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MAJOR ARTICLE

Vivax Malaria Chemoprophylaxis: The Role of Atovaquone-Proguanil Compared to Other Options

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Background. Atovaquone-proguanil is considered causal prophylaxis (inhibition of liver-stage schizonts) for *Plasmodium falciparum*; however, its causal prophylactic efficacy for *Plasmodium vivax* is not known. Travelers returning to nonendemic areas provide a unique opportunity to study *P. vivax* prophylaxis.

Methods. In a retrospective observational study, for 11 years, Israeli rafters who had traveled to the Omo River in Ethiopia, a highly malaria-endemic area, were followed for at least 1 year after their return. Malaria prophylaxis used during this period included mefloquine, doxycycline, primaquine, and atovaquone-proguanil. Prophylaxis failure was divided into early (within a month of exposure) and late malaria.

Results. Two hundred fifty-two travelers were included in the study. Sixty-two (24.6%) travelers developed malaria, 56 (91.9%) caused by *P. vivax*, with 54 (87.1%) cases considered as late malaria. Among travelers using atovaquone-proguanil, there were no cases of early *P. falciparum* or *P. vivax* malaria. However, 50.0% of atovaquone-proguanil users developed late vivax malaria, as did 46.5% and 43.5% of mefloquine and doxycycline users, respectively; only 2 (1.4%) primaquine users developed late malaria ($P < .0001$).

Conclusions. Short-course atovaquone-proguanil appears to provide causal (liver schizont stage) prophylaxis for *P. vivax*, but is ineffective against late, hypnozoite reactivation–related attacks. These findings suggest that primaquine should be considered as the chemoprophylactic agent of choice for areas with high co-circulation of *P. falciparum* and *P. vivax*.

Keywords. *Plasmodium vivax*; *Plasmodium falciparum*; atovaquone-proguanil; mefloquine; primaquine.

Malaria remains one of the most important infectious concerns among travelers. According to the multinational GeoSentinel registry, malaria is the most frequently diagnosed cause of febrile illness among ill-returning travelers [1], and is a leading cause of infectious mortality among travelers [2].

The main focus of malaria chemoprophylaxis is the prevention of *Plasmodium falciparum* malaria, which causes most malaria cases and most fatalities [3]. Although historically known as "benign tertian malaria," *P. vivax* can cause severe disease, and is clinically similar to severe *P. falciparum* malaria [4, 5] *Plasmodium vivax* is geographically more widespread than *P. falciparum*, is the cause of 41% of all malaria cases outside Africa, and is the leading cause of malaria in the World Health Organization American and Western Pacific regions [3].

These statistics are also seen in travelers, where in 2011, *P. vivax* accounted for 28% of all malaria cases in the United States and was the dominant species in malaria acquired outside Africa [6]. In Australia and New Zealand, *P. vivax* is the leading cause of malaria in travelers [7, 8]. In fact, GeoSentinel data had shown that *P. vivax* malaria is present in most African regions, including West Africa [9].

Atovaquone-proguanil is one of the most popular malaria prophylactic agents. It has excellent efficacy and tolerability, with a low potential for severe adverse effects [10]. Atovaquone-proguanil inhibits not only the blood stage of *P. falciparum*, but also its liver stage, for which activity it is considered causal prophylaxis for this pathogen [11]. Atovaquone-proguanil's causal prophylactic activity obviates the need for weeks of post-travel prophylaxis, which is essential for blood stage agents such as doxycycline or mefloquine [12]. However, atovaquone-proguanil's effects on the liver stages *of P. vivax* are undetermined.

In *P. vivax* malaria, hypnozoites are present in the liver, causing late-onset malaria with attacks occurring months to years after exposure. Primaquine was shown to be a good hypnozoiticidal agent in the 1950s, when mass prophylaxis in returning Korean war soldiers practically eliminated the problem of late-onset vivax malaria [13].

The problem of hypnozoite reactivation–related, late-onset *P. vivax* malaria creates difficulties in the study of malaria prophylaxis in endemic populations, as it is almost impossible to distinguish between *P. vivax* reinfection or relapse [14]. Published prospective trials on *P. vivax* prophylaxis in endemic

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countries reported a follow-up period of only 1 month after chemoprophylaxis [15, 16], and were thus unable to detect any late relapses. It is therefore impossible to assess atovaquone-proguanil's potential as a "comprehensive prophylaxis," meaning effective against early and late malaria for both falciparum and vivax malaria. In this regard, returning travelers are the best target population to assess drug efficacy, as all malaria events, including late-onset malaria, can be attributed to the initial exposure and the true efficacy of chemoprophylaxis can be established.

