



Effectiveness and Tolerability of the ASAQ versus AL Association in Children 6-59 Months for the Treatment of Uncomplicated *P. falciparum* Malaria in Massakory (Chad)

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Abstract: *Background and Objective:* Artemisinin-based combination therapies are the first-line antimalarial drugs used to treat uncomplicated *Plasmodium falciparum* malaria in many endemic countries worldwide. This study was conducted to assess the efficacy and tolerability of two fixed-dose formulations of artesunate-amodiaquine and artemether-lumefantrine for the treatment of *Plasmodium falciparum* malaria in Chad. *Methodology and Results:* A two-arm single cohort study was conducted assessing the efficacy artesunate-amodiaquine and artemether-lumefantrine for the treatment of children with uncomplicated falciparum malaria. This study was carried out from December 14, 2019 to March 14, 2020 at the Massakory I Health Center in Chad. Primary efficacy endpoint was day 28, parasitological cure rate. Secondary endpoints were parasite and fever clearance times and tolerability. A total of 113 patients were included, including 56 in the artesunate-amodiaquine arm and 57 in the artemether-lumefantrine arm. In intention to treat these patients, the Adequate Clinical and Parasitological Response on day 28 were 100% for the two groups. No early treatment failure was observed. The drugs were well tolerated and no serious adverse events were noted. *Conclusion:* Both forms of Artemisinin-based combination therapy were still effective and safe in the treatment of uncomplicated *P. falciparum* malaria in Chad. Further studies are warranted in different regions of Chad for monitoring of drug resistance.

Keywords: Simple Malaria, Artésunate-Amodiaquine, Artemether-Lumefantrine, *Plasmodium falciparum*, Massakory, Chad

1. Introduction

Malaria remains an important public health problem in tropical and subtropical countries. It is estimated that there were 216 millions clinical cases of malaria and around 445,000 deaths in 2016, of which nearly 92% were in Africa, according to data from the World Health Organization [1]. Almost 85% of malaria deaths worldwide in 2018 were concentrated in 20 countries in the WHO Africa region and India. Nigeria alone accounted for nearly 24% of these deaths, followed by the Democratic Republic of the Congo (11%), the United Republic of Tanzania (5%), as well as Angola, Mozambique and Niger (4% each). It is estimated that nearly 24 millions children in sub-Saharan Africa suffered from *P. falciparum* malaria infections in 2018.

Since then, great strides have been made to reduce malaria-related morbidity and mortality. Artemisinin-based combination therapy (ACT) has been recommended for the treatment of uncomplicated falciparum malaria in almost all areas, as recommended by the WHO, since the emergence and spread of multidrug-resistant strains of *Plasmodium falciparum* [2]. ACT combines a fast-acting but rapidly eliminated artemisinin derivative with a long-lasting partner drug. Artesunate-Amodiaquine (ASAQ) and Artemether-Lumefantrine (AL) are the first-line drugs for uncomplicated *P. falciparum* malaria in Africa. ACT therapy indeed shows high efficacy, but clinical resistance to artemisinin, manifested by delayed parasite clearance, was first reported in Pailin, western Cambodia in 2009 [3], this resistance has

spread to all the countries of the Greater Mekong sub-region [4, 5]. The presence of resistance to Artemisinin partner drugs has caused treatment failure with Piperaquine (DHA-PPQ), AL, etc. [4, 6, 7].

Therefore, it is important and necessary to study the emergence and distribution of artemisinin and partner drug resistance in order to guide public health measures and rational administration at the level of local communities. Protecting the effectiveness of recommended treatments for malaria is a top priority for malaria-endemic countries as well as the global malaria control community.

In Chad, since the adoption of ACTs in its first-line treatment policy for uncomplicated malaria in 2005, Artemether-Lumefantrine and Artesunate-Amodiaquine have been widely used. WHO recommends that all countries regularly monitor the emergence or spread of resistant parasites. Therapeutic efficacy studies remain the gold standard for guiding drug policy. Regular performance of Therapeutic Effectiveness Tests (TET) every two years, coupled with molecular studies, is an effective way to monitoring drug resistance in endemic countries. This study was conducted to assess the efficacy and tolerability of two fixed-dose formulations of ACT, Artesunate-Amodiaquine and Artemether-lumefantrine for the treatment of *P. falciparum* malaria in Chad. This study shows that they are effective for the treatment of uncomplicated malaria with the Adequate Clinical and Parasitological Response which was 100% in both groups.

