EDITORIALS

Tafenoquine — A Radical Improvement?

Nicholas J. White, F.R.S.

Plasmodium vivax is a major cause of malaria in the Americas, the Horn of Africa, and Asia. *P. vivax* malaria has a propensity to recur (relapse), often multiple times, after resolution of the initial illness. This may cause substantial medical complications and contribute to death.[1] Relapses arise from the dormant parasite stage in the liver (the hypnozoite). The only available drug that clears hypnozoites, thereby providing "radical cure," is the 8-aminoquinoline primaquine. In this issue of the *Journal*, two studies report on the radical curative efficacy of tafenoquine, a newly registered, slowly eliminated, single-dose 8-aminoquinoline.[2,3] It's been a long time coming.

The first 8-aminoquinoline, pamaquine (also known as plasmoquine or plasmochin), was synthesized in 1924. Pamaquine had useful asexual-stage activity against *P. vivax* and, when given in sufficient doses, prevented relapse,[4] but these doses had substantial side effects. The high rates of *P. vivax* relapse among soldiers fighting in the Asian theaters of the Second World War prompted intense research that yielded two slightly better 8-aminoquinolines — pentaquine and isopentaquine. Then came primaquine, which had fewer side effects and was more effective. Primaquine was rushed into service during the Korean war, and the adult-dose regimen that was recommended then (15 mg base per day for 14 days) has since remained unchanged for nearly 70 years. Taken with food, primaquine has few gastrointestinal side effects; however, like all the other antimalarial 8-aminoquinolines, it has a potentially dangerous adverse effect. Primaquine causes dose-dependent oxidant hemolysis in persons who have glucose-6-phosphate dehydrogenase (G6PD) deficiency (indeed, it was the investigation of "primaquine sensitivity" that led to the discovery of G6PD deficiency).[5] There are more than 180 different polymorphic genetic variants of G6PD deficiency, which confer different levels of enzyme deficiency (and thus severities of oxidant hemolysis). Prevalences range from 1 to 35%, with an average of 8 to 10%, in regions where malaria is endemic. G6PD deficiency is X-linked. Affected female homozygotes and male hemizygotes are fully deficient, whereas female heterozygotes are genetic mosaics. Their blood contains a mixture of G6PD-deficient and G6PD-normal erythrocytes (average ratio, 50:50). G6PD deficiency can be readily identified with the use of simple screening tests, such as the NADPH fluorescent "spot test" or recently developed rapid tests. These tests indicate whether the blood has less than 30 to 40% of normal G6PD activity and thus identifies hemizygotes, homozygotes, and the more severely affected female heterozygotes. Unfortunately, G6PD testing is not widely available, and only a small proportion of patients with *P. vivax* malaria are tested. This has substantially limited the deployment of primaquine.

Tafenoquine (WR 238605) was developed at the Walter Reed Army Institute of Research in the 1980s. It has been given to more than 4000 participants in different studies. Tafenoquine solves the potentially important problem of poor adherence to daily primaquine by providing a radical cure in a single dose. This major operational advantage is also its weakness. The slow elimination (terminal half-life of approximately 15 days), which allows single-dose treatment, means that

in patients with G6PD deficiency, hemolysis of the older erythrocytes continues until all susceptible cells have been destroyed. In contrast, primaquine (half-life of approximately 5 hours) can be stopped at the first sign of clinically significant hemolysis (usually the development of hemoglobinuria). Even with point-of-care testing, tafenoquine would still pose a significant risk to female heterozygotes who would be reported as "normal" by the screening tests but could still undergo substantial hemolysis.[6] For this reason, tafenoquine is restricted to patients with greater than 70% of normal G6PD activity. This means that a quantitative assessment of G6PD activity must be performed before tafenoquine is used. Although point-of-care quantitative tests have been developed, they have not yet been tested extensively under field conditions.

The two current studies showed that with appropriate G6PD testing, tafenoquine can be given safely. Early concerns over vortex keratopathy, a type of corneal deposit, have receded. Tafenoquine effectively prevented recurrences of *P. vivax* malaria. Assessing radical curative efficacy in areas where malaria is endemic poses several challenges. Follow-up needs to be sufficient to capture the majority of relapses, which may occur up to a year after the primary illness. The proportion of patients who have a relapse varies depending on geography, the degree of previous exposure, and immunity. Furthermore, relapses cannot be distinguished reliably from recrudescences or reinfections with the use of parasite genotyping alone because relapses can derive either from the sporozoite inoculation, which caused the primary infection, or from activation of hypnozoites from previous infections. In the two current studies, which included follow-up periods of 6 months, the efficacy of tafenoquine in preventing recurrence of *P. vivax* malaria was similar to that of the standard 14-day regimen of primaquine in South America and the Horn of Africa, but efficacy was lower with tafenoquine than with primaquine in Southeast Asia. Earlier studies of single adult doses of tafenoquine of up to 600 mg showed a clear dose–response relationship.[7] The rates of relapse among patients with *P. vivax* infections in East Asia and Oceania are generally higher than elsewhere, and these patients require higher doses of primaquine to attain the maximum radical curative efficacy. The lower efficacy of tafenoquine in Southeast Asia is therefore perhaps not surprising, and it suggests that a higher dose should be evaluated in that region. The requirement for accurate quantitative G6PD assessments and the current prescribing restrictions (pregnancy, lactation, or age younger than 16 years) will limit the potential deployment of tafenoquine, at least in the immediate future. The developers of tafenoquine deserve credit for persevering with this potentially valuable antimalarial drug, despite the difficulties, but it is too early to say whether tafenoquine can be used safely on a large scale in routine practice and thus fulfill its promise as a radical improvement in the treatment of malaria.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, and the Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom.

1. Douglas NM, Lampah DA, Kenangalem E, et al. Major burden of severe anemia from non-falciparum malaria species in southern Papua: a hospital-based surveillance study. PLoS Med 2013;10(12):e1001575.
2. Lacerda MVG, Llanos-Cuentas A, Krudsood S, et al. Single-dose tafenoquine to prevent relapse of *Plasmodium vivax* malaria. N Engl J Med 2019;380:215-28.
3. Llanos-Cuentas A, Lacerda MVG, Hien TT, et al. Tafenoquine versus primaquine to prevent relapse of *Plasmodium vivax* malaria. N Engl J Med 2019;380:229-41.
4. Sinton JA, Bird MW. Studies in malaria, with special reference to treatment: plasmoquine in the treatment of malaria. Indian J Med Res 1928;16:159-77.
5. Recht J, Ashley E, White N. Safety of 8-aminoquinoline antimalarial medicines. Geneva: World Health Organization, 2014 (https://www.who.int/iris/bitstream/10665/112735/1/9789241506977_eng.pdf?ua=1).
6. Rueangweerayut R, Bancone G, Harrell EJ, et al. Hemolytic potential of tafenoquine in female volunteers heterozygous for glucose-6-phosphate dehydrogenase (G6PD) deficiency (*G6PD Mahidol* variant) versus G6PD-normal volunteers. Am J Trop Med Hyg 2017;97:702-11.
7. Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, et al. Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. Lancet 2014;383:1049-58.

DOI: 10.1056/NEJMe1816383