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Retrospective observational study of the use of artemether-lumefantrine in the treatment of malaria in Japan

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ABSTRACT

Background: The Research Group on Chemotherapy of Tropical Diseases, Japan, introduced artemether–lumefantrine (AL) in late 2002, mainly for treating uncomplicated *Plasmodium falciparum* malaria. Because AL was on the market in Japan in March 2017, the effectiveness and safety of AL were analyzed to help medical personnel use AL optimally.

Methods: Case report forms submitted by the attending physicians were analyzed. When necessary, direct contact with the attending physicians was made to obtain detailed information.

Results: Effectiveness analysis was performed for 62 cases and safety analysis was performed for 66 cases. In *P. falciparum* malaria, the overall cure rate was 91.1% (51/56), of which the cure rates for Japanese and non-Japanese patients were 82.1% (23/28) and 100% (28/28), respectively. The successfully treated cases included severe *P. falciparum* malaria, with parasite densities exceeding 500,000/μL. Adverse events were reported in 14 patients, including delayed hemolytic anemia which occurred in the top four highest parasitemic cases.

Conclusions: AL treatment failure in *P. falciparum* malaria may not be rare among non-immune individuals, including Japanese. The possibility of delayed hemolytic anemia, which occurs preferentially in high parasitemic cases, should be considered following AL treatment.

1. Introduction

Medical clinicians are more likely than ever to encounter patients with tropical diseases because of increasing global exchanges, including those involving tropical and subtropical countries. Malaria, especially that caused by *Plasmodium falciparum* infection, is potentially fatal, and prompt diagnosis and adequate treatment are critically important, especially in non-endemic countries.

In malaria-endemic countries, parenteral artemisinins and artemisinin-based combination therapies (ACTs) are increasingly used because of the high level of evidence for superior efficacy [1]. Artemisinins kill malaria parasites more rapidly than other antimalarials, acting even on the immature ring-form parasites, which results in prompt parasite clearance and symptom resolution. Artemether–lumefantrine (AL) is one of the fixed-dose oral ACTs and has been used for uncomplicated *P. falciparum* malaria in endemic as well as non-endemic industrialized countries [2–4].

In Japan, a number of essential medicines for treating tropical and

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parasitic diseases, including malaria, have not been licensed. To circumvent foreseeable treatment difficulties, the Research Group on Chemotherapy of Tropical Diseases (RG-CTD) was established in 1980 under the Ministry of Health (renamed the Ministry of Health, Labor, and Welfare) aimed at importing nationally unlicensed medicines and making them available to patients who need them. Since then, RG-CTD has been conducting observational studies on the use of the drugs, which were designed primarily for patients who needed access to unlicensed medicines in Japan, because no compassionate use program covering acute infectious diseases has been formulated in the pharmaceutical administration policy in Japan.

Despite the fact that administration of the drugs by the Research Group was not performed under a strict clinical research protocol, our reports on the effectiveness and safety of the medicines have contributed significantly to the licensing of drugs for parasitic and tropical diseases in Japan. For example, we published reports on the effectiveness and safety of the antimalarials atovaquone–proguanil [5,6] and primaquine [7], and these drugs were eventually licensed and marketed in February 2013 and June 2016, respectively.

As a major part of our activity, we started importing AL tablets in late 2002, and AL use has gradually increased since the introduction. Previously, we reported a preliminary study on 50 cases treated with AL alone on behalf of RG-CTD in Japanese [8], and some of the current authors (S.K., T. Ko., Y.M., Y. Kato) analyzed AL-treated cases seen in their hospital [9], which was also published in Japanese. These reports expressed some concern over treatment failure and delayed hemolytic anemia, and AL tablets were finally licensed and marketed in Japan in March 2017.

In this study, we conducted a detailed study on the effectiveness and safety of AL in malaria treatment using our whole data set obtained from 2003 until 2017 to help physicians use AL optimally for treating imported malaria.

2. Patients and methods

2.1. Use of antimalarial drugs by the Research Group on Chemotherapy of Tropical Diseases (RG-CTD)

RG-CTD has been involved in introducing nationally unlicensed medicines for tropical and parasitic diseases. Upon introduction, each medicine is examined at the National Institute of Health Sciences, Tokyo, to ensure that it meets Japanese quality standards. After confirmation of quality, the medicines are used in registered hospitals across Japan. Previously tested Riamet® combination tablets (20 mg of artemether and 120 mg of lumefantrine per tablet, Novartis Pharmaceuticals) were purchased and imported by one of the authors.