A unique opportunity to study malaria chemoprophylaxis emerged following a series of rafting trips made by Israelis to the Omo River in southern Ethiopia, where a malaria attack rate of about 50% was repeatedly documented among the travelers [17, 18]. Our aim was to compare the efficacy of different chemoprophylactic agents against early and late malaria.

METHODS

This was a retrospective, observational study. From 1996 to 2006, annual rafting trips to the Omo River in southern Ethiopia were organized by a single Israeli tour operator who followed a uniform agenda. These were 2-week rafting trips along a 300-km stretch of the river, starting each year during the same season (September–October) when river conditions are most suitable for rafting. During the trip, the participants would camp every night on the river banks. All travelers in these trips were referred for pretravel counseling, including malaria chemoprophylaxis and vaccination. In addition, travelers were reminded throughout the trip by tour operators to use insect repellents, to sleep in screened tents, and to adhere to their malaria chemoprophylaxis recommendations.

The chemoprophylactic agents used during the study period included mefloquine, doxycycline, primaquine, and atovaquone-proguanil. Initially, either mefloquine or doxycycline was used; however, after the recognition of *P. vivax* malaria in this region [17], primaquine chemoprophylaxis was recommended [18]. Primaquine, however, was not readily available in Israel for several years, and atovaquone-proguanil was registered in Israel in 2003.

In Israel, malaria is a notifiable disease. All cases of malaria are reported to the Ministry of Health, where diagnoses and speciation are confirmed. All malaria cases were diagnosed by microscopy. Since 2003, polymerase chain reaction for final speciation was added [19]. The registry of malaria cases from 1996 to 2010 was evaluated, and all cases occurring in travelers who participated in Omo River rafting trips were included. In addition, all travelers were interviewed by telephone, to evaluate whether a diagnosis of malaria had been made since the trip. They were also questioned about the use of chemoprophylaxis during their rafting trip, and whether they had traveled to malaria-endemic countries after the index trip.

Cases were divided into groups, according to the chemoprophylactic regimen used:

1. Weekly mefloquine, beginning 1–2 weeks before the trip and continuing for 4 weeks after return.
2. Daily doxycycline, beginning a day before the trip and continuing for 4 weeks after return.
3. Daily atovaquone-proguanil, beginning 1 day before the trip and continuing for 1 week after return.
4. Daily primaquine, beginning 1 day before the trip and continuing for 3 days after return. The dose of primaquine recommended changed during the study period. Until 1999, a daily dose of 15 mg base was recommended. This was then changed to the currently recommended dose of 30 mg.

Travelers who used >1 drug were excluded from the analysis.

Early malaria was defined as a malaria attack occurring within 1 month after return from the Omo River, and all other cases were designated as late malaria.

For statistical analysis, Fisher exact test and Student *t* test were used to analyze categorical and continuous variables, respectively.

The study was approved by the Sheba Medical Center institutional review board.

RESULTS

During an 11-year period, 252 Israeli travelers participated in Omo River rafting trips. The male/female ratio was 1.86 and their age ranged from 21 to 65 years. None of the 252 travelers had further travel to malaria-endemic areas during the follow-up period.

Primaquine was used by 145 (57.5%) travelers, mefloquine by 54 (21.5%), atovaquone-proguanil by 30 (11.9%), and doxycycline by 23 (9.1%) travelers. In 3 cases, primaquine was given as terminal prophylaxis after mefloquine use and these travelers were excluded from the analysis.

Sixty-two travelers developed malaria, an overall malaria attack rate of 24.6%, with 57 (91.9%) cases caused by *P. vivax* and 5 (8.1%) cases by *P. falciparum*. The outcome of all malaria cases was favorable without any fatalities.

The distribution of malaria cases per chemoprophylaxis used is detailed in Table 1. The overall failure rate was 49.0%, 52.2%, and 56.7% for travelers treated with mefloquine, doxycycline and atovaquone-proguanil, while primaquine had a failure rate of 5.5% ($P < .0001$ in comparison to each of the other agents).

Early malaria occurred in 8 patients (12.9%): 5 were caused by *P. falciparum* and 3 by *P. vivax* (Table 1). The percentage of early cases was 0.0%, 0.0%, 4.1%, and 8.7% in those who were treated with atovaquone-proguanil, mefloquine, primaquine, and doxycycline, respectively, a difference that was not statistically significant. All 6 cases of early malaria among primaquine

Table 1. Malaria Infection in Omo River Rafters

Chemoprophylaxis Used	No. of Travelers	Early Malaria (at <1 mo)			Late Malaria (at up to 1 y)		All Malaria Cases	
		P. falciparum	*P. vivax*	Early Prophylaxis Failure Rate	*P. vivax*	Late Prophylaxis Failure Rate	All Malaria Cases	Overall Prophylaxis Failure Rate
Atovaquone-proguanil	30	0	0	0.0%	17	56.7%	17	56.7%
Mefloquine	51[a]	0	0	0.0%	25	49.0%	25	49.0%
Doxycycline	23	1	1	8.7%	10	43.5%	12	52.2%
Primaquine	145	4[b]	2[b]	4.1%	2	1.4%	8	5.5%
Total	249	5	3	3.2%	54	21.7%	62	24.9%

[a]Three additional travelers used consecutive mefloquine and primaquine and were excluded from the analysis.

