

Artemether–lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria

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Abstract: The World Health Organization strongly recommends artemisinin-based combination therapy (ACT) regimens for the treatment of uncomplicated *Plasmodium falciparum* malaria cases in endemic areas. Among the combinations of compounds that are available at present, excellent results have been obtained for the artemisinin derivative artemether, in a combination galenic preparation with lumefantrine (artemether–lumefantrine, AL). Here, the pharmacological properties and the therapeutic options of both substances are briefly reviewed and a cursory overview is given on recent trials that have compared the therapeutic effects of AL in the standard 6-dose regimen with other antimalarials and combinations. In order to ensure the most achievable and reliable adherence and compliance of children in the treatment of malaria, a dispersible formulation of AL is now attainable. Recent reports on the emergence of resistance to ACT regimens in Asia, however, are alarming.

Keywords: artemether, lumefantrine, malaria, *Plasmodium falciparum*, dispersible formulation, treatment, therapy

Introduction

According to the 2008 World Malaria Report of the World Health Organization,¹ an estimated 247 million confirmed clinical episodes of malaria were documented in 2006 world-wide. However, and with respect to partly ineffective notification structures and the likelihood of underreporting cases in several malaria-endemic countries, the 5th to 95th percentile uncertainty interval is wide and ranges from 189 million to 327 million cases. More than 880,000 fatalities due to *Plasmodium falciparum* malaria occurred in 2006, 91% of these in subSaharan Africa (SSA) and 85% occurring among children under 5 years of age.¹ Indeed, every 36 seconds a patient dies from malaria. The promotion of artemisinin-based combination therapy (ACT) regimens in recent years as, in terms of effectiveness and the low probability of rapidly evolving resistance to such combinations, a first-line strategy to treat uncomplicated falciparum malaria has under the pronounced advocacy of WHO officially been adopted in all but three countries (Cape Verde, Dominican Republic, French Guyana) and the territory of Swaziland by June 2008. This does, however, not necessarily imply strict routine use of ACT in countries which have officially adopted the WHO suggestion, and compounds to which resistance has emerged (eg, chloroquine, sulfadoxine–pyrimethamine) are still widely used.

The active components and the galenic formulations of ACT combinations vary. At present, the formulations artemether–lumefantrine (AL), artesunate–amodiaquine, artesunate–mefloquine and artesunate–sulfadoxine–pyrimethamine are available and

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recommended for treatment of malaria. Any preferential choice of one of these combinations in a region of intended implementation must critically depend both on the proven efficacy and the degree of parasite resistance to one of the components, either presently established or anticipated to manifest and spread in the foreseeable future. One of the most important issues of a memorandum of understanding that was endorsed and signed by the manufacturer Novartis and WHO in 2001 implies that AL (Coartem®) should be available at cost price in malaria-endemic areas.

Artemisinin

Artemisia annua (qīnghāo [青蒿], syn. sweet wormwood, sweet Annie, sweet sagewort, annual wormwood) is a medicinal herb native to temperate areas of Asia, but naturalized throughout the world. *A. annua* grows with a single stem about 2 m tall, has alternating branches with fern-like leaves, yellow flowers, and a dulcet fragrance of camphor. In central China, especially in the province Hubei, the stems of *A. annua* are still today used as food in a salad-like form. The product is a slightly bitter salad with strong acid overtones from the spiced rice vinegar used as marinade. It is considered a delicacy and is more expensive to buy than meat.

Extracts of *A. annua* have been in use medically, in particular in the treatment of feverish conditions, but also of hemorrhoids, by Chinese herbalists for centuries. The extracts and their potency are referred to in both the *Recipes for 52 Kinds of Diseases* which were unearthed from the Mawangdui Han Dynasty tomb in Changsha 168 B.C.,² and in the *Zhou Hou Bei Ji Fang* (中醫救治術精華; *Handbook of Prescriptions for Emergency Treatments*), written in 340 A.D. by Ge Hong of the Eastern Jin Dynasty. In 1596, artemisinin was mentioned by Li Shizhen as being effective in the treatment of malaria, although appropriate diagnostic tools for malaria were unavailable at that time.

