Therapeutics and Clinical Risk Management

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REVIEW

Update on the efficacy, effectiveness and safety of artemether–lumefantrine combination therapy for treatment of uncomplicated malaria

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
16 December 2009
Number of times this article has been viewed

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Abstract: Artemether–lumefantrine is one of the artemisisnin-based combination therapies recommended for treatment of uncomplicated *falciparum* malaria. The drug combination is highly efficacious against sensitive and multidrug resistant *falciparum* malaria. It offers the advantage of rapid clearance of parasites by artemether and the slower elimination of residual parasites by lumefantrine. The combination can be used in all populations except pregnant mothers in the first trimester where safety is still uncertain. There are still concerns about safety and pharmacokinetics of the drug combination in children, especially infants, pregnant mothers and drug interactions with mainly non-nucleoside reverse transcriptase inhibitors and protease inhibitors used for HIV therapy.

Keywords: artemether–lumefantrine, efficacy, effectiveness, safety, malaria

Introduction

Malaria is a febrile illness caused by intracellular protozoa of the genus *Plasmodium*, and transmitted by the bite of an infected female mosquito of the genus *Anopheles*. *Plasmodium* species that cause disease in humans include: *P. falciparum, P. vivax, P. malariae*, *P. ovale*, and *P. knowlesi. P. falciparum* is the most prevalent and most virulent. Worldwide, malaria is one of the most important causes of morbidity and mortality. Approximately 2.2 billion people are exposed to malaria every year of whom about 300 to 500 million develop disease. In 2006, there were 247 million cases of malaria, causing nearly 1 million deaths, mostly among African children.[1] Malaria deaths are responsible for almost 3% of the world's disability-adjusted life years, not counting the considerable and imprecisely quantified burden due to morbidity and disability.[2] In addition to causing significant morbidity and mortality, malaria significantly contributes to poverty through lost productivity and economic loss on antimalarial treatment. African countries spend US$12 billion annually on malaria, with individual African families spending up to 25% of their income on malaria prevention and control. Malaria has slowed economic growth in African countries by 1.3% per year. As a result of the compounded effect over 35 years, the gross domestic product for African countries is now up to 32% lower than it would have been in absence of malaria.[3]

Reduction in malaria-associated morbidity and mortality largely depends on provision of prompt, effective, safe and affordable antimalarial drugs. Resistance to antimalarial drugs poses a significant challenge to malaria control programs in sub-Saharan Africa. Multi-drug resistance to sulfadoxine–pyrimethamine (SP) and chloroquine was described extensively in sub-Saharan Africa. The World Health

Organization (WHO) recommends use of artemisinin-based combination treatments (ACT) as first-line therapy. The ACTs combine fast-acting artemisinins with another structurally unrelated and more slowly eliminated compound which permits elimination of residual malarial parasites.[4–6] Of the 81 countries with endemic *P. falciparum*, 77 have now adopted the WHO recommendation.[7] Commonly used ACTs are artemether–lumefantrine (AL), amodiaquine–artesunate (AQAS), mefloquine–artesunate, dihydroartemisin–piperaquine (DP) and napthoquine–artemisinin. In this review we provide an update on efficacy, effectiveness and safety of AL for treatment of uncomplicated malaria.

Pharmacology of artemether–lumefantrine

A 6-dose regimen of artemether (20 mg) co-formulated with lumefantrine (120 mg) is recommended; with first and second doses taken 8 hours apart, the third dose taken 24 hours after the first and the remaining doses 12 hours apart. The 6-dose regimen is superior to the 4-dose regimen.[8,9] Artemesinin from which artemether is derived is obtained from the Chinese herb sweet wormwood (*Artemisua annua*). Artemisinins have the most potent and rapid onset of antiparasitic activity against all *Plasmodium* species that infect humans.

