Published in final edited form as:
Am J Trop Med Hyg. 2003 July ; 69(1): 14–18.

CLINICAL TRIAL OF ORAL ARTESUNATE WITH OR WITHOUT HIGH-DOSE PRIMAQUINE FOR THE TREATMENT OF VIVAX MALARIA IN THAILAND

Udomsak Silachamroon, **Srivicha Krudsood**, **Sombat Treeprasertsuk**, **Polrat Wilairatana**, **Kobsiri Chalearmrult**, **Hla Yin Mint**, **Pannamas Maneekan**, **Nicholas J. White**, **Victor R. Gourdeuk**, **Gary M. Brittenham**, and **Sornchai Looareesuwan**
Department of Clinical Tropical Medicine and Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Wellcome Trust, Mahidol University Oxford Tropical Medicine Research Programme Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Center for Sickle Cell Disease, Howard University, Washington, District of Columbia

College of Physicians and Surgeons, Columbia University, Harkness Pavilion, New York, New York

Abstract

We studied prospectively 801 Thai patients admitted to the Bangkok Hospital for Tropical Diseases with acute, symptomatic *Plasmodium vivax* malaria to determine the optimum duration of treatment with oral artesunate and the safety, tolerability, and effectiveness of a high dose of primaquine in prevention of relapse. Patients were randomly assigned to one of four treatment groups: 1) a five-day course of artesunate (Group A5); 2) a seven-day course of artesunate (Group A7); 3) a five-day course of artesunate plus a 14-day course of high-dose primaquine (0.6 mg/kg, maximum dose = 30 mg) (Group A5 + P); and 4) a seven-day course of artesunate plus a 14-day course of high-dose primaquine (Group A7 + P). During 28 days of observation, *P. vivax* reappeared in the blood of 50% of those who received artesunate alone (Groups A5 and A7), compared with none of those who received primaquine (Groups A5 + P and A7 + P; $P < 0.0001$). Adverse effects were confined to the 13 patients with a deficiency for glucose-6-phosphate dehydrogenase; high-dose primaquine (0.6 mg/kg of base a day) had to be stopped in four (31%) patients because of a significant decrease in the hematocrit. The combination of five days of artesunate and 14 days of primaquine is a highly effective and generally well-tolerated treatment regimen for vivax malaria in Thailand.

Reprint requests: Prof. S. Looareesuwan, tmslr@mahidol.ac.th.
Authors' addresses: Udomsak Silachamroon, Sombat Treeprasertsuk, Polrat Wilairatana, Kobsiri Chalearmrult, Hla Yin Mint, Pannamas Maneekan, and Sornchai Looareesuwan, Department of Clinical Tropical Medicine and Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand, Telephone: 66-2-247-1688, Fax: 66-2-245-7288, tmslr@mahidol.ac.th. Srivicha Krudsood, Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand. Nicholas J. White, Wellcome Trust Mahidol University Oxford Tropical Medicine Research Programme Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand. Victor R. Gourdeuk, Center for Sickle Cell Disease, Howard University, 2121 Georgia Avenue, NW, Washington, DC 20059. Gary M. Brittenham, College of Physicians and Surgeons, Columbia University, Harkness Pavilion, Room HP568, 630 West 168th Street, New York, NY 10032-3795.

INTRODUCTION

Of the four protozoan species of the genus *Plasmodium* that cause infection in humans, *P. falciparum* and *P. vivax* are responsible for most cases of malaria. In Thailand three decades ago, *P. falciparum* caused approximately 80% of infections and *P. vivax* 20%, but by 1998 the proportions had become equal.[1] Thailand and most of southeast Asia are areas of low malaria transmission, individuals gain relatively little acquired immunity, asymptomatic parasitemia is unusual, and acute falciparum or vivax malaria may occur at any age.[2] The *P. falciparum* parasites prevalent in Thailand are the most drug-resistant in the world,[3] and for effective treatment the use of artemisinin derivatives is necessary.[4] Although chloroquine-resistant *P. vivax* has been reported in this region,[5–7] almost all acute vivax infections can still be treated with chloroquine successfully in Thailand.[8] To prevent relapses of *P. vivax* arising from persistent liver stages (hypnozoites), radical treatment with primaquine is required. Standard doses of primaquine (0.25 mg/kg of base a day for 14 days) do not prevent all relapses in Thailand. Increased dose regimens of primaquine need evaluation.[9]

