

Tafenoquine and its potential in the treatment and relapse prevention of *Plasmodium vivax* malaria: the evidence to date

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Abstract: Despite declining global malaria incidence, the disease continues to be a threat to people living in endemic regions. In 2015, an estimated 214 million new malaria cases and 438,000 deaths due to malaria were recorded. *Plasmodium vivax* is the second most common cause of malaria next to *Plasmodium falciparum*. Vivax malaria is prevalent especially in Southeast Asia and the Horn of Africa, with enormous challenges in controlling the disease. Some of the challenges faced by vivax malaria-endemic countries include limited access to effective drugs treating liver stages of the parasite (schizonts and hypnozoites), emergence/spread of drug resistance, and misperception of vivax malaria as nonlethal. Primaquine, the only 8-aminoquinoline derivative approved by the US Food and Drug Administration, is intended to clear intrahepatic hypnozoites of *P. vivax* (radical cure). However, poor adherence to a prolonged treatment course, drug-induced hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, and the emergence of resistance make it imperative to look for alternative drugs. Therefore, this review focuses on data accrued to date on tafenoquine and gives insight on the potential role of the drug in preventing relapse and radical cure of patients with vivax malaria.

Keywords: vivax malaria, radical cure, schizonts, hypnozoite, primaquine

Introduction

Among *Plasmodium* species causing malaria in humans, *Plasmodium falciparum* and *Plasmodium vivax* are the most common causes of malaria. Despite progress in reducing global malaria incidence by 37%, an estimated 214 million new cases of malaria and 438,000 deaths caused by the disease were recorded in 2015. Africa was the most severely affected region, with 88% of global malaria incidence followed by Southeast Asia where 10% of the global incidence was reported.¹⁻³

P. vivax is the second most common cause of malaria in humans next to *P. falciparum*. In 2015, an estimated 13.8 million new cases were reported globally. The highest vivax incidence was recorded in Southeast Asia (74%), followed by the Eastern Mediterranean Region (11%) and Africa (10%).^{2,3} Surprisingly, 80% of global vivax malaria cases were reported from three countries, Ethiopia, India, and Pakistan.¹ Even though *P. vivax* is widely distributed, its global incidence rate is wrongly perceived to be low. Some factors that explain underestimation of vivax malaria incidence include microscopic misreading as falciparum in co-endemic areas and presence of undetectable parasitemia among symptomatic patients and liver hypnozoites among asymptomatic patients.^{2,4-11}

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Hypnozoites and relapse of malaria

Human infection with *Plasmodium* species starts when sporozoites are injected into the blood circulation while female *Anopheles* mosquito feeds on human blood. These sporozoites then migrate shortly to the liver hepatocytes and enter the exoerythrocytic cycle, in which high numbers of schizonts are produced mitotically. Within 5–15 days of liver infection, thousands of merozoites are released and enter blood circulation. The merozoites then infect red blood cells (RBCs), and this constitutes the erythrocytic cycle that repeats many times in a course of single malaria episode. The erythrocytic cycle produces an average of 8–32 new merozoites and gametocytes per infected RBC. When female *Anopheles* mosquitoes feed on blood of infected individuals, these gametocytes are ingested and begin sporogonic phase in the gut of mosquitoes, thereby perpetuating vivax infection (Figure 1).^{8,9,12–17}

However, a few hepatic schizonts of *P. vivax* and *Plasmodium ovale* hibernate instead of migrating to the vascular RBCs. These dormant stages, called hypnozoites, are capable of reactivation and could cause relapse of malaria weeks, months, or even years after the first malaria episode.^{8,9,12} The underlying mechanisms for reactivation are not thoroughly understood. However, factors related to relapse of malaria include the adaptive trait of the parasites, geographical variations, the presence of other febrile illness,

and dose of the injected sporozoites.^{9,18,19} A pooled analysis of data from studies published in English that included 87,000 patients with acute vivax malaria reported that ~20% of the patients experienced malaria relapse, with a relapse rate ranging from 0% to 100%.¹⁹ Studies have also identified that the events of vivax relapse are associated with patient and parasite factors.^{20,21}

Malaria interventions

Global malaria incidences reduced from 262 million in 2000 to 214 million in 2015. The World Health Organization has also planned to eliminate malaria in more than 20 countries by 2025 through implementation of integrated malaria control programs that use interventions such as vector control, effective diagnosis, and use of artemisinin-based combinations therapies.^{1,3,22,23} Moreover, RTS, S, a recombinant protein-based malaria vaccine, which has been approved by the European Medicines Agency, with a protective efficacy of ~26% in young infants and 36% in children,²⁴ may also be integrated with other tools in malaria control.

