PharmaNote®

Volume 25, Issue 2 November 2009

AN OVERVIEW OF ANTIMALARIAL AGENTS: FOCUS ON COARTEM®

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Malaria is an infectious disease transmitted predominantly through the bite of an infected female Anopheline mosquito. Of the parasitic species that infect humans, *Plasmodium vivax*, *P. malariae*, *P. ovale*, and *P. falciparum*, the latter causes the most severe form of the disease and may lead to anemia, renal failure, pulmonary edema or gastroenteritis.[1] Malaria preferentially affects pregnant women and children under 5 years of age. Immunocompromised individuals are associated with higher parasite densities and a higher probability of more severe and fatal malaria infections.[2] Temperate climates as well as rainy seasons conducive for mosquito growth are additional risk factors that contribute to malaria transmission.

Malaria, a treatable and preventable disease, has also been called a disease of poverty as it is mainly found in the poorest regions of the world & developing countries.[3] According to the 2008 World Malaria Report, there are an estimated 247 million cases and nearly 1 million deaths worldwide.[3] Although malaria occurs in over 90 countries, the majority of cases (91%) are found in Sub-Sahara Africa. While the prevalence in the United States has increased, as of 2007, malaria has accounted for merely 1505 cases and only 1 death.[4] An estimated $1800 million is spent on direct costs of treatment and disease prevention as well as indirect cost including lost time due to morbidity and premature mortality.[5] This heavy financial burden can hinder the economic and community growth throughout developing regions.

Management of malaria pharmacotherapy has likewise grown increasingly complex as resistance to traditional drug therapy has emerged resulting in an increase in financial cost and difficulty in achieving a cure. This article will review the efficacy of established pharmacologic treatment options, as well as Coartem® (artemether and lumefantrine), a Novartis manufactured agent approved by the FDA in April 2009 for the management of uncomplicated malaria. This article will also address prevention, prophylaxis and treatment recommendations for international travelers.

PARASITIC LIFE CYCLE

Following a bite from an infected Anopheline mosquito, sporozoites are released from their salivary glands into the host's circulation. Sporozoites aggregate in human hepatic tissue where they can mature into tissue schizonts.[6] Eventually, these tissue schizonts rupture and release their content containing merozoites that specifically target and invade erythrocytes.[7] The parasites within the erythrocytes ultimately develop into schizonts. The cycle continues as schizonts release merozoites, merozoites attack additional erythrocytes, and parasites within erythrocytes mature into schizonts. Finally, circulating merozoites develop into gametocytes that are ingested from the

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host by a new mosquito.[6] It is important to note that when the tissue schizonts of *P. malariae* and *P. falciparum* rupture, all forms of the parasite exit the liver. However, the tissue parasite of *P. vivax* and *P.ovale* can remain dormant in the liver in a stage known as hypnozoites. Lingering parasites can result in relapses of erythocytic infection that can occur months to years after the initial attack.[5]

ESTABLISHED PHARMACOLOGIC TREATMENTS

Established antimalarial treatment options are classified based on the stage in the parasite life cycle that they inhibit. For example, hepatic tissue schizonticides target the liver stages of the parasite; treatment options include atovaquone & proguanil (Malarone®) & primaquine. Hypnozoiticides are active against the dormant forms of *P. vivax* and *P. ovale* and include primaquine. Lastly, blood schizonticides target the asexual blood stages of the parasite and include chloroquine (Aralen®), mefloquine (Lariam®), Malarone®, tetracyclines, and primaquine. Table 1 summarizes the mechanism of action, treatment indication, dosing regimen, common adverse events and cost of these agents.

