

Drugs for the treatment of malaria in the Kingdom of Saudi Arabia

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ABSTRACT

تعتمد علاجات الملاريا الحالية على استخدام التركيبات القائمة على الأرتيميسينين. أما في المملكة العربية السعودية، فيتم استخدام المزيغ من بيرميثامين/السلفادوكسين/الارتيسونات كخط اولي لمعالجة الملاريا غير المصحوبة بمضاعفات، بينما يستخدم لومفانترين/مادة ارتيميشير (كوارتيم®) كخيار ثان. علاج الملاريا الحادة يعتمد على استخدام الكينين أو الارتيسونات. بينما علاج الملاريا الحادة يعتمد على استخدام الكينين المضادة للملاريا القديمة والارتيسونات (مشتقات الأرتيميسينين). ويتم جلب معظم حالات الملاريا للمملكة العربية السعودية، من خلال العمال المهاجرين من شبه القارة الهندية والجزء الشرقي من أفريقيا. نتيجة لذلك تكون معظم الطفيليات قد تعرضت للأدوية المضادة للملاريا قبل المجيء إلى البلاد. وهكذا، فإن المعرفة بنمط المقاومة لهذه الأدوية خارج البلاد يمكن أن يسهم بإدارة أفضل لهذا المرض. في هذا الاستعراض، قد قمنا بتلخيص معرفتنا الحالية على أنماط الفعالية والمقاومة للأدوية المضادة للملاريا المستخدمة حالياً، كما تم مناقشة أيضا العلاجات.

Current malaria treatments are based on the use of artemisinin based combinations. In the Kingdom of Saudi Arabia, the combination of pyrimethamine/sulfadoxine/artesunate is the first line of treatment of uncomplicated malaria, while lumefantrine/artemether (Coartem®) is used as a second option. The treatment of severe malaria rests on the use of quinine or artesunate. In Saudi Arabia, most cases of malaria are imported, mainly from emigrant workers from the Indian subcontinent and the Eastern part of Africa. As a result, most parasites might have been exposed to antimalarials prior to coming to the country. Thus, knowledge of the pattern of resistance to these drugs outside the country could contribute to better management of the disease. In this review, we have summarized our current knowledge on the efficacy and resistance patterns of currently used antimalarials. Alternative treatments that could be used against malaria in the Kingdom are also discussed.

Saudi Med J 2013; Vol. 34 (6): 569-578

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Malaria is a global public health priority, and remains the biggest cause of mortality and morbidity. The disease is prevalent in the developing world, mainly in Sub-Saharan Africa, and primarily affects children under the age of 5. Several initiatives, such as Roll Back Malaria and the Malaria Eradication Research Agenda have been promoted to reduce the burden of malaria. In the past few years, a decrease in malaria mortality has been reported in several endemic areas.¹⁻³ However, a recent investigation indicates that the real burden of malaria has been underestimated, especially in children aged 5 years or older.³ For instance, it is estimated that more than one million malaria attributed deaths occurred in 2010 alone.³ Thus, malaria remains a global public health priority.

In the Kingdom of Saudi Arabia (KSA), an extensive effort, started in the 1940s, has led to a substantial decrease of malaria cases in many parts of the country. In the Eastern and Northern provinces for instance, malaria has been eliminated since no local transmission has been observed for many years.⁴ Most cases are imported malaria, through emigrants who form the workforce in the country. For instance, in 2009, out of 2333 reported malaria cases, only 58 (1.7%) were local cases, the rest were imported.⁴ In the Eastern Province, out of 700 malaria cases in 2011, 99.1% were imported and only 0.9% were from Saudi citizens (Dr Al-Zahrani, unpublished data). Most local

infections occur in the South-western regions of Jazan and Aseer, and the predominant species is *Plasmodium falciparum* (*P. falciparum*).⁴ Imported cases came from the neighboring countries of Yemen and Sudan and the Indian subcontinent (India and Pakistan). Yemenites and Sudanese predominantly carry *P. falciparum*, while travellers from India and Pakistan are infected with *Plasmodium vivax* (*P. vivax*) alone or in co-infection with *P. falciparum*.⁴⁻⁶ The malaria parasite has an intrinsic ability to quickly develop resistance against antimalarials. As a result, the World Health Organization (WHO) recommended that antimalarial treatment be based on the use of combinations of 2 drugs that have different modes of action, as a strategy to delay or slow down the onset of resistance. Artemisinin has been selected as the drug of choice in such combinations, and these are now known as artemisinin based combinations, ACTs.⁷