Vector control

In sub-Saharan Africa, ~50% of the population used either insecticide-treated mosquito nets or indoor residual spraying to prevent malaria in 2013.^{3,25} Despite emergence of

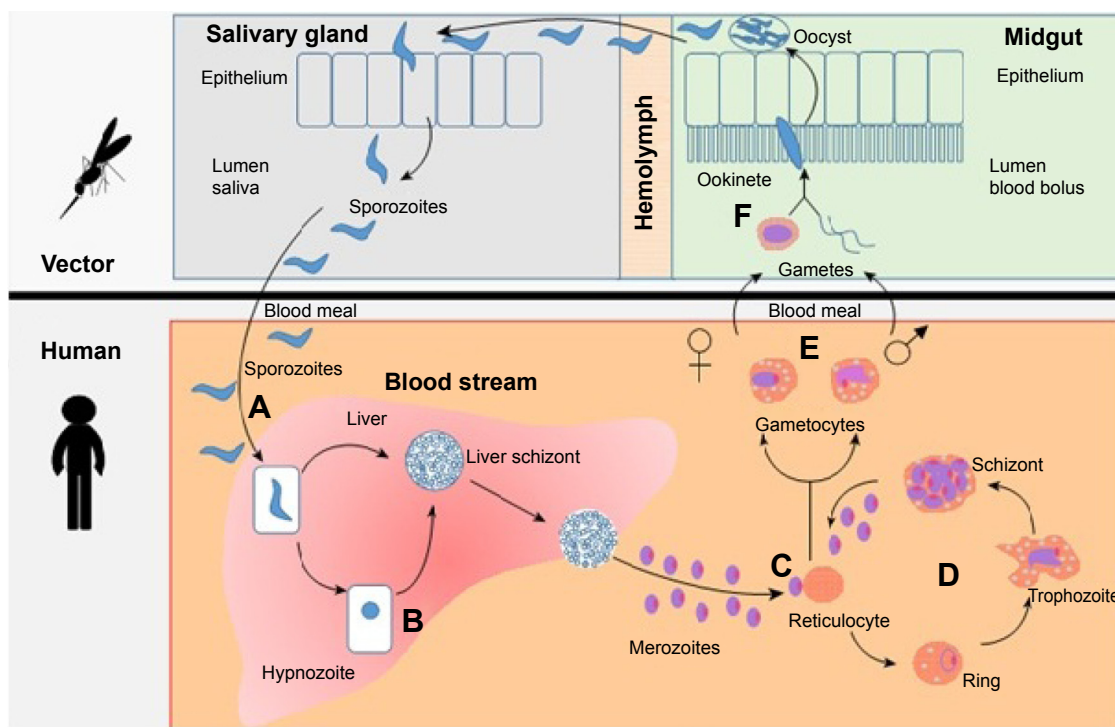


Figure 1 Life cycle of *P. vivax* and hypnozoite.

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Abbreviation: *P. vivax*, *Plasmodium vivax*.

pyrethroid-resistant *Anopheles* mosquitoes (mainly *Anopheles gambiae* and *Anopheles funestus*) worldwide, countries such as Ethiopia, Zambia, and Rwanda have reduced malaria incidence by more than two-thirds compared to what was projected for the countries between 2000 and 2011. Similarly, 4% of global and 7% of African populations were protected from malaria by indoor residual spraying in 2013.^{2,26–30}

