

EDITORIAL COMMENTARY

The antimalarial activity of tafenoquine in falciparum malaria

Nicholas J. White, M.D., FRS

¹Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; ²Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, Oxford University, United Kingdom.

It is almost one hundred years since the first 8-aminoquinoline antimalarial (pamaquine or plasmoquine) was introduced into medicine [1]. This discovery was the successful result of an innovative chemical screen in canaries infected with *Plasmodium relictum* (which may have been the first high throughput screen in the pharmaceutical industry). The 8-aminoquinoline class of compounds has remarkable antimalarial properties. They inhibit pre-erythrocytic (liver stage) development (and so they are effective chemoprophylactics), they have blood stage activity (providing additional activity in treatment regimens for vivax and ovale malaria with artemisinin combination treatments [ACTs] or chloroquine), they kill mature gametocytes of *Plasmodium falciparum* (in endemic areas primaquine is given in single low dose of 0.25mg base/kg together with ACTs to reduce the transmission potential of falciparum malaria), and they have unique radical curative properties (preventing relapses of vivax or ovale malarias). However, despite a century of investigation and use in billions of treatments, it is still not clear exactly how these venerable antimalarial drugs work. Recent studies show that metabolism to reactive oxidative intermediates is necessary for their antimalarial activity [2-4]. These active metabolites are also responsible for the major 8-aminoquinoline toxicity; hemolysis in people with glucose 6 phosphate dehydrogenase deficiency. As G6PD deficiency is so common in malaria endemic areas whereas testing is often unavailable, this potential for hemolytic toxicity

Correspondence: Nicholas J. White, M.D., FRS nickw@tropmedres.ac

© The Author(s) 2023. Published by Oxford University Press on behalf of Infectious Diseases Society of America. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com This article is published and distributed under the terms of the Oxford University Press, Standard Journals Publication Model (https://academic.oup.com/journals/pages/open_access/funder_policies/chorus/standard_publication_model)

is a major limitation to 8-aminoquinoline general use for preventing relapses (radical cure) of vivax or ovale malaria [5]. It contributes substantially to the difficulty in eliminating *Plasmodium vivax*.

Primaquine has been the only widely deployed 8-aminoquinoline since the 1950s. In general, primaquine has fared well with relatively few reports of serious toxicity and good tolerability (if taken with food which avoids abdominal discomfort) but, because G6PD testing is often unavailable, it is underused [5]. Primaquine is eliminated rapidly so radical cure regimens require 7 to 14 days of once or twice daily treatments. These can be operationally challenging. Extending a long line of antimalarial chemotherapy research, in 1978 the US Army discovered a slowly eliminated 8-aminoquinoline which we now call tafenoquine. Tafenoquine was engineered to be slowly eliminated -the terminal elimination half-life is approximately 15 days compared with 5 hours for primaquine [6]. After a long and difficult program of development tafenoquine has now been licensed in some countries for both prophylaxis and treatment. Tafenoquine has the substantial advantage of providing a radical cure regimen in a single oral dose [7] (although that dose for adults should probably be 450 mg base equivalent rather than the currently recommended 300mg [4]). Vivax malaria is often a major cause of illness in children and tafenoquine is not yet licensed for children but there seems no reason why this label extension will not be approved [8].

In-vivo primaquine has good blood stage activity against *P. vivax* [9], but weak activity against *P. falciparum* [10]. Testing these drugs in ex-vivo systems is compromised by the need to generate their active metabolites. The parent drugs have very weak or no activity. During the development of tafenoquine it was estimated that its asexual stage activity against *Plasmodium falciparum* was better than for primaquine [11]. In this edition Barber and colleagues have used their well-established controlled human infection with malaria (CHIM) [12] to evaluate the in-vivo blood stage activity of tafenoquine against *P. falciparum* [13]. The pharmacodynamic measure was malaria parasite clearance measured by serial quantitative PCR [14]. Pathogen densities in the blood in malaria are sufficient for quantitation at levels which are up to three orders of magnitude lower than those which cause illness ('pyrogenic densities'). Drug assessments can therefore be made in volunteers who are infected but remain well. Rates of parasite clearance are accelerated by effective drugs and can be used as comparative pharmacodynamic measures in pharmacometric assessments [15]. In general parasite clearance in malaria is a first-order process. Thus, a single rate constant derived from the slope of the log-linear decline in parasite densities can be used to describe antimalarial activity. In falciparum malaria this log-linear decline is confounded by sequestration, in which the erythrocytes infected with *P. falciparum* cytoadhere to vascular endothelium after the first third of their approximate two days asexual cycle [16]. The compound result is a declining wave form. Resolution in this study of tafenoquine blood stage activity is insufficient to determine whether or not this is a confounder (i.e. whether or not tafenoquine has ring stage activity). Nevertheless, the results show clearly that tafenoquine has moderately good blood stage activity against *P. falciparum*.

[13], confirming earlier assumptions. This CHIM model [12] has proved valuable in the early clinical assessment of antimalarial drugs. Although the healthy volunteers are not ill, and have therefore not activated their innate host-defense mechanisms to the extent that a patient sick with malaria has, the results in the CHIM model across antimalarial drugs generally do reflect the activities observed in treatment studies.

