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ARTESUNATE VERSUS ARTEMETHER FOR THE TREATMENT OF RECRUDESCENT MULTIDRUG-RESISTANT FALCIPARUM MALARIA

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Abstract. The therapeutic efficacy and toxicity of artesunate (2mg/kg/day for five days, then 1 mg/kg/day for two days: total = 12 mg/kg) was compared with that of artemether (4 mg/kg followed by 2 mg/kg/day for two days, then 1 mg/kg/day for four days: total = 12 mg/kg) for the treatment of recrudescent multidrug-resistant falciparum malaria in an open randomized trial in 443 patients living on the western border of Thailand. Parasite and fever clearance times were similar in both groups; within 48 hr 94% (95% confidence interval [CI] = 91–96%]) of the treated patients were aparasitemic and 93% (95% CI = 89–96%) were afebrile. Symptom resolution and resolution of hepatomegaly were slightly slower in the artesunate group; adjusted hazards ratio = 1.5 (95% CI = 1–2.0, $P < 0.01$) and 2.2 (95% CI = 1.4–8, $P = 0.04$), respectively. There was no significant difference in times to resolution or development of anemia or splenomegaly between treatment groups. By day 28, 3% (95% CI = 0.3–5%) of the patients treated with artesunate and 6% of those treated with artemether (95% CI = 2–9%) had recurrent infections ($P = 0.3$). Both regimens were very well tolerated, with no significant adverse effects attributable to either derivative. Overall, these data suggest that the two oral artemisinin derivatives are safe, highly effective, and result in equivalent therapeutic responses in the treatment of drug-resistant falciparum malaria.

On the western border of Thailand, *Plasmodium falciparum* has developed resistance to nearly all the available antimalarial drugs. Mefloquine has been the treatment of choice for uncomplicated falciparum malaria in this region since 1985, but nearly 50% of the patients now fail with high dose (25mg/kg) mefloquine when given alone.[1] These recrudescent infections have a higher failure rate when retreated with mefloquine again, and constitute the reservoir and driving force for drug resistance.[2]

The artemisinin derivatives are the most potent antimalarial compounds available for human use.[3] They have excellent efficacy against multidrug-resistant strains of *P. falciparum* and they are very well tolerated. Although more than a million people have now been treated with artemisinin, or one of its derivatives, there is still no consensus concerning the most appropriate dose, treatment regimen, or choice of derivative. The antimalarial efficacy of oral artesunate in uncomplicated malaria appears to be a function of the duration of therapy.[4,5] Recrudescence rates are unacceptably high in patients given less than five days of treatment. Combined treatment with mefloquine improves efficacy and allows shorter courses of artesunate to be given.[6,7] Since 1994, a combination regimen (MAS3) of mefloquine (25 mg/kg) plus a three-day course of artesunate (12 mg/kg) has become the treatment of choice for uncomplicated falciparum malaria in this area.[1] The recrudescence rate by day 63 with this treatment is less than 10%,[8] but patients whose infections do recur are symptomatic and their management poses a difficult problem. Re-treatment with mefloquine again increases the risk of severe neuropsychiatric reactions.[9] The combination of quinine and tetracycline over a seven-day period provides an alternative that remains $\geq$ 80% effective,[10] but compliance is poor, and tetracycline cannot be given to young children and pregnant women (who comprise a significant proportion of treatment failures). Although oral artesunate is the most widely used of the artemisinin derivatives, an oral formulation of artemether is also available.[3] There has been no previous large comparison of the two derivatives alone to establish their relative merits. We report a large study comparing seven-day courses of artesunate and artemether (total dose of 12 mg/kg) in patients with recrudescent, uncomplicated, multidrug-resistant falciparum malaria.

METHODS

Study site. This trial was conducted from July 1993 to August 1995 in Shoklo, a camp for displaced persons of the Karen ethnic minority. Due to security problems, the study site was transferred to Maela (a larger camp 60 km from Shoklo) in September 1995. Both camps are situated along the Thai-Burmese border in areas of seasonal low transmission malaria where approximately 50% of infections are caused by *P. falciparum*. Further details on the epidemiology of malaria in Shoklo have been reported elsewhere.[11] Standard treatment of primary *P. falciparum* infection in this area was mefloquine (25 mg base/kg) until mid 1994, and thereafter mefloquine (25 mg/kg) plus artesunate, 4 mg/kg/day for three days.

