Artesunate + amodiaquine versus artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in the Colombian Pacific region: a noninferiority trial

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ABSTRACT

Introduction: In Colombia, there are no published studies for the treatment of uncomplicated *Plasmodium falciparum malaria* comparing artemisinin combination therapies. Hence, it is intended to demonstrate the non-inferior efficacy/safety profiles of artesunate + amodiaquine versus artemether-lumefantrine treatments. **Methods:** A randomized, controlled, open-label, noninferiority ($\Delta \leq 5\%$) clinical trial was performed in adults with uncomplicated *P. falciparum* malaria using the 28-day World Health Organization validated design/definitions. Patients were randomized 1:1 to either oral artesunate + amodiaquine or artemether-lumefantrine. The *primary* efficacy endpoint: adequate clinical and parasitological response; *secondary* endpoints: - treatment failures defined per the World Health Organization. Safety: assessed through adverse events. **Results:** A total of 105 patients was included in each group: zero censored observations. Mean (95%CI - Confidence interval) adequate clinical and parasitological response rates: 100% for artesunate + amodiaquine and 99% for artemether-lumefantrine; the noninferiority criteria was met ($\Delta = 1.7\%$). There was one late parasitological therapeutic failure (1%; artemether-lumefantrine group), typified by polymerase chain reaction as the *MAD20 MSP1* allele. The fever clearance time (artesunate + amodiaquine group) was significantly shorter (p=0.002). Respectively, abdominal pain for artesunate + amodiaquine and artemether-lumefantrine was 1.9% and 3.8% at baseline (p=0.68) and 1% and 13.3% after treatment (p<0.001). **Conclusions:** Uncomplicated *P. falciparum* malaria treatment with artesunate + amodiaquine is noninferior to the artemether-lumefantrine standard treatment. The efficacy/safety profiles grant further studies in this and similar populations.

Keywords: Artesunate-amodiaquine combination. Artemether-lumefantrine combination. Efficacy. Safety. Malaria-falciparum. Colombia.

INTRODUCTION

Malaria is a widespread tropical parasitic disease characterized by a large worldwide morbidity burden. In 2009, estimates of 225 million malaria cases (781,000 deaths) worldwide, 1.1 million cases in the Americas (1,300 deaths), and 79,252 cases in Colombia (12 deaths) were reported by the World Health Organization (WHO)[1]. *Plasmodium falciparum* accounts for 25% of the malaria cases in Colombia[1]; yet, this percentage increases to 75% in the Pacific region. This phenomenon is partially explained by the high (26.4%) prevalence of hemoglobinopathies and Duffy-negative (Fy-) phenotypes in the predominantly African-descent population[2]. As a consequence, more than half of the national *P. falciparum* cases are reported in this region[3]. **Figure 1** presents selected geographic, demographic, and malaria statistics for Quibdó and Tadó, two municipalities in the Chocó department, located in the Colombian Pacific region[1,4-6].

Early antimalarial measures included Anophelinae subfamily vector control and the folkloric use of quinine- and artemisinin-based monotherapy[7]. Reports of *in vitro* and *in vivo P. falciparum* resistance to chloroquine (CQ) in South America, including the Colombian Pacific region, have been published[8-10]. Due to the increasing worldwide CQ resistance reports, the most current antimalarial treatment recommended by WHO is combination therapy with two or more blood schizonticidal drugs. As opposed to monotherapy, this approach improves treatment outcome and decreases de novo resistance. Nonetheless, it increases treatment-related adverse events and costs[11].

Artemisinin derivatives - such as arthemeter, artemotil, artesunate, and dihydroartemisinin - are active against all four *Plasmodium* species, are generally well tolerated, and have been shown to reduce the transmissibility of malaria by decreasing gametocyte carriage[11]. Four artemisinin combination therapies (ACT) are currently recommended by WHO[11]: artemether-lumefantrine (AL), artesunate + amodiaquine (AS+AQ), artesunate + mefloquine (AS+MQ), and artesunate + sulfadoxine-pyrimetamine (AS+SP). The Colombian Ministry of Social Protection (CMSP; former Ministry of Health) implemented WHO recommendation of ACT with the use of AL as the first-line standard of care for confirmed uncomplicated *P. falciparum* malaria cases. In 2009, 1.28 million doses of AL were administered in Colombia[1].

