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ORIGINAL RESEARCH ARTICLE

Safety Profile of Artemether-Lumefantrine: A Cohort Event Monitoring Study in Public Health Facilities in Tanzania

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Abstract

Background and Objective Artemisinin combination therapies such as artemether-lumefantrine (AL) are effective for first-line treatment of uncomplicated acute *Plasmodium falciparum* malaria. However, the safety profile of AL in large populations has not been fully assessed. The objective of this study was to establish the safety of AL in public health facilities in Tanzania using the Cohort Event Monitoring (CEM) method.

Methodology Patients who presented to public health facilities in four regions of Tanzania who were prescribed AL were enrolled in a CEM study, a prospective, observational cohort study to establish a profile of adverse events (AEs) for the medicine when used in routine clinical practice. Pre- and post-treatment forms were used to record baseline information and new health events before and 7 days after treatment.

Results A total of 8040 patients were enrolled in the study, of whom 6147 were included in the analysis. Following treatment initiation, a total of 530 AEs were reported in 6 % (383) of the patients. The most frequent post-treatment AEs were in alimentary system (42 %), including vomiting, nausea, diarrhoea, abdominal pain and anorexia, followed by AEs in the neurological system (25 %). Causality assessment of the events showed that 51.9 % (275/530) were possibly related to AL. There was a significant difference in the frequency of AEs by age-group with an increase in the number of AEs as age increased ($P < 0.001$). There was no statistically significant difference in the frequency of the events between males and females ($P = 0.504$). The AE profile was consistent with the AEs reported in the product information and in other studies; no new adverse drug reactions were identified. The majority of the reported AEs were the same as the symptoms of malaria and therefore indistinguishable from the underlying disease.

Conclusions The safety profile of AL for treatment of malaria continues to be favourable. CEM as a pharmacovigilance tool has proven to provide reliable safety data in a short period.

Key Points

The artemether-lumefantrine safety profile continues to be favourable.

The Cohort Event-Monitoring method is a reliable pharmacovigilance tool.

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1 Introduction

Artemisinin-based combination therapies (ACTs) are being widely used in sub-Saharan Africa for first-line treatment and management of uncomplicated *Plasmodium falciparum* malaria. Artemether-lumefantrine (AL) was introduced in Tanzania as a first-line treatment for uncomplicated *P. falciparum* malaria in 2006, in line with the World Health Organization (WHO) treatment guidelines, and was made available in public and faith-based healthcare facilities under subsidy for affordability to the majority of the population [1–3].

AL is generally considered to be safe and well tolerated in the treatment of uncomplicated *P. falciparum* malaria [4–8]. However, safety data from clinical trials may not reflect real-life experience due to patient exclusions and small sample sizes. Population-based post-marketing surveillance of medicines in a real-life setting is necessary to detect some of the adverse drug reactions (ADRs) that could have been missed during clinical trials.

The spontaneous reporting system, which forms the basis of the WHO Programme for International Drug Monitoring, is widely used by national pharmacovigilance centres to collect information on the safety profile of medicines. Despite the benefits of the spontaneous reporting system as a tool for capturing post-marketing safety data, the method has a number of limitations, including under-reporting, reporting biases and an unknown denominator (the number of patients exposed to each medicine is usually unknown, so the frequency of specific ADRs cannot be estimated) [9–12].

The WHO Global Individual Case Safety Report (ICSR) Database, VigiBase®, contains limited post-marketing safety data for ACTs from Africa and from other malaria-endemic countries [13]. Obtaining adequate information on the safety profile of AL is of paramount importance considering the large number of ACT courses that are being deployed globally each year, with approximately 20 million doses of AL being administered annually in Tanzania alone [14, 15].

WHO has proposed a method of active post-marketing surveillance for monitoring the safety of new medicines used in public health programmes known as Cohort Event Monitoring (CEM) [16–18]. The CEM approach has the potential to detect previously unknown or unsuspected ADRs and identify possible risk factors since all AEs are recorded, not only suspected ADRs, while the defined cohort enables the frequency of known and newly detected ADRs to be estimated. This study was conducted to assess the safety profile of AL in a large cohort of patients receiving treatment for malaria in public health facilities in Tanzania.

2 Methodology

2.1 Study Design, Sites and Population

This was a prospective, observational cohort study which involved an active surveillance of malaria patients commencing AL treatment to systematically capture all adverse events (AEs) experienced after treatment. The CEM method has been described in detail elsewhere [16]. A total of 19 health facilities in four regions (Mwanza, Dar es Salaam, Arusha and Pwani) were selected as monitoring sites for the study. Their locations were based on the catchment of the Tanzania Food and Drugs Authority (TFDA) National Pharmacovigilance Centre, TFDA zonal offices as well as regional pharmacovigilance centres to allow close and efficient follow-up of the facilities. The health facility needed to be accessible and to have a continuous supply of AL, and the healthcare providers needed to be willing to participate in the monitoring programme (including data collection and patient follow-up).