Patients. Patients with slide-confirmed falciparum malaria recurring within 63 days of a previously documented case of falciparum malaria were enrolled in the study if they or their parents gave informed consent. Pregnant women, children weighing < 5 kg, and patients with signs of severity or concomitant disease requiring hospital admission were all excluded. The study was approved by the Ethical Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, and by the Karen Refugee Committee, Mae Sot, Thailand.

Study procedures. On admission a questionnaire was completed recording details of symptoms and their duration, and the history of previous antimalarial medication (since health structures in the camp are the only source of anti-

malarial drugs in this area, the history is a reliable guide to pretreatment). Patients were categorized as being symptomatic if they were febrile or reported one of the following: headache, feeling ill, nausea, vomiting, muscle pain, or joint pain. A full clinical examination was done and blood was taken for parasite count, hematocrit, and white blood cell count. Parasite counts were determined on Giemsa-stained thick films and recorded as the number of parasites per 500 white blood cells. Patients were examined daily thereafter until they became aparasitemic and then seen weekly for nine weeks. Patients who failed to attend were traced by a home visitor. At each clinic appointment, a full physical examination was performed, the symptom questionnaire was completed and, at the weekly visits, blood was taken for hematocrit and parasite count. A brief neurologic examination was also performed at baseline and then at each weekly clinic visit. This included tests for coordination (heel-toe ataxia), fine finger dexterity (ability to pick up a tablet), hearing (using a 256-Hz tuning fork), as well as an assessment for nystagmus and balance (standing with feet together). Blood for malaria parasite cultures was taken on admission in a random selection of 32 patients, and *in vitro* antimalarial drug sensitivity profiles were determined on the freshly cultured isolates using the ^{3}H-hypoxanthine uptake inhibition method.[12]

Antimalarial drug regimens. Patients were allocated at random to receive either 1) As7: oral artesunate (Guilin No. 1 Factory, Guangxi, People's Republic of China), 2 mg/kg/day once a day for five days followed by 1 mg/kg/day once a day for two days (total dose = 12 mg/kg corresponding to 31.4 nmol/kg), and 2) Am7: oral artemether (Kunming Pharmaceutical Factory, Kunming, People's Republic of China), 4 mg/kg on the first day, followed by 2 mg/kg/day once a day for two days and then 1 mg/kg/day once a day for four days (total dose = 12 mg/kg corresponding to 40.3 nmol/kg).

Children weighing $<$ 20 kg received the exact weight adjusted dosage as crushed tablets mixed with water and given immediately by spoon or with a syringe. Patients above this weight received the weight-adjusted dose to the nearest quarter tablet. Drug administration was observed in all cases and, if vomiting occurred in less than 30 min, drug administration with the full dose was repeated. If vomiting occurred between 30 and 60 min, half the dose was repeated. No retreatment was given for vomiting after 60 min.

Recrudescent infections. A blood smear was taken from any patient complaining of fever or illness during the follow-up. A treatment failure was defined as the presence of *P. falciparum* on the blood smear between days 7 and 63 of follow up. These patients were retreated with a standard seven-day course of quinine (10 mg of salt/kg three times a day) and tetracycline (4 mg/kg/ four times each day) if they were more than eight years of age, or with seven days of artesunate alone (total dose = 12 mg/kg) if they were $\leq$ eight years old. Patients recrudescing again following retreatment were treated with artesunate (total dose = 12 mg/kg) to which tetracycline was added if the patient was more than eight years of age.

Adjusting for reinfections. Since the study was conducted in an area of malaria transmission, recrudescences could not be distinguished reliably from reinfections. The proportion of new infections should have been the same in both treatment groups and does not therefore preclude comparison of failure rates. Further information was available from an epidemiologic survey conducted simultaneously, but only in the first year of study in Shoklo camp, and was not available for the second phase of the study in Maela. Although blood samples for parasite genotyping were not collected routinely on admission and at the time of recrudescence when the study was started, paired blood samples were available in 10 cases of apparent recrudescence (from blood taken for parasite culture). These were analyzed by polymerase chain reaction genotyping using primers for merozoite surface proteins-1 and -2 and glutamate-rich protein as described previously to investigate the proportion of treatment failures attributable to true recrudescence.[13]

Statistical analysis. Data were analyzed using SPSS for Windows (SPSS Software, Gorinchem, The Netherlands). Categorical data were compared by calculating the chi-square value with Yates' correction or by Fisher's exact test. Normally distributed continuous data were compared by the Student's *t*-test and analysis of variance. Data not conforming to a normal distribution were compared by the Mann-Whitney U test or Kruskal-Wallis analysis of variance.

