Advances In the Treatment of Malaria

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Abstract: Even at the start of the third millennium, malaria continues to have a significant impact on mortality and disability rates. The rise of drug-resistant P. falciparum and, to a lesser extent, P. vivax strains in the majority of the malaria endemic areas was facilitated by the improper sequential use of medication monotherapy in the past, rendering the majority of anti-malarial ineffective. The majority of P. falciparum malaria infections have been successfully treated over the past ten years with a novel combination approach based on artemisinin derivatives (ACT), which may have an impact on resistance and has already been infrequently seen in South East Asia, serves as a barrier to the broad implementation of this technique. Even though quinine still has value if artesunate is not readily available, parenteral artesunate has now established itself as the gold standard of care for severe malaria. While we wait for an effective anti-malarial vaccine to become available, the appropriateness of suppository artesunate use before the referral is being closely watched.

Keywords: Drug resistance of malaria plasmodia, uncomplicated P. falciparum malaria, severe malaria

Introduction and Historical Outline

The correct management of clinical malaria cases is a complex issue that has to take into account different targets that may be differently prioritized according to the various clinical and epidemiological situations:

a. to prevent progression of uncomplicated malaria patients to severe life threatening complications (P. falciparum but also P. vivax);

b. to prevent mortality of patients with severe malaria (P. falciparum but also P. vivax and P. knowlesi);

c. to prevent relapses when appropriate (P. vivax, P. ovale);

d. to limit the spreading of the infection/disease in the population;

e. to limit as much as possible the emergence of plasmodium resistant strains.

Considering the complex biological cycle of malaria plasmodia, the ideal drug to meet the clinical targets should have the following properties:

- to act rapidly against the replicating blood erythrocytic asexual forms, primarily schizonts, that are responsible for the clinical manifestation of the disease (parasitological cure);

- to act against liver hypnozoites, when appropriate (radical cure).

In endemic areas, furthermore, the ideal drug to meet the epidemiological targets should have the following properties:

- to act against the sexual forms (gametocytes) that are responsible for the transmission of the infection in the population via the vector mosquitoes; this gametocidal effect is time-sensitive because the appearance of sexual forms is delayed of several days from the clinical malaria attack;

- to avoid selecting plasmodia resistant strains (high resistance barrier).

No significant advancement in malaria chemotherapy occurred until the first decades of the XX century after Francesco Torti in Italy first proposed quinine's selective therapeutic effectiveness against malaria plasmodia. Up until recently, a single drug regimen was employed to treat malaria attacks, and new drug combinations were only recently made accessible due to the advent of resistance to the old compounds. Pamaquine and chloroquine were first found in Germany in 1924 and 1934, respectively. Proguanil, pyrimethamine, primaquine, sulphonamides, mefloquine, and halofantrine were then discovered in England in 1944, the United States in 1956, and Germany again in 1956.

Since the early 1960s, when P. falciparum with diminished sensitivity to chloroquine first arose in South-East Asia and Colombia and subsequently quickly expanded to almost all P. falciparum endemic areas, the effectiveness of monotherapy has been called into question. After it, all antimalarial medications targeting P. falciparum and, to a lesser extent, P. vivax experienced the same side effects.

At the end of the 20th century, the strong anti-parasite efficacy of the long-known Chinese malarial remedy artemisinine and its derivatives was scientifically demonstrated, both on blood asexual and sexual forms (gametocytes). Furthermore, in line with other major infectious diseases such as tuberculosis and HIV infection, the value of combination treatment to lessen the chance of a natural resistant strain to emerge was clearly established and new combination treatments tested (atovaquone-proguanil, chlorproguanil-dapsone).

Extensive randomized clinical trials demonstrated the superiority of artemisinin-based combination treatments (ACT) in terms of fever and parasitological clearance times as well as clinical outcomes. Therefore, the current standard of care for both complicated and uncomplicated malaria is artemisinin-based treatment, which satisfies the majority of the qualities of the "ideal antimalarial drug" listed above.

Drug resistance of malaria plasmodia

The WHO defines medication resistance to malaria as "a parasite strain's ability to survive and/or multiply despite the proper administration and absorption of an antimalarial drug in the normally recommended dose."

