

Case Report

Artemether–Lumefantrine Treatment Failure in a *Falciparum* Malaria Patient in Tunisia

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Keywords

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- Treatment failure
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Abstract

Aim: Malaria, especially that caused by *Plasmodium falciparum*, is one of the most important infectious diseases in the world, and its control is hampered by increasing resistance of malaria parasites to available drugs.

Case: We report a case of possible clinical failure of artemether-lumefantrine treatment in a 26-year old Tunisian traveler with uncomplicated *P. falciparum* malaria imported from Cote d'Ivoire.

Conclusion: This was a first reported case of treatment failure of artemether-lumefantrine in Tunisia.

INTRODUCTION

Malaria, especially that caused by *Plasmodium falciparum*, is one of the most important infectious diseases in the world, and its control is hampered by increasing resistance of malaria parasites to available drugs. Artemisinin-based combination therapy (ACT), especially artemether-lumefantrine, is known to be the best treatment [1]. Many studies have reported artemisinin combination therapies (ACTs) to be the best antimalarial drugs available, due to their efficacy and potential to lower the emergence of resistance. It is now first-line therapy for uncomplicated malaria in endemic areas with multidrug resistant *Plasmodium falciparum* [2]. We report a case of possible artemether-lumefantrine clinical failure in a Tunisian traveler with uncomplicated *P. falciparum* malaria imported from Cote d'Ivoire.

CASE PRESENTATION

A 26-year old Tunisian man, four days after coming back from two months travel business in Cote d'Ivoire, was admitted to the Infectious Diseases Department because of high fever, headache and vomiting lasting for five days. He didn't take any prophylaxis for malaria. On admission, he was conscious, febrile at 39.3°C with a pulse rate of 120 beats/min, a blood pressure at 110/60 mm Hg and peripheral oxygen saturation: 99%.

Blood samples showed thrombocytopenia, renal failure and elevated bilirubin levels (Table 1). Peripheral blood smear was

positive for *Plasmodium falciparum* with 5.6% parasitemia. The combination drug Coartem® (artemether-lumefantrine 20/120 mg) was started following manufacturer advice: 6 dose regimen of 4 tablets at 0, 6, 18, 30, 42, 54 hours. Within 48 hours the patient was afebrile and a control of biochemical tests and blood smear showed resolution of abnormalities and negativity of parasitemia on the eleventh day. After 14 days he was readmitted to the Infectious Diseases Department with high fever, jaundice and vomiting. On examination, the patient had a body temperature at 38.7°C without any other clinical findings. Blood test results are summarized in Table 1 (blood results).

Blood smear was performed and resulted positive for *Plasmodium falciparum* with 0.8% parasitemia. The recrudescence of *P. falciparum* after treatment with artemether-lumefantrine is represented in (Figure 1).

Oral quinine 600 mg three times per day was started and continued for 7 days. The outcome was favorable and the patient was discharged after 7 days in good clinical condition and the blood smear was negative for *Plasmodium*. The patient did not report other febrile episodes.

DISCUSSION

Malaria is one of the major public health problems worldwide causing more than one million deaths each year. It is widespread in hot humid regions of Africa, Asia, and South and Central America [3].

Table 1: Blood Results.

	Admission 1	Admission 2
Leucocytes (/mm ³)	5500	3500
Hemoglobin (g/dl)	13,8	11,2
Hematocrit	35	32,8
Platelets (/mm ³)	18000	58000
AST (U/l)	43	81
ALT (U/l)	38	186
Total bilirubin (μmol/l)	70,3	62,9
Creatinine (μmol/l)	137	126
C-reactive protein (mg/l)	240,5	56,5

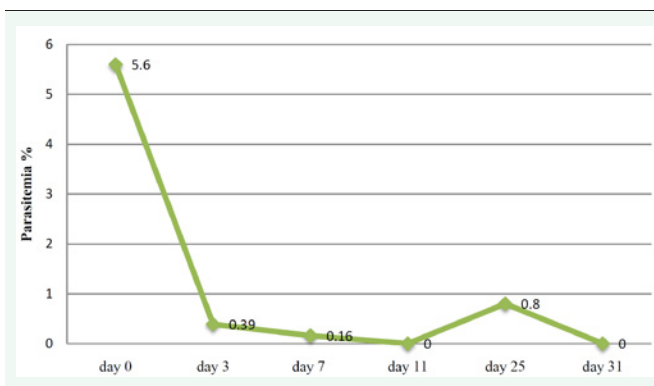


Figure 1 Recrudescence of *P. falciparum* in a traveller treated with artemether-lumefantrine.

Accordingly, the WHO recommends that treatment policies for *falciparum* malaria in all countries experiencing resistance to monotherapy should be combination therapies containing artemisinin derivatives. Artemether, lumefantrine is the most used worldwide, it is well tolerated and fast acting [4]. The two components of the fixed combination are mutually complementary. Artemether reduces parasitaemia, and lumefantrine eliminates residual parasites [4].

Previous four-dose regime was associated with 15% treatment failure, whereas, the now recommended six-dose regime showed, in a recent pooled analysis, a 28-day PCR-corrected parasitological cure rate of 97% in malaria endemic areas [5,6].