The ACTs have been adopted by the Saudi Ministry of Health. The combinations of pyrimethamine/sulfadoxine/artesunate (PM/SD/ART) and lumefantrine/artemether (LM/ATM), also known as Coartem®, have been selected as first and second lines of treatment for uncomplicated falciparum malaria, and quinine and artesunate are used for the management of severe malaria due to *P. falciparum*.⁴ Overall, these drugs are efficacious to treat malaria in the country. For instance, in the Eastern province, no case of malaria (*P. falciparum*) treatment failure has been reported in the last 2 years (Dr Zahrani, personal communication). However, these drugs have been used extensively outside the KSA, and cases of resistance against these drugs have been reported. For instance, PM/SD is no longer effective in Africa and Asia,⁸ resistance to artemisinin is now emerging in South East Asia, and there is concern that this resistance may spread to other parts of the world.^{9,10} On the other hand, *P. vivax* malaria is treated with the combination of chloroquine (an old antimalarial used to treat *P. falciparum* malaria, which is also active against the *P. vivax* blood stage) and primaquine.¹¹ *Plasmodium vivax* is characterized by the existence of dormant forms in the liver of the host, and these forms are effectively cleared by primaquine,¹² hence, the use of the combination of chloroquine and primaquine. However, resistance of *P. vivax* against chloroquine is now emerging in Asia, threatening the treatment of *P. vivax*.¹³ Since the bulk of malaria cases in KSA are imported, most parasites might have been exposed to antimalarials prior to coming to KSA. Thus, knowledge of the pattern of resistance to these drugs outside KSA could contribute to better management of the disease. In this review, we have summarized our current knowledge on the efficacy and resistance

patterns of antimalarials used in the KSA (PM/SD, artemisinin, Coartem® and quinine). Also discussed, are alternative treatments that could be introduced in the Kingdom. Table 1 summarizes current drugs used in the treatment of malaria, Table 2 presents information pertaining to the mechanism of antimalarial resistance, and Table 3 provides the dosages and main side effects of antimalarials.

Pyrimethamine/sulfadoxine/artesunate in the treatment of *Plasmodium falciparum*. Pyrimethamine/sulfadoxine belongs to the class of antifolate drugs, since it blocks the synthesis or conversion of folate derivatives. Folate derivatives are important cellular cofactors for the production of deoxythymidylate (dTMP), thus, synthesis of DNA.^{14,15} This pathway is so critical that *P. falciparum* relies completely on the de novo synthesis pathway of dTMP, since it cannot salvage pyrimidine from the exogenous medium.^{14,15} The most important enzymes, with regard to antifolate activity, are dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS). All drugs that target DHPS are sulpha-based and they include sulfonamide (sulfadoxine, SD) and sulfone (dapson, DDS). Combinations of inhibitors of DHFR and DHPS are synergistic (the presence of one increases the activity of the other), and this led to the development of the combination of PM and SD as an antimalarial, also known as Fansidar®. This drug combination was used extensively first in South East Asia in the 1970s, as a replacement for chloroquine (CQ). However, resistance to it emerged relatively quickly, within a few years.⁸ To improve its efficacy, the drug was combined with mefloquine (another antimalarial) under the name of Fansimef.¹⁶ However, the spread of resistance to PM/SD, and to some extent, to mefloquine, led to the withdrawal of this combination.¹⁷

Mechanisms of resistance. Pyrimethamine/sulfadoxine resistance is attributable to parasites that carry point mutations at codons 108 (Ser to Asn), 51 (Asn to Ile), and 59 (Cys to Arg) of the dhfr gene, and these are triple mutant parasites. Resistance is augmented by the selection of point mutations at codons 437 (Ala to Gly) and/or 540 (Lys to Glu) or 437 and/or 581 (Ala to Lys) of the dhps gene. High levels of in vivo PM/SD resistance are associated with the selection of mutation at codon 164 (Ile to Leu) of dhfr.⁸ Genotyping of dhfr and dhps has been widely used to monitor the emergence and selection of resistance to PM/SD in various malaria endemic areas, including the KSA.¹⁸

