 remained free of parasitemia. Two of those subjects had recurrent parasitemia at day 56, indicative of relapse. In our study, all 19 subjects with *P. vivax* malaria had prompt clearance of fever and parasitemia, and none had recurrent parasitemia during the 28-day follow-up period. In previous studies from this region that have included primaquine therapy, recurrent *P. vivax* parasitemia occurred in 15% of the subjects treated with chloroquine [12]. Given the high risk of therapeutic failure with chloroquine against *P. vivax* in Papua (>50%), our findings suggest that treatment with atovaquone/proguanil for 3 days, followed by primaquine for 14 days, may be an effective alternative to chloroquine for patients with chloroquine-resistant *P. vivax* malaria.

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