Chapter

Treatment of Malaria Infection and Drug Resistance

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Abstract

Malaria is a public health challenge that requires prompt treatment for those infected to make a full recovery. Treatment of malaria infection is to be started as soon as a diagnosis is confirmed. Antimalarial medications are administered to prevent and also to treat malaria. The type of medication used and the duration of therapy is dependent on the type of malaria-causing *plasmodium species*, the severity of the symptoms, geographical area where malaria infection occurred and the medication used to prevent malaria and whether there is pregnancy. Treatment of malaria from public health perspective is to reduce transmission of the infection to others, by reducing the infectious reservoir and to prevent the emergence and spread of resistance to antimalarial medicines. Medications used in the treatment of malaria infection come from the following five groups of chemical compounds: quinolines and aryl amino alcohols, antifolate, artemisinin derivatives, hydroxynaphthoquinones and antibacterial agents. The treatment of malaria is not initiated until the diagnosis has been established through laboratory testing. Artemisinin-based Combination Therapy (ACTs) has been used for the treatment of uncomplicated malaria. ACTs are also to enhance treatment and protect against the development of drug resistance. IV artesunate is used in the treatment of severe malaria, regardless of infecting species.

Keywords: Malaria, treatment, drug resistance, ACTs, drugs and plasmodium specie

1. Introduction

Plasmodium species are protozoan parasites that cause malaria, a life-threatening infectious ailment in humans. Five different species of *Plasmodium* are known to infect man: *P. falciparum, P. malariae, P. ovale, P. vivax* and *P. knowlesi*. *Plasmodium falciparum* is the commonest malaria-causing parasite in the World Health Organization (WHO) African Region, accounting for 99.7% of estimated malaria cases in 2018, as well as in the WHO Eastern Mediterranean Region (71%), the WHO Western Pacific Region (65%), and WHO South-East Asia Region (50%).

Plasmodium falciparum causes a serious form of malaria infection. *Plasmodium falciparum* parasite is known to be responsible for the vast majority of malaria morbidity and mortality in Africa [1].

Plasmodium vivax, causes most of the malaria infections in the Americas (75%). Also, about 53% of the malaria cases found in Southeast Asiais caused by *P. vivax*.

In addition, *P. vivax* presents some challenges as compared to *Plasmodium falciparum* which includes; shortage of accurate diagnostics and its ability to remain dormant in a person's liver among others [2].

Plasmodium malariae is found worldwide and causes a mild form of malaria. It is not as harmful as that caused by *P. falciparum or P. vivax*. Clinical signs associated with P. malariae include fevers that reoccur just about three-day intervals (a quartan fever) and longer than the two-day (tertian) intervals of the other malarial parasites [3]. *Plasmodium malariae* gives rise to a chronic infection that in some cases can last for a long period. The *P. malariae* parasite has diverse variations between it and the other Plasmodium parasites, one being that maximum parasite counts are normally low as compared to those in patients infected with *P. falciparum* or *P. vivax* [4].

Plasmodium ovale causes tertian malaria in humans. It is rare compared to *P. falciparum* and *P. ovale* and substantially less dangerous than *P. falciparum*. *P. ovale* has recently been shown by genetic methods to consist of two subspecies, *P. ovale curtisi* and *P. ovale wallikeri* [5]. *P. ovale* can infect persons who are negative for the Duffy blood group. This is common in many residents of sub-Saharan.

Africa. This accounts for the significant prevalence of *P. ovale* in most of Africa rather than *P. vivax* [6].

Plasmodium knowlesi causes malaria in humans and other primates. The natural warm-blooded hosts of *P. knowlesi* are various monkeys and humans can be infected by *P. knowlesi*. It closely resembles *Plasmodium vivax* as well as other *Plasmodium* species that infect primates other than humans. Individuals with *P. knowlesi* infection can develop uncomplicated or severe malaria comparable to that brought about by *Plasmodium falciparum*. Diagnosis of *P. knowlesi* infection is burdensome as *P. knowlesi* very closely looks like other species that infect humans [7].