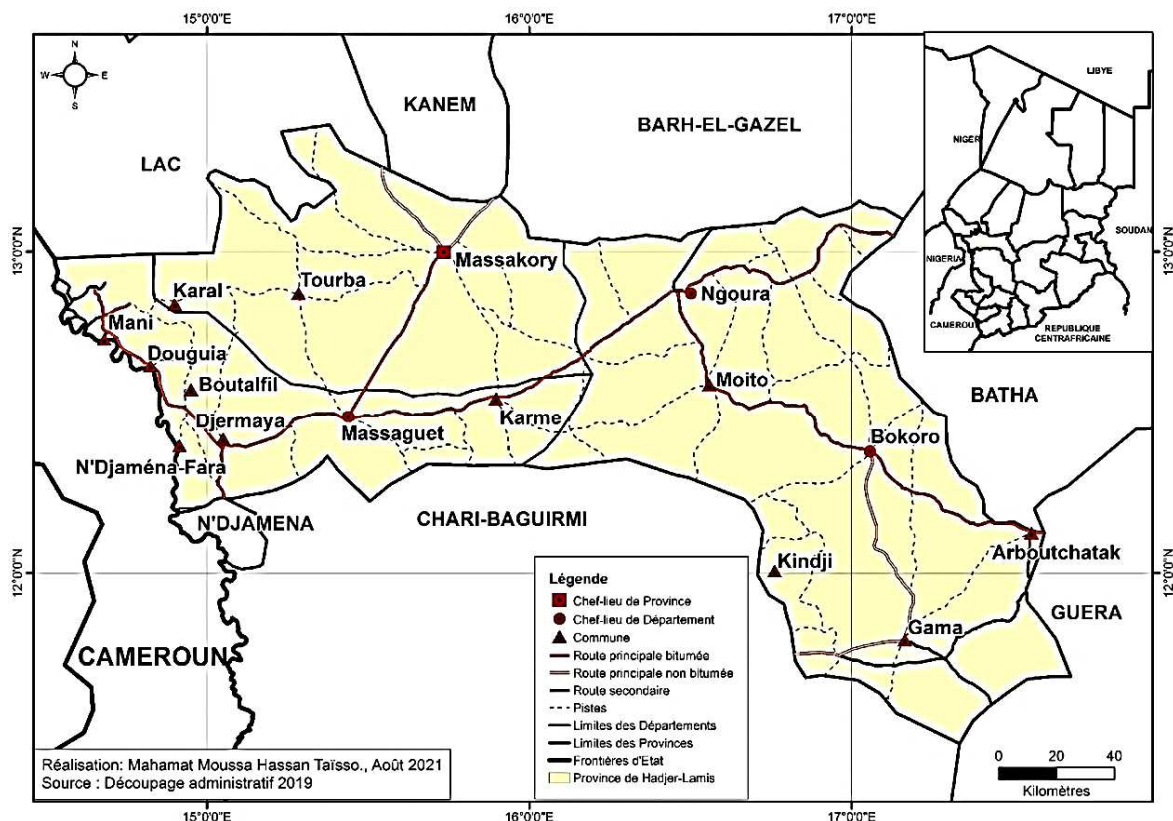


Figure 1. Map of Massakory, Chad.

2. Materials and Methods

2.1. Type, Period and Study Location

This was a two-arm single cohort study (ASAQ-AL). The patients are split into two groups corresponding to the two molecules tested. After the medication is drawn, a unique code is assigned to each patient until discharge (D28). The study was carried out from December 14, 2019 to March 14, 2020 at the Massakory I Health Center (Maplink Latitude: 13.0016804 Longitude: 15.7286011), located in the city of Massakory about 160 km at the North exit from N'Djamena (figure 1). Massakory is the capital of the Province of Hadjer Lamis and department of Dagana. The Center covers an area of responsibility with 46 rural villages and 9 urban districts, the number of the population is estimated at 15,122 in 2015. The number of monthly consultations varies from 1,000 to 2,500 respectively in the dry and rainy seasons.

2.2. Target Population of the Study

The study focused on patients with uncomplicated *P. falciparum* malaria, aged 6 to 59 months, who came for consultation at the Massakory health center and who had met the criteria for inclusion of the protocol. This age group is often vulnerable to all diseases, especially malaria because of their weak immune system. This group provides a better appreciation of the therapeutic efficacy of ASAQ and AL.

2.3. Procedure and Sample Collection

The population of this study was infant aged to 6-59

months, and presenting with acute, symptomatic, uncomplicated *P. falciparum* malaria. They were recruited according to the WHO inclusion criteria (absence of severe malnutrition, axillary temperature of $\geq 37.5^{\circ}\text{C}$ or history of fever in the last 24 hours, asexual *P. falciparum* density 2,000-200,000/ μL , and ability to swallow oral medication), and exclusion criteria (severe vomiting, history or evidence of clinically systematic significant disorders, other febrile conditions, hypersensitivity or adverse reactions to anti-malarial, history of use of any other anti-malarial agent within four weeks prior to start of the study). Subject informed consent was requested prior the study. Subjects who withdrew early were not replaced. Eligible subjects were blindly, randomly assigned equally to one of the two treatment groups (ASAQ-AL).

ASAQ₁ manufactured by SANOFI (batch number 8MA127, expiration date 01/01/2021) is dosed as 25 mg Artesunate / 67.5 mg Amodiaquine body weight for infants (3-11 months) and ASAQ₂ (Batch number 8MA153, expiration date 01/01/2020) is dosed in 50 mg Artesunate / 135 mg Amodiaquine for small children (3-5 years). ASAQs were prescribed based on the child's body weight once a day for 3 days.

AL is manufactured by CILPA (batch number B / NID73883, expiration date 09/01/2020), is dosed in 20 mg Artemether / 120 mg Lumefantrine. The treatment was administered twice a day for three days. All medication taken under the supervision of the doctor for possible side effects. (The dosage is given in the following table 1).

