Annals of Parasitology 2017, 63(2), 127–131
doi: 10.17420/ap6302.96

Original papers

Comparison of effectiveness of two different artemisinin-based combination therapies in an area with high seasonal transmission of malaria in Burkina Faso

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ABSTRACT. In Sahelian countries such as Burkina Faso, malaria transmission is seasonal with a high incidence of transmission during the rainy season. This study aimed to compare the effectiveness of the two recommended treatments (Artemether-Lumefantrine and Artesunate-Amodiaquine) for uncomplicated malaria in Burkina Faso regarding this seasonal variation of malaria transmission. This is part of a randomized open label trial comparing the effectiveness and safety of Artemether-Lumefantrine *versus* Artesunate-Amodiaquine according to routine practice in Nanoro. Patients with uncomplicated *falciparum* malaria were recruited all year round and followed-up for 28 days. To distinguish recrudescences from new infections, dried blood spots from day 0 and day of recurrent parasitaemia were used for nested-PCR genotyping of the polymorphic loci of the merozoite surface proteins 1 and 2. Seasonal influence was investigated by assessing the treatment outcomes according to the recruitment period of the patients. Two main groups (dry season versus rainy season) were defined following the seasonal characteristics of the study area. In Artemether-Lumefantrine group, the uncorrected cure rate was 76.5% in dry season versus 37.9% in rainy season. In Artesunate-Amodiaquine group, this was 93.3% and 57.1% during dry and rainy seasons, respectively. After PCR adjustment, the cure rate decreased from 85.9% in dry season to 75.0% in rainy season in Artemether-Lumefantrine group. In Artesunate-Amodiaquine group, it was 93.3% in dry season and 80.7% during the rainy season. During the rainy season around 50% of patients had a new malaria episode by Day 28. The cure rate of both Artemether-Lumefantrine and Artesunate-Amodiaquine treatments was higher in dry season compared to rainy season due to high incidence of re-infections during the rainy season. For this reason, in addition to the curative effect, the post-treatment prophylactic effect should be taken into account in the choice of antimalarial regimens.

Key words: effectiveness, artesunate-amodiaquine, artemether-lumefantrine, season, malaria

Introduction

Despite numerous efforts to control malaria, it still remains a public health burden, killing over 584000 people annually worldwide [1]. In Burkina Faso, malaria represents the major cause of health facilities attendance and hospitalizations [2]. After the emergence and spread of Chloroquine resistance, the national malaria control program of Burkina Faso adopted Artemether-Lumefantrine (AL) and Artesunate-Amodiaquine (ASAQ) as first line treatments for uncomplicated malaria. The efficacy studies have shown that these combinations are efficacious and well tolerated [3]. However, according to routine practices there is a lowering of their cure rate and around 50% of treated patients develop a new malaria episode within 28 days [4,5]. This phenomenon constitutes an important challenge for the control of the disease by raising the cost allocated for malaria control. Burkina Faso is a Sahelian country and malaria transmission is considered as seasonal with a peak of high

transmission during the rainy season (RS) [6,7]. Due to this seasonality, clinical trials and most of malaria control activities such as indoor residual spray were concentrated during that period of the year. A study carried out in Nanoro showed that although there was a reduction of malaria transmission, it still represents an important febrile illness during the dry season (DS) [8]. We conducted a study in Burkina Faso in which patients were recruited all year along for the assessment of the effectiveness and safety of AL *versus* ASAQ [5]. Findings of this study confirming the high incidence of reinfection by day 28 was published elsewhere [5].

The present report aims to compare the effectiveness of these two treatments for uncomplicated malaria regarding this seasonality of malaria transmission in Burkina Faso.

Materials and Methods

The study was carried out in Nanoro health district which is located in the central-west part of Burkina Faso. The characteristics of the study area have been described in detail elsewhere [5,9]. Briefly, malaria transmission is seasonal with of peak of high transmission between October-November. *P. falciparum* is the principal malaria species and its transmission is mainly assured by mosquitos belonging to *Anopheles gambiae* complex [8,10]. Samples for this investigation were collected from patients attempting pharmacovigilance clinical trial (reference A70283). Patients of all age groups were recruited in two health facilities (Nanoro and Nazoanga) of Nanoro health district (NHD) for the assessment of the effectiveness and safety of AL *versus* ASAQ according to routine practices in Burkina Faso. Methodology and results of this clinical trial have been published elsewhere [5]. Briefly, 680 (n=340 for AL and n=340 for ASAQ) patients were recruited and were followed-up for 28 days with scheduled visits at days 3, 7, 14, 21 and 28. Treatment outcomes were assessed after 28 days of follow-up according to WHO protocol [11]. The occurrence of uncorrected and adjusted adequate clinical and parasitological response (uACPR and aACPR) in each treatment group was recorded monthly regarding to the recruitment period of the patient. An aggregate into a period of three months was defined on the basis of the seasonal characteristics (December-February = DS with harmattan wind, February-May = DS with drought, Jun-August = RS with maximal rainfalls, September-November = RS minimal rainfalls).