In vivo resistance to artemisinin derivatives has only been reported in Southeastern Asia[12,13], not in Africa or the Americas. Treatment with AS+AQ has been used in Africa for the treatment of *P. falciparum* malaria with very good efficacy, safety, and cost-effectiveness profiles[14,15]. This combination has been previously studied in Colombia[16], but to date, no reports comparing its efficacy with other ACT have been published for this country. This clinical trial was designed to test the noninferiority efficacy profile of AS+AQ versus AL standard therapy for the treatment of patients with uncomplicated *P. falciparum* malaria in the municipalities of Quibdó and Tadó, both in the Chocó department located in the Colombian Pacific region. The safety profiles of both treatments were also compared.

A

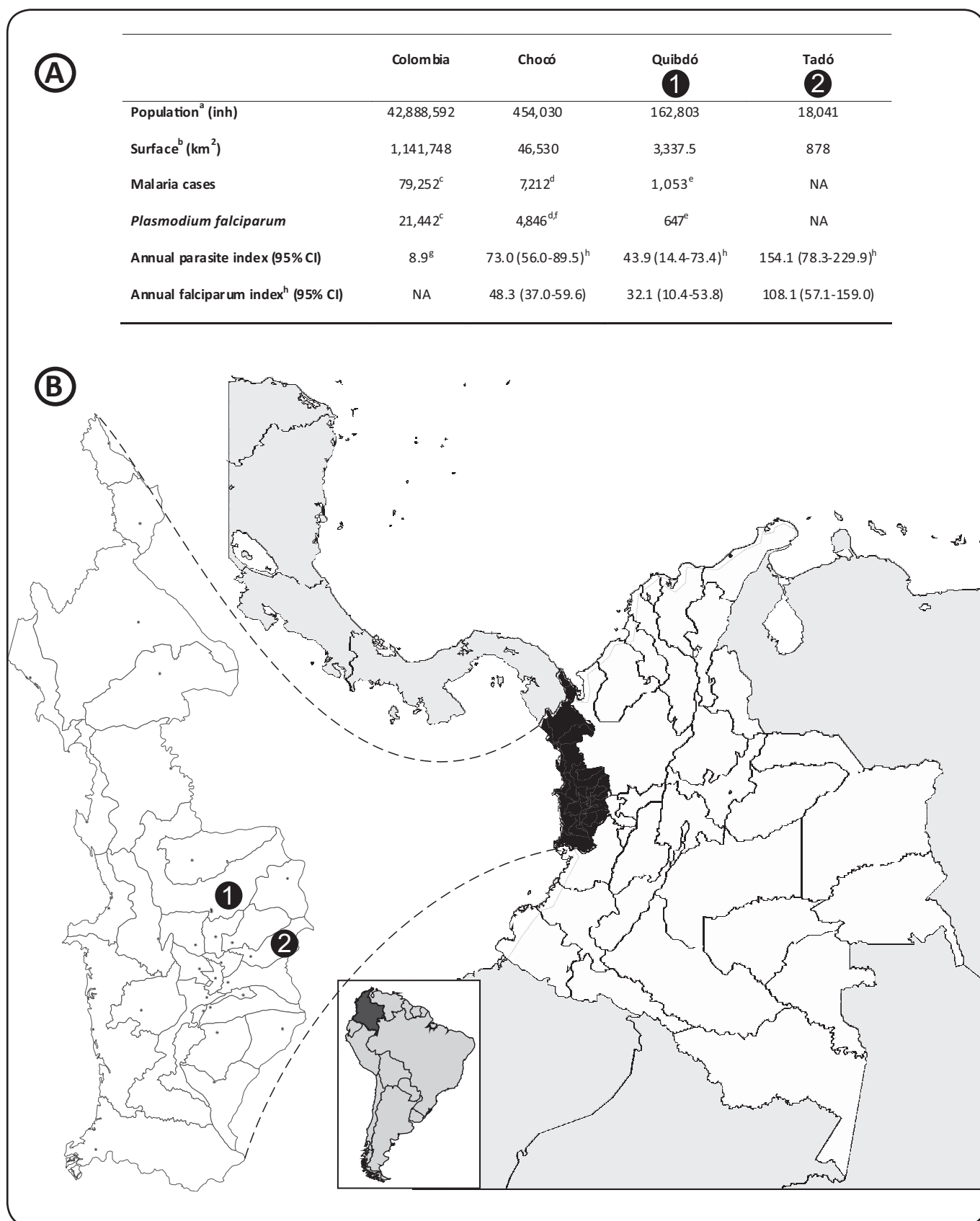|	Colombia	Chocó	Quibdó ❶	Tadó ❷
Population[a] (inh)	42,888,592	454,030	162,803	18,041
Surface[b] (km²)	1,141,748	46,530	3,337.5	878
Malaria cases	79,252[c]	7,212[d]	1,053[e]	NA
Plasmodium falciparum	21,442[c]	4,846[d,f]	647[e]	NA
Annual parasite index (95% CI)	8.9[g]	73.0 (56.0-89.5)[h]	43.9 (14.4-73.4)[h]	154.1 (78.3-229.9)[h]
Annual falciparum index[h] (95% CI)	NA	48.3 (37.0-59.6)	32.1 (10.4-53.8)	108.1 (57.1-159.0)

