



Artesunate–mefloquine: a malaria treatment for African children?

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Artesunate–mefloquine is one of five artemisinin-based combination therapy (ACT) formulations recommended by WHO for the treatment of uncomplicated falciparum malaria worldwide.¹ The scaled-up deployment of ACTs in Africa during the past 10 years, and their substitution in place of failing monotherapies, particularly chloroquine and sulfadoxine–pyrimethamine, has contributed to the reduction in levels of malaria transmission,² and currently, no other therapy is as effective. The artemisinin component has a short-lived but powerful action to reduce the malaria parasite count, reducing the chance of severe disease and death and onward transmission of the infection. The partner antimalarial drug has a slower elimination half-life, producing a post-treatment prophylactic effect, which conveys additional benefit in high-endemic settings. Alarming, the emergence of artemisinin-tolerant parasites in south-east Asia is now well documented. One strategy to prevent the spread of artemisinin resistance is to have a range of ACT formulations available for use in a given setting, so that the parasite population is not over-exposed to the pressure of any single drug combination.¹

Despite its recommendation for use in Africa, artesunate–mefloquine is absent from treatment guidelines and unregistered in many African countries. Policy makers need to be sure that their decisions regarding drug deployment are well informed. Extensive use of artesunate–mefloquine and mefloquine monotherapy, mainly in southeast Asia, has shown that notable drug-attributed effects are early vomiting, during the treatment course, and self-limiting neuropsychiatric effects, most commonly dizziness and insomnia.^{3–7} Concerns about a paucity of data on tolerance and efficacy of artesunate–mefloquine in children, who carry the greatest burden of malaria cases in Africa, might contribute to the rarity of its use.

In *The Lancet Infectious Diseases*, Sodiomon Sirima and colleagues⁸ describe the findings of a phase 4, multicentre, open-label trial assessing non-inferiority of the efficacy and safety of a fixed-dose formulation of artesunate–mefloquine (developed by the Drugs for Neglected Diseases initiative and the Brazilian public health laboratory Farmanguinhos in 2002). This

formulation has age-based, rather than weight-based dosing, facilitating its use in resource-poor settings. The once-daily dose is expected to promote adherence and to reduce the possibility of dosing errors. The comparator drug was artemether–lumefantrine, which is the ACT used most commonly in Africa.

With 944 participants from Tanzania, Burkina Faso, and Kenya, aged between 6.0 months and 59.8 months, this is the largest study assessing artesunate–mefloquine in African children with uncomplicated falciparum malaria. The prolonged follow-up period of 63 days incorporated the long elimination half-life (2–3 weeks) of mefloquine. In the per-protocol analysis, the PCR-corrected rate of adequate clinical and parasitological response at 63 days was 90.9% (370 of 407 patients) in the artesunate–mefloquine group and 89.7% (365 of 407 patients) in the artemether–lumefantrine group. Artesunate–mefloquine was non-inferior to artemether–lumefantrine (treatment difference 1.23%, 95% CI –2.84% to 5.29%) and both parasite and fever clearance times were indistinguishable between groups after 48 h, with some suggestion that initially rates were faster in the artesunate–mefloquine group. There was no increase in microscopic gametocyte clearance rate with artesunate–mefloquine and re-infection was delayed longer with artesunate–mefloquine than with artemether–lumefantrine, as reported previously in a similar setting.⁹

The investigators found no difference between treatment groups in the frequency of early vomiting (16% on any study day), and it reduced during the 3-day course. This result accords with findings in other populations that vomiting is less frequent if the 25 mg/kg dose of mefloquine is divided evenly over the 3 treatment days.⁶

Few neurological adverse events occurred in either treatment group. This finding has to be put into context. As Sirima and colleagues note, the trial was not powered for specific safety outcomes. During the long period of safety follow-up, 63 days, plus three more visits over 63 days after treatment failure, neuropsychiatric adverse event monitoring was encouraged, but it was not systematic. In children younger than 5 years,

standardised assessment of neuropsychiatric status is challenging, not least logistically, in a trial of this size.^{3,10} Detailed assessment was done in young children (with mean age 3 years) in a single-arm study in Cameroon,⁵ in which 3.8% of 213 children had a mild-to-moderate drug-related neuropsychiatric event after treatment with artesunate-mefloquine, the most common of which was sleep disorder.

