CHAPTER IV

CLINICAL EFFICACY OF MONOTHERAPY OF HIGH DOSE DIHYDROARTEMISININ OR COMBINATION THERAPY OF HIGH DOSE DIHYDROARTEMISININ AND MEFLOQUINE IN VIETNAMESE PATIENTS WITH UNCOMPLICATED FALCIPARUM MALARIA

1. Introduction

Dihydroartemisinin (DHA) is a semi-synthetic derivative of artemisinin and has been used in clinical treatment of patients with falciparum malaria in many tropical countries in the world, especially those in the Asian region (WHO, 1995). DHA is considered as a potent antimalarial drug against *P. falciparum* parasites (de Vries and Dien TK, 1996). The expenditure for production of DHA is cheaper, compared to that of other artemisinin derivatives (Brossi *et al.*, 1988). This drug is therefore considered to be the most applicable for using in developing countries.

Artemisinin derivatives have been used clinically in two approaches, *i.e.*, monotherapy and combination therapy with other antimalarials (Davis *et al*, 2005). For monotherapeutic regimens, DHA has been used in treatment courses of 3 to 5 days. The radical cure rate of monotherapy with artesunate, artemether, and DHA were reported as high as 90% in some clinical trials (Looareesuwan *et al*, 1992, 1996; Karbwang *et al.*, 1998a; Schwarz *et al.*, 2005), but were as low as 80% or lesser in other reports (Hien and White, 1993; Alin *et al.*, 1995; Alin *et al.*, 1996; Borrmann *et al.*, 2003; Gomez *et al.*, 2003).

The artemisinin derivatives have short half-lives, *e.g.*, 40-60 minutes for DHA (Hien and White, 1993; Benakis *et al.*, 1997; Davis *et al.*, 2005). These drugs are rapidly excreted after administration. In addition, the decline of DHA concentrations in plasma during a 5-day oral treatment course with artesunate was reported in patients with acute uncomplicated falciparum malaria (Khanh *et al.*, 1999). Despite their short residence time in the body, continuous reduction in parasite

density in malaria patients treated with artemisinin derivatives was recorded. This may be explained by the "post-antiparasitic" activity of the artemisinin derivative drugs. In theory, the efficacy of DHA could therefore be enhanced by the increase of treatment dose or by the prolongation of treatment course, or both.

We conducted an open randomized comparative study of the high dose monotherapy of DHA and the combination of high dose DHA with mefloquine (MQ) for the treatment of acute uncomplicated falciparum malaria in Vietnamese patients.

2. Patients and methods

2.1 Patients

The study was conducted at Binh Thuan and Binh Phuoc Provinces in the south of Vietnam. Binh Thuan Province is an area composing of mountains and plain fields which is considered as the joining province between the central and the southern part of Vietnam. Some malaria endemic areas are located in this province in the new economic zones and in villages at the foot of mountain. Malaria season is generally during June and December. In this province, the study was conducted at 3 sites: Bac Binh District Hospital, and Mepu and Song Luy Village Health Care Centers. Binh Phuoc Province locates near the border between Vietnam and Cambodia. This area is specialized for development of rubber plantations and farms for black pepper cultivation. The study was conducted during January 2002 and July 2003 at the health care center of the 11^{th} rubber farm of the Phu Rieng rubber plantation company. The workers of the plantation and inhabitants living in surrounding areas often come to the health care center for malaria diagnosis whenever signs/symptoms of malaria appear. In both provinces, malaria is the main disease among infectious diseases, in which *P. falciparum* and *P. vivax* account for the same incidence rates.

