

## Short Communication

# First Case of Treatment Failure of Artemether-Lumefantrine in a Japanese Traveler with Imported Falciparum Malaria

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**SUMMARY:** Artemether-lumefantrine, a tablet formulation of these respective antimalarial compounds, has been developed for the treatment of patients with drug-resistant malaria worldwide. Many studies have shown that it is most effective of the antimalarial compounds in shortening the fever and parasite clearance times. However, several treatment failures have been reported. These failures are believed to be a consequence of poor bioavailability of the lumefantrine component when ingested without fatty food. This paper reports the first case of such treatment failure of imported malaria in Japan in a 58-year-old Japanese man who showed recrudescence of *Plasmodium falciparum* after treatment with artemether-lumefantrine. The drug was administered to the patient in 6 doses, each time without fatty food and on a seemingly empty stomach. It is believed that treatment failure was due to poor absorption and a subsequent low plasma concentration of lumefantrine. Although artemether-lumefantrine has not been approved for use in Japan and is thus not commonly used there at present, it is thought to be the most promising drug of choice for the treatment of drug-resistant malaria. Taking an appropriate dosage and providing patients with proper instructions on taking the drug concurrently with fatty food are required for effective treatment with artemether-lumefantrine.

Artemisinin-based combination therapies (ACTs) have been reported to be the best antimalarial drugs available in recent years (1). Artemisinin enhances efficacy and has the potential to lower the rate at which resistance emerges and spreads (2). Artemether-lumefantrine, a tablet formulation of the antimalarial compounds artemether and lumefantrine (formerly benflumetol), has been approved in a large number of countries. It is a well-tolerated, fast-acting, and effective blood schizontocidal drug used primarily in the treatment of uncomplicated falciparum malaria that is resistant to other antimalarials (3). Initial clinical-parasitological response relies mainly on artemether, whereas lumefantrine effects a radical cure (4). Lumefantrine is known to be poorly absorbed in the fasting state. Co-administration with a relatively small amount of fat is required to ensure its maximum absorption (5). Five cases of uncomplicated falciparum malaria have been successfully treated by artemether-lumefantrine at the International Medical Center of Japan in Tokyo. In this report, the first case of treatment failure with artemether-lumefantrine is reported in a Japanese patient with imported falciparum malaria. The patient may not have been properly administered the drug with the necessary amount of fat.

A 58-year-old Japanese man was admitted to the International Medical Center of Japan on December 28, 2006, because of high fever, general fatigue, and epigastralgia. Prior to admission, the patient had suffered 2 days of febrile illness after returning from a 3-month stay (September 22 to December 11) in Sierra Leone as a consultant for an official development assistance program. The patient had a medical history of hepatitis A, dengue fever, and gastric ulcer and had not used any chemoprophylaxis against malaria.

Upon admission, the patient's body temperature was 38.6°C, his pulse rate was 72 beats/min, and his blood pressure was 146/88 mmHg. Initial laboratory test results were almost normal except for a high C-reactive protein (CRP) of 6.5 mg/dl and a low platelet count of  $11.7 \times 10^4/\mu\text{l}$  (Table 1). A peripheral blood smear showed 2.78% parasitemia with

Table 1. Laboratory data upon initial admission

Hematology	
Leukocytes	4,960/ $\mu\text{l}$
Neutrophil	88.1%
Lymphocyte	7.1%
Monocyte	4.0%
Eosinophil	0.4%
Basophil	0.4%
Erythrocytes	$489 \times 10^4/\mu\text{l}$
Hemoglobin	15.2 g/dl
Hematocrit	43.9%
Platelets	$11.7 \times 10^4/\mu\text{l}$
Blood chemistry	
AST	41 IU/l
ALT	42 IU/l
LDH	247 IU/l
$\gamma$ -GTP	56 IU/l
Total bilirubin	0.7 mg/dl
BUN	14.9 mg/dl
Creatinine	0.89 mg/dl
Uric acid	5.8 mg/dl
Sodium	137 mEq/l
Potassium	3.5 mEq/l
Chloride	101 mEq/l
C-reactive protein	6.5 mg/dl

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase;  $\gamma$ -GTP,  $\gamma$ -glutamyl transpeptidase; BUN, blood urea nitrogen.