2. Treatment of malaria and drug resistance

Malaria is an entirely preventable and treatable ailment. The choice of therapy is dependent mainly on the infecting species, the severity of infection, age of the patient, and susceptibility of parasites to antimalarial therapies, the cost and availability of medicines. The aim of malaria treatment is to ensure rapid and total elimination of the *Plasmodium* parasites from the patient's blood to help prevent the progression of uncomplicated malaria to complicated illness that leads to malaria-related anemia and death. From a public health perspective, treatment is meant to reduce transmission of the infection to others, by reducing the infectious reservoir and preventing the emergence and spread of resistance to antimalarial medicines [8, 9].

Drugs used in the treatment of malaria infection come from the following five groups of chemical compounds: quinolines and aryl amino alcohols, antifolate, artemisinin derivatives, the hydroxynaphthoquinones and antibacterial agents [10].

i. **Quinolines** include 4-aminoquinolines (chloroquine, amodiaquine and piperaquine), 8-aminoquinolines (e.g., primaquine and pamaquine) belong to the quinolines. **Chloroquine** (**Figure 1**), a 4-aminoquinoline manifests its antimalarial activity mostly on the mature trophozoites stage of the parasite by causing inhibition of the hemozoin (Hz) formation from hemoglobin digestion. Free heme causes lysis of membrane and parasite death. The side-effects of chloroquine include pruritus, skin-rashes, cephalgia, gastrointestinal disturbances and rarely bone marrow suppression, alopecia and convulsions [11]. Chloroquine was withdrawn from use because of a

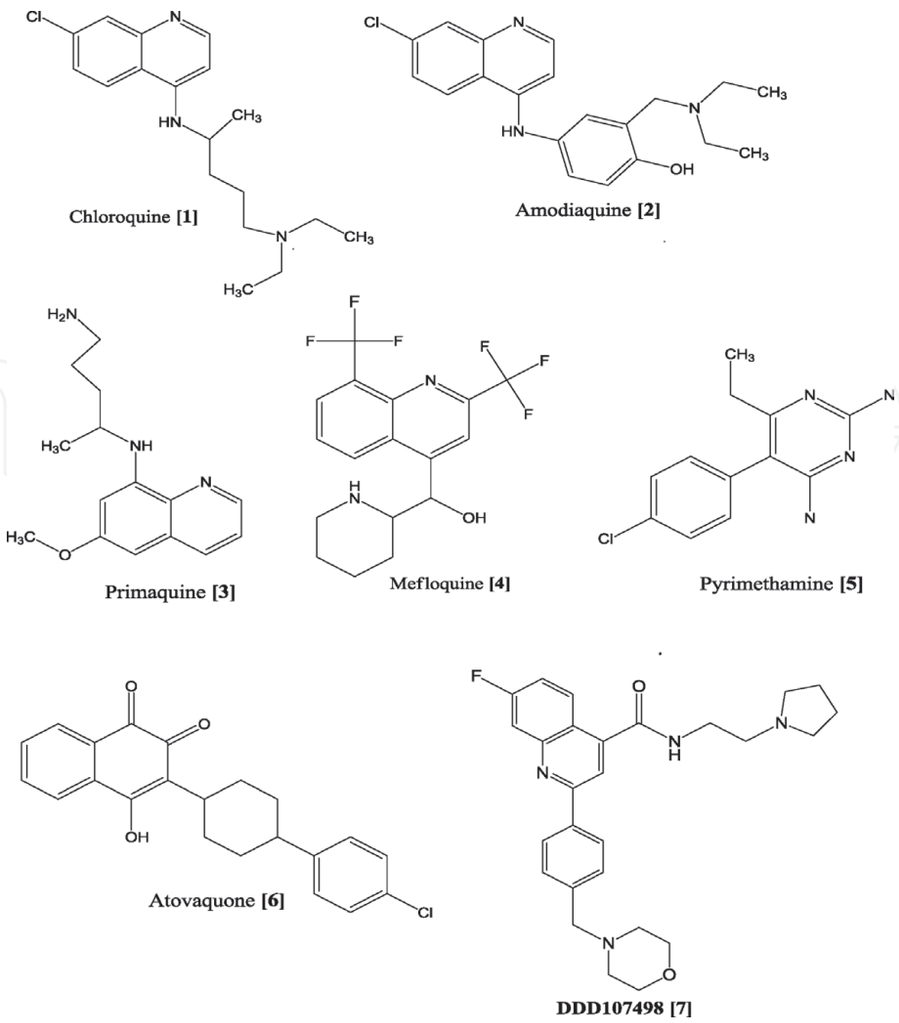

Figure 1.
Chemical structures of some synthetic compounds used as antimalarial.