Laboratory analyses. Giemsa stained thick and thin films from Day 0 and day of recurrent parasitaemia were double read by qualified microscopists. Parasite density was determined by counting the number of asexual forms against the number of white blood cells. A negative microscopic result was declared if no malaria parasite was found after examination of 100 thick film fields. PCR genotyping of merozoite surface proteins (*msp1* and *msp2*) from the dried blood spots was used to differentiate between recrudescence and new infection as described

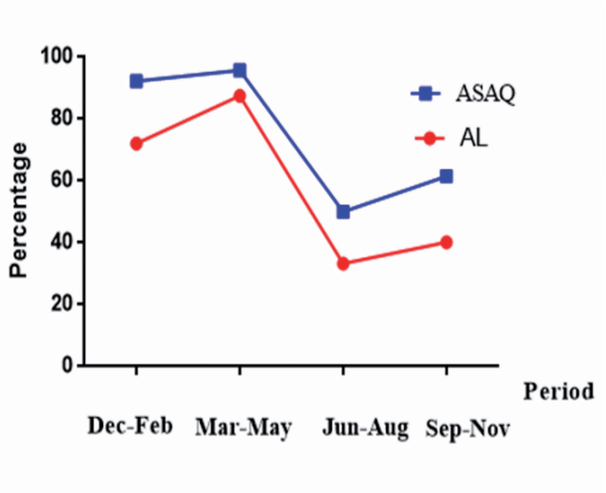

Fig. 1: Temporal variation of PCR uncorrected Adequate Clinical and Parasitological Response by treatment group

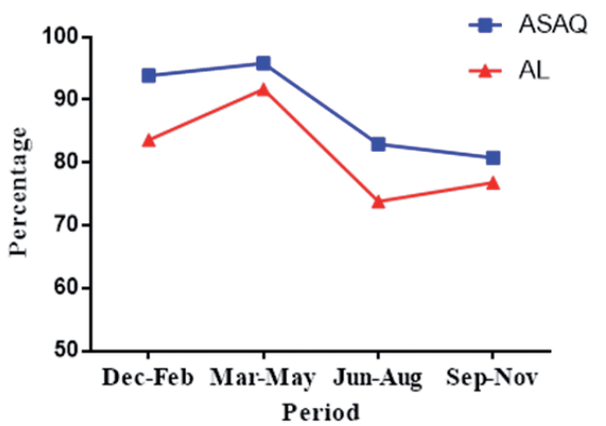

Fig. 2: Temporal variation of PCR corrected Adequate Clinical and Parasitological Response by treatment group

Table 1. Patients age, level of parasitaemia, gametocyte carriage, and multiplicity of infection by transmission season

Characteristics	Dry season n=174	Rainy season n=486	P- value
Age of patients in years, median (P25–P75)	3.2 (1.6–5.0)	3.2(1.7–4.9)	0.435
Gametocytes carriers, n (%)	10 (5.7)	34 (7.0)	0.571
Geometric mean parasite density/µL (CI)	20791 (17160–25191)	35694 (32382–39344)	0.0001
Multiplicity of infection	2.0 (1.3)	2.5(1.4)	0.0001

previously [12]. Briefly, DNA was extracted from dried blood using Qiagen columns according to manufacturer's instructions. 5 µL of DNA template were used for a primary PCR using primers flanking the outer parts of *msp1* block 2 and the central block of *msp2*. One µL of this primary PCR product was used as template for the second PCR round using primers specific to allelic families: K1, MAD20, RO33 for *msp1* and IC3D7 and FC27 for *msp2*. Five µL of the nested PCR product were used for revelation of DNA fragments by ethidium bromide stained 3% agarose gel electrophoresis.

Statistical analysis. The clinical data entry was performed by trained team in an ACCESS database. PCR genotyping results were entered separately from clinical data in an EXCEL database. Data were analysed using the software package STATA (IC) version 10.0 software. The statistical analysis was mainly descriptive. T-test and chi-square tests were used to compare means and the temporal fluctuation of the parameters respectively. The mean number of parasite genotypes by clinical isolate was considered as the Multiplicity of infection (*MOI*) [13]. The difference was considered as statistically significant when p-value was less than 0.05.