Malaria diagnosis

Accurate diagnosis and prompt treatment of all patients with proper antimalarial drugs is one of the essential components of malaria control and elimination strategies. Early diagnosis and treatment of acute cases is the primary approach to reduce mortality and morbidity.^{31,32} Diagnosis of malaria is done based on a defined set of criteria. Even though any patient with acute febrile illness should be a malaria suspect, the criteria, particularly the parasite density, may vary with the level of malaria transmission intensity. The World Health Organization also recommends that parasitological confirmation of malaria cases should be done with either microscopy or rapid diagnostic test in order to improve care of parasite-positive patients.^{33–35}

Current approaches applied for controlling *P. falciparum* malaria may not be effective against *P. vivax*. Control program against *P. vivax* is proven to be a formidable task due to lack of suitable diagnostic tools to detect low vivax parasitic loads during blood stage, presence of hypnozoites, and lack of effective whole stage drugs against vivax.^{2,7,11,19,36}

Treatment of uncomplicated vivax

Chloroquine (CQ) is still the first line of treatment for malaria due to *P. vivax* infection³⁷ although CQ-resistant *P. vivax* has been identified in various countries.³⁸ A review of ten nonrandomized trials showed that the therapeutic success of CQ at 28 days of follow-up ranges from 49.2% to 96.2%.³⁹ In addition to CQ, *P. vivax* and *P. ovale* infections require treatment with primaquine (PQ) for radical cure because of the presence of hypnozoites in their life cycles. In areas with CQ-resistant *P. vivax*, artemisinin-based combinations therapies containing piperazine, mefloquine, or lumefantrine are the recommended treatments.^{40,41} Artemisinin-based combinations therapies are also effective^{37,42–44} for treatment of malaria due to coinfection with multiple species.^{43–45} Radical treatment with PQ is needed for *P. vivax* or *P. ovale* coinfections.³⁷

Treatment of complicated vivax

P. vivax is considered relatively benign disease,⁴⁶ even though manifestations such as severe anemia and acute respiratory distress syndrome are encountered occasionally.⁴⁷ A recent

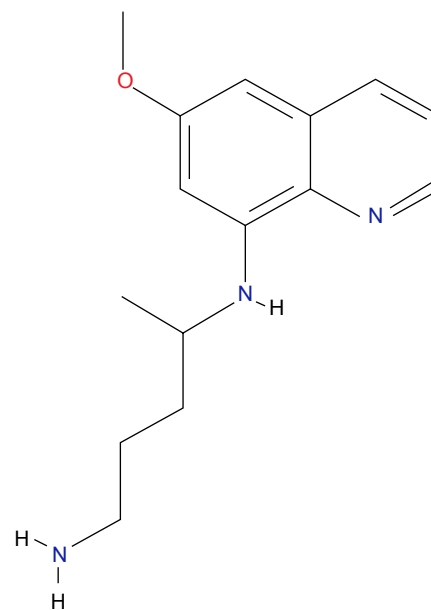


Figure 2 Chemical structure of PQ.⁹⁹
Abbreviation: PQ, primaquine.

systematic review highlights a marked increase of reported cases of severe vivax in certain *P. vivax*-endemic regions of the world.⁴⁷ Patients with severe vivax malaria are treated aggressively with either parenteral cinchona alkaloids, ie, quinine or quinidine, or artemisinin derivatives, preferably intravenous artesunate.⁴⁸

P. vivax infections that recur after drug treatment may be a recrudescence of asexual blood-stage parasites that survived drug treatment, reinfection from new mosquito inoculation, or relapse due to hypnozoites.⁴¹

Patients with vivax malaria may benefit from the major blood schizonticidal agents only for clinical cure. Similarly, chemoprophylaxis with blood schizonticidal agents provides only suppressive (clinical) prophylaxis.⁴⁹ Hence, a drug targeting the hepatic stages of primary schizonts and secondary schizonts (hypnozoites) would be critical for causal prophylaxis, terminal prophylaxis/presumptive anti-relapse therapy (PART), and radical cure of infection caused by vivax malaria.⁵⁰ PQ, a synthetic derivative of quinine,⁵¹ has been instrumental in these aspects⁵² (Figure 2).