Artemether acts rapidly with half-life of 1 to 3 hours, whereas lumefantrine has a half-life of 3 to 6 days and is responsible for preventing recurrent parasitemia.[10] Artemether and lumefantrine have different modes of action and act at different points in the parasite life cycle.[11,12] Artemether interferes with parasite transport proteins, disrupts parasite mitochondrial function, inhibits angiogenesis and modulates host immune function.[13] Lumefantrine is an aryl-amino alcohol[14] that prevents detoxification of heme, such that toxic heme and free radicals induce parasite death.[12] Oral formulations of AL are available as tablet and dispersible formulations which have similar pharmacokinetic (PK) properties.[15,16] Artemether and lumefantrine differ in rates of absorption and elimination. Artemether is rapidly absorbed reaching peak plasma concentrations within 2 hours post dose.[11,17] It is metabolized rapidly by cytochrome P450 (CYP) 2B6, CYP3A4 and possibly CYP2A610 to dihydroartemisinin (DHA) which in turn is converted to inactive metabolites primarily by glucoronidation via UGT1A1, 1A8/9 and 2B7.[14] The metabolite DHA reaches peak plasma concentration within 2 to 3 hours post dosing.[11] Both artemether and DHA offer potent antimalarial properties causing significant reduction in asexual parasite mass of approximately 10,000-fold per reproductive cycle, with prompt resolution of symptoms.[18,19]

Lumefantrine is absorbed and cleared more slowly, acting to eliminate residual parasites that may remain after artemether and DHA have been cleared from the body and thus prevent recrudescence.[11,12] Lumefantrine is highly lipophilic, thus absorption is enhanced with a fatty meal; its absorption occurs 2 hours after intake reaching peak plasma concentration after 3 to 4 hours[20] with an elimination half life of 4 to 10 days.[20,21]

Food enhances absorption of both artemether and lumefantrine although this effect is more apparent for lumefantrine.[11,20] Administration of AL with high-fat meal increased bioavailability of both artemether and lumefantrine by 2-fold and 16-fold respectively.[11] Premji et al in an evaluation of the typical fat content of African diets noted that total fat intake is 15 to 30 g/day during breast feeding, >10 g/day in the post weaning phase and 30 to 60 g/day in a normal diet and this is adequate for optimal efficacy of lumefantrine.[22]

However, the effect of food on AL absorption is of concern because patients with malaria usually have anorexia, vomiting and low food intake. Lumefantrine is metabolized by N-debutylation mainly by CYP3A410 to desbutyl-lumefantrine with 5- to 8-fold higher antiparastic effect than lumefantrine. The key PK determinant of cure is the area under the concentration time curve (AUC) of the longer-acting lumefantrine.

Efficacy and effectiveness of AL

Efficacy of the 6 dose regimen of AL judged by elimination of malaria parasites using the 28-day polymerase chain reaction (PCR)-corrected cure rates and resolution of symptoms, has been demonstrated in semi-immune and non-immune populations in Asia and Africa to be consistently greater than 95%, with rapid parasite and symptom clearance and significant gametocidal effect.[15,23–27] Many studies in Africa and Asia have demonstrated AL to be as efficacious as other ACTs when used in pediatric and adult populations with differing immunity. PCR-corrected day 28 and day 42 cure rates range between 91% and 100% using evaluable patient analysis.[28–62] Correction by PCR enables differentiation between recurrence and recrudescence of the initial infection from re-infection. A few cases of treatment failure were recorded after AL treatment, but these were mostly re-infections.[29,32,33,38] This is of particular concern in areas with very intense malaria transmission where antimalarial drugs with longer half-life may offer the advantage of preventing re-infection. Lumefantrine with an estimated elimination half-life of 4 to 10 days offers post-treatment antimalarial prophylaxis of up to 4 weeks. Studies showed

both AL and DP to be highly efficacious for treatment of uncomplicated malaria, although DP was superior to AL at preventing new malaria infections.[33,34,38,50] In addition to excellent efficacy and effectiveness, AL has demonstrated significant gametocidal effects.[34,42,48,51] A meta-analysis of 32 randomized trials showed AL to be one of the most effective ACTs with 28-day parasitological cure rates of 97.4%.[63]

