Malaria- hope on the horizon

Gogtay NJ

Department of Clinical Pharmacology Seth G. S. Medical College and K. E. M. Hospital, Parel, Mumbai - 400012, India.

Correspondence:
Nithya Gogtay, MD
E-mail:
nithyagogtay@gsmc.edu

Malaria is a major international public health problem, and the disease affects more than 500 million people and causes 2-3 million deaths each year. Despite its already enormous toll of suffering, deaths due to malaria are increasing as a consequence of drug resistance.[1] The global resurgence of malaria can be attributed to a variety of factors- insecticide resistance in the Anopheles mosquito, resistance of *Plasmodium falciparum* to affordable first line anti malarials, deterioration of national control programs and increased movement of populations secondary to increase in international travel and tourism. South-east Asia as a region has been particularly hard hit by the development of parasites initially resistant to chloroquine, then to sulfadoxine-pyrimethamine, then to mefloquine and to a certain extent quinine.[2] The Roll Back Malaria (RBM) campaign launched in 1998, with the stated goal to halve malaria deaths worldwide by 2010 is being confounded by the problem of drug resistance.[3] However, despite the grim scenario, there is reason to be optimistic.

Considerable impetus to the management of malaria today has been given by the artemisinin (qinghaosu) derivatives first isolated in 1971 by Chinese chemists. These drugs have a rapid onset of action, and resistance of *Plasmodium falciparum* to these compounds has not yet been reported.[4] An additional advantage is their ability to reduce gametocyte carriage and therefore infectivity. The International Artemisinin study group in a recent meta-analysis studied individual patients' data (N=5948) from 16 randomized trials of acute, uncomplicated *Plasmodium falciparum* malaria where artesunate had been added to the standard treatment. They showed that the addition of 3 days of artesunate substantially reduced treatment failure, recrudescence and gametocyte carriage without an increase in serious adverse events.[5] The rationale for treating malaria with combination therapy is the same as for diseases such as AIDS, and tuberculosis where patients given two or more robust and highly effective drugs are less likely to encounter drug resistance and fail treatment which brings both clinical and public health benefits. The advantages of the artemisinin combination treatments (ACT) makes it likely that many countries will now look at ACT as a viable treatment option.

A parasite of perhaps equal importance is *Plasmodium vivax*, the causative agent of benign tertian malaria. *Plasmodium vivax* has the widest global distribution and is responsible for more than 50% of malaria cases in Central and South America, Asia and the Indian subcontinent.[6] However, research into the biology and management of *P vivax* has been limited perhaps due to greater emphasis on *Plasmodium falciparum* and also in part due to the lack of a continuous in vitro culture system for the parasite. The clinical management of vivax malaria today has assumed greater importance for two reasons- the emergence of chloroquine resistant *Plasmodium vivax* and the declining efficacy of primaquine as an anti-relapse agent.[7-10] Although the incidence of both remains low, the number of anti-relapse drugs for vivax is limited. Of the 8-aminoquinolines, primaquine is likely to remain an important anti-relapse drug for sometime, but other drugs in this class such as tafenoquine and bulaquine hold promise as potential anti-relapse therapies.[11,12]

Although challenges for the effective control and treatment of malaria are great, so are the current opportunities. Our understanding of the biology of the malarial parasite is growing at a rapid pace. A landmark in the fight against malaria was passed recently with the publication of the complete genome sequence of *Plasmodium falciparum* in combination with that of the malaria vector Anopheles gambiae.[13,14] Analysis of the genome sequence data of the malarial parasite led to the identification of the DOXP (1-deoxy-xylulose 5 phosphate) pathway, a pathway present in bacteria and plants but not in humans. A drug targeting the pathway fosmidomycin originally developed for the treatment for urinary tract infections has shown cure rates of 88-89% in falciparum malaria after 4-5 days of treatment.[15,16] A project to sequence the complete genome of *P vivax* is in progress and is expected to be completed shortly. It is hoped that the vivax genome sequence will prove to be as valuable as the *Plasmodium falciparum* genome sequence.[17] Considerable advances have also been made in vaccine technology and immunology. The rate of clinical assessment of candidate malaria vaccines is increasing; in the past 5 years, the number of groups doing such research has increased from three to 11. Worldwide, funding for malaria vaccines has increased recently from USD 50 million to around USD 60-70 million.[18] However, much remains to be accomplished. While the ACT is attractive, additional research into their comparisons with other combinations, cost-effectiveness and the issue of safety in pregnancy still need to be addressed. Traditionally, implementation of national malaria policies is done by public health departments.[2] However, it is important to remember that provi-

sion of malaria care by private practitioners can be vastly different and their involvement in policy making is crucial. Finally, for a disease where millions of lives are at stake each year, the value of working in partnership at all levels, cannot be overemphasized.

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