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Single-dose radical cure of *Plasmodium vivax*: a step closer

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Almost 40% of the world's population is at risk of *Plasmodium vivax* infection, with 70–390 million clinical episodes occurring each year.[1] Unlike *Plasmodium falciparum*, *P vivax* forms hypnozoite stages, which can lie dormant in the liver for months or even years before emerging to cause malaria relapses. The risk, frequency, and timing of these relapses vary with the geographical location of infection and host immunity.[2] The chronic relapsing nature of the disease can cause severe anaemia, miscarriage in pregnant women, malnutrition, and developmental delay in young children; the associated morbidity and economic burden of these manifestations is considerable.[3]

A radical cure for malaria requires treatment that targets both the erythrocytic and liver stages of infection. For more than 60 years, radical cure of *P vivax* has relied on primaquine —the only licensed antimalarial with proven hypnozoitocidal activity. However, primaquine has several major shortcomings. It can cause severe haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked disorder present in 1–40% of the population.[4] WHO guidelines recommend a 14-day primaquine regimen, but since treatment is usually unsupervised, adherence is generally poor, limiting effectiveness and public health benefit.[5] Tafenoquine was designed as a synthetic analogue of primaquine with a slower elimination time, allowing shorter courses to be given. Despite its pragmatic advantages over current options, progress in bringing tafenoquine to market has been slow. It has been 20 years since the first reports of its schizontocidal efficacy in rodent malaria[6] and 10 years since the early clinical studies.[7]

In *The Lancet*, Alejandro Llanos-Cuentas and colleagues[8] present a much anticipated comparative study of single-dose tafenoquine for the radical cure of *P vivax*. This multicentre, double-blind, phase 2b clinical trial randomly allocated 329 patients to receive one of six regimens: a single dose of 50 mg, 100 mg, 300 mg, or 600 mg tafenoquine, 14 days of primaquine (15 mg per day), or placebo. All patients received chloroquine for 3 days to ensure initial clearance of the erythrocytic stages of the parasites. The primary objective was to show superiority of chloroquine plus tafenoquine over chloroquine alone, as assessed by recurrence of *P vivax* infection within 6 months. The results are impressive: 6 months

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after being assigned chloroquine plus tafenoquine 300 mg, 89·2% (95% CI 77–95) of patients remained free from *P vivax* recurrence compared with only 37·5% (23–52) of patients assigned to chloroquine alone. The 600 mg dose offered little benefit (91·9% [80–97] efficacy) over the 300 mg dose, and the lower tafenoquine doses were significantly worse (both <58%). As expected, the proportion of patients who had recurrent *P vivax* infection after chloroquine monotherapy varied substantially between sites, ranging from 10% in India, to 44% in Thailand, 83% in Brazil, and 88% in Peru. The superiority of tafenoquine 300 mg was apparent at all sites except India, where the sample size was small and risk of recurrence low.

Clinical trials of antirelapse treatment are challenging to do and difficult to interpret.[9] Latency can result in *P vivax* relapses occurring a year or more after the primary infection, so long-term follow-up is necessary.[10] Furthermore, relapse with homologous recurrences are more likely to be asymptomatic. In the study by Llanos-Cuentas and colleagues,[8] follow-up was curtailed at 6 months, and in the latter half of follow-up routine visits were 30–60 days apart. Hence a proportion of relapses might have gone undetected, either because they were transient or occurred after the end of the study. Conversely, prolonged follow-up in an endemic setting increases the risk of reinfection with new strains of *P vivax*. No tests to discriminate reliably between recrudescence, relapse, or reinfection are available.[11] These factors confound estimates of absolute antirelapse efficacy. However, in this randomised study,[8] confounders should have been equally distributed between treatment groups, allowing the authors to conclude the superiority of tafenoquine compared with patients receiving no hypnozoitocidal treatment.