Microscopic diagnosis of malaria allows appropriate regimens for the treatment of *P. falciparum* and *P. vivax* malaria to be prescribed.[3,4] However, in many circumstances malaria is diagnosed principally by clinical criteria, and reliable clinical differentiation of falciparum malaria from vivax malaria is not possible.[10] In addition, mixed infections are common in Thailand. For example, of 994 patients admitted to the Bangkok Hospital for Tropical Diseases with the initial microscopic diagnosis of *P. vivax* malaria alone, 104 (10.5%) subsequently developed *P. falciparum* malaria following drug treatment for *P. vivax* malaria.[11] Conversely, 30% of patients with the initial microscopic diagnosis of falciparum malaria alone subsequently develop vivax malaria.[12,13] Thus, drugs effective against both species of malaria are needed. Radical cure of *P. vivax* malaria requires treatment with primaquine because the hypnozoites are insensitive to all antimalarial drugs other than the 8-aminoquinolines. Accordingly, we carried out a trial designed to determine for infection with *P. vivax* in Thailand 1) the optimum duration of treatment with artesunate (five or seven days) and 2) the safety, tolerability, and effectiveness of a high dose of primaquine (0.6 mg/kg of base a day for 14 days) in the prevention of relapse.

MATERIALS, AND METHODS

Patients

This study included all patients admitted to the Bangkok Hospital for Tropical Diseases in Bangkok, Thailand with acute symptomatic *P. vivax* malaria between February 1999 and July 2001. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (Bangkok, Thailand). Each participant gave fully informed consent. The inclusion criteria for the study were an age of 15 years or older, willingness to give informed consent, a body weight of at least 40 kilograms, and an agreement to remain in the hospital for 28 days. Patients who were pregnant were excluded, as were those with concomitant *P. falciparum* infection, patients with associated severe vital organ dysfunction, those with a history of drug hypersensitivity or of taking antimalarials during the two-week period prior to admission. A known deficiency for glucose-6-phosphate dehydrogenase (G6PD) was not an exclusion criterion, but patients with a history of dark urine or significant hemoglobinuria related to primaquine treatment during the course of a previous episode of malaria were excluded.

Procedures

After clinical evaluation and examination of thick and thin blood smears to establish the diagnosis, baseline blood samples were obtained for hematologic and biochemical studies.

Patients were then randomly assigned to one of four treatment groups: 1) a five-day course of artesunate (50 mg of salt/tablet; Guilin No. 1 Factory, Guangxi, People's Republic of China): a single dose of oral artesunate, 200 mg, on the first day, followed by single daily doses of oral artesunate, 100 mg, for the next four days (Group A5); 2) a seven-day course of artesunate: a single dose of oral artesunate, 200 mg, on the first day, followed by single daily doses of oral artesunate, 100 mg, for the next six days (Group A7); 3) a five-day course of artesunate plus a 14-day course of primaquine (7.5 mg of base per tablet; Thai Government Pharmaceutical Organization, Bangkok, Thailand): a single dose of oral artesunate, 200 mg, on the first day, followed by single daily doses of oral artesunate, 100 mg, for the next four days, after which primaquine (0.6 mg/kg, maximum dose = 30 mg) was given once a day for 14 days (five-day course of artesunate plus primaquine; Group A5 + P); and 4) a seven-day course of artesunate plus a 14-day course of primaquine: a single dose of oral artesunate, 200 mg, on the first day, followed by single daily doses of oral artesunate, 100 mg, for the next six days, after which primaquine (0.6 mg/kg, maximum dose = 30 mg) was given once a day for 14 days (seven-day course of artesunate plus primaquine, Group A7 + P). Randomization was performed by block randomization. Patients successfully treated with artesunate alone for five or seven days were given a course of primaquine (15 mg/day for 14 days) at follow-up on the 28th day of the study to complete their radical cure. Primaquine was given after a meal or soft drink. Oral acetaminophen (0.5−1.0 g every four hours) was given for a temperature ≥38°C.