Development of the combination of pyrimethamine/sulfadoxine/artesunate. In Africa, PM/SD was introduced in the 1990s for malaria treatment, as a

replacement for chloroquine. However, in South East Asia, resistance to this combination emerged within a few years, and by the mid-2000s,⁸ this drug was withdrawn in most African countries and replaced by ACT.¹⁹ However, in some parts of Africa, mainly in Western Africa, the efficacy of PM/SD was still acceptable until the early 2000s. As a result, the combination of PM/SD/ART has been evaluated. Several clinical trials of PM/SD/ART have been carried out in comparison either with PM/SD alone, PM/SD with amodiaquine, or with lumefantrine/artemether. While the efficacy of the combination was improved compared to the use of PM/SD monotherapy,²⁰ the data showed limited efficacy in areas where PM/SD resistance was high.²¹⁻²³ This combination is efficacious only in areas of high PM/SD efficacy.^{20,24-28} In many central Middle East Asian countries, PM/SD remains relatively efficacious, since it has not been widely used. As a result, the combination

of PM/SD/ART has been adopted as a first line of treatment of uncomplicated malaria in Afghanistan, Iran, Pakistan, Tajikistan, Yemen, and India among others; Sudan and Somalia, the neighboring African countries to the KSA, have also adopted PM/SD/ART as a first line of treatment.²⁹ Clinical evaluations of the combination have shown a relatively good efficacy in Sudan,³⁰ Ethiopia,²⁷ Afghanistan and Pakistan,³¹ and Iran.³² However, experience in South Asia and Africa indicates that use of PM/SD is associated with a rapid selection of resistance as a result of mutations in dhfr and dhps.⁸ Thus, though used in combination with artesunate, resistance to PM/SD will eventually emerge, which will lead to a decrease in the efficacy of PM/SD/ART. For instance, in some endemic sites in India, a high rate of failure to PM/SD monotherapy has been already demonstrated,³³ and recently, a report has emerged on the reduced efficacy of PM/SD/ART in another site.³⁴

Table 1 - Drugs used in the treatment of malaria.

Antimalarials	General remarks	Saudi Arabia	Asian countries	African countries	Level of resistance world wide	References
<i>Uncomplicated falciparum malaria</i>						
PM/SD/ART	PM/SD is an old drug that has been combined with ART	1 st line of treatment	1 st line of treatment in middle East Asian countries	PM/SD is no longer in used in most African countries	Resistance is common to PM/SD in Africa and South East Asia	4, 8, 20-34
LM/ATM (Coartem®)	The first artemisinin drug combination	2 nd line of treatment	1 st line of treatment in some Asian countries	1 st line treatment	Very effective, the only concern is the emergence of resistance to artemisinin	4, 44-47
PYR/ART	New drug combination	-	-	-	-	55-62
PQP/DHA	New drug combination	-	-	-	-	64-68
<i>Severe falciparum malaria</i>						
Quinine	The oldest antimalarial	1 st line treatment	No longer recommended in South East Asia	No longer recommended	Decrease efficacy	4, 51-54
Artesunate	New evidence showing its efficacy	2 nd line treatment	1 st line treatment in South East Asia	1 st line treatment in Africa	Emergence of resistance in South East Asia	70
<i>Vivax malaria</i>						
CQ + PMQ	Old drug combination	1 st line treatment	1 st line treatment	-	Emergence of resistance to CQ	11-13
PM/SD/ART	Evidence that it could be used against vivax, but cannot clear hypnozoite forms of vivax	-	-	-	-	11, 42
LM/ATM (Coartem®)	Evidence that it could be used against vivax, but cannot clear hypnozoite from of vivax	-	-	-	-	50
PQP - Piperazine, SD - sulfadoxine, ART - artesunate, PYR - Pyronaridine, DHA - dihydroartemisinin, PM-pyrimethamine, CQ- chloroquine, LM - Lumefantrine, ATM - artemether, PMQ- primaquine						

Thus, resistance to PM/SD will likely emerge first in these countries before appearing in the Kingdom. Thus, information on the pattern of PM/SD efficacy in these countries would be important in the management of malaria in the Kingdom (Table 1).