The combination drug artemether-lumefantrine is highly effective in Africa [5]

However, the wide spread use of artemisinin-based combination therapies (ACTs) could have a major impact on the treatment of malaria [2].

In fact the two drugs are mutually protective, and indeed there was no in vitro evidence for the development of resistance in the small number of recrudescence isolates. Since they have different mechanisms of action, the chances that drug-resistant parasite mutants would survive are reduced considerably. The residual tail of lumefantrine concentrations that persists after elimination of artemether does provide a potential selective

pressure to the development of resistance if new infections are acquired during this period.

But high failure rates were seen in Cambodia (13,5% in 2006), where the emergence of lumefantrine resistance could not be excluded and could be explained by the cross resistance between mefloquine and lumefantrine [7]. We report a case of possible clinical failure of artemether-lumefantrine in a tunisian traveler with imported uncomplicated *Plasmodium falciparum* malaria. To our knowledge three previous case of treatment failure of artemether-lumefantrine in *Plasmodium falciparum* malaria imported [1,4,8].

These failures had been speculated to be due to sub-optimal lumefantrine concentrations. Because of lumefantrine is highly lipophilic and bioavailability depends on concurrent food intake. Also different sets of parasite populations have been suggested to have caused the recurrent episodes.

According to WHO classification of treatment outcome in high-transmission areas (2009), our patient must be considered a late clinical failure (clinical manifestations and presence of parasitemia between day 4-28).

Clinical symptoms were more pronounced because of the parasite densities higher at recrudescence or diagnostic delay [8].

Many studies conclude that decreasing effect of artemether-lumefantrine was indeed seen in an area of decreasing malaria transmission and immunity. That's why, drugs chosen for treatment of *P. falciparum* malaria, especially in non-immune highly vulnerable individuals such as children and travellers, should preferably be efficacious enough to allow for single missed doses or uneven drug absorption. However, in endemic areas, partial immunity is likely to contribute to the effect of antimalarial drugs and thus overestimate cure rate [8,9].

Our laboratory could not perform an in vitro antimalarial susceptibility test, so the therapy with oral quinine was chosen in the suspicion of inefficacy of the combination artemether-lumefantrine.

CONCLUSION

The treatment failure described here might have been due to reduced sensitivity to lumefantrine but suboptimal concentrations of lumefantrine and a missed dose cannot be fully ruled out.

So, patients must be well informed to seek prompt care in the event of fever the weeks after completing artemether-lumefantrine treatment.

REFERENCES

- Mizuno Y, Kato Y, Kudo K, Kano S. First case of treatment failure of artemether-lumefantrine in a Japanese traveler with imported *falciparum* malaria. *Jpn J Infect Dis.* 2009; 62: 139-141.
- Kabanyanyi AM, Mwita A, Sumari D, Mandike R, Mugittu K, Abdulla S. Efficacy and safety of artemisinin-based antimalarial in the treatment of uncomplicated malaria in children in southern Tanzania. *Malar J.* 2007; 6: 146.
- Greenwood BM, Fidock DA, Kyle DE, Kappe SH, Alonso PL, Collins FH,

- et al. Malaria: progress, perils, and prospects for eradication. *J Clin Invest*. 2008; 118: 1266-1276.
- Ernestina C. Repetto, Antonio Traverso, Claudio G. Giacomazzi. Possible Clinical Failure of Artemether-Lumefantrine in an Italian Traveler with Uncomplicated Falciparum Malaria. *Mediterr J Hematol Infect Dis*. 2011; 3: 201104.
 - Vugt MV, Wilairatana P, Gemperli B, Gathmann I, Phaipun L, Brockman A, et al. Efficacy of six doses of artemether-lumefantrine (benflumetol) in Multidrug-resistant plasmodium falciparum malaria. *Am J Trop Med Hyg*. 1999; 60: 936-942.
 - Makanga M, Bassat Q, Falade CO, Premji ZG, Krudsood S, Hunt P, et al. Efficacy and safety of artemether-lumefantrine in the treatment of acute, uncomplicated Plasmodium falciparum malaria: a pooled analysis. *Am J Trop Med Hyg*. 2011; 85: 793-804.
 - Dondorp AM, Nosten F, Yi P, Das D, Phyto AP, Tarning J, et al. Artemisinin resistance in Plasmodium falciparum malaria. *N Engl J Med*. 2009; 361: 455-467.
 - Anna Färnert, Johan Ursing, Thomas Tolfvenstam, Josea Rono, Lillemor Karlsson, Elda Sparrelid, et al. Artemether-lumefantrine treatment failure despite adequate lumefantrine day 7 concentration in a traveller with Plasmodium falciparum malaria after returning from Tanzania. *Malaria J*. 2012; 11:176.
 - Borrmann S, Sasi P, Mwai L, Bashraheil M, Abdallah A, Muriithi S, et al. Declining responsiveness of Plasmodium falciparum infections to artemisinin-based combination treatments on the Kenyan coast. *PLoS One*. 2011; 6: 26005.

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