The study protocol was reviewed and approved by the Ethics Committee of Cho Ray Hospital, Vietnam. Inclusion criteria included males or females aged at least 15 years with acute uncomplicated falciparum malaria with asexual parasitemia density between 1,000 - 200,000/μl, and with written informed consent for study

participation and completion of follow-up schedule. Exclusion criteria included patients with *P. vivax* or mixed infection with other *Plasmodia* species, pregnant women, women having babies in breast feeding period, patients with severe and complicated conditions, patients unable to take oral medication, those having allergic history with mefloquine or artemisinin derivatives, and those who had received artemisinin derivatives in previous 24 hours, or taking mefloquine, tetracycline, doxycycline in previous 7 days, or quinine in previous 12 hours.

Eligible patients were randomly assigned by randomization code to receive one of two antimalarial treatment regimens. The random codes were made based on the block of 4 with a ratio of 1:1 between the two treatments. Each code was put in a tightly closed separate envelop, with an ordinal number on the outside of envelop. The number of envelops were given to study sites as the multiple of block of 4. At each study site, patients were allocated to receive the randomized treatment codes, starting from the lowest ordinal number.

The sample size was calculated with the Epi-Info Program version 3.3.2. in order to get the clinically significant difference between the two regimens. This calculation of 86 cases (43 cases for each regimen) was based on the assumption that the recrudescence rate following treatment with DHA-MQ combination regimen (5%) was about 25% lower than that of the 5-day DHA monotherapy (30%). These recrudescence rates were based on the previous studies in the same study areas (Sy *et al.*, 1993; Bich *et al.*, 1996; Hung *et al.*, 1997; Hung, personal communication). With the strictly follow-up, the rate of drop-out cases was estimated to be 5%. Therefore, the final sample size was 90 cases, 45 cases for each regimen.

2.2 Treatment administration

The eligible patients were randomized to receive one of the two regimens as follows: (i) the 5 day-monotherapy regimen of DHA with a total dose of 900 mg divided as 300 mg daily in the first 2 days (0 h, 24 h) followed by 100 mg daily for the next 3 consecutive days (48 h, 72 h, and 96 h), or (ii) the DHA-MQ combination regimen given as 300 mg DHA at 0 h, followed by 300 mg DHA and 750 mg MQ at 24 h. If patients had vomiting within one hour after drug administration, a full dose of drug was repeated.

DHA capsules (100 mg/capsule) were kindly provided by Dr. F.H. Jansen of the Drafa-Pharma Pharmaceutical Company, Brussels. Mefloquine (Euphaquine®) tablets (250 mg/tablet) were kindly supported by Prof. Kesara Na-Bangchang, Pharmacology and Toxicology Unit, Faculty of Allied Health Sciences, Thammasat University, Thailand.

2.3 Clinical assessments

Patients had general physical examination for baseline data at enrollment. All clinical symptoms, *e.g.*, spleen enlargement, hepatomegaly, anemia, jaundice, nutritional status, as well as functional symptoms such as loss of appetite, fatigue, headache, nausea, tinnitus, were recorded as baseline signs/symptoms in the patient record forms (PRFs) of hospital or in the case report forms (CRFs) generated for the study. The progress of treatment as well as occurrence of adverse events was evaluated based on the comparison with corresponding baseline signs/symptoms. The axillary body temperature was recorded before drug administration and every 8 hours until 3 consecutive times of normal temperature ($\leq 37.5^{\circ}C$). Pulse and blood pressure were measured every 8 hours or twice *per* day. Patients underwent re-examination at least twice *per* day during the treatment time at the study sites. Patients were discharged from the hospital/health care centers only when they had completed the treatment and were well recovered from all signs/symptoms of malaria, with 3 consecutive negative blood smears with *P. falciparum*. All study drugs were given directly to patients by responsible physicians or nurses.

2.4 Laboratory assessments

At the health care center of the 11th Phu Rieng rubber farm, the facilities for hematology and biochemistry tests were not available. At the Mepu and Song Luy Health Care Centers, only hematology tests for red blood counts and white blood counts with cell differentiation were performed on day 0 (at enrollment time into the trial) and day 2. At Bac Binh Hospital, hematology (complete blood count) and biochemistry (transaminases, bilirubin, BUN, and albumin) tests were performed on days 0 and 2.