The adverse effects associated with PM/SD/ART are generally nausea, vomiting, anorexia, and diarrhoea. In addition, cutaneous manifestations can be observed and include pruritus, photosensitivity reactions, exfoliative dermatitis, erythema nodosum, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Long administration can cause depression of hematopoiesis and anemia, due to interference with folic acid metabolism, and in glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur.²⁹

Pyrimethamine/sulfadoxine against Plasmodium vivax. As stated earlier, the treatment of *P. vivax* still rests on the use of chloroquine in combination with primaquine.²⁹ Pyrimethamine/sulfadoxine has never been recommended for treatment of vivax malaria based on earlier studies that *P. vivax* was intrinsically resistant to this drug combination.³⁵ *Plasmodium vivax* is often co-infected with *P. falciparum* in relatively equal frequencies.³⁶ Therefore, *P. vivax* has been unintentionally exposed to PM/SD during treatment of *P. falciparum* infection, resulting in progressive selection

of PM/SD-resistant *P. vivax*.³⁷ This has been proven by molecular studies on antifolate resistance, that PM/SD exerts a selective pressure against dhfr and dhps genes, in areas where PM/SD has been used for falciparum infections.³⁸ Thus, PM/SD could have an anti-vivax effect. Since then, several clinical trials have indicated the relative good efficacy of PM/SD against *P. vivax*.³⁹ As we shall discuss in the next section, artemisinin derivatives are active against *P. vivax*, thus, the combination of PM/SD/ART would be effective against *P. vivax* in areas where PM/SD is relatively efficacious. However, in the treatment of *P. vivax*, the challenge remains the clearance of the liver forms (hypnozoite forms), which can only be achieved with the use of primaquine (PMQ). Thus, physicians should bear in mind that the use of PM/SD/ART does not provide a radical cure from infections of *P. vivax*. Under such circumstances, recurrent infections of *P. vivax* malaria could occur in patients who have not returned to endemic areas, while in KSA.

Chloroquine/primaquine in the treatment of Plasmodium vivax. *Plasmodium vivax* is characterized by the existence of 2 forms, the erythrocytic and the exoerythrocytic forms. The latter forms, exoerythrocytic, develop in the liver and are also known as hypnozoites. These forms are dormant and are insensitive to most antimalarial drugs, thus are associated with the relapse of *P. vivax*. The main challenge in the treatment of *P. vivax* is the clearance of these hypnozoites.^{40,41} As

Table 2 - Proposed mechanisms of resistance to commonly used antimalarials.

Antimalarial	Mechanisms of resistance	References
<i>Uncomplicated falciparum malaria</i>		
PM/SD/ART	Point mutations in dhfr and dhps genes for PM and SD. Not defined yet but single polymorphism in chromosomes 10,13,14 for artemisinin has been reported.	8, 74, 76
LM/ATM (Coartem®)	Presence of wild type Pfmdr1 and Pfcr1. Single polymorphism in chromosomes 10,13,14 for artemisinin has been reported	49, 74, 75
PYR/ART	Not defined yet for PYR. Single polymorphism in chromosomes 10,13,14 for artemisinin has been reported	74, 75
PQP/DHA	Not defined yet for PQP. Single polymorphism in chromosomes 10,13,14 for artemisinin has been reported	74, 75
<i>Severe falciparum malaria</i>		
Quinine	PfNHE-1 polymorphism	51
Artesunate	Single polymorphism in chromosomes 10,13,14 for artemisinin has been reported	74, 75
<i>Vivax malaria</i>		
CQ+ PMQ	Pvcrt and Pvmdr1 in vivax for CQ. Not defined yet for PMQ	42
PM/SD/ART	Point mutations in dhfr and dhps genes for PM and SD.	37, 38
LM/ATM (Coartem®)	Not defined yet.	-
dhfr - dihydrofolate reductase gene, dhps - dihydropteroate synthase, Pfmdr1 - <i>Plasmodium falciparum</i> multidrug resistant protein 1, Pfcr1 - <i>Plasmodium falciparum</i> chloroquine resistance transporter, PfNHE-1 - <i>Plasmodium falciparum</i> sodium hydrogen exchanger -1, Pvcrt - <i>Plasmodium vivax</i> chloroquine resistance transporter, Pvmdr1 - <i>Plasmodium vivax</i> multidrug resistant protein 1, PM - Pyrimethamine, PQP - Piperaquine, SD - sulfadoxine, ART - artesunate, PYR - Pyronaridine, PQP - Piperaquine, DHA - Dihydroartemisinin, LM - Lumefantrine, ATM - artemether, CQ - Chloroquine, PMQ - primaquine		