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*Plasmodium falciparum*. Chest X-ray and electrocardiographic findings were normal. The patient was administered artemether-lumefantrine (20/120 mg), 4 tablets each for 6 doses, at 0, 7, 24, 37, 48, and 61 h, based on the manufacturer's advice. Within 37 h of treatment, blood microscopy was negative for parasites, and the patient was afebrile. He appeared clinically well 61 h after beginning treatment.

However, 21 days after initial admission, he was re-admitted to our hospital with a temperature of 39.3°C. Microscopy revealed 0.52% *P. falciparum* parasitemia. We chose atovaquone-proguanil, which has already been proposed as a first-line therapy in Africa, and for which an elevated rate of resistance has not been widely reported in studies undertaken in endemic areas (6). After a 3-day course of atovaquone-proguanil treatment, the patient recovered clinically, and repeat blood microscopy was negative for parasites. Mefloquine was not used for the recrudescence of parasites because we had done in vitro mefloquine susceptibility testing with the patient's parasitized blood from the first admission and found that the parasites were resistant to the drug (data not shown).

The World Health Organization (WHO) recommends ACTs for the treatment of uncomplicated malaria because multi-drug-resistant (MDR) malaria has spread widely throughout the world, particularly in Southeast Asia (7). Artemisinin and its derivatives act extremely rapidly to reduce parasite biomass and clinical symptoms. They have broad stage specificity and also act to reduce gametocyte carriage. However, short courses of treatment lead to a relatively high failure rate. Therefore, it has been recommended that artemisinin derivatives be combined with another antimalarial drug with a longer half-life to destroy any residual parasites.

Artemether-lumefantrine is now one of the most popular formulations of ACT. Artemether is rapidly absorbed and eliminated and its use results in a rapid and considerable reduction of parasite biomass and in the resolution of malaria symptoms. Lumefantrine, with its delayed absorption and slower clearance, eliminates residual parasites (8). The efficacy of the combination is therefore dependent on the number of parasites remaining after artemether has been eliminated and the duration for which lumefantrine plasma concentrations exceed the minimum inhibitory concentration against the parasites. In this case, artemether-lumefantrine proved to be very effective in treating the patient's first episode by reducing his initial parasitemia and body temperature within 37 h. Although the drug has not yet been approved for use in Japan, it should be considered the first drug of choice in treatment of the acute phase in patients with imported malaria, particularly from regions where MDR malaria is endemic.

Resistance to artemisinin has not been formally confirmed, but reduced sensitivity has been reported in China and Vietnam (9,10). In vitro monitoring over time has shown no clear evidence of resistance to artemisinin and its derivatives in many parts of the world. In fact, a case report in the United Kingdom showed that treatment failure of artemether-lumefantrine was possibly due to the poor absorption of lumefantrine (11). Another study in Cambodia showed that the successful treatment rate increased by 15% when treatment was supplemented with fatty food, and that patients successfully treated had significantly higher plasma concentrations of lumefantrine than those failing treatment (12). However, other studies predicted that amplification of *pfmdr1* alleles may potentially represent a further development towards resistance with increased selection pressure of lumefantrine in Africa (13,14). In African children, the rates

of treatment failure at day 28 using artemether-lumefantrine ranged from 0 to 3.3% for the combination therapy (15). However, at present there are no reports of in vivo resistance to artemether-lumefantrine in Sierra Leone (16). Thus, it is believed that the treatment failure in the patient described in this study could not be due to resistance to the combination therapy, but rather by the failure of the lumefantrine component.

Patients with acute malaria are frequently nauseated and anorexic, making it difficult for them to comply with dietary advice. In fact, the patient in this study ingested artemether-lumefantrine when he was in a fasting state. For example, the first 4 doses were taken at 17:00 (on admission, 0 h), at 24:00 midnight (7 h), at 17:00 the following day before dinner (24 h), and at 06:00 the next morning before breakfast (37 h). Thus, the initial and acute phase treatments were not perfectly administered. After clinical improvement and the return to a normal diet, the absorption of lumefantrine may have increased (5,17). However, the 5th dose was at 17:00 before dinner (48 h), and the 6th dose was at 06:00 (61 h). Although an in vitro lumefantrine resistance test was not performed and measurement of the plasma concentration of lumefantrine was not feasible, the recrudescence of the *P. falciparum* parasites may have been due to the poor absorption and subsequent low plasma concentration of the lumefantrine. The authors conclude that this first reported case of treatment failure with artemether-lumefantrine in Japan highlights the importance of taking each dose with a small amount of fat to ensure maximum absorption of the lumefantrine.

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