Oral temperature and pulse and respiratory rates were measured every four hours until resolution of fever and thereafter every 6−12 hours; blood pressure was measured once a day. Monitoring for signs and symptoms of malaria was conducted daily for the first seven days of admission and weekly thereafter. Patients with a G6PD deficiency in groups 3 and 4 were closely monitored during the period of primaquine administration: their hematocrit values were assessed daily, and they were examined for clinical evidence of intravascular hemolysis or hemoglobinuria.

Fever clearance time was defined as the time from the start of a patient's treatment until the oral temperature decreased to less than 37.5°C and remain at or below this level for 48 hours. Parasite clearance time was defined as the time from the start of a patient's treatment until the patient's first negative blood film with the blood film then remaining negative for 24 hours.

All patients were hospitalized for 28 days or until the reappearance of parasites. Patients in whom *P. vivax* parasitemia reappeared after initial parasite clearance were considered to have failed treatment. These patients were then treated with the hospital's standard regimen for vivax malaria: chloroquine (30 mg base/kg in a single dose) and primaquine (15 mg base once a day for 14 days). Patients found to be co-infected by asexual forms of *P. falciparum* were treated with either quinine combined with tetracycline for seven days or artesunate (600 mg) followed by mefloquine (25 mg/kg). These patients were excluded from the analysis of the 28-day cure rates.

Laboratory studies

Pretreatment investigations included a complete blood count (red blood cell count, hemoglobin, hematocrit, total white blood cell count, differential count, and platelet count); estimations of total and direct bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, albumin, globulin, and aspartate and alanine aminotransferases; and a urinalysis. These tests were repeated on days 7, 14, 21, and 28. A screening test for a G6PD deficiency was conducted on admission. Thick and thin blood films were examined for malaria parasites before treatment and then every 12 hours until negative; thereafter, thick films were examined daily until either the reappearance of *P. vivax* or *P. falciparum* or the 28th

day. Parasite counts per microliter of blood were determined by counting the number of asexual parasites per 200 white blood cells (thick films) or per 1,000 red blood cells (thin films); blood films were considered negative if no parasites were seen in 200 oil-immersion fields of a thick blood film.

Statistical analysis

Continuous variables are summarized as means and standard deviations and were compared by one-way analysis of variance. A geometric mean was used to express the parasite count. The efficacy of the drug regimens was compared by the chi-square test.

RESULTS

Patients

Eight-hundred one patients were studied: 206 received a five-day course of artesunate (Group A5), 201 received a seven-day course of artesunate (Group A7), 196 received a five-day course of artesunate plus a 14-day course of primaquine (Group A5 + P), and 198 received a seven-day course of artesunate plus a 14-day course of primaquine (Group A7 + P). Most of the patients had contracted malaria on the Thailand-Myanmar border. Demographic, clinical, and pretreatment laboratory data are shown in Table 1. There were no significant differences between the treatment groups ($P > 0.1$).

Following treatment, 186 patients (49 in Group A5, 42 in Group A7, 54 in Group A5 + P, and 41 in Group A7 + P) sought discharge from the hospital before follow-up day 28 because of social reasons, not because of the drug treatment or its side-effects. These patients were excluded from the analysis of the 28-day cure rates. The median day of early discharge from the study was day 14 in groups 1, 2, and 4 and day 16 in group 3. All patients who sought discharge before day 28 were asymptomatic and free of parasitemia before their discharge from the hospital.