B

FIGURE 1 - **A: Selected geographic, demographic, and malaria data in Colombia. B: Geographic situation of the Colombian Pacific regions of Quibdó and Tadó.**
[a]Adjusted. [b]From Wikipedia. Available from: www.wikipedia.com. [c]In 2009. [d]In 2008. [e]In 2001. [f]Malaria cases were calculated multiplying the percentage of *Plasmodium falciparum* cases (67.2%) by the total number of malaria cases (7,212). [g]In the 1994-2004 period. [h]In the 1998-2006 period. **inh.:** inhabitants; **NA**: not available in the sources reviewed; **CI:** confidence interval.

METHODS

Design

This was a randomized, controlled, open-label clinical trial using the WHO-validated design for noninferiority efficacy in uncomplicated *P. falciparum* malaria[17], with the additional recommendations by the Pan-American Health Organization (PAHO)[18]. Even though this was an open-label clinical trial, blinding was kept for the staff performing patient follow-up and for the laboratory technicians reading the thick blood smears, as recommended by the United States Food and Drug Administration (FDA) protocol[19].

A sample size of 210 subjects (105 in each treatment arm) was calculated based on an estimated 95% efficacy for both treatments, a 5% (range 1% - 11%) proportion of failures to treatment, a two-sided 5% alpha error, an 80% statistical power, and a 5% estimated loss of patients to follow-up.

Patients

Patients were eligible if they were 18 years of age or older, had an axillary temperature >37.5ºC or history of fever in the absence of another cause of fever in the 48h previous to the initial study visit (day 0), and a *P. falciparum* monoinfection with 250 to 100,000 asexual parasites/μL, confirmed by microscopy.

Patients were excluded if they were unable to swallow oral medication, presented more than 2 vomiting episodes in the 24h previous to day 0, had a history of hypersensitivity to any of the protocol drugs, or presented severe chronic hematologic, hepatic, or renal illness, determined by the physician in the initial visit. WHO-defined clinical manifestations of severe malaria (ie, prostration, impaired consciousness, respiratory distress, multiple convulsions, circulatory collapse, abnormal bleeding, jaundice, hemoglobinuria) precluded the participation in this study, as well as women who tested positive in a urine pregnancy test.

All eligible patients were included once their written informed consent was obtained, and they were randomized 1:1 to either treatment group through a random-numbers table. A monthly interim analysis was performed by an external Data Safety Monitoring Board to assess the therapeutic failures as defined by WHO[17] and ensure an ethical conduct of the study. The Board would also terminate the study if the efficacy of any study drug was below 90% after consecutively treating 60 patients.

