



ANTIMALARIAL DRUGS AND THEIR MODE OF ACTIONS

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ABSTRACT

Malaria is a life threatening parasitic disease and is considered as a complex and overwhelming public health problem. For long, prevention and treatment of the disease heavenly depend on Prophylaxis and chemotherapy using different synthetic drugs which target some specific organells or stages in the life cycle of the parasite. Therefore, the aim of this paper was to exhaustively review the state of knowledge on antimalarial drugs and their mode of action. Antimalarial drugs fall in to three classes based on their action on the parasite, these are Quinolines(Quinine, Chloroquine, Amodiaquine, Primaquine, Mefloquine and Lumefentrin), Antifolate (Pyrimethamine, Proguanil and Sulfadoxine), Artemisinin, Artusenate, Artemether and Areether) and Hydroxynaphthaquinones (Atovaquine). Based on their action on different developmental stages of the parasite, the antimalarial drugs are classified as Hypnozoiticide, which act on the liver stage of P.vivax and P.ovale e.g Primaquine, Blood schizonticide which act on the erythrocytic stage of the parasite(e.g Chloroquine), Gametocytocide (artemisinins and primaquine) which attack the gametocyte stage and Sprontocide (e.g Pyrimethamine) which prevent the development of oocyte and multiplication of the parasites in the mosquito gut when ingested with the blood of the human host (e.g., primaquine, chloroguanide, pyrimethamine). For most of these antimalarial drugs, their exact mechanism of action is yet to to be properly elucidated, but there exist several hypotheses behind their mode of action. For Quinolines it is believed that they interfere with Haemoglobin digestion which leads to the generation of toxic heme that accumulate in the digestive vacuole thereby interfering with or inhbiting proper functioning of protein, consequently lead to the death of the parasite. Antifolate interfere with folate metabolism while Artemisinin and it derivatives are thought to interfere with normal functioning of Mitochondria of the parasite. For effective prevention and Treatment,

combination therapy using different classes of drugs should be encouraged in order to drastically avoid the risk development of resistance by the parasite.

Keywords: *Quinolines, Antifolate, Artemesinin, Plasmodium falciparum, Mechanism of action*

INTRODUCTION

Malaria is a life threatening parasitic disease and is considered as a complex and overwhelming public health problem. The disease is a serious burden particularly to low and a middle- income country like Nigeria and is one of the major contributor to morbidity and mortality (Alister et.al.2012). The infection begins when a *Plasmodium* infected female anopheline mosquito probes for a blood meal and injects the sporozoites into the dermis. The Sporozoites then migrate to the liver, infect hepatocytes, and remain in a clinically silent stage (Gunanidhi et.al.,2010; Friedrich and Kai, 2017). After which they move and invade the red blood cell and start the erythrocytic cycle. Pathology associated with malaria disease arises from *Plasmodium* parasite infection and replication within red blood cells (RBCs) (Olivrer et.al.,2018).

This disease is present in 106 countries and among these 99 have ongoing transmission of malaria. According to WHO (World Health Organization) estimation there were 216 million malaria cases was reported worldwide (Kondapalli et.al.,2012). Malaria is estimated to kill nearly one million people annually, with most of the deaths occurring in children under 5 years of age in sub-Saharan Africa. Additionally, pregnant women and newborns have reduced immunity and therefore are vulnerable to severe complications of malaria infection and disease (Mebrahtu,2015). More than 90% of the worlds' malaria cases occur in sub-Saharan Africa and the transmission rate and the degree of severity are worse in *Plasmodium falciparum* malaria (Wogu and Obasahan, 2014). Nigeria alone accounts for nearly 25% of the total malaria burden within Africa (Muhammad and Napthali,2014). In Nigeria also, the disease is responsible for 60 % outpatient visits to health facilities, 30 % childhood death, 25 % of death in children under one year, 11 % maternal death (Chinyere et.al.,2012), and indirectly contributes to additional 11% of maternal deaths mainly by being a leading cause of anaemia in pregnancy (Augustine et.al., 2012). One of the key malaria control interventions is vector control which includes the use of insecticide treated nets (ITNs), the other key interventions being prompt diagnosis and effective treatment of malaria cases as well as Indoor Residual Spraying (IRS) (Envuladu et.al.,2012). Synthetic antimalarial drugs are the focus