decline in effectiveness resulting from resistant strains of the plasmodium parasite and fatal side effects [12]. *Plasmodium* parasite resistance against chloroquine and treatment failure is associated with multiple mutations in *Plasmodium falciparum* chloroquine-resistant transporter (PfCRT), a protein that probably functions as a transporter in the parasite's digestive vacuole membrane which results in reduced intracellular drug concentrations [13]. Chloroquine is currently on the Model List of Essential Medicines (MLEM) for the treatment of *P. vivax* infection in regions where resistance has not developed [14]. **Amodiaquine [2]**, also a Mannich base 4-aminoquinoline and its mechanism of action involve the suppression of the breakdown of hemoglobin. The drug also suppresses the glutathione-dependent destruction of ferriprotoporphyrin IX in the malaria parasite, leading to the accumulation of this peptide, which is unsafe to the survival of the parasite. Amodiaquine is therapeutically potent as compared to chloroquine in treating chloroquine-resistant *Plasmodium falciparum* malaria infections. These two drugs were widely used in the past for both prophylaxis and treatment of malaria. However, amodiaquine has serious adverse effects of hepatitis and agranulocytosis associated with its long-term use and therefore not generally recommended in malaria treatment [15]. Resistance to amodiaquine by plasmodium parasite has been associated with single nucleotide polymorphism (SNP) alleles *pfcrt* 76 T, *pfmdr1* 86Y, 184Y and 1246Y (c). Also, PfCRT, has been found to contribute to resistance to amodiaquine [16].

Primaquine [3] is a member of the 8-aminoquinoline range of antimalarials that includes tafenoquine and pamaquine. Primaquine is mainly used in the treatment of *P. vivax* or *P. ovale* malaria, specifically to get rid of the inactive liver forms of these parasites (hypnozoites). To achieve this, a 14-day course of primaquine is required [17]. The usual adverse effects associated with the administration of primaquine include nausea, vomiting, and stomach cramps. The most dangerous adverse effect of primaquine is haemolysis in patients who are deficient in Glucose-6-phosphate dehydrogenase (G6PD) enzyme, Africans or Caucasians of Mediterranean descent. Primaquine is the only antimalarial currently recommended as a therapy in *P vivax* malaria [18]. Resistance to primaquine is known to occur due to CYP-4502D6 mutation, which affects its metabolism and activation [19].

Piperaquine is a bisquinoline compound which was first synthesized in the 1960s and was widely used in China and Southeast Asia (Indochina) as a preventive agent for treatment purposes for over 20 years. Due to resistant strains of *P. falciparum* and the introduction of artemisinin-based antimalarial products, the usage of piperaquine declined [20]. Currently, piperaquine is used in combination with dihydroartemisinin to treat malaria [21]. Piperaquine resistance has been reported and the genetic markers plasmepsin 2 (*pfpm2*), exonuclease (*pfexo*) and chloroquine resistance transporter (*pfcrt*) genes are implicated for the resistance [22].

Mefloquine [4] is a quinoline methanol compound that resembles quinine and it is active against the asexual stages of malaria; however, its precise mode of action is not known. Mefloquine is therapeutically potent as a preventive agent against malaria and is extensively used in therapy against chloroquine-resistant *P. falciparum* malaria infection. Mefloquine is effective against all five strains of malaria parasites known to affect humans [23]. Frequent treatment using mefloquine is associated with asymptomatic, transient serum enzyme elevations in up to 18 per cent of patients. Adverse reactions such as skin-rash and autoantibody formation are also rare. Reported side effects of mefloquine include nausea, vomiting, abdominal pains, dizziness, neurotoxic effects and chronic neuropsychiatric adverse effects [24, 25]. Mefloquine is currently not widely used due to the perception of central nervous system toxicity [23]. Resistance to mefloquine result from increased amplification in *pfmdr1* in falciparum malaria [26].