The study was carried out between September 2009 and June 2012. All patients who presented to the selected health facilities and were diagnosed with malaria, either presumptively based on clinical presentation or confirmed by microscopy or malaria Rapid Diagnostic Test (mRDT), and who were prescribed AL were eligible for enrolment. There were no exclusion criteria other than unwillingness to participate in the study. The target was to consecutively enrol patients within the study period to reach a minimum cohort of 8000 patients from all sites; a cohort of this size would have the power to detect a rare ADR (i.e. an ADR that occurs at a frequency of less than 0.1 %) with >95 % probability. Patients who gave verbal consent to participate in the study were enrolled; in the case of children, verbal consent was obtained from parents or guardians.

2.2 Drug Administration

The fixed-dose combination tablet containing artemether 120 mg plus lumefantrine 20 mg for oral administration was prescribed. The standard regimen involved six doses of four tablets each twice per day for adults and children (weighing above 35 kg). The first dose started on day zero followed by other doses at 8, 24, 36, 48 and 60 h, comprising a 3-day regimen. Depending on body weight, a dose of one to three tablets was prescribed at the same time intervals for children weighing less than 35 kg.

2.3 Data Collection

Pre- and post-treatment questionnaires were used for data collection as shown in the supplementary material (Online

Resource 1). A team comprised of clinicians, nurses and pharmaceutical personnel working at Outpatient Departments (OPD) at each facility and zonal pharmacovigilance focal persons were trained for data collection.

Information recorded at treatment initiation included: demographic data, contact information, malaria-related symptoms and signs at presentation, current and past medical conditions, medications (including all medicines taken during the preceding 7 days) and malaria laboratory test results. In addition, all new medical events that had started within the preceding 7 days were also recorded to enable comparison with new events that were subsequently recorded following treatment initiation. The AL regimen and other medicines prescribed at the first visit were also recorded on the Treatment Initiation Form. At enrolment, each patient was assigned a code number and issued with a CEM ID card for identification during follow-up visits.

Patients were requested to return to the health facility 7 days after initiation of treatment with AL for follow-up. Patients were interviewed by the healthcare provider and asked about any new or worsening symptoms they may have experienced since starting AL. Treatment outcome was also recorded, based on symptom resolution and without further diagnostic testing (mRDT or microscopy). In the event that a patient could not return for follow-up, a CEM focal person endeavoured to contact the patient by mobile phone. If a patient was concerned about any new or worsening symptoms, he or she could report to the health facility earlier than the recommended time. Patients who experienced AEs or other complications after the study period were encouraged to report to their usual healthcare provider using the routine spontaneous reporting system and were managed as per existing healthcare procedures.

An AE is defined as "any untoward medical occurrence that may present during treatment with a medicinal product but which does not necessarily have a causal relationship with this treatment" [19]. The AEs collected from patients were graded as mild, moderate or severe by the clinician at the facility based on their clinical judgement. The completed pre- and post-treatment forms were collected and submitted to TFDA HQ where the data was entered into CemFlow, a data management tool that was being developed by the Uppsala Monitoring Centre, in collaboration with WHO, specifically for use in CEM studies. Data security was assured by keeping the completed data collection forms in a limited access area and the electronic data in CemFlow was password protected.

2.4 Data Analysis

CemFlow uses a unique CEM terminology, which is based on the terminology developed by the former New Zealand Intensive Medicines Monitoring Programme (IMMP), to code the events. The CEM terminology has a five-level hierarchy and is mapped to MedDRA (Medical Dictionary for Regulatory Activities) [20] for consistency with international standards. The trained pharmacovigilance staff at TFDA National Pharmacovigilance Centre assigned the CEM terminologies during data entry. Co-morbid diseases, past medical history and laboratory tests were coded using the MedDRA dictionary. Monitored and concomitant medications were coded using the WHO Drug Dictionary [21, 22].

Individual reports were carefully reviewed by pharmacovigilance specialists at the TFDA and each reported event was assessed according to the WHO-UMC Causality Assessment system to establish the likelihood of a causal relationship between the reported event and the use of AL [23]. Factors that were taken into consideration in the assessment include: time-to-onset of the event, dechallenge and rechallenge information, alternative explanations such as the condition for which the medicine was given (malaria), other concurrent diseases and concurrent medications, and the known pharmacological properties of the drug. Causality was assessed for each event as 'Certain', 'Probable', 'Possible', 'Unlikely', 'Unclassified' or 'Unassessable'.

2.5 Statistical Analysis

The Excel outputs from the CemFlow database were imported into the IBM SPSS Statistics software version 16 [24] for statistical analysis. Chi square tests were used for categorical variables and Student's t test was used to determine statistical significance for continuous variables and comparisons between groups where appropriate. The statistical significance was set at $p < 0.05$. The events were ranked by frequency (per 1000 patients).

