

Investment in antimalarial drug development is bearing fruit



Front-line antimalarial drugs (the artemisinin-based combination therapies) are failing in southeast Asia, making the need for novel antimalarials more pressing than ever.¹⁻³ In *The Lancet Infectious Diseases*, two studies of DSM265,^{4,5} a plasmodium dihydroorotate dehydrogenase inhibitor, are reported. This novel antimalarial, discovered by a team at the University of Texas Southwestern, is in phase 2 clinical development for the prophylaxis and treatment of malaria.⁶

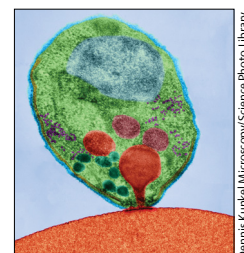
James S McCarthy and colleagues⁴ report antimalarial activity, pharmacokinetics, tolerability, and safety of DSM265 in the first human challenge studies, using a new approach to predict the optimal dose for treatment. Study participants received an intravenous infusion of erythrocytes infected with *Plasmodium falciparum*. Sub-microscopic parasite densities were tracked using ultrasensitive PCR methods and DSM265 was given when a pre-defined parasitaemia threshold was reached. This approach enabled in vivo estimation of the minimum inhibitory concentration⁷ (albeit in participants whose host defences had not been activated by malaria illness), providing a more rational basis for dose selection than the standard approach taken in the past, which relied on a combination of educated guesswork from preclinical studies and in vitro assessment and trial and error using clinical endpoints. Parasitocidal efficacy of DSM265, expressed as the log₁₀ parasite reduction ratio at 48 h, measured 1.55 (95% CI 1.42–1.67), which was lower than that of a 10 mg/kg dose of mefloquine given to controls at 2.34 (95% CI 2.17–2.52). In their study, peak DSM265 concentrations were reached between 1.5 h and 4 h after administration and the elimination half-life was estimated at 86–118 h, making it a possible contender for a single curative dose antimalarial treatment if it is combined with a more potent partner drug with comparable elimination kinetics.

In the second report, Mihály Sulyok and colleagues⁵ show that DSM265 was well-tolerated and gave at least 7 days complete protection from malaria infection in five healthy volunteers when given less than 24 h before venous inoculation with *P falciparum* sporozoites, but this protection dropped to around 50% when the dosing interval before inoculation was prolonged to 7 days. Pharmacokinetic parameters were similar to those estimated in the treatment study (median t_{max} 3 h,

elimination half-life 57–183 h) but there was notable inter-participant variability in drug exposure that correlated with parasitological efficacy.

What do these studies tell us about the future of DSM265? In healthy volunteers this is a medium potency, slowly eliminated, well-tolerated antimalarial. If these results are confirmed in acute malaria then it would be a suitable partner drug used in combination with a more rapidly effective agent for malaria treatment. The path through pre-clinical and clinical development appears to have been relatively untroubled but there is still some way to go before registration. Tolerability, safety, and efficacy in larger numbers of symptomatic patients with naturally acquired infections will need to be confirmed, as well as efficacy against non-falciparum species. Even after registration, knowledge gaps are likely to remain, such as whether the chosen dose is as effective in pregnant women and young children, two groups typically neglected in pivotal clinical trials of new drugs. The relatively short period of protection against infection it affords when used as prophylaxis makes it unlikely to be used as a preventive strategy in pregnant women and children in endemic areas in the future. However, if the dose can be optimised to permit weekly administration it would be a possible candidate for the travellers' market, where it could replace mefloquine which continues to fall out of favour.

The Achilles heel of all anti-infective drugs is the eventual selection of resistance in the target pathogen, and here DSM265 looks vulnerable. The propensity for development of resistance to DSM265 has already been assessed in vitro by exposing laboratory Dd2 strains of *P falciparum* to DSM265 continuously. The lowest number of parasites needed to select a resistant parasite was around 2 × 10⁶, which is lower than for atovaquone, a drug known for its low threshold for resistance emergence following antimalarial treatment. A point mutation in the dihydroorotate dehydrogenase gene (G181C) was associated with a 13 times higher IC₅₀ compared with parasites with wild-type enzyme.⁶ This vulnerability raises concerns about the longevity of this compound and reinforces the importance of combining it with one or more suitably matched partners for clinical use.



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Investment in the antimalarial pipeline is finally bearing fruit. Substantial achievements have been made in antimalarial drug development as a result of collaborative endeavours between the public and private sectors and variations on this model are being adopted in the search for new antibiotics.^{8,9} DSM265 looks to be a promising antimalarial of the future. But the looming crisis of untreatable malaria being faced in southeast Asia and reports of untreatable bacterial infections from elsewhere show us that current models of anti-infective drug development are not keeping pace with the loss of drugs to resistance. Drastic action is needed.

Elizabeth Ashley

Myanmar Oxford Clinical Research Unit, Yangon, Myanmar
liz@tropmedres.ac

I declare no competing interests.

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