[b]Cases occurred in travelers using primaquine 15 mg.

users occurred when the primaquine dosage was 15 mg base daily. After the dose was increased to 30 mg base daily (as currently recommended by the Centers for Disease Control and Prevention), there were no further cases of early malaria among primaquine users.

Fifty-four (87.1%) cases represented late infection, which developed 2–9 months after return, and all were caused by *P. vivax*. The difference in the attack rate for late malaria according to the chemoprophylaxis used was pronounced: malaria occurred in 1.4% of primaquine users, whereas 56.7%, 49.0%, and 43.5% of atovaquone-proguanil, mefloquine, and doxycycline, respectively, developed late malaria ($P < .0001$ for comparisons of primaquine to all other agents). These results are illustrated in Figure 1.

DISCUSSION

Atovaquone-proguanil is a relatively new antimalarial agent, and the latest to be introduced into the market. It is highly effective against blood stage parasites and is therefore considered a treatment option for acute uncomplicated malaria [20], maintaining its efficacy, even in areas with multidrug-resistant parasites [21]. Its popularity as chemoprophylaxis for travelers results from its good tolerability, and its liver stage activity, which allows for the recommendation of only 1 additional week of therapy postexposure [11, 22, 23]. Recently, even shorter courses were suggested for the use of atovaquone-proguanil without any loss of efficacy [12]. However, most research on atovaquone-proguanil has involved *P. falciparum* malaria, and its effects on nonfalciparum malaria have been less explored.

The life cycle of both *P. vivax* and *P. falciparum* includes sequential liver and then erythrocytic/blood stages, with resulting incubation periods of about 12 days for *P. falciparum* and 14 days for *P. vivax* [24]. The complete absence of early malaria among our atovaquone-proguanil users confirms its position as causal prophylaxis—that is, inhibiting the liver schizont stage of *P. falciparum*—and suggests it has a similar effect on *P. vivax* liver schizonts. In this respect, our results are in line with previously published clinical trials that reported 84% and 96% protective efficacy for atovaquone-proguanil against early *P. vivax* malaria among nonimmune Indonesians and Colombians, respectively [15, 16].

However, a unique aspect of *P. vivax* (and *Plasmodium ovale*) infection is the formation of hypnozoites, which are viable parasite cells that remain dormant within hepatocytes. Hypnozoites can reactivate and cause a late malaria relapse up to several years after exposure. Among Israeli and US travelers, 60%–80% of *P. vivax* malaria occurs with such a late onset, occurring despite using the recommended chemoprophylaxis [14]. This phenomenon is completely missed by clinical trials conducted in malaria-endemic countries, as the usual follow-up period is 1 month [15, 16].

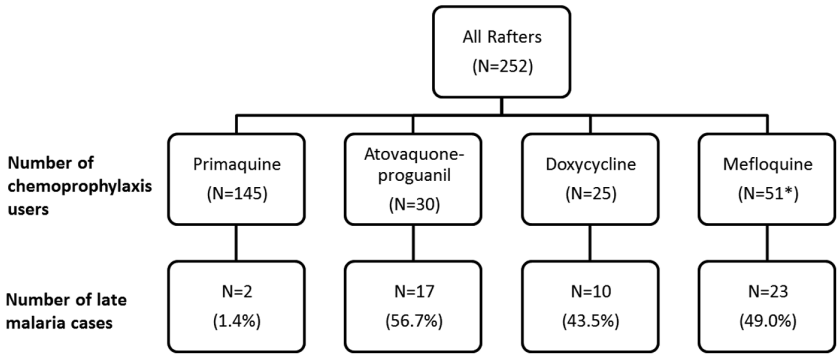

Figure 1. Distribution of late malaria cases among Omo River rafters according to chemoprophylactic agent used. *Three additional travelers used consecutive mefloquine and primaquine and were excluded from the analysis.