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Medication resistance for malaria is described by the WHO as "a parasite strain's ability to survive and/or multiply despite the proper administration and absorption of an antimalarial drug in the normally recommended dose."

Traditionally, resistance spreads in two stages. The parasite population that is actively reproducing first spontaneously produces a mutant clone. Unless it is exposed to pressure from a selective drug that can kill sensitive parasites but not blood-circulating resistant forms that later evolve into gametocytes with the potential to spread in the population (second step), this clone is typically less fit than the wild-type sensitive ones and tends to disappear. In low transmission environments where the majority of parasite-carrying patients are symptomatic and hence subject to therapy, this occurrence is typically more likely to occur initially.

This is likely the cause of the chloroquine and pyrimethamine-resistant strains first emerging in South-East Asia in the early 1960s before migrating to the continent of Africa.4 This is further supported by the hypothesis that Asian P. falciparum strains have a higher propensity to mutation.

A combination strategy to limit resistance has been proposed in the 1990s using a rapidly acting and potent drug able to achieve a fast reduction of parasitic burden (limiting the intrinsic probability of genetic mutation), with few residual parasites exposed to high concentrations of the long-acting partner drug (thus limiting the selective potential of low dr).5 Artemisinin and its derivatives, which are today regarded as the cornerstone of malaria treatment, have been identified as the rapidly acting component of these combinations, thereafter referred to as Artemisinin Combination Therapies (ACT).

Unfortunately, resistance to artemisinin derivatives has been reported, once again in South East Asia, as a potential result of drug abuse both in combination and in monotherapy, forcing the World Health Organisation to implement a Global Plan for Artemisinin Resistance Containment (GPARC).

Artemisinin and artesunic acid-based combination therapy (ACT).

The 1970s Chinese programme known as "Project 523" obtained artemisinin, a sesquiterpene trioxane lactone, from the plant Artemisia annua.8 Its derivatives (artesunate, arteether, and arteether) work through a mechanism that is essentially unknowable, rendering them nearly invincible against P. falciparum. It has a greater impact on early immature gametocyte stages and ring stages than other antimalarial medications, but not on extra-erythrocytic forms like sporozoites, liver schizontes, or merozoites. The common active metabolite dihydroartemisinin, which is produced by artemisinin and its derivatives, has a very rapid effect and a high killing rate; the parasite reduction ratio (PRR), which measures the fractional reduction for each asexual life cycle (which lasts 48 hours), is in the order of 104. Even when the baseline total parasite burden is >1012 (100,000/l or 2% parasitemia), such an activity profile would indicate a dramatic cure (eradication of every parasite from the host) after 7-8 days.11 Non-clinical observations12 demonstrate that absorption is good and quick regardless of the route of administration (Tmax is 0.5–1 hours after oral assumption, whereas intramuscular injection causes slower absorption and longer sustained plasma levels after repeated administrations with potential for increased toxicity).

Artemisinin combination treatment (ACT), which combines artemisinin-based medications with longer-acting antimalarial medications, has been developed to address this issue. The ACTs benefit from the companion drug's favourable pharmacokinetic characteristics and the artemisinin derivative's strong and quick beginning activity, which after a brief course of treatment continues to act on low level parasitaemia until radical cure.11,17 According to WHO recommendations, a 3-day treatment of artemisinin can reduce the parasite burden by 90%. The partner drug should ideally be chosen from a group of anti-malarial medications that are still effective (ensuring at least an 80% cure rate on their own) and have a shorter half-life to expose replicating parasites to sub-therapeutic drug levels that might facilitate the emergence of resistant parasites. Because of this, East Asia and Sub-Saharan Africa may choose different companion medications.

Artemisinins are typically thought to have low toxicity. Clinical data show a decreased toxicity in malaria patients compared to healthy volunteers, contrary to animal (on rats) research that revealed damage on the haematopoietic system with a reversible decrease in reticulocytes.21 When oil-based arteether and arteetherol were administered at large intramuscular dosages in toxicological experiments using beagle dogs, QTc prolongation was observed at a considerable level.22 However, therapeutic intravenous bolus doses of artesunate (2.4 mg/kg) had no impact on the QTc interval in humans.

