A new antimalarial candidate

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‘Mother Nature gave us the cinchona alkaloids and qinghaosu. World War II led to the introduction of chloroquine, chloroguanide (proguanil), and eventually amodiaquine and pyrimethamine. The war in Vietnam brought mefloquine and halofantrine. These drugs are all we have available now to treat malaria. It is difficult to see where the next generation of antimalarial drugs will come from... there is little pharmaceutical industry interest in developing new antimalarial drugs; the risks are great, but the returns on investment are low... If drug resistance in P. falciparum continues to increase at the current rate, malaria may become untreatable in parts of Southeast Asia by the beginning of the next millennium.’

—N. J. White


Eradication of malaria has been a difficult task and there have been various socio-economic/political as well as biochemical reasons for this. Research in this area, whether on the genome sequencing of the protein of the parasite, finding new medicines, or developing vaccine has been met with difficulties due to variations in the parasite depending on the endemic region and drug resistance. A report in the recent issue of Nature describing the synthesis and activity of a new drug, RBX-11160 or OZ-277, an alternative to the natural product drug artemisinin, appears to be a positive step in the direction towards cost-effective combat route against malaria. Here I provide some information about malaria and the efforts which have gone in developing the new drug.

Malaria has been known since ancient times. It was centuries before the true causes of the symptoms of malaria were understood. Previously, it was thought that ‘miasma’ (bad air or gas from swamps – ‘mal air ia’) caused the disease. Surprisingly, in view of this, some ancient treatments were remarkably effective. Details of this disease can be found even in the ancient Indian medical literature like the Charaka Samhita. An infusion of qinghao (Artemisia annua) has been used for at least the last 2000 years in China, although its active ingredient (artemisinin) has only recently been scientifically identified. Before the 15th century, the antifebrile properties of the bitter bark of Cinchona ledgeriana were known in Peru. Quinine, the active ingredient of this potion was first isolated in 1820 by the pharmacists. Although people were unaware of the origin of malaria and the mode of its transmission, protective measures against the mosquito have been used for many hundreds of years. The inhabitants of swampy regions in Egypt were recorded as sleeping in tower-like structures out of the reach of mosquitoes, whereas others slept under nets as early as 450 BC. An earlier examination of a 5th century cemetery on the outskirts of Rome (Lungano, Umbria) containing bodies of babies and foetuses which have been buried together, reports that the bones of the oldest infant showed the presence of DNA of malaria parasite. This is the earliest malaria DNA ever to be identified.

The distribution of malaria varies greatly from country to country and within the countries themselves. In 1990, 75% of all recorded cases outside of Africa was concentrated in nine countries, namely India, Brazil, Afghanistan, Sri Lanka, Thailand, Indonesia, Vietnam, Cambodia and China. Systematic control of malaria started after the discovery of the malaria parasite by Laveran in 1889 (Nobel Prize for Medicine in 1907), and the demonstration by Ross in 1897 that the mosquito was the vector of malaria. These discoveries quickly led to control strategies and with the invention of DDT (p,p’-dichlorodiphenyltrichloroethane) during World War II and the notion of global eradication of the disease. Effective and inexpensive drugs of the chloroquine group were also synthesized around this time.

Malaria is caused by protozoan parasites of the genus Plasmodium, which breed in water. Four species of Plasmodium can produce the disease in its various forms, viz. Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae. Amongst the four, P. falciparum untreated can lead to fatal cerebral malaria. Malaria parasites are transmitted from one person to another by the female anopheline mosquitoes. The parasites are developed in the gut of the mosquito and are transmitted each time it takes blood from a human being. The male mosquitoes do not transmit the disease, as they feed only on plant juices. There are about 380 species of anopheline mosquitoes, but only 60 or so are known to transmit the parasite.

The infection is set with a mosquito bite and the sporozoites are then carried by the blood to the liver where they invade the cells and multiply asexually. After 9–16 days, the merozoites emerge from the liver and infect the red blood cells. The infection gets further transmitted via gametocytes back to the mosquitoes when the next mosquito bites and the whole cycle follows. The merozoites also get attached to the endothelium of the blood vessels, where they multiply again, progressively breaking down the red cells. This induces bouts of fever and anaemia in the infected individual. In cerebral malaria, the infected red cells obstruct the blood vessels in the brain. Other vital organs can also be damaged, often leading to the death of the patient. In the same manner, they get attached to the placenta and get transferred to the foetus and hence, in pregnant women, the disease is responsible for a substantial number of miscarriages and low-birthweight babies.