Parasite, fever, and symptom clearance times and the resolution of other signs (anemia [hematocrit $<$ 30%], hepatomegaly, splenomegaly), and the risk of treatment failure were all evaluated by survival analysis with cumulative incidences calculated by the product limit method and compared by the Mantel-Haenszel log rank test. Cox regression analysis was used to determine the contribution of different variables to recovery.

RESULTS

Between July 1993 and June 1996, 443 patients with acute uncomplicated falciparum malaria that had failed treatment (i.e., recrudesced following primary treatment within the previous 63 days) were enrolled into the trial. Thirty-two patients were excluded from the study: two patients in the As7 group were excluded because they had not received malaria treatment in the preceding 63 days (i.e., they were primary and not recrudescent infections), and two patients in the Am7 group were excluded because their admission slides contained *P. vivax* and not *P. falciparum.* An additional 28 patients (7%) were excluded for failing to complete a full course of treatment (15 in the As7 group and 13 in the Am7 group). Poor compliance was more likely in males compared with females (relative risk [RR] = 2.4, 95% confidence interval [CI] = 1.1–5.7, $P = 0.04$). The median (range) total doses administered were 425 (72–800) mg in the artesunate group and 400 (72–720) mg in the artemether group ($P = 0.7$). This corresponds to 1.11 (0.1–2.09) versus 1.34 (0.24–2.42) mmol, respectively ($P < 0.001$).

Although the baseline characteristics and *in vitro* drug sensitivity profiles were similar for both treatment groups and both camps (Tables 1 and 2), 59% (123 of 207) of the patients in the artesunate group had received treatment for their primary infection within the preceding 28 days compared with only 48% (97 of 204) in the artemether group ($P = 0.02$). Recrudescences following mefloquine can occur up to 63 days following treatment, but new infections may also

TABLE 1
Admission variables of patients

	Treatment group*	
	AS7	AM7
No. of subjects enrolled	207	204
Males	107 (52%)	112 (55%)
Age (years)		
Median (range) in years	15 (0.3–66)	15 (0.6–58)
<5	37 (18%)	32 (16%)
5–14	66 (32%)	69 (34%)
>14	104 (50%)	103 (51%)
Weight (kg)	36 (6–68)	32 (5–60)
Camp		
Shoklo	183	180
Maela	24	24
Temperature (°C)		
Mean (SD)	37.8 (1.1)	37.8 (1.1)
≥38°C	118 (57%)	111 (55%)
Hematocrit (%)		
Mean (SD)	33.0 (6.0)	33.3 (5.8)
Hematocrit <30%	60 (32%)	51 (27%)
Geometric mean (range) parasite count/μl	5,341 (30–252,000)	4,548 (24–208,000)
Previous treatment		
Mefloquine	93	85
Mefloquine + three days of artesunate	82	84
Quinine	20	26
Artesunate or Artemether	12	9
Time since last treatment		
Median (range) days	27 (3–67)	29 (3–68)†

* AS7 = oral artesunate, 2 mg/kg/day once a day for five days followed by 1 mg/kg/day once a day for two days. AM7 = oral artemether, 4 mg/kg on the first day, followed by 2 mg/kg/day once a day for two days, then 1 mg/kg/day once a day for four days.
† $P = 0.03$.

occur. However, new second infections rarely occur within 28 days of receiving a therapeutic dose of mefloquine in this area. Thus, 220 of the patients had definite recrudescent infections at enrollment, and in the remaining 223 a new second infection was possible. Twenty-eight (6.8%) patients had failed two or more treatment courses prior to enrollment (12 in the artesunate group and 16 in the artemether group). There was no significant difference between treatment groups in compliance with follow-up.