The major active ingredient of *A. annua*, a sesquiterpene lactone (qinghaosu, artemisinin), was first isolated and chemically analyzed in detail in 1972 by Chinese researchers and its antimalarial activity was proven in both mice and primates. The active ingredient is found in the glandular trichomes of the plant leaves, stems and inflorescences, and congregates in the upper portions of the plants at new growth. It can be extracted with low boiling point solvents, eg, diethylether. Subsequently, in 1984 scientists at the Walter Reed Army Institute of Research crystallized the active component of *A. annua*. Artemisinin and its derivatives artemether, artesunate, arteether and others have since successfully been used to clear plasmodia, the causative

infectious agents of malaria, from the blood more swiftly than do other drugs: artemisinin is indeed the fastest acting antimalarial available today. In particular, artesunate and artemether are known to clear parasitemias more rapidly than chloroquine, atovaquone–proguanil, mefloquine, quinine and sulfadoxine–pyrimethamine. Successful and accelerated clearance applies, most importantly, also to otherwise resistant plasmodial strains. By inhibiting the maturation of plasmodial trophozoites, artemisinins efficiently prevent sequestration of parasitized erythrocytes in the microvasculature and, thus, impair disease progression. In contrast to the early belief that artemisinins modify the heme metabolic pathway we know now that the *P. falciparum* encoded sarcoplasmic–endoplasmic reticulum ATPase is most likely their true target.³

Clinically relevant and applicable artemisinins are rapidly metabolized *in vivo* to the biologically active dihydroartemisinin which has an elimination half-life of approximately 45 minutes. Artemisinins also lack the quinine-associated property to induce life-threatening hypoglycemia.

In addition to its strong antimalarial effectiveness, *A. annua* has also been claimed to exhibit considerable anticancer properties. The active ingredients appear to be selectively toxic to distinct breast cancer cells⁴ and some forms of prostate cancer, and exciting results have been reported from experiments with leukemia cells⁵ and other cancer cells.⁶ Furthermore, *A. annua* is effective in killing young adult worms in infections with the several species of the trematode *Schistosoma*, which may cause human schistosomiasis.⁷ Standard therapy regimens of these conditions with artemisinin derivatives have, in contrast to human malaria management, not yet been established. Respective options are, however, under study.

Artemether

As artemether is now the most widely used artemisinin derivative in the treatment of malaria, we will refer in the following to that particular derivative if not indicated otherwise.

Artemether is fat-soluble and readily absorbed within 2 hours after oral application. It is remarkably well tolerated, and peak serum levels occur within 1 hour of an oral dose and persist for up to 4 hours. The terminal phase elimination half-life is less than 1 hour. Co-administration with grapefruit juice and fat increases bioavailability.⁸ Artemether is demethylated by cytochrome P450 (CYP3A4)-mediated metabolic transformation.⁹ Dihydroartemisinin also exhibits antiparasite effects and is cleared rapidly, largely through the bile system.

The inherent advantage of artemether, but also of all other artemisinins, is its rapid effect on all asexual erythrocytic stages of the malaria parasite and on the sexual gametocytes. It prevents gametocyte development by its effect on trophozoites and on early (stage I–III) gametocytes.¹⁰ In studies of more than 5000 malaria patients in Thailand it was convincingly demonstrated that gametocyte carriage occurred significantly less frequent among individuals who were treated with artemisinin derivatives than among those treated with mefloquine.¹¹ Thus, apart from the extraordinary clinical benefit to the individual patient, efficient transmission of plasmodia is inhibited.¹²

The safety profile of artemether is remarkably good and the substance appears to be less toxic than quinine or chloroquine. Reports from clinical trials on serious adverse effects (SAEs) are scarce and include type 1 hypersensitivity reactions in about 1 out of 3,000 patients as well as drug-induced fever, hypotension, tinnitus, transient and clinically insignificant reticulocytopenia, neutropenia, elevated SGOT and SGPT plasma levels, bradycardia and ECG abnormalities. In particular, a prolongation of the QT interval has been observed.¹³ Gastrointestinal disturbances such as nausea, abdominal pain, diarrhea after oral application, dark urine, sweats, jaundice and somnolence and dizziness, pain at the site of the injection, skin reactions, and fever may occur rarely. All adverse events are reversible.

