FIRST-EVER DRUG COMPOUND DEVELOPED ON AFRICAN SOIL, AN ANTIMALARIAL, TO MOVE TO HUMAN TRIALS

Researchers at MIM also presented new insights into preventing artemisinin resistance in Africa, squelching resistance in Southeast Asia and extending the life of ACTs

DURBAN, SOUTH AFRICA (8 OCTOBER 2013) — A promising next-generation drug has been approved to move to Phase I human trials in 2014. The development was announced by researchers today at a major conference on malaria that also presented efforts to stop growing resistance by malaria parasites to artemisinin in Southeast Asia and to keep artemisinin combination therapies effective for as long as possible. Other researchers in West Africa reported on work to test the safety of multiple administration of a new ACT, Pyramax (pyranoridine-artesunate), which was recently approved by the European Medicines Agency.

These new findings were among many announced at the Sixth Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference—the world's largest gathering of malaria experts—taking place in Durban, South Africa, 6-11 October 2013. At the conference, researchers also reported on research using mobile phone text messages to increase compliance with malaria drug dosing and preliminary research on counterfeit drugs in six countries in Africa and Asia.

The next-generation antimalarial compound, MMV390048, underwent a year of preclinical development after discovery in 2012 by a project team led by researchers with the Drug Discovery and Development Centre (H3-D) at the University of Cape Town, South Africa. International project partners included the Eskitis Institute at Griffiths University (Australia), the Swiss Tropical and Public Health Institute (Switzerland), Monash University (Australia), Syngene (India) and the Switzerland-based Medicines for Malaria Venture (MMV).

The researchers were able to identify the mode of action the compound uses against the parasite and show that it is a truly novel mechanism. With resistance constantly biting at the heels of research against malaria, researchers say it is essential to fully understand how new drugs work so any potential future issues with resistance can be addressed.

MMV390048 is the first drug compound discovered and researched on African soil for clinical development for any disease. "It is our hope that this drug will go all the way to market and fulfill its promise," said Kelly Chibale, founder and director of H3-D. "But whether it does or not, this work shows that pessimism about Africa is sometimes unfounded. This research, for Africans by Africans, shows the excellence in science that exists on the continent."

EXTENDING USEFULNESS OF CURRENT ARTEMISININ THERAPIES

While researchers have not yet detected artemisinin resistance in Africa, frontline malaria drugs are already failing in Southeast Asia. Public health officials are putting in place measures to ensure that current malaria therapies remain useful in Africa for as long as possible.

In a September 2011 update on artemisinin resistance, WHO articulated the need for new treatment alternatives for Cambodia, given the alarming rise in treatment failure. It listed pyronaridine-artesunate (Pyramax®), quinine + doxycycline for 7 days, and atovaquone-proguanil (Malarone®) + primaquine as potential options.

Although Pyramax has already been shown to be as effective as current standard artemisinin combination therapies in Southeast Asia and Africa, authorities still need to understand the health effects of repeated administration of ACTs in regions where patients might suffer multiple episodes of malaria within the same year.

A longitudinal study comparing the incidence rates of uncomplicated malaria episodes in children and adults treated with repeated ACT therapy is being carried out in three countries in West Africa. Researchers presented interim data at MIM that showed the safety of repeated treatment courses of Pyramax in over 50 patients.

“Until new classes of antimalarial drugs become available, we must do all we can to make sure the parasite does not become resistant to artemisinin-based treatments,” said Issaka Sagara of the University of Bamako, Mali, who is part of the West African Network for Clinical Trials of Antimalarial Drugs (WANECAM) project. “One promising strategy is to encourage the use of a mix of artemisinin combination therapies in a region, as long as all the artemisinin combinations are equally safe and effective.”

In addition, researchers and clinicians are seeking to preserve the therapeutic life of ACTs for as long as possible. The extent to which patients are prescribed the correct dose of a drug is a key component in ensuring drug effectiveness. Not only can inadequate dosage result in treatment failure, but it may arguably contribute to the spread of resistance by encouraging resistant parasites to outcompete those that are still susceptible to the medication. In most cases, the dosage is probably accurate, according to the researchers. However, there are subpopulations—like malnourished children or pregnant women—for whom achieving adequate drug concentrations can be especially difficult and who are at particular risk of being under-dosed.