Therapeutic responses

Fever and parasite clearance times were rapid, and similar in all four groups (Table 2). There were no early treatment failures. Of the 615 patients who completed the follow-up on day 28, 158 had a reappearance of *P. vivax* in their blood. All of these had not received primaquine ($P < 0.0001$), giving an average recurrence rate of 50% and the 28-day cure and failure rates. During the follow-up period, none of these patients had asexual forms of *P. falciparum* in blood films.

Adverse effects

Forty-four patients were found to be deficient for G6PD: 18 of them received primaquine (Groups A5 + P and A7 + P) (Table 1). Five of the 18 left the hospital prior to finishing treatment. Nine patients completed their treatment without difficulty, but four had a significantly reduced hematocrit that prompted their doctors to stop administration of primaquine. They were withdrawn on day 7, day 4, day 6, and day 6 after initial primaquine treatment. The decreases in hematocrit were 16%, 13%, 14%, and 8%, respectively. This compares with a mean (SD) change in hematocrit of 0.79% (4.28) in patients who were not G6PD deficient. Some patients had nausea, vomiting, or abdominal discomfort that was self-limited or needed symptomatic treatment. No other adverse effects were associated with primaquine; specifically, no cyanosis, abdominal cramps, hypertension, arrythmias, central nervous system disturbances, granulocytopenia, agranulocytosis, and leukocytosis were reported or observed.

DISCUSSION

In areas of Asia where both *P. falciparum* and *P. vivax* are prevalent, chloroquine and primaquine should not be used for treatment of vivax malaria if co-infection with multidrug-resistant *P. falciparum* cannot be excluded and follow-up ensured. Even with expert microscopic diagnosis, approximately 10% of patients initially considered to have *P. vivax* malaria alone will subsequently develop *P. falciparum* malaria following drug treatment for *P. vivax*.[11,14] Because artemisinin derivatives are active against both species, we examined regimens with an artemisinin derivative as the blood schizontocide for the treatment of acute malaria and primaquine as the hypnozoiticide for prevention of relapse. In an earlier study evaluating the activity of artesunate alone against *P. vivax* infection, a five-day regimen (200 mg on the first day and 100 mg on the following four days) cleared parasitemia rapidly, but vivax malaria reappeared in more than 60% of the patients within 28 days.[15] In this study, we also examined the effect of a seven-day regimen, but the additional two days of artesunate produced no significant increase in the cure rate assessed at 28 days. With either five or seven days of artesunate treatment, vivax malaria reappeared in roughly half the patients by day 28. With southeast Asian strains of *P. vivax*, both the average relapse interval and the average time to recrudescence are approximately three weeks.[15] Thus, in an individual patient, differentiation between relapse and recrudescence following administration of a rapidly eliminated antimalarial is not possible. In this series, it is likely that most, and possibly all, recurrent parasitemias resulted from relapses. Artesunate is even more active against *P. vivax* than against *P. falciparum*, but in infections with the latter species seven-day regimens of artesunate alone give ≥90% cure rates. Furthermore, primaquine prevented all recurrent parasitemias.

Because a proportion of vivax infections in Thailand now seem to be refractory to standard doses of primaquine (0.25 mg/kg of base a day for 14 days),[9] we examined the effectiveness, tolerability, and safety of a higher dose of primaquine (0.6 mg/kg of base a day for 14 days) in prevention of relapse. The addition of this higher dose of primaquine to either the five- or seven-day treatment with artesunate prevented the reappearance of vivax malaria in all patients by day 28. The 28-day period of observation is too short to detect later relapse, but in an earlier study with a 12-week follow-up period, high-dose primaquine prevented the reappearance of vivax malaria in 33 (94%) of 35 patients.[8]