In animals, intramuscular injection of artemether can cause neurotoxicity, in particular neuronal damage in brain stem nuclei,^{14,15} most likely due to sustained blood concentrations of artemether after injection of the oily drug. Neurotoxic effects in mice are less pronounced when artemether is given orally, although higher blood concentrations are achieved via the parenteral route.¹⁶ However, these findings were not confirmed to occur in humans.¹⁷ Artemisinins have shown toxic potential, but no teratogenic potential, in animal models and are thus contraindicated in the first trimester of pregnancy if alternatives are obtainable.¹⁸

Overdosage of artemether has not been reported to date. Experiments with large doses of artemether, however, suggest the occurrence of cardiac irregularities, eg, prolongation of the QTc interval and arrhythmias (mostly tachycardia), and disturbances of the central nervous system. An ECG should be documented prior to the initiation of treatment in all cardiac patients. Clinicians who are confronted with situations of artemisinin overdosage should examine gait and balance as well as alterations of the ocular motility and of peripheral reflexes. An antidote to artemether is not at hand.

As the half-life of artemether is extremely short, a safe cure cannot be relied on unless multidose treatment has been applied, eg, for 7 days with plasma levels above the minimal parasitocidal concentration. The use of artemisinins in monotherapy of malaria is, however, not recommended as it is associated with high incidences of recrudescence infection. In addition, combined treatment with a second drug is critically important in order to prevent the development of artemisinin resistance. The WHO has announced in 2006 that 13 pharmaceutical companies have agreed to comply with the prudent recommendation to phase out single-drug artemisinin medicines for oral malaria treatment. Complying companies include the leading producers of high quality artemisinin-based substances. They will now focus their marketing efforts primarily on combinatory drugs (artemisinin-based combination therapy, ACT).

Resistance to artemisinins

In experimental laboratory settings, the induction of persistent high-level resistance to artemisinins in *P. falciparum* is difficult to achieve. Rodent malarias, but also *P. falciparum* with a 5- to 10-fold reduced susceptibility, could be selected *in vitro*.¹⁹ *P. falciparum* multidrug resistance gene 1 (*Pfmdr1*) is associated with slight but significant reductions in susceptibility to artemisinins.²⁰ *In vitro* data from French Guyana and Senegal indicate that inhibitory concentrations (IC) 50 values as high as 117 nmol/L and 45 nmol/L, respectively, were associated with mutations (S769N) in the SERCA-type PfATPase6.²¹ Data were collected in areas of unrestrained and unsupervised oral artemisinin application. Data that come from Cambodia and its border to neighboring Thailand are of concern as well. In this cradle area of drug resistance development and multidrug-resistant *P. falciparum*, treatment failure to artesunate-mefloquine as well as AL already exceeds 10%,²² whereby it is unclear whether resistance to partner compounds of the artemisinins play a prominent role.²³ Other investigators have found, in the very same area, a persistent high sensitivity of *P. falciparum* to artesunate-mefloquine, but steadily decreasing parasitological responses to artesunate, and an increase in gametocyte carriage of patients.²⁴ Nevertheless, artemisinin derivatives have been used in this region for more than 30 years now and, most likely, exerted considerable cumulative evolutionary pressure on *P. falciparum*. Until now, *in vitro* resistance of parasite isolates appears to be inducible.²⁰ A most recent alarming study from the Thai–Cambodian border raises, however, concern in this matter and clearly indicates the urgent need of appropriate containment measures.²⁵

Table 1 Countries by WHO region which have adopted artemether–lumefantrine (AL) as first-line drug policy for the treatment of uncomplicated falciparum malaria¹⁸

WHO region	Country
Africa	Angola, Benin, Botswana ^a , Burkina Faso ^a , Central African Republic ^a , Chad ^{a,b} , Comoros, Ethiopia, Gambia, Guinea-Bissau ^a , Kenya, Malawi, Mali ^a , Mozambique ^a , Namibia, Niger, Nigeria, Rwanda, South Africa, Togo, Uganda, United Republic of Tanzania ^b , Zambia, Zimbabwe ^a
Western Pacific	Papua New Guinea ^a , Philippines ^a , Vanuatu ^a

^aPolicy adopted but not fully implemented. ^bAL adopted, but not exclusively; other ACTs in use as well.