The hope of global eradication of malaria was almost abandoned in 1969, when it was recognized that this was unlikely ever to be achieved. Ongoing control programmes remain essential in endemic areas. Malaria is currently endemic in as many as 91 countries, with small pockets of transmission occurring in further eight countries. P. falciparum is the predominant parasite. More than 120 million clinical cases and over 1 million deaths occur in the world each year (in the whole world more than 1 million deaths, up to 500 million attacks of acute illness, up to 50,000 cases of neurological damage, up to 400,000 episodes of severe anaemia in pregnancy, and up to 300,000 low birth weight babies). Eighty per cent of the cases occur in sub-Saharan Africa, where malaria accounts for 10 to 30% of
all hospital admissions and is responsible for 15 to 25% of all deaths of children under the age of five. Around 800,000 children under the age of five die from malaria every year, making this disease one of the major causes of infant and juvenile mortality.

Malaria thus has social consequences and is a heavy burden on economic development. It is estimated that a single bout of malaria costs a sum equivalent to over 10 working days in Africa. The cost of treatment is between $US 0.08 and 5.30, according to the type of drugs prescribed as determined by local drug resistance. In 1987, the total ‘cost’ of malaria—health care, treatment, lost production, etc. was estimated to be $US 800 million for tropical Africa alone, and this figure is currently estimated to be more than $US 1800 million.

The significance of malaria as a health problem is increasing in many parts of the world. Epidemics are even occurring around traditionally endemic zones and in areas where transmission had been eliminated. These outbreaks are generally associated with deteriorating social and economic conditions, and the main victims are the underprivileged rural populations. Demographic, economic and political pressures compel entire populations (seasonal workers, nomadic tribes and farmers migrating to newly-developed urban areas or new agricultural and economic developments) to leave malaria-free areas and move into endemic zones. People who are non-immune are at high risk of severe disease. Unfortunately, these population movements and the intensive urbanization are not always accompanied by adequate development of sanitation and health care. In many areas, conflict, economic crises and administrative disorganization can result in the disruption of health services. The absence of adequate health services frequently results in a recourse to self-administration of drugs, often with incomplete treatment. This is a major factor in the increase in resistance of the parasites to previously effective drugs.

Malaria is complex, but it is a curable and preventable disease. Lives can be saved if the disease is detected early and treated adequately. It is known what action is necessary to prevent the disease and to avoid or contain epidemics and other critical situations. The technology to prevent, monitor, diagnose and treat malaria exists. It needs to be adapted to local conditions and applied through local and national malaria control programmes.

The antimalarial drugs can be classified according to their chemical structures (Table 1).

The traditional antimalarial drugs can also be classified according to their activity in the human body and their effectiveness/ineffectiveness.

Tissue schizonticides for causal prophylaxis: These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of infection can be theoretically prevented. Pyrimethamine and primaquine have this activity. However, since it is impossible to predict the infection before clinical symptoms begin, this mode of therapy is more theoretical than practical.

Tissue schizonticides for preventing relapse: These drugs act on the hypnozoites of P. vivax and P. ovale in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.

Blood schizonticides: These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in antimalarial chemotherapy. They include chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulphadoxine, sulphones, tetracyclines, etc.

Gametocytocides: These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of infection to the mosquito. Chloroquine and quinine have gametocytocidal activity against P. vivax and P. malariae, but not against P. falciparum. Primaquine has gametocytocidal activity against all plasmodia, including P. falciparum.

Sporontocides: These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action.