Reduced susceptibility to mefloquine has been documented in African parasites, particularly in west Africa.¹¹ Consistent surveillance of molecular resistance markers, in-vitro susceptibility, and in-vivo treatment responses will be important when monitoring the effect of introducing the fixed-dose combination. Additional pharmacokinetic data from Africa could complement the current consensus that adjustment of the dose of mefloquine in children is not necessary.⁴

Three issues merit operational consideration in the African setting of higher malaria transmission. First, there is an increased risk of neuropsychiatric effects if the treatment course of artesunate-mefloquine is repeated within 60 days.^{1,12} Indeed, Sirima and colleagues report that 444 (48%) of 933 children in their study were retreated with an alternative rescue treatment within 63 days, similar to proportions recorded by other investigators.¹³ The risk of repeated treatment should be investigated in well designed cohort studies;¹³ furthermore, awareness of this risk should be incorporated in training initiatives for health-care providers. Second, because of drug interaction,¹ the effects of previous mefloquine exposure on the efficacy of artemether-lumefantrine treatment should be assessed. Finally, comparison studies exploring cost-effectiveness in African countries will be important.

Further complementary studies would optimise the safe delivery of a fixed-dose combination of artesunate-mefloquine to African children, but its increased availability could offer an efficacious treatment with rapid

action and prolonged protection from re-infection; an important resource in the fight against malaria.

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I declare no competing interests.

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- 1 WHO. Guidelines for the treatment of malaria. Third edition. Geneva: World Health Organization, 2015. <http://www.who.int/malaria/publications/atoz/9789241549127/en/> (accessed May 14, 2016).
- 2 Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature* 2015; **526**: 207–11.
- 3 Luxemburger C, Price RN, Nosten F, Ter Kuile FO, Chongsuphajaisiddhi T, White NJ. Mefloquine in infants and young children. *Ann Trop Paediatr* 1996; **16**: 281–86.
- 4 Schlagenhauf P, Adamcova M, Regep L, Schaerer MT, Bansod S, Rhein HG. Use of mefloquine in children - a review of dosage, pharmacokinetics and tolerability data. *Malar J* 2011; **10**: 292.
- 5 Frey SG, Chelo D, Kinkela MN, et al. Artesunate-mefloquine combination therapy in acute *Plasmodium falciparum* malaria in young children: a field study regarding neurological and neuropsychiatric safety. *Malar J* 2010; **9**: 291.
- 6 Ashley EA, Lwin KM, McGready R, et al. An open label randomized comparison of mefloquine-artesunate as separate tablets vs. a new co-formulated combination for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand. *Trop Med Int Health* 2006; **11**: 1653–60.
- 7 Tine RC, Faye B, Sylla K, et al. Efficacy and tolerability of a new formulation of artesunate-mefloquine for the treatment of uncomplicated malaria in adult in Senegal: open randomized trial. *Malar J* 2012; **11**: 416.
- 8 Sirima SB, Ogutu B, Lusingu JP, et al. Comparison of artesunate-mefloquine and artemether-lumefantrine fixed-dose combinations for treatment of uncomplicated *Plasmodium falciparum* malaria in children younger than 5 years in sub-Saharan Africa: a randomised, multicentre, phase 4 trial. *Lancet Infect Dis* 2016; published online July 15. [http://dx.doi.org/10.1016/S1473-3099\(16\)30020-2](http://dx.doi.org/10.1016/S1473-3099(16)30020-2).
- 9 Sagara I, Diallo A, Kone M, et al. A randomized trial of artesunate-mefloquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria in Mali. *Am J Trop Med Hyg* 2008; **79**: 655–61.
- 10 Staedke SG, Jagannathan P, Yeka A, et al. Monitoring antimalarial safety and tolerability in clinical trials: a case study from Uganda. *Malar J* 2008; **7**: 107.
- 11 Fall B, Camara C, Fall M, et al. *Plasmodium falciparum* susceptibility to standard and potential anti-malarial drugs in Dakar, Senegal, during the 2013–2014 malaria season. *Malar J* 2015; **14**: 60.
- 12 Phillips-Howard PA, ter Kuile FO. CNS adverse events associated with antimalarial agents. Fact or fiction? *Drug Saf* 1995; **12**: 370–83.
- 13 Wanzira H, Kakuru A, Arinaitwe E, et al. Longitudinal outcomes in a cohort of Ugandan children randomized to artemether-lumefantrine versus dihydroartemisinin-piperaquine for the treatment of malaria. *Clin Infect Dis* 2014; **59**: 509–16.

A malaria vaccine in children with HIV

Plasmodium falciparum is the major cause of malaria cases and deaths globally, particularly in sub-Saharan Africa where HIV is also highly prevalent.^{1,2} The primary target population of a malaria vaccine is young

children, and more than 2 million children in sub-Saharan Africa are infected with HIV.² Therefore, many HIV-infected children could benefit from a malaria vaccine, especially because HIV might increase the



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