Treatments

Patients were randomized to either treatment group receiving the fixed-dose oral ACT. The AS+AQ (Coarsucam®; SANOFI, France; AS 540mg + AQ 200mg per tablet) schedule consisted of 2 tablets on Day 0, followed by two additional 2-tablet doses on days 1 and 2. The AL (Coartem®; Novartis Pharma AG, Switzerland; artemether 80mg + lumefantrine 480mg per tablet) schedule consisted of 4 tablets on Day 0, followed by five additional 4-tablet doses at 8, 24, 36, 48, and 60h after the initial dose.

All of the drug doses were administered by the research staff at the health care facility on an outpatient basis if the patient was considered suitable (ie, mobilization to and from the health care facility was possible), or the research staff provided the study patients with the remaining doses per domiciliary visits. A number of patients who could not be closely monitored by the previously mentioned approaches were managed on an inpatient basis to ensure the administration of all the treatment doses. After the drug administration, patients were observed during 30min for adverse events or vomiting. Patients who presented vomiting within this period were then provided with another dose of the study drugs and were observed for 30 additional minutes. If a second vomiting episode occurred, the patient was excluded from the study and initiated on standard parenteral therapy for severe malaria, as defined by the CMSP guidelines.

Concomitant treatment with acetaminophen was provided to patients presenting axillary temperature ≥39ºC. Follow-up visits and procedures were scheduled per WHO protocol (ie, on days 1, 2, 3, 7, 14, 21, and 28)[17]. Nonetheless, patients were instructed to visit the health care facilities if they felt any worrisome discomfort or symptom (including, but not limited to fever, malaise, headache, and vomiting). In case of a first-line therapeutic failure as defined by WHO[17], an oral second-line therapeutic combination of quinine (10mg/kg every day for 7 days) and primaquine (single 45-mg dose) was administered, and a polymerase chain reaction (PCR) was performed to typify the *MSP1* gene alleles and distinguish true therapeutic failures from reinfections.

Endpoints

The primary efficacy endpoint was the adequate clinical and parasitological response (ACPR), defined as absence of parasitemia on day 28, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure.

Secondary efficacy endpoints included treatment failures as defined by WHO protocol[17]. Early treatment failure (ETF) was defined as severe malaria on days 1, 2, or 3 in the presence of parasitemia; parasitemia on day 2 higher than on day 0, irrespective of axillary temperature; or parasitemia on day 3 with axillary temperature ≥37.5ºC or ≥25% of parasite count on day 0. Late treatment failure was further divided into clinical or parasitological. Late clinical treatment failure (LCTF) included patients who did not previously meet any of the ETF criteria and had parasitemia on any day between days 4 and 28 with either severe malaria, or axillary temperature ≥37.5ºC (or history of fever), or parasitological failures. Patients who did not meet ETF and LCTF criteria who had parasitemia on any day between days 7 and 28 and axillary temperature <37.5ºC were considered as having a late parasitological treatment failure (LPTF). In order to determine if a therapeutic failure was due to the drug administered and not due to a reinfection, all three failure rates (ie, ETF, LCTF, LPTF) were analyzed as PCR-unadjusted (crude) and PCR-adjusted.

Other efficacy measurements included mean parasitemia on Day 1 and mean parasite, fever, and gametocyte clearance times. An exploratory endpoint was the analysis of possible risk factors for therapeutic failures (ie, age, previous antimalarial therapy, and initial parasitemia). Safety was assessed through patient spontaneous report of adverse events and serious adverse events at follow-up or at any unscheduled visits.

Statistical analysis

The per-protocol population data values were entered in duplicate in a WHO-standardized[17] Excel spreadsheet (The Microsoft Corporation; Redmond, WA). Noninferiority of AS+AQ versus AL was

assumed if the lower limit of the 95% confidence interval (CI) for the treatment difference was greater than 5% for the mean parasitological cure rate at day 28 or any of the secondary efficacy endpoints. This 5% noninferiority margin (Δ) approximates the treatment difference in parasitological cure rates at day 28 that might be expected from discrepancies in disease treatment[20,21]. Secondary efficacy endpoints were summarized through descriptive statistics (ie, percentages, means, geometric means for parasitemia counts, standard deviations [SDs], and 95% CIs). The Kaplan-Meier analysis method was used to calculate the mean time to failure and to estimate failure rates. The two-sided p values for the comparisons between the two groups were calculated using GraphPad (GraphPad Software, Inc.; La Jolla, CA). The statistical tests applied to the secondary efficacy endpoints were the two-tailed Fisher exact test for the comparison of two proportions and the Student t test with 208 degrees of freedom for the comparison of two means.

