

## PfATP4 inhibitors to treat malaria- worthy successors to qinghaosu?

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Progress in controlling malaria has slowed in recent years and the annual death toll remains above 400 000, with most deaths caused by *Plasmodium falciparum*.<sup>1</sup> The joint threats of increasing resistance to insecticides, the artemisinin (qinghaosu) derivatives, and almost all other antimalarials in current use make the development of new classes of antimalarials a high priority.

In the last ten years the malaria parasite cation ATPase PfATP4 was identified as a promising target for novel antimalarials by phenotypic screening.<sup>2</sup> It plays a role in maintaining low intracellular sodium cation concentrations in *Plasmodium falciparum*.<sup>3</sup> Inhibition of PfATP4 disrupts Na<sup>+</sup> homeostasis and is lethal for the parasite. One PfATP4 inhibitor, the spiroindolone cipargamin, is already in Phase 2 clinical development.<sup>4</sup> The appeal of this new class of compounds lies in their rapid parasitocidal effect, a property previously only possessed by the pre-eminent artemisinin derivatives, and their transmission-blocking activity.

In this issue of The Lancet Infectious Diseases Aditya Gaur, James McCarthy and colleagues report their findings from related phase 1a and phase 1b studies of SJ733, a novel PFATP4 inhibitor.<sup>5</sup> The efficient design of these two complementary studies is a good example of how far antimalarial clinical drug development has come. The phase 1a study conducted in the United States in healthy adults without malaria describes the tolerability, safety and pharmacokinetics of ascending-dose SJ733 and its main metabolite in the fed and fasting state. In the phase 1b pharmacokinetic-pharmacodynamic study of 17 malaria-naïve healthy adults in Queensland, participants were inoculated with a known concentration of *P. falciparum* infected erythrocytes and two doses of SJ733 were evaluated (150 mg and 600 mg). The lower dose was predicted to be sub-therapeutic and was given to enable estimation of the minimal inhibitory concentration (MIC) of SJ733, which permits a more evidence-based approach to dose-setting than in the past.<sup>6</sup>

The results of the two studies indicate that absorption of SJ733 is dose-limited with exposure plateauing at doses above 600mg. The elimination half-life of the 600 mg dose in the phase 1b study was moderate at a median [min, max] of 17.5 [11.9, 41] hours. This has implications for how the drug can be further developed. In the recent past, target product profiles for new antimalarials have aimed for single dose treatments,<sup>7</sup> effectively ruled out for SJ733 by these findings. This is not a major limitation as worldwide three-day treatments of malaria are the norm. The parasite clearance results were encouraging. Parasite clearance half-lives were comparable to those of susceptible infections treated by the artemisinin derivatives but longer than following cipargamin treatment (Table). They were calculated from sequential parasite densities estimated by ultrasensitive PCR in non-immune study participants. The

slower parasite clearance, coupled with the high MIC compared to cipargamin raises the question as to whether SJ733 at maximally absorbed doses is as active as other PfATP4 inhibitors.<sup>8</sup> Estimating the MIC and parasite clearance in patients with malaria in endemic areas would help to resolve this.

Gametocytes were detectable in some patients at the end of therapy, however infectivity was not assessed.

Safety and tolerability results in these small numbers of participants were reassuring. Four participants to the phase 1b study had rises in liver transaminases, including one increase in alanine aminotransferase >14 times the upper limit of normal. These occurred predominantly in patients in the lower dose arm in whom early parasite recrudescence occurred and were attributed to malaria. This is plausible, however will need to be monitored in future studies. There were signals of hepatotoxicity in early studies of cipargamin and a dose-escalation study (NCT03334747) focusing on hepatic safety is underway in several African countries.

As the authors note, study participants were overwhelmingly male, indicating that relaxing inclusion criteria alone is not effective in correcting gender imbalance in first-in-human studies, likely due to fears of teratogenicity.<sup>9</sup>

Assessing the propensity for resistance to develop to the PfATP4 inhibitors was not an objective of this research. Other investigators have succeeded in inducing resistance to SJ733 using CRISPR/Cas9-based genome editing tools, which signals the importance of protecting this new compound by combining it with other antimalarials.<sup>10</sup> Now that piperazine resistance is established in Southeast Asia the choice of partner drugs is very limited. There is a tension between the need to expedite development of new antimalarial drug combinations by while doing everything possible to 'resistance-proof' the constituent drugs and maximise their useful therapeutic life.

Over the last 20 years most of the new combination therapies that have been registered have come from related classes of compounds. Only now are new molecules progressing through the development pipeline. Rapid parasite killing was the pharmacodynamic hallmark of the artemisinin derivatives before resistance emerged and underpins their enormous success. Seeing this property replicated in new unrelated drug classes like the PfATP4 inhibitors is cause for optimism.

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EAA and APP declare no conflicts of interest.

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Table Comparison of characteristics of SJ733 with other fast-acting antimalarial drugs

	Artefenomel	Artesunate before 2008 <sup>a</sup>	Artesunate after 2008	Cipargamin	Ganaplacide	SJ733 (600mg dose)
Drug class	Synthetic trioxolane	Artemisinin derivative		PFATP4 inhibitor	Imidazolopiperazine	PFATP4 inhibitor
PCT <sub>½</sub> (hr) <sup>b</sup>	3-6	3-2	5-29	0-9	3-51	3-56
Elimination Half-life (hr)	46-62	<1		20-8	42-5-70-7	17-5
Adverse events	Raised creatine phosphokinase	Allergic reactions (<1/3,000)		Raised aminotransferases	Raised aminotransferases	Raised aminotransferases
Resistance	Kelch-13 mutations	Kelch-13 mutations		PfATP4 mutation	PfCARL gene mutations	PfATP4 mutations
MIC <sup>c</sup>	4-1 ng/mL	2-2 ng/ml		0-13 ng/mL	58 ng/mL	122 ng/mL

<sup>a</sup> Before emergence of the kelch-13 mutations causing artemisinin resistance

<sup>b</sup> PCT<sub>1/2</sub> Time taken to clear half the parasite density (median). For SJ733 this is estimated from qPCR-derived parasite density data in a controlled human infection model. All others are from microscopy-derived parasite densities in patients with natural infections.

<sup>c</sup> Minimal Inhibitory Concentration-Lowest concentration of an antimicrobial agent that will inhibit the visible growth of a microorganism