Malaria prophylaxis

Causal prophylaxis

So far, eight clinical studies with different research designs, including experimental challenge studies, controlled trials, and prospective observational studies, have been conducted to evaluate the efficacy of PQ in preventing malaria. The results from these studies showed PQ's protective efficacy against vivax malaria at 30 mg/d to be >85%.⁵⁰ In these

studies, PQ was started 1 day before travel to an endemic area and continued throughout the stay in the area as well as for 7 days after return. However, PQ is not being used as a causal prophylactic agent in many countries up until now.⁵³

Terminal prophylaxis

Terminal prophylaxis is alternatively called PART. PQ is used for PART with a regimen of 15 mg/d orally for 14 days immediately after the individuals have traveled out of vivax-endemic areas.⁵⁴ Terminal prophylaxis is considered for persons who have resided for prolonged periods (eg, ≥ 6 months) in high-risk vivax-endemic areas or who experience intense exposure to *P. vivax*.⁵⁰

Radical cure

A standard PQ therapy of 15 mg/d orally for 14 days has been reported to fail in preventing relapse in different geographic locations such as the Solomon Islands, Southeast Asia, Brazil, Colombia, Guyana, Guatemala, Somalia, Ethiopia, Afghanistan, and elsewhere.^{50,55} These reports may not represent actual failures of the 15 mg daily regimen since the extent of adherence to the recommended regimen and quality of the medications were not confirmed in these studies.

A meta-analysis evaluated the efficacy of PQ in preventing vivax malaria recurrence in 59,735 patients.⁵⁵ A marked heterogeneity was noted in the study design and particularly on PQ dosing. Despite differences in design, it was possible to draw a conclusion from 87 clinical trials selected for the systematic review. Three dose ranges of PQ, expressed as total doses per kilogram, were considered. The dose ranges included very low (< 2.5 mg/kg body weight), low (> 2.5 mg/kg– < 5.0 mg/kg body weight), and high (≥ 5.0 mg/kg body weight). The median rate of recurrence following very low dose of PQ in 44 studies was 25% (range, 0%–90%) at 4–6 months, whereas in 82 studies following low dose of PQ, the recurrence was 6.7% (range, 0%–59%) at 4–6 months. High-dose PQ regimens assessed in 28 treatment arms were associated with a median recurrence rate of 0% (range, 0%–15%) at 1 month. Some strains of *P. vivax* may also show inherent resistance to 15 mg/d regimen without any previous exposure to PQ. Taking all these into consideration, higher doses of PQ (30 mg base for 14 days; 420 mg total dose) are administered to prevent relapse in some regions.^{50,56}

Why PQ use is not at its maximum?

Even though PQ was licensed for use in 1952 for the prevention and cure of malaria, its use is not maximized to the need of the society.⁵⁷ The major factor that limits the wide usage

of PQ is the high risk of hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.⁵²

Hemolysis related to G6PD deficiency

Polymorphisms of the G6PD gene are numerous, with G6PD deficiency due to single-point mutations, deletions, insertions, and rarely, splicing variants.⁵⁸ Approximately 400 variant alleles have been described.⁵⁹ The overall prevalence of G6PD deficiency allele across malaria-endemic countries is estimated to be 8.0% (interquartile range, 7.4–8.8). Using the 2010 population data, this corresponds to 220 million males (interquartile range, 203–241) and an estimated 133 million females (interquartile range, 122–148), including 17 million homozygous females.⁶⁰

Treatment of 22 G6PD-deficient patients in Thailand with a 3-day course of CQ followed by PQ, 15 mg/d for 14 days, resulted in a significant reduction in hematocrit. The treatment did not result in blood transfusion.⁶¹ Another report from Brazil revealed the risks of hemolysis in 18 patients who were referred to a tertiary care unit after therapy with PQ (0.5 mg/kg/day for 7 days) for radical cure. All patients had jaundice, 14 patients had dark urine, and one patient presented with low urinary output. Blood transfusion was required in 12 out of the 18 patients included in the study due to PQ-induced hemolysis. A patient who developed severe renal failure required hemodialysis. The study confirmed that all the abovementioned adverse phenomena were associated with the patients' G6PD deficiency.⁶² The association between the extent of PQ-induced hemolysis and the dose of PQ as well as degree of G6PD deficiency is well established.⁴⁰ Hence, it is recommended that patients are tested for G6PD deficiency before treatment with PQ and many countries restrict the use of PQ, including single-dose treatment, for the gametocidal purpose.⁶³

