Artemether-Lumefantrine Compared to Atovaquone-Proguanil as a Treatment for Uncomplicated *Plasmodium falciparum* Malaria in Travelers

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Abstract. Atovaquone-proguanil (AP) and artemether-lumefantrine (AL) are both treatments for uncomplicated *Plasmodium falciparum* malaria, but comparative clinical trials are lacking. We performed a retrospective analysis, comparing treatment failure and fever clearance time in non-immune travelers with uncomplicated *P. falciparum* malaria, treated with AP or AL. Sixty-nine patients were included during 2001–2013: 44 in the AP group and 25 in the AL group. Treatment failure was observed in 6 of 44 (13.6%) and 1 of 25 (4.0%) patients in the AP and AL groups, respectively. Six treatment failures were observed in travelers from West Africa. Fever clearance time was 44 ± 23 h in AL group versus 77 ± 28 h in AP group, ($P < 0.001$). Hospitalization time was significantly shorter in the AL group; 3.8 ± 1.3 versus 5.1 ± 2.8 days in the AP group ($P = 0.04$). In conclusion, travelers with uncomplicated *P. falciparum* malaria recover faster on AL than on AP. The AL should probably be the drug of choice for this population.

INTRODUCTION

Malaria is the most common cause of hospitalization as a result of a febrile disease in returning travelers,¹ with around 30,000 malaria cases reported in travelers annually.² Travelers from non-endemic origin have no immunity to the disease and therefore the mortality rates are even higher compared with the endemic population.¹

Plasmodium falciparum is the major cause of severe malaria and its treatment is complicated by the emergence of resistant strains. Several treatment options are available for *P. falciparum* malaria in developed countries.³ For uncomplicated *P. falciparum* malaria these include quinine plus doxycycline/clindamycin, high-dose mefloquine, or the two newer drug-combinations: atovaquone-proguanil (AP) and artemether-lumefantrine (AL). The AP and AL are probably the best current options as they are both considered to be safe and effective, have a short course of oral treatment (3 days), few adverse effects, and only a few reports on emergence of resistance.^{3–6}

The AP has been shown to be safe and effective for uncomplicated malaria in returning travelers, and was found to be superior to mefloquine and halofantrine (a drug not commonly used in developed countries any more).^{7,8} However, in recent years there have been reports of treatment failure with both clinical and laboratory resistance shown.^{9,10}

Artemisinin derivatives are considered to be the fastest and most potent current malaria treatment.¹¹ In 2006 the World Health Organization (WHO) declared artemisinin combination therapy (ACT) such as AL to be the regimen of choice for treating *P. falciparum* malaria in Africa,¹² because of its relatively low cost and high efficiency. To date, few treatment failures have been reported.^{13–15} A recent study evaluated the tolerability and efficacy of a standard 6 doses course of AL in non-immune patients and found a 96% cure rate.¹⁶

The relative efficacy of AP and AL has not been evaluated in head-to-head clinical trials. The aim of this study was to compare, for the first time, the treatment outcome of uncom-

plicated malaria in non-immune travelers, treated with either AP or AL.

METHODS

The study design was a retrospective cohort analysis. We reviewed medical records of malaria patients who were hospitalized at the Sheba Medical Center between the years 2001, the year AP was first administered, and until 2013. The following data were extracted from patients' medical records: demographic data, laboratory characteristics, fever clearance time (hours), treatment outcome, and hospitalization time (days).

The study was approved by the Ethical committee of Sheba Medical Center.

Inclusion criteria. The patient population included adult (18 years of age and older) non-immune Israeli travelers, who returned from malaria-endemic countries, were hospitalized with *P. falciparum* malaria, and were treated by either AL or AP as a single drug.

Exclusion criteria. Tourists, immigrants, and foreign workers from malaria-endemic countries, and patients who did not receive their treatment in Israel were excluded from the study.

Treatment regimen. Patients with uncomplicated *P. falciparum* malaria (as per WHO criteria¹²) received oral treatment. All antimalarial treatment was given as inpatient observed therapy. The treatment decision was based on drug availability: between the years 2001 and 2009 all the patients were treated with AP as the drug of choice. Between the years 2009 and 2013 all the patients were treated with AL, unless it was not available, and then they received AP (AL is still not licensed in Israel and was delivered to our hospital under special institutional review board).