Effectiveness of AL may be influenced by poor adherence to the 3-day, 6-dose regimen and the food requirements for AL absorption. Clinical and parasitological responses to AL were similar with both supervised and unsupervised treatment in Uganda.[64] The supervised treatment arm received AL with fatty food while the unsupervised arm received AL as outpatient treatment with nutritional advice. Unsupervised treatment resulted in lower concentrations of lumefantrine with increased risk of early reinfection.[4,64] In Uganda and Nigeria adherence to correct AL dose and duration prescribed to febrile children by community medicine distributors was greater than 80% and crude parasitological failure rates varied from 3.7% in Uganda to 41.8% in Nigeria and PCR-adjusted parasitological cure rate was 90.9% in Nigeria and 97.2% in Uganda.[6] Differences in crude rates may be due to differences in re-infection rates. A recent study of uncomplicated malaria in Uganda showed adherence to AL was 94.5% compared to that quinine of 85.4% with high unadjusted cure rates of AL of 96% vs 64% for quinine.[65]

In multidrug-resistant areas, day 7 lumefantrine concentration was a useful surrogate marker for AUC and concentrations of less than 280 ng/mL predicted treatment failure.[17,20] However, results from areas with lumefantrine-sensitive parasites showed no treatment failures despite day 7 concentrations less than 280 ng/mL in 45% of all patients, and re-infections occurred among patients with day 7 concentrations below 400 ng/mL and those who received a lower dose of lumefantrine per kilogram body weight.[4]

Safety of AL

Safety and tolerability of AL has been assessed in clinical trials in Asia and Africa. Most adverse events are mild or moderate, mostly affecting gastrointestinal and nervous systems; however, most are typical of the symptomatology of malaria or concomitant infections.[15,24–27,66] Serious adverse events were unlikely and were unrelated or most unlikely to be related to study medication.[15,29–31,33,34,36,38,39,41–43,46–51,53,54,67] Two meta-analysis concluded that AL is well tolerated, with mild or moderate adverse events mostly affecting gastrointestinal and nervous systems. Ototoxicity associated with AL has been reported recently in a few cases;[68,69] however, this was not confirmed in a study that investigated hearing sensation following AL treatment.[31] Lumefantrine possesses a similar chemical structure to halofantrine which is known to cause cardiac arrhythmia; however, safety studies have not shown lumefantrine to be cardiotoxic or to prolong QTc interval.[67,70] Other studies and a review of 15 trials concluded that AL did not cause hematological adverse events, although pre-clinical trials suggested the repeated exposure to AL may affect blood cell counts.[71]

Safety assessment has been conducted during treatment of single episodes of malaria. Safety concerns become more important when AL is administered over the counter, which commonly results in overdiagnosis and overtreatment of malaria, and when patients get recurrent infections requiring repeated treatment. Overdiagnosis of malaria is common in malaria-endemic areas.[72] There are no standard guidelines for evaluating drug safety and tolerability in antimalarial trials.[64] Establishing systems for pharmacovigilance in areas where AL is frequently prescribed is of utmost importance and several challenges exist.[73]

AL use in children

Vomiting, which may be due to disease-related nausea or taste of the medication, may influence drug intake especially in children. A more palatable dispersible formulation of AL is now available and has been shown to be as efficacious as the currently used crushed tablet in infants and children, and with similar safety and PK profile.[15] Pediatric dosing of AL is deduced from adult-based regimens adjusted for body weight, with little consideration for maturational effects on drug absorption and metabolism. Although diet and nutritional status are important determinants of PK processes, drug responses and toxicity, there are few relevant data for AL in this patient group. In resource-constrained areas, children may not be weighed at each clinic visit and dosing in such settings is usually based on age as a proxy measure for weight. Besides research on therapeutic dose levels based on body weight, there is urgent need for evidence-based translation of weight based dosing regimens to regimens that can be based on age, as the majority of fevers in malaria endemic areas are treated with over-the-counter antimalarial drugs without involvement of the formal health sector. Age-based dose regimens are more practical than weight-based regimens, but will inevitably result in a greater proportion of children receiving either too much or too little drug. This is a particular concern with lumefantrine, which has a narrow therapeutic margin between effective and toxic concentrations. This dosing consideration is especially important in malnourished,

