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Drug Resistance Against Antimalarial Drugs

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ABSTRACT

In this short communication, we have discussed about killer disease malaria and drug resistance caused by many popular drugs. Malaria is oldest and very important parasitic disease in mankind from ancient times. Millions of people are at high risk of this disease every year. This disease has become major cause of morbidity and mortality in this world because of emergence of resistance to first line drugs. Because of development of resistance of old drug molecules and therapies, WHO recommends combination therapies for the treatment of malaria. This short communication will highlight the reason of resistance along with new findings of molecules against resistance developed molecules in the market. Artemisinin combination therapies are first line treatment for all *Plasmodium falciparum* parasites in malaria endemic countries of the world according to WHO recommendations. Malaria eradication will become a battle in the world with urgent need of new drug molecule or therapy to combat against this disease leading to effective global malaria control programme.

Keywords: Malaria, Drug resistance, Artemether, ACT Artemisinin combination therapy.

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INTRODUCTION

Now days, the killer disease malaria continues to hunt millions of people in different terrains of the world. The "KING of DISEASES ", malaria is transmitted by mosquitoes and infects red blood cells [1]. The World Health Organization estimates that about 3.2 billion people - almost half of the world's population - are considered to be at risk of malaria. According to World Health Organization, In September 2015, there were an estimated 214 million cases of malaria and 438,000 malaria-linked deaths taken place [2]. Malaria is an endemic disease because multidrug resistance developed by *Plasmodium falciparum*. Malaria remains the leading cause of death with approximately 300 million clinical cases annually resulting in an estimated 2,300,000 deaths, primarily in children [3, 4]. In India, malaria is responsible for around 20 lakhs clinical cases and about 500 deaths in a year. In West Bengal alone, malaria is responsible for around 28,500 clinical cases in a year out of which 10% cases are of *Plasmodium falciparum* parasite [5]. Thus, it is a major public health problem in India. It is an infectious disease caused by a parasite of the genus *Plasmodium*. There are four species in the world which can cause malaria like *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Out of these four, *Plasmodium falciparum* is the dreaded one and is associated with high mortality [6]. Past records suggest malaria has infected humans since the beginning of mankind. The name "malaria" (meaning bad air in Italian) was first used in English in 1740 by H. Walpole. The term was shortened to "malaria" in the 20th century. C. Laveran in 1880 was the first to identify the parasites in human blood. R. Ross in 1889 discovered that mosquitoes transmit the malaria. His pioneering work on establishing the main features of the parasitic life cycle earned the Ross the Nobel Prize in medicine in 1902 [7]. The parasites are transmitted in humans by the bite of an infected female mosquito (*Anopheles*) [8]. The malaria parasites multiply extremely rapidly in the human liver. At certain point, they leave the liver and infect red blood cells (erythrocytes). *Plasmodium* replication takes place in the erythrocytes, the red blood cells burst and new red blood cells are infected by the parasites. Symptoms associated with malaria range from very mild ones to severe disease and even death. *P. falciparum* is the main cause of severe clinical malaria and death. Malaria begins as a flu-like illness 8-30 days after infection [9]. The disease can be categorized as uncomplicated or complicated (severe) malaria. Symptoms include fever (with or without other indications such as headache, muscular aches and weakness, vomiting, diarrhoea, coughing) [10]. Typical cycles of fever, shaking chills and drenching sweats may then develop. Destruction of the erythrocytes leads to severe anemia. Persons infected with *P. falciparum* are

at great risk of dying when severe malaria occurs. Severe malaria develops when *P. falciparum* infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. Especially cerebral malaria – which is caused by parasites blocking the blood vessels in the brain and leads to abnormal behavior, impairment of consciousness, seizures, coma or other neurological abnormalities often results in the death of the patient.

For decades, drug resistant has been major challenge in treatment of malaria. Drug resistance has been reported in three of the five Plasmodium species that is, P. falciparum, P. vivax and in P. malariae which are the mail causative agents for malaria in human being. First of all, WHO identified the drug resistance in 1967 i.e as the ability of a parasite strain to survive or reproduce regardless of the administration and absorption of a drug when it is given in doses that are equal to or higher than those usually recommended but within the tolerance range of the given subject It was later modified in this term of drug resistance by Bruce-Chwatt *et al* . to include ''the amount of the drug which is active against a given parasite must be able to gain access to the parasite or the infected erythrocyte for the length of the time necessary for its natural reaction''. Drug resistance usually leads to a delay or failure to clear asexual parasites from the peripheral blood that eventually enable production of gametocytes which are responsible for transmission of the resistant genotype. After the official recommendation by the WHO in 2001;resistance in vivo has been reported in all anti malarial drugs, except Artemisinin and its derivatives. Drug resistance necessitates the use of drugs which are more expensive and may have dangerous side effects.