3 Results

3.1 Cohort Size

Eight thousand and forty (8040) patients were enrolled in the CEM study. 172 patients (2.1 %) were lost to follow-up and a further 1721 patients (21.4 %) were subsequently excluded from the analysis because of invalid data collection forms (incomplete data, details of medicines missing and unrecognized terminologies/abbreviations used), leaving a total of 6147 patients to be included in the analysis.

3.2 Characteristics of the Patients Included in the Study

Table 1 shows the demographic characteristics of the patients included in the CEM of AL in Tanzania.

Table 1 Characteristics of patients ($N = 6147$) included in the Cohort Event Monitoring of artemether-lumefantrine in Tanzania (2009–2012)

Characteristic	Value
Gender	
Male	2924 (47.6)
Female	3159 (51.4)
Sex not recorded	64 (1)
Age (years)	
0–4 years	1836 (29.9)
5–14 years	869 (14)
15–18 years	344 (5.6)
19–49 years)	2514 (40.9)
≥50 years	451 (7.3)
Age unknown	133 (2.2)
Mean (SD) age	19.8 (17.9)
Median age	18
Mean (SD) age in females	21.5 (17.8)
Mean (SD) age males	18.1 (18)

Values are expressed as *n* (%) unless specified otherwise

3.3 Pre-treatment Events

Patients presented with a total of 13,583 events at baseline. The most frequently reported events were fever 4802 (78.1 %), headache 2492 (40.5 %), malaise 1083 (17.6 %) and vomiting 1037 (16.9 %), consistent with the presentation of malaria. The pre-treatment events are summarized in Table 2.

3.4 Co-morbid Conditions

A total of 407 concurrent conditions were reported at baseline. The most common co-morbid condition was 'flu'/cold 161 (2.6 %), followed by HIV/AIDS 57 (0.9 %), tonsillitis 39 (0.6 %), pneumonia 27 (0.4 %), and hypertension 12 (0.2 %), as summarized in Table 3.

3.5 Concomitant Medication

A total of 25 different types of medications were co-administered during treatment with AL among the enrolled patients. The most commonly administered concomitant medications were paracetamol—66 (1.1 %), co-trimoxazole—25 (0.4 %) and zinc—12 (0.2 %), as summarized in Table 4.

3.6 Post-treatment Events

The AEs reported following treatment initiation are summarized by clinical category in Table 5. A total of 530 AEs were reported by 383 patients (6 %) at the follow-up interview. The ten most frequently reported AEs (expressed as frequency per 1000 patients) were headache

Table 2 Frequency of pre-treatment events in the 7 days before artemether-lumefantrine initiation in the Cohort Event Monitoring of artemether-lumefantrine in Tanzania (2009–2012) [$N = 6147$]

Pre-treatment events	Number of events	% of patients
Fever	4802	78.1
Headache	2492	40.5
Malaise	1083	17.6
Vomiting	1037	16.9
Coughing	722	11.7
Joint pain	654	10.6
Diarrhoea	560	9.1
Abdominal pain	389	6.3
Loss of appetite	263	4.3
Dizziness	211	3.4
Nausea	165	2.7
Back pain	112	1.8
Chest pain	107	1.7
Rhinorrhoea	99	1.6
Pain body	84	1.4
Fatigue	60	1.0
Chills	52	0.8
Hypoventilation	42	0.7
Abdominal discomfort	40	0.7
Anorexia	33	0.5
Convulsions	32	0.5
Palpitations	32	0.5
Neck pain	30	0.5
Rash	26	0.4
Shivering	25	0.4
Bitter taste	24	0.4
Chest tightness	23	0.4
Painful micturition	23	0.4
Sore throat	23	0.4
Gastritis	21	0.3
Mouth ulcers	20	0.3
Swelling extremities	18	0.3
Limb pain	17	0.3
Sweating	17	0.3
Cold	15	0.2
Itching	13	0.2
Numbness extremities	13	0.2
Hypertension	12	0.2
Arthralgia	11	0.2
Faintness	11	0.2
Pallor	10	0.2
Others (less than 10 cases)	160	2.6

Table 3 Co-morbid conditions in patients enrolled in the Cohort Event Monitoring of artemether-lumefantrine in Tanzania (2009–2012) [$N = 6147$]