in the treatment and prevention of malaria infection (Muturi, et.al.,2016).Antimalaria drugs act on different intracellular targets. The majority of them interfere with digestive vacuoles (DVs) while others affect other organelles, namely, apicoplast and mitochondria (Zaid,et.al.,2014). With regard to the antimalarial treatment policy, the objective is to reduce morbidity and mortality by ensuring rapid complete cure of infection, in addition to curtailing the transmission of malaria by reducing the parasite reservoir of infection and infectivity (Eric, et. al., 2015). Most antimalarial drugs target the erythrocytic stage of malaria infection, which is the phase of infection that causes symptomatic illness. Treatment of the acute blood stage infection is necessary for malaria caused by all malaria species. In addition, for infection due to *Plasmodium ovale* or *Plasmodium vivax*, terminal prophylaxis is required with a drug active against hypnozoites which can remain dormant in the liver for months and, occasionally, years after the initial infection (Mebrahtu,2014).

Antimalarial are used in three different ways, prophylaxis, treatment of *falciparum* malaria and treatment of non-*falciparum* malaria .Prophylactic antimalarials are used by almost exclusively travellers from developed countries who are visiting malaria endemic countries. Treatment protocols for *falcifarum* malaria vary depending on the severity of the disease, fast acting parenteral drugs are best for severe life threatening disease. In addition, treatment protocols for *falciparum* malaria vary geographically and depend on the resistance profile for strains in particular regions. Non-*falciparum* malarias, in contrast are rarely drug resistant (Muheet et.al, 2013). Antimalarial drugs have two key roles for malaria control. First, prompt and effective treatment of malaria prevents progression to severe disease and limits the development of gametocytes, thus blocking transmission to mosquitoes. Second, drugs can be used to prevent malaria in endemic populations, including various strategies of chemoprophylaxis, intermittent preventive therapy, and mass drug administration (Reetika and Bechan 2019).

Over the past 60-70 years, since the introduction of synthetic antimalarials, drugs from the following classes of compounds have found to be for clinical usage (Mebrahtu, 2015). These compounds include Quinoline and Aryl alcohol (which comprises of Quinine, Chloroquine, Amodiaquine, Primaquine, Mefloquine and Lumefentrin), Antifolate (Pyrimethamine, Proguanil and Sulfadoxine) Artemisinin and its derivatives (Artemisinin, Artusenate, Artemether and Areether) and Hydroxynapthaquinones (Atovaquine) (Makoah, and Gabriel, 2013).

Anti-malarial drugs can be classified by their action on different stages of the malaria parasite:

- a. Hypnozoitocides: act against quiescent liver stage hypnozoites from *P. ovale* and *P. vivax* infections (primaquine)
- b. Blood schizonticide (chloroquine, sulphadoxine-pyrimethamine, quinine, mefloquine and artemisinins)
- c. Gametocytocide (artemisinins and primaquine)
- d. Sporontocides: prevent the development of oocyst and multiplication of the parasites in the mosquito gut when ingested with the blood of the human host (e.g., primaquine, chloroguanide, pyrimethamine). (Xhamla et.al.,2017; Esperanca et.al.,2010).

MATERIALS AND METHODS

Literature Search

In order to obtain reliable and authentic research and published articles on the topic the following data bases were visited; PubMed, Web of Knowledge, EMBASE, Web of Science, Scopus, Google scholar, World Health Organization's WHOLIS and Medline. In addition Sci.Hub. was used to access some publications that were very difficult to access with the other data bases.

Search Terms Used

Search terms that were directly or indirectly linked to Antimalarial drugs and their mode of action were used in order to generate relevant research papers. The following search terms were specifically used; Antimalarial drugs, Quinolines, chloroquine, sulphadoxine-pyrimethamine, quinine, mefloquine and artemisinins, artemisinins and primaquine, Hypnozoitocides, Blood schizonticide, Gametocytocide, Sporontocides, Antimalarial drugs and their mode of action. All research papers generated were carefully and critically analysed and scrutinised, after which the papers were grouped and classified based on the various headings and Subheading of the title of the review topic.