MATERIALS AND METHOD

There are so many factors responsible for the drug resistance. Genetic mutations may be the main cause for drug resistance and are independent of drug effect. The onset of resistance occurs in two phases. In the first phase, an initial genetic event produces a resistant mutant (de novo mutation) in which a new genetic trait gives the parasite a survival advantage against the drug .In the second phase, the resistant parasites are then selected and start to multiply, which finally ends with a parasite population no longer being susceptible to treatment. In case of few drugs, there is involvement of single point mutation for cause of resistance however for various other drugs multiple site mutation is required. The acquired mutations allow the survival or reproduction of the resistant parasite whereas drug pressure will eliminate susceptible ones. Antimalarial drug resistance typically arises when there are spontaneous mutations that are selected by different concentrations of anti-malarial drug that impart deferential inhibition to

distinct genetic parasite types, i.e. the drug concentrations are sufficient to reduce the susceptible parasite population, but can either not inhibit multiplication or cause less inhibition of the mutants. Drug resistance to several antimalarials is sometimes either due to changes in drug accumulation or efflux mechanisms (chloroquine, amodiaquine, quinine, halofantrine, mefloquine resistance) or due to decreased affinity of the drug target which may result from point mutations in the respective genes that encode these targets (pyrimethamine, cycloguanil, sulphonamide, atovaquone, artemisinin resistance).

Artemisinin drugs are the first line treatment, and are used indiscriminately for self treatment of suspected uncomplicated malaria, so we can expect to see malaria forms resistant to Artemisinin soon according to WHO Drug resistant *P. falciparum* was first reported in Thailand in 1961. Various *P. falciparum* strains have now attained resistance to all commonly use and generally available antimalarial drugs. In man, the problem of the resistance to the common anti malarial drugs, such as chloroquine and the decreasing effectiveness of quinine is mainly limited to *P. falciparum* infection; chloroquine remains the treatment of choice for *P. Vivax* [11].

The development of resistance to front line drugs such as chloroquine and antifolates as well as decreased efficacy of mefloquine, even quinine in malaria endemic regions has led to introduction of traditional medicines and artemisinin derivatives as front line drugs. Alternative drugs, such as mefloquine and atovaquone - proguanil, are too expensive to be used to treat malaria in rural Africa. Furthermore, there are several reports that describe treatment failure of malaria because of the resistance of *P. falciparum* to the action of more expensive / newer drugs, such as the atovaquone-proguanil combination. It will most likely be only a matter of time before these drugs, too, become ineffective against *P. falciparum*. Although, Artemisinin, plant based drug molecule are particularly more active than any other anti malarial, reducing the number of parasites by approximately 10^4 per cycle, they need to be taken for seven days period in mono therapy for complete cure. The difficulty in adherence to this regimen as well as use of sub optimal doses would result in recrudescence and development of resistance and is major concern. This has led to Artemisinin derivative based combination therapies in a three day course regimen. Among several Artemisinin based combination, Curcumin combination therapy was found to be more effective and safe in preventing parasite recrudescence. Therefore, there will be an urgent need for affordable and effective treatment alternatives. Traditional medicines are widely used especially in areas of poverty or where there is no access to medical treatment. In the face of drug resistance, side effects and long therapy, researchers are turning to traditional medicines to provide a starting point for development of new drugs [12].

Artemisinin derivatives are available as mono-therapy but usually applied in combination with others also in clinical treatments of malaria. World Health Organization guidelines for the treatment of uncomplicated falciparum malaria recommend the use of this artemisinin-based combination therapy, and approved by Swiss medic in December 2008 and recently approved by the United States Food and Drug Administration. Zambia was the first African country to adopt artemether/lumefantrine (commonly called Coartem) as first-line therapy in national malaria treatment guidelines in 2002. Clinical records show that by 2008, the rates of in-patient malaria cases and deaths decreased by 61% and 66%, respectively, compared with the 2001-2002 reference period. In South Africa also the number of malaria-related outpatient cases and hospital admissions to each fall by 99% from 2001 to 2003, and malaria-related deaths decreased by 97% over the same period. The efficacy of the six-dose regimen of Coartem has been confirmed in many different patient populations around the world, consistently achieving 28-day polymerase chain reaction-corrected cure rates of >95% in the evaluable population, rapidly clearing parasitaemia and fever, and demonstrating a significant gametocidal effect, even in areas of widespread parasite resistance to other antimalarials. Coartem is much more effective than quinine, the classical antimalarial. Randomized clinical trial in Uganda shows cure rate of malaria as high as 96% in the Coartem-treated group compared with 64% for the quinine group. For Plasmodium vivax infection, combination with piperaquine is more effective than Coartem [11].

