Review Article

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Combinational Chemotherapy: A Proven Regimen for Treatment of *Plasmodium falciparum Malaria*

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Malaria is found to be a serious parasitic disease whose treatment involves varied number of drugs like Chloroquine, Pyremethamine and Mefloquine. However a number of resistance cases where found due to spontaneous mutations, reflecting the failure in malaria therapy. This has resulted in a high childhood and infant morbidity, mortality rate, increased social and economic costs. And so for effective treatment combinational therapy had proven to be superior means which involves a variety of combinations like Artemether-Lumefantrine, Mefloquine-Artemisinin which are highly effective and had overcome the problem of resistance due to mutations.

Key words: *Plasmodium falciparum Malaria*, Drug resistance, Mefloquine, Chloroquine, Combinational therapy.

INTRODUCTION

Malaria is acknowledged to be by far the most important tropical parasitic disease, causing great suffering and loss of life. More than two billion people, nearly 40% of the world's population are at risk. The treatment of malaria has to keep pace with the evolution of resistance acquired by malarial parasites. Plasmodium falciparum, which is responsible for causing severe forms of the disease, is also adept at developing resistance to drugs there by decreasing their efficacy in treatment over a period of time. Over the last generation, falciparum malaria has become widely resistant to a number of common antimalarial drugs [1,2].By drug resistance one mean when adequate blood concentrations of the drug are no longer able to kill a previously susceptible parasite. Drug resistance arises by the evolutionary selection of spontaneously arising mutants that are drug insensitive. When one kills all sensitive parasites, by definition the ones remaining are drug insensitive[3].

The basis of all malaria treatment is a sound diagnosis. Most febrile patients do not have malaria and most malaria patients in India do not have *P.falciparum* but *P.vivax*. Clinical diagnosis of malaria is usually incorrect and cannot be the basis of any rational treatment plan. This review of treatment of *falciparum malaria* will make no sense what so ever unless one proceeds from a solid diagnosis obtained by a blood film examined Microscopically by a trained observer which may some times be replaced by a rapid chromatographic blood test strip for malaria antigen[4,5].

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Anti-Malarial Drug Resistance and Consequences

Increasing resistance of P.falciparum malaria to anti malarial drugs is posing a major threat to the global world. This situation is worsening, with the geographic spread of resistance widening to previously unaffected areas and a remorselers increase both in prevalence and degree of drug resistance.

The cure of disease caused by malaria and its consequences has been documented in terms of childhood mortality[6], Anemia[7], Maternal and Infant morbidity and mortality[8] , neurologic disability[9,10] economic and social costs.[11,12,13] Further, the overall transmission of malaria increases. Studies have shown that patients who remain parasitaemic produce more gametocytes than those who are cured. [14]. And also certain drugs such as sulfadoxime-pyrimethamine (SP) increase production of gametocytes.

The economic impact of the disease increases, not only because more patients need treatment but also because more absent from work, school and more die as a result of infection. For example, in India the economic loss to malaria

was estimated to be between 0.5 and 1 billion USD a year [15].

Anti malarial drug, resistance may present as a treatment failure in an Individual patient, but more commonly, it makes its presence known by increasing the apparent number of malarial infections[16]. Individuals appear to be getting multiple infections, when in reality they have a single infection that is suppressed by inadequate treatment followed by a parasite recrudescence. At a community level this is demonstrated by increasing malaria rates, appearance of malaria in previously well- controlled areas and malaria epidemics in marginal transmission zones.[17, 18,19,20,21].

Reasons for Drug Resistance

Not all treatment failures represent drug resistance, critical questions to be asked when confronted by a falciparum malaria patient who has failed chemotherapy include whether the drug is genuine or expired, was the drug in the correct dosage actually taken by the patient and whether the administered drug was absorbed from gastrointestinal tract . Unfortunately, counter fit anti malarial drugs are common in Asia and those participating in this form of " pharmacological manslaughter" often produce very convincing fakes that closely resemble the real article excepting they include no active drug [22] . Many anti malarial drugs are not highly bio-available which is particularly of concern when a sick patient is poorly tolerant of any oral intake [23]. The important reason for the drug resistance is through spontaneous genetic mutation shown by *P. falciparum* parasites. The mutations are not induced by drugs themselves and for most drugs, the precise site of each mutation is not known. This is because the mode of action of most antimalarials is largely known or poorly understood. However, for certain drugs such as SP, the mutations that confer resistance to the parasite have been characterized. A series of mutations in DHFR encoding gene will enable the parasite to survive the action of pyrimethamine. Successive mutations in DHPS gene (on chromosome 8) will in turn confer resistance to the sulfadoxine component [24]. For drugs such as chloroquine (cq), mefloquine and other quinolines (halofantrine, quinine), the mechanism of resistance is probably multigenic. The gene encoding for the protein pfCRT (chromosome 7) has been associated with resistance to chloroquine[25], while mutations and number of copies of the gene encoding for pfmdr1 seem to be implicated in the resistance to mefloquine [26]. Because these mutations are spontaneous (and not induced), they are more likely to occur when there are large numbers of individual parasites (large parasite bio mass) as during the acute phase of the disease. This is when the selection of resistant mutants occurs: the denovo selection. [27]

Finally, these mutations allowing the parasite to resist the action of the drug will be transmitted to other hosts by the gametocytes. The level of transmission, vector capacity, in-vector recombination of genes, and multiplicity of clones per infection, are all-important factors that will influence the speed at which resistance will emerge and spread.

Drugs of Choice

There are many a drug used for treatment of the falciparum malaria from past several decades. Each of them having their own specificity and action but none of them proved to be the best. Here are some brief description of drugs and there statistics.

