Primaquine and *Plasmodium vivax* Malaria Recurrence in Brazil

Brian Greenwood, M.D., and Chris Drakeley, Ph.D.

Attempts to control malaria have been making good progress in South America, and two countries, Paraguay and Argentina, have recently been certified by the World Health Organization (WHO) as having achieved elimination of malaria. Brazil has the highest incidence of malaria in South America,[1] with 143,381 indigenous cases of malaria recorded in 2021, of which 84% were attributed to *Plasmodium vivax*. The elimination of *P. vivax* infection, which is critical to eliminating malaria, is challenging because of the ability of the parasite to persist in the liver as a quiescent hypnozoite and subsequently cause recrudescence months or years later.[2,3]

Until recently, primaquine was the only licensed antimalarial drug that could kill hypnozoites, but primaquine has now been joined by tafenoquine, which has the advantage of being given as a single dose.[4] Primaquine is not recommended for use in pregnant women or in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, in whom the drug may cause severe hemolytic anemia. The primaquine regimen that is currently recommended by the WHO for the prevention of *P. vivax* relapse is administered over a 14-day period and varies according to the prevalent strain in the particular climatic zone, with a total dose of 3.5 mg per kilogram of body weight (0.25 mg per kilogram per day) for strains endemic in temperate climates and a total of 7 mg per kilogram (0.5 mg per kilogram per day) for the frequently relapsing tropical strains endemic in East Asia and Oceania.[5] To find the safest, most effective, and most acceptable regimen for the prevention of *P. vivax* recrudescence, researchers have conducted many clinical trials of various other primaquine regimens, including 7-day administration and weekly doses given during an 8-week period.[6]

In this issue of the *Journal*, Chamma-Siqueira et al.[7] report the results of a study involving 254 Brazilian patients 5 years of age or older that evaluated the efficacy of three primaquine regimens in preventing the recurrence of *P. vivax* malaria in Amazonia. All the patients received initial treatment with chloroquine after being assigned to one of three groups. Those in group 1 (63 patients) were instructed to take a daily dose of 0.5 mg per kilogram of primaquine for 7 days (total dose, 3.5 mg per kilogram) with unobserved receipt, those in group 2 (96 patients) were assigned to receive the same regimen given under direct observation, and those in group 3 (95 patients) received the same daily dose administered under observation for 14 days (total dose, 7.0 mg per kilogram). Patients with severe malaria were excluded, as were patients with G6PD deficiency. Three recurrences of *P. vivax* infection occurred by day 28; these infections may have been due to chloroquine resistance, because plasma levels of chloroquine were high at the time of the recurrence. Seventy later recurrences were recorded. By day 168, the percentage of patients without *P. vivax* recurrence was 58% (95% confidence interval [CI], 44 to 70) in group 1, 59% (95% CI, 47 to 69) in group 2, and 86% (95% CI, 76 to 92) in group 3. Differences between group 1 and 3 and between group 2 and 3 were both significant (P<0.001). No major safety signals were observed.

Genotyping with the use of seven microsatellites was performed to try to determine whether recurrent infections were homologous or heterologous with respect to the original infection. Although this approach has some limitations,[3] it indicated that in the per-protocol analysis, homologous parasite recurrence occurred in 12 of 53 patients (23%) in group 1, in 17 of 78 patients (22%) in group 2, and in 4 of 79 patients (5%) in group 3, findings that further highlight the superiority of the higher-dose regimen.

Genotyping of the gene encoding cytochrome P450 2D6 (CYP2D6) was performed in samples obtained from 252 patients, of whom 22 patients in group 2 had phenotypes indicative of low or intermediate primaquine metabolism. By day 168, 64% of these patients remained free of recurrence, as compared with 54% of those with a

normal phenotype; in group 3, the corresponding percentages were 79% and 88%. Although the number of patients with low or intermediate metabolism was low, these findings suggest that the CYP2D6 genotype does not have any major effect on the efficacy of primaquine.

The study reported by Chamma-Siqueira et al. provides convincing evidence that in Brazil, a daily 14-day course of primaquine (total dose, 7.0 mg per kilogram) administered under observation was more effective than a 7-day course of the same daily dose, regardless of whether the administration was observed or unobserved. Adoption of the 14-day course of treatment would benefit patients in Brazil, but the administration of 14 days of treatment under direct observation could be difficult to achieve, especially in remote communities in Amazonia where the incidence of malaria can be high and where access to G6PD testing may not be readily available. Increasing the availability of reliable, rapid point-of-care tests for G6PD deficiency would allow for the use of the higher dose of primaquine or the use of tafenoquine in mass or targeted drug administration campaigns conducted as part of an elimination program,[8] but such administration would need to be carefully established. This study shows that when primaquine is administered at the right dose for a sufficient period of time, it is an effective treatment to prevent the recurrence of *P. vivax* malaria in South America.

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

From the Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London.

1. World malaria report 2021. Geneva: World Health Organization, 2021.
2. Robinson LJ, Wampfler R, Betuela I, et al. Strategies for understanding and reducing the *Plasmodium vivax* and *Plasmodium ovale* hypnozoite reservoir in Papua New Guinean children: a randomised placebo-controlled trial and mathematical model. PLoS Med 2015;12(10):e1001891.
3. Auburn S, Cheng Q, Marfurt J, Price RN. The changing epidemiology of *Plasmodium vivax:* insights from conventional and novel surveillance tools. PLoS Med 2021;18(4):e1003560.
4. 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.
5. WHO guidelines for malaria. Geneva: World Health Organization. February 18, 2022 (https://www.who.int/publications/i/item/guidelines-for-malaria).
6. Milligan R, Daher A, Graves PM. Primaquine at alternative dosing schedules for preventing relapse in people with Plasmodium vivax malaria. Cochrane Database Syst Rev 2019;7:CD012656.
7. Chamma-Siqueira NN, Negreiros SC, Ballard S-B, et al. Higher-dose primaquine to prevent relapse of *Plasmodium vivax* malaria. N Engl J Med 2022;386:1244-53.
8. Nekkab N, Lana R, Lacerda M, et al. Estimated impact of tafenoquine for Plasmodium vivax control and elimination in Brazil: a modelling study. PLoS Med 2021;18(4):e1003535.

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