Ethical considerations

After thorough considerations and reviews, the Ethics Committee of the National University of Colombia School of Medicine approved the study protocol, which was registered under the number CE-095. The National Institute of Drug and Food Surveillance (INVIMA) also reviewed and approved the study protocol (under the code # 626421). Patient confidentiality was kept and the trial was conducted according to the ethical principles stated in the sixth revision of the Declaration of Helsinski[22] and the applicable Colombian laws and regulations.

RESULTS

The target recruitment of 210 patients was achieved from August 2008 to September 2009, without deaths, censored observations, or losses to follow-up. Hence, the per-protocol analysis set is the same as the Kaplan-Meier analysis set. There were no protocol violations, and the Data Safety Monitoring Board found no reasons to interrupt the study during interim analyses.

Table 1 shows the baseline demographic and clinical characteristics of the study population. The mean ages for both study groups were similar, and the male-to-female ratio was well balanced. In both treatment groups, more than 80% of the population was of African descent, most patients came from the municipality of Tadó, and more than 90% was affiliated with the social security system. Globally, 126 patients reported a previous episode of malaria, 18 of which occurred in the previous year. Eighty-four patients received either study treatment in an inpatient basis during the trial. Overall, the duration of malaria symptoms ranged from 4 to 17 days, with a mean (SD) of 4.2 (3.1) days for the AS+AQ group and 4.5 (2.6) days for the AL group (p=0.45).

TABLE 1 - Baseline demographic and clinical characteristics.

	AS+AQ (n=105)		AL (n=105)		
	n	%	n	%	P value
Age, years, mean (SD)	38.4	14.5	36.7	13.4	0.40
Males, n (%)	59	56.2	52	49.5	0.41
Body weight, kg, mean (SD)	63.9	8.0	65.3	6.6	0.16
Height, m, mean (SD)	1.61	0.05	1.62	0.06	0.19
Body mass index, kg/m², mean (SD)	24.5	2.4	24.8	2.6	0.39
African descent ethnicity, n (%)	89	84.8	95	90.6	0.30
Municipality, n (%)					
Tadó	84	80.0	80	76.2	0.62
Quibdó	21	20.0	25	23.8	-
Social security affiliation, n (%)	97	92.3	95	90.6	0.81
Previous history, n (%)					
malaria	68	64.8	58	55.2	0.20
fever	105	100.0	105	100.0	>0.99
Malaria evolution time, days, mean (SD)	4.2	3.1	4.5	2.6	0.45
Symptoms at inclusion (day 0), n (%)					
fever	105	100.0	105	100.0	>0.99
cephalea	105	100.0	105	100.0	>0.99
shivers	103	98.1	105	100.0	0.50
diaphoresis	103	98.1	105	100.0	0.50
myalgias	103	98.1	105	100.0	0.50
abdominal pain	2	1.9	4	3.8	0.68
vomiting	2	1.9	4	3.8	0.68
Axillary temperature, ºC, mean (SD)	38.3	0.5	38.2	0.4	0.53
Parasitemia, asexual parasites/iL, mean (SD)	6,887	9,464	4,693	6,225	0.048
Patients with gametocytes, n (%)	2	1.9	14	13.3	0.003

AS: artesunate; **AQ**: amodiaquine; **AL**: artemether-lumefantrine; **SD**: standard deviation.

TABLE 2 - Secondary efficacy results.