Co-morbid conditions	Frequency	% of patients
Flu/cold	161	2.6
HIV infection	57	0.9
Tonsillitis	39	0.6
Pneumonia	27	0.4
Hypertension	12	0.2
Urinary tract infection	9	0.1
Upper respiratory tract infection	8	0.1
Dysmenorrhoea	6	0.1
Amenorrhea	5	0.1
Candidiasis	5	0.1
Fungal infection	5	0.1
Gynaecological pain	5	0.1
Arthritis	4	0.1
Asthma	4	0.1
Ear infection	4	0.1
Genital infection	4	0.1
Helminthic infection	4	0.1
Skin infection	4	0.1
Vaginal infection	4	0.1
Abscess	3	0.05
Gastroenteritis	3	0.05
Oral thrush	3	0.05
Pelvic inflammatory disease	3	0.05
Tinea	3	0.05
Bronchitis	2	0.03
Conjunctivitis	2	0.03
Diabetic complication	2	0.03
Failure to thrive	2	0.03
Malnutrition	2	0.03
Psychosis	2	0.03
Typhoid	2	0.03
Wound sepsis	2	0.03
Others	9	0.1

HIV human immunodeficiency virus

(23.3), vomiting (11.1), nausea (9.4), diarrhoea (5.9), malaise (5.9), anorexia (4.9), abdominal pain (4.7), fever (4.2), arthralgia (2.6) and rash (2.3). The majority (78.5 %) of these post-treatment events started on the same day as AL treatment initiation. Only 0.6 % (4) of the reported AEs were serious and reported as life threatening, and included cardiac arrest (1), seizure (1), dyspnoea (1) and wound sepsis (1). The AEs reported were mostly mild—341 (64.3 %), and moderate—140 (26.4 %) with only a few—49 (9.2 %) that were considered severe.

Table 4 Medications co-administered with artemether-lumefantrine 7 days before and during treatment in patients enrolled in Cohort Event Monitoring of artemether-lumefantrine in Tanzania (2009–2012) [$N = 6147$]

Type of medication	Number of patients
Paracetamol	66
Co-trimoxazole	25
Zinc	12
Quinine	8
Gentamycin	6
Erythromycin	5
Ciprofloxacin	4
Diclofenac	4
Ringer's lactate	4
Aspirin	3
Mebendazole	3
Oral rehydration salts	3
Vitamin B complex	2
Cloxacillin	2
Ibuprofen	2
Levofloxacin	2
Metronidazole	2
Promethazine	2
Tetracycline	2
Amoxycillin + cloxacillin	1
Azithromycin	1
Chloramphenicol	1
Omeprazole	1
Phenobarbitone	1
Tinidazole	1

3.7 Events by Age Group and Gender

There was no statistically significant difference in the overall frequency of reported AEs between males and females (84.1 AEs per 1000 male patients and 89.2 AEs per 1000 female patients, $p = 0.504$); cough was the only AE with a statistically significant difference in reporting frequency by sex, being more frequently reported in males, as shown in Table 5.

The overall frequency of reported AEs varied significantly by age group, with the highest frequency of events reported in elderly patients (122 AEs per 1000 patients), followed by adults (99.4 per 1000 patients) and adolescents (81.4 per 1000 patients). Overall, there was a significant association between the reporting of AEs and age group ($p < 0.001$). Headache was the only AE with a statistically significant difference in reporting frequency by age-group, with the frequency being lower in children aged less than 15 years than in adults aged over 18 years.

Table 5 Number and frequency of post-treatment adverse events (AEs) by age group and sex in patients enrolled in the Cohort Event Monitoring of artemether-lumefantrine in Tanzania (2009–2012)