RESULT AND DISCUSSION

Quinoline

Historically, Quinolines are among the most important antimalarial drugs ever used (Margarida, et.al., 2005). Quinoline-containing antimalarial drugs, such as Quinine, Chloroquine, Amodiaquine, Primaquine, Mefloquine and Lumefantril (Kondapalli et.al.,2012). Despite problems associated with drug resistance and side effects, quinolines remain widely used for the treatment of severe malaria

and malaria prophylaxis (Lindi, et.al, 2009). Despite the fact that, quinolones have been used as specific antimalarial therapy for more than 300 years (David et. al.,1996). The molecular basis of the action of these drugs is not completely understood, but they are thought to interfere with hemoglobin digestion in the blood stages of the malaria parasite's life cycle (Foley and Tilley, 1998) but some are believed to target the hepatic stage(Margarida, et.al, 2005). During this stage, the parasite needs to degrade hemoglobin. Hemoglobin digestion releases free heme that is toxic to the parasite, so it is then polymerised to nontoxic hemozoin. Antimalarial quinolines are thought to interfere with this polymerisation and kill the malaria parasite by the accumulation of toxic free heme.

The ingestion and digestion of most of the host cell's haemoglobin is a vast and energetically expensive process for the parasite. Another problem for the parasite is remaining heme (Ferriprotophyrin IX) that is released upon digestion of haemoglobin chain. Free Ferriprotophyrin IX (heme) causes lethal to the membranes and proteins and its efficient disposal is critical importance to the parasite. Ferriprotophyrin IX is not destroyed enzymatically, but instead is converted to a crystalline substance called haemazoin or malaria pigment that is harmless to the parasite. The process of haemazoin is of great interest to malariologist, not least, because it is thought to be the target of some of the quinolone antimalarials (Bray, et. al., 2005).

Quinine

Quinine, a quinoline derivative, is used in many African countries as second-line treatment for uncomplicated malaria, as an alternate first-line treatment of severe malaria, and for treatment of malaria in the first trimester of pregnancy(Jelagat et.al,2012). Quinine has been used to treat malaria for hundreds of years and is still effective in treating *P. falciparum* and other parasites, particularly when combined with other drugs, although its efficacy is declining in some endemic regions .The first quinolone antimalarial drug quinine was alkaloid extracted from cinchona tree (Sandeep and Shailja, 2014). Quinine was the only effective agent for the treatment of malaria until 1930s. Due to its undesirable side effect, because of it high toxicity, it is now mainly used to as an intravenous injection to treat severe malaria (Mebrahatu, 2015) as in this case, the preferred route (Ane et.al,2001). Most often Quinine is combined with a second agent to shorten the duration of therapy and thus minimize the adverse effects (Luiz et.al,2018).

Quinine act in a manner similar to chloroquine but with some differences, in the sense that chloroquine causes clumping of malaria pigment while Quinine

antagonises that. quinine is a weaker base than chloroquine, as such it has less affinity for heme, implying that mechanisms other than ion transport into the food vacuole and heme-drug interaction are required for the action of the drugs, but it has been shown to inhibit heme polymerization and heme catalase activity (Muheet et.al.,2013).

Chloroquine

Chloroquine is a derivative of quinine, first synthesised in 1934 and introduced as a drug of choice for treatment of non-severe or uncomplicated malaria and for chemoprophylaxis in 1950s (Makoah, et.al, 2013). The drug is a remarkable antimalarial compound that is rapidly active against the blood (sexual) stages of all the four species of human malaria, its cheap, well tolerated and requires only two or three days treatment for cure (White,1998). It is the first synthetic antimalarial drug and first in the class quinolone (Dylan and Junior, 2014). Chloroquine is particularly prepared because of its efficacy, stability, low cost and ease to manufacture. Its first use was initially ignored as it was said to be toxic to people. Chloroquine, like other members of quinolone family, mainly interferes with detoxification of heme in digestive vacuole.

Chloroquine, exists in unprotonated form, CQ, monoprotonated form, CQ⁺ and diprotonated form, CQ⁺⁺ form. Unprotonated form of chloroquine is membrane permeable and it freely diffuses into the red blood cell. It then continues to diffuse into the Digestive Vacuole. Once Chloroquine has diffused into the Digestive Vacuole it is protonated. Protonation of Chloroquine makes it impermeable to the membrane as most charged substances do not cross the membrane. As a result of this, chloroquine accumulates in the Digestive Vacuole. Charged chloroquine in the Digestive Vacuole is believed to bind to hematin, which is a by-product of hemoglobin breakdown. This binding prevents the incorporation of hematin into the hemozoin crystal. Lack of incorporation therefore leaves the hematin free. Hematin will therefore interfere with the process of detoxification within the parasite. Lack of detoxification therefore allows the toxins to build up which will eventually damage the *Plasmodium* membrane.