2.5 Parasitological assessments

The parasitemia were examined on blood smears taken from finger tips of patients. Blood smears were done on admission, then every 8 hours after the start of drug administration until 3 consecutive times of negative blood smears. Thereafter, blood smears were done daily until discharged. All blood smears were stained with Giemsa and examined by experienced laboratory technicians of the study sites. The parasites were count over 200 white blood cells in the thick blood smear. The parasitemia density was calculated based on the estimation of an average of 8,000 white blood cells *per* microliter of blood and expressed as number of parasites *per* microliter of blood. The presence of gametocytes in blood smear was qualitatively recorded as positive or negative. Blood examination was also performed during follow-up on days 7, 14, 21, and 28 for the 5-day DHA monotherapy and additionally on days 35, and 42 for patients in the DHA-MQ combination regimen. All blood smears were retained and re-checked by expert microscopists of the Malaria Division of Ho Chi Minh City. The results obtained from these experts are considered as standard values. If there were discrepancies in parasite density between technicians of the study sites and the experts of Malaria Division of Ho Chi Minh City, the data from the reviewing experts were accepted for analysis.

2.6 Patients' follow-up

Patients were discharged after treatment completion and having the initial clinical cure. All patients were requested to come back to the health facilities for blood examination and assessment of clinical signs/symptoms of malaria on days 7, 14, 21, and 28 for the DHA monotherapy group and for an additional 2 weeks on days 35, and 42 for the DHA-MQ combination group. At each visit, patients had a general physical examination and blood smears taken for parasitemia inspection.

2.7 Evaluation of treatment outcomes

Initial clinical cure was defined as the combination of the parasite clearance, the defeverescence, and the complete absence of clinical symptoms of malaria. The fever clearance time (FCT) is defined as the time from the beginning of treatment until the first time of three consecutive normal temperature records ($\leq$ 37.5°C). The

parasite clearance time (PCT) is defined as the time from the beginning of treatment until the first time of three consecutive negative blood smears for *P. falciparum* parasite. The radical cure or sensitive response of either treatment regimen was defined as an initial negative parasitemia by day 7 without any recrudescence up to day 28 for the 5-day DHA monotherapy or day 42 for the DHA-MQ combination regimen. The early RI (grade I resistance) response was defined as an initial negative parasitemia with reappearance of parasite before or on day 14; the late RI response was defined when the parasitemia reappeared after day 14. The RII (grade II resistance) response was defined as parasite density reduced by at least 75% (or less than 25% of the initial parasitaemia sustained) by 48 hours after treatment, then resurgence, without parasite clearance by day 7. The RIII (grade III resistance) response was defined as absence of clinical response or parasite density reduced by less than 75% of an initial value by 48 hours without clearance by day 7 (WHO, 1973).

2.8 Adverse effects

Clinical and laboratory adverse effects were recorded in relation to treatment administration by comparing adverse events with causality 'likely' to that of the baseline signs/symptoms of malaria, as well as any change in laboratory values.

2.9 Data management and analysis

At Bac Binh Hospital, the main source documents were the PRFs including all laboratory records. The source data of patients in the PRFs were transcribed carefully by the study physicians to the CRFs. Some data such as temperatures, blood pressures, and parasitemia densities were directly recorded into the CRFs.

In the health care centers where there were no PRFs, the patient administrating books were used as source documents. The patients' data entering included the ordinal numbers of patient admitted, date of admission, gender, age, address, results of malaria parasite, treatments given, and date of discharge. The CRFs were also used as source documents for other data, *i.e.*, patient history, drug treatment monitoring, clinical/laboratory findings, fever monitoring chart, parasitemia follow-up table, *etc.* The heads of the health care centers were responsible for filling data in the CRFs.