Clinical category/AE	Number (frequency[a]) of AEs ($N = 6147$)	Number (frequency[a]) of AEs by age group[b]					Number (frequency[a]) of AEs by sex[c]	
		0–4 years ($N = 1836$)	05–14 years ($N = 869$)	15–18 years ($N = 344$)	19–49 years ($N = 2514$)	≥50 years ($N = 451$)	Male ($N = 2924$)	Female ($N = 3159$)
Total	530 (86.2)	86 (46.8)	48 (55.2)	28 (81.4)	250 (99.4)	55 (122)	246 (84.1)	282 (89.2)
Alimentary								
Vomiting	68 (11.1)	37 (20.2)	12 (13.8)	2 (5.8)	9 (3.6)	4 (8.9)	27 (9.2)	40 (12.7)
Nausea	58 (9.4)	3 (1.6)	4 (4.6)	5 (14.5)	31 (12.3)	5 (11.1)	30 (10.3)	28 (8.9)
Diarrhoea	36 (5.9)	9 (4.9)	6 (6.9)	1 (2.9)	9 (3.6)	4 (8.9)	15 (5.1)	21 (6.6)
Anorexia	30 (4.9)	3 (1.6)	2 (2.3)	1 (2.9)	11 (4.4)	2 (4.4)	19 (6.49)	11 (3,48)
Abdominal pain	29 (4.7)	1 (0.5)	4 (4.6)	1 (2.9)	18 (7.2)	5 (11.1)	14 (4.8)	15 (4.7)
Heartburn	7 (1.1)	–	–	–	5 (2.0)	2 (4.4)	5 (1.7)	2 (0.6)
Gastritis	3 (0.5)	–	–	–	3 (1.2)	–	–	3 (0.9)
Mouth ulcer	1 (0.2)	–	–	–	–	1 (2.2)	1 (0.3)	–
Constipation	1 (0.2)	1 (0.5)	–	–	–	–	1 (0.3)	–
Neurological								
Headache	143 (23.3)	5 (2.7)*	8 (9.2)	8 (23.3)	92 (36.6)	16 (35.5)	61 (20.9)	82 (26)
Seizure	1 (0.2)	1 (0.5)	–	–	–	–	–	1 (0.3)
Deafness	1 (0.2)	–	–	–	1 (0.4)	–	1 (0.3)	–
Body pain	1 (0.2)	1 (0.5)	–	–	–	–	1 (0.3)	–
Mental health								
Malaise	36 (5.9)	2 (1.1)	–	1 (2.9)	23 (9.1)	4 (8.9)	17 (5.8)	19 (6.0)
Autonomic								
Fever	26 (4.2)	6 (3.3)	8 (9.2)	1 (2.9)	5 (2.0)	4 (8.9)	9 (3.1)	17 (5.4)
Sweating	1 (0.2)	–	–	–	–	1 (2.2)	–	1 (0.3)
Chills	1 (0.2)	1 (0.5)	–	–	–	–	1 (0.3)	–
Skin								
Rash	14 (2.3)	6 (3.3)	1 (1.2)	1 (2.9)	5 (2.0)	–	6 (2.1)	8 (2.5)
Pruritus	9 (1.5)	–	–	–	4 (1.6)	1 (2.2)	4 (1.4)	5 (1.6)
Musculoskeletal								
Arthralgia	16 (2.6)	–	–	3 (8.7)	12 (4.8)	1 (2.2)	8 (2.7)	8 (2.5)
Back pain	2 (0.3)	–	–	–	2 (0.8)	–	1 (0.3)	1 (0.3)
Circulatory								
Dizziness	11 (1.8)	–	1 (1.2)	1 (2.9)	7 (2.8)	2 (4.4)	3 (1.0)	8 (2.5)
Chest pain	3 (0.5)	–	–	–	2 (0.8)	1 (2.2)	1 (0.3)	2 (0.6)
Cardiac arrest	1 (0.2)	–	–	–	–	1 (2.2)	–	1 (0.3)
Hypertension	1 (0.2)	–	–	–	1 (0.4)	–	–	1 (0.3)
Dyspnoea	1 (0.2)	–	–	–	–	–	1 (0.3)	–
Palpitations	1 (0.2)	–	–	–	1 (0.4)	–	1 (0.3)	–
Respiratory								
Cough	13 (2.1)	5 (2.7)	1 (1.2)	2 (5.8)	5 (2.0)	–	10 (3.4)*	3 (0.9)
Urological								
Urinary infection	2 (0.3)	–	–	1 (2.9)	–	–	–	2 (0.6)
Urine abnormal	2 (0.3)	–	–	–	–	–	2 (0.7)	–
Eye								
Eye pain	2 (0.3)	–	1 (1.2)	–	1 (0.4)	–	1 (0.3)	1 (0.3)

Table 5 continued

Clinical category/AE	Number (frequency[a]) of AEs ($N = 6147$)	Number (frequency[a]) of AEs by age group[b]					Number (frequency[a]) of AEs by sex[c]	
		0–4 years ($N = 1836$)	05–14 years ($N = 869$)	15–18 years ($N = 344$)	19–49 years ($N = 2514$)	≥50 years ($N = 451$)	Male ($N = 2924$)	Female ($N = 3159$)
Vision reduced	1 (0.2)	–	–	–	0 (0.0)	1 (2.2)	1 (0.3)	
Others	8 (1.3)	5 (2.7)	–	–	3 (1.2)	–	5 (1.7)	2 (0.6)

* Statistically significant difference between groups

[a] Frequency expressed as number of events per 1000 patients

[b] Age was not recorded in 133 study participants (including 63 events)

[c] Sex was not recorded in 64 study participants (including two events) so the denominator for both sexes combined is 6083 with a total of 528 events