Table 1. ASAQ and AL dosing regimen.

| Body weight (age) | Day 0 | Day 1 | Day 2 |
|-----------------------------------|-----------------|----------------|----------------|
| Artesunate-Amodiaquine (ASAQ) | | | |
| 5 to 9 kg (<3 years) | 1 tab 2x / day | 1 tab 2x / day | 1 tab 2x / day |
| 9 to 18 kg ($\geq 3 - 8$ years) | 2 tab * | 2 tab * | 2 tab * |
| Artemether-Lumefantrine (AL) | | | |
| 5 to 15 kg (<3 years) | 1 tab x 2 / day | tab 2x / day | 1 tab 2x / day |
| 15 to 25 kg ($\geq 3 - 8$ years) | 2 tab x 2 / day | 1 tab 2x / day | 1 tab 2x / day |

*Or 1 tab containing 50 mg of artesunate and 135 mg of amodiaquine.

The same dose of drug was re-administered if the patient vomited within 30 minutes after administration. Any patient who persistently vomited after second dosing of drug within 30 minutes was excluded from the study and treated with intravenous quinine or intramuscular artesunate according to national guidelines. Paracetamol has been given to any patient with a body temperature above 38°C . The patients were regularly followed up to D28 and underwent a clinical examination with control of blood smear and axillary temperature measurement on D0, D1, D2, D3, D7, D14, D21 and D28. Capillary blood on filter papers (Wattman 3) was collected systematically from all patients on the day of inclusion D0 and during follow-up after D7 in the event of therapeutic failure.

The protocol that was carried out during this study was validated by the National Malaria Control Program (NMCP).

This study is part of the WHO recommendations to test first and second line drugs used for the management of uncomplicated malaria.

2.4. Microscopic Blood Examination

To confirm compliance with the inclusion and exclusion criteria, each child had a blood sample taken for the Parasite Density (PD) count during screening Day zero (D0) and on days 1, 2, 3, 7, 14, 21, 28 follow-up. The labeling of the samples was anonymous (screening number, day of follow-up, date). Blood is drawn on a slide for thin and thick smear. Cookies and candies were distributed to the children; soap scoops and travel expenses were given to parents.

The parasite density (PD) is calculated according to the following formula where PD (μL) = $N \times 8,000 / X$

(PD: parasite density; N: number of parasites counted; X: number of leukocytes counted).

Slide is considered negative when examination of 1000 leukocytes or 100 fields containing at least 10 white blood cells per field does not show any asexual form of parasite.

The internal quality control were carried out by a team of physicians and parasitologists respectively from the University Hospital and Faculty of Health Sciences of the Ministry of Higher Education, Research and Innovation (Chad).

2.5. Primary Endpoint

The proportion of patients with early Adequate Clinical and Parasitological Response (ACPR), Treatment Failure designated as Early Treatment Failure (ETF), Late Clinical Failure (LCF), or Late Parasitological Failure (LPF).

2.6. Secondary Endpoint

The frequency and nature of the side effects.

2.7. Data Analysis

The Excel™ spreadsheet developed by WHO was used for data management and analysis. The data were analyzed using the following two methods: Kaplan-Meier method, and

“Per Protocol” analysis ACPR percentages were calculated with a 95% confidence interval.

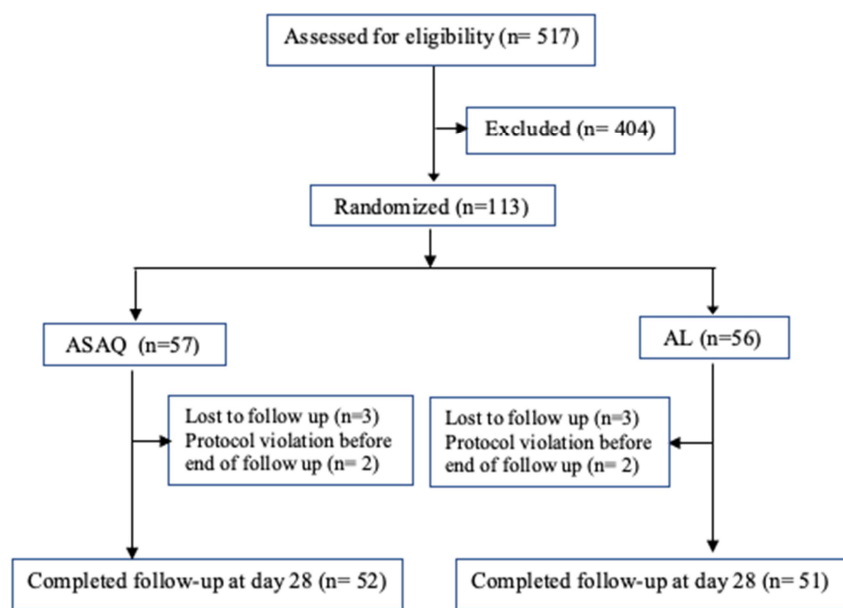
2.8. Ethical Considerations

Before the start of the study, the protocol falling within the framework of the WHO recommendations aimed at testing drugs, in particular ACTs used in 1st and 2nd line, received the approval of the Ministry of Public Health and National Solidarity. Public as well as the authorization of the ethics committee through a research authorization from the Ministry of Higher Education, Research and Innovation of Chad. All parents or legal guardians of the children received a clear explanation of the study and informed consent was obtained.

3. Results

3.1. Population Profile

A total of 113 patients were recruited for uncomplicated malaria during the study period. These patients received ASAQ (n = 57) or AL (n = 56) as treatment after randomization. Among them, 103 out of 113 included were followed up to D28, including 51 in the AL group against 52 in the ASAQ group (shown in Figure 2).