Results

During the study period, 502 patients were recruited in RS *versus* 178 in DS and this difference was due to the high incidence of malaria cases during the RS. Samples from patients whose treatment outcomes are not available were excluded from this study (n=20). Parasite density, gametocytes carriage prevalence and the number of different parasites genotypes co-infecting individuals were higher in RS than in DS (Table 1). The occurrence of these two factors (high parasitaemia and multiplicity of infection) during RS could have an impact on reducing the cure rate of ACT during that period.

A similar temporal trend of uACPR was observed for both AL and ASAQ treatment groups. The highest cure rate was observed in DS between March and May while lowest was observed during the RS (Fig. 1). In AL group, uACPR was 76.5% during the DS *versus* 37.9% [Risk difference (95% CI)=38.6 (27.7–49.4), p<0.0001] in RS (Table 2). In ASAQ group, uACPR decreased from 93.3% to 57.1% [Risk difference (95% CI)=36.1 (26.2–46.0), p<0.0001] during DS and rainy RS, respectively. The same trend was observed after adjustment by PCR (Fig. 2). After AL treatment, aACPR was 85.9% *versus* 75.0% [Risk difference (95% CI)=10.8 (1.8–19.9), p=0.0360] during DS and RS, respectively. In ASAQ group, it was 93.3% in DS and 80.7% [Risk difference (95% CI)=12.6 (4.0–21.1), p=0.0104] during RS.

Discussion

Our findings show the high risk of re-infection

Table 2. Adequate Clinical and Parasitological Response (ACPR) of Artemether-Lumefantrine (AL) and Artesuante-Amodiaquine (ASAQ) by transmission season

Treatment outcome		Dry season	Rainy season	Risk difference	P-value
AL	Unadjusted ACPR n(%)	65 (76.5)	94 (37.9)	38.6 (27.7–49.4)	<0.0001
	Adjusted ACPR n(%)	73 (85.9)	186 (75.0)	10.8 (1.8–19.9)	0.0360
ASAQ	Unadjusted ACPR n(%)	83 (93.3)	136 (57.1)	36.1 (26.2–46.0)	<0.00001
	Adjusted ACPR n(%)	83 (93.3)	192 (80.7)	12.6 (4.0–21.1)	0.0104

during RS and more than 50% of treated patients with AL and ASAQ developed a new malaria episode within 28 days during that period. Obviously, this difference between DS and RS is due to environmental conditions which are not favourable for malaria transmission because of desiccation destroying larval habitats during DS [14,15]. From these findings the big question is how to tackle this phenomenon of high incidence of reinfection during RS which at the same time highlights a limitation of preventive methods such as bed-net use. A study carried out in Ghana showed an incidence of parasitaemia ranging from 4.7/infection/person/year during the DS to 7.1 during wet season [16]. The same trend of higher recurrent parasitaemia during the RS compare to DS was previously observed in a study carried out in Bamako [17]. This raises the issue of post-treatment prophylactic effect of ACT. Therefore we postulate that the use of a long-acting ACT could help to tackle this problem and the choice of an antimalarial regimen should take into account the intensity of malaria transmission. In poor resource settings with high malaria transmission, in addition to the curative effect, the post-treatment prophylactic effect of an antimalarial treatment is of great interest. This could mean that in Sahelian countries such as Burkina Faso with a pronounced seasonality of malaria transmission, ASAQ and AL could be most appropriate during DS. However during the high transmission period (RS) the use of a longer-acting treatment could be most beneficial by reducing the repeated treatments over the time whose effect on decreasing drug sensitivity has been suggested [18]. The latter could also help reduce the financial burden of malaria.

The cure rate of both AL and ASAQ treatments was higher in dry season comparing to rainy season due to high incidence of re-infections during the rainy season. For this reason, in addition to the curative effect, the prophylactic effect should be taken into account in the choice of an antimalarial regimen.

Acknowledgements

We are grateful to the study participants and the staff of the Nanoro Health District for their acceptation and good collaboration. We acknowledge Sanofi Aventis, WHO-TDR and the Institute of Tropical Medicine, Belgium for the financial support of the study. We are grateful to Matthew Cairns for his helpful contributions in designing this study. Many thanks to Prof. Umberto d'Alessandro and Dr. Ambrose Talisuna for their contribution to the study protocol finalization.

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Received 15 November 2016
Accepted 14 March 2017