Other adverse effects associated with PQ

Though not a major reason for abandoning the use of PQ, individuals taking PQ can develop additional adverse effects such as gastrointestinal discomfort and methemoglobinemia.⁵⁴ Administration of 22.5–30 mg of PQ per day resulted in mild-to-moderate abdominal cramps in 10%–12% of patients.⁵² Standard PQ therapy elevates methemoglobin levels slightly⁵⁴ and could be treated with intravenous methylene blue. However, in the presence of G6PD deficiency, patients may not respond to treatment.⁶⁴

Need for high dose for a better outcome

Evidence for failure of the standard PQ regimen, which is 15 mg/d orally for 14 days, in preventing relapse emerged

from experimental challenge with the Chesson strain of *P. vivax*. This strain was isolated from an American soldier infected in New Guinea in 1944.⁶⁵ Another trial in Thailand demonstrated reduced efficacy of a 15 mg PQ regimen in preventing relapse.⁶⁶ A study in Germany also demonstrated that infection acquired on the islands of New Guinea had a high risk of relapse after PQ therapy.⁶⁷ The higher dose required to tackle PQ-resistant vivax in radical cure or terminal prophylaxis would increase dose-dependent adverse effects from the drug.

Tafenoquine: the next generation 8-aminoquinoline

Currently available antimalarial drugs are stage specific. Drugs such as PQ have activity mainly on hypnozoites and hence help in preventing relapse, while drugs such as CQ have effect on blood stages (asexual stages), which makes it important for clinical cure of patients with malaria. This fact should attract researchers to work further in discovering and developing products that target multiple stages of the *Plasmodium*. Efforts are also being exerted to come up with a better alternative drug that can be used in treatment failures due to resistance and that shorten treatment duration. As an example, PQ's liabilities include prolonged treatment duration; increasing trend of failing treatments, particularly at 15 mg/d regimen; and the risk of hemolytic anemia in G6PD-deficient patients. These identified gaps in PQ treatment should put a pressure on the scientific community to search for alternative interventions that can fill these gaps.

The 8-aminoquinoline tafenoquine (TQ; WR 238605) was discovered by scientists at the Walter Reed Army Institute of Research in 1978. It is currently being developed in a collaborative approach between GlaxoSmithKline and Medicines for Malaria Venture.⁶⁸

Pharmacokinetics of TQ Bioavailability and absorption

First-time-in-humans safety and pharmacokinetics study showed that the time to peak concentration (t_{max}) of TQ is 13.8 hours. This study speculated that the prolonged absorption from the gut could be due to absorption at distal gastrointestinal tract combined with the drug's slow clearance.⁶⁹ In a Phase I trial involving 156 individuals taking different doses of TQ, it was demonstrated that TQ is slowly absorbed. The median t_{max} values for TQ were 15 hours for the 300 mg dose and 12 hours for the 600 mg and 1,200 mg doses. Area under the curve and maximum concentration observed (C_{max}) exhibited moderate intersubject variability.⁷⁰

Bioavailability of TQ increases when the drug is taken with high-fat meal.⁷¹ From a population kinetics study of TQ in Thai soldiers, it was demonstrated that food affects the amount of TQ absorbed, rather than the rate of absorption.⁷²

Distribution

TQ has a large volume of distribution (~2,560 L) and a low clearance (~6 L/h).⁶⁹ Though body weight affects the plasma concentration in general, females tended to achieve higher drug concentrations compared to males of equivalent weight.⁷³ The concentration of TQ in whole blood is approximately twofold higher than the corresponding concentration in plasma. In individuals with a normal hematocrit of 45%, the drug concentration in the erythrocytes is estimated to be threefold higher than that in plasma. However, there is no change in accumulation of the drug in RBCs over time.⁶⁹ Little is known about the distribution of TQ to extra vascular tissues in human beings, but animal study showed that the drug is highly distributed to the liver. Area under the curve up to the last measurable concentration (AUC_{last}) in the liver after intravenous administration is ~80 times more than that in the plasma.⁷⁴