The inexpensive cost, ease of accessibility & the management of malaria by a single agent, has lead to increased resistance to the previously mentioned antimalarial treatment options. Resistance to chloroquine, the drug choice for malaria since 1946, was first documented in 1957. pyrimethamine and sulfadoxine was recommended to replace chloroquine but resistance was reported within the same year the drug was introduced.[6] Similarly, resistance to mefloquine was reported only five years after its introduction.[6] Widespread misuse of these agents has likewise facilitated the emergence of *P. falciparum* resistance to nearly all currently available antimalarials.[7] As a result, the World Health Organization opposes single agent antimalarial treatment despite the temptation to reduce the cost for the patient.[8] Currently, the recommendation is for two or more schizonticidal agents with independent mechanisms of actions as well as molecular targets. This approach should result in synergistic effects of these two agents.[3]

COARTEM®

Resistance has emerged to all antimalarial classes except a novel class known as artemisinins.[9] However, decreased parasite clearance times have been shown in areas where an artemisinin is used as monotherapy compared to artemisinin combination therapy (ACT) ($p<0.001$).[10] In order to delay or prevent emergence of resistance, artemisinins are combined with one of several longer-acting drugs including amodiaquine, mefloquine, sulfadoxine/pyrimethamine or lumefantrine.[6] Although successfully used internationally for several years, Coartem® is the only ACT agent FDA approved for treatment of acute, uncomplicated malaria infections in adults and children (weighing at least 5kg) within the United States.

Coartem®, an artemisinin-based, fixed combination antimalarial consists of 20 mg artemether and 120 mg lumefantrine. Combining the two medications in one tablet prevents both single agent use and facilitation of subsequent resistance. These two drugs synergistically interfere with the use of hemoglobin by the parasite.[11] Additionally, these two agents are effective in eliminating the parasite from the host but by differing mechanisms. Artemether rapidly reduces 95% of the parasite population. However, the short half life of artemether, renders the Coartem® inappropriate for prophylatic therapy. Lumefantrine's long half life, (t ½ 4 days) allows it to eliminate residual, very low resistance risk parasites.[12] Table 2 summarizes the pharmacokinetics, effective treatment dose, relative side effects of Coartem®. The reported cost was determined by average prices from local pharmacies. However, in order to make the medication more accessible for developing countries, Norvatis has subsidized the cost to around $0.9 to $1.40 for a treatment course of a child up to 7 years old and around $ 2.4 per adult treatment dose.[13]

Efficacy

Coartem® usually is given over six days in multidrug resistant areas. However, to ease administration in regions where *P. falciparum* is not multidrug resistant, a four day regimen appeared to be equally effective and cost saving. A head-to-head, double blind study conducted by Van Vugt et al., examined the 28 day cure rate, with two six-dose regimens compared to a four-dose regimen of Coartem® in 359 patients. A 28 -day cure rate was defined as the proportion of patients with clearance of asexual parasitemia within 7 days of initiation of trial treatment, without subsequent relapse within 28 days after starting study treatment. The results showed that the six-dose administration schedule was more effective than the four-dose regimen of Coartem® in adolescents and adults with uncomplicated *P. falciparum* malaria. [14] The 28-day cure rates were 96.9% and 99.12% for the two six-dose regimens compared to 83.3% for the four-dose regimen ($p < 0.001$). Makanga et al, conducted a comparable study in children and infants (n=544) which provided similar results.[15] The corrected 28 day cure rates were 93% and 96% compared to 61% and 76%

Table 1. Comparison of antimalarial drug therapy options.