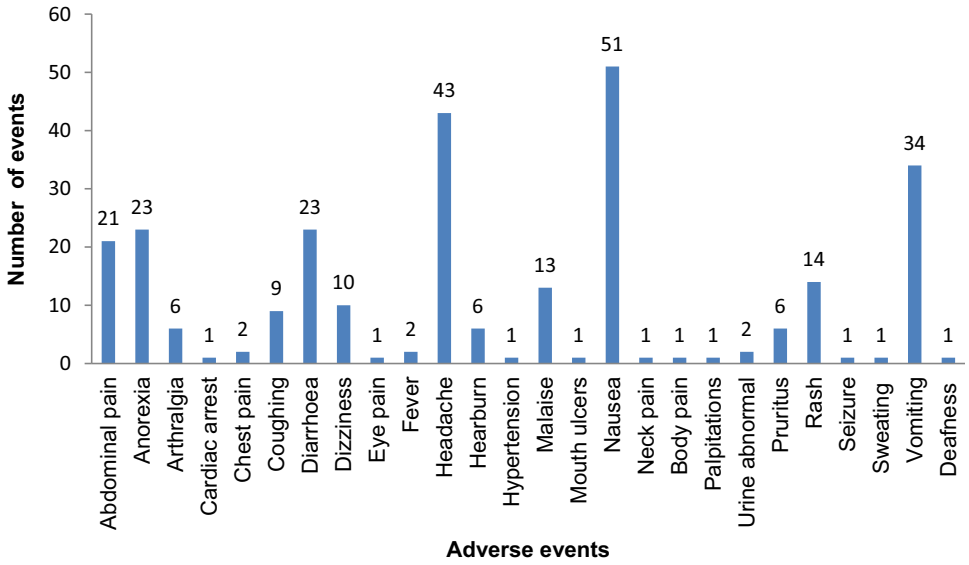

Fig. 1 Post-treatment events classified as possibly related to artemether-lumefantrine in Cohort Event Monitoring in Tanzania (2009–2012)

The most frequently reported AEs in children aged less than 5 years were: vomiting (20.2 per 1000), diarrhoea (4.9 per 1000), fever and rash (both 3.3 per 1000). Vomiting (13.8 per 1000), fever and headache (both 9.2 per 1000) were the most frequently reported AEs in children aged 5–14 years. Adolescents aged 15–18 years most frequently reported headache (23.3 per 1000), nausea (14.5 per 1000) and arthralgia (8.7 per 1000), while adults most frequently reported headache (36.6 per 1000), nausea (12.3 per 1000) and malaise (9.1 per 1000). Patients aged over 50 years most frequently reported headache (35.5 per 1000), nausea and abdominal pain (both 11.1 per 1000). Table 5 summarizes the frequency of AEs by age-group and sex.

3.8 Causality Assessment

Assessment of causality indicated a 'possible' causal relationship to AL for 275 (51.9 %) of the 530 events that were reported at follow-up; 252 events (47.5 %) were assessed as 'unlikely' to be related to AL and the remaining three events (0.6 %) could not be assessed due to a lack of information. No events were assessed to have a 'probable' or 'certain' causal relationship. The most common events that were assessed as possibly caused by AL were: nausea ($n = 51$), headache ($n = 43$), vomiting ($n = 34$), diarrhoea ($n = 23$), anorexia ($n = 23$) and abdominal pain ($n = 21$) (Fig. 1).

3.9 Outcome of the Events

At day 7 of patient follow-up, 83.1 % of AEs were reported to have resolved, 7.9 % were resolving, 3 % had resolved with sequelae, 4.5 % of the events had not resolved and the outcome was not reported at the time of follow-up for the remaining 1.5 % of the reported events.

4 Discussion

In this CEM study of artemether-lumefantrine, a cohort of 6147 male and female patients of various age groups (mean age of 19.8 years) was successfully followed up 7 days after commencing treatment for uncomplicated malaria.

Six percent of the cohort reported a total of 530 AEs at the follow-up interview; the remaining 94 % of the cohort reported no new events, suggesting that AL was generally well tolerated by patients in this Tanzanian cohort during the 7-day follow-up period. Of the 530 AEs reported at the follow-up visit, 99.3 % were not serious, nearly two-thirds were reported as mild and over 90 % had either resolved or were resolving at the time of the follow-up interview on day 7. These findings are consistent with the manufacturer's product information sheet [25], which states that 'most adverse reactions were mild, did not lead to discontinuation of study medication, and resolved'. These findings are also consistent with a Nigerian CEM study that compared the AE profile of two ACTs, artemether + lumefantrine (AL) and artesunate + amodiaquine (AA): among the 1068 patients who received AL, 176 events were reported during a 7-day follow-up period, none of which were reported as serious, and 87 % of events reported for either combination had resolved or improved within the 7-day monitoring period [26].

The most frequently reported AEs at the follow-up interview were headache, vomiting, nausea, diarrhoea, malaise, anorexia, abdominal pain and fever. These events are also common symptoms of malaria, so it is difficult to differentiate whether the reported AEs were caused by the disease for which the medicine was prescribed or by the medicine itself. The similarity of treatment-emergent AEs to the symptoms of malaria was also noted in a review of clinical trials that included a total of over 6300 patients treated with AL [27]. The review showed that AL is generally well tolerated with the majority of reported AEs affecting either the gastrointestinal or nervous system; few adverse events were considered by the investigators to be drug-related, while the majority were assessed as being caused by malaria [27].

