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Editorial
Ferroquine Advances

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Multidrug resistant (MDR) malaria continues its gradual but relentless spread. Despite the recent loss of dihydroartemisinin–piperaquine combination therapy in Cambodia,[1] the Medicines for Malaria Venture and their network of collaborators continue determined and effective pursuit of new antimalarials. Their response to this emerging threat has been nothing short of remarkable, licensing several important new therapies, and moving an impressive slate of development candidates into clinical trials in only a decade.[2] Although ferroquine is a desperately needed candidate to treat MDR *Plasmodium falciparum*, its developers face a daunting and unenviable challenge. They must balance the need to eradicate resistant infections with the need to prevent rare but potentially fatal complications. Difficult decisions may lie ahead.

As Supan and others demonstrate in this month's edition of the *American Journal of Tropical Medicine and Hygiene,* the approach has been methodical and deliberate. Carefully estimating the risk of rare events from small clinical trial populations is no simple task. The level of focus and attention to detail demonstrated here are imperative. The inherently higher safety bar imposed by developing long-acting antimalarials can add greatly to study time, cost, and complexity. As a result, most recent antimalarial successes have come from novel short-acting agents.[3,4] Few if any new candidates have emerged to replace the work horses lumefantrine, mefloquine, and piperaquine.

Given ferroquine's promise, safety issues are thoroughly explored in the present work. Hepatotoxicity has been a key liability identified in prior studies. The ability to monitor post-treatment liver function in malaria endemic areas is generally limited and often nonexistent. In the present report, there were more mild-to-moderate alanine aminotransferase (ALT) elevations indicating acute liver injury associated with use of ferroquine than with amodiaquine, including two events graded as potentially clinically significant. Fortunately, bilirubinemia denoting synthetic liver function impairment was not seen. Simultaneous ALT and bilirubin elevations have been found to predict a high risk of fulminant liver failure (often referred to as Hy's law). Even when ALT and bilirubin elevations are seen in clinical trials, liver failure requiring transplantation remains a vanishingly rare (though potentially fatal) event at the population level. Although Hy's law was not met for ferroquine, ALT elevations seen weeks after therapy, and the lack of an apparent dose response were concerning, and could hamper prediction of hepatotoxicity. A mitigating factor seen in earlier ferroquine studies was the lack of a clear food effect on drug pharmacokinetics. While this does not help with predicting outcomes, it lowers the risk of inadvertently high drug levels following a meal.

Cardiac repolarization injury, evidenced by QT-interval prolongation, is also common with ferroquine and related compounds such as chloroquine and piperaquine. Like liver injury, the lack of a clear concentration-response for QT prolongation in the present data set is concerning, while the lack of apparent food-effect seen previously somewhat mitigating. Also as with liver injury, electrocardiographic monitoring capacity is limited in malaria-endemic areas. Although QT-interval prolongation results only rarely in the unstable cardiac arrhythmia know as torsades de pointes, this event often proves fatal. Yet the clinical significance and true torsadogenic risk of 4-aminoquinoline-induced repolarization injury remain unclear and apparently low. Dosing interval appears to be an important factor. Despite moderate-to-severe QT prolongation observed with compressed 2-day courses of dihydroartemisinin–piperaquine in a recent study,[5] liability was reduced when the same dose was divided into a standard 3-day course.[6] Further, the qualitative appearance of EKG tracings suggested that the U-wave rather than T-wave may have been prolonged. Thus, apparent QT-interval prolongation could actually be due to blockade of the less well characterized Ik_1 ion channel, which is thought to be less torsadogenic than blockade of the Ik_r or hERG channel.[6] Whether this property explains the notable lack of clinically significant 4-aminoquinoline-induced sudden cardiac death reported in the literature remains to be seen, but should be further explored as part of ongoing ferroquine development.