AGENT	MECHANISM OF ACTION	INDICATION	KINETICS	TREATMENT DOSE	SIDE EFFECTS	COST[a]
atovaquone + proguanil (Malarone®)[b]	Works synergistically to inhibit the electron transport & collapse the mitochondrial membrane	Treatment & prophylaxis of drug resistant *P.falciparum* or *P. vivax*	F: Variable M: Enterohepatic circulation E: Feces $t_{½}$: 2-3 days: adults & 1-2 days in children	A: 4 adult tabs po qd x 3 days P: 5-8kg: 2 peds tabs po qd x 3 d 9-10kg: 3 peds tabs po qd x 3 d 11-20kg: 1 adult tab po qd x 3 d 21-30kg: 2 adult tabs po qd x 3d 31-40kg: 3 adult tabs po qd x 3d > 40 kg: 4 adult tabs po qd x 3d	Abdominal pain (17%), N/V (12%)	$4.93
	Inhibits DNA synthesis & depletes folate cofactors	Treatment of *P.falciparum* & *P. vivax* when used w/ Atovaquone	F: Variable M: Hepatic to active metabolite E: Urine $t_{½}$: 12-21 hrs			
chloroquine (Aralen®)	Interfere w/ lysosomal degradation of Hb & digestive function of malarial parasites	Treatment & prophylaxis for *P. vivax*, *P.ovale*, *P. malariae*, & CQ-sensitive *P. falciparum*	F: Rapid M: Partially hepatic E: Urine $t_{½}$: 3-5 days	CYP2D6 substrates, drugs that prolong QT interval	CNS, GI, CV, ocular, dermatological disturbances	$4.97
hydroxychloroquine	Interferes w/ lysosomal degradation of Hb & digestive function of malarial parasites	Treatment & prophylaxis for *P. vivax*, *P.ovale*, *P. malariae*, & CQ-sensitive *P. falciparum*	F: Rapid absorption M: Hepatic E: Urine $t_{½}$: 32-50 days	CYP 2D6 substrates, methotrexate, antacids	CNS, CV, dermatological & ocular disturbances	$3.78
mefloquine (Lariam®)	Inhibits replication of asexual erythrocytic parasites by raising pH & inhibiting nucleic & protein synthesis	Prophylaxis of drug-resistant *P. falciparum* or *P. vivax*	F: Well absorbed M: Extensively hepatic E: Bile & feces $t_{½}$: 21-22 days	A: 684 mg base po as initial dose, followed by mg 456 base po given 6-12 hrs after initial dose P: 13.7 mg base/kg po as initial dose, followed by 9.1 mg base/kg po given 6-12 hrs after initial dose.	N/V (3%)	$10.58
quinine[c]	Disrupts replication & transcription; depresses O_2 uptake & carbohydrate metabolism	Treatment against CQ-resistant *P. falciparum*	F: Readily absorbed M: Hepatic E: Urine $t_{½}$: 10-13 hrs: adult, 3 hrs healthy children, 12 hrs w/ malaria	A: 542 mg base po tid P: 8.3 mg base/kg po tid x 3 or 7 days	CNS, CV, photosensitivity, muscle weakness	

Table 1 (continued). Comparison of antimalarial drug therapy options.

AGENT	MECHANISM OF ACTION	INDICATION	KINETICS	TREATMENT DOSE	SIDE EFFECTS	COST[a]
pyrimethamine + sulfadoxine (Fansidar®)[d]	Pyrimethamine inhibits DHF reductase; Sulfadoxine inhibits dihydropteroate synthase	Used as adjunctive therapy for CQ-resistant *P. falciparum*	F: Well absorbed M: Hepatic E: Urine $t_{½}$: 80-95 hrs	A: 2—3 tablets po x 1 P: 5-10 kg: ½ tablet po x 1 11-20 kg: ½ tablet po x 1 21-30 kg: 1 & ½ tablets po x 1 31-45 kg: 2 tablets po x 1 > 45 kg: 3 tablets po x 1	Stevens-Johnson syndrome, rash	
primaquine	Interferes w/ plasmodial DNA	Prophylaxis of drug-resistant *P. falciparum* or *P. vivax*	F: Well absorbed M: Hepatically to active form E: Urine $t_{½}$: 3-10 hrs	300mg base po every day for 14 days	Anemia	$2.07
Tetracyclines: doxycycline (Vibramycin®, Doryx®)	Slow acting blood schizontocide	Prophylaxis or adjunctive therapy for CQ-resistant *P. falciparum*	F: Rapid M: Chelate formation Hepatic E: Urine & feces $t_{½}$: 12-15 hrs	A: 100 mg po bid x 7 days P: 2.2 mg/kg po every 12 hrs x 7 days	Stevens-Johnson syndrome, rash	$0.25

A: Adult dose, CV: cardiovascular, E: elimination, F: oral bioavailability, M: metabolism, N/V: nausea & vomiting , P: Pediatric dose, t½: half life

[a]Cost per single tablet accessed from http://www.drugstore.com. Accessed 7/12/09

[b]Malarone: Adult tab = 250 mg atovaquone/ 100 mg proguanil; Peds tab = 62.5 mg atovaquone/ 25 mg proguanil

[c]Used w/ doxycycline

[d]Fansidar®: Available as 25mg Pyrimethamine; 500mg Sulfadoxine

Table 2. Overview of Coartem® (artemether/lumefantrine).