Patients with a G6PD deficiency are generally excluded from primaquine treatment trials because of the risk of adverse reactions.[16] However, we decided that G6PD-deficient individuals could be investigated safely since the variants of G6PD deficiency that are prevalent in Thailand (G6PD Viangchan (871G>A), G6PD Canton (1376G>T), G6PD Mahidol (487G>A) and G6PD Kaiping (1388G>A))[17] are generally mild, and the patients were carefully monitored in the hospital. In the present study, patients tolerated primaquine well and adverse effects were confined to the subpopulation of patients with G6PD deficiency. Among the 13 who completed the 28 day study, the high dose primaquine (0.6 mg/kg of base) had to be stopped because of a decrease in the hematocrit in four (31%). For comparison, in another recent study at the Bangkok Hospital for Tropical Diseases, all 22 patients receiving a standard dose of primaquine (0.25 mg/kg of base) completed the 14-day course.[18] These results suggest that even in Thailand, where the prevalent variants of G6PD deficiency are relatively mild, a substantial proportion of patients with G6PD deficiency will be unable to tolerate high-dose primaquine. For patients with G6PD deficiency, the use of a standard dose of primaquine with observation for later relapse may provide a better therapeutic option.

A combination of five days of artesunate plus 14 days of high-dose (0.6 mg base/kg/day) primaquine is a highly effective regimen for vivax malaria in Thailand. For the treatment of

falciparum malaria, seven-day courses of artesunate are preferable,[19] although the five-day regimen is sufficient to cure subclinical *P. falciparum* infections co-existing with *P. vivax*. Thus, as an empirical treatment of suspected malaria in this region, where laboratory confirmation cannot be obtained, this regimen would be highly effective. In patients with a G6PD deficiency, the use of high-dose primaquine would require careful monitoring of the hematocrit, but a standard dose of primaquine with close observation for later relapse could also be considered as a therapeutic alternative.

Acknowledgments

We are grateful to the staff of the Hospital for Tropical Diseases for their help and support. Nicholas J. White is a Wellcome Trust Principal Fellow.

Financial support: This study was supported by the Thailand-Tropical Diseases Research Programme (T2), Department of Medical Science, Ministry of Public Health, Thailand, National Institutes of Health grant R01 AI-51310, and the Tak Malaria Initiative supported by the Bill and Melinda Gates Foundation.