To facilitate causality assessment, all new symptoms that had developed in the 7 days prior to treatment initiation were recorded at the initial visit as 'pre-treatment events'; information was also collected on concurrent and past medical conditions and current medicines. The WHO-UMC System for Standardized Case Causality Assessment takes into consideration alternative explanations for the reported events in addition to the plausibility of the time-to-onset (both pathologically and pharmacologically), the result of dechallenge (and rechallenge) if applicable, and the known pharmacology of the drug. Using this system, approximately half of the events were assessed to have a 'possible' causal relationship to AL while almost as many were assessed as 'unlikely' to be caused by the drug. None of the reported events were assessed to have a stronger causal relationship ('probable' or 'certain') to AL.

Overall, there was no statistically significant difference in the frequency of AEs between males and females; however, cough was reported more frequently in males ($p < 0.05$). The frequency of reported AEs increased significantly with increasing age group, from 46.8 events per 1000 patients aged 0–4 years to 122 events per 1000 patients aged 50 years and over. This finding is not surprising as the increased risk of ADRs in older patients due to changes in pharmacodynamics and pharmacokinetics have been well documented [28, 29].

Vomiting was the most frequently reported AE in all children aged up to 14 years; in children aged less than 5 years, diarrhoea, fever, rash, headache and cough were also among the most frequently reported AEs, while in children aged 5–14 years the most frequently reported events also included fever, headache, diarrhoea, nausea and abdominal pain. The AEs observed in children in this study are similar to those observed in pre-marketing clinical trials, whereby pyrexia, cough, vomiting, anorexia and headache were the most frequently observed treatment-emergent AEs in children [25]. The results are also consistent with the findings of a systematic review of AL in children aged less than 18 years that included a total of 6000 patients, in which cough was very commonly reported (frequency of at least 1/10), while coryza, vomiting, anaemia and diarrhoea were all commonly reported (frequency between 1/10 and 1/100) [30]. Similarly, a pooled analysis of eight clinical trials of AL in children weighing 5–25 kg that aimed to compare the safety and efficacy of four- and six-dose regimens, reported that the most frequent AEs observed with both regimens included cough, anaemia, anorexia, vomiting, hepato-splenomegaly, headache and diarrhoea [31].

Adults most frequently reported headache, nausea, malaise and abdominal pain. The most frequent AE described in the manufacturer's product sheet for adults is headache, followed by anorexia, dizziness, asthenia, arthralgia, myalgia, nausea, pyrexia, chills and sleep disorder [25]. These AEs are also similar to those reported in a pooled analysis of clinical trial data that included a total of 598 adult and adolescent patients aged over 12 years who were treated with the six-dose regimen of AL: the most frequently reported AEs were headache, asthenia, dizziness, myalgia, arthralgia, nausea, anorexia and fatigue [32]. The most frequent AEs reported by patients in the cohort aged over 50 years were headache, nausea, abdominal pain, vomiting, diarrhoea, fever and malaise.

Neurological events comprised 27.5 % ($n = 146$) of the reported post-treatment AEs. The majority of these events were headache ($n = 143$), but there was also one case each of seizure, deafness and body pain. Forty-three of the reported headache events were assessed as possibly related to AL, while the remainder was assessed as unlikely to be related. The seizure occurred in a child and was assessed as possibly related to AL, but may also have been explained by the underlying febrile illness that was being treated. One case of deafness was experienced in an adult male who had 'flu', fever and headache within the 7 days prior to AL treatment initiation and these other conditions might account for the deafness despite the temporal relationship to starting AL. The deafness was mild and resolved within 24 h. Of note, neurotoxicity has been associated with artemether in preclinical studies and with case reports in the literature [33–36]. The body pain experienced by one child occurred on the day treatment was started and was classified as possibly related; the pain had resolved at the follow-up visit. Body pain is also a symptom of malaria and therefore difficult to distinguish whether it was related to AL or to the underlying infection.

Lumefantrine is chemically related to halofantrine, which has been associated with significant QTc prolongation; cardiac safety has been investigated during the preclinical and clinical development of AL, and lumefantrine is considered to pose a low risk of cardiotoxicity compared to halofantrine [27, 37, 38]. In this study, a total of 3.2 % ($n = 17$) of the AEs reported at follow-up belonged to the circulatory clinical category of which 16 were classified as possibly related to AL. The most common circulatory AE was dizziness (11 cases); other circulatory AEs included chest pain (three cases), hypertension (one case) and palpitations (one case), all of which were not serious. There was also one serious case of cardiac arrest, which occurred 2 days after treatment initiation in a 55-year-old female who presented with fever at baseline and was treated presumptively for malaria with AL. No prior medical history was reported and the case was assessed as possibly related to AL based on the temporal relationship.

