EDITORIAL

Artemisinin Partial Resistance and the Treatment of Severe Malaria

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One of the greatest threats to the control of malaria is the emergence of artemisinin partial resistance (ART-R) in *Plasmodium falciparum,* the most virulent human malaria parasite, in multiple countries in Africa.[1] Artemisinins are rapid-acting antimalarial therapeutic agents that are the key components of artemisinin-based combination therapy, which combines an artemisinin derivative with a longer-acting partner drug to treat uncomplicated falciparum malaria. Artemisinin-based combination therapies are the standard of care for this indication. In addition, the artemisinin derivative artesunate, provided intravenously or intramuscularly, is the standard of care to treat severe falciparum malaria, offering significantly improved survival compared with the prior standard, quinine, in African children.[2] Artemisinin partial resistance is manifest as delayed parasite clearance after treatment and was first identified in Southeast Asia in 2008.

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Artemisinin partial resistance is mediated principally by variants in the *P falciparum* kelch 13 (K13) protein; any of approximately 20 K13 variants are associated with clinical delayed parasite clearance after therapy and enhanced survival in the ring survival assay, an in vitro marker of the clinical phenotype.[1] The emergence of ART-R in Southeast Asia was followed by development of resistance to key partner drugs, notably piperaquine, which resulted in high rates of treatment failure for dihydroartemisinin-piperaquine in Cambodia.[3]

More recently, ART-R was observed independently in Rwanda,[4,5] Uganda,[6,7] and Eritrea and Ethiopia,[8,9] with different K13 variants emerging in each country and spreading to surrounding countries.[1] The clinical implications of ART-R in Africa are not yet clear. In clinical trials of uncomplicated malaria in Rwanda,[5] Eritrea,[8] and Tanzania,[10] the presence of validated ART-R K13 variants was associated with delayed parasite clearance, but not treatment failure based on standard World Health Organization criteria, probably because resistance to artemisinin-based combination therapy partner drugs was not present. However, for the treatment of severe malaria, artemisinins are provided initially as monotherapy (parenteral artesunate followed by an oral artemisinin-based combination therapy after a patient has stabilized). An important concern regarding ART-R is its potential effect on the efficacy of parenteral artesunate to treat severe malaria. However, because the incidence of malaria in regions of Southeast Asia with ART-R parasites is relatively low, and therefore severe malaria is uncommon, it has not been possible to study the effect of ART-R on the treatment of severe malaria in this area.

Of great concern, with the emergence of ART-R in sub-Saharan Africa, where approximately 95% of malaria morbidity and mortality occurs, thousands of children with severe falciparum malaria due to ART-R parasites will be treated with parenteral artesunate. An urgent priority is determining the effect of ART-R in parasites now circulating in Africa on the treatment of severe malaria.

A short report by Henrici et al[11] published in this issue of *JAMA* offers initial insights relevant to this concern. The article describes outcomes for 100 hospitalized children aged 6 months to 12 years in Jinja, Uganda, who were treated for complicated malaria; 41% met World Health Organization criteria for severe malaria, and the remainder had other complications requiring hospital admission. Validated K13 variants that predict ART-R were present in 10 of the 100 cases. These were the markers of ART-R that are most prevalent in Uganda,[7] including *A675V* (8 patients) and *C469Y* (2 patients). According to time to parasite clearance or calculated parasite clearance half-life, the *A675V* variant was associated with delayed parasite clearance after treatment with intravenous artesunate. The 2 patients infected with *C469Y* mutant parasites had rapid parasite clearance. Two patients required extended therapy because of greatly delayed parasite clearance, but only 1 of these patients was infected with K13 mutant (*A675V*) parasites. Thus, not surprisingly, ART-R was associated with delayed parasite clearance after therapy, but, in the relatively small sample studied, infection with parasites with ART-R variants was not associated with poorer clinical outcomes than infection with parasites without these variants.

Another interesting result of this study was that 10% of patients experienced recrudescence (recurrent malaria caused by the same parasite strain, based on molecular genotyping, as the initial infection) after therapy with intravenous artesunate followed by artemether-lumefantrine. This treatment efficacy is unexpectedly poor compared with that in numerous studies of artemisinin-based combination therapy for uncomplicated malaria, but experience with the long-term efficacy of treatment for severe malaria is limited. Recrudescence was not associated with the K13 genotypes of infecting parasites, so the results offer caution about overall efficacy of treatment for severe falciparum malaria, but not evidence of the effect of K13 variants on treatment outcomes.

The study by Henrici et al[11] offers valuable information: ART-R K13 variants were associated with delayed parasite clearance. However, because of its small sample size and limited characterization of treatment outcomes, the study was unable to answer the most important question concerning ART-R and severe malaria: do patients infected with ART-R parasites have poorer clinical outcomes after treatment with parenteral artesunate compared with patients infected with drug-sensitive parasites? Poorer outcomes associated with ART-R would not be surprising because children often present for care

with advanced disease, and rapid action of artesunate is likely critical to provide speedy resolution of life-threatening effects of severe falciparum malaria, presumably explaining why parenteral artesunate provided superior results compared with parenteral quinine (a slower-acting drug) in prior trials.[2] If ART-R is indeed associated with poorer outcomes, changes in management strategies may be needed. Thus, an urgent priority is the conduct of clinical trials of adequate size and design to answer the key question posed earlier. One such trial is ongoing. The SMAART study (ISRCTN14711763) is a multisite prospective observational/nested case-control study of children hospitalized with severe malaria with 6-month follow-up, including rigorous measures of parasite clearance, plasma lactate clearance, and case fatality among children with severe malaria treated with intravenous artesunate. The study includes 2 sites in northern Uganda (Soroti Regional Referral Hospital, Soroti and Dr Ambrosoli Memorial Hospital, Kalongo), where prevalence of the *C469Y* and *A675V* variants is high. Results of this ongoing study, which are expected in 2025, will allow direct testing of the hypothesis that severe malaria with ART-R parasites is associated with poorer clinical outcomes than severe malaria with wild-type parasites.

If ART-R does lead to poorer treatment outcomes, as hypothesized, the appropriate response will not be straightforward. Rapid-acting alternatives to intravenous artesunate will probably not be available for several years. Cipargamin, a novel compound that, like artesunate, acts rapidly against ring-stage parasites, is now in phase 2 clinical trials for the treatment of severe falciparum malaria (NCT04675931). The drug selects readily for resistance due to variants in its target, *P falciparum PfATP4*,[12] but combining it with an effective partner drug or following immediate use of cipargamin with a slower-acting efficacious regimen may circumvent resistance development. For uncomplicated malaria, new approaches under consideration for the treatment of ART-R malaria include instituting multiple concurrent first-line antimalarial regimens within a country, informed by the understanding that certain artemisinin-based combination therapy partner drugs counteract development of resistance to other partner drugs[13]; using triple artemisinin-based combination therapy, including an artemisinin plus 2 unrelated partner drugs[14]; or using nonartemisinin treatments, a number of which are currently under study.[15] Similar approaches will be appropriate for the treatment of severe malaria as long as at least 1 component of a combination offers rapid activity against ring-stage parasites, as seen with artesunate and cipargamin.

Sorting out the best means of treating severe malaria in the setting of ART-R will be challenging, but the first step in this process is determining whether currently circulating ART-R parasites are preventing effective treatment. Thus, trials to determine the effect of ART-R on the efficacy of parenteral artesunate to treat severe malaria are an urgent priority.

ARTICLE INFORMATION

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