ii. **Arylaminoalcohols.** Quinine, quinidine, mefloquine, lumefantrine and halofantrine, belong to the arylamino alcohols**. Quinine** is a drug obtained from the stem bark of the cinchona tree and was the first therapy used for malaria [27]. The most common adverse effects of quinine involve a group of symptoms called cinchonism; headache, vasodilation and sweating, nausea, tinnitus, hearing impairment, vertigo or dizziness, blurred vision, and interference in color perception. Quinine is a common cause of drug-induced disorders, including thrombocytopenia and thrombotic microangiopathy [28]. Quinine can also have severe adverse effects involving multiple organ systems, among which are immune system effects and fever, hypotension, haemolytic anemia, acute kidney injury, liver toxicity, and blindness. Quinine excites the secretion of insulin and may lead to hyperglycaemia which is a risk in pregnancy [29]. The mode of action of quinine is not clear but it is believed to interfere with the parasite's ability to breakdown hemoglobin leading to the inhibition of self-generated formation of beta-haematin (haemozoin or malaria pigment) which is a poisonous product of the breakdown of hemoglobin by the parasite [10]. Quinine is currently not used as front-line therapy for malaria due to the high-quality evidence

of the efficacy superiority of artesunate over quinine in adults and children with severe malaria [21]. There is currently inadequate data on resistance to quinine in malaria therapy [30, 31].

iii. **Antifolate**. The principal antifolates are pyrimethamine **[5]** (PYR), proguanil (PG; broken-down *in vivo* to the active form cycloguanil [CG]) and Dapsone. The sulfa drugs, the most significant of the antifolate are the outstanding, sulfadoxine (SDX), and the sulfone, dapsone. Antifolates were initially made available in the late 1960, and established to be of long-term use, particularly, as a low-cost substitute to combat the CQ-resistant parasites that were distributed across Africa from the late 1970s onwards [32]. Currently, antifolate are not widely used as a preventative therapy because of high levels of resistance [33]. Resistance to *antifolate* drugs is linked to point mutations in the dihydrofolate reductase domain of the dihydrofolate-thymidylate synthetase (DHFR-TS) gene and dihydropteroate synthase region of the pyrophosphokinase-dihydropteroate synthetase (PPK-DHPS) gene of the *malaria* parasite [34].

iv. **Hydroxy naphthoquinones** have been widely investigated over the past 50 years for their anti-malarial effect [35]. Atovaquone **[6]** is a hydroxyl naphthoquinone that is used in combination with proguanil for prophylaxis and therapy of uncomplicated malaria [36]. Atovaquone has outstanding anti-malarial property but demonstrates poor pharmaceutical activities, such as poor bioavailability and high plasma protein binding. The mechanism of action of atovaquone is through the prevention of the electron transport system at the level of cytochrome BC1 complex. Atovaquone also ensures the breakdown of the parasite mitochondrial membrane potential. Atovaquone is used as a fixed-dose combination with proguanil for the treatment of uncomplicated malaria. No serious or life-threatening adverse effects have been reported. Hydroxy naphthoquinones are taken one dose per day and for 7 consecutive days [6, 37]. Resistance to naphthoquinones has been attributed to a single-point mutation in the cytochrome b (*Pfcytb*) gene [38].

v. **Artemisinin** and its derivatives (Artesunate, Artemether, and Dihydroartemisinin) represent a new category of antimalarials. Fixed-dose formulations (combining two different active ingredients co-formulated in one tablet, Artesunate-Amodiaquine and Artemether-Lumefantrine are ideally favored and recommended over co-blistered, co-packaged or loose tablet combinations since it enhances adherence to treatment and cuts down the possible use of the individual components of co-blistered drugs as monotherapy [39]. The WHO advocates for the use of artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria caused by the *P. falciparum* parasite. ACTs are the most therapeutically potent antimalarial medicines available today [40]. The current trend in the treatment of uncomplicated malaria caused by *P. falciparum* is the use of ACTs with one of the following artemisinin-based combination therapies:

- Artesunate+Amodiaquine (AS-AQ)
- Artemether+Lumefantrine (A-L)

- Dihydroartemisinin+Piperaquine (DHAP).
- Artesunate+Mefloquine
- Artesunate+ Sulfadoxine+Pyrimethamine [32].