ASAQ: artésunate amodiaquine, AL: artéméter-luméfantrine

Figure 2. Distribution of patients by treatment group and exclusion during follow-up.

3.2. General Characteristic of the Study Population

The children's temperatures varied between 36°C and 40.9°C with an average of 38.6 (1.4) for the AL group and between 36°C and 40.8°C with an average of 38.5 (1.3) for the ASAQ group; Children's weights varied between 7.7 kg and 22.8 kg in the AL group with an average of 14 kg and between 5 kg and 20.4 kg in the ASAQ group with an average of 12 kg.

Of the 56 patients included in the AL group, 32 were male, ie an M/F sex ratio of 1.3; in the ASAQ group, the sex ratio

M/F is 1.2.

The age of the patients varied between 6 months and 59 months. Children aged 48 to 59 months were the most represented respectively with 30.08% in the AL group against 18.58% in the ASAQ group. (Figure 3)

The parasite density (PD) at D0 varied between 2,080 and 35,000 for the AL group against 2,100 and 35,640 for ASAQ. The highest PDs represented 40.35% and 35.71% respectively for ASAQ and AL (figure 4).

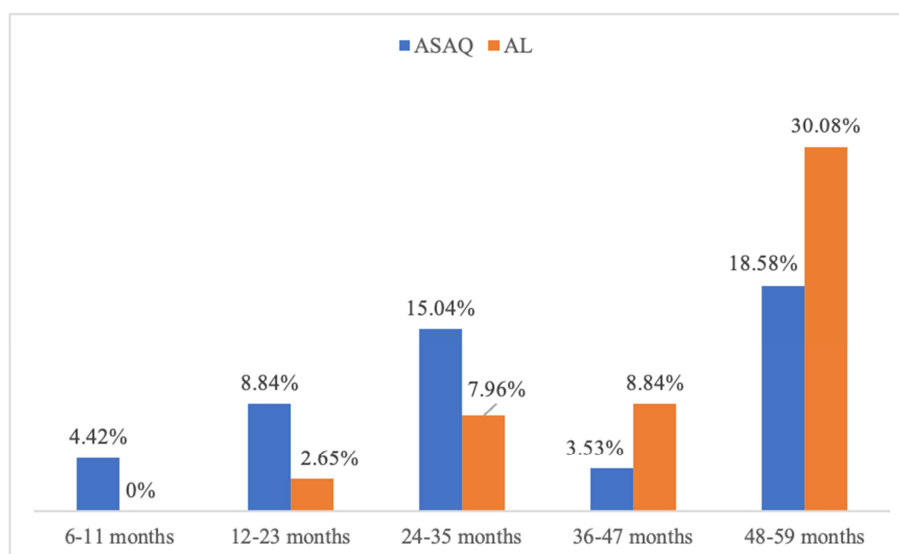


Figure 3. Distribution of patients by age group in the two treatment groups.

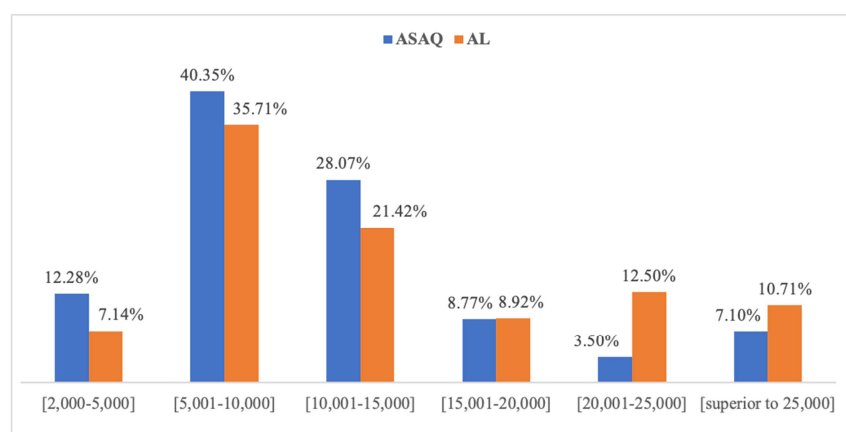


Figure 4. Distribution of patients according to parasite density class and treatment group.

Table 2. Clinical and para-clinical characteristics of the study population.

| Characteristics | Molecules | |
|--|--------------|---------------|
| | AL | ASAQ |
| Number of patients | 56 | 57 |
| Male (M) | 32 | 32 |
| Female (F) | 24 | 25 |
| Ratio M/F | 1.3 | 1.2 |
| Age (years) | | |
| Average (sd)* | 3.6 (1.2) | 2.7 (1.4) |
| Extreme (min-max) in year | 1 – 5 years | 0.5 – 5 years |
| Weight (kg), day 0 | | |
| Average weight (kg) (sd) | 14 (3.3) | 12 (3.6) |
| Extreme (min-max) in kg | 7.7-22.8 | 5-20.4 |
| Temperature (°C), day 0 | | |
| Average temperature (sd) °C | 38.6 (1.4) | 38.5 (1.3) |
| Extreme (min-max) °C | 36-40.9 | 36-40.8 |
| Parasitaemia (μL), day 0 | | |
| Geometric mean parasitaemia (asexual parasites / μL) | 11,712 | 9,534 |
| Extreme (min-max) (asexual parasites / μL) | 2,080-35,000 | 2,100-35,640 |

*sd: standard deviation, day 0: first day of inclusion and follow-up of patients.