Table 3 - Antimalarial combinations used to treat malaria, their dosage and their major side effects.

Type of malaria disease	Antimalarials	Dosage	Most common side effects	Ref.
Uncomplicated falciparum malaria	PM/SD/ART	Single administration PM/SD (1.25/25 mg base/Kg bw) on day 1 ART 4mg/Kg bw per day for 3 days	Nausea, vomiting, anorexia and diarrhea, cutaneous manifestations can be severe and include pruritus, photosensitivity reactions, exfoliative dermatitis, erythema nodosum, toxic epidermal necrolysis and Stevens-Johnson syndrome	4, 29
	LM/ATM (Coartem®)	Tablet of 120 mg LM and 20mg ATM. Tablets are given by weight: 1 for 5-14 kg/2 for 14-24 Kg/3 for 24-34Kg/4 for >34Kg	Mild nausea, abdominal discomfort, headache and dizziness	4, 29
	PYR/ART	One tablet containing 180 mg of PYR and 60 mg of ART per day for 3 days (adult dose)	Anemia, eosinophilia, neutropenia, increased platelet count, bradycardia, abdominal pain, vomiting	59
	PYR/ART	One tablet containing 160 mg of PQP and 60 mg of ART per day for 3 days (adult dose)	Anaemia, headache, heart rhythm disturbances (ECG changes or noticing unusually fast heart beats or palpitations), fever, general weakness	68
Severe falciparum malaria	Quinine	20mg/Kg loading dose over 4 hours followed by 10mg/Kg over 4 hours /8 hours (maximum dose 1800mg) for 7 days. Complete cure is obtained with a dose of 200mg doxycycline, followed by daily doses of 100mg for 7-10 days (adult dose)	Tinnitus, impaired high tone hearing, headache, nausea, dizziness and dysphoria, visual disturbances. Hypoglycemia is common in the treatment of severe malaria.	4, 29
	Artesunate	2.4mg/Kg intravenous or intramuscular on day 0, and then at 12 hours and 24 hours, then once a day until patient is able to tolerate oral medication	Mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopenia, neutropenia, elevated liver enzyme values, and electrocardiographic abnormalities	29
Vivax malaria	CQ+ PMQ	10 mg base/kg orally at once, followed by 5 mg base/kg at 6, 24, and 48 hours, combined with 0.25mg/Kg of PMQ taken daily with food for 14 days	The most important adverse effect is hemolytic anemia in patients with Glucose-6 phosphate dehydrogenase deficiency (G6PD) deficiency due to PMQ. Mild dizziness, nausea, vomiting, abdominal pain and itching can also be observed.	29
	PM/SD/ART	Single administration PM/SD (1.25/25 mg base/Kg bw) on day 1, and ART 4mg/Kg bw per day for 3 days	Same as in <i>Plasmodium vivax</i>	
	LM/ATM (Coartem®)	Tablet of 120 mg LM and 20mg ATM. Tablet are given by weight: 1 for 5-14 kg/2 for 14-24 Kg/3 for 24-34Kg/4 for > 34Kg	Same as in <i>Plasmodium vivax</i>	

PM - Pyrimethamine, PQP - Piperaquine, SD - sulfadoxine, ART - artesunate, PYR - Pyronaridine, PQP - Piperaquine, DHA - Dihydroartemisinin, LM - Lumefantrine, ATM - artemether, CQ - Chloroquine, PMQ - primaquine

a result, treatment of this infection combines anti-erythrocytic and anti-hypnozoite drugs.