	AS+AQ (n=105)		AL (n=105)		
	n	%	n	%	P value
Parasite clearance time, days	1	1.2	2	3.2	0.23
Fever clearance time, hours	8	12.3	48	32.1	0.002
Therapeutic failure, n (%)					
early	0	0.0	0	0.0	>0.99
late clinical	0	0.0	0	0.0	>0.99
late parasitological	0	0.0	1	1.0[a]	>0.99
Time to negative gametocytemia, days	2	1.3	4	4.5	<0.001
Parasitemia[b,c] asexual parasites/iL					
day 1	181.8	247.5	182.1	668.8	0.76
Temperature, ºC					
day 1	37.2	0.5	37.0	0.4	0.05
day 2	37.1	0.5	37.2	0.4	0.05
day 3	37.0	0.5	37.0	0.4	0.05
day 7	37.0	0.5	37.2	0.4	0.05
day 14	36.8	0.5	37.2	0.4	0.05
day 21	37.1	0.5	37.0	0.4	0.05
day 28	37.0	0.5	37.0	0.4	0.05

All values are mean (SD), unless otherwise specified. [a]Genotyped through PCR as the *MAD20 MSP1* allele. [b]No asexual parasites were reported in either group on days 2, 3, 7, 14, 21, and 28. [c]Geometric means and SDs are reported for this variable. **AS**: artesunate; **AQ**: amodiaquine; **AL:** artemether-lumefantrine; **SD**: standard deviation.

In both study groups, all patients presented with fever and cephalea with more than 98% presenting with diaphoresis and myalgia. Baseline abdominal pain and vomiting were reported in less than 4% of patients in each group **(Table 1)**.

When compared to AL, AS+AQ had a noninferiority margin of 1.7%. The primary efficacy endpoint, ie, ACPR, was not significantly different (p>0.99) for AS+AQ (100%; 95% CI 96.6%-100%) when compared to AL (99%; 95% CI 94.8%-100%). All the secondary efficacy variables are presented in **Table 2**. None of the treatment failure secondary efficacy endpoints (ie, ETF, LCTF, and LPTF) was significantly different for the comparison of the two study groups. Only one PCR-confirmed LPTF (1%) was reported in the AL group, which adequately responded to the second-line treatment of quinine and primaquine and corresponded to the *MAD20 MSP1* haplotype. Although the mean parasite clearance time was not statistically significant between the study groups, the mean fever clearance times showed a significantly earlier response in the AS+AQ group (p=0.002). **(Table 2).**

Spontaneously reported adverse events were limited to epigastric burning sensation in 1 (1%) patient in the AS+AQ group versus 14 (13.3%) patients in the AL group (p<0.001). No hospitalizations or deaths related to malaria or its complications, study treatments, adverse events, or any other cause occurred during the study.

DISCUSSION

To the best of researchers' knowledge, this is the first noninferiority trial comparing AS+AQ to standard AL therapy performed in the Colombian Pacific region. The primary efficacy endpoint-ie, a non-inferiority margin of less than 5%-was met.

Studies reporting similar crude ACPRs when AS+AQ and AL are used have been published. A Cochrane meta-analysis of 50 studies[23] and a meta-analysis including 8 studies in Africa[24] concluded that there is enough evidence to suggest that AL more effectively increases crude ACPR rates.

Regarding PCR-corrected ACPRs, Jansen et al performed a meta-analysis of 32 trials comparing the four WHO-recommended ACT[25]. In this multi-treatment, random-effects Bayesian analysis, AS+AQ and AL treatments had PCR-corrected ACPRs of 88.5% and 97.4%, respectively. The authors explained that this difference was due to the inclusion of results from South Asian studies, where ACT drug resistance has been reported[12,13]. These results were not necessarily inferior, as proven through an odds ratio analysis for the PCR-corrected ACPR[25].

On the other hand, Zwang et al demonstrated that PCR adjustment yields inconsistent ACPR rate results[14]. These authors performed an analysis of 26 studies (n=5,942) comparing AS+AQ to other ACT in a pooled sub-Saharan African population. Crude ACPR rates of 78.3% for AS+AQ and 83.2% for the other ACT were reported. However, when PCR adjustment was applied, the mean (95% CI) ACPR rates were superior: 93.9% (93.2%-94.5%) for AS+AQ and 94.8% (93.8%-95.6%) for the other ACT.