Artemisinin-based Combination Therapy (ACTs) has been used since the year 2004 for the treatment of uncomplicated malaria. This initiative was important because the malaria parasite became resistant to Chloroquine and other monotherapies. Artemisinin is administered in combination with a second, long-acting antimalarial to enhance treatment and protect against the development of drug resistance [33]. Quite recently the malaria parasite has developed resistance to artemisinin. Reasons for artemisinin resistance include uncontrolled use of artemisinin-based combination therapy (ACT), mobile populations and migrants, artemisinin monotherapy, the use of subtherapeutic levels of artemisinin, substandard and counterfeit drugs, high treatment cost, and co-use of artemisinin derivates as prophylactic agents [41].

2.1 New product under development

DDD107498 is a compound with the chemical name 6-Fluoro-2-[4-(4-morpholinylmethyl) phenyl]-N-[2-(1-pyrrolidinyl) ethyl]-4-quinolinecarboxamide. It is a novel chemical compound developed based on a 2, 6-disubstituted quinoline-4-carboxamide scaffold against the blood stage of the multi-drug-sensitive *Plasmodium falciparum* 3D7 strain. The compound has a powerful and wide spectrum of antimalarial activity against varied life-cycle phases of the *Plasmodium* parasite, with better pharmacokinetic activities and a satisfactory safety profile. DDD107498 has sub-micromolar efficacy against parasites. The compound has shown marked activity against 3D7 strain parasites. DDD107498 averted the development of trophozoites and schizonts. It is also effective against several drug-resistant strains. It is more effective as compared to artesunate in (*ex vivo)* assays against a range of clinical isolates of both *P. falciparum* and *P. vivax* and is not toxic to human cells [42–44]. DDD107498 which is now called M5717 entered the first stages of human clinical trials in 2017 (**Figure 1**).

3. Guidelines for the treatment of malaria

Ideally, treatment of malaria should not be initiated until the diagnosis has been established by laboratory testing. Therefore, without prior laboratory testing to confirm the presence of the parasite, treatment, should only be reserved for extreme circumstances, such as strong clinical suspicion of severe disease in a setting where there are no prompt laboratory services to confirm a diagnosis. The following factors should act as a guide in the treatment of malaria:

- the Plasmodium species causing the infection;
- the clinical condition of the patient;
- the anticipated drug responsiveness of the infecting parasite as determined by the geographic location where the infection was acquired; and
- the previous utilization of antimalarials, including those taken for malaria chemoprophylaxis [45].

Treatment of malaria is dependents on the species responsible for the malaria, as well as on the seriousness of the disease. The World Health Organization's protocols for the treatment of malaria provides recommendations on topics such as:

- Treatment of uncomplicated malaria caused by *P. falciparum*
- Treatment of uncomplicated malaria caused by *P. vivax*
- Treatment of severe malaria
- Mass drug administration

4. Modes of treatment

Treatment of malaria involves two principal concepts which are suppressive and radical treatments.

4.1 Suppressive treatment

The symptoms of malaria are relieved by suppressing the erythrocytic stage of the parasitic development in the suppressive treatment. This involves the administration of appropriate blood schizonticidal agents. In all cases of non-falciparum malaria (*P. vivax*, *P. ovale*, P. malariae and *P. knowlesi*), it consists of the administration of chloroquine. Also, presumptive treatment for malaria involves administration of blood schizonticidal medicines, such as chloroquine, to suspected cases of malaria, followed by full treatment after confirmation. This plan of action has been abandoned in recent years [45].

4.2 Radical treatment

Radical treatment involves the administration of primaquine to all confirmed cases of malaria [45].

5. Treatment of uncomplicated malaria caused by *P. falciparum*

Uncomplicated malaria is defined as a patient having symptoms of malaria and a positive parasitological test (microscopy or RDT) but with no clinical manifestation of severe malaria. The clinical goals of treating uncomplicated malaria are to seek to the total elimination of all parasites from the body as rapidly as possible followed by preventing progression to severe disease. The public health goals of treatment are to prevent onward transmission of the infection to others, prevent the emergence and spread of resistance to antimalarial medicines [46].