During hemoglobin digestion, heme is released in large quantities. Heme released in this process lyses the cells and it is therefore not safe to have it in the body. Heme further produces oxygen radicals and inhibits other metabolic processes. It is therefore necessary to remove heme the moment it is produced. The process of heme removal involves accumulating heme into large molecules called hemozoin. The whole process of heme detoxification happens in the food vacuole. Heme is therefore the main target for chloroquine. Chloroquine attaches itself to

heme and this process prevents biocrystallization of heme into hemozoin. Accumulation of heme will eventually lead to the killing of the parasite due to its accumulation to high toxic levels.

Amodiaquine

Amodiaquine is a 4-aminoquinoline similar to chloroquine that has been widely used in the past to treat and prevent malaria. Following serious toxicity associated with use as prophylaxis, it was withdrawn by the WHO from the list of drugs for the treatment of malaria during 1990-1996 and then reinstated. However, it is still used in West, Central and East Africa. The widespread increase of resistance to chloroquine in *Plasmodium falciparum* has resulted in renewed interest in amodiaquine (AQ) as a replacement for chloroquine in the treatment of malaria, especially in sub-Saharan Africa. Although AQ belongs to the same chemical class of compounds as chloroquine, the 4-aminoquinolines, this drug often shows adequate clinical-parasitological efficacy in chloroquine-resistant infections (Mariga et.al.,2004).

After absorption, orally administered AQ is rapidly metabolized to desethylamodiaquine (DAQ) and other derivatives of lesser antimalarial significance. Clinically, the antimalarial activity of AQ is exerted mainly through DAQ (Mariga et.al.,2004). This is due to the higher concentration-time profile and the longer half-life of between 9-18 days, (Barka et.al 2018) compared to those of the parent compound. It also acts by binding to the parasite and preventing the production of DNA and RNA and, subsequently, the synthesis of protein (Peace et.al.,2015).

Primaquine

Primaquine has been used since early 1950s and is the mostspread 8-aminoquinoline antimalarial drugs, it is extensively used in radical treatment of *Plasmodium vivax* and *Plasmodium malariae* and also as a single-dose gametocytocide in *plasmodium falcifarum* malaria (WHO,2015). Primiquine is the only commonly used anti-malarial drugs that kills mature gametocyte, the life cycle stage responsible for the transmission of malaria from the human to mosquitoes (Ingrid et.al.,2015). In addition, it currently holds a unique place in antimalarial therapeutics. It's the only generally available drugs kills hypnozoite (radical curative activity) in *vivax* and *ovale* and the only drug with potent activity against mature gametocytes of *Plasmodium falcifarum* (WHO,2014). It acts by inhibiting the mitochondrial electron transport. The main limitation to its use has been haemolytic toxicity. The 8- aminoquinoline antimalarials produce

dose dependant acute haemolytic anaemia (AHA) in individuals with Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency (WHO,2012).

Mefloquine

Mefloquine (MQ) is a quinoline class of antimalarial agents used for chemoprophylaxis and the treatment of malaria. MQ has two chiral centers and can exist in two diastereomeric forms. However, it is clinically used as an enantiomeric mixture of the erythro isomer. MQ has been in clinical usage for malaria for more than three decades. It is readily available, inexpensive, and is on the World Health Organization's list of essential medicines. Despite its clinical use for decades, the precise mechanism of action of MQ was not determined (Gautam and Conor,2018).

Mefloquine is active against asexual forms of the four species of plasmodium that infect humans. It has some activity against the sexual forms (gametocytes) of *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*, but its ineffective against gametocyte of *Plasmodium falcifarum* and exoerythrocytic liver form of plasmodium species.

Mefloquine is a potent antimalarial drug of the arylamino alcohol class that is chemically related to quinine. It is only available as an oral preparation. Mefloquine is highly lipid-soluble, and is metabolized largely in the liver; it has an elimination half life of 2–3weeks.¹(Smith and Black, 1999).

