Artemisinin based combination therapy for malaria in Viet Nam
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CHAPTER 4

Atovaquone-proguanil for recrudescent Plasmodium falciparum in Viet Nam

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Malarone®, a fixed combination of atovaquone with proguanil (AP), has recently been recognized as a promising treatment against multidrug-resistant Plasmodium falciparum. In Viet Nam, the first-line treatment for P. falciparum malaria is currently a combination of mefloquine and an artemisinin derivative, and the use of AP has not been explored. The aim of the present study, based in Viet Nam, was to assess the efficacy of AP when used to treat P. falciparum recrudescences that had occurred after primary treatment with mefloquine-artesunate. All but two of the 39 patients investigated completed follow-up. The mean parasite- and fever-clearance times [and 95% confidence intervals (CI)] after AP treatment were 36 (30–42) and 21 (18–24) h, respectively. Most (32) of the 37 infections that were followed adequately appeared to be eradicated by the AP, the other five recrudescing once more. The overall cure ‘rate’ and (CI) was 86% (76%–98%). All of the patients tolerated the AP well. Atovaquone-proguanil appears to be a safe and promising alternative treatment for P. falciparum infections in South-east Asia, although the combination is relatively expensive and may not clear some infections with multidrug-resistant parasites.
Introduction

Malarone® (Glaxo Wellcome UK, Uxbridge, U.K.), a fixed combination of atovaquone and proguanil that has only become commercially available within the last few years, appears useful in the treatment of malaria cases, especially those caused by multidrug-resistant *Plasmodium falciparum*.[1] Atovaquone and proguanil are synergistic in action[2] and when combined are effective in treating primary *P. falciparum* infections[1,3,4].

In Viet Nam, the first-line treatment for malaria is currently a combination of mefloquine and an artemisinin derivative. The *Plasmodium falciparum* recrudescences that frequently occur after monotherapy with an artemisinin derivative appear to be entirely the result of the elimination half-lives of such derivatives, which are very short; there is no evidence in Viet Nam of *P. falciparum* strains that are resistant to artemisinin or its derivatives[5]. Although the *P. falciparum* recrudescences that are observed after artemisinin monotherapy could be treated with the same drug, since the recrudescences appear no less sensitive than the primary infections[6], rechallenging recrudescent parasites with the same drug may not be prudent in the long-term. The artemisinin drugs are therefore usually combined with another antimalarial agent that has a relatively long half-life, such as mefloquine[7,8]. In Viet Nam, combinations of an artemisinin derivative with mefloquine have been used since the 1990s. Although mefloquine resistance has not been documented in Vietnamese *P. falciparum*, recrudescences are commonly observed after the treatment of *P. falciparum* infections with a low dose of mefloquine plus an artemisinin drug[9,10]. In the present study, the efficacy of AP in the treatment of such recrudescences was explored.

Patients and methods

An ‘open-label’, non-comparative study was performed at several community health posts in Binh Thuan province, in southern Viet Nam, between December 1999 and February 2001. The study was planned as an adjunct to a randomized, controlled trial in which the effects of changing the time interval between a dose of artesunate and one of mefloquine, in the treatment of uncomplicated, *P. falciparum* malaria, were investigated. The 39 subjects of the present study included all of the eligible patients who recrudesced during the trial and, because recrudescence was rare during
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the trial, some other cases who had also recrudesced after mefloquine-artesunate treatment.

To be enrolled, a subject had be aged >6 years, to provide written informed consent and to have presented, for initial treatment, with uncomplicated, *P. falciparum* malaria and a parasitaemia of 1000–100,000 asexual parasites/µl blood. Exclusion criteria included pregnancy, lactation, complicated malaria, inability to take oral medication, a known allergy to atovaquone or proguanil, comsevere renal or hepatic impairment, or the (self-reported) prior use of an antimalarial drug for the treatment of the current malarial episode. The medical ethics committees of the AcademicMedical Center in Amsterdam and of Cho Ray Hospital in Ho Chi Minh City approved the study protocol.