REFERENCES

1. Chareonviriyaphap T, Bangs MJ, Ratanatham S. Status of malaria in Thailand. Southeast Asian J Trop Med Public Health. 2000; 31:225–237. [PubMed: 11127318]
2. Luxemburger C, Kyaw Ley Thew, White NJ, Webster HK, Kyle DE, Maelankiri L, Chongsuphajaisiddhi T, Nosten F. The epidemiology of malaria in a Karen population on the western border of Thailand. Trans R Soc Trop Med Hyg. 1996; 90:105–111. [PubMed: 8761562]
3. Brockman A, Price RN, van Vugt M, Heppner DG, Walsh D, Sookto P, Wimonwattrawatee T, Looareesuwan S, White NJ, Nosten F. *Plasmodium falciparum* antimalarial drug susceptibility on the north-western border of Thailand during five years of extensive use of artesunate-mefloquine. Trans R Soc Trop Med Hyg. 2000; 94:537–544. [PubMed: 11132385]
4. Looareesuwan S, Olliaro P, White NJ, Chongsuphajaisiddhi T, Sabcharoen A, Thimasarn K, Nosten F, Singhasivanon P, Supavej S, Khusmith S, Wyling S, Kanyok T, Walsh D, Leggat PA, Doberstyn EB. Consensus recommendation on the treatment of malaria in Southeast Asia. Southeast Asian J Trop Med Public Health. 1998; 29:355–360. [PubMed: 9886127]
5. Tan-ariya P, Na-Bangchang K, Tin T, Limpaibul L, Brockelman CR, Karbwang J. Clinical response and susceptibility in vitro of *Plasmodium vivax* to the standard regimen of chloroquine in Thailand. Trans R Soc Trop Med Hyg. 1995; 89:426–429. [PubMed: 7570887]
6. Marlar-Tan, Myat-Phone-Kyaw, Aye-Yu-Soe, Khaing-Khaing-Gyi, Ma-Sabai, Myint-Oo. Development of resistance to chloroquine by *Plasmodium vivax* in Myanmar. Trans R Soc Trop Med Hyg. 1995; 89:307–308. [PubMed: 7660445]
7. Baird JK, Waidy I, Fryauff DJ, Sutanihardja MA, Leksnan B, Widjaya H, Kysdarmanto, Subianto B. *In vivo* resistance to chloroquine by *Plasmodium vivax* and *Plasmodium falciparum* at Nibire, Irian Jaya, Indonesia. Am J Trop Med Hyg. 1997; 56:627–631. [PubMed: 9230793]
8. Looareesuwan S, Wilairatana P, Glanarongran R, Indravijit KA, Supeeranontha L, Chinnapha S, Scott TR, Chulay JD. Atovaquone and proguanil hydrochloride followed by primaquine for treatment of *Plasmodium vivax* malaria in Thailand. Trans R Soc Trop Med Hyg. 1999; 93:637–640. [PubMed: 10717754]
9. Looareesuwan S, Buchachart K, Wilairatana P, Chalermrut K, Rattanapong Y, Amradee S, Siripipat S, Chullawichit S, Thimasan K, Ittiverakul M, Triampon A, Walsh DS. Primaquine-tolerant vivax malaria in Thailand. Ann Trop Med Parasitol. 1997; 91:939–943. [PubMed: 9579214]
10. Luxemburger C, Nosten F, Kyle DE, Kiricharoen L, Chongsuphajaisiddhi T, White NJ. Clinical features cannot predict a diagnosis of malaria or differentiate the infecting species in children living in an area of low transmission. Trans R Soc Trop Med Hyg. 1998; 92:45–49. [PubMed: 9692150]
11. Mason DP, Krudsood S, Wilairatana P, Viriyavejakul P, Silachamroon U, Chokejindachai W, Singhasivanon P, Supavej S, McKenzie FE, Looareesuwan S. Can treatment of *P. vivax* lead to a

unexpected appearance of falciparum malaria? Southeast Asian J Trop Med Public Health. 2001; 32:57–63. [PubMed: 11485096]

12. Looareesuwan S, White NJ, Chittamas S, Bunnag D, Harinasuta T. High rate of *Plasmodium vivax* relapse following treatment of falciparum malaria in Thailand. Lancet ii. 1987:1052–1054.
13. Krudsood S, Chokejindachai W, Silachamroon U, Phumratanaprapin W, Virayavejakul P, Bussaratid V, Looareesuwan S. Clinical malaria and treatment of multidrug resistance falciparum in Thailand. Jpn J Trop Med Hyg. 1999; 27:181–188.
14. Mayxay M, Pukrittayakamee S, Chotivanich K, Imwong M, Looareesuwan S, White NJ. Identification of cryptic coinfection with *Plasmodium falciparum* in patients presenting with vivax malaria. Am J Trop Med Hyg. 2001; 65:588–592. [PubMed: 11716119]
15. Pukrittayakamee S, Chantra A, Simpson JA, Vanijanonta S, Clemens R, Looareesuwan S, White NJ. Therapeutic responses to different antimalarial drugs in vivax malaria. Antimicrob Agents Chemother. 2000; 44:1680–1685. [PubMed: 10817728]
16. Baird JK, Wiady I, Sutanihardija A, Suradi, Purnomo, Basri H, Sekartuti, Ayomi E, Fryauff DJ, Hoffman SL. Short report: therapeutic efficacy of chloroquine combined with primaquine against *Plasmodium falciparum* in northeastern Papua, Indonesia. Am J Trop Med Hyg. 2002; 66:659–660. [PubMed: 12224570]
17. Nuchprayoon I, Sanpavat S, Nuchprayoon S. Glucose-6-phosphate dehydrogenase (G6PD) mutations in Thailand: G6PD Viangchan (871G>A) is the most common deficiency variant in the Thai population. Hum Mutat. 2002; 19:185. [PubMed: 11793482]
18. Buchachart K, Krudsood S, Singhasivanon P, Treeprasertsuk S, Phophak N, Srivilairit S, Chalermrut K, Rattanapong Y, Supeeranuntha L, Wilairatana P, Brittenham G, Looareesuwan S. Effect of primaquine standard dose (15 mg/day for 14 days) in the treatment of vivax malaria patients in Thailand. Southeast Asian J Trop Med Public Health. 2001; 32:720–726. [PubMed: 12041544]
19. McIntosh HM, Olliaro P. Treatment of uncomplicated malaria with artemisinin derivatives. A systematic review of randomised controlled trial. Med Trop (Mars). 1998; 58 suppl 3:57–58. [PubMed: 10212900]