The spread of artemisinin resistance westwards has also been addressed.²⁶ Discrepancies between *in vivo* and *in vitro* data require careful exploration. Parasite isolates from most other parts of the world are still highly sensitive to artemisinins. We are, however, expecting now the first data sets from Kenya where corresponding studies on artemisinin resistance are being performed. *In vitro*, the median IC50 for dihydroartemisinin and artesunate are usually below 10 nmol/L. IC50s for artemether and artemisinin are typically 2 to 3 times and 5 to 10 times higher, respectively.²⁰

To delay the imminent emergence of resistance, artemisinins are now combined with longer-acting drugs, in particular with amodiaquine, mefloquine, sulfadoxine–pyrimethamine or with lumefantrine. The addition of long-acting drugs to artemisinins causes the elimination of residual parasites that were not readily disrupted by the fast-acting artemisinin. The combinatory drug that has been studied best so far is lumefantrine.

Lumefantrine

Lumefantrine (previously referred to as benflumetol) is a substance with distinct blood schizontocidal activities against a wide range of plasmodia, including *P. falciparum* and all other human plasmodia. Lumefantrine, a fluorene (benzindene) derivative (a-(dibutylaminomethyl)-2,7-dichloro-9-(p-chlorobenzylidene)-5-fluorenemethanol), is an aryl-amino alcohol with intriguing similarities to other antimalarials (quinine, halofantrine, mefloquine). It has, however, and in contrast to these substances, never routinely been used as monotherapy in malaria. Lumefantrine originates, as does artemether, from malaria research in China. It was synthesized in the 1970s by the noncommercial Academy of Military Medical Sciences in Beijing²⁷ and its effectiveness against all *Plasmodium* species that are pathogenic to humans has been documented and evaluated in several studies.⁹

Lumefantrine is highly lipophilic and resorption commences approximately two hours after administration. Peak plasma levels are found 6 to 8 hours after administration,

whereby plasma levels may vary considerably between individuals.²⁸ Concomitant consumption of food, in particular the intake of fat at a minimum amount of about 1.2 g/dose of lumefantrine,²⁹ enhances the bioavailability of both artemether and lumefantrine by the factors 2 and 16, respectively. Concerns that fat contents of meals in sub-Saharan Africa might not suffice for ample bioavailability of AL with convincing cure rates have been addressed in a recent review article and have been contradicted.³⁰ However, an anecdotal case report indicates that insufficient fat intake or even starvation may result in treatment failure.³¹

The precise mode of the efficacy of lumefantrine on plasmodia is not fully understood. It results, most likely, from the interaction of heme, a degradation product of the hemoglobin metabolism, with the active ingredients in the digestive vacuole of the malaria parasite. It may, however, also interfere with the synthesis of nucleic acids and proteins. The activity of lumefantrine is slower than that of artemisinins and the recrudescence rate is low when the substance is given as recommended. Lumefantrine binds strongly to lipoproteins and has a terminal phase elimination half-life of approximately 86 hours.⁹ In dogs and rats, a direct glucuronidation takes place *in vivo* after oxidative biotransformation. In human liver microsomes, lumefantrine is N-dibutylated by CYP3A4³² and, *in vitro*, lumefantrine inhibits at appropriate plasma concentrations significantly the activity of CYP2D6.

The pharmacokinetic properties of lumefantrine are reminiscent of characteristics of halofantrine, with variable oral bioavailability profiles, considerable augmentation of oral bioavailability through concomitant consumption of fat, and a terminal elimination half-life of 2 to 3 days in healthy volunteers and 4 to 6 days in patients with clinically relevant *P. falciparum* infections.³³

Artemether–lumefantrine: the fixed-dose formulation

The rationale of using ACT is as follows: different half-lives of ACT compounds, with extremely short half-lives of

artemisinin derivatives and long half-lives of the partner drugs cause a pharmacokinetic imbalance. The rapid onset of action of artemisinins reduces the biomass of the parasite within a short period of time. The remaining parasites are subject to elimination through the partner drug. This mode of action has proven highly effective. It implies, however, that the efficacy of ACTs critically depends on the parasite's sensitivity to the non-artemisinin partner drug. In order to minimize the development of ACT resistance, fixed co-formulations are superior to two separate or co-blistered drugs, as fixed combinations explicitly exclude artemisinin monotherapy. Currently, 100 million ACT treatments are prescribed per year, approximately 75% of them with AL. AL is now registered in 79 countries. The second largest share of the market has artesunate–amodiaquine as a co-blistered formulation which is expected to be replaced in due time by a fixed-dose combination produced by Sanofi-Aventis.³⁴ Given that approximately 300 million malaria treatments are needed annually, the number of ACTs to be distributed could readily double by 2012. Taking into account the current absence of clinically significant resistance to these ACTs outside Cambodia and Thailand, they are likely to be the most commonly used ACTs for the next few years to come.