Clinical and parasitologic responses. Parasite and fever clearance times were almost identical following treatment with As7 or Am7 (Table 3). After 48 hr, 346 (94%) of 370 patients had cleared their initial parasitemia and 184 (93%) of 198 were afebrile. However, symptom clearance time was significantly longer in the As7 group; 42% (64 of 151) were asymptomatic by day 2 compared with 61% (86 of 142) in the Am7 group (RR = 1.4, 95% CI = 1.1–1.8, $P < 0.01$). Two independent risk factors were found to delay symptom clearance: an age < 5 years (adjusted hazards ratio [AHR] = 2.1, 95% CI = 1.6–2.8, $P < 0.001$) and a parasite count on admission greater than 10,000/μl (AHR = 1.5, 95% CI = 1.1–2.1, $P = 0.008$). After adjusting for these factors, the AHR for delayed symptom clearance time in the As7 group was 1.5 (95% CI = 1.2–2.0, $P = 0.01$).

The mean time for the resolution of admission anemia in the 111 patients (30%) with anemia (hematocrit < 30%) on presentation was 21 days (95% CI = 15–26) in the As7 group and 14 days (95% CI = 11–18) in the Am7 group ($P = 0.07$). Two patients (one in each group) required a blood transfusion. Of the 267 patients without anemia on admission, 21% (17 of 83) of the patients in the As7 group subsequently developed anemia in the first two weeks of follow-up compared with 12% (11 of 89) in the Am7 group ($P = 0.15$).

Hepatomegaly was present in 18% (36 of 205) of the As7 group and 16% (33 of 202) of the Am7 group on admission. The time to resolution of hepatomegaly was significantly faster in the Am7 group with an AHR of 2.2 (95% CI =

TABLE 2
In vitro drug sensitivity profiles (ng/ml) of 32 parasite isolates collected on admission*

	Chloroquine	Quinine	Mefloquine	Halofantrine	Dihydroartemsinin
Median IC_{50} (range)	102 (59–317)	480 (6–1,108)	61 (8–169)	14 (3-59)	1.3 (0.26–7.7)

* IC_{50} = 50% inhibitory concentration.

TABLE 3
Treatment response

	Treatment group*	
	(AS7)	(AM7)
Compliance		
Completed day 7	205 (99%)	200 (98%)
Completed day 28	172 (83%)	166 (81%)
Completed day 42	151 (73%)	151 (74%)
Completed day 63	115 (55%)	119 (58%)
Clearance times†		
Parasite–days	1.7 (1.6–1.8)	1.64 (1.6–1.7)
Fever–days	1.6 (1.4–1.8)	1.4 (1.3–1.6)
Symptom–days	3.9 (3.5–4.4)	3.1 (2.7–3.5)‡
Resolution of anemia–days	21 (15–26)	14 (11–18)
Resolution of splenomegaly–days	38 (26–50)	21 (16–26)
Resolution of hepatomegaly–days	40 (30–51)	22 (15–30)§
Overall cumulative proportion of patients with recurrent infections (%)¶		
Day 7	0%	0%
Day 28	5% (2–8)	8% (4–12)
Day 42	14% (8–19)	16% (11–23)
Day 63	27% (19–35)	31% (23–39)

* For definitions of treatment group, see Table 1.
† Mean (95% confidence intervals); derived from group survival tables, in those with parameter present on admission.
‡ $P < 0.01$.
§ $P = 0.04$.
¶ % (95% confidence intervals). These comprise reinfections and recrudescences.

1.01–4.8, $P = 0.04$) (Table 3). There was no significant difference in the times to resolution of a palpable spleen ($P = 0.1$).

Failure rates. There was no significant difference in the failure rates between the As7 or Am7 groups (Table 3). The cumulative crude failure rates (not adjusted for reinfections) assessed at day 28 were 4.6% (8 of 172) for the As7 group and 7.8% (13 of 166) for the Am7 group ($P > 0.2$). Overall, the median time to recurrence of infection was 39 days (range = 14–66 days). After correcting for background reinfections in the 363 patients from Shoklo camp, where concurrent malaria incidence data were available, the overall adjusted failure rates were 4% (95% CI = 2–7) by day 28, 11% (95% CI = 8–15) by day 42, and 22% (95% CI = 17–28) by day 63. Adults (age greater than 14 years) were at greater risk of recurrent infection, but only after day 42 (RR = 2.0, 95% CI = 1.2–3.3, $P < 0.01$).

Genotyping of the primary and recrudescent infections was only possible in 10 cases. In these the median time to recurrence of the infection was 35 days (range = 19–63 days). True recrudescence was found to have occurred in only one case, a patient treated with As7 who failed at day 19.