Drug protocol. The AP (Malarone [GlaxoSmithKline, Uxbridge, United Kingdom]), a fixed combination tab of 250 mg atovaquone and 100 mg proguanil—4 tabs orally once daily for a total of 3 days. The AL (Coartem, [Novartis Pharma Ltd., Basel, Switzerland]), a fixed combination tab of artemether 20 mg and lumefantrine 120 mg, 4 tabs orally at 0 and 8 hours, and then twice daily for a total of six doses.

Patients were evaluated 4 weeks after hospital discharge, to ensure absence of recrudescence. Patients with recurrent fever were asked to return to the hospital for reevaluation.

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TABLE 1
Patient characteristics according to treatment regimen

	Total (N = 69)	Artemether-lumefantrine (N = 25)	Atovaquone-proguanil (N = 44)	P value
Age (years, mean $\pm$ SD)	43.0 $\pm$ 14.1	45.0 $\pm$ 14.7	41.0 $\pm$ 13.8	0.26*
Male gender (%)	93%	92%	95%	1†
Time from fever onset to treatment (days, mean $\pm$ SD)	4.0 $\pm$ 6.4 (N = 63)	3.1 $\pm$ 1.9 (N = 24)	4.6 $\pm$ 7.7 (N = 39)	0.36*
Country of acquisition				1.00†
Africa	65 (94%)	24 (96%)	41 (93%)	
West Africa	47 (68%)	18 (72%)	29 (66%)	
East Africa	17 (25%)	6 (24%)	11 (25%)	
Asia	4 (6%)	1 (4%)	3 (7%)	
India	3 (4%)	1 (4%)	2 (5%)	
Thailand	1 (1%)	0 (0%)	1 (2%)	
Laboratory results on admission‡				
WBC	5.63 ($\pm$ 2.1)	5.6 ($\pm$ 2.1)	5.7 ($\pm$ 2.0)	0.95*
NEUT%	71.9 ($\pm$ 13.1)	73.5 ($\pm$ 13.1)	70.9 ($\pm$ 13.4)	0.44*
HGB	13.9 ($\pm$ 1.8)	14.1 ($\pm$ 1.6)	13.8 ($\pm$ 1.8)	0.44*
PLT	122.1 ($\pm$ 75.5)	122.6 ($\pm$ 70.8)	121.8 ($\pm$ 79.0)	0.97*
Cr	1.2 ($\pm$ 0.3)	1.2 ($\pm$ 0.3)	1.1 ($\pm$ 0.2)	0.03*
SGPT (ALT)	51.6 ($\pm$ 47.6)	51.4 ($\pm$ 55.4)	51.8 ($\pm$ 42.4)	0.97*
SGOT (AST)	50 ($\pm$ 47.32)	51.1 ($\pm$ 52)	49.2 ($\pm$ 44.9)	0.87*
LDH	350.3 ($\pm$ 187.8)	389.9 ($\pm$ 259.4)	325.6 ($\pm$ 121.8)	0.18*
Total Bilirubin	1.5 ($\pm$ 1.2)	1.3 ($\pm$ 0.6)	1.64 ($\pm$ 1.4)	0.26*

*t test for equality of means

†Fisher test.

‡WBC = white blood count; NEUT% = neutrophil percentage; HGB = hemoglobin; PLT = platelets; Cr = serum creatinine; SGPT = serum glutamic pyruvate transaminase; SGOT = serum glutamic oxaloacetic transaminase; LDH = serum lactate dehydrogenase.

Clinical and epidemiological data, including age, sex, place of birth, place of infection, laboratory results, and the time between fever onset and treatment onset (days) were recorded and compared between the two groups. Primary outcomes included fever clearance time (hours)—the time between treatment initiation and defervescence below 37.5°C and treatment failure. Treatment failure was defined as deterioration to severe malaria, or failure to clear parasitemia after 3 days of treatment (early failure), or recrudescence of fever and parasitemia within 1 month of presentation (late failure). Patients that failed their initial treatment were not included in the fever clearance time calculations.

A secondary outcome was hospitalization time.

Statistical analysis. Patient data were extracted from medical records and analyzed with SPSS 19.0 (IBM Corporation, Armonk, NY) statistical software. Patients were divided into two groups based on treatment type: AP and AL. Continuous variables distribution, such as fever clearance time, was assessed for normality using the Kolmogorov-Smirnov test (cutoff at $P < 0.01$). Continuous variables with normal distribution were described as mean $\pm$ SD and compared with the *t* test for independent samples. Non-normal distribution continuous variables were described as median and compared with the Mann-Whitney *U* test. Categorical variables such as treatment failure (yes/no) were compared by treatment exposure using the Fisher test.