The combination of artemether with lumefantrine was developed in China and first evaluated in the 1960s. Based on the good results, Novartis was involved in the production and distribution of AL as Coartem[®] or Riamet[®]. It was the first fixed-dose antimalarial drug combination of an artemisinin derivative with an unrelated co-substance, in terms of biochemical and pharmacological properties. First, tablets containing 20/120 mg AL were introduced as a 4-dose regimen (total dose: 80/480 mg AL) to be administered at 0, 8, 24 and 48 hours of treatment. Pharmacokinetic–pharmacodynamic (PK–PD) data, however, suggested that the main PK determinant of cure was either the area under the actual plasma lumefantrine concentration time curve (AUC) or, as a proxy, the concentration of lumefantrine at day 7.²⁷ Lumefantrine plasma concentrations at day 7 of >500 ng/mL are required to result in cure rates of more than 90%, but such success could not be reproducibly and reliably achieved with the 4-dose regimen. To increase the AUC, a 6-dose regimen was then tested and proved highly effective and well tolerated in adults when each 4 tablets were given at 0, 8, 24, 36, 48 and 60 hours of the treatment course.³⁵ When comparing the 6-dose regimen over 60 hours with the 6-dose regimen over 96 hours with tablets given at 0, 8, 24, 48, 72 and 96 hours, the 28-day cure rates were still slightly higher.³⁵

In children, appropriately bodyweight-adjusted AL doses are recommended. Children with weights of ≥ 5 / <15 kg, ≥ 15 / <25 kg and ≥ 25 / <35 kg should receive 1, 2 and 3 tablets, respectively, per time point. Demographic variables such as gender, body weight, age and ethnicity do not appear to affect the pharmacokinetics of AL. If vomiting occurs within one hour of administration, an equal dose of AL should be given again.

Artemether–lumefantrine: drug interactions

Administration of AL together with ketoconazole, a potent CYP3A4 inhibitor, resulted in elevated plasma levels of artemether, dihydroartemisinin and lumefantrine. These increases were, however, considered clinically insignificant,³² as were decreases in the lumefantrine AUC when mefloquine, a CYP3A4 substrate as well, was simultaneously given to healthy individuals.³⁶ As antiretroviral drugs are powerful modulators of CYP enzymes, validated pharmacokinetic data on their interactions with AL are now urgently needed. Patients who are undergoing antiretroviral treatment should be examined regularly during a treatment course with AL.

When switching from AL to quinine during a treatment course, the long elimination half-life of lumefantrine must be considered and careful ECG monitoring is essential. Pretreatment with mefloquine does not modify the plasma concentration of artemether or the ratio artemether–dihydroartemisinin. However, a significant decline of plasma lumefantrine levels may occur, most likely due to a mefloquine-induced decreased resorption that is induced by diminished production and output of bile.

Artemether–lumefantrine: side effects, cautions and contraindications

AL is tolerated very well in the majority of cases. A tolerability superior to that of mefloquine alone or to the combination of mefloquine with artesunate has repeatedly been observed.^{37,38} Adverse effects that were reported include gastrointestinal irritations, headache, dizziness, fatigue, sleep disturbances, rash, palpitations, myalgia and arthralgia.³⁹ Evidence of cardiotoxicity, which may be expected due to structural similarities of lumefantrine with mefloquine, quinine, and halofantrine, is weak. In fact, in healthy volunteers as well as in patients, clinical studies could not demonstrate significant changes in the QTc interval, or a correlation between plasma lumefantrine levels and QTc intervals.^{40,41} One study has

indicated a modestly increased risk of QTc prolongation when AL was given to healthy individuals together with quinine intravenously.³² Data on cardiotoxicity of artemisinin derivatives in general, and of artemether in particular, have shown clinically insignificant ECG abnormalities in <1.3% of more than 2600 patients who were surveyed.¹³ However, as in several studies asymptomatic prolongations of the QTc intervals have been described, the manufacturing company has decided to restrain from recommending AL for patients with recognized cardiac arrhythmias and for patients who are on medications potentially affecting the QTc interval. Studies of patients with renal or hepatic impairment have not been conducted so far.