The data were analyzed with the Epi-Info Program version 3.3.2. The Kolmogorov-Smirnov test was used to specify the distribution of the quantitative data such as age, weight, height, parasite density, fever clearance time, parasite clearance time, *etc.* in the two treatment regimens. Normally distributed data were presented as means and standard deviations (SD), and comparison of difference between the two groups was performed using student's *t* test. The qualitative data, *e.g.*, proportion of gender, radical cure rate, recrudencence rate, of two treatment groups were compared using the Chi-Square test. Differences were considered statistically significant at the $p \leq 0.05$.

3. Results

3.1 Patient characteristics

A total of 91 patients were recruited into the trial; 2 patients were excluded from the final analysis (1 with mixed infection of *P. falciparum* and *P. vivax* parasites, and 1 with severe and complicated falciparum malaria). One patient in the DHA-MQ group had high but clinically non-significant values of transaminases (SGOT: 87 U/l and SGPT: 75 U/l), and bilirubin (6.4 mg/dl) on the day of hospital admission. A total of 89 patients were therefore recruited into the final analysis.

Forty-five patients (11 females and 34 males) were treated with a 5-day monotherapy with DHA and 44 patients (10 females and 34 males) with combination therapy with DHA-MQ. Forty-seven cases were admitted to the health care center of the 11th rubber farm, Phu Rieng Company in Binh Phuoc Province, and 42 cases were admitted to 3 health facilities in Binh Thuan Province. The mean age of patients was 29 years (29 ± 11, mean ± SD). Most of the patients had been staying for more than 1 year in malaria areas (95.5%). Thirty-four patients (77%) in each group came to the health facilities after 1 - 2 episodes of malaria.

There was no difference in clinical signs/symptoms of malaria between the two treatment groups (**Table 5**). **Table 6** presents results of the laboratory findings (hematology and biochemistry). There were three patients in the DHA-MQ regimen group with red blood cell counts below 3,500,000/µl. Three patients in each group

had white blood cell counts less than 5,000/μl. Only the levels of SGOT were found significantly different between the two groups. There was no significant difference in hematology and biochemistry values between the two patient groups.

3.2 Clinical responses

All patients had fast recovery from signs/symptoms of malaria within 1 - 3 days following treatment. The fever clearance times (FCT) for DHA monotherapy and DHA-MQ combination therapy were 23.3 ± 13.4 h and 26.2 ± 19.8 h (mean ± SD), respectively ($p > 0.05$). Fever clearance within 48 h after treatment was observed in more than 90% of the patients in both groups. No RII, RIII responses were found in all patients. The parasite clearance times (PCT) for DHA monotherapy and DHA-MQ combination therapy were 35.3 ± 17.4 h and 37.8 ± 19.2 h (mean ± SD), respectively ($p > 0.05$). There was no significant difference in PCT95% and PCT50% values between the two regimens (**Table 7**).

3.3 Parasitological response

Table 7 presents details of parasitological response between the two treatment regimens. There were 12 patients who had reappearance of parasitemia by day 28 in the 5-day DHA monotherapy regimen (26.7%) and 5 had reappearance of parasitemia by day 42 in the DHA-MQ combination regimen (11.4%) ($p = 0.07$). All recrudesced patients were treated with the current standard combination regimen of CV8 (DHA + piperaquine + primaquine + trimethoprim; 4 tablets on day 1 divided into 2 times and 2 tablets *per* day for the next two days) or the monotherapy regimen of artesunate for 7 days (4 mg/kg body weight on day 1 and 2 mg/kg body weight on the following days). The 28-day cure rate in the DHA-MQ combination group was significantly higher (43/44 cases, 97.7%) than that of the DHA-5 day monotherapy (34/45 cases, 75.6%) ($p = 0.003$). The survival analysis (**Figure 4**) of cure rate by time showed that the DHA-MQ combination had significantly higher cure rate compared to that of the 5-day DHA monotherapy ($p = 0.003$, Kaplan Meier analysis). When data were stratified by study site, there was no significant difference in cure rate between two regimens, except for the Phu Rieng Health Care Center, where the

combination regimen had significantly higher cure rate (91.7%) compared to that of the DHA monotherapy (60.8%), ($p = 0.012$).