Chloroquine is active against the erythrocytic forms while primaquine (PMQ) is the only available drug that is efficacious against hypnozoites. Since the 1950s, the combination of CQ and PMQ has remained the only available option for the complete treatment of vivax malaria.¹¹ There is now compelling evidence that the efficacy of CQ against *P. vivax* is

reducing in most endemic areas where this disease is prevalent. For instance, emergence of resistance has been reported in Africa (Ethiopia and Madagascar), in India subcontinent and South East Asia.¹¹ The mechanisms of resistance to chloroquine are associated with polymorphisms in the *P. vivax* mdr1 (Pvmdr1) and *P. vivax* crt (Pvcrt) genes.⁴² Various antimalarials have proven to be active against CQ-resistant *P. vivax* erythrocytic forms, including mefloquine, halofantrine,

artesunate, pyronaridine and piperazine;¹¹ however, as stated earlier, the challenge remained in clearing the hypnozoite forms. Hypnozoites are sensitive to PMQ, an 8-aminoquinoline drug, however, its use is associated with side effects (Table 3). Indeed, it can cause life-threatening hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients. New 8-aminoquinolines, analogs of PMQ, exerting less side effects are being investigated, and some of them, such as bulaquine and tafenoquine, have reached advanced clinical development stages.¹¹ Several investigations indicate that artemisinin combinations are efficacious to clear erythrocytic forms of vivax (see next sections). Thus, in response to the spread of CQ resistant *P. vivax*, the use of the artemisinin based combinations, in conjunction with PMQ is being advocated.^{11,43} Thus, in the near future, as evidence of CQ resistance mounts, it is likely that PMQ with artemisinin based combination will become the mainstay of *P. vivax* treatment.⁴³

Coartem® in the treatment of Plasmodium falciparum. The combination of lumefantrine (LM) and artemether (ATM, an artemisinin derivative), also known as Coartem®, was introduced in the mid-2000s, as the first line of treatment of uncomplicated malaria in many African countries.⁴⁴ In KSA, Coartem® is the second line of treatment (Table 1).⁴

Coartem® has proven effective to clear *P. falciparum* malaria in areas where multi-resistance parasites are common, such as in the Burma-Thai border, in South East Asia.⁴⁵ The efficacy of Coartem® was also demonstrated in several malaria endemic areas in India.^{34,46,47} However, several studies indicated that the use of Coartem® selects quickly for LM-tolerant parasites. These are parasites that can grow in the presence of sub-therapeutic concentrations of LM.⁴⁸ In Africa, these LM-tolerant parasites are wild-type at codon 86 of Pfmdr1 (asparagines at codon 86, [Pfmdr_N86]), and to some extent, wild-type Pfcr1, lysine (K) at position 76 (Pfcr1_K76), the 2 genotypes associated with CQ susceptibility.⁴⁸ In Asia, these parasites, in addition to containing Pfmdr_N86, have an increase in Pfmdr1 copy number.⁴⁹ In vitro, investigations have shown this in vivo tolerance is less susceptible thus, LM-tolerant parasites are more susceptible to CQ.⁴⁸ This inverse relationship raises the possibility of re-introducing CQ once LM resistance is common.⁴⁸ However, since Coartem® is still highly effective, it remains to be seen whether the selection of LM resistance would lead to the restoration of CQ susceptibility. We have recently reviewed this concept of LM tolerance.⁴⁸

Coartem® is generally well tolerated. Reported side effects are generally mild-nausea, abdominal discomfort,

headache and dizziness, and cannot be distinguished from symptoms of acute malaria (Table 3).²⁹

Coartem® in the treatment of Plasmodium vivax. Coartem® has also proven effective against blood stages of *P. vivax* in several Asian countries including India, China, and Thailand.⁵⁰ Thus, the use of this drug in the treatment of *P. falciparum* would also clear the *P. vivax* blood stage. However, as we discussed, radical cure of *P. vivax* requires the clearance of the liver stage (hypnozoite forms), which can be achieved with the addition of primaquine. Thus, the combination of Coartem® and primaquine could be used for the radical cure of *P. vivax*.