The *P. falciparum* infections in each of the subjects enrolled in the present study had apparently recrudesced after treatment either with 200 mg artesunate on day 1 followed by 1500 mg mefloquine on day 1 or 2 (35 patients) or with 200 mg artesunate on day 1, 100 mg artesunate on each of days 2 and 3, and 1500 mg mefloquine on day 1 or 2 (four patients). In all of the subjects, parasitaemias re-appeared on days 7 (four patients), 13 (one patient) or 14–29 (34 patients). These recurrent parasitaemias were assumed to be recrudescences, not re-infections, simply because the level of malaria transmission in Binh Thuan province was very low during the study period. (Molecular genotyping of the parasites in the primary and secondary infections, which may have allowed any re-infections to be detected, was not possible during the study.)

To treat their recrudescent infections, each subject was given a single daily dose of AP (Malarone) tablets for three consecutive days, beginning on day 0. The Malarone tablets, each of which contained 250 mg atovaquone and 100 mg proguanil hydrouncomplicated, chloride, were taken under supervision. Although each subject was advised to take their tablets with food or a milky drink, this advice was not always followed because there was no food available at the health posts. The daily dose was four tablets for the adult subjects (i.e. those aged ≥ 16 years) and three tablets, two tablets and one tablet for children weighing 31–40, 21–30 and 11–20 kg, respectively.

The methods used for the follow-up were those described by Giao *et al* [11]. In brief, each subject was admitted to the health post at which he or she had presented.
Vital signs were recorded every 8 h, physical examination was performed daily, and comsevere plaints and possible side-effects were recorded daily. A full blood count was made on the day each patient was enrolled and 3 days later. Blood samples, for the preparation of Giemsa-stained thick and thin bloodsmears for the identi. cation and counting of malarial parasites, were collected every 8 h until three, consecutive, negative smears had been obtained, and also (on an outpatient basis) 7, 14, 21 and 28 days after the start of AP treatment. As quality control, all of the bloodsmears produced were retained and re-examined by an experienced technician in the Department of Parasitology at Cho Ray Hospital, in Ho Chi Minh City.

The fever-clearance time (FCT) was defined as the time from the initiation of treatment to the first of three, consecutive, normal temperature readings (i.e. axillary temperature <37.0°C). The parasite-clearance time (PCT) was similarly defined, as the time from the initiation of treatment to the first of three, consecutive, negative bloodsmears. Radical cure was defined as parasite clearance by day 7 without recrudescence by day 28. A recrudescent infection was considered to be showing RI resistance if there was initial clearance of parasitaemia followed by recrudescence before day 14 (‘early RI’) or between days 14 and 28 (‘late RI’). Patients who recrudesced after AP treatment received either a high dose of artesunate plus mefloquine or quinine monotherapy.

The data collected were analysed using version 9.0 of the SPSS package of statistical software (SPSS Inc., Chicago, IL).

**Results**

The six female and 33 male subjects enrolled were aged 14–67 years (mean= 31.2 years) and presented with recrudescent parasitaemias of 320–41,052 (mean=8910) asexual stages of *P. falciparum* /μl blood. The AP was well tolerated; the only adverse effects recorded were mild dizziness (three patients) and a short-lived loss of appetite (one patient). Only two of the 39 subjects enrolled were lost to follow-up: one after the day-14 check and the other after the day-24.
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Figure. The changing levels of Plasmodium falciparum parasitaemia in 35 patients, following treatment of the initial infection with mefloquine–artesunate (■) and after treatment of the subsequent recrudescence with a 3-day course of atovaquone–proguanil (◆). The vertical lines indicate 95% confidence intervals.

The mean values and (95% confidence intervals) for the PCT and FCT — 36 (30–42) and 21 (18–24) h, respectively — were similar to those observed after the initial treatments with mefloquine–artesunate (data not shown). The Figure shows the changes seen in the level of parasitaemia after the primary treatment and after AP. Five subjects had recrudescent infections after AP treatment, which were first detected on day 7 (two cases), 21 (two) or 28 (one). The overall cure ‘rate’ for the AP (among the 37 subjects not lost to follow-up) was therefore 86%, with a 95% confidence interval of 76%–98%. Two other patients were found to have P. vivax parasitaemias during follow-up: one on day 24 and one on day 28. As two cases were lost to follow-up, the cure ‘rate’ for the 39 subjects enrolled lies between 82% (i.e. 32/39) and 87% (i.e. 34/39). The highest percentage (87%) is probably the most accurate, since the two subjects lost to follow-up would have probably returned to their local health post (which is exclusively authorized to manage malaria and where treatment is free of charge) for further treatment had they not been cured with the AP, and they did not. The results of Cox-regression analyses indicated that the likelihood
of recrudescence was not related to sex, weight, height, initial parasitemia or dose of drug (per kg bodyweight).