The WHO recommends that children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) are to be treated with one of the following recommended ACTs:

- Artemether + Lumefantrine
- Artesunate + Amodiaquine
- Artesunate + Mefloquine

- Dihydroartemisinin + Piperaquine
- Artesunate + Sulfadoxine–Pyrimethamine (SP).

The duration of ACT treatment regimens should provide 3 days' treatment with an artemisinin-derivative [46].

Pregnant women with uncomplicated *P. falciparum* malaria during the first trimester are to be treated for 7 days with quinine + clindamycin. Also, infants weighing less than 5 kg are to be treated with an ACT at the same mg/kg body weight target dose as for children weighing 5 kg. In addition, people with HIV/AIDS and having uncomplicated *P. falciparum* malaria, should avoid artesunate + SP if they are also receiving co-trimoxazole, also, they are to avoid artesunate + amodiaquine if they are also receiving efavirenz or zidovudine [46].

6. Treatment of uncomplicated malaria caused by *P. vivax*

The utilization of artemether-lumefantrine, atovaquone-proguanil, or quinine sulfate with doxycycline or tetracycline (or clindamycin for pregnant women and children <8 years old), are recommended treatment for uncomplicated malaria caused by *P. vivax*. Also, mefloquine can be used if no other options are available. In addition, primaquine phosphate can be used in combination with any of the medication options for treatment of the acute phase of infection [46].

7. Treatment of severe malaria

Patients with clinical manifestations and features of severe malaria; coma, hemoglobin of less than 7 g/dL, acute kidney injury, acute respiratory distress syndrome, shock, acidosis, jaundice should be treated promptly and aggressively with parenteral antimalarial therapy regardless of the species of malaria noted. All patients with severe malaria, regardless of infecting species, should be treated with intravenous (IV) artesunate [47].

The objective of management of severe malaria infection is to prevent deaths from the direct effect of the disease or its complications through the use of appropriate emergency supportive measures, diagnostics and the recommended anti-malaria medications. The goals of management of severe/complicated malaria are to provide:

- Urgent treatment of life-threatening problems.
- Anti-malarial treatment which is specific for severe/complicated malaria.
- Appropriate supportive care throughout illness [47].

8. Mass drug administration

Mass drug administration (MDA) is defined as the provision of a therapeutic dose of an effective anti-malarial medication to the entire target population, irrespective of infection status or symptoms. The MDA is a strategy recommended by the WHO for the elimination of *Plasmodium falciparum* malaria in areas approaching interruption of transmission, as well as where multidrug resistance is present,

given the prerequisites of good access to case management, effective vector control and surveillance, and limited potential for reintroduction [48].

9. Conclusion

The treatment of malaria infection involves the utilization of various medicines and combinations however, the choice of medication is dependent on several factors, including the specific species of parasite identified, the severity of symptoms, and determination of drug resistance based on the geographic area. The anti-malarial used are administered in pill form or as an intravenous depending on the above factors. The most commonly utilized antimalarial medications are artemisinin, its derivatives and combinations. Artemisinin's are more effective acting anti-malarial agents killing young parasites. It has also been used successfully for the treatment of severe malaria. In cases of parasite resistance to drugs, combination therapies are used. In addition, malaria parasites, such as *P. vivax* and *P. ovale*, have liver stages where the parasite can live in the body for an extended period and reactivate at a later date causing a relapse of the infection. In situations like this, a second medication to prevent a relapse in the future is administered.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Abbreviations

ACT	Artemisinin-based Combination Therapy
CG	Cycloguanill
CQ	Chloroquine
CYP	Cytochrome
DHFR-TS	Dihydrofolate-Thymidylate Synthetase
G6PD	Glucose-6-phosphate dehydrogenase
MLEM	Model List of Essential Medicines
PfCRT	*Plasmodium falciparum* chloroquine resistant transporter
PG	Proguanil
PPK-DHPS	Pyrophosphokinase-Dihydropteroate Synthetase
PYR	Pyrimethamine
RDT	Rapid Diagnostic Test
SDX	Sulfadoxine
SNP	Single Nucleotide Polymorphism
WHO	World Health Organization

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