pre-school children and during onset of puberty when physiological variations in bodyweight by age are greatest. Earlier experience with SP and DP suggests that lack of clear guidance on age-based dosing as part of the regulatory process contributes to considerable variation in recommended age-based dose regimens,[74,75] potentially resulting in poor, but widely used regimens, particularly for young rapidly growing children who bear the brunt of the malaria burden. Different age-based regimens are already being used in countries that have recently switched to ACTs. These concerns apply also to young infants <6 months old or of <5 kg body weight. Most ACTs are contra-indicated in this group because of lack of safety data, even though these children are at considerable risk. In western Kenya 50% of infants not protected by insecticide-treated mosquito nets had their first infection by 3 months.[76] In southern Mozambique, an estimated 9% of out-patient visits for uncomplicated malaria in children less than 5 years of age are children aged <6 months. Infants in endemic areas have the highest burden of severe malarial anemia, blood transfusions and death.[77,78] Thus, programmatically implemented ACTs will end up being widely used in children <6 months even though the label does not provide guidance for this age group.

Malaria and AL use in pregnancy

Pregnant women with malaria, symptomatic and asymptomatic alike, should be treated without delay with effective and safe antimalarial drugs in order to reduce risks for adverse outcomes for both mother and fetus.[79] AL is a very attractive alternative because it is highly effective, acts rapidly and is well tolerated. However, there is insufficient information on safety and efficacy of ACTs in pregnancy, including exposure in the first trimester.[79,80] Early data indicated that artemisinins were embryotoxic and potentially teratogenic in several animal species without maternal toxic effects or impaired fertility, and more recent studies have confirmed these findings.[79]

Artemisinin derivatives have shown embryo-toxic effects in animal reproductive toxicology studies.[81] The mechanism of embryo-toxicity is thought to occur through depletion of embryonic erythroblasts causing severe anemia and cell damage and death due to hypoxia.[81] The most sensitive time window for embryo-toxicity in humans is between weeks 4 to 10. From these data ACTs are not indicated for malaria treatment in the first trimester of pregnancy unless no alternatives exist. There is increasing experience with artemisinin derivatives in second and third trimesters with no evidence of adverse outcomes in more than 1000 prospectively followed pregnancies.[82,83] WHO Malaria Treatment Guidelines of 2006 recommend use of ACTs in pregnant women in the second and third trimester of gestation. None of the studies on AL use in pregnancy have reported increased risk of serious maternal adverse events, adverse birth outcomes or neuro-developmental deficits. However all these studies were underpowered to detect rare adverse outcomes.[84] Data from Sudan from a cohort of women who reported use of artemisinins in first trimester and were followed up until delivery and their babies followed up till 1 year of age showed that most delivered apparently healthy babies at full term with no congenital malformations and no maternal deaths, and none of the babies died during their first year of life.[85] A prospective observational study was conducted recently in Zambia which evaluated safety of AL and SP in pregnant women who received AL and SP to treat symptomatic *falciparum* malaria. Data from 1001 pregnant women and fetuses/newborns indicated that the incidence of perinatal death, spontaneous abortion, neonatal mortality, premature delivery, stillbirth and low birth weight is similar after pregnancy exposure to AL compared to SP.[86]