Arteether, arteetherol, and artellic acid oral administration have all been associated with fatal neurotoxicity in animals, but only after prolonged drug exposure that was not equivalent to that attained with therapeutic courses as advised for people.24 After receiving artesunate parenterally, incidences of late hemolysis have recently been documented.25 This phenomenon, whose underlying mechanism is still not entirely understood, was also observed in vitro in the 1980s26 and in an animal model.27 It is more pronounced at high doses of artemisinin derivatives and necessitates a longer period of patient follow-up.

Treatment:

Uncomplicated P. falciparum malaria

To treat patients with uncomplicated malaria, the World Health Organisation (WHO) encouraged several clinical trials assessing the effectiveness of artemisinin-based combinations employing different partner medications (ACTs) in several continents at the end of the 1990s.

In the years that followed, a sizable body of convincing evidence about the advantages of ACTs in achieving parasitological (parasite clearance time) or clinical (fever clearance time, survival) endpoints28,29 gathered. ACTs are currently recommended as first-line treatments for pregnant women only in the second and third trimesters; during early pregnancy, the use of an ACT is only permitted if the recommended treatments (a seven-day course of quinine plus clindamycin or quinine monotherapy if clindamycin is not available) is not available or has failed, with artesunate plus clindamycin being the second-line treatment) is not available or has failed.3 Monitoring of unintentional exposure to artemisinins during the first trimester of pregnancy is done.33, but further research is required.

Atovaquone-proguanil (table 1) is also regarded as one of the first-line options for travelers returning to non-endemic areas34,3 and for regions with confirmed artemisinin resistance, provided that it has not been used for prophylaxis. Proguanil interferes
with parasite DNA synthesis, blocking plasmodial dihydrofolate reductase, whereas atovaquone affects the mitochondrial membrane potential. They outperform mefloquine and have a 98% cure rate when used together. The medicine is not officially advised for usage during pregnancy, despite the limited data suggesting that the risk of birth abnormalities linked with atovaquone-proguanil exposure does not exceed 3 times the one reported in the general population.

Uncomplicated non-Plasmodium falciparum malaria

It's crucial to stress that any case of uncomplicated malaria coming from regions where resistance is reported should be treated as Plasmodium falciparum malaria, especially since ACTs and atovaquone-proguanil are effective against blood stages of non-falciparum Plasmodium species. This is especially true in cases where P. falciparum cannot be excluded (such as co-infection cases or mixed species malaria).

However, chloroquine continues to be the gold standard of treatment for P. malariae, P. ovale, and P. vivax malaria when P. falciparum infection is confirmed excluded. It is advised to administer a total dose of 25 mg/kg (10 mg/kg at T0, followed by 5 mg/kg at 6, 24, and 48 hours; alternatively, administer 10 mg/kg on the first and second days, followed by 5 mg/kg on the third). P. vivax, however, is shown declining sensitivity in a few particular regions. Even though the risk of treatment failure with this medication, as well as with primaquine, is still largely unknown, monitoring activity since the first P. vivax chloroquine resistance report in 198948 has shown resistant strains primarily in South-East Asia49, but also in East Africa50 and Central and South America51. The knowledge of P. falciparum resistance enables a justifiable expectation of things getting worse. Chloroquine is well-tolerated and safe for both children and pregnant women.