One case of mild chest pain occurred 1 day after treatment initiation in an adult male patient who presented with fever and headache and was also on antiretrovirals (ARVs) and fluconazole. The case was assessed as possibly related to AL due to time plausibility; however, his other conditions were likely to have caused the event. The second case of mild chest pain occurred 2 days after treatment initiation in an elderly patient who was treated presumptively for malaria when he presented with dizziness and headache; he was also started on amoxycillin and aminophylline for asthma on the same day. Despite the temporal relationship to starting AL, the chest pain could also have been attributed to the asthma so the relationship was assessed as possible. The third case of chest pain occurred 6 days after treatment initiation in a female adult patient who had presented with malaise, headache and fever at baseline and was positive for malaria on microscopy. The case was assessed as possibly related to AL.

In addition to malaria, some patients (6.6 %) were diagnosed with other conditions at the initial visit and were prescribed other medicines together with AL. Consequently, some of the events that have been reported at the follow-up interview might also have been attributable to other medicines.

Overall, 25 different types of medication, besides AL, were taken either during the 7-day comparator period prior to starting AL or concurrently with AL. The majority of these concomitant medicines were antibiotics (48 %), including fluoroquinolones and macrolides. The prescribing information for AL recommends caution, including monitoring of the QT interval, when medicines that prolong the QT interval such as fluoroquinolone and macrolide antibiotics are used together with AL; however, it was observed that in practice patients were prescribed these medicines without additional monitoring being done.

The CEM method provides exposure information (the denominator) for the monitored medicine, which enables the frequency of the AEs to be calculated, providing an advantage when compared to the routine spontaneous reporting system [16]. CEM has provided the National Pharmacovigilance Centre at Tanzania Food and Drugs Authority with reliable safety data in a short time. The CEM study was conducted in a small number of health facilities across four regions in Tanzania and from these monitoring sites a total of 530 AEs were reported, of which 275 were assessed as possibly related to AL. By contrast, it is worth noting that in the same period only 89 ADRs were reported for AL from the remaining 21 regions in Tanzania through the routine spontaneous reporting system. CEM is based on the Prescription Event Monitoring (PEM) method that has been established and practiced in New Zealand and the UK for many years, where it has provided safety data quickly and has enabled the detection of signals for ADRs [39–41]. This study has shown that CEM can be conducted in Tanzania and can provide a useful profile of adverse events for a drug that is widely used in the local population.

However, some challenges were encountered during the implementation of CEM including a lack of commitment by healthcare providers who were overburdened with forms to complete for various other programmes. Another challenge was the causality assessment of the AEs, many of which overlapped with the symptoms of malaria and were difficult to distinguish from the underlying disease.

Limitations of this study included misrepresenting and under-reporting of some adverse events due to third-party reporting (where adults reported AEs for their children).

The degree to which these factors may have affected the results of our study was not assessed. Another limitation was the inability to detect abnormal laboratory test results or electrocardiographic disturbances since these investigations are not part of the routine follow-up for patients with malaria in Tanzania. This study was conducted in real-life healthcare settings in Tanzania with quite a number of challenges such as limited resources, work overload, staff turnovers and different staff qualifications. This limitation contributed to having some of the sites not to perform well in the completion of questionnaires despite training and frequent supervision, which led to some forms being invalid.

5 Conclusion

The safety profile of the antimalarial drug combination artemether-lumefantrine remains favourable for the treatment of uncomplicated *P. falciparum* malaria. No major safety concerns were observed in the 7 days following treatment initiation with AL in a cohort of 6147 patients in Tanzania. Most of the observed AEs were already documented elsewhere.

CEM has proven to be a useful tool for pharmacovigilance in Tanzania. The methodology can be used to complement the spontaneous reporting system for monitoring the safety of medicines of public health interest in the future.

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Compliance with Ethical Standards

Ethical Considerations Cohort Event Monitoring of medicines is part of drug safety monitoring and is under the jurisdiction of Tanzania Food and Drugs Authority (TFDA) as per the Tanzania Food, Drugs and Cosmetics Act, Cap 219 section 5 (C) [42]. The study was endorsed by TFDA Pharmacovigilance Technical Committee. This study was observational and did not interfere with the routine practice in health facilities. However, all patients were informed of the purpose of undertaking the monitoring and were requested to provide verbal consent as per requirements [43]. Ethical principles for conducting medical research were considered during implementation of the programme.

Conflicts of interest Ms. Alambo K. Mssusa, Mr. Adam M. Fimbo, Dr. Alex F. Nkayamba, Mr. Henry F. Irunde, Mr. Hiiti B. Sillo, Dr. Danstan H. Shewiyo, Dr. Geraldine Hill and Prof. Omary M. Minzi declare they have no direct conflicts of interest.

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