Pregnancy has been associated with reduced plasma concentrations of AL which have a significant impact on treatment outcome since plasma concentrations of lumefantrine, after elimination of artemether, are an important determinant of cure.[87,88] A study that evaluated PK of AL in pregnant women with recrudescent uncomplicated multidrug resistant *falciparum* malaria demonstrated that pregnant women in second and third trimester had lower concentrations of artemether, dihydroartemisinin and lumefantrine, and elimination of lumefantrine was more rapid than reported previously in non-pregnant adults.[87,89] Another study that compared artesunate monotherapy to AL for treatment of uncomplicated *falciparum* malaria in second and third trimesters demonstrated that the standard 6-dose AL regimen was well tolerated and safe but efficacy was inferior to that of 7-day artesunate monotherapy and was unsatisfactory for general deployment in this geographic area. PK parameters measured in this study showed low drug concentrations in later pregnancy which could possibly explain the poor treatment outcomes.[89] There is need for further studies to determine the optimum dose regimen and efficacy of AL in pregnancy.

AL use in HIV-infected populations

Human immunodeficiency virus (HIV)-infected individuals are at high risk for acquiring malaria parasitemia, with the risk increasing as immunity declines.[90–93] Evidence for this interaction is more consistent in pregnant women of all gravidities.[94–96] HIV-1 infected pregnant women have a higher prevalence of peripheral parasitemia and placental malaria[95,96]

and their infants experience higher postnatal mortality when both diseases are present.[97,98] Therefore, offering adequate and efficacious antimalarial treatment and prevention is extremely important for this high risk group. Little is known about efficacy and safety of antimalarial drugs in HIV-infected individuals and much less on interaction between antimalarial and antiretroviral (ARV) drugs, and reliable data are urgently needed. Few studies have examined the effect of HIV infection on response to antimalarial treatment and these have yielded conflicting results.[99–103] Most studies have shown that HIV-infected individuals have higher risk of experiencing antimalarial treatment failure due to re-infections.[101,103] Birku et al demonstrated decreased clearance of parasites by artemisinin treatment in HIV-infected patients with malaria.[104] In Zambia, HIV-infected adult patients with CD4 counts of 300/μL and below had higher risk of getting recrudescent malaria than HIV-infected patients with higher CD4 counts and HIV-uninfected patients.[103] Recent studies, however, suggest that the threshold for an increased risk of malaria treatment failure (new infections or recrudescence) probably lies at 400 CD4 cells/μL.[105,106] Following the latest WHO guidelines for sub-Saharan Africa this malaria vulnerable population should be protected by cotrimoxazole prophylaxis or highly active ARV therapy (HAART). There are concerns about safety of AL treatment in HIV-infected patients concomitantly receiving HAART. The standard first-line HAART regimens in many sub-Saharan countries where malaria is endemic are made up of a non-nucleoside reverse transcriptase inhibitor (NNRTI) backbone with 2 nucleoside reverse transcriptase inhibitors (NRTI). The second-line HAART regimen is made up of a protease inhibitor (PI) backbone and 2 NRTIs. Knowledge of the metabolism of ARVs and AL suggests that there is potential for PK drug–drug interactions.[107] For example, PIs like lopinavir/ritonavir (LPV/r) are among the most potent inhibitors of cytochrome P450 (typically CYP 3A4) metabolism, while NNRTIs (efavirenz and nevirapine) are also substrates of cytochrome P450 and usually these two induce but occasionally efavirenz inhibits some P450 isoforms. Although poorly studied the risk of clinically significant interactions involving AL and ARVs is considerable[108] and may result in high concentrations with excessive toxicity or reduced concentrations with reduced efficacy and risk for development of resistance to AL. The potential for interactions between ARVs and antimalarials have been shown in a study of healthy volunteers where AQAS was co-administered with the NNRTI efavirenz. In the first 2 study participants, the AUC for AQAS increased by 100% to 300% and alanine and aspartate transferase levels increased markedly above the upper limit of normal, suggesting hepatoxicity. This led to recommendations that AQAS should be avoided in patients receiving EFV. In a recent study of uncomplicated malaria in Uganda, treatment of HIV-infected children with AQAS was associated with markedly higher risk of neutropenia compared with treatment of HIV-uninfected children. The risk of neutropenia was higher in participants with concurrent ARV use, especially zidovudine, and in those with a history of repeated doses of AQAS.[109] These clinical observations demonstrate the need for thorough examination of the nature of interaction between ARVs and ACTs. An interaction is expected between lumefantrine and both EFV and PIs that could potentially lead to increased levels of lumefantrine (Figure 1); no data are available. The potential interactions with NVP are less clear but co-administration could reduce lumefantrine levels. A study that investigated the PKs of AL when administered with LPV/r in HIV-uninfected healthy volunteers demonstrated that the PK of lumefantrine is influenced by LPV/r, resulting in 2- to 3-fold increases in lumefantrine AUC, and trends towards decreases in artemether maximum concentration (C_{max}) and AUC were noted during co-administration. Decreases in DHA AUC were observed during co-administration without changes in DHA: artemether AUC ratios. The authors concluded that co-administration of AL and LPV/r can be carried out for patients co-infected with malaria and HIV.[110] This study did not address safety concerns with co-administration, which need to be considered in future studies among individuals living in malaria-endemic regions.

