

and WR99210 is 2.50-6.89 nM (Mean \pm SD = 3.91 \pm 1.17, n = 47). The 715-bp and 238-bp PCR products of complete and partial sequences of *dhfr* gene were successfully amplified. The 715-bp fragment was analyzed by *Pvu* II restriction enzyme digestion and DNA sequencing while the 238-bp fragment was analyzed with *Alu* I restriction endonuclease. The results of PCR-RFLP analysis and DNA sequencing revealed 3 groups of mutant alleles i.e. double, triple and quadruple mutations, which are associated to pyrimethamine and WR99210 responses. Relationships between different *dhfr* genotypes and their EC₅₀ values of pyrimethamine and WR99210 were investigated. Results indicate that all mutant genotypes exhibiting pyrimethamine tolerant phenotypes were more sensitive to WR99210. These results promise new means of controlling vivax malaria. (*This work was supported by the University Development Committee (UDC)*).

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AZITHROMYCIN COMBINATION THERAPY WITH ARTESUNATE OR QUININE FOR THE TREATMENT OF UNCOMPLICATED FALCIPARUM MALARIA IN ADULTS. PRELIMINARY RESULTS FROM A RANDOMIZED PHASE 2 CLINICAL TRIAL IN THAILAND

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Azithromycin is a macrolide antibiotic that may have a role as an antimalarial due to its safety in children and experience with use in pregnancy. The study was designed as a phase II open label, randomized 28-day inpatient study of acute, uncomplicated falciparum malaria, comparing the safety and efficacy of 2 azithromycin - artesunate combinations with 2 azithromycin-quinine regimens in 100 adult patients: 1.) 3 days of azithromycin (AZ) 750 mg BID plus artesunate (AS) 100 mg BID 2.) 3 days of AZ 1000 mg QD plus AS 200 mg QD 3.) 3 days of AZ 750 mg BID plus quinine (QN) 10 mg/kg BID 4.) 3 days of AZ 500 mg TID daily plus QN 10 mg/kg TID.

After completion of 50 subjects the treatment failure rates, parasite clearance times (PCT), and fever clearance times (FCT) were compared in a preliminary efficacy analysis. The 28-day cure rates for the 4 groups were 100 (95%CI: 71.5 - 100), 100 (95%CI: 73.5 - 100), 72.7 (95%CI: 39.0 - 94.0), and 91.7% (95%CI: 61.5 - 99.8), respectively. No failures were seen in either of the artesunate arms, two RIIs and one RI failure in the BID quinine arm, and one RI in the TID quinine arm. With a mean PCT and FCT of 34 \pm 12 and 26 \pm 18 hours the artesunate combinations led to a significantly (P<0.001) faster clinical and parasitological improvement than the quinine arms (80 \pm 34 and 60 \pm 39 hours, respectively). No drug-related SAEs were seen and the drug combinations were well tolerated and safe.

In vitro results suggest that the early failures in the quinine arms were associated with decreased susceptibility to quinine as well as with mefloquine resistance. All treatment failures had 50% inhibitory concentrations (IC₅₀s) for quinine consistently above average. Interestingly both

cases of RIII were also highly mefloquine resistant, a drug that is widely used in Thailand and that is known for its cross-resistance with quinine.

In conclusion, these preliminary data suggest that azithromycin-artesunate, even when given only once daily for 3 days, as well as azithromycin-quinine TID may be safe and highly efficacious combination treatments for uncomplicated falciparum malaria.

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COMPARATIVE EFFICACY OF INTRAVENOUS ARTESUNATE AND ARTELINATE IN AN UNCOMPLICATED MODEL AND SEVERE PRIMATE MALARIA MODEL

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Plasmodium coatneyi is a primate malaria whose schizonts sequester in the tissues of the lung, heart and brain, mimicking *Plasmodium falciparum* infection. Using a severe malaria model of *P. coatneyi* in splenectomized rhesus, we found that parasitemias reach high densities ($> 1,000,000/\mu\text{l}$) and the infection is uniformly fatal, if untreated. We validated a treatment window for rescue with parenteral antimalarials using quinine, and here we report comparison of efficacy testing with the two candidate intravenous artemisinin, sodium artesunate (AS) and artelinate lysine salt (AL). Animals were randomized to receive artesunate and artelinate by IV bolus injection for 3 days, in dose-escalation cohorts targeted to achieve 100% parasite clearance. 5 animals received quinine intramuscularly with 20% mortality, and mean parasite clearance time of 5.6 days. Artesunate (4, 6 or 8 mg/kg) was associated with an 11% mortality, and rapid parasite reduction ($> 99.99\%$) with complete parasite clearance in 66%, 50% and 100% of animals, respectively. All animals had recur-descence (mean 4.5 days). Equimolar doses of artelinate (5.9, 8.8 and 11.8 mg/kg) also resulted in a rapid, 4-log reduction in parasitemia, but no animals successfully cleared their parasitemia. Higher doses (23.6 and 47 mg/kg) were associated with increased mortality, despite no life-threatening toxicities noted in healthy rhesus at these doses. The most effective doses (8 mg/kg AS; 11.8 mg/kg AL) were tested in a cohort of monkeys with uncomplicated *P. coatneyi* infection. All AS-treated animals cleared with eventual recur-descence (mean 6 days). Only 2 of 8 AL-treated animals cleared parasitemia with recur-descence within 1-2 days. Unexpectedly, three AL-treated animals developed a shock-like syndrome after treatment, with no clear etiology. In summary, while both drugs rapidly cleared parasitemia, artesunate was more effective in both the severe and uncomplicated models. In view of this and other studies, artesunate has been chosen for advanced clinical development.

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