Quinine in the treatment of severe Plasmodium falciparum. Quinine has been used widely to treat severe malaria in almost all malaria endemic areas, and it is still used for this purpose in KSA (Table 1). This drug (in combination with antibiotics) has also been proposed as a second line treatment (in the case of ACT failure) in the treatment of uncomplicated *P. falciparum* malaria in many African countries.²⁹ Quinine resistance has been reported both in Africa and South East Asia,⁵¹ and this led to the investigation of the artemisinin derivative artesunate as a possible alternative for the treatment of severe malaria. The efficacy of intravenous artesunate with quinine was compared in a large multicentre randomized trial in Asian patients (mainly adults) suffering from severe malaria (South East Asian Quinine Artesunate Malaria Trial [SEAQUAMAT]).⁵² A significantly reduced mortality rate was observed from 23.1% in the quinine group to 14.2% in the artesunate group, a relative reduction of 38.6%.⁵² Another major multinational clinical trial of intravenous artesunate versus quinine was conducted in children, in 9 sub-Saharan Africa countries (AQUAMAT).⁵³ The data clearly showed that the development of coma, convulsions, and the deterioration of coma score were all significantly less frequent in the artesunate group than in the quinine group, and overall, the mortality rate was lower in the artesunate group. Similar observations were made based on meta-analysis of data from several clinical trials of artesunate versus quinine.⁵⁴ All this information led to the recommendation of intravenous artesunate as the drug of choice in the treatment of severe malaria. In KSA, in addition to quinine, intravenous artesunate monotherapy has been recommended for the treatment of severe malaria, the choice between quinine or artesunate being based on drug availability.⁴ However, in the light of this new information on the high efficacy of artesunate in severe malaria, artesunate could be made the first option. Quinine causes a complex of

symptoms known as cinchonism, which is characterized in its mild form by tinnitus, impaired high tone hearing, headache, nausea, dizziness, and dysphoria, and sometimes disturbed vision. Vomiting, abdominal pain, and diarrhea can also be noticed (Table 3).

Potential drugs in the pipeline for malaria treatment. Two other ACTs, the combination of pyronaridine/artesunate (PYR/ART) and piperazine/dihydroartemisinin (PQP/DHA), have been investigated as potential replacements for Coartem®.

Pyronaridine/artesunate. Pyronaridine is an acridine derivative and a Mannich base, synthesized in China and used in the treatment of uncomplicated malaria in the 1970s.⁵⁴ This drug was evaluated in clinical trials in the mid-1990s in Africa, with encouraging results.⁵⁶ It has now been combined with artesunate (ART), under the name of Pyramax®, and clinical evaluations of this combination have been carried out in 8 different African malaria endemic areas. A 3-day fixed combination of PRN and ART has proven effective and safe to clear malaria infection.^{57,58} This combination has been recently registered by the European Medicine Agency (EMA) for the treatment of uncomplicated malaria.⁵⁹ Thus, it is now part of the drug armamentarium against *P. falciparum* malaria. As stated earlier, PYR is also active against *P. vivax* in vitro,⁶⁰ and an early investigation indicated its efficacy in clearing the blood stage infection of *P. vivax*.⁶¹ Recently, in a Phase III investigation, the combination of PYR/ART has proven efficacious in clearing *P. vivax* blood stage infection, a clear indication that this could also be used for *P. vivax* treatment.⁶² Pyronaridine/artesunate is well tolerated, and the most commonly adverse effects are anemia, eosinophilia, neutropenia, increased platelet count, bradycardia, abdominal pain and vomiting, hypoglycemia, and headache (Table 3).⁵⁹

Piperazine/dihydroartemisinin. Piperazine is a bis-chloroquine molecule developed in China in the 1990s. It has been used as monotherapy for the treatment of malaria infections in the 1980s. However, by the late 1980s, cases of resistance were common.⁶³ To overcome the spread of resistance, PQ was then combined with other antimalarial drugs. The first combination that was used contained PQ, primaquine (PMQ), trimethoprim, and DHA. Although the combination proved efficacious,⁶⁴ concerns about the risk/benefit ratio of PMQ led to its removal. Then, uncertainty regarding the antimalarial activity of trimethoprim resulted in a change to the current combination of PQ and dihydroartemisinin (DHA).⁶⁵ This combination, also known as Eurartesim®, has undergone successful clinical evaluations in both Africa and Asia.^{66,67} Like Pyramax®,

this combination has recently been registered by the European Medicine agency (EMA) for the treatment of uncomplicated malaria.⁶⁸ This combination is also efficacious against erythrocytic forms of *P. vivax*. This drug combination is well tolerated. Side effects are minor, and the most frequent are headache, prolonged QTc interval on the ECG, anemia, eosinophilia, sinus tachycardia, asthenia, pyrexia, and decreased red blood cell count (Table 3).⁶⁸