Table 3. Distribution by sex and treatment group.

| Drugs | | | |
|---------------|-------------|---------------|-----------------|
| Gender | AL (n = 56) | ASAQ (n = 57) | Total (n = 113) |
| Male | 32 | 32 | 64 |
| Female | 24 | 25 | 49 |
| M/F sex ratio | 1.3 | 1.2 | |

3.3. Therapeutic Efficacy of AL and ASAQ at Day 28

Table 4. Responses to treatment on D28 according to the two treatment groups.

| Parameters | AL | | ASAQ | | |
|--------------|--------|-------|----------|--------|-------|
| | Number | % | IC | Number | % |
| ETF | 0 | 0.0 | 0.0-7.0 | 0 | 0.0 |
| LCF | 0 | 0.0 | 0.0-7.0 | 0 | 0.0 |
| LPF | 0 | 0.0 | 0.0-7.0 | 0 | 0.0 |
| ACPR | 51 | 100.0 | 93-100.0 | 52 | 100.0 |
| Number total | 51 | | | 52 | |

ACPR: Adequate Clinical and Parasitological Response; ETF: Early Treatment Failure; LCF: Late Clinical Failure and LPF: Late Parasitological Failure.

At D28 the RCPA was 100% for the two groups AL and

ASAQ. LPF, LCF and ETF were 0% each for the two groups (AL: IC between 0.0-7.0 and ASAQ: IC between 0.0-6.8).

3.4. Tolerance

Table 5. Distribution of patients according to thermal clearance.

| Temperature (T°) | AL | | ASAQ | |
|------------------|---------|----|---------|----|
| | Average | n | Average | n |
| D0 | 38.63 | 56 | 38.47 | 57 |
| D1 | 37.19 | 55 | 37.31 | 56 |
| D2 | 36.75 | 55 | 36.65 | 56 |
| D3 | 36.74 | 54 | 36.71 | 54 |
| D7 | 37.04 | 53 | 36.95 | 54 |
| D14 | 36.96 | 51 | 37.05 | 52 |
| D21 | 37.01 | 51 | 37.03 | 52 |
| D28 | 36.96 | 51 | 37.08 | 52 |

Before treatment on D0, the mean temperatures were 38.63°C in the AL group against 38.47°C in the ASAQ group. After treatment on D3, the mean body temperature was 36.74°C in the AL and ASAQ group. At D28 they were 36.91 in AL against 37.08 in ASAQ.

Table 6. Parasite clearance during follow-upst.

| Parasite Density (day) | AL | | ASAQ | |
|------------------------|------------------|----|------------------|----|
| | Average (ap*/µL) | n | Average (ap*/µL) | n |
| D0 | 13711.4 | 56 | 11292 | 57 |
| D1 | 3063.3 | 31 | 1782 | 23 |
| D2 | 31.1 | 13 | 51.7 | 6 |
| D3, D7, D14, D21, D28 | 0 | 0 | 0 | 0 |

*asexual parasites.

On D0 the mean parasite densities in the two groups were 13711.4 in the AL group against 11292 in the ASAQ group; the densities were zero from D3 to D28.

Table 7. Proportion of the most frequent adverse events.

| Adverse events | AL (n=56) | | ASAQ (n=57) | | n (%) |
|----------------|-----------|------|-------------|------|------------|
| | n | % | n | % | |
| Abdominal pain | 3 | 5.3 | 4 | 7 | 7 (06.7%) |
| Asthenia | 8 | 14.2 | 7 | 12.2 | 15 (13.5%) |
| Vomiting | 3 | 5.3 | 0 | 0 | 3 (02.9%) |
| Diarrhoeas | 4 | 7.1 | 3 | 5.2 | 7 (06.7%) |
| Anorexia | 7 | 12.5 | 8 | 14 | 15 (13.5%) |
| cough | 3 | 5.3 | 2 | 3.5 | 5 (04.8%) |
| Total | 28 | 50 | 24 | 42.1 | 52 (50.4%) |

The most common adverse events were asthenia and anorexia with a similar percentage of 13.5% in the two groups (AL and ASAQ) followed by 6.7% abdominal pain and diarrhoeas in both groups. Vomiting was only seen in the AL group.

4. Discussions

This study aimed at evaluating the therapeutic efficacy and safety of Artemether-Lumefantrine (AL) and Artesunate-Amodiaquine (ASAQ) combinations in the management of uncomplicated *P. falciparum* malaria at the level of health centers from Massakory (Figure 1). These two therapeutic

combinations based on artemisinin are included in the list of drugs of the national policy for the management of malaria in Chad since 2005. They are also subsidized by the government and its development partners. To meet the WHO recommendations on regular efficacy tests in order to guarantee an effective and tolerated treatment of these combinations and above all that their evaluations must be as regular and continuous in order to avoid the emergence of resistance to *P. falciparum* to these antimalarial drugs. For this reason, it is important to have data on the efficacy of ACTs in Chad on the one hand and on the other hand to assess the level of resistance to these two molecules.