In Colombia, Osorio et al. have reported similar 100% mean (95% CI: 89.1%-100%) PCR-adjusted ACPR rates for AS+AQ treatment in the Colombian Pacific region[16]. From the comparison of these data and the findings in this study, we infer that the crude and PCR-corrected ACPR rates found for adults treated with AS+AQ in the Colombian

Pacific region are not different from those previously described. Even though AL is the standard treatment for uncomplicated *P. falciparum* malaria in Colombia, no literature discussing its ACPR rates in this country could be found in the literature reviewed.

No ETFs were found in either group. This can be explained by the rapid clinical improvement observed with all ACTs[26]. In the analysis performed by Zwang et al., the comparison of AS+AQ with AL yielded differences in the crude failure risks. The adjusted hazard ratio (95% CI) for AL was 0.79 (0.57-1.10), yielding a nonsignificant PCR-adjusted failure risk[14]. Neither LCTF nor LPTF were observed in the AS+AQ group, yielding a 0% failure rate.

The single LPTF corresponded to the *MAD20 MSP1* haplotype, a native allele of the *MSP1* gene, confirming a true failure rather than a reinfection. This polymorphic gene have been demonstrated as a marker of natural selection, rather than *P. falciparum* transmission dynamics, and its loci determine the variation in allele frequencies among populations[27,28]. In another regions of Colombia, it has been demonstrated that MAD20 haplotype with a 187-base-pair band is present in all of the samples analyzed, while the K1 and RO33 haplotypes were not found in these regions[29]. Based on similar reports from Colombian regions[30,31], Barrera et al concluded that *MSP1* is not a good marker for genetic diversity studies in Colombia[29].

Geometric mean parasitemia on day 1 was not statistically significantly different between AS+AQ and AL (p=0.76). When compared with the baseline geometric mean parasitemia, the 24h mean change was statistically significant for either group (p<0.001).

Compared with AL, mean fever clearance time was significantly lower (p=0.002) for AS+AQ. This significant fever clearance difference for the comparison of AS+AQ and AL have also been reported by Koram et al (p=0.006)[32]. In this report, the proportion of patients treated with AS+AQ that remained febrile at Day 2 was significantly lower when compared to those treated with AL, similar to a finding previously reported in another larger study (2.8% versus 6.3%, respectively; p=0.001)[14]. Even though the clinical relevance of small but significant differences in fever clearance times is arguable, it seems evident that ACT in general[26], and AS+AQ in particular, offer a faster relief from the febrile state and the associated inflammatory response.

The correlation between parasitemia and fever clearance times has been verified in other reports[14,33]. The study by Zwang et al. found that parasitemia and fever percentages of patients treated with AS+AQ were, respectively, 66.4% and 7.4% on day 1; 8.5% and 2.4% on day 2; 1.8% and 2.4% on day 3; and 0.6% on day 7. This group demonstrated that parasitemia clearance time is significantly (p=0.001) longer in patients with higher parasitemia at day 0. Also, the risk of being parasitemic at day 3 was not different in patients treated with AS+AQ or any other ACT (2.9% versus 2.6%; p=0.48)[14].

Whether the adverse events are truly attributable to the antimalarials or to malaria itself is still debatable. Some symptoms reported as adverse events are present at baseline and are exacerbated with antimalarial treatment. Gastrointestinal adverse events have been previously reported for both treatments. Compared to baseline, no significant differences were found between gastrointestinal spontaneously reported adverse events after starting either treatment. However, the proportion of patients presenting gastrointestinal adverse events was significantly higher (p<0.001) in the AL treatment group.

One of the limitations of this trial is that the efficacy profile of AL is influenced by the wide between-individual variation of lumefantrine pharmacokinetics-absorption is poor when not taken with fatty foods[34]. On the other hand, inconsistencies in AS+AQ efficacy profiles worldwide are influenced by the previous use of amodiaquine in endemic countries, such as Colombia. These areas present with high rates of parasitological failures with ACPR, which reflect good immunity and dangerously poor antimalarial efficacy[33].