4. Discussion

The study showed that DHA was well tolerated with no clinical significant adverse drug reaction. Fever and parasitemia were cleared within 3 days after treatment in almost all patients. The aim of this trial was to observe the high efficacy in radical cure rate of the 5-day DHA monotherapy when using with a high total dose of 900 mg. However, it was observed that the 28-day cure rate of 5-day DHA monotherapy was as low as 73.3%.

DHA was initially used as monotherapy in malaria treatment with low dose (*i.e.*, 240 mg) and short course (*i.e.*, 3 days) in 25 patients with the cure rate of as low as 52% (Li *et al.*, 1994). The cure rates were increased to 94% and 98% when the total doses were increased to 360 and 480 mg with the extension of the courses of treatment to 5 and 7 days in 50 and 205 Chinese patients with uncomplicated falciparum malaria, respectively (Li *et al.*, 1994). With the high dose of 600 mg DHA given over 5 days, the cure rates of 80 - 92% were achieved in Thai patients with acute uncomplicated falciparum malaria (Wilairatana *et al.*, 1998).

In Vietnam, the cure rate of DHA at 600 mg given over 5 days was 87.5% during the year 1997 - 1998 (Hung, personal communication). All of these data suggest that high doses of DHA may improve the cure rate and prevent the occurrence of drug resistance. In the present study, however, the concept of using high dose of DHA seems unsuccessful. This could be due to several reasons including (i) the inadequately high dose to give the good efficacy, (ii) the pharmacokinetic factors, *i.e.*, low bioavailability of oral DHA, or enzyme induction resulting in low plasma DHA concentration, and (iii) the resistance of *P. falciparum* parasite to DHA after a long time of clinical usage of artemisinin and derivatives in Vietnam (Giao *et al.*, 2001).

There were very few pharmaceutical formulations of oral DHA and their pharmacokinetic studies (Na-Bangchang *et al.*, 1997; Hung *et al.*, 1999). Up to now, there has been no bioequivalence study for the oral DHA formulations. The original Chinese oral DHA formulation Cotecxin®, which was by far the most widely used

formulation, provided a benchmark against which other formulation may be compared. The oral DHA formulation used in the present study was Arenco-nv® (Brussels). It seems that there was no difference in pharmacokinetic properties (with the same high-performance liquid chromatographic method with electrochemical detection) between two DHA formulations, Arenco-nv® (Brussels) and Cotecxin® (China), in Thai and Vietnamese healthy volunteers, respectively (Na-Bangchang *et al.*, 1997; Hung *et al.*, 1999). The t_{max} and $t_{1/2z}$ were approximately similar between two formulations, *i.e.*, around 1.5 and 2 h, respectively. The C_{max} and AUC of DHA were also comparable between Thai and Vietnamese healthy subjects. Thus, low absorption of the DHA formulation was not taken into account in the less treatment efficacy of DHA in the current study

