SHORT REPORT: TAFENOQUINE FOR THE TREATMENT OF RECURRENT
PLASMODIUM VIVAX MALARIA

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Abstract. Tafenoquione was used to treat Plasmodium vivax malaria cases who had previously failed treatment with chloroquine and primaquine. Chloroquine was followed by a loading dose of tafenoquione (200 mg base/day for 3 days) and 200 mg a week was given for 8 weeks. One of 27 treated patients relapsed after 6 months of observation. A standard course of primaquine administered with 8 weeks of tafenoquione may be more effective than chloroquine with primaquine (22.5 mg/day for 14 days) in preventing additional P. vivax relapses. Larger studies are required to optimize the combination, but our findings suggest that an extended use of tafenoquione may be required to prevent relapses of primaquine-tolerant strains of P. vivax malaria.

The treatment of Plasmodium vivax malaria is of particular concern in the southwestern Pacific region with evidence of relative resistance of the parasite to conventional treatment with primaquine. The Australian Defense Force (ADF) has recently deployed large numbers of troops to Bougainville (Papua New Guinea) and East Timor on peacekeeping missions. During the initial phase of the East Timor deployment in 1999, more than 7,000 ADF personnel were deployed taking 100 mg of doxycycline daily for malaria prophylaxis and primaquine post-exposure prophylaxis. However, they experienced an inordinate number of malaria infections (> 400) mostly after return to Australia. The cure rate of soldiers returning from East Timor who were treated with chloroquine, 1,500 mg for 3 days and primaquine, 22.5 mg/day for 14 days, for their first relapse of P. vivax malaria was 53% (40 of 75). These infections required increasing doses of primaquine to adequately prevent relapse.

In an effort to eliminate these primaquine-tolerant parasites, we evaluated chloroquine and an extended treatment course of tafenoquione (formerly known as WR 238605), a primaquine analog, to see whether such a regimen would be more efficacious than chloroquine and primaquine. We report the effectiveness and tolerability of this open-label, prospective use of tafenoquione given over 8 weeks as treatment for P. vivax malaria after a standard course of chloroquine (1,500 mg total dose) to treat the acute attack. We attempt to determine whether this course of tafenoquione would prevent further relapses among healthy non-immune adult Australians who had developed acute P. vivax malaria and had already experienced at least one relapse.

The study was conducted entirely with ADF personnel who had microscopically confirmed P. vivax malaria. This group included one female member. The average age and weight at onset of treatment was 26 years and 79 kg, respectively. The proposal to conduct this treatment trial was reviewed and approved by the Australian Defense Human Research Ethics Committee, and each individual patient signed an informed consent and information sheet and their treatment was approved by the Australian Therapeutics Goods under the auspices of the Therapeutics Goods Act (1989), Section 19(1).

Initial management was with chloroquine 600 mg (base), followed by 300 mg six hours later, 300 mg the following day, and a final 300 mg on the third day.

Prior to administration of tafenoquione, glucose-6-phosphate dehydrogenase status was confirmed to be normal from the patient’s medical records and the female patient was tested for pregnancy. Patients were then administered a loading dose of tafenoquione, 200 mg base/day for 3 days, followed by a maintenance dose of 200 mg tafenoquione once a week for 8 weeks. The tafenoquione course was selected on the basis of the lengthy elimination half-life for tafenoquione of 2 weeks, which would lead to persistent drug blood concentrations to at least the median time to relapse (approximately 90 days) noted previously in this population. Further support for the 8-week tafenoquione treatment course is the high effectiveness of a single 45 mg-dose of primaquine administered once a week for 8 weeks against Chesson P. vivax infections. Observation throughout the eight weeks of active treatment included clinical assessment, blood films for parasitemia, and blood samples collected for measurement of plasma tafenoquione concentrations.

The primary endpoint of this pilot study was the development of a clinical episode of P. vivax infection within six months of commencing the tafenoquione treatment course. Any subject developing symptoms of malaria during treatment or follow-up phases was required to have Giemsa-stained thick and thin film blood slides prepared with duplicate slides sent to the Australian Army Malaria Institute for confirmation.

Blood samples collected (4 mL using EDTA as the anticoagulant) for drug analysis were centrifuged at 2,500 rpm for 10 minutes. The separated plasma was transferred to plastic tubes for storage at −20°C or less and on completion of the treatment course the samples were then sent to AMI on dry ice and stored at −80°C until analyzed. Plasma tafenoquione concentrations were measured by reversed-phase high-performance liquid chromatography, with fluorescence detection, as previously described.