A) Chloroquine (Cq)

Introduced in the 1940's proven to be early drug for treatment of all kinds of malaria. For nearly a generation after its introduction, chloroquine successfully cured both *falciparum* and *vivax* malaria, greatly simplifying any malaria drug decision [19,28,29] but today resistance to drug occurs wherever *falciparum* occurs. The resistance was first detected almost simultaneously in Colombia and Thailand in 1961. And the evidence of resistance is increased mortality. When patients are treated with ineffective drugs such as cq, some deteriorate and succumb to the

increasing parasites biomass, as been shown in a recent trial conducted in India[30]. Africa has seen a very significant Increase in malaria mortality with the spread of resistance to cq[31].

B) Anti- Folate Drugs:- Pyrimethamine And Sulfadoxine (SP)

Owning to the chloroquine resistance the use of anti – folate drugs became most prominent in different areas of the world. They produce their action by blocking parasites synthesis of tetrahydrofolate thus stopping nucleic acid synthesis. Sequential blockages of the synthesis pathway using both dihydrofolate reductase by pyrimethamine and dihydropteroate synthatase by sulfadoxine can often produce a cure. [32, 33,34,35].

Unfortunately, falciparum parasites are able to quickly accumulate multiple genetic mutations producing enzymes resistance to such drugs. In Thailand during 1970's, SP failed as the primary therapy in a very short period of times once it was in general use[16]. The same resistance genes have rapidly spread across Asia and to Africa such that treatment in a single administration of Sulfadoxine or Pyrimethamine often fails to cure uncomplicated falciparum infections [35,36,37]. One more evidence is on the south-African Mozambique border malaria control was rapidly been lost in the phase of wide spread SP resistance[38,36].

C) Mefloquine [mq]

It is a potent, long acting blood – schizontocide, which may have some sporonticidal activity [39].Its mechanism of action has not been clearly defined. The postulated mechanisms includes formation of drug-heme complex that is toxic to parasite and change in pH of parasite food vacuoles making digestion of hemoglobin difficult. It is proved to be effective in treatment of cq-sensitive and cq-resistant as well as SP-resistant and even quinine resistant falciparum parasites. However, reports of mefloquine failure have started emerging [39,40,41,42]. In retrospect, it is possible to see that mefloquine resistant parasites pre-existed the introduction of mefloquine[43]. In practical terms this meant that wide spread use of mq – allowed the selection of multiple drug- resistant falciparum parasites[16,44]. And therefore, all these drugs are of incomplete use in treatment of *P.falciparum malaria*.

New Strategies to Prevent Spread of resistance: Combinational Chemotherapy

The widespread resistance of *P.falciparum* to cq in India precludes the use of this drug in treatment of severe malaria[45]. SP and mq cannot be used as primary drugs for management of severe malaria as they are oral drugs. (Therapy in severe malaria should always be parentral due to in ability to take oral medication and the uncertain bioavailability of oral medication)[46,47]. Additionally resistance to these drugs in India is rising (SP-North eastern states, west Bengal, Andhra Pradesh; mq – Mumbai, surat) [48]. Therefore, the essential choice is to have a combinational therapy, of artemisinin derivatives, with other drugs.

By this combinational therapy, we can over come multiple – drug resistance that occurs when a parasite that already is resistant to one class of anti – malarials develops resistance to another separate class of drugs.

Combinational chemotherapy in malaria is typically found when a rapidly acting drug (artemisinin) is combined with a slower acting drug (mefloquine etc;) given over enough time (atleast four parasites generations which is about eight days) to kill any residual parasites[2]. When two effective drugs are used, the probability of selecting a mutant parasite with resistance to both drugs is very unlikely. Currently available combinations which have been proven affective in field trials include quinine – tetracycline, chlorproguanil – dapsone, artemether-

lumefantrine and previously mentioned atovaquone- proguanil [49,50,51,52].

Looareesuwan et al[53] have reported better response rates with mefloquine – qinghaosu (Artemisinin) combination than with mefloquine alone. The choice of artemisinin and its partner drug have led to several ACT's (Artemisinin-based combination therapies) being evaluated. Artemether – lumefantrine is a co-formulated ACT that is highly efficacious and many countries in Africa now use this combination. Artesunate – mefloquine was recently introduced in Burma as first – line treatment and DHA – piperaquine showed similar efficacy to Artesunate – mefloquine although the later was less effective in preventing gametocytemia[54]. The drug Artemisinins act rapidly, safe, well tolerated, have a high intrinsic effectiveness, reduce gametocyte carriage and thus a good transmission blocking agents. Thus, it became a wide range of choice.

It is sometime suggested that the efficacy and tolerability of new drugs should be assessed in each and every area before deployment. This is unrealistic and unnecessary for ACT.

These regimens (mefloquine – artesunate, coartem®, artekin®) have been shown to be effective against the most resistant parasites in the world, so they should be effective everywhere. The safety of Artesunates alone or in combination has been assessed in more patients than with any other anti malarial agent.

CONCLUSION

Drug- resistant malaria remains the greatest challenge to any malaria – control program. The focus of management today relies on the use of combinations rather then mono therapy. Since the parasites have to mutate at several sites for it to become resistant to the combination, this prolongs life of the drugs used.

The development of individual drugs such as Isoquine and Aminoquinoline with an improved safety profile, DB289 an aromatic diamide and OZ 277 a synthetic artemisinin derivative hold the promise that new drugs and their combinations will become widely available in the next few years[55].

The time for change has come. It is essential to stop treating malaria cases with in affective drugs and break the vicious circle of resistance. Otherwise, we will lose the last drugs that we have and will be confronted in Asia, as in Africa, with a malaria disaster [56].

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