The term hypnozoites-killing medication must be used in addition to a drastic cure since P. ovale and P. vivax suggest a latent hepatic stage (hypnozoites). The 8-amino quinolines (bloque, primaquine, and tafenoquine)52 are currently the only molecules with significant activity against this parasite stage. Their mechanism of action is unclear, but it is likely focused on damaging the parasite's mitochondrial membrane and interfering with the parasite's DNA structure. Since being initially approved by the FDA in 1952 as an anti-malarial medication, only primaquine has been available on the market. The other 8-amino quinoline medications are still being studied, although they appear to have safer profiles than primaquine (bloque has less oxidative toxicity) and better pharmacokinetic properties (tafenoquine has a longer half-life). The danger of severe intravascular hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (G6PDH), which can be fatal for people with the Mediterranean B version of the X-chromosome gene, is the greatest safety worry concerning the usage of primaquine. The activity of glucose-6-phosphate dehydrogenase must then be determined before primaquine is administered. In cases of severe deficiency (WHO classes I and II; less than 10% residual enzyme activity), the medication is contraindicated. Primaquine 0.75 mg base/kg body weight may be safely taken once weekly for 8 weeks in individuals with mild-to-moderate G6PDH deficiency (WHO class III; 10–60% residual activity);3 in persons without G6PDH deficiency (WHO classes IV and V; > 60% enzyme activity). Adult dosages of daily drugs typically range from 0.25 mg per kilogram of body weight to 15 mg per day for 14 days. However, regional variations exist in the ability of such low primaquine doses (5 mg/kg total dose) to prevent P. vivax relapses.58 When treating Asian P. vivax strains, the Centres for Disease Control and Prevention (CDC) and other authors currently advise increasing the adult dosage to 0.5 mg/kg of body weight daily (maximum 30 mg divided into 2 doses) for 14 days. Primaquine should not be taken by pregnant women, regardless of their G6PDH status, because it is impossible to know the fetus's G6PDH status with confidence and there is a chance that severe hemolysis and hydrops fetalis could occur. On the other hand, if both the mother's and the child's G6PDH activity is sufficient, lactating women can take the medication. It is the Primaquine also exhibits a synergistic impact when paired with chloroquine against blood stages. However, in regions with P. vivax chloroquine resistance where G6PDH activity testing is not readily available, the use of an ACT regimen (with the exclusion of artesunate plus sulfadoxine-pyrimethamine) seems to be more appropriate.3,61 However, in this instance as well, only a primaquine course ensures a complete recovery from hypnozoites.

The most recent malaria agent to affect humans is Plasmodium knowlesi. It is microscopically identical to P. malariae and can even be mistaken for early trophozoites of P. vivax or P. falciparum.62 As with other non-falciparum malaria, uncomplicated P. knowlesi infection may be treated with chloroquine. Although there is currently no official recommendation for the treatment of P. knowlesi infection, there is evidence that other medications, such as mefloquine, quinine, atovaquone/proguanil, and sulfadoxine-pyrimethamine, may be effective against P. knowlesi.

Severe malaria

Plasmodium falciparum infection is typically the source of severe malaria, as determined by clinical or laboratory criteria as stated in Table 2 or by high parasitemia (2% in non-immune individuals; 5% in patients in endemic areas). A growing body of research suggests that other Plasmodium species, particularly P. vivax, have the potential to cause more severe forms of infection. Even after adopting the standard intravenous anti-malarial regimens, the case-fatality ratio is significant (about 10%), particularly in youngsters. When suitable intravenous therapy is expected to be delayed for longer than 6 hours, a pre-referral treatment is advised because patients might deteriorate extremely quickly, with the largest risk of death occurring in the first 24 hours, especially in the case of pediatric patients.

Clinical symptoms:

Conditions defining severe malaria case in plasmodium infection (ref: 3). Severe malaria is defined, in the absence of other obvious cause, when P. falciparum asexual parasitemia is accompanied by one or more of the following clinical or laboratory features.

<table>
<thead>
<tr>
<th>Clinical features:</th>
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<tbody>
<tr>
<td>impaired consciousness or unrousable coma</td>
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<tr>
<td>prostration, i.e. generalized weakness so that the patient is unable to walk or sit up without assistance</td>
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<tr>
<td>failure to feed</td>
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</table>
Clinical features:
- multiple convulsions – more than two episodes in 24 h
- Deep breathing, respiratory distress (acidotic breathing)
- circulatory collapse or shock, systolic blood pressure < 70 mm Hg in adults and < 50 mm Hg in children
- clinical jaundice plus evidence of other vital organ dysfunction
- hemoglobinuria
- abnormal spontaneous bleeding
- pulmonary edema (radiological)

Laboratory findings:
- hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
- hemoglobinuria
- hyperparasitaemia (> 2% or 100 000/μl in low transmission areas or > 5% or 250 000/μl in high stable malaria transmission areas)
- hyperlactatemia (lactate > 5 mmol/l)
- renal impairment (serum creatinine > 265 μmol/l).

To provide effective monitoring and treatment of organic dysfunctions, severe malaria should be treated as a medical emergency and perhaps handled in intensive care units (ICU).