Since patients treated with artesunate were 1.3 (95% CI = 1.04–1.5)-fold more likely to have received prior treatment within the previous 28 days ($P = 0.02$), i.e., they were more likely to be true recrudescences, a *post hoc* analysis was carried out on the 220 patients who had recrudesced within 28 days. Compared with the remainder (i.e., those patients with infections that recrudesced later), these patients with definite recrudescences were more likely to be less than 5 years of age (RR = 2.1, 95% CI = 1.3–3.5, $P = 0.02$), to be anemic on presentation (RR = 1.7, 95% CI = 1.2–2.3, $P = 0.003$), to have a palpable spleen (RR = 1.6, 95% CI = 1.04–2.3, $P = 0.04$), and have lower parasite counts (geometric mean = 3,877/μl [95% CI = 4,037–6,024] versus 6,490/μl [95% CI = 4,852–8,680], respectively, $P = 0.01$). There was no significant difference in any of the baseline parameters between the 123 patients in the As7 group and the 97 in the Am7 group. Patients in the Am7 group were more likely to have a second recrudescence during subsequent follow-up (RR = 1.1, 95% CI = 1.0–1.2, $P = 0.05$) but were quicker to recover from anemia (12 days [95% CI= 9–16] versus 23 days [95% CI = 16–30], $P = 0.02$), hepatomegaly (20 days [95% CI = 13–28] versus 40 days [95% CI = 29–52], $P = 0.03$), and splenomegaly (18 days [95% CI = 12–24] versus 45 days [95% CI = 32–58], $P = 0.04$). There was no difference in the parasite, fever, or symptom clearance times.

Re-treatment. Of the 68 patients who experienced an additional recrudescent or recurrent infection, 32 were re-treated with a seven-day regimen of quinine and tetracycline (Q7T7) (of whom nine failed again), three with quinine alone (of whom one failed again), 10 with a repeat course of artesunate (As7) (of whom 3 failed again), six with a seven-day regimen of artesunate and tetracycline (As7T7) (of whom two failed again) and one with mefloquine plus three days of artesunate (this patient failed again). Sixteen could not be followed in the course of their re-treatment.

Of the 16 patients who failed re-treatment, seven received As7T7 (one failed again, but was retreated successfully with the same regimen), six were re-treated with a As7 (of whom two failed again to be successfully treated with As7T7), one patient was successfully re-treated with Q7T7, and two were successfully treated with mefloquine plus seven days of artesunate.

Adverse effects. Seven (0.2%) of the 2,877 doses of artesunate and artemether administered were vomited within 1 hr (four artesunate and three artemether). Vomiting occurred in 0.7% (3 of 3,411) of the patients on the day of admission compared with 0.2% (4 of 2,466) on the subsequent days ($P = 0.06$).

Minor adverse effects attributable to the drug regimen were estimated from those patients in whom the symptom was absent on admission, but developed during follow-up. By day 7 when the patients completed their course of treatment, all had made a symptomatic recovery from the acute malaria. At this time, there was no significant difference between treatment groups in the incidence of dizziness (3%, 4 of 129), diarrhea (0.3%, 1 of 349), nausea or vomiting (3%, 5 of 183), anorexia (5%, 6 of 126), and rash or itching (2%, 6 of 296). These figures were not significantly different from the incidence of complaints reported at day 28 or day 63, suggesting that the symptoms were not attributable to the administration of the qinghaosu derivatives.

During the course of drug administration (days 1–6), there were nine reported cases of balance disturbance (seven patients were unable to stand with their feet together and two were unable to walk heel to toe). Two patients reported hearing loss, but this was present prior to receiving any medication; one recovered by day 3 and in the other, hearing loss was reported throughout follow-up. From day 7 onwards there was no report of neurologic adverse effects.

Two patients in the As7 group died. One of these patients, a 17-year-old man, had had a three-month history of swollen ankles, and peripheral paresthesia. He was seen on day 14 of follow-up and was apparently well, but two days later had a sudden onset of dyspnea and palpitations while digging in the forest. A post-mortem diagnosis of probable adult beriberi was made. The other patient was a 35-year-old woman who made a rapid and uneventful recovery from her malaria and was followed until day 35 of follow-up with no adverse sequelae. She was reported as having returned to Burma and died two weeks later. No further details were available.