Mefloquine may inhibit merozoite invasion and interact with protein involved with parasite membrane lipid trafficking and nutrient uptake. Like other quinolone (e.g Chloroquine), mefloquine binds to haem, forming complex that may also be toxic to the parasite.

Atovaquone

Atovaquone is a naphthoquinone with a potent anti protozoal activity against plasmodium (Roalan, et.al.,1997).Atovaquone is the end product of half a century of research by many groups who researched the antiparasitic properties of numerous structurally related compounds, the drug is used as a fixed-dose combination with proguanil (Malarone) for treating children and adults with uncomplicated malaria or as chemoprophylaxis for preventing malaria (Gemma, et.al.,2013). It is also effective for preventing falcifarum malaria in lifelong residents of malaria endemic countries (Birthe,et.al.,2000). A combination of atovaquone and proguanil has been found to be quite effective in treating malaria, with little evidence of the emergence of resistance when atovaquone was used as a single agent (Indresh and Akhil,1999).

Its mode of action is original, blocking the electron transport chain of the parasite's mitochondria. Used on its own, atovaquone has limited value, as shown by a significant relapse rate. Its association with proguanil has shown excellent efficacy on acute malaria in numerous clinical trials, due to a synergistic effect. AP is also widely used as an efficient and well-tolerated chemoprophylaxis for travelers (Hugues et.al.,2013). It selectively inhibits the electron transport through the parasite mitochondrial cytochrome *bc1* complex and collapses the mitochondrial membrane potential at concentrations far lower than those at which the mammalian system is affected (Michael et.al.,2005). It is also thought to deplete the intracellular nucleotide pools by inhibiting dihydroorotate dehydrogenase, an enzyme for de novo pyrimidine synthesis (Sarah et.al.,2020).

ANTIFOLATE

The antifolates were the first class of anti-metabolites to enter the clinics 65 years ago (Michele,et.al., 2012). Antifolate combination of pyrimethamine and sulfadoxine is the last affordable drug combination available for the wide-scale treatment of plasmodium falcifarum malaria in Africa (Nzila, et. al.,2000). The principal antifolate drugs used against malaria are pyrimethamine, proguanil and the sulfa drugs, the most important of which are the sulfonamide, sulfadoxine and the sulfone, dapson (Ingrid and John,2010). Pyrimethamine is an important chemotherapeutic agent used alone in the prevention of malaria and in combination with sulphonamide in the treatment of malaria (Thomas,et.al.,1984). Antifolate antimalarial drugs interfere with folate metabolism, a pathway essential to malaria parasite survival. This class of drug include effective causal prophylactic and therapeutic agents, some of which act synergistically when used in combination (Aric and Christopher, 2005).

Antifolate agents act on folate metabolism of the parasite, with regard to the target enzyme they inhibit, the antifolates are divided in to two classes, inhibitors of dihydropteroate synthase (DHPS)(class I antifolates) such as Pyramethamine, Proguanil and Chloroproguanil and inhibitors of dihydrofolate reductase (DHFR) (class II antifolate) such as sulfadoxine and Dapson (Mebrahtu, 2015). The combination of DHPS and DHFR inhibitors is synergistic hence their use in combination in the treatment of malaria (Alexis, 2006).

The combination of sulfadoxine/ Pyramethamine was introduce in 1967 as a synergistic antimalarial drug and replaced Chloroquine as a first-line treatment of plasmodium falcifarum in many part of Africa (Makoah and Gabriele, 2013). sulfadoxine/ Pyramethamine is recommended for treatment of malaria in pregnancy(Federal Ministry of Health,2010) .In combination therapy, two or

more drugs with independent mode of action and different target in the parasite are used together. This delays the development of resistance to the component drugs, thereby prolonging the life span of still effective antimalarial drugs (Osei-Akoto, et al., 2009).

ARTEMISININ

Artemisinin and its derivatives were introduced in the 1980s (Paloque, et al., 2016), these are a group of antimalarials derived from the *Artemisia annua* tree (annual wormwood). These include e.g. artesunate, artemether, dihydroartemisinin, artelinic acid, arteminol and artemotil. They can only be used as part of combination therapies. Multi-drug resistance has increasingly become a major impediment to malaria control, although, the discovery and evaluation of artemisinin in China in the 1970s has strengthened the global efforts to combat malaria (Ngo, et al., 2010). Artemisinin combination therapy is recommended as first-line anti-malarial treatment, they are extremely safe and effective after three days of dosing, and currently there is no alternative to artemisinins for the treatment of malaria (Makoah and Gabriel, 2013).