What are the therapeutic implications of these findings? Pharmacometric modelling based on the study results suggests that the currently recommended adult dose of 300mg would be insufficient to provide reliable cure of a symptomatic infection [13]. But Tafenoquine would not be used alone for the treatment of symptomatic malaria, it would be combined with other drugs. In all malarias it would provide additional blood stage activity and so would provide “resistance protection” to the co-administered slowly eliminated antimalarial drug. For falciparum malaria triple ACTs (as opposed to the current two drug combinations) are currently under consideration in order to protect our few available antimalarial drugs as artemisinin resistance spreads [18]. For the treatment of a mixed infections, adding tafenoquine to an ACT would provide useful additional blood stage activity to ACTs as well as the hypnozoitocidal activity. In some areas where *P. vivax* relapse rates following *P. falciparum* infections are very high [17], a case could be made for adding a radical cure regimen to all falciparum malaria treatments. In these various contexts of potential use tafenoquine would only be a suitable addition if quantitative G6PD testing was available to ensure the potential recipients had >70% of normal G6PD activity. Finally, there is increasing appetite again for mass treatment as a malaria elimination accelerator. As discussed by Barber et al [13] mass treatments with primaquine have been used to eliminate vivax malaria [19]. Tafenoquine would be simpler to administer and its greater *P. falciparum* activity would be a bonus, although the need to conduct accurate mass quantitative G6PD testing would be a substantial operational obstacle – and the risk of serious hemolysis if mistakes occurred would be considerable.

NOTES

Funding: I am a Wellcome Trust Principal Fellow: 223099/Z/21/Z

Conflicts of Interest: none

References

1. Mühlens P. Die behandlung der natuerlichen menschlichen malaria-infektionen mit Plasmochin. Arch Schiffs-u Tropenhyg 1926; 30: 25–32.
2. Pybus BS, Marcsisin SR, Jin X, et al. The metabolism of primaquine to its active metabolite is dependent on CYP 2D6. Malar J. 2013 ;12: 212.
3. Camarda G, Jirawatcharadech P, Priestley RS et al. Antimalarial activity of primaquine operates via a two-step biochemical relay. Nature Communications. 2019; 10: 3226.

4. Watson JA, Commons RJ, Tarning J et al. The clinical pharmacology of tafenoquine in the radical cure of *Plasmodium vivax* malaria: An individual patient data meta-analysis. *Elife*. 2022;11: e83433.
5. Recht J, Ashley E, White N. Safety of 8-aminoquinoline antimalarial medicines. World Health Organization, Geneva, 2014.
6. Thakkar N, Green JA, Koh GCKW, Duparc S, Tenero D, Goyal N. Population Pharmacokinetics of Tafenoquine, a Novel Antimalarial. *Antimicrob Agents Chemother*. 2018; 62: e00711-18.
7. 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: 229-241.
8. Vélez ID, Hien TT, Green JA et al. Tafenoquine exposure assessment, safety, and relapse prevention efficacy in children with *Plasmodium vivax* malaria: open-label, single-arm, non-comparative, multicentre, pharmacokinetic bridging, phase 2 trial. *Lancet Child Adolesc Health*. 2022; 6: 86-95.
9. Dow G, Smith B. The blood schizonticidal activity of tafenoquine makes an essential 355 contribution to its prophylactic efficacy in nonimmune subjects at the intended dose 356 (200 mg). *Malar J* 2017; 16: 209
10. Pukrittayakamee S, Chantira A, Simpson JA et al. Therapeutic responses to different antimalarial drugs in vivax malaria. *Antimicrob Agents Chemother*. 2000; 44: 1680-5.
11. Arnold J, Alving AS, Hockwald RS et al. The antimalarial action of primaquine against the blood and tissue stages of falciparum malaria (Panama, P-F-6 strain). *J Lab Clin Med*. 1955; 46: 391-7.
12. McCarthy JS, Sekuloski S, Griffin PM, et al. A pilot randomised trial of induced blood-stage *Plasmodium falciparum* infections in healthy volunteers for testing efficacy of new antimalarial drugs. *PLoS One* 2011; 6: e21914.
13. Barber BE, Abd-Rahman AN, Webster R, et al Characterizing the blood stage antimalarial activity of tafenoquine in healthy volunteers experimentally infected with *Plasmodium falciparum*. *Clin Infect Dis* 2023;
14. Marquart L, Baker M, O'Rourke P, McCarthy JS. Evaluating the pharmacodynamic effect of antimalarial drugs in clinical trials by quantitative PCR. *Antimicrob Agents Chemother* 2015; 59: 4249-59
15. White NJ. Assessment of the pharmacodynamic properties of antimalarial drugs in vivo. *Antimicrob Agents Chemother*. 1997; 41: 1413-22.
16. White NJ. Malaria parasite clearance. *Malar J*. 2017; 16: 88.
17. Commons RJ, Simpson JA, Thriemer K, et al. Risk of *Plasmodium vivax* parasitaemia after *Plasmodium falciparum* infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2019; 19: 91-101.
18. Dhorda M, Amaratunga C, Dondorp AM. Artemisinin and multidrug-resistant *Plasmodium falciparum* - a threat for malaria control and elimination. *Curr Opin Infect Dis*. 2021; 34: 432-439.
19. Kondrashin A, Baranova AM, Ashley EA, Recht J, White NJ, Sergiev VP. Mass primaquine treatment to eliminate vivax malaria: lessons from the past. *Malar J*. 2014; 13: 51.