MECHANISM OF ACTION	Works synergistically to interfere with nucleic acid & protein synthesis	
INDICATION	Treatment for drug-resistant *P. falciparum*	
PHARMACOKINETICS	Artemether*:* F: Rapid absorption M: Hepatic E: Urine $t_{½}$: 2-3 hours	Lumefantrine*:* F: Slower absorption M: Hepatic E: Feces $t_{½}$: 3-6 days
TREATMENT DOSE	A 3-day treatment for a total of 6 oral doses for both adult & pediatrics. Patient should receive the initial dose, followed by the second dose 8 hrs later, then 1 dose PO bid for the following 2 days. • 5 - <15 kg: 1 tablet per dose • 15 - <25 kg: 2 tablets per dose • 25 - <35 kg: 3 tablets per dose • >35 kg: 4 tablets per dose (total of 24 tablets)	
SIDE EFFECTS (%)	• HA (56%) • Palpitations (18%) • N/V (17%)	
COST	$10.50 per tablet or $89.56 for 24 tablets (6 dose adult treatment)	

E: elimination, F: oral bioavailability, M: metabolism, $t_{½}$: half life, HA: headache, N/V: nausea & vomiting

($p < 0.0001$) for the six-dose and four-dose regimen respectively.

Gametocyte reduction may be equally if not more important than a 28-day cure rate for an active infection. Sutherland et al. investigated the amount of gametocyte reduction between treatment with Coartem® or a combination of chloroquine (CQ)/ sulfadoxine pyrimethamine (SP). This single-blind, randomized controlled trial was conducted in children ages 1-10 with acute uncomplicated falciparum malaria. Children were randomized to receive standard doses (see Table 2) of either a combination of CQ/SP (n= 91) or a six dose regimen of Coartem® (n=406). There is known resistance to chloroquine, so it was combined with SP in attempt to extend its usefulness since SP remains effective in 95% of this patient population. The major endpoints were gametocyte carriage rates, as well as the potential for children carrying gametocytes 7 days post treatment to infect mosquitoes.[16] Children treated with Coartem® were significantly less likely to carry gametocytes during follow-up than children treated with CQ/SP ($p < 0.001$ at each of days 7, 14, and 28; relative risk 6.15; 95% CI: 4.10–9.23). Additionally, 28 days post treatment, children treated with Coartem® compared to CQ/SP carried the parasites for a shorter time (0.3 and 4.2 days respectively; $p < 0.0001$), and their blood was less able to infect mosquitoes ($p < 0.001$). This study is significant since it showed that while a treatment cure is important, it should be viewed only as the initial goal. The second and equally important goal should be a reduction in gametocyte carriage rates and therefore a reduction in transmission of *P. falciparum* malaria infections to surrounding regions.[17]

In the case where CQ & SP resistance is prevalent and not the current standard of care, both amodiaquine plus SP and amodiaquine plus artesunate, have been compared to Coartem® to determine which of these therapeutic options are more efficacious. A single-blind, randomized clinical trial was conducted in 329 Ugandan children ages 1-10.[18] Patients were randomized to treatment with standard doses of amodiaquine/SP (n=111), amodiaquine/artesunate (n=113), or Coartem® (n=105).[18] The primary outcome was the 28 day risk of recurrent parasitemia (early treatment, late clinical or late parasitological failure). Primary outcomes were classified as: early treatment failure (complicated malaria or failure to respond to therapy on days 0-3), late clinical failure (complicated malaria or fever and parasitemia on days 4-2), late parasitological failure (asymptomatic parasitemia on days 7-28), or adequate clinical and parasitological response (absence of parasitemia on day 28). Each episode of uncomplicated malaria was unad-

justed or adjusted by genotyping to distinguish between recurrence and a new infection. The secondary outcomes measured change in gametocyte carriage and hemoglobin levels. Additionally, hemoglobin levels were measured to monitor anemia as a predictor of malaria burden.[19]