Resistance to artemisinin and the future of ACTs.

As we discussed earlier, artemisinin derivatives form the backbone of malaria treatment, and most currently used antimalarial combinations (and those registered recently) contain an artemisinin derivative. Artemisinin derivatives have short half-lives (less than one hour), but have a rapid killing rate, leading to a parasite reduction biomass by a rate of $>10^{10}$ within the first 24 hours.⁶⁹ Thus, it was thought that resistance to artemisinins would be very slow to develop because of brief parasite exposure to sub-therapeutic levels of the drug. However, recent data have shown the emergence of artemisinin resistance in South East Asia. Clinical studies have clearly demonstrated a prolonged time to parasite clearance in patients treated with ART, leading to the emergence of parasites with reduced in vivo susceptibility to ART.⁷⁰ This development is a matter of great concern, and current strategies have been proposed to control and contain the spread of resistance of artemisinins to other malaria endemic areas.^{9,10} Several studies have been dedicated to studying the mechanisms of artemisinin resistance. Polymorphisms in Pfmdr1, at codons 86, 184, 1034, 1042, and 1246, alone or in combination, and increased copy numbers of this gene have been associated with reduced levels of artemisinin derivatives in vitro by 2-fold.⁷¹ However, in vivo, these changes are not associated with reduced susceptibility.⁷²

PfATPase6, an analogue of the mammalian sarco/endoplasmic reticulum Ca²⁺ ATPases (SERCAs), has been proposed to contribute to reduced artemisinin activity in vitro.^{73,74} However, this gene has not been associated with a decrease in artemisinin efficacy in South East Asia.⁷² Recent studies has shown that decreased efficacy of artemisinin could be associated with genetic changes in regions of chromosomes 10, 13, and 14,^{75,76} however, further studies are still warranted to identify genetic markers associated with resistance to this important antimalarial.

Artemisinin derivatives are safe and remarkably well tolerated.²⁹ However, mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopenia, neutropenia, and

elevated liver enzyme values can be observed (Table 3). Neurotoxicity has been reported in animal studies, but has not been substantiated in humans.³⁰

In conclusion, the endemicity of malaria is low in KSA, and most cases of malaria are from emigrant workers from Asia and the Eastern part of Africa. Antimalarials that are recommended in KSA are also widely used in most of these countries. As a result, the efficacy of antimalarials in KSA could be compromised if resistance to these drugs is high in the countries of the emigrant workers. For instance, PM/SD/ART is the current first line of treatment of uncomplicated *P. falciparum* malaria, however, cases of reduced efficacy of PM/SD have already been reported in India and Pakistan. Coartem® is recommended as a second line treatment in KSA (in the case of failure of PM/SD/ART). So far, most clinical investigations have shown the high efficacy of this drug in most malarial endemic areas. However, the main concern over this drug and other artemisinin-based combinations (such as PM/SD/ART) is the emergence of resistance to artemisinin derivatives, which have been reported in South East Asia. If resistance to artemisinin derivatives spreads to other malaria endemic areas, the concept of artemisinin-based combination will be compromised. Quinine is reserved for the treatment of severe malaria in KSA. However, recent data indicate a higher efficacy of artesunate (an artemisinin derivative) over quinine in severe malaria, and in most malaria endemic areas, artesunate is now used to treat severe malaria. Thus, this drug could also become central in the treatment of severe malaria in KSA.

Acknowledgment. Dr. Alexis Nzila is grateful to King Fahd University for financial support. The author wish to express their gratitude to Dr. Assad Thukair for his helpful contribution to the manuscript.

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