Initial reports on irreversible audiometric changes in humans treated with AL have raised concern.⁴² Further careful evaluation in a randomized trial, however, has not confirmed any detrimental effects of standard oral regimens of AL on peripheral hearing or brainstem auditory pathways in patients with falciparum malaria.⁴³

According to the manufacturer, approximately 20 distinct SAEs were observed in more than 1800 patients treated. These include severe anemia in children, pneumonia, hepatitis, and one case of hemolytic anemia and others, all of which could even have been caused by the malaria infection itself.¹³ Because of the unavailability of validated data, AL should not be given to pregnant or breast-feeding women and clinicians should use AL in these patients only when alternatives are either not obtainable or contraindicated.¹⁸ This applies also to children with body weights less than 5 kg. Overall, the tolerability and safety profile of AL is favorable, while drug interactions should be subject to clinical notice and trigger further research.

Procurement of artemether–lumefantrine by WHO

AL has been included in the *WHO Model List of Essential Medicines* for adults and children (<http://www.who.int/medicines/publications/essentialmedicines/en/>), a list of essential medicines compiled by a group of independent experts who select basically essential drugs according to their public health relevance, evidence of efficacy and safety, and competitive cost-effectiveness. Novartis, the manufacturer of AL, and WHO have formally agreed to collaborate in order to increase the access to AL in developing countries. Through this collaboration, WHO intends to achieve a broad and equitable availability of safe and effective malaria treatment and, in addition, contribute to the control of drug resistance. In its function as a technical adviser to member states, WHO

wants to contribute to both national drug policy changes and rational drug use.

Despite strong efforts to modify the properties and galenics of AL, it still has a limited shelf-life of 24 months only. This requires efficient distribution infrastructures on all levels of health care systems. The problem applies in particular to those developing countries which have adopted AL as first-line drug for the treatment of uncomplicated falciparum malaria. These countries face the challenge of supplying AL to remote primary health care facilities and to assure correct storage of sufficient amounts of the medicines.

Most recent data indicate that AL tablets may be chemically and physically stable well beyond the stated shelf-life even under tropical, ie, warm, conditions.⁴⁴ These data should, however, not pave the way for a permissive attitude about the stability of AL tablets, but rather lead to thorough investigation and examinations and, if possible, chemical and galenic improvement.

UNICEF and other official agencies as well as non-governmental organizations have established direct procurement agreements with Novartis to supply AL at the cost that was negotiated by WHO. As a direct consequence, a smaller proportion of AL was procured through WHO in 2007.¹

Soluble formulations of artemether–lumefantrine for children

A 3-day, 6-dose regimen of AL is efficacious and safe both in adults and children.^{45,46} Infants and children can safely be treated when weighing 5 kg or more. AL was found to have an efficacy of 90% or more in African children at day 28 of treatment. This was even true under unsupervised outpatient conditions when nutritional advice, namely intake with fatty food, was given.⁴⁷ Young children are, especially if they are sick, not able to swallow the AL tablets. In everyday practice, crushing of the tablets and administering them with water is the typical solution of this problem. This, however, results in a bitter tasting solution, potentially compromising tolerability and compliance. To overcome these problems, dispersible tablets (Coartem® Dispersible) have been tailored for exclusive pediatric use by Novartis in collaboration with Medicines for Malaria Venture (MMV). The main features of Coartem® were maintained as far as possible, in particular the strength of the dosage (20 mg A/120 mg L) per dispersible tablet. The sweetened and cherry-flavored dispersible tablets have to be added to a small amount of water and administered without delay orally once disintegrated to a suspension. Rinsing the water glass is recommended to ensure complete administration.