Artemisinin forms the most important class of antimalarial drugs currently available, particularly because of their effectiveness against parasite resistant to almost all other classes of antimalarial (Antifolate and Quinoline), and it is one of the few classes of drug that is useful to treat severe malaria that is resistant to chloroquine (Sanjeev et al., 2004). Since 2001, the World Health Organization (WHO) has recommended the use of artemisinin-based combination therapy (ACT) in countries where *P. falciparum* is resistant to CQ, SP, and amodiaquine (AMQ) (Aminata, et al., 2016), but observations of longer artemisinin (ART) parasite clearance times (PCTs) in Southeast Asia are widely interpreted as a sign of potential ART resistance (Whitney, et al., 2016).

Forty years ago, effort by a consortium of Chinese scientists supported by the Chinese government, to combat malaria led to the discovery of a powerful antimalarial drug, artemisinin. In contrast to cinchona alkaloids, such as quinine, which only kill mature parasites, artemisinin is effective in killing nearly all asexual as well as sexual stages of the parasite (Jian and Bing, 2010). Another advantage of artemisinin derivatives is their ability to kill gametocytes, hence interrupting malaria transmission (Robert and Jane, 2011). In addition, artemisinin can kill malaria parasites within minutes with a parasite reduction ratio of approximately 10,000 per erythrocytic cycle, resulting in rapid clinical responses (White, 2008).

The food vacuole appears to be the target of artemisinin antimalarials (Philiph, 2013), but the actual mechanism of action of artemisinin is ambiguous,

unlike quinolone-based antimalarials for example (Chloroquine) which have only one well-documented mechanism of action, artemisinin kills malaria parasite by generating more than one type of cytotoxic intermediate. Several hypotheses have been proposed to explain their mode actions, include alkylation of heme by carbon-centered free radical, interference with protein such as the Sarcoplasmic/Endoplasmic calcium ATPase (SERCA) as well as damaging of normal mitochondrial function (Jian and Bing, 2010).

Early diagnosis and prompt effective treatment—key components of all national malaria control strategies—were seriously compromised during the early 1990s by resistance to widely used monotherapies. The use of oral artemisinin-based monotherapies the long- term usefulness ACTs by fostering the emergence and/or spread of resistance to artemisinin. To contain this risk and to ensure high cure rate for *P. falcifarum* malaria, WHO recommends the withdrawal of oral artemisinin-based monotherapies from the market and replacement by ACTs as endorsed by world health assembly in 2007 (WHO, 2012).

Combination drug treatment practices are common in treating many infectious diseases such as TB, HIV infection and cancers, and the general principle is applicable to malaria. The rationale behind ACT is that the chance of parasites simultaneously developing resistance because of genetic mutations to two drugs with different modes of action is much lower than the chance of parasites developing resistance to single drugs (F.M.O.E,2010).

The concept of combination therapy is based on the synergistic or additive potentials of two or more drugs, to improve therapeutic efficacy and delay resistance to the individual component of the combination and to also overcome the threat of resistance of *plasmodium falciparum* to monotherapies. Combination therapy (CT) with antimalarial drugs is the simultaneous use of two or more blood schizontocidal drugs with independent mode of action and different biochemical target in the parasites(i.e. the partner drugs in a combination must be independently effective) (WHO, 2001).