AL use in patients with co-morbidity

Treatment of tuberculosis is often a minimum of 6 months including 2 months of intense rifampicin-based treatment. Patients may concomitantly develop malaria requiring treatment with AL. There are currently no published data on interactions of rifampicin and AL. Rifampicin is a potent inducer of hepatic cytochrome and may influence the PKs of AL since both drugs are metabolized by CYP 450.[111] Theoretically co-administration of rifampicin with AL may result in decreased concentrations of AL resulting in decreased efficacy (Figure 1). Data on these PK drug interactions are very scarce, thus the need for more studies. One study evaluated effects of concomitant administration of AL with a potent CYP 3A4 inhibitor. Artemether, DHA, and lumefantrine PKs were altered by ketoconazole. AUC and C_{max} increased for all 3 compounds and terminal half-life increased for artemether and DHA. None of the changes in

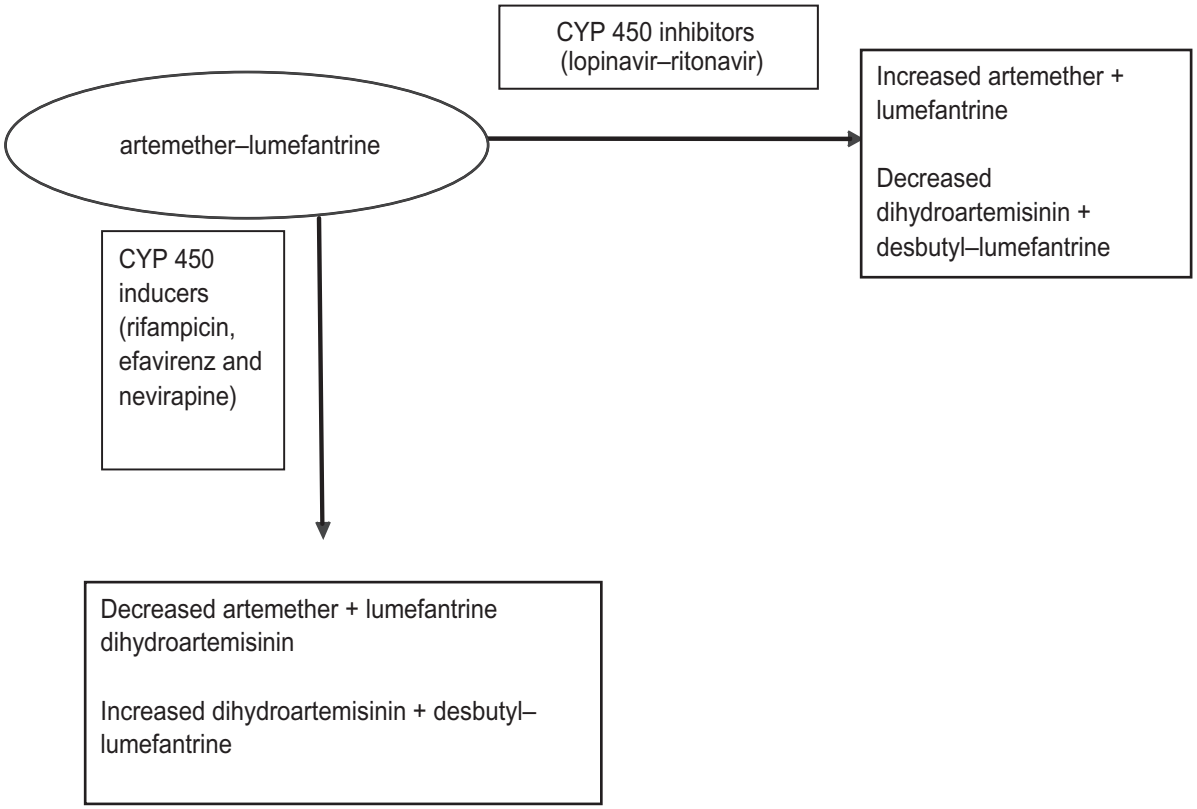

Figure 1 Summary of potential pharmacokinetic interactions between artemether–lumefantrine and commonly prescribed inducers and inhibitors of CYP 450.

PK parameters were greater than the changes observed in healthy volunteers taking AL with a high-fat meal. There was no increase in observed side effects or electrocardiographic changes. The authors concluded that dosage adjustments of AL do not appear to be necessary with concomitant ketoconazole administration.[112]

AL resistance

Antimalarial drug resistance has been defined as "the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the subject." This definition was later modified to specify that the drug in question must gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action."[113] Antimalarial drug resistance is heightened in individuals with lower immunity, such as children less than 5 years, pregnant women, non-immune immigrants to malarious areas, malnourished individuals and HIV-infected patients.[113] Reduced immunity allows the survival of a residuum of parasites that are able to survive treatment, and as such reduced immunity may further increase the development, intensification and spread of resistant strains.