Our study site was chosen on the basis that Massakory is a malaria endemic area. Malaria transmission is continuous and hardly ever stops throughout the year during the dry season. Massakory are home to many ponds that are veritable breeding grounds, thus exposing the population to infesting bites from mosquitoes, the main vectors of malaria transmission. During the rainy season, the formation of water pockets following rainfall and the retention of water in the vicinity of dwellings also contribute to this mode of transmission.

We recorded a total of 113 patients during our study, of which 64 (56.6%) were male and 49 (43.4%) female for a sex ratio of 1.3. The sex ratio was 1.3 in the AL group and 1.2 in the ASAQ group. This male predominance was also found by Hamadou B et al [8]. Our study, on the other hand, differs from that of Souleymane Issa M et al who found a rate of 44.8% with a sex ratio of 0.81 [9]. These results cannot be statistically significant because malaria affects both sexes.

All the children included in the study were aged 6 to 59 months. The vast majority were in the age group [48-59 months], ie 31% for the AL group and 18.5% for the ASAQ group. However, the results of our study showed that all age groups ranging from 6 months to 59 months are affected by malaria. No age group is spared, which leads us to believe that children under five are vulnerable to malaria.

The two study molecules (AL and ASAQ) are homogeneous and comparable. This study shows that they are effective for the treatment of uncomplicated malaria with the adequate clinical and parasitological responses (ACPR) which was 100% in both groups. The evaluation of the effectiveness of ACTs in the neighboring countries of Chad also showed good effectiveness of ASAQ and AL. Particularly in Democratic Republic of Congo De Wit M. et al, found similar results (95% ASAQ and 99% AL) [10]. Issa I et al in Niger found results showing adequate clinical and parasitological responses with respectively 93.1% and 94.1% for AL and ASAQ [11]. In the rest of Africa Sow D et al, and in Asia Ashley EA et al, Takala H et al. attesting to the constant efficacy of the AL and ASAQ combinations with efficacy rates always above 95% [12, 4, 7]. In Mali, the work of Ibrahim M. L. et al, showed that the adequate clinical and parasitological response is respectively 94.8% for AL and 97.1% for ASAQ [13]. Unlike Tinto H. et al. and Sondo P. et al in Burkina Faso showed a low cure rate on D28 [14, 15]. These results could indicate a decrease in sensitivity of *P.*

falciparum to these two molecules.

On D0, the mean temperature of the patients was 38.6 °C in the AL group and 38.5 in the ASAQ group (before treatment). At the end of treatment on D2, the mean temperature rose to 36.7 in AL and to 36.6 in the ASAQ group (Table 4). This significant drop in mean body temperature made it possible to determine the thermal clearance, which is 48 hours. This shows the effectiveness of the two CTAs used in our study. A decrease in the proportion of febrile patients was noted in both arms after the first day of treatment. Only 7.6% of patients in the ASAQ arm and 9.2% in the AL arm were febrile on the second day of treatment, but the difference was not significant ($p = 0.62$) [11].

The mean parasitaemia in the two treatment groups was similar on D0. Parasite clearance was in both molecules less than 72 hours and the two groups were comparable in the elimination of asexual forms of *Plasmodium falciparum* from the blood. The reduction in parasitaemia, which was satisfactory from the start of treatment in both groups, shows us that these artemisinin-based combinations would effectively help reduce the parasite burden responsible in part for the progression from uncomplicated malaria to the severe form. The results of Issa I *et al* in Niger showed rapid parasite clearance in both groups 48 h after the first dose [11]. Only 7 (8.9%) patients in the AL arm and 4 (5.3%) in the ASAQ arm had residual parasitaemia on the second day without significant difference ($p = 0.55$). The differences observed may have had effects on the comparison of efficacy, especially since it is reported in the literature that factors such as age, level of parasitaemia on admission or immune status may, in some cases, influence parasite clearance [7, 16, 17].

Adverse events were relatively more frequent in the ASAQ group compared to the AL group and consist mainly of abdominal pain and vomiting. Monitoring of anorexia, asthenia and headache. However, serious adverse events were not encountered (Table 7). These minimal adverse events are reported in most studies involving amodiaquine and are believed to be largely due to the drug's mechanism of action and its bitter taste. In Chad Tchoufiene (2013) observed the same signs dominated by vomiting (54.5%) in the ASAQ group [18], Souleymane Issa M observed in Pala (2017) all adverse events mild a predominance of loss of appetite (10.3%) followed by cough (7%) abdominal pain and vomiting (3.5%) [9]. No severe adverse events have also been reported as Touré *et al* in 2012 did not record any severe adverse effects but some signs described above in the occurrence of asthenia, abdominal pain and vomiting are respectively in 14%, 7% and 6% of cases [19]. Issa I *et al* (2020) to Mali found that the number of patients on AL and ASAQ treatment who developed an adverse reaction are 7.6% and 28%, respectively [11]. However, these various minor side effects observed are similar to those usually described in the tolerance assessment of ACTs, Nji A. M. *et al* (2015) to Cameroon. In this study, the most commonly observed side effects are vomiting, abdominal pain, dizziness and diarrhea [17]. These adverse effects correspond to those most frequently encountered during treatment with ACT by

Bassi P *et al* to Nigéria (2016), Grandesso F *et al*, Ibrahim ML *et al* in Niger (respectively 2018 and 2016) [20, 21]. Overall the two therapeutic regimens were well tolerated, the side effects being so minor, it is also important to mention them [23-26].