The high level of recrudescence and reinfection rates present in the department of Chocó further limit the extrapolation of these findings. PCR genotyping of polymorphic genes-such as the merozoite surface protein 1 and 2 (MSP1 and MSP2, respectively) precursor and the glutamate-rich protein (PF10_0344) genes-allow a reliable description of seasonal recrudescence patterns[33], though many times the results are commonly missing or indeterminate[22,29]. Distinguishing recrudescence from reinfection can be a difficult task and there is no current consensus on how data should be analyzed[22]. The way the outcome measure is reported, the analyses performed, and the geographic location can partially explain the results variation[23;24]. In everyday clinical practice, PCR genotyping increases the surveillance costs[34], which is a major limitation in developing countries. Regarding safety limitations, the use of adverse events spontaneous reports introduces data production bias.

Besides a 10% failure rate, the WHO recommendations for changing first-line therapy should address other factors in further pharmacokinetic, in vitro, and molecular studies[17]. The noninferior efficacy demonstrated for AS+AQ compared to other ACT in general and to AL in particular, pose a viable alternative for the treatment of *P. falciparum* malaria in the Chocó department. The easier administration schedule and the robust efficacy and safety profile also favor the use of AS+AQ in this and similar settings. Being the most cost-effective treatment in prevention strategies, as it was previously demonstrated in sub-Saharan Africa[15], treatment with AS+AQ would grant savings in the treatment costs of uncomplicated *P. falciparum* malaria. Treatment of uncomplicated *P. falciparum* malaria with AS+AQ also has high compliance rates, with or without health care staff supervision[35].

In sum, the treatment of uncomplicated *P. falciparum* malaria with AS+AQ was noninferior to the AL standard treatment. Caution should be exerted when extrapolating the study results, as these apply to the sui generis settings of the Chocó department. The efficacy and safety profiles of AS+AQ make its use a plausible alternative treatment of uncomplicated *P. falciparum* malaria in the Colombian Pacific region.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

FINANCIAL SUPPORT

ABSTRACT IN PORTUGUESE

Artesunato + amodiaquina *versus* artemether-limefantrina para o tratamento da malaria não complicada por *Plamodium falciparum* no Pacifico Colombiano: um estudo de não inferioridade

Introdução: Na Colômbia não existem estudos publicados sobre o tratamento da malária não complicada por *Plasmodium falciparum* comparando as terapias combinadas com artemisinina. Destarte, quer se demonstrar a não inferioridade dos perfis de eficácia/segurança dos tratamentos com artesunato+amodiaquina *versus* artemeter-lumefantrina. **Métodos**: Foi realizado um estudo clínico de não inferioridade (Δ≤5%), aleatório, controlado, aberto, em adultos com malária não complicada por *P. falciparum* usando o desenho validado de 28 dias e os desenhos validados/definidos pela Organização Mundial da Saúde. Os pacientes foram aleatorizados (1:1) para ambos artesunato+amodiaquina ou artemeter-lumefantrina orais. Critérios primários de eficácia: resposta clínica e parasitológica adequada; Criterios de eficácia secundários: as falhas de tratamento definidos pela Organização Mundial da Saúde. A segurança: avaliada através de eventos adversos. **Resultados:** Foram incursos 105 pacientes em cada grupo: zero observações censuradas. As taxas médias da resposta clínica e parasitológica adequada (95% IC - intervalo de confiança): 100% para artesunato+amodiaquina e 99% para artemeter-lumefantrina; atingiu-se o critério de não inferioridade (Δ=1.7%). Houve uma falha terapêutica parasitológica tardia (1%; grupo artemeter-lumefantrina), caracterizada mediante reação em cadeia da polimerase como o alelo *MAD20 MSP1.* Tempo de remissão da febre (grupo artesunato+amodiaquina), foi significativamente mais curto (p=0.002). Dor abdominal, para artesunato+amodiaquina e artemeter-lumefantrina, respectivamente, 1.9% e 3.8% (p=0.68) na linha de base, 1% e 13.3% pós-tratamento (p<0.001). **Conclusões:** O tratamento com artesunato+amodiaquina da malária não complicada por *P. falciparum* é não inferior ao tratamento normal com artemeter-lumefantrina. Os perfis de eficácia/segurança justificam estudos adicionais nesta e outras populações semelhantes.

Palavras-chaves: Combinação de artesunato-amodiaquina. Combinação de artemeter-lumefantrina. Eficácia. Segurança. Malária-falciparum. Colômbia.

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