Resistance to artemisinins has not been confirmed although reduced sensitivity has been reported in China and Vietnam.[114,115] Treatment failures occurring after AL treatment are thought to be due to poor absorption with reduced concentrations.[116,117] AL selects for the *P. falciparum* multidrug resistance gene (PfMDR1) N86, the chloroquine-susceptible allele which has been proposed as a marker for lumefantrine resistance.[118] In Tanzania, treatment with AL was associated with selection of newly infecting parasites containing the *pfmdr1* 86N allele,[118] which has been associated with decreased in vitro sensitivity to artemisinins and lumefantrine.[119]

Factors that lead to development, intensification and distribution of antimalarial drug resistance can broadly be classified as: factors leading to treatment failure (incorrect dosing regimen, non-compliance, substandard drugs and misdiagnosis), human behavior, parasite and vector biology, and drug PKs.[113] In sub-Saharan Africa antimalarial drugs are readily available outside public health services, in pharmacies, drug shops and private practitioners' clinics.

Quality of antimalarials is a serious concern and counterfeits may be found in some of these units. In Southeast Asia half of the samples of artemisnins obtained from most countries were counterfeit.[11,120] In sub-Saharan Africa substandard antimalarials were found in 7 countries.[121,122]

Conclusion

There is increasing evidence of very high efficacy and effectiveness of AL for treatment of uncomplicated malaria. Continued health education on correct use of AL and surveillance of effectiveness is necessary to prevent and detect emergence of drug resistance. There is need to develop strong systems for pharmacovigilance to increase the evidence base on safety of AL especially in pregnant mothers and infants weighing less then 5 kg. PK studies especially on drug interactions with ARV drugs are urgently needed.

Disclosures

None of the authors declare conflicts of interest.

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