Regardless of the plasmodium species that is causing the disease, the mainstay of severe malaria therapy is immediate, parenteral, and potent anti-malarial treatment with the primary objectives of preventing death and disability and, only secondarily, recrudescence. Since 2006, the WHO has advised using intravenous artesunate as a first-line treatment method wherever possible, as opposed to intravenous quinine. Systematic reviews have shown that artesunate is effective in lowering case fatality rates independent of age or location after multicenter trials have shown considerable superiority of artesunate over quinine both in South-East Asia and among children in Africa (RR 0.71). Due to this, i.v. artesunate is now regarded as the gold standard of care, despite the lack of registration with a global drug regulatory agency and the possibility of decreased availability outside of Asia. It should be noted that the Guilin Pharmaceutical Company Ltd., Shanghai, China-produced non-GMP (Good Manufacturing Practices) i.v. artesunate used in the SEQUAMAT and AQUAMAT studies has recently been prequalified by WHO. There are currently significant efforts being undertaken to make a GMP intravenous artesunate formulation accessible for clinical usage in Western nations. A formulation that is now licensed by the FDA as an experimental medicine and may be ordered directly from the CDC has undergone Phase I trials at the Walter Reed Army Institute of Research (WRAIR) in the United States. However, also pharmaceutical companies (e.g. Sigma-Tau, Italy) are investing in GMP-standard i.v. artesunate production programs and on 2007 the European Medicines Agency assigned the Orphan Medicinal Drug Designation to the drug.

**Treatment of severe malaria**

<table>
<thead>
<tr>
<th>Dosage/body weight</th>
<th>Notes</th>
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<tr>
<td><strong>Parenteral Drug</strong></td>
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<tr>
<td>i.v. Artesunate</td>
<td>2.4 mg/kg at 0,12,24 then once a day Available as single-dose vial containing drug as a sterile dry-filled powder and a single-dose vial of a buffer solution to be reconstituted in a clear colorless 10 mg per mL solution. Adding 5 ml of normal saline solution it can be administered direct i.v. over 1 to 2 minutes into an established i.v. line.</td>
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<tr>
<td>i.v. Quinine</td>
<td>20 mg*/kg (loading dose) then 10 mg/kg &gt; at 8-h intervals * Quinine doses are usually prescribed as quinine dihydrochloride salt (10 mg of salt = 8.3 mg of quinine base). contra-indicated if previous blackwater fever or quinine hypersensitivity or cardiac arrhythmia are known avoid loading dose if oral quinine or mefloquine has been given within 24 hours or if QT interval at baseline ECG is &gt;25% each dose in 10 ml/kg of saline or 5% dextrose solutions (maximum concentration 60mg/ml) rate-controlled infusion not exceeding 5 mg salt/kg body weight per hour (2–4 hrs) never by intravenous bolus injection → lethal hypotension reduce quinine dose to 5–7 mg/kg if infusion last for more than 48 hrs or if pt develops renal failure monitor blood glucose levels and electrocardiographic features</td>
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<tr>
<td>Pre-referral drugs</td>
<td>5 to 8 kg 1supp. 50 mg given once and followed as soon as possible by parenteral therapy</td>
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<tr>
<td>Dosage/body weight</td>
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<tr>
<td><strong>Suppository artesunate</strong></td>
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<tr>
<td><strong>50,100,400 mg</strong></td>
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<tr>
<td>9 to 19 kg</td>
<td>1 supp.100 mg</td>
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<td>20 to 29 kg</td>
<td>2 supp 100 mg</td>
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<tr>
<td>30 to 39 kg</td>
<td>3 supp 100 mg</td>
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<tr>
<td>40 to 59 kg</td>
<td>1 supp 400 mg</td>
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<tr>
<td>60 to 80 kg</td>
<td>2 supp 400 mg</td>
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<tr>
<td>&gt;80 kg</td>
<td>3 supp 400 mg</td>
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| i.m. Quinine      | Dilute 300 mg quinine (usually corresponding to 1 ml) into 5ml of sterile water for injection or saline (not dextrose) in the same syringe, that now contains 50mg quinine/ml |
| i.m. Artemether   | 3.2mg/kg                          |

**References**