5. Conclusion

The two combinations form of ACT remain effective in the treatment of uncomplicated *P. falciparum* malaria in Chad. The RCPA was 100% for both molecules. Fever and parasite clearance times were 48 hours and 72 hours respectively. Tolerance to AL and ASAQ were generally good. However, regular monitoring of the effectiveness of these combinations is desirable to prevent treatment failures according to WHO recommendations in the fight against uncomplicated *P. falciparum* malaria in children from 6 months to 59 months. It is desirable that this work can be repeated in the various health centers in Chad in order to monitor the therapeutic efficacy of the antimalarial drugs used. Further studies are warranted in different regions of Chad for monitoring of drug resistance.

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References

- [1] World Health Organization (WHO). (2017). World malaria report 2017. Geneva (<http://apps.who.int/iris/bitstream/10665/259492/1/9789241565523-eng.pdf>, accessed 19 December 2019) ISBN 978-92-4-156552-3.
- [2] World Health Organization. (2009). Methods for surveillance of antimalarial drug efficacy. World Health Organization. <https://apps.who.int/iris/handle/10665/44048> accessed 19 December 2019.
- [3] Noedl, H., Se, Y., Schaefer, K., Smith, B. L., Socheat, D., & Fukuda, M. M. (2008). *Evidence of Artemisinin-Resistant Malaria in Western Cambodia. New England Journal of Medicine*, 359 (24), 2619–2620.
- [4] Ashley, E. A., Dhorda, M., Fairhurst, R. M., Amaratunga, C., Lim, P., Suon, S., Sreng, S., Anderson, J. M., Mao, S., Sam, B., Sopha, C., Chuor, C. M., Nguon, C., Sovannaroeth, S., Pukrittayakamee, S., Jittamala, P., Chotivanich, K., Chutasmit, K., Suchatsoonthorn, C., Runchaoen, R.,... Tracking Resistance to Artemisinin Collaboration (TRAC) (2014). Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *The New England journal of medicine*, 371 (5), 411–423.
- [5] Menard, D., & Dondorp, A. (2017). Antimalarial Drug Resistance: A Threat to Malaria Elimination. *Cold Spring Harbor perspectives in medicine*, 7 (7), a025619.