The idea behind the therapeutic effect of ACT is that the Artemether rapidly kills most of the Plasmodium parasites, and those that survive are subsequently killed by a high concentration of the companion drug. One of the main advantages of combination therapy is the likelihood that this strategy will reduce the chances of an infectious agent becoming resistant to the action of the drugs. In the case of malaria, combination therapy has been applied since around 1990. This strategy is being hampered because the *Plasmodium* parasite has developed resistance, as a result of monotherapy, to certain components of currently applied combination drugs. The efficacy and very short half-life (<6 hours) of the Artemisinin derivatives make it less likely that resistance develops. Results indicate significant differences between the pharmacokinetic parameters employed, particularly of artemether (2.1±0.03) as control with short elimination half-life and artemether – lumefartrine (2.3±0.01h-1) with longer elimination half-life. These significant variations might be attributed to the enhanced effect of the combined drugs possibly due to synergistic effect. The independent antimalarial activity of both lumefantrine and artemether is enhanced by their combination which has been shown to potentiate the blood schizontocidal

effects. It is also effective against drug-resistant strains of *P. falciparum* malaria. Comprehensive *in-vitro* studies using laboratory-maintained and fresh-field parasite isolates from different malaria endemic areas have shown marked synergy of the two components. Results of comparative clinical trials indicate that COMETHER™ also clears gametocytes more rapidly than non-artemisinin antimalarial [9, 11].

RESULTS AND DISCUSSION

The summarize of this discussion risk of recrudescence in accordance with WHO, Because it recommends the use of Artemisinin-based combination therapies (ACTs) in order to ensure high cure rates of *Plasmodium falciparum* malaria and the withdrawal of oral Artemisinin monotherapies from the market. The use of single-drug Artemisinin treatment – or monotherapy – hastens development of resistance by weakening but not killing the parasite. When used correctly in combination with other anti-malarial drugs in Artemisinin Combination Therapies (ACTs), Artemisinin is nearly 95% effective in curing malaria and the parasite is highly unlikely to become drug resistant. ACTs are currently the most effective medicine available to treat malaria. Additionally, to anticipate and prevent the onset and spread of drug resistance in the long term, WHO urges the global malaria research community and the pharmaceutical industry to rapidly invest in the design of the next generation of anti malarial drugs (WHO release,19th Jan, 2006). New products of ACTs are in pipeline shown in Table 1[13]. By creating ACTs with multiple-drug combinations and transmission blocking components, resistance can be prevented. "Our biggest concern right now is to treat patients with safe and effective medication and to avoid the emergence of drug resistance. "If we lose ACTs, we'll no longer have a cure for malaria," by WHO and it will probably be at least ten years before a new one can be discovered.

Table 1: All Available pipelines of Artemether based combination therapy

Active ingredients	Partnership	Product name
Artesunate mefloquine	Far Manguinhos, DNDi1	
Artesunate amodiaquine	Sanofi aventis, DNDi	Coarsucam
Artesunate pyronaridine	Shin Poong, MMV2	Pyramax
Artesunate ferroquine	Sanofi aventis	Ferroquine
Artemether lumefantrine	Novartis, MMV	Coartem
Dihydroartemisinin Piperaquine	Sigma au, MMV; Chongqing, Holley	Eurartesim, Artekin; Duocotexin
Artesunate sulfadoxine/ pyrimethamine		

CONCLUSION

The biggest concern all over the globe is to treat patients with safe and effective medications and to avoid the emergence of drug-resistant malaria parasites. However, the emergence of vector

resistance to widely used insecticides and parasite resistance to first-line drugs including artemisinin combination therapy has resulted in a rise in malaria incidence in many endemic areas, which has called for development of new therapeutic and technology approaches to combat the disease and impede drug resistance. More progress and better understanding in terms of scientific research and innovation is needed to develop these novel technologies as tools to reduce the occurrence and resistance in malaria.

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