Table 2 Therapeutic effects of artemether–lumefantrine (6-dose regimen; standard tablets of 20/120 mg AL) in children in malaria-endemic areas with uncomplicated falciparum malaria – comparison to other antimalarial compounds

Drugs tested vs AL	Country	n	Main conclusion	Score ^a	Reference
AS-SMP-PYR	Cameroon, Mali, Rwanda, Sudan	1,384	Similar effectiveness, efficacy and tolerability	+/-	52
AQ-AS	Ghana	246	Equal clinical and parasitological responses; more late clinical failures with AL; AL less well accepted	-	53
CQ-SUL-PYR AS-SUL-PYR DHA-PIP DHA-PIP	Papua New Guinea	482	AL most effective	+	54
DHA-PIP	Kenya	146	Faster parasite clearance with AL	+	55
AS-MQ	Mali	470	Similar cure rates; more new infections after treatment with AL	-	56
AS-AQ	Ghana	227	Both equally effective and well tolerated	+/-	57
AS-AQ AS-CPG-DAP DHA-PIP	Ghana Uganda	534 414	Similar effectiveness and tolerability Similar efficacy; higher risk of reinfection in AL group, higher risk of gametocytemia in AL group; equally well tolerated	+/- -	58 59
AS-AQ	Nigeria	132	Equal efficacy and safety	+/-	60
AS-AQ	Tanzania	157	Similar efficacy after PCR adjustment		61
AQ-SUL-PYR DHA-PIP	Burkina Faso	559	Similar risk of genotype-adjusted treatment failure, equally well tolerated	+/-	62
SUL-PYR	Nepal	99	AL more effective than comparison drug	+	63
AQ-SFL-PYR	Nigeria	181	Similar efficacy, tolerability, and gametocyte-carrier rate; faster parasite clearance in the AL group	+	64
AS-SUL-PYR	Sudan	160	Both regimens highly effective	+/-	65
AS-AQ AS-MQ AQ-SUL-PYR DHA-PIP	Senegal Uganda	955 421	All combinations after PCR correction similarly effective and well tolerated Higher risk of recurrent parasitemia and gametocytemia in the AL group	+/- -	66 67
AQ-SUL-PYR AQ-AS DHA-PIP	Uganda Indonesia	601 774	AL was the most efficacious treatment Both equally safe and effective after PCR correction; higher risk of reinfection in the AL group	+	68 69
AQ-SUL-PYR	Burkina Faso	521	AL less effective	-	70
AQ-SUL-PYR	Rwanda	500	AL more efficacious than comparison drug	+	71
MQ-AS	Cambodia	190	Lower cure rates in AL, possibly due to low levels of lumefantrine in blood or lumefantrine resistance	-	23

(Continued)

Table 2 (Continued)

Drugs tested vs AL	Country	n	Main conclusion	Score ^a	Reference
AS-SUL-PYR AS-AQ	Republic of Congo	298	Better efficacy and fewer reinfections in the AL group	+	72
AS-SMP-PYR	Mali	606	Same efficacy/safety profile as AL; both well tolerated	+/-	73
AS-AQ	Uganda	408	Equal efficacy; AL superior in preventing new infections	+	74
AS-AQ	Angola	137	Equal efficacy	+/-	75
AS-AQ	Nigeria	119	Equally high efficacy and tolerability	+/-	76
AS-SUL-PYR	Sudan	143	Equally high efficacy and tolerability	+/-	77
AS-MQ	Thailand	490	Equally high efficacy	+/-	78
AS-AQ	Tanzania (Zanzibar)	408	Equal efficacy; AL superior in preventing new infections	+	79
CQ-SUL-PYR AS-MQ	Bangladesh	364	Both ACTs effective, well tolerated, reduced gametocyte carriage	+/-	80
CQ SUL-PYR AS-AQ	Ghana	168	Rapid fever, parasite and gametocyte clearance in the studied ACTs	+/-	81
CQ-SUL-PYR	The Gambia	497	AL reduced risk of gametocyte-carriage and gametocyte density post-treatment	+	82
AQ AQ-SUL-PYR AS-AQ	Tanzania	1811	Best effectiveness and least recrudescences in the AL group	+	83
AS-MQ	Lao People's Democratic Republic	108	Equally high efficacy and tolerability	+/-	84
CQ-SUL-PYR AS-MQ	Lao People's Democratic Republic	330	Both ACTs highly effective	+/-	85
AS-MQ	Thailand	219	Similar efficacy and tolerability	+/-	86
AS-MQ	Thailand	200	AL equally effective but better tolerated	+	87

Notes: Randomized, comparative efficacy and/or efficiency trials found in PubMed when search terms "artemether AND lumefantrine" were entered are included in the table. Only trials that were published in English are considered.