The clinical study on the use of nationally unlicensed drugs described in the clinical research proposal approved at the principal investigator's institution (currently H. Maruyama, University of Miyazaki, Clinical Study Permission No. 2012-006) was approved by the research ethics committee of each participating hospital. Prior to the use of AL tablets, written informed consent was obtained from each patient, with clear explanation that AL tablets were not licensed in Japan. After completing the treatment, each attending physician submitted a formulated case report form to RG-CTD, as was previously done with atovaquone-proguanil [5,6] and primaquine [7].

2.2. Diagnosis and enrollment of patients

Diagnosis was made on blood smears stained with standard Giemsa staining in all cases. Smears were examined microscopically for malaria parasites at each hospitals. Some smears were cross-checked by more than one authors. In addition to blood smears, rapid diagnostic tests, including Binax NOW® (Alere Scarborough, Inc., Scarborough, ME, USA) and SD Malaria Antigen Pf® (Standard Diagnostics, Inc., Konggido, South Korea), were also used in some cases. Polymerase chain reaction analysis was performed, especially when mixed-species infection was suspected.

Choice of treatment was primarily made by the treating physicians. However, they generally referred to the standard treatment guidance edited by RG-CTD and/or consulted directly with experienced members of RG-CTD about the treatment, when necessary.

Among malaria patients who took at least one dose of AL from 2002 until 2017, those who received other antimalarials prior to or with AL were excluded, and the remaining patients were subjected to safety analysis. Among patients for the safety analysis, those who completed the six-dose regimen of AL (4 tablets twice a day for 3 days) were subjected to effectiveness analysis.

2.3. Data analysis

Basic analysis on the drug's effectiveness and adverse events was performed by using case report forms that were filled by the attending physicians. The patients' personal data recorded in the case report forms included age, sex, body weight, nationality, purpose of travel, and country of disease acquisition. When more detailed information was necessary, direct contact with the attending physician was made.

Severe/complicated malaria was defined according to the definitions outlined by the United Kingdom's committee [10], with the exception of a high parasitemia ≥ 5% (parasite density ≥ 250,000/μL in our study), as suggested by the guidelines in the United States [11] and Germany [12]. Delayed hemolytic anemia was defined mainly according to Arguin et al. [13] who modified the definition originally proposed by Jauréguiberry et al. [14]: a > 10% decrease in hemoglobin (Hb) levels and an increase in lactate dehydrogenase to > 390 U/L, or an increase of > 10%, at ≥ 7 days after initiation of AL treatment. We did not include a decreased haptoglobin level, which is not routinely measured in Japan.

Treatment failures were defined on the basis of Sondén et al. [15] with slight modification; 1) early failure in which parasite clearance was not achieved within day 7 of treatment initiation, 2) late failure (recrudescence) in which parasites reappeared in the circulation ≥ 7 days after a microscopy-negative interval.

Statistical analysis was performed by using the Mann-Whitney *U* test or Fisher's exact test. (GraphPad Prism 6, GraphPad Software, Inc.). P-values of less than 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Between 2003 and 2017, AL was administered to 89 malaria patients who were all > 18 years old. Among these 89 patients, 23 were administered additional antimalarial medicines, such as quinine and/or artesunate suppository, prior to or with AL. These patients were excluded from the study. The remaining 66 patients were subjected to safety analysis in which 62 patients who completed the six-dose regimen of AL were subjected to effectiveness analysis.

The characteristics of the 66 patients are summarized in Table 1; the median age was 38 years, and > 80% were male patients. Approximately half of the patients were Japanese (34/66), and most (28/32) of the non-Japanese people were from sub-Saharan African countries. The purposes of travel among the Japanese patients included business, mission for the Japan International Cooperation Agency, vacationing, and volunteer activities. Non-Japanese patients acquired infections while visiting friends and relatives from Japan or in their home country before visiting Japan for business or job training. *P. falciparum* malaria accounted for 59 patients, including 4 mixed infections (2 with *P. vivax* and 2 with *P. ovale*). Regarding the country of infection of the 59 *P. falciparum* patients, 57 were infected in sub-Saharan countries.