The C_{max} of oral DHA formulation (Cotecxin®) at the dose of 60 mg and 240 mg in Vietnamese malaria patients were 490 ± 200 ng/ml and 862 (345-2,280) ng/ml, respectively (Benakis *et al.*, 1996; Hung, personal communication). With the assumption of the same bioequivalence between two formulations of DHA, Cotecxin® tablets and Arenco-nv® capsules, the C_{max} of oral DHA formulation (Arenco-nv®) at the dose of 300 mg on the first day of treatment in this trial could be estimated as equal as or higher than that in the two above trials. The maximum level of *in vitro* inhibition concentration (IC_{99}) of DHA was reported as 7.5 ng/ml (Wongsrichanalai *et al.*, 1997). The parasitemia was continuously declined even when DHA concentration was lower than the maximum *in vitro* IC_{99}. Thus, the minimum parasiticidal plasma concentration (MPC) of DHA could be lower than the maximum *in vitro* IC_{99} (White 1997). This matter leads to the concept of the presence of the post-antiparasitic effect (PAE) of DHA. In the field of antibiotic drugs, those having PAE are classified as concentration-dependent antibiotic activity. Such antibiotics, *i.e.*, gentamycin, amikacin, are required to give in high dose at less frequent dosing interval. In this trial, the higher dose of DHA was used, the higher C_{max} concentrations were expected to be achieved, but the radical cure rate was still low. The PAE may therefore be inadequate for DHA to achieve the optimal efficacy in treating malaria. The low efficacy of DHA monotherapy, even when the total dose was increased, indicates that artemisinin derivatives should not be used alone in treatment of *P. falciparum* malaria. The study showed that the cure rate of high dose (900 mg totally) DHA monotherapy in 5 days

was not superior to that of lower dose (600 mg totally) DHA monotherapy with the same time course. More rational dosing regimens for DHA in monotherapy approach are needed to improve treatment efficacy without adverse reactions.

The treatment duration was on the other hand an important factor that should be considered in order to kill all residual parasites that escaped from the PAE action of DHA. Shorter treatment courses are associated with higher recrudescence rates (Nguyen *et al.*, 1993; Sy *et al.*, 1993; Brian *et al.*, 2002). The artemisinins act very rapidly, reducing parasitemia by a factor of 10^4 with each cycle. Thus, for a parasite burden of 10^{12}, three cycles are required to abolish parasitemia. The artemisinins are rapidly eliminated, and daily administration for a period of six to seven days (three cycles) is needed (Baird, 2005; WHO, 1998). The results of some other studies, however, showed that extending the duration of treatment course with artemisinin alone may not be rational (Brian *et al.*, 2002; Giao *et al.*, 2001). Monotherapy with artemisinin and its derivatives initiate a very fast recovery but do not prevent recrudescence. The high recrudescence rate seen with artemisinin monotherapy is usually attributed to the short half-life of artemisinins, which is further shortened by the increased drug clearance that develop during repeat dosing and/or convalescence of malaria (Alin *et al.*, 1996; Hassan *et al.*, 1996a; Ashton *et al.*, 1998a,b,c; Khanh *et al.*, 1999; Newton *et al.*, 2000; Teja-Isavadharm *et al.*, 2001). Improvement in therapeutic effect of DHA might therefore be enhanced with dose increasing and/or time extending monotherapy regimen or with combination regimen.

There have been no reports of clinical resistance to the artemisinin drugs so far but the World Health Organization in 1997 reported the reduced susceptibility of falciparum parasites to artemisinin in Yunnan Province in China in border areas with Lao PDR and Myanmar, due to the migration and the self-treatment increase in this area (WHO, 1997). All risk factors contributed to the emergence of resistance to other antimalarial drugs may also play some role in the emergence of artemisinin resistance. In this trial, the clinical efficacy of DHA used alone was lower than that reported in previous studies (Sy *et al.*, 1993; Hung *et al.*, 1997; Hung, personal communication; Giao *et al.*, 2001). This may suggest the need to follow up the emergence of artemisinin resistance of *P. falciparum* parasites in Vietnam.

To prevent the development of drug resistance, the combination regimens of artemisinin derivatives with other long-acting antimalarials, such as mefloquine, are recommended. DHA can rapidly reduce parasite density to very low level at a time when drug level of MQ is still maximal. This greatly reduces the parasites surviving initial treatment, the exposure to suboptimal level of the longer acting drug, the gametocytogenesis, the transmission rate, and the drug resistance. The treatment efficacy could therefore be improved. The present study showed that the cure rate of DHA-MQ combination regimen with high dose DHA in a 2-day treatment course was comparable to that achieved a long time ago in Vietnam (Hung *et al.*, 1997). Additionally, no adverse events were found even with high dose of DHA.