Thirty-one patients were enrolled and commenced study medication; 27 patients completed the full tafenoquione treatment. Treatment was terminated early for four patients when all tafenoquione clinical trials were suspended by the sponsor (GlaxoSmithKline) because of an unexpected adverse event (vortex keratopathy) occurring in a long-term prophylaxis trial being conducted concurrently. Of the 27 patients who
completed treatment, 17 were recruited after their second clinical episode of *P. vivax* malaria, 7 after their third episode, and 3 after their fourth episode. There were no serious adverse events reported in this study and no withdrawals because of adverse events. The eight-week regimen of tafenoquine was well-tolerated. Only one patient subsequently relapsed, which represents a cure rate of 96.3% (26 of 27). The patient (a 25-year-old man) was found to have parasitemia 126 days after onset of tafenoquine treatment. Prior to joining this study, he had had three previous episodes of malaria beginning with a single case of *P. falciparum* malaria after four months deployment in East Timor. This was treated with quinine and doxycycline. He continued doxycycline prophylaxis for an additional one month prior to returning to Australia. On arrival in Australia, he received primaquine, 7.5 mg three times/day for 14 days, an approximate total dose of 5 mg/kg. His first episode of *P. vivax* malaria began within six weeks of beginning primaquine. He was treated with chloroquine and another course of primaquine (22.5 mg/day for 14 days). His second episode of *P. vivax* malaria began three months later. This episode was treated with chloroquine. He provided consent to enter the study and began tafenoquine treatment seven weeks later after having been treated with chloroquine weekly in the interim. His post-tafenoquine *P. vivax* parasitemia was treated with the same initial course of chloroquine. The parasitemia subsided quickly and he was then treated with weekly chloroquine, 300 mg of chemosuppression for an additional six months.

Four patients (three successfully treated and the treatment failure) who completed the full bleeding schedule were tested for plasma tafenoquine concentration. The mean plasma tafenoquine concentration profiles of these patients are shown in Figure 1. The steady-state mean ± SD plasma tafenoquine concentration was 247 ± 75 ng/mL after eight weeks of tafenoquine administration in the three patients who were successfully treated. Compared with these patients, the soldier who failed tafenoquine treatment had lower plasma tafenoquine concentrations up to six weeks after initiation of treatment.

In 1999, the ADF compared the effectiveness of tafenoquine (400 mg/day for 3 days) and primaquine (22.5 mg/day for 14 days) for post-exposure prophylaxis of *P. vivax* malaria. Tafenoquine was well tolerated and found to be equally effective as the longer course of primaquine in preventing *P. vivax* malaria. Recently, a dose ranging study of tafenoquine (total dosage = 500–3,000 mg) given from one to seven days with chloroquine (1,500 mg over 3 days) was found to be more efficacious than chloroquine and primaquine (15 mg/day for 14 days) in treating *P. vivax* malaria.

The level of cross-resistance between primaquine and tafenoquine is unknown. In searching for an optimal tafenoquine treatment regimen, a study in Thailand comparing chloroquine and tafenoquine (three different regimens of tafenoquine) and chloroquine and low-dose primaquine (15 mg/day for 14 days) showed that the rate of protective efficacy was markedly higher after chloroquine and tafenoquine treatment. Of the patients with *P. vivax* malaria who completed at least 8 weeks of follow-up, 1 of 46 patients relapsed on chloroquine and tafenoquine, 8 of 10 patients relapsed on chloroquine only, and 3 of 12 patients relapsed on chloroquine and primaquine. Notwithstanding these encouraging findings, caution needs to be exercised because *P. vivax* relapses may occur up to more than six months after acute infections and that a higher dose of primaquine (30 mg/day for 14 days) might have prevented more relapses.

The patient relapsing in this study after chloroquine and tafenoquine treatment had markedly lower plasma tafenoquine concentrations for the first six weeks after commencing tafenoquine treatment compared with those who where successfully treated with the drug combination. His low plasma tafenoquine concentrations suggest that he experienced difficulty in absorbing the drug after the commencement of treatment. Doses as low as 600 mg have been effective in treatment of *P. vivax* malaria. However, low tafenoquine concentrations have been implicated in treatment failures with tafenoquine. It is thus probable that the combination of a highly primaquine-tolerant *P. vivax* strain and low plasma tafenoquine concentrations contributed to the patient not being cured on the extended tafenoquine regimen.

In conclusion, a standard course of chloroquine administered with 8 weeks of treatment with tafenoquine may be more effective than chloroquine with primaquine at a dose of 22.5 mg/day for 14 days and comparable to 30 mg/day for 14 days in preventing further *P. vivax* relapses. The extended tafenoquine regimen needs to be evaluated against the more effective dose of primaquine (30 mg/day for 14 days). Larger studies are required to optimize the combination of chloroquine and tafenoquine, but our findings suggest that an extended use of tafenoquine may be required to prevent relapses of primaquine-tolerant strains of *P. vivax* malaria.

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