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TRIAL WATCH

Next-generation antimalarial from phenotypic screen shows clinical promise

Results from a Phase II trial show that KAE609, a potential first-in-class antimalarial drug, rapidly clears malaria parasites from the blood (*N. Engl. J. Med.* **371**, 403–410; 2014).

Although many antimalarial drugs are available, the emergence of resistance is an ongoing problem. Worryingly, resistance to artemisinin — the key component of the current first-line drug combinations — has recently emerged in Southeast Asia, and so the need for new drug classes is pressing.

About 8 years ago, many groups seeking such drugs started to focus on phenotypic screening, which has "been incredibly fruitful in terms of generating hits and leads," says Tim Wells, Chief Scientific Officer of the Medicines for Malaria Venture in Geneva, Switzerland. "Around 80% of the compounds in preclinical or Phase I at the moment have come from phenotypic screening," he says. KAE609 is the first antimalarial compound identified using such screens to demonstrate efficacy in clinical trials.

KAE609, a spiroindolone discovered by a public–private partnership (*Science* **329**, 1175–1180; 2010), targets P-type cation-transporter ATPase4 (PfATP4), a membrane transport protein that regulates sodium homeostasis and thus the osmoregularity of the parasite. "The target was known, but nobody would have ever set up an ion-channel screen in malaria to look for inhibitors," says Wells. He estimates that about 5% of the ~30,000 antimalarial compounds identified through phenotypic screening also target PfATP4.

In the Phase II trial, patients with malaria caused by either *Plasmodium falciparum* ($n = 11$) or *P. vivax* ($n = 10$) parasites were treated with KAE609 for 3 days. "The surprising thing was how quickly the parasitaemia resolved," says Nick White, a Professor in the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, and a lead investigator in the trial. The median parasite clearance time was 12 hours in each cohort, with a median parasite half-life of 0.95 hours. By comparison, <1% of historical patients who had been treated with artemisinin showed a parasite half-life of 1 hour or less; artemisinin is by far the fastest-working antimalarial drug currently available.

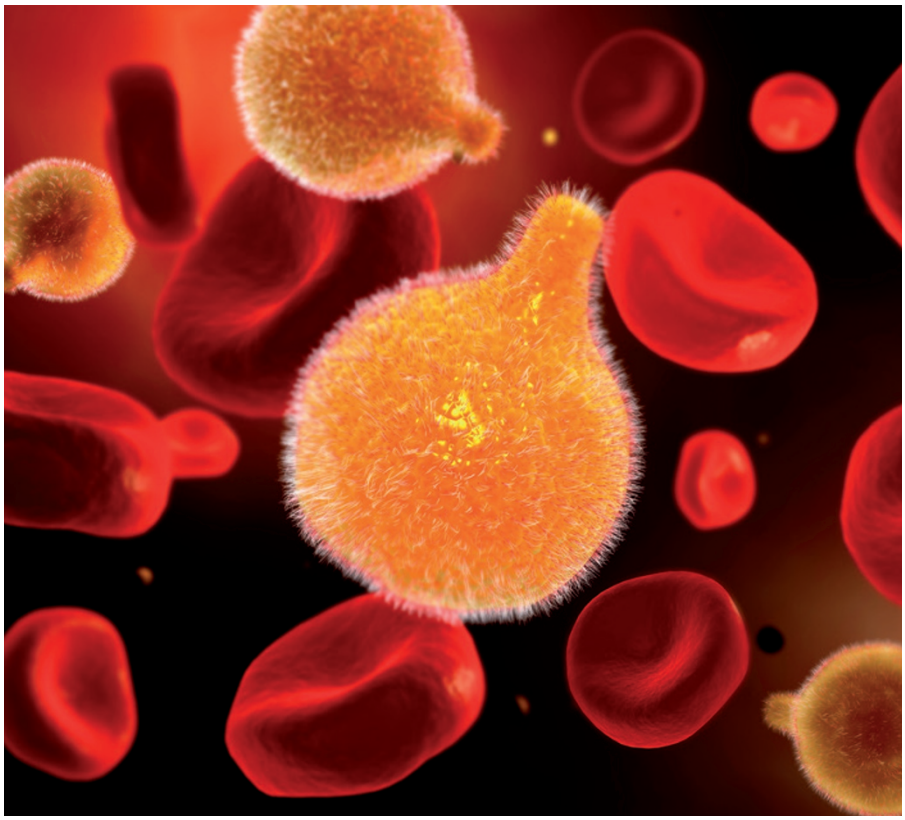
Both artemisinin and KAE609 target all stages of the life cycle of malaria parasites and this is probably the reason for their speedy parasite clearance. White surmises that KAE609 is "blowing up the parasite literally, making it like a little hard balloon," which is then removed by the spleen.

As with other antimalarials, resistance to KAE609 seems likely to be an issue. "Mutations in *pfatp4* seem to occur reasonably readily and not be too deleterious to the parasite, so we're worried about resistance," explains White. KAE609 "would have to be deployed only in combination with something else."

The drug is now being further investigated in a Phase II dose-finding trial. "The problem with other antimalarial drugs is that not enough attention has been paid to dose," says White. Some of these drugs have therefore been approved and registered at doses that are too low. "We don't want to make that mistake with this one," he says.

Pending the outcomes of clinical trials, Novartis hopes to submit KAE609 for approval in 2017. Given the continuing emergence of artemisinin resistance, an antimalarial with a novel target would be a welcome arrival.

Megan Cully



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