5. Conclusion

The aims of treatment in uncomplicated falciparum malaria are to cut short the morbidity of an acute episode of illness and to clear the infection entirely so that it does not recur, with a minimum of adverse effects. Combination therapy with drugs with different modes of action is the preferred approach to malaria treatment to inhibit the emergence and spread of parasite resistance to each component of the combination. In Vietnam, mefloquine is used as the first choice in combination with artemisinins for treatment of confirmed falciparum malaria (Sy *et al.*, 1993; Hung *et al.*, 1997; Peter *et al.*, 2000). DHA-MQ combination regimen resulted in a rapid clearance of parasitemia and produced a radical cure. DHA-MQ combination regimen also reduced the dose and duration of artemisinin derivative treatment and therefore improved compliance, a factor that can lead to inadequate drug intake and treatment failure.The strategy on early diagnosis and treatment of malaria with artemisinin-based combination regimens (ACTs) has contributed a major role to malaria control in Vietnam (Hung *et al.*, 1997).

Table 5 Baseline clinical characteristics of patients; data are presented as number or mean ± SD

	DHA monotherapy n = 45	DHA-MQ combination therapy n = 44
Gender		
Female/Male	11/34	10/34
Province		
Binh Thuan	22	20
Binh Phuoc	23	24
Hospital/Health Center		
Bac Binh	8	6
Mepu	9	10
Song Luy	5	4
Phu Rieng	23	24
Age (yrs)	29.3 ± 11.9	28.5 ± 10.1
Weight (kg)	49.0 ± 5.7	48.9 ± 5.5
Height (cm)	159.7 ± 6.7	158.5 ± 6.7
Duration of stay in malaria endemic area (yrs)	8.3 ± 7.5	8.0 ± 6.5
Number of malaria episodes before admission (n)		
1 - 2	34	34
3 - 6	8	9
7 -10	3	1
Clinical symptoms (n, %)		
Headache	41 (91.1%)	43 (97.7%)
Fatigue	36 (80.0%)	35 (79.5%)
Anorexia	33 (73.3%)	29 (65.9%)
Arthralgia	9 (20.0%)	8 (18.2%)
Diarrhea	0 (0%)	2 (4.5%)
Nausea	1 (2.2%)	5 (11.3%)
Chill	40 (88.9%)	35 (79.5%)
Hepatomegaly	1 (2.2%)	1 (2.3%)
Splenomegaly	2 (4.4%)	4 (9.1%)

Table 6 Baseline laboratory characteristics of patients; data are presented as number, mean ± SD or median (range)

	DHA monotherapy n = 45	DHA-MQ combination therapy n = 44
Red blood cells (/μl)	n = 22	n = 20
	3,981,818 ± 153,177	3,875,000 ± 261,322
≤ 3,500,000	0 case	3 cases
White blood cells (/μl)	n = 22	n = 20
	6,927 ± 1,189	6,530 ± 1,270
≤ 5,000	3 cases	3 cases
Neutrocytes (%)	n = 22	n = 20
	61.0 ± 11.2	62.1 ± 8.5
SGOT (U/l)	n = 8	n = 6
	11.0 (3.0 – 23.0)	21.5 (11.0 – 87.0)*
SGPT (U/l)	n = 8	n = 6
	12.0 (6.0 – 40.0)	22.0 (6.0 – 75.0)
Bilirubin (mg/dl)	n = 8	n = 6
	0.9 (0.7 - 1.5)	1.0 (0.8 - 6.4)
Protein (g/dl)	n = 8	n = 6
	7.0 (5.8 - 8.0)	6.2 (5.8 - 7.2)
Creatinine (mg/dl)	n = 8	n = 6
	0.9 (0.7 - 1.1)	1.1 (0.8 - 1.2)
Glucose (mg/dl)	n = 8	n = 6
	99 (83 – 209)	115 (88 – 182)

* $p = 0.044$ (Mann-Whitney U test), significant difference between the two groups.