RESULTS

During the study period of 2001–2013, 69 patients met the inclusion criteria and were included in the study: 44 in the AP group and 25 in the AL. Age (mean $\pm$ SD) was 43 $\pm$ 14 years, and there was a remarkable male predominance (93%).

Clinical and epidemiological characteristics, and complete blood count and blood chemistry tests did not differ significantly between the two treatment groups (Table 1). Time from fever onset and treatment initiation was 4.6 $\pm$ 7.7 (mean $\pm$ SD) days in the AP group and 3.1 $\pm$ 1.9 (mean $\pm$ SD) days in the

AL group, a difference that was not statistically significant. Most malaria cases in both groups were imported from Africa, especially from West Africa (Table 1).

Six (13.64%) cases of treatment failure were recorded in the AP group, and one (4%) in the AL group ($P = 0.41$). In the AP group, three patients failed to clear their fever and blood parasites, despite a full dose of AP treatment. Three more had cleared their fever, but had a recrudescence within 1 month of discharge. Of the six AP failure cases, one patient was treated with AL, two received mefloquine, and two quinine + doxycycline. The sixth patient progressed to severe malaria despite AP treatment, and the treatment was changed to intravenous treatment. All six patients recovered completely. In the AL group the one case of treatment failure was diagnosed with recrudescence 2.5 weeks after fever clearance. This patient had inadvertently received only five doses of AL. He subsequently received AP treatment, cleared his fever within 48 hours, and recovered uneventfully.

All treatment failure cases had returned from Africa, six from West Africa, and one from East Africa (AP group). The treatment failure rate in West Africa was 17% in AP group (5 of 30) and 4.5% in AL (1 of 22) (Table 2).

TABLE 2
Outcome parameters according to treatment allocation

	Artemether-lumefantrine	Atovaquone-proguanil	P value
Fever clearance time	(N = 23*)	(N = 38*)	
Mean ($\pm$ SD) (hours)†	44 ($\pm$ 22.7)	77 ($\pm$ 28)	< 0.001†
Median (hours)	48	72	
Treatment's failure	(N = 25)	(N = 44)	
Number	1	6	0.41‡
Percentage	4%	13.64%	
Hospitalization time	(N = 23)	(N = 37)	
Average (days)	3.8 ($\pm$ 1.3)	5.14 ($\pm$ 2.8)	0.04†
Median (days)	4	6	

*Seven patients (6 in AP group and 1 in AL group) had failed to clear their fever and therefore had no fever clearance time. One patient in AL group was afebrile at admission, and therefore was excluded from fever clearance time calculation.

†t test for Equality of Means.

‡Fisher test.

FIGURE 1. Fever clearance time: a survival analysis Kaplan Meier curve for fever clearance time in patients who received Atovaquone-proguanil (black curve) or Artemether-Lumefantrine (grey curve) for uncomplicated *Plasmodium falciparum* malaria.

Fever clearance time was 44 ± 22.7 (mean $\pm$ SD) hours in the AL group and 77.0 ± 28.0 (mean $\pm$ SD) hours in the AP group ($P < 0.001$) (Table 2). A Kaplan Meier survival analysis also showed that fever clearance time was significantly faster in the AL group (log-rank $P < 0.001$) (Figure 1).

In seven cases from the AP group data regarding complete defervescence time were missing. In these cases we used the minimum follow-up time as a surrogate of fever clearance time and further examined worst case scenario sensitivity analysis and calculated the fever clearance time difference without these seven patients. By all methods of calculation the AP group had a statistically significant longer fever clearance time.

Hospitalization time was significantly shorter in the AL group: 5.1 ± 2.8 (mean $\pm$ SD) versus 3.8 ± 1.3 (mean $\pm$ SD) days in the AP group (P value = 0.04) (Table 2).