DISCUSSION

The artemisinin derivatives are being used increasingly in the treatment of drug-resistant malaria in Southeast Asia. Drug resistance has increased alarmingly in this area of the world over the past two decades.[14] The artemisinin derivatives have proved effective against *P. falciparum* resistant to mefloquine, and now, in combination with mefloquine, have become the treatment of choice for falciparum malaria in these drug-resistant areas. We have shown recently that there is no significant difference between artemether and artesunate when combined with mefloquine for the treatment of primary infections with multi-drug resistant *P. falciparum.*[1] In the present study, we have compared the efficacy of artesunate and artemether in the treatment of patients with recrudescent infections, a group with a particularly high failure rate. Mefloquine was not used, so this is the first large comparison of efficacy of the two artemisinin derivatives used alone.

The therapeutic response to the two drugs was similar. Both were well tolerated and cleared fever, symptoms of disease, and peripheral parasitemia rapidly. Although fever and parasite clearance rates were identical in the two large and well-matched groups, there was a difference in the rates of symptom resolution and the speed with which hepatomegaly resolved. Artesunate was slightly slower in this regard than artemether. This is may be attributable to the differences in the dose regimens. Artemether recipients received 4 mg/kg in the first 24 hr compared with 2 mg/kg in the artesunate group, and in $>$ 90% of the patients, symptoms, signs, and parasitemia had resolved within two days. The maximum effect on parasite clearance with artesunate has been observed at a dose of 2 mg/kg (Angus BJ, White NJ, unpublished data), but these findings should be taken in context with the considerable interindividual variability in plasma concentration profiles following the oral administration of this drug.[15] Some patients receiving 2 mg/kg may therefore have had suboptimal (i.e., less than the minimum parasiticidal concentration) blood concentrations in the first day of treatment. Furthermore, artemether was give at a 28% higher dose in molar terms. Thus, the initial molar dose of artemether was 2.6 times greater than that of artesunate. Overall, these data suggest that the two drugs have equivalent antimalarial efficacy and that a higher dose of artesunate (4 mg/kg) on admission might facilitate a rapid early parasite reduction in some patients and a faster clinical response.

Recrudescent infections are generally more difficult than primary infections to treat. However, it is not possible to comment on the relative efficacy of the artemisinin derivatives because different drug regimens are used for primary and recrudescent infections.

In an area of malaria transmission, it is difficult to distinguish recrudescence of an infection (i.e., a treatment failure) from acquisition of a new infection. Previously, when assessing antimalarial efficacy in primary infections at this study site, we have subtracted population malaria incidence rates for the period of study from the observed recurrence rate to estimate the true recrudescence rate. After adjusting for reinfection in this way, estimated recrudescence rates increased from 4% on day 28 to 22% by day 63. Thus, 69% (47 of 68) of apparent failures occurred after day 28, which could be taken to suggest that delayed recrudescence is occurring with these regimens. This is at variance with previous experience, which indicates that most recrudescences following treatment with short-acting antimalarials occur within a month of treatment.[16] The finding that adults in this study were at greater risk of failure (although only after day 42) is also at variance with our previous studies, which have shown that children are generally more likely to fail their treatment.[8,17] An alternative and more likely explanation for these observations is that the true background reinfection rate assessed from the remaining population in this study has been underestimated. Patients who have had falciparum malaria in the preceding 63 days represent a high-risk subgroup who are more likely to be reinfected than the general population from whom the survey data was gathered.[11] This increased risk is associated with travel outside the camp into the surrounding malarious forest for the purpose of work, and accounts also for the greater risk of recurrent infection in adults rather than children. This is supported by the parasite genotyping in 10 cases, which showed that only one of the true recurrences resulted from a true recrudescence. This occurred on day 19. The nine other apparent failures occurring after this time were reinfections. If all true failures are assumed to have occurred by day 28, then the overall cumulative failure rates would be nearer 4% rather than 22%.

The mean time to resolution of anemia was slower in the artesunate-treated patients. These drugs are known to suppress reticulocytosis, but in other studies this has not trans-

lated into anemia.[18] Further investigations will be needed to determine whether there are true differences in the hematologic response to these two closely related compounds.

Both artemether and artesunate were very well tolerated. All symptoms were attributable to malaria rather than to the drugs themselves. These two artemisinin derivatives are rapidly and reliably effective. Although combination therapy with mefloquine (or other antimalarials) would be preferable for first-line treatment, seven days of monotherapy is satisfactory for the treatment of recrudescent multidrug-resistant falciparum malaria.

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