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Mini Review

Prospects of Control of Malaria

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Malaria, a tropical disease caused by protozoa of genus Plasmodium is really a concern for centuries. More than 40% of world's population are suffering from Malaria.[1] It is one of the leading cause of morbidity and mortality in the tropics. There are 300-500 million cases of Malaria occurring each year, of which 500 million attacks are of acute illness, 50,000 cases of neurological damage, 400,000 episodes of severe Anaemia in Pregnancy, and 300,000 are low birth weight babies. Around 800,000 children under five years of age die each year of Malaria.[2] It has been estimated to represent 2.3% of the global disease burden and 9% being in Africa. It is especially important in pregnant women and children under the age of five years.[3] In Bangladesh, Malaria is hyper-endemic in Chittagong Hill Tracts and has been proven to be an insurmountable and inpenetrable bastion of *Plasmodium falciparum*.[4]

The morbidty and mortality are increasing, not because of ineffective treatment of severe Malaria, but because of ineffective first-line oral treatment. In addition, transmission of resistant strains is facilitated by events of unsuccessful treatments.[5] Absence of adequate health services frequently results in a re-course to self-administration of drugs, often with incomplete or improper treatment. This was found as a major factor in the increase in resistance of parasites to previously sensitive drugs.[6]

Definitive diagnosis is made by the demonstration of the parasites in thin and thick peripheral blood films. The serological tests are of value in epidemiological surveys and screening potential blood donors. The standard one is the Indirect Fluorescent Antibody (IFA) test using species-specific antigens. The Enzyme Linked Immunosorbent Assay (ELISA) is done for *P. falciparum*. Falciparum malaria can be diagnosed by non-microscopic methods e.g., Parasight F and ICT (immunochromatographic test) malaria Pf tests as well.[7]

Chloroquine is the drug of choice in an acute attack of Malaria. However, in Chloroquine-resistant areas, patients are treated with Quinine sulphate or Quinine hydrochloride followed by the Wulfadoxine and Pyrimethamine combination or Tetracycline or Mefloquine. Amodiaquine and Quinidine are alternative drugs in cases where patient can not tolerate Quinine. In cases of potentially dangerous complications e.g., Cerebral Malaria, immediate intravenous administration of Quinine or Chloroquine is indicated. Primaquine is also given to achieve radical cure of vivax and ovale Malaria.[8]

New antimalarial drugs

As there is an alarming situation of spread of multidrug resistance, new antimalarials to control Malaria are absolutely needed. Artemisinin is a new drug developed by the Chinese scientists from a plant called 'Qinghaosu' (*Artemisia annua*). It is effective in all strains of Plasmodium including multidrug-resistant Malaria. But it showed some toxicities in experimental animal models.[3] Several derivatives of Artemisinin have been developed for clinical use such as Artesunate, Artemether and Arteether. Artesunate as suppositories for severe cerebral Malaria and Artemether and Arteether for parenteral treatment.[9] Artemether is effective as parenteral Quinine and is a practical alternative.[10] Presently,

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WHO recommends that Artemether should not be used as a first line treatment in Africa, in order to delay the development of resistance to this valuable class of antimalarial compound. Treatment with Artemether was associated with a significantly lower mortality rate than treatment with Quinine in Vietnamese adults with severe falciparum Malaria.[11] Artemisinin compounds act rapidly, stop parasite development and prevent subsequent cytoadherence.[12] Both cytoadherence and rosetting are thought to be important pathophysiological mechanisms involved in severe Malaria. Artemisinin and related compounds are preferable to Quinine because of safety, speed of effects and ease of administration.[9]

A phase I clinical trial of Arteether for intramuscular injection showed the injection to be well tolerated. Subsequently, phase II studies in adult, non-severe, multidrug-resistant falciparum Malaria patients in Thailand were also completed and showed the drug to be well tolerated. The phase III clinical trial has started with 200 severe falciparum Malaria patients in Africa and Asia.[3]

Pyronaridine, another antimalarial drug, is highly effective in Chloroquine-resistant *P. falciparum* and *P. vivax.* It is less toxic than Chloroquine but very expensive. In one study in Africa, the cure rate of Chloroquine was 44% whereas the cure rate for Pyronaridine was 100%. So, with the increasing inefficacy of Chloroquine, emergence of Pyrimethamine-resistance of *P. falciparum* in Cameroon and elsewhere, doubts about the safety of Amodiaquine and *in vivo* cross-resistance in Asia, Pyronaridine may be a cost-effective alternative in future.[13]