DISCUSSION

Malaria is the most common cause of fever and hospitalization in returned travelers from Africa.¹ Four approved regimens are available in developed countries for the treatment of uncomplicated *P. falciparum* malaria: atovaquone-proguanil (AP), artemether-lumefantrine (AL), quinine + doxycycline/clindamycin, high-dose mefloquine (chloroquine use is restricted to very few areas where chloroquine sensitivity is maintained).¹⁷ Of these four regimens AP and AL have the advantages of a short course of therapy, good tolerability, and few side effects, proven efficacy and as yet rare resistance. The AP was patented by Glaxo-Wellcome in 1999. It is registered in most developed countries (including Israel) for malaria prophylaxis and for the treatment of uncomplicated malaria. The AL was introduced later to the pharmacopoeia, but had since been declared by the WHO as the drug of choice for treating malaria in Africa.¹² The relative efficacy of AP and AL has not been evaluated in head-to-head clinical trials. Previous non-comparative studies in non-immune population had suggested that AL has a parasite clearance time around 32–41.5 hours and fever clearance time around 24–36.8 hours.^{16,18} This appears to be much shorter than for AP, which had a parasite clearance time around 63–79.2 hours and

fever clearance time around 60.3–88.8 hours.^{7,8} On the other hand, in a recent study describing the experience with different regimens for uncomplicated malaria in multiple European hospitals, AP and AL were found to have similar fever and parasite clearance time (48 and 72 hours, respectively).¹⁹ It should be noted however, that the majority of patients in this study were immigrants visiting friends and relatives, and may not have constituted a non-immune population.

In our study we showed a 13.6% failure rate with AP, whereas only one patient (4%) (who had received an incomplete regimen) had failed to be cured by AL. Although this difference did not reach statistical significance, it should be a source of concern. In recent years several reports have documented AP treatment failure with laboratory evidence of resistance.^{9,10,20} To date, very few treatment failures had been documented with AL.^{13–15} Some reported AL failures may have been due, as in our case, to incomplete drug administration rather than to parasite resistance.^{13,15}

Our study also showed that the fever clearance time was 44 ± 22.7 hours in patients treated with AL. Although somewhat longer than that reported in previous AL studies,^{16,18} it was shorter by 33 hours (a 57% reduction) than the fever clearance time on AP, which was 77 ± 28.0 hours (similar to that seen in other AP studies).^{7,8} This difference in favor of AL was statistically highly significant. Our results differ from a European retrospective study that showed similar fever clearance time for both drugs.¹⁹ It should be noted, that patients included in our study were all from a non-immune population, whereas most patients in the European study were immigrants and travelers visiting friends and relatives. Because the fever clearance times we found for both drugs are consistent with those found in other studies that individually measured either AP or AL fever clearance time, we believe they represent a significant difference between the two regimens in non-immune populations.

The secondary outcome measured in our study was hospitalization time. A significant 1.3 days difference was found in the hospitalization time in favor of AL. This outcome is probably the result of more rapid defervescence and patient recovery on AL. The ACTs are known to provide the most potent, and fastest available parasitocidal antimalarial regimen. A

shorter hospital stay is likely to be associated with advantages for the patient and the healthcare system alike, and to be cost-effective as well.

Our study has several limitations. This was not a prospective, randomized, controlled trial. However, because treatment allocation changed according to drug availability during the study period, selection bias is unlikely. Furthermore, we were able to show that the groups were similar in all other epidemiological and clinical parameters, except for the choice of drug. Validating these results in a prospective study is recommended, but in the absence of any economic incentive it must rely on governmental initiative rather than on pharmaceutical companies.

The patients in our study were mostly men who returned from Africa, and whether the superiority of AL also extends to cases in malaria acquired elsewhere, and in women is theoretically not established. However, travel to Africa entails the highest risk of malaria acquisition, and in all likelihood, imported malaria from Africa will continue to form the bulk of cases seen in developed countries.

CONCLUSIONS

In non-immune travelers with *P. falciparum* malaria, AL is associated with more rapid defervescence and shorter hospital stay than AP. The high failure rate of AP treatment (especially in West Africa) is a cause of concern, and should be validated by further prospective studies. We believe that AL should be considered the drug of choice for treating travelers with *P. falciparum* malaria acquired in Africa. Thus, the WHO recommendation for the treatment of malaria in the local population should be applied to returning travelers as well.

Received April 23, 2014. Accepted for publication June 11, 2014.

Published online November 4, 2014.

Disclosure: This study was performed in partial fulfillment of the M.D. thesis requirements of the Sackler Faculty of Medicine, Tel Aviv University.

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