^aScoring refers to the comparisons of AL with other components; +, -, +/-, AL superior, inferior, equal, respectively, to the comparison drugs; ^bchildren and adults.

Abbreviations: AL, artemether–lumefantrine; ACT, artemisinin combination therapy; n, number of randomized study participants; AS, artesunate; CPG, chlorproguanil; CQ, chloroquine; DAP, dapson; DHA, dihydroartemisinin; MQ, mefloquin; PIP, piperazine; PYR, parimethamine; SFL, sulfalene; SMP, sulphamethoxy-pyrazine; SUL, sulfadoxine.

In a randomized, multicenter, non-inferiority, investigator-masked clinical trial including 899 children in Benin, Mali, Kenya, Tanzania/Zanzibar and Mozambique, the 28-day parasitological cure rate (PCR corrected) in the per-protocol analysis was 97.8% (95% confidence interval [CI], 96.3 to 99.2) for dispersible tablets and 98.5% (95% CI, 97.4 to 99.7) for the administration of crushed tablets.⁴⁸ In the intention-to-treat analysis of this study, these figures were 95% and 96.2%, respectively. The safety profile of dispersible AL tablets also equals that of the standard tablets. The costs of this formulation are identical to those of the standard formulation. Several African countries have already approved the dispersible galenics of AL. Novartis has now applied for the inclusion of Coartem[®] Dispersible in the *WHO Model List of Essential Medicines for Children*, a step that appears reasonable and justified.

Another soluble formulation, a dry powder containing 15 mg Artemether and 90 mg Lumefantrine per 5 mL of

liquid after reconstitution (Co-Artesiane[®]; Dafa Pharma), was successfully tested against AL standard tablets in a randomized, controlled, open-label trial in Kenya.⁴⁹ The results of this study did also not indicate any differences in cure rates or safety, though they had a lower statistical power to do so.

Trials on the efficacy of artemether-lumefantrine in children

Table 2 lists clinical trials from Africa and Asia in which the therapeutic effects and/or the tolerability and/or the risk of reinfections of the 6-dose AL regimen with standard tablets in children in malaria-endemic areas with uncomplicated falciparum malaria were compared to that of other antimalarials. The studies listed in Table 2 are based on a NCBI-PubMed review with the search terms "artemether AND lumefantrine" and did not adhere to the stringent selection criteria which are applied for the meta-analyses of the Cochrane Infectious Diseases Group Specialized

Register. Notably, in several studies only small numbers of participants were enrolled.

Although the conclusions that came from the various comparative studies are partly inconsistent and, in some cases, dependent on inherent differences in reporting, they clearly demonstrate the favorable tolerability, high efficacy and adequate parasitological responses to ACT in general and in particular to the standard 6-dose regimen. In the majority of the comparisons, the overall evaluation of AL appears superior to the comparison substances. In those studies where AL was rated inferior to the comparison drug or drug combination it is worth to note that in all studies, except one, artemisinin derivatives were part of the comparison. The overall good effectiveness and tolerability is in line with the 2005 Cochrane Database Systematic Review,⁵⁰ which concludes that, after evaluation of 9 clinical trials, the 6-dose regimen of AL appears to be more effective than antimalarial regimens not containing artemisinin derivatives.

Conclusion

Although resistance now appears to be emerging, ACT treatment is still the best choice that we have at present for the treatment of uncomplicated *P. falciparum* malaria, both in disease of children and adults. It is sufficiently well tolerated and effective and some degree of resistance against the constituent components has only recently been reported. This situation certainly requires attentive monitoring and the development of containment strategies. The dispersible formulation of AL for use in pediatric malaria is an important and favorable improvement, as it will certainly enhance the compliance of affected children and of the parents who care for them. However, we are desperately waiting for the effective (at best 99% or so) malaria vaccine, which is not in sight yet. Recent encouraging observations on the RTS,S/AS01E vaccine that is still undergoing evaluation in several regions show an adjusted efficacy rate of 53%.⁵¹ Until comprehensive coverage with an effective vaccine we have to cope with and explore and improve all available and attainable preventive and therapeutic options in order to reduce the intolerable burden of malaria.

Disclosures

The authors have no conflicts of interest to disclose.

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