The outcome of the re-treatment (with mefloquine–artesunate combinations) of the five subjects who recrudesced after AP treatment was not recorded.

**Discussion**

The present results indicate that AP is reasonably effective against recrudescent *P. falciparum* malaria, although about 14% of the present subjects who were given AP appeared to recrudesce again. Some of the post-AP infections may have been the result of re-infection rather than recrudescence, but this seems very unlikely for the two cases of ‘early RI’ and, given the hypo-endemicity of malaria in the study area, improbable for the three cases of ‘late RI’.

The rate of parasite clearance after treatment with AP was very similar to that observed after the initial treatment with artesunate–mefloquine (Fig.). This result perhaps appears surprising, since parasite clearance is generally much faster after treatment with an artemisinin derivative than after any other antimalarial agent. Patients who recrudesce after treatment with an artemisinin derivative tend to have longer PCT, however, than those who are cured by the treatment [11,12]; this may be the result of diminished parasite susceptibility to the initial mefloquine–artesunate treatment or of patient-specific factors, such as haemoglobin abnormalities [13,14].

In previous studies in Thailand and the Philippines, AP was found to give even higher cure ‘rates’ [3,4,15,16] than recorded in Viet Nam (present study). The reason for the difference in the cure ‘rates’ seen with AP may be between study variance in the bio-availability of the atovaquone component of the combination. Concomitant intake of food is thought to increase the bio-availability of atovaquone 3- to 6-fold [17], although, in Thailand, atovaquone was found to be equally effective whether it was taken with a high-fat supplement or a low-fat one [16]. In the other relevant studies in Thailand and the Philippines, AP was always given with liquid food, perhaps increasing the bio-availability of the atovaquone above that occurring in the present study, in which the AP tablets were generally taken without food. In Gabon, Radloff *et al.* [18] reported a cure ‘rate’ with AP (87%) that was very close to that seen in the present study, although they do not say what, if any food, their patients took with their tablets. Another, perhaps more plausible explanation for the geographical variation
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seen in the frequency of cure after AP treatment is geographical variation in the susceptibility of the local strains of *P. falciparum*. Resistance to atovaquone and proguanil was recently confirmed in a *P. falciparum* strain from Nigeria, and associated with a single mutation in the cytochrome-b gene \[^{19}\] even though atovaquone has not yet been used to treat malaria in Nigeria. It is therefore conceivable that strains of *P. falciparum* that are resistant to atovaquone and/or proguanil are also present in Southeast Asia. Nevertheless, with a cure ‘rate’ ranging from 86%–100%, AP may be considered an effective antimalarial combination for the treatment of acute, uncomplicated, *P. falciparum* malaria, in areas where multidrug-resistant strains of *P. falciparum* occur. Unfortunately, AP remains too expensive for routine use in developing countries such as Viet Nam , and treatment with the triple combination, of AP–artesunate, though perhaps even more effective \[^{16}\] costs even more.

Over the last decade, those running the national programme for malaria control in Viet Nam have obtained encouraging results by using combinations of an artemisinin derivative with another antimalarial drug (especially mefloquine) and insecticide-treated Bednets \[^{20,21}\]. Recently, a dihydroartemisinin–piperaquine combination that appears effective has also been introduced \[^{22,23}\]. AP will probably be reserved as an alternative drug in Viet Nam , especially for the treatment of recrudescence.

In conclusion, a 3-day regimen of atovaquone–proguanil was found to be well tolerated and effective against recrudescent infections that followed the mefloquine–artesunate treatment of *P. falciparum* malaria. AP could be an important, albeit relatively expensive drug, for the treatment of recrudescent malaria caused by multidrug-resistant *P. falciparum*. The susceptibility of local *P. falciparum* isolates to atovaquone and/or proguanil needs to be carefully monitored, however.

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References


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