The combination of Chlorproguanil/ Dapsone led to a phase II pilot study in Kenya by Tropical Disease Research (TDR). This study indicated that 3-day treatment with the combination may be an alternative to treatment with Sulphadoxine/ Pyrimethamine.[3] It has been postulated that if drug resistance in falciparum Malaria continues to increase at the current rate, Malaria may become untreatable in parts of Southeast Asia by the beginning of next millennium.[14]

The drawback of Artemisinin derivatives is short half-life (3-5 hours). So, when used as monotherapy, a treatment as long as 5 days is required for complete elimination of parasites. They are then preferentially used in combination with other antimalarial agents such as Sulphadoxine-Pyremethamine[15] or Mefloquine[16,17] to increase cure rates and to shorten the duration of therapy in order to minimize the emergence of resistant parasites.[18]

However, the relatively high cost and erratic supply of natural parent compound, Artemisinin enhances necessity for the development of new synthetic and cheaper endoperoxide based antimalarials, e.g., Trioxalones. RBX-11160 or OZ-277, as an alternative to natural product drug Artemisinin, appears to be a positive step in the direction towards cost-effective combat route against Malaria.[14] It has been tested *in vitro* on laboratory strains (Chloroquine-sensitive and Chloroquine-resistant strains) of *P. falciparum*: all IC_{50} values obtained were below 30nM, without any significant difference between resistant and sensitive strains.[19]

Malaria vaccines

The development of an effective vaccine represents one of the most important approaches to provide a cost-effective intervention for Malaria control. Several vaccine candidate antigens and their genes have been identified and some vaccines have progressed to clinical trials.[20] There are three main types of vaccines: (i) asexual blood stage vaccines; (ii) transmission blocking (gametocyte) vaccines; and (iii) pre-erythrocytic vaccines. Merozoite surface protein-1 (MSP-1) and Spf 66 were the leading candidate antigens and have undergone clinical trial.[3] Several other vaccine candidates, including erythrocyte binding antigen- 175 (EBA-175), serine repeat antigen (SERA), apical merozoite antigen-1 (AMA-1) are in the stages of preclinical development.[3]

Spf 66, a multi-component synthetic peptide with amino acid sequences derived from three *P. falciparum* asexual erythrocytic stage proteins. This vaccine has undergone extensive trial and was found to be safe and immunogenic.[21, 22] In Tanzania, it showed protective efficacy in 31% in children aged 1-5 years.[23] However, results from a study in the Gambia failed to demonstrate protection against Malaria in infants of 6-11 months of age.[24] The results from a recent study in children of 2-15 years old in Thailand indicated no protection.[25] One further trial, among infants in Tanzania is in progress.[20] Inspite of mixed results, the field trials conducted till now with Spf 66 have had an impact on thinking and the

design of vaccine trials in naturally exposed population.[3]

NYVAC- Pf 7, an engineered, attenuated Vaccinia virus, multi-stage, multi-component *P. falciparum* vaccine which includes a transmission-blocking-vaccine candidate Pfs-25 together with six additional leading candidate antigens. The phase I/II safety, immunogenicity and efficacy of this vaccine was studied in 1995.[3] If these engineered vaccines become successful, it would provide a particularly cost-effective means to deliver multi-antigens in one vaccine to elicit both humoral and cellular immune responses.

The Pfs-25 is one of the most promising *P. falciparum* transmission-blocking vaccine candidates under development by TDR. A phase I trial showed that it is safe.[3] In addition a second phase trial was done in the USA designed to test the 'prime boost concept' whereby the volunteers, who were vaccinated with NYVAC- Pf 7, are boosted with one dose of recombinant Pfs-25. Several other candidates including Pfs-28, Pfs-230 and Pfs-48/45 are also under investigation by the TDR.[3]

One promising vaccine candidate RTS-S, consists of sporozoite-coated proteins expressed in Hepatitis B surface coat, is currently underway with the TDR for field-trial in Gambia. The pre-erythrocytic vaccines are combined with the basic vaccine to form a multi-component vaccine.[3]

DNA vaccine: In addition to these conventional polypeptide vaccines, advances in DNA vaccines are also being applied to Malaria. It is easier to synthesise, manipulate and store DNA than peptides, making DNA vaccines an attractive option for future vaccine studies.[26]

In future, it may be possible to genetically engineer mosquitoes to make them resistant to Malaria parasites or unable to transmit it.[26]

Due to advances in molecular biology techniques, it will be easy to make early diagnosis of Malaria based on DNA probes and monoclonal antibodies and thereby treatment can be initiated promptly.[27]

There is much hope that newer drugs, vaccine(s) and future achievements of research in mosquito genetics, biochemistry and especially molecular biology will eventually be able to produce new weapons against Malaria. However, this success cannot be achieved by new technical tools alone. The proper use of tools will depend on the individual national ability of the third world countries to relieve the poverty of the large population.

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