Table 7 Clinical and parasitological responses of patients; data are presented as number or mean ± SD

	DHA monotherapy n = 45	DHA-MQ combination therapy n = 44
Initial clinical response (n)	45	44
Fever clearance time (h)	23.3 ± 13.4	26.20 ± 19.80
6 – 24 h (cases)	33	26
25 – 48 h (cases)	9	15
> 48 h (cases)	3	3
Parasite clearance time 100% (h)	35.3 ± 17.4	37.80 ± 19.20
Parasite clearance time 95% (h)	26.6 ± 20.9	23.90 ± 14.60
Parasite clearance time 50% (h)	8.3 ± 7.1	7.90 ± 5.30
Parasitological response (n, %)		
Radical cure	33 (73.3%)	39 (88.6%)
Early R1	1 (2.2%)	0
Late R1	11 (24.4%)	5 (11.4%)
Cure rate by time (n, %)*		
d.14	45 (100%)	44 (100%)
d.21	40 (88.9%)	43 (97.7%)
d.28	34 (75.6%)	43 (97.7%)
d.35	/	41 (93.2%)
d.42	/	39 (88.6%)
Radical cure rate/study site**		
Bac Binh	5/8 (62.50%)	4/6 (66.70%)
Mepu	9/9 (100%)	10/10 (100%)
Song Luy	5/5 (100%)	3/4 (75.00%)
Phu Rieng***	14/23 (60.8%)	22/24 (91.7%)

* Kaplan Meier curve analysis, $p = 0.003$

** Data are presented as number of cases with radical cure over the total cases

*** Significant difference, $p = 0.012$

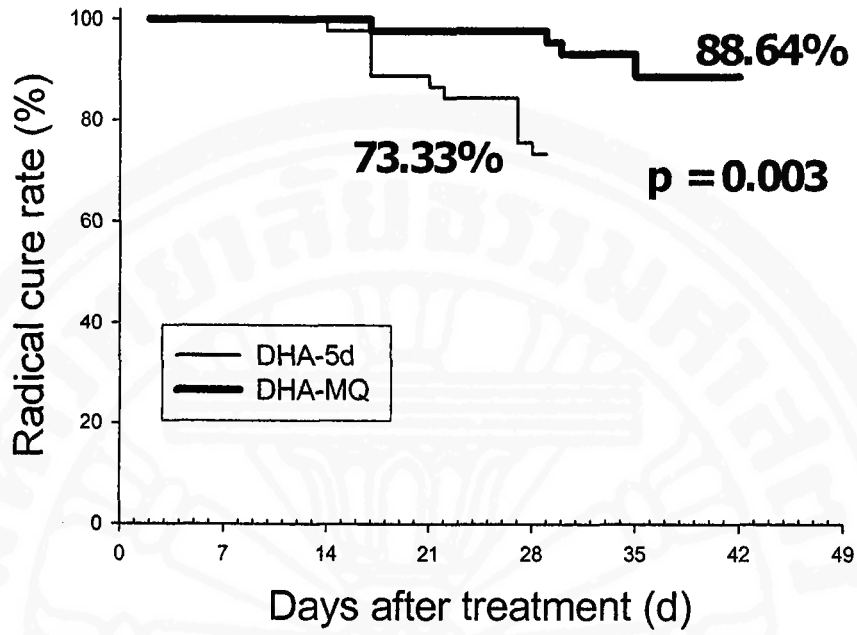

Figure 4 Radical cure rates of two regimens, 5-day DHA monotherapy and DHA-MQ combination therapy, in uncomplicated falciparum malaria. The radical cure rate of DHA-MQ combination regimen is significantly higher than that of 5-day DHA regimen ($p = 0.003$).