It had been previously shown that patients with established *P. vivax* malaria who were treated with atovaquone-proguanil cleared their parasitemia, but relapse did occur [24]. This suggested that when hypnozoites are already present in the liver, atovaquone-proguanil is not effective. Taking atovaquone-proguanil as prophylaxis prior to malaria exposure, however, theoretically might be able to prevent the establishment of hypnozoites in the liver. Our study showed almost identical rates of late-onset *P. vivax* malaria—that is, hypnozoite reactivation, for atovaquone-proguanil and for the blood stage (suppressive) agents such as mefloquine and doxycycline. This indicates that whereas atovaquone-proguanil is schizonticidal for *P. vivax*, it does not prevent the formation of liver hypnozoites, even when administered before sporozoite inoculation into the liver. This is highly suggestive that hypnozoites were preformed in the mosquito prior to inoculation to the liver.

Published data on the effects of atovaquone-proguanil on *P. vivax* hypnozoite formation is limited to several case reports and short case series. Several returning travelers and soldiers have developed late *P. vivax* (or *P. ovale)* malaria despite atovaquone-proguanil prophylaxis [25–29]. On the other hand, among a group of 31 travelers to northwestern Ethiopia, none of the 11 travelers who took atovaquone-proguanil developed late *P. vivax* malaria, whereas about half of those taking doxycycline or mefloquine did [30]. This result is in contrast to our findings, but may reflect random effects due to the small number of cases.

Our study clearly demonstrates the superiority of primaquine over all other chemoprophylactic agents currently recommended for the prevention of malaria, in people who travel to areas highly endemic for both *P. falciparum* and *P. vivax*. While all other recommended drugs, including atovaquone-proguanil, failed in approximately half the cases, the primaquine failure rate was 5.5%, and if only failures with the currently recommended 30 mg primaquine base dose are considered, the failure rate was only 1.4%.

Primaquine was shown to be an effective prophylactic agent against *P. vivax* in human volunteers in the early 1950s [31]. More recently, primaquine was reevaluated as malaria prophylaxis, with similar short-term efficacy demonstrated against both *P. falciparum* and *P. vivax* (88%–94% and 85%–92% prevention, respectively) [32, 33]. However, in both studies patients were followed for only 4 weeks postexposure, and therefore the issue of late infection was not addressed at all. In a previous study, we have shown that primaquine offered far better long-term malaria protection than either mefloquine or doxycycline [18]. The present study reaffirms these results and extends them also in comparison to atovaquone-proguanil.

Primaquine has several limitations as malaria chemoprophylaxis and failures are rare but do occur even with currently recommended doses, and may be associated with CYP2D6 polymorphism, as persons with poor/intermediate metabolizer profile may fail to metabolize primaquine to its active metabolite [34]. In Israel, about 17% of the population may harbor this polymorphism, but it is highly variable among different Israeli ethnic backgrounds [35, 36]. In addition, primaquine can interact with multiple medications via CYP2D6. The main, potentially severe, side effect of primaquine is acute hemolysis in people with glucose-6-phosphate-dehydrogenase (G6PD) deficiency and pretravel screening for G6PD is mandatory prior to primaquine use; this also precludes its use in pregnant women [37].

Our study has several limitations. It was not a prospective randomized interventional study; however, malaria chemoprophylaxis studies in travelers must involve very large numbers of subjects considering the low overall incidence of malaria in this population. Such studies are therefore unlikely to be pursued outside large-scale military or humanitarian deployments to hyperendemic areas. Furthermore, in prospective malaria chemoprophylaxis studies to date, follow-up has been usually limited to 1 month postexposure, and in the absence of a prolonged follow-up period, all late infections of *P. vivax* (and *P. ovale*) malaria will be missed. In fact, had the follow-up in our study been limited to 1 month postexposure, the efficacy of all agents would have been deemed to be excellent, approaching 100%. The retrospective design and the absence of drug blood levels prevents the exclusion of noncompliance as a cause of prophylactic failure; however, we believe this to be unlikely as atovaquone-proguanil is one of the better tolerated chemoprophylactic agents and noncompliance would have reduced its efficacy against early malaria, as well as late, hypnozoite reactivation–derived malaria.

CONCLUSIONS

Long-term follow-up of travelers to the Omo River in Ethiopia has shown a high incidence of late (ie, hypnozoite reactivation related) attacks of *P. vivax* malaria, despite the use of commonly recommended prophylaxis, including atovaquone-proguanil. Although atovaquone-proguanil provides liver stage prophylaxis against *P. vivax* malaria, only primaquine has demonstrated activity against hypnozoite reactivation–related *P. vivax* malaria.

Despite the perception that vivax malaria compared to falciparum malaria is much easier to prevent due to lesser degree of drug resistance, its complex life-cycle within humans, including the hypnozoite formation, makes complete prevention much more challenging. Primaquine is therefore the only drug that currently provides "comprehensive" prophylaxis. New drugs that lack the metabolic disadvantages of primaquine, but that preserve its activity against both early and late malaria, are needed.

Note

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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