Artemisinin partner drug choice remains a further challenge which the developers have proactively addressed. Given widespread artemisinin resistance in southeast Asia, the plan to switch from artesunate to artefenomel[4] moving forward represents an important and rational decision. Combining ferroquine with artesunate would effectively result in the introduction of ferroquine monotherapy in artemisinin resistant areas. While a ferroquine–artofenomel combination will almost certainly have significant initial potency, the speed at which recent ACT failures have emerged in southeast Asia[1] warrants thoughtful and deliberate deployment. Assuming eventual regulatory success, use should be reserved in favor of therapies which remain effective in a given region. Ferroquine combinations as first-line agents should be limited to areas with documented clinical ACT failures, and lack of viable alternatives. Implementation should be carefully coordinated with, regulated, and monitored by host-nation public health authorities.

The choice of clinical dose will be a critically important one, and the present work represents a wealth of data to support transparent decision-making. The focus of safety efforts should be on better understanding the mechanisms of hepatic and cardiac toxicities. The unpredictable nature of serious hepatic and cardiac events warrants further drug-interaction

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studies to mitigate risks from concomitant administration. This is particularly critical as many nations continue to suffer from large unregulated markets for drug distribution. Polypharmacy is common in the setting of acute illness, and some commonly used agents including antipyretics, antihistamines, and others may have harmful interactions. Because adverse effects and interactions will be unmonitorable with widespread use, detailed safety evaluation should be continued through development. A strong recommendation to avoid concomitant use of hepatotoxic and QT-prolonging drugs is likely to be part of the eventual product label. Educating health workers who prescribe and administer antimalarials will be a critical task for authorities implementing use in national malaria programs. Ferroquine development will be closely watched moving forward as the delicate balance between safety and efficacy is sought. If successful, ferroquine's developers will have achieved a major victory in the fight against malaria.

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REFERENCES

1. Saunders D, Vanachayangkul P, Lon C, 2014. Dihydroartemisinin-piperaquine failure in Cambodia. *N Engl J Med 371:* 484–485.
2. Burrows JN, Duparc S, Gutteridge WE, Hooft van Huijsduijnen R, Kaszubska W, Macintyre F, Mazzuri S, Möhrle JJ, Wells TNC, 2017. New developments in anti-malarial target candidate and product profiles. *Malar J 16:* 26.
3. Leong FJ, Li R, Jain JP, Lefèvre G, Magnusson B, Diagana TT, Pertel P, 2014. A first-in-human randomized, double-blind, placebo-controlled, single-and multiple-ascending oral dose study of novel antimalarial Spiroindolone KAE609 (Cipargamin) to assess its safety, tolerability, and pharmacokinetics in healthy adult volunteers. *Antimicrob Agents Chemother 58:* 6209–6214.
4. Charman SA, Arbe-Barnes S, Bathurst IC, Brun R, Campbell M, Charman WN, Chiu FC, Chollet J, Craft JC, Creek DJ, Dong Y, Matile H, Maurer M, Morizzi J, Nguyen T, Papastogiannidis P, Scheurer C, Shackleford DM, Sriraghavan K, Stingelin L, Tang Y, Urwyler H, Wang X, White KL, Wittlin S, Zhou L, Vennerstrom JL, 2011. Synthetic ozonide drug candidate OZ439 offers new hope for a single-dose cure of uncomplicated malaria. *Proc Natl Acad Sci USA 108:* 4400–4405.
5. Lon C, Manning J, Vanachayangkul P, So M, Sea D, Se Y, Gosi P, Lanteri C, Chaorattanakawee S, Sriwichai S, Chann S, Kuntawunginn W, Buathong N, Nou S, Walsh DS, Tyner SD, Juliano JJ, Lin J, Spring M, Bethell D, Kaewkungwal J, Tang D, Chuor CM, Satharath P, Saunders D, 2014. Efficacy of two versus three-day regimens of dihydroartemisinin-piperaquine for uncomplicated malaria in military personnel in northern Cambodia: an open-label randomized trial. *PLoS One 9:* e93138.
6. Vanachayangkul P, Lon C, Spring M, Sok S, Ta-Aksorn W, Kodchakorn C, Pann ST, Chann S, Ittiverakul M, Sriwichai S, Buathong N, Kuntawunginn W, So M, Youdaline T, Milner E, Wojnarski M, Lanteri C, Manning J, Prom S, Haigney M, Cantilena L, Saunders D, 2017. Piperaquine population pharmacokinetics and cardiac safety in Cambodia. *Antimicrob Agents Chemother 61:* e02000–e02016.