- [6] Ménard, S., Ben Haddou, T., Ramadani, A. P., Arief, F., Iriart, X., Beghain, J., Bouchier, C., Witkowski, B., Berry, A., Mercereau-Puijalon, O., & Benoit-Vical, F. (2015). Induction of Multidrug Tolerance in *Plasmodium falciparum* by Extended Artemisinin Pressure. *Emerging infectious diseases*, 21 (10), 1733–1741.
- [7] Takala-Harrison, S., & Laufer, M. K. (2015). Antimalarial drug resistance in Africa: key lessons for the future. *Annals of the New York Academy of Sciences*, 1342, 62–67.
- [8] Hamadou Bouare. (2018). Test d'efficacité Thérapeutique de la combinaison Arthemeter-Lumefantrine (AL) et Artesunate-Amodiaquine (ASAQ) dans le traitement du paludisme simple a *P. falciparum* à Sélingué et à Missira en 2016. These Med: Université da Bamako (Mali), 120 p.
- [9] Souleymane ISSA M, Clément KH, Denis MM, et al. (2017) Therapeutic Efficacy of Artesunate-Amodiaquine and Polymorphism of *Plasmodium falciparum* k13-Propeller Gene in Pala (Tchad). *Int J Open Access Clin Trials* 1 (1): 1.
- [10] Mari De Wit, Anna Louise Funk, Krystel Moussally, David Aksanti Nkuba, Rubbis Siddiqui, Karla Bil, Erwan Piriou, Aldert Bart, Patrick Bahizi Bizozza and Teun Bousema. (2016). In vivo efficacy of artesunate-amodiaquine and artemether-lumefantrine for the treatment of uncomplicated *falciparum malaria*: an open-randomized, non-inferiority clinical trial in South Kivu, Democratic Republic of Congo. *Malaria Journal*, 15 (1).
- [11] Issa Ibrahima, Ibrahim Maman Laminou, Eric Adehossi, Daou Maman, Saidou Boureima, Hama Kadri Harouna, Hamadou, Hassan Hamidou, Aboubacar Mahamadou, Idrissa Yacouba, Jackou Hadiza, Ilagouma Amadou Tidjani (2020) Study of therapeutic and therapeutic efficacy tolerance of artemether-lumefantrine and artesunate-amodiaquine in Niger. *Bull Soc Pathol Exot* doi 10.3166 / bspe-2020.
- [12] Sow D, Ndiaye JL, Sylla K, et al (2016) Evaluation of the efficacy and safety of artesunate-amodiaquine, dihydroartemisinin-piperaquine and artemether-lumefantrine combinations for the treatment of uncomplicated *Plasmodium falciparum* malaria in Senegal. *Med Santé Trop* 26 (1): 45-50.
- [13] Ibrahim ML, Sadou F, Daou M, et al (2016) Comparison of therapeutic efficacy and tolerance of artemether-lumefantrine and artesunate-amodiaquine combinations in Niger. *Mali Med* 31 (1): 1-7.
- [14] Tinto, Halidou, Diallo Salou, Issaka Zongo, Issa Guiraud, Innocent Valea, Adama Kazienga, Hervé Kpoda, Herman Sorgho, Jean-Bosco Ouédraogo, Tinga Robert Guiguemdé and Umerto D'Alessandro. (2014). Effectiveness of artesunate-amodiaquine vs. artemether-lumefantrine for the treatment of uncomplicated *falciparum malaria* in Nanoro, Burkina Faso: a non-inferiority randomised trial. *Tropical Medicine & International Health*, 19 (4), 469–475.
- [15] Sondo, P., Derra, K., Diallo-Nakanabo, S., Tarnagda, Z., Zampa, O., Kazienga, A., Valea, I., Sorgho, H., Owusu-Dabo, E., Ouédraogo, J. B., Guiguemde, T. R., & Tinto, H. (2015). Effectiveness and safety of artemether-lumefantrine versus artesunate-amodiaquine for unsupervised treatment of uncomplicated *falciparum malaria* in patients of all age groups in Nanoro, Burkina Faso: a randomized open label trial. *Malaria journal*, 14, 325.
- [16] Houh, Y. K., Kim, K. E., Park, S., Hur, D. Y., Kim, S., Kim, D., Bang, S. I., Yang, Y., Park, H. J., & Cho, D. (2017). The Effects of Artemisinin on the Cytolytic Activity of Natural Killer (NK) Cells. *International journal of molecular sciences*, 18 (7), 1600.
- [17] Nji, A. M., Ali, I. M., Moyeh, M. N., Ngongang, E.-O., Ekollo, A. M., Chedjou, J.-P.,... Mbacham, W. F. (2015). Randomized non-inferiority and safety trial of dihydroartemisinin-piperaquine and artesunate-amodiaquine versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Cameroonian children. *Malaria Journal*, 14 (1), 27.
- [18] Tchoufiene P. (2013). Efficacité et tolérance de Coarsucam® dans le traitement du paludisme simple à *Plasmodium falciparum* (étude sur 117 enfants de 6-59 mois à Koyom; Mayo Kebbi Est). Thèse de doctorat en médecine, Université de N'Djaména (Tchad), 60 p.
- [19] Toure, O. A., Assi, S. B., N'Guessan, T. L., Adji, G. E., Ako, A. B., Brou, M. J., Ehouman, M. F., Gnamien, L. A., Coulibaly, M. A., Coulibaly, B., Beourou, S., Bassinka, I., Soumahoro, A., Kadjo, F., & Tano, M. A. (2014). Open-label, randomized, non-inferiority clinical trial of artesunate-amodiaquine versus artemether-lumefantrine fixed-dose combinations in children and adults with uncomplicated *falciparum malaria* in Côte d'Ivoire. *Malaria journal*, 13, 439.
- [20] Bassi P, Osakwe AI, Suku C, et al (2016) Cohort event monitoring of patients treated for uncomplicated malaria with artemisinin-based combination therapies in selected hospitals and community pharmacies in Nigeria. *Niger Postgrad Med J* 23 (4): 172-181.
- [21] Grandesso F, Guindo O, Woi Messe L, et al (2018) Efficacy of artesunate-amodiaquine, dihydroartemisinin- piperaquine and artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Maradi, Niger. *Malar J* 17 (1): 52.
- [22] Odhiambo G, Bergmann-Leitner E, Maraka M, Wanjala CNL, Duncan E, Waitumbi J, et al (2019) Correlation Between Malaria-Specific Antibody Profiles and Responses to Artemisinin Combination Therapy for Treatment of Uncomplicated Malaria in Western Kenya. *J Infect Dis*; 219 (12): 1969-79.
- [23] Faye, B., Kuété, T., Kiki-Barro, C. P., Tine, R. C., Nkoa, T., Ndiaye, J. L., Kakpo, C. A., Sylla, K., El Menan, H., Gaye, O., Faye, O., Same-Ekobo, A., & Moussa, K. (2012). Multicentre study evaluating the non-inferiority of the new paediatric formulation of artesunate/amodiaquine versus artemether/lumefantrine for the management of uncomplicated *Plasmodium falciparum* malaria in children in Cameroon, Ivory Coast and Senegal. *Malaria journal*, 11, 433.
- [24] Schramm, B., Valeh, P., Baudin, E., Mazinda, C. S., Smith, R., Pinoges, L., Dhorda, M., Boum, Y., 2nd, Sundaygar, T., Zolia, Y. M., Jones, J. J., Comte, E., Houzé, P., Jullien, V., Carn, G., Kiechel, J. R., Ashley, E. A., & Guérin, P. J. (2013). Efficacy of artesunate-amodiaquine and artemether-lumefantrine fixed-dose combinations for the treatment of uncomplicated *Plasmodium falciparum* malaria among children aged six to 59 months in Nimba County, Liberia: an open-label randomized non-inferiority trial. *Malaria journal*, 12, 251.
- [25] Lingani, M., Bonkian, L. N., Yerbanga, I., Kazienga, A., Valéa, I., Sorgho, H., Ouédraogo, J. B., Mens, P. F., Schallig, H., Ravinetto, R., d'Alessandro, U., & Tinto, H. (2020). In vivo/ex vivo efficacy of artemether-lumefantrine and artesunate-amodiaquine as first-line treatment for uncomplicated *falciparum malaria* in children: an open label randomized controlled trial in Burkina Faso. *Malaria journal*, 19 (1), 8.