

Tafenoquine versus Primaquine to Prevent Relapse of *Plasmodium vivax* Malaria

TO THE EDITOR: Cytochrome P-450 2D6 (CYP2D6) screening has been used to improve the safety and efficacy of primaquine to prevent the clinical relapse of *Plasmodium vivax* malaria on the recommendation of the Centers for Disease Control and Prevention.¹ Tafenoquine, a primaquine analogue, requires CYP2D6-mediated metabolic activation for antimalarial efficacy.² In the trial by Llanos-Cuentas et al. (Jan. 17 issue)³ on the prevention of relapse of *P. vivax* malaria, we note that the reported percentages of patients in whom treatment with either primaquine or tafenoquine had failed were similar to percentages of predicted CYP2D6 reduced-function phenotypes in comparable geographic or ethnic populations.⁴ Although the participants in the trial by Llanos-Cuentas et al. were not all screened for CYP2D6 status, Baird et al. recently estimated that 38.8% of the population living at risk of *P. vivax* infection are unable to receive safe and effective primaquine therapy because of glucose-6-phosphate dehydrogenase (G6PD) deficiency and reduced CYP2D6 function.⁵ We therefore recommend that CYP2D6 allelotyping be included in future clinical studies of tafenoquine to address unresolved safety and efficacy concerns before this drug is widely used for *P. vivax* eradication or prophylaxis in travelers worldwide.

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TO THE EDITOR: The value of an antirelapse therapy for *P. vivax* malaria depends on the number of relapses averted and adherence to and toxicity of the medication regimen. Southeast Asia has the highest rates of relapse, with the majority of *P. vivax* cases being caused by relapses.¹ The prevention of relapse with conventional low-dose primaquine (total dose, 3.5 mg per kilogram of body weight) is considered unsatisfactory in Southeast Asia, so high-dose regimens (total dose, 7 mg per kilogram of body weight) are recommended.^{2,3} Nevertheless, the meta-analysis in the trial by Llanos-Cuentas et al. showed that a single 300-mg dose of tafenoquine was inferior to low-dose primaquine in Southeast Asia. Corroborating the efficacy of high-dose primaquine, we estimated that the percentage of patients in Southeast Asia in whom supervised treatment with high-dose primaquine had failed (7-day and 14-day regimens combined), with adjustment for reinfection, is 2.6% (80% credible interval, 2.0 to 3.5) at 1 year of follow-up.⁴ Although single-dose regimens promote adherence, we believe that primaquine is safer than tafenoquine in patients with G6PD deficiency because treatment can be stopped at the first sign of serious hemolysis. Looking ahead, could a regimen of primaquine followed by tafenoquine provide an efficacious yet safe and practical option for anti-relapse therapy?

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THE AUTHORS REPLY: Quinn and McCarthy suggest that screening for CYP2D6 status should be performed before tafenoquine administration. This is unfeasible for an acute infection in low-resource settings where genotyping is not available. A prospective planned analysis of CYP2D6 status and its effect on drug efficacy was performed in our trial, as well as that by Lacerda et al.¹ We confirmed the previously described relationship between CYP2D6 metabolizer status and primaquine efficacy but found no effect on outcomes of tafenoquine use, an observation consistent with other published data.² Unlike primaquine, tafenoquine has not been shown to require CYP2D6-mediated metabolism to result in a radical cure (i.e., clearance of *P. vivax* parasitemia and hypnozoites) in experimental or clinical studies.^{1,2}

Watson and Taylor suggest that tafenoquine is inferior to primaquine in Southeast Asia. In fact, our meta-analysis concluded that noninferiority of tafenoquine to primaquine could not be shown owing to the wide 95% confidence intervals. No adjustments for multiple comparisons were made in the analyses according to region, and conclusions with regard to the statistical significance of findings within subgroups cannot be made. Note that the meta-analysis was conducted in the per-protocol population, in which 99% of the participants adhered to the primaquine

regimen. Published data from Southeast Asia show notably lower primaquine adherence (24%), with a corresponding reduction in efficacy.³ Thus, the efficacy of primaquine plus chloroquine observed in the participants from Southeast Asia in our trial (in which the interventions were administered under supervision) is unlikely to translate to programmatic interventions in which unsupervised therapy is the norm. Conversely, the efficacy of single-dose tafenoquine is likely to be maintained. The use of primaquine as a surrogate G6PD test would be inappropriate; even a single dose of primaquine can precipitate hemolysis in G6PD-deficient persons, which can continue for days even after treatment is stopped.⁴ We believe that appropriate quantitative G6PD testing before the use of any 8-aminoquinoline drug should be mandatory.

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Since publication of their article, the authors report no further potential conflict of interest.

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One-Year Outcomes after PCI Strategies in Cardiogenic Shock

TO THE EDITOR: In their randomized trial, Thiele et al. (Nov. 1 issue)¹ reported that 1-year mortality was 50.0% for culprit-lesion-only percutaneous coronary intervention (PCI) and 56.9% for multi-vessel PCI in patients with acute myocardial infarction and cardiogenic shock (relative risk, 0.88; 95% confidence interval [CI], 0.76 to 1.01). Be-

cause the P value for their comparative test was greater than 0.05, the authors concluded that “mortality did not differ significantly between the two groups at 1 year of follow-up.”

In contrast, a Bayesian analysis shows that there is a posterior probability of 0.965 that culprit-lesion-only PCI is associated with a lower prob-