Results demonstrated that the unadjusted 28-day risk of treatment failure for individual episodes of malaria were 26.1% (95% CI, 21.1-32.1) for amodiaquine/SP, 17.4% (95% CI: 13.1-23.1) for amodiaquine/artesunate, and 6.7% (95% CI, 3.9-11.2) for Coartem®. Likewise, the risks of treatment failures (adjusted by genotyping) due to recurrence, were significant: 14.1% (95% CI: 10.3-19.2) for amodiaquine/SP, 4.6% (95% CI: 2.5- 8.3) for amodiaquine/artesunate, and 1.0% (95% CI: 0.3-4) for Coartem® ($p< 0.008$ for all pairwise comparisons, except amodiaquine plus artesunate vs Coartem® $p=0.05$).

The changes in the hemoglobin levels from day 0 to day 14 were not significantly different between treatment groups, however the prevalence of gametocytes were lowest with Coartem® (3.5%) compared to amodiaquine/artesunate (6.1%) or amodiaquine/SP (14%) (amodiaquine/SP versus amodiaquine/artesunate, $p<0.05$; amodiaquine/SP versus Coartem®, $p<0.05$). For both the primary and secondary outcomes, Coartem® was significantly more effective as a treatment option against uncomplicated falciparum malaria.

Based on malarial resistance patterns, populations exist where treatment options may be equally effective as Coartem®. A randomized, open label study conducted by Sagara et al, compared standard treatment doses of artesunate-sulfamethoxypyrazine-pyrimethamine (AS-SMP) given every 24 hours (n =476), AS-SMP given every 12 hours (n=458), and the 6 dose treatment of Coartem® (n=458).[20] The primary endpoint was the 28-day cure rates and secondary endpoints were early treatment failure, late clinical failure, late parasitological failure, adverse events (clinical and laboratory abnormalities), anemia (hemoglobin value<10 g/dl), clearance rate of fever and parasitemia, and gametocyte carriage.

Although no statistically significant difference ex-

Table 3. Summary of clinical trials for treatment of *P. falciparum* malaria infections.

TRIAL	DESIGN	TREATMENT	OUTCOME(S)	CONCLUSION
Van Vugt, et al.[14] (1999)	RDB	4 dose Coartem® (n=120) vs two 6 dose Coartem® (n=118, 121)	Primary: 28 day CR	6 dose > 4 dose regimen of Coartem® w/ no difference in tolerability & safety.
Sutherland, et al.[16] (2005)	RC	Chloroquine/ sulphadoxine-pyrimethamine (n= 91) vs. 6 dose Coartem® (n=406)	Primary: 28 day CR Secondary: gametocyte carriage & infectious rate of mosquitoes	Patients treated w/ Coartem® less likely to carry gametocytes 28 days following treatment than those receiving CQ/SP ($p < 0.0001$). Coartem® > CQ/SP for gametocytes densities, time ($p < 0.0001$) & infectious rate of mosquitoes at day 7 ($p < 0.001$) vs. CQ/SP.
Dorsey G, et al.[18] (2007)	RSB	Amodiaquine/SP (n=111) & amodiaquine/artesunate (n=113) vs. 6 dose Coartem® (n=105).	Primary: 28-day risk of treatment failure Secondary: Gametocyte carriage	28-day risk of treatment failure, unadjusted & adjusted for genotyping lowest for Coartem®. Prevalence of gametocytes lowest w/ Coartem® (amodiaquine/SP vs amodiaquine/artesunate, $p < 0.05$; amodiaquine /SP vs Coartem®, $p < 0.05$).
Sagara, et al.[20] (2009)	ROL	AS-SMP every 24hrs (n =476), AS-SMP every 12hrs (n=458) vs. 6 dose Coartem® (n=450)	Primary: 28-day CR Secondary: Incidence of AE	No difference in primary endpoints. Incidence of vomiting was 7.0%, 4.6% and 2.2% for AS-SMP 12 hr, AS-SMP 24 hr & Coartem® group respectively. Incidence of diarrhea was 3.3%, 0.6% and 1.3% for the AS-SMP 12-hr, AS-SMP 24 hr & Coartem® group respectively .
Hatz, et al.[21] (2008)	OL	128 patients treated w/ 6 dose Coartem®	Primary: 28-day CR Secondary: Gametocyte carriage	28 day CR was 96% (95% CI 90.8-98.7). Gametocytes carriage reduced from 20.6% on days 0-3 to no gametocytes present on days 8 to 42.