TABLE 1

Demographic, clinical, and laboratory pretreatment data*

	Group A5	Group A7	Group A5 + P	Group A7 + P
Number	206	201	196	198
Sex (male/female)	148/58	139/62	135/61	136/62
Mean age in years (SD)	25.8 (9.1)	26.3 (10.4)	26.1 (9.6)	26.5 (9.6)
Fever				
Mean duration in days (SD)	5.4 (5.3)	5.2 (4.8)	5.1 (6.0)	5.4 (9.9)
Mean highest temperature in °C (SD)	38.6 (1.0)	38.5 (2.4)	38.6 (0.9)	38.6 (2.2)
Percentage of patients with				
First attack	45.7	46.1	50.0	43.5
Hepatomegaly	22.3	15.4	15.9	13.6
Splenomegaly	11.7	7.0	11.3	9.6
Geometric mean parasite count (/μL)	6,089	6,096	4,925	5,903
Baseline laboratory data, mean (SD)				
Hemoglobin (g%)	12.2 (2.2)	12.1 (2.2)	12.2 (2.3)	12.0 (2.1)
WBC count (/μL)	6,035 (1,878)	6,026 (2,001)	5,967 (1,771)	5,782 (1,902)
BUN (mg%)	14.9 (6.4)	16.1 (9.2)	14.5 (6.0)	15.1 (5.3)
Creatinine (mg%)	0.95 (0.18)	0.98 (0.25)	0.96 (0.21)	0.95 (0.16)
Total bilirubin (mg%)	1.62 (1.05)	1.56 (1.09)	1.44 (0.85)	1.68 (1.08)
AST (IU/L)	34 (23)	39 (53)	38 (32)	38 (36)
ALT (IU/L)	37 (38)	40 (65)	45 (74)	39 (47)
Albumin (g%)	3.96 (0.47)	3.92 (0.58)	3.98 (0.47)	4.00 (0.43)
Number of patients with G6PD deficiency	14	12	6	12

*WBC = white blood cell; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; G6PD = glucose-6-phosphate dehydrogenase.

TABLE 2

Therapeutic responses

	Group A5	Group A7	Group A5 + P	Group A7 + P
No. of patients completing 28 days follow-up	157	159	142	157
No. of patients discharged before 28 days follow-up	49	42	54	41
Cure rate at 28 days (%)	47.8	52.2	100.0*	100.0*
Failure rate during 28 days (%)	52.2	47.8	0.0	0.0
Fever clearance time, hours, mean (SD)	21.1 (20.5)	21.7 (19.2)	23.6 (24.4)	21.6 (19.3)
Parasite clearance time, hours, mean (SD)	39.3 (9.4)	39.6 (11.7)	37.7 (10.1)	38.8 (9.5)

* $P < 0.0001$.