Tafenoquine, like primaquine, is an 8-aminoquinoline compound with potential to cause substantial haemolysis in patients with G6PD deficiency, and its long elimination half-life increases the risk of an extended period of haemolysis. Reassuringly, tafenoquine was well tolerated with no evidence of increased adverse events compared with the other treatments. In fact, the mean fall in haemoglobin a week after treatment with tafenoquine 300 mg was 0·6% (95% CI −8·9 to 4·4), compared with 2·2% (−6·4 to 2·1) after chloroquine alone and 1·4% (−5·9 to 0·8) after chloroquine plus primaquine. However, the study excluded patients with G6PD enzyme activity below 70%, and patients younger than 16 years. The crucial question is whether the benefits of tafenoquine in reduction of recurrent *P vivax* can outweigh the risk of haemolysis in a large enough population to ensure public health benefit. A reliable point-of-care test for G6PD deficiency will need to be developed to identify patients with unacceptable risk of haemolysis if prescribed tafenoquine.

An equally important question is whether a single dose of tafenoquine is as good as recommended treatments. Overall, the efficacy of tafenoquine 300 mg was 89·2% compared with 77·3% (95% CI 63–87) for primaquine; however, this difference should be interpreted with caution because the comparison was not defined a priori. Additionally, only the first 3 days of primaquine were supervised, so incomplete treatment might have resulted in a proportion of treatment failures. Furthermore, low-dose primaquine (total dose 3·5 mg/kg) is recognised to be less efficacious than high-dose primaquine regimens (total dose >6 mg/kg).[9] The efficacy of tafenoquine will need to be compared formally with both low-dose and high-dose primaquine regimens in phase 3 clinical studies.

Llanos-Cuentas and colleagues should be congratulated for completing a challenging clinical trial and providing the first convincing evidence that a single dose of tafenoquine 300 mg can deliver high hypnozoitocidal efficacy across a range of endemic settings. If subsequent clinical trials can confirm safety and comparative efficacy against current treatment options, and the drug can be deployed widely to patients, then a single-dose tafenoquine radical cure has potential to transform *P vivax* therapeutics and become a major contributor to malaria elimination.

References

1. Gething PW, Elyazar IR, Moyes CL, et al. A long neglected world malaria map: *Plasmodium vivax* endemicity in 2010. PLoS Negl Trop Dis. 2012; 6:e1814. [PubMed: 22970336]
2. White NJ. Determinants of relapse periodicity in *Plasmodium vivax* malaria. Malar J. 2011; 10:297. [PubMed: 21989376]
3. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax malaria: neglected and not benign. Am J Trop Med Hyg. 2007; 77(suppl):79–87. [PubMed: 18165478]
4. Howes RE, Piel FB, Patil AP, et al. G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. PLoS Med. 2012; 9:e1001339. [PubMed: 23152723]
5. Baird JK, Hoffman SL. Primaquine therapy for malaria. Clin Infect Dis. 2004; 39:1336–45. [PubMed: 15494911]
6. Peters W, Robinson BL, Milhous WK. The chemotherapy of rodent malaria. LI. Studies on a new 8-aminoquinoline, WR 238,605. Ann Trop Med Parasitol. 1993; 87:547–52. [PubMed: 8122915]
7. Walsh DS, Wilairatana P, Tang DB, et al. Randomized trial of 3-dose regimens of tafenoquine (WR238605) versus low-dose primaquine for preventing *Plasmodium vivax* malaria relapse. Clin Infect Dis. 2004; 39:1095–103. [PubMed: 15486831]
8. 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. 2013 published online Dec 19. http://dx.doi.org/10.1016/S0140-6736(13)62568-4.
9. John GK, Douglas NM, von Seidlein L, et al. Primaquine radical cure of *Plasmodium vivax*: a critical review of the literature. Malar J. 2012; 11:280. [PubMed: 22900786]
10. Sutanto I, Tjahjono B, Basri H, et al. Randomized, open-label trial of primaquine against vivax malaria relapse in Indonesia. Antimicrob Agents Chemother. 2013; 57:1128–35. [PubMed: 23254437]
11. Price RN, Auburn S, Marfurt J, Cheng Q. Phenotypic and genotypic characterisation of drug-resistant *Plasmodium vivax*. Trends Parasitol. 2012; 28:522–29. [PubMed: 23044287]

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