In many instances, there have been reports that the malaria parasite is becoming resistant to drugs such as chloroquine, which has been the staple of malaria treatment since the 1960s. More recently, the most effectively used drugs have been based on artemisinin (the traditional Chinese remedy). This is a molecule which contains a pharmacophoric peroxide bond in a unique 1,2,4-trioxane heterocycle (Figure 1). Available evidences suggest that artemisinin and related peroxide antimalarial drugs exert parasitidal activity subsequent to reductive activation by heme released as a result of haemoglobin digestion by the malaria-causing parasites. Unfortunately, artemisinin family of drugs suffer from (a) chemical (e.g. semisynthetic availability, purity and cost), (b) biopharmaceutical (e.g. poor bioavailability and limiting pharmacokinetics), and (c) treatment (e.g. non-compliance with long treatment) issues, and hence have not been available for malaria treatment on a larger scale.

The recent discovery in the area of antimalarial drugs deals with the synthesis of RBX-11160 or OZ-277, which has been developed by the Indian pharmaceutical company Ranbaxy in a multinational project venture. This synthetic drug is somewhat structurally related to the natural product artemisinin, as the derivatives of the latter are the most potent drugs that are available which kill the drug-resistant P. falciparum parasite rapidly in

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<th>Table 1. Classification of antimalarial drugs according to chemical structure</th>
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<td>Aryl amino alcohols</td>
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<td>4-aminoquinolines</td>
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<td>Folate synthesis inhibitors</td>
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<td>8-aminoquinolines</td>
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<td>Antimicrobials</td>
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<td>Naphthoquinones</td>
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all stages. As the extraction of the natural product artemisinin is expensive, a synthetic analogue of it was termed as a target. The endoperoxide bridge in artemisinin was considered as the major cause of its antimalarial activity, and hence the major challenge was to synthesize molecules containing this linkage. Unfortunately, until now, problems related to either the stereoselectivity or the scaling up of the synthesis of the target molecules have not been successfully addressed. Also, keeping high antimalarial activity of such molecules changed with the stereoselectivity and also substrate specifically.

In a recent study by Vennerstrom et al., it was found that the trioxolanes, which are produced by exposure of alkenes to ozone, would be the ideal starting point for a new generation of antimalarial drugs. In view of stabilizing metabolically these five-membered, unstable, heterocyclic rings, the substituents needed to be tethered are bulky (e.g. adamantain moiety). To make it suitable for therapeutic use, this bulky organic molecule also needs to be made water-soluble by adjusting the substituents. All these points have been taken care during the synthesis of the drug RBX-11160 or OZ-277 (Figure 1). Since this drug contains the same active group as in artemisinin, the proposed mechanism of the drug is essentially the same (Figure 1). The endoperoxide generates free radicals in the parasite by interacting with the ferrous ions of the heme, which react with the proteins of the parasite thus subsequently killing the parasite. This happens to the parasite during all stages of the life cycle. The presence of carbon-centred free radicals during the action of the drug similar to its counterpart artemisinin was proven by the researchers by spin-trapping technique used to monitor free radicals.

The Ranbaxy Chief Executive Officer, Brian Tempest in a recently released company statement said, ‘Our scientists are excited to be able to work on a drug that could save millions of lives’. This drug, as of now, has entered clinical trials in the UK. If the new drug is as cheap as claimed by the inventors, then it would be a cost-effective and pragmatic substitute to artemisinin combination therapy, which costs presently about US$ 2 per dose, an amount beyond the reach of many sufferers in poor countries.

In all situations, control programmes should be based on four objectives: (i) the provision of early diagnosis and prompt treatment to all people at risk; (ii) selective application of sustainable preventive measures, including vector control adapted to local situations; (iii) an immediate, vigorous and wide-scale response to epidemics, and (iv) the development of reliable information on infection risk, living conditions of concerned populations, and vectors.

There are many successful vaccines against viruses and bacteria. But there are no vaccines for human parasites due to their complexity. First, they have much larger genomes coding for more proteins. Secondly, they have multistage life cycles expressing different proteins at different times. In such cases, recombinant protein vaccine would be required. Finally, the most effective vaccine would need to induce response in both antibody and T-cells. Thus, in short, the vaccine may have to be directed against multiple proteins at different stages of the life cycle at the same time. And such a vaccine would be more beneficial to the residents than the tourists in disease-endemic area. We only hope that the discovery of such vaccines will become a reality soon and the eradication of malaria will be possible.


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