Research at the Harvard School of Public Health examined ways to ensure patients complete the course of medication. In the study, which was presented at MIM, patients enrolled in a free mobile phone health information system and were reminded to take their medication by either six long or six short text messages in 12-hour intervals. By looking at pill counts and household drug inventories, researchers found that short text message reminders—more so than long ones—increased adherence to ACT regimens.

SURVEILLANCE AND MONITORING: TRIP WIRES FOR RESISTANCE

Other sessions at MIM this week discussed early identification of drug resistance and the need for better methods of detecting extended parasite clearance—an indicator of possible resistance. Early detection of resistance would mean faster interventions to stop the spread of drug-resistant parasites.

A study in Mali looked at the rate of parasite clearance in parasites isolated from patients undergoing artesunate monotherapy. “No sign of resistance was observed there yet,” said Carol Hopkins Sibley, co-founder and scientific director of the WorldWide Antimalarial Resistance Network (WWARN).

“Scientists across Africa are looking for signs of resistance—almost a trip wire for setting off an alarm,” Sibley continued.

They are also interested in looking for a molecular marker that might be a more efficient way to identify resistance to artemisinin and to the drugs that are paired with ACTs. Recent studies in Southeast Asia are providing more clues on how to identify parasites that are resistant to artemisinin. According to Sibley, two new “fast and effective tests” will help speed up the process of identifying resistance and most importantly one test can be used by field clinicians, even with a simple laboratory, to identify parasite clearance rates.

Resistance to artemisinin is now indicated in Myanmar, and is widely acknowledged as a serious threat to global efforts to eliminate the disease. Arguably, one of the key drivers of this has been the widespread availability and use of partial courses of oral artemisinin monotherapy (oAMT) in the informal private sector. In an effort to ameliorate this threat, Population Services International implemented an emergency replacement program, flooding the market with heavily subsidized ACTs and supporting the effort with intensive communication campaigns. At the same time, the Ministry of Health banned further importation of oAMT.

After only 12 months of implementation, significant changes in the availability and market share of oAMT versus ACTs were observed. National ACTwatch surveys—auditing over 3,500 outlets—found that the availability of ACTs had increased from 27 percent to 63 percent, while the availability of oAMT had decreased from 51 percent to 36 percent. Significant changes in relative market share were also

observed, particularly among pharmacies, retail stores and informal drug vendors (which had historically provided the bulk of oAMT).

"The market share of quality-assured ACT relative to oAMT among these priority outlets increased from only 3.2 percent to a staggering 73.1 percent," said Chris White, program director for malaria at Population Services International (PSI). "The results demonstrate that a sustained price subsidy, when combined with an enforced ban on oAMT importation and intensive behavior change communications, can bring about rapid changes in antimalarial markets within the Greater Mekong Sub-region where artemisinin drug resistance has emerged."

Other studies provide insights into the use of poor quality ACTs, which pose a continuous threat to malaria patients. A recent preliminary study offered hope. It examined the frequency of substandard, falsified and degraded artemisinin-derivative-containing drugs found at pharmacies, patent medicine vendors (PMVs) and clinics in Rwanda, Ghana (Kintampo), Tanzania, Nigeria (Enugu and Ilorin), Equatorial Guinea (Bioko Island) and Cambodia. Of the 9,000 ACTs analyzed, few were found to be substandard.

"The fact is that of these six countries, only two had falsified artemisinin derivative-containing drugs," said Harparkash Kaur, lecturer in pharmacology at the London School of Hygiene and Tropical Medicine. "And even in those two African countries, we found less than three percent falsified drugs."

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The Multilateral Initiative on Malaria (MIM) (http://www.mimalaria.org/eng/), launched in Dakar, Senegal in 1997, is an international alliance of organizations and individuals seeking to maximize the impact of scientific research against malaria in Africa to ensure that research findings yield practical health benefits. The MIM conference in Durban follows successful conferences held in Yaoundé, Cameroon, in November 2005, and in Nairobi in October 2009. The MIM Secretariat is currently hosted by the Biotechnology Centre of the University of Yaoundé I/Amsterdam Medical Centre.

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