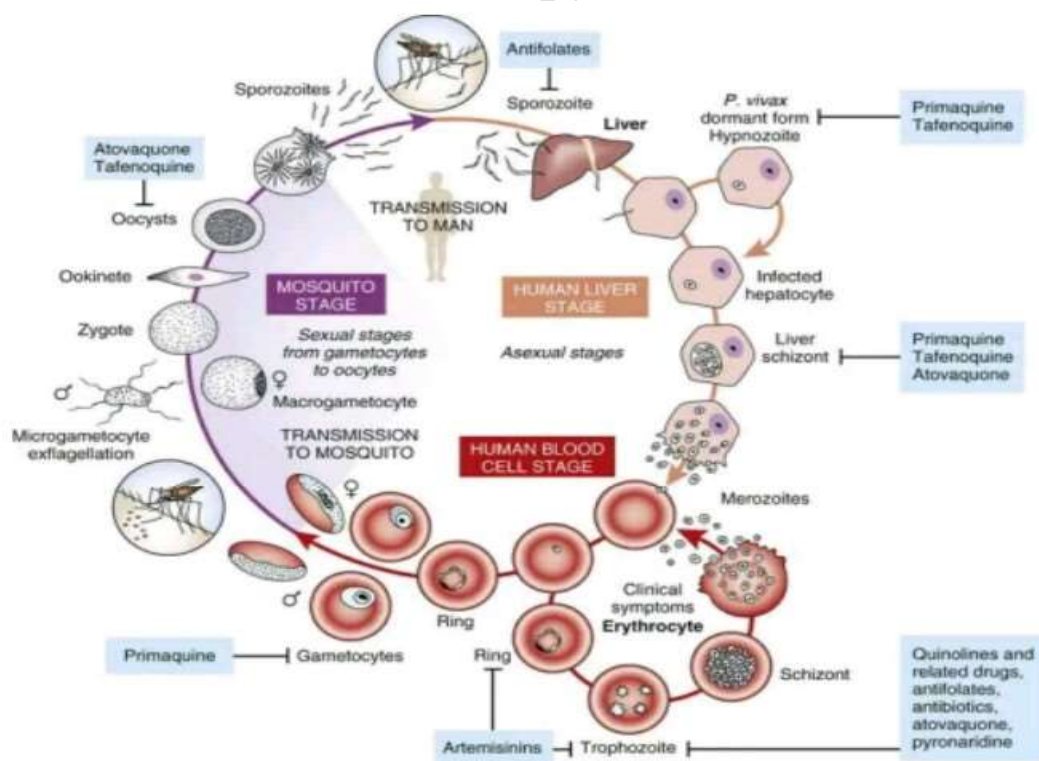
To eliminate at least 90% of the parasitaemia, a 3-day course of the artemisinin is needed to cover up to three post-treatment asexual cycles of the parasite. This leaves a much smaller number of parasites (10%) for the partner drug to kill while its concentration in plasma remains high.Parasite resistance to drug monotherapy prompted the WHO to recommend dual or triple therapy, which combines molecules with independent modes of action or distinct target enzymes. Drug combination is usually more effective and in the event of resistance to one component, the second one kills residual resistant parasites. However, some combination therapy, such as sulfadoxine-pyrimethamine plus chloroquine or amodiaquine, must be avoided due to the high levels of resistance established to these drugs already extensively used in monotherapy (Paloque,2016).

ACTs recommended by WHO are:Artesunate + amodiaquine, Artemether + lumefantrine ,Artesunate + mefloquine, Artesunate + sulfadoxine-pyrimethamine and Dihydrortemisinin + piperazine (Robert and Jane, 2011).

Artemether-Lumefantrine is the first artemisinin-based combination therapy registered in industrialised countries (Christoph, et.al.,2008). The artemisinin component of the combination reduces the gametocyte carriage of a patient by acting particularly on young gametocyte, thereby blocking malaria transmission, but they do not prevent transmission of the mature gametocyte present at the time of treatment (Bousema et.al., 2006). Presently, most malaria endemic countries in Africa including Nigeria have changed their first line antimalarial treatment from CQ or SP to amodiaquine combined with artesunate or the combination of artemether and lumefantrine (Folarin et. al., 2008).

World Health Organisation has recommended Artemisinin-based Combination Therapies (ACTs) as the first line treatment for uncomplicated malaria since 2001, and during the past decade, most malaria-endemic countries shifted their national treatment policies to ACTs (World Health Organisation, 2010). Artemisinin-based combination treatment (ACTs) are now generally accepted as the best treatment for uncomplicated falcifarum malaria, they are rapidly and reliably effective (Francois and Nicolas, 2007). The global malaria situation has shown substantial improvement after massive deployment of preventive and curative tools, including artemisinin-based combination therapy (The, et.al.,2007).

The figure below shows different classes of antimalarial drugs and their target stage in the life cycle of the parasite.



CONCLUSION

Prevention and treatment of malaria still depends on synthetic antimalarial drugs as up to now there is no available vaccine for the disease. The antimalarial drugs falls in different classes and target different developmental stage of the parasite.

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