C: controlled; CR: cure rate; DB: double blind; OL: open label; R: randomized; SB: single blind

isted for primary endpoints, a higher incidence of side effects, such as vomiting and diarrhea, was observed in the AS-SMP 12 hour group. The incidence of vomiting was 7.0% (n = 458), 4.6% (n = 476) and 2.2% (n = 450) for AS-SMP 12 hour group, AS-SMP 24 hour group and Coartem® group respectively. Additionally, the incidence of diarrhea was 3.3%, 0.6% and 1.3% for the AS-SMP 12-hour group, AS-SMP 24 hour group and Coartem® group respectively. While this confirms that antimalarial treatment should be tailored according to local drug sensitivity patterns, it also highlights the importance of secondary factors in selecting appropriate therapy. Patients on Coartem® experienced fewer side effects and were able to tolerate treatment better than patients taking AS-SMP every 12 or 24 hours. Tolerability of anti-malarial treatments may determine compliance and therefore efficacy and outcome of treatment.

While Coartem® has been used extensively in endemic countries, it has also been shown to be effective in non-immune travelers in an open-label, non-comparative study, conducted by Hatz et al.[21] Patients were described as non-immune if they did not have an acute *P. falciparum* infection diagnosed during the last 5 years and have either not spent long periods during the 5 years before the study in malaria-endemic areas or spent their first 5 years of their life in malaria-endemic areas. These 124 patients were treated with the standard six-dose regimen of Coartem®. The primary endpoint, parasitological cure rate, was 96% at the end of 28 days (95% CI 90.8-98.7). Gametocytes were also reduced from 20.6% on days 0-3 to no gametocytes present on days 8 to 42. Additionally, Coartem® was well tolerated with the main adverse events reported as headache (29.1%), insomnia (13.3%) and diarrhea (13.3%). However, these adverse events were not compared to placebo and since these adverse are commonly seen with malaria, they may merely be signs or symptoms of malaria and not Coartem®.

Table 3 summarizes the clinical trials for treatment of *P. falciparum* malaria infections.

Recommendations for Travelers

Travelers visiting malaria dense areas should take necessary precautions to prevent from contracting malaria. Preventative measures include wearing long sleeve shirts and pants as well as using insecticides when going outdoors. Long-lasting insecticidal nets can also be used over bedding. Additionally, travelers should determine what, if any, prophylaxis medication are recommended based on the resistance patterns within that country. Prophylaxis treatment must be started before travel, and used continuously while abroad, and for four weeks after leaving malaria-endemic areas. Lastly, travelers should be counseled on how to initiate treatment if they suspect malarial symptoms such as unexplained persistent headaches, weakness, vomiting, or diarrhea.

For additional information on traveling precautions & malaria, visit CDC on the web:

http://www.cdc.gov/malaria

Summary

Malaria is a preventable disease that has resulted in nearly one million unnecessary deaths within the last year. Monotherapy treatments with previously established agents lead to the growing resistance of nearly all parasitic forms, but most importantly *P. falciparum*. FDA-approved Coartem® is currently effective in treating uncomplicated malaria due to *P. falciparum* in the United States although it has been used worldwide for several decades. Although reducing treatment time may reduce cost short term, care must be taken to prevent facilitation of resistance.

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