Metabolism and excretion

Like PQ,⁷⁵ the activation of TQ needs metabolism by cytochrome P450 2D6 (CYP2D6) liver microsomal enzyme.^{76,77} This was demonstrated by the lack of the anti-malarial activity of TQ in CYP2D6 knockout mice when given at a dose of 3 mg/kg and the partial restoration of its antimalarial activity in humanized CYP2D6 knockin mice.⁷⁶

A metabolite of TQ, 5,6 *ortho*-quinone TQ, has been identified from animals taking the drug (Figure 3). The level of 5,6 *ortho*-quinone TQ is high after administration of TQ in wild-type extensive metabolizer phenotype. This report from laboratory animals shows the association between CYP2D6 metabolism and TQ pharmacokinetics. The findings in the laboratory animals could suggest that TQ is metabolized by CYP2D6 in human beings in whom the isoenzyme shows polymorphism.⁷⁷

Pharmacodynamics of TQ Plasmodium stages affected by TQ

An in vitro test evaluating the activity of 8-aminoquinolines showed that TQ has an average 50% inhibitory concentration (IC_{50}) of 0.436 μ M (range, 0.059–1.47 μ M) against blood stages of seven *P. falciparum* clones and strains (NIG59, NIG9171, D6, W2, TM91C235, WR75-235, and TM91C40).⁷⁸

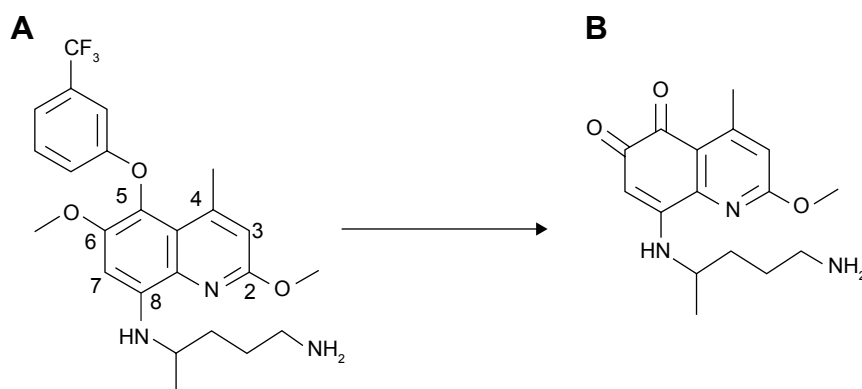


Figure 3 Metabolism of TQ (A) to 5,6 *ortho*-quinone TQ (B) in the presence of 2D6 isoenzyme.⁷⁷
Abbreviation: TQ, tafenoquine.

Another study evaluated an *in vitro* activity of TQ and PQ in wild isolates of *P. falciparum* from Djibouti, Gabon, and Senegal, where the isolates are CQ resistant. The IC₅₀ values for TQ were in the range of 0.9–9.7 μM for the Djiboutian isolates, 0.6–33.1 μM for the Gabonese isolates, and 0.5–20.7 μM for the Senegalese isolates.⁷⁹ PQ's activities were inferior to those of TQ.

A study from Thailand investigated the transmission blocking potential of TQ. The study evaluated the efficacy of TQ against the sporogonic stage of vivax parasite after letting mosquitoes feed on gametocytemic blood containing TQ. TQ reduced the transmission of the parasite to the mosquito at doses of ≥ 25 mg/kg.⁸⁰

Mechanism of action

TQ is a prodrug that needs activation to quinone TQ metabolite through metabolism by CYP2D6 (Figure 3).⁷⁶ The mechanism of action of TQ is not yet precisely known. Research Councils UK⁸¹ demonstrated the metabolites of 8-aminoquinolines to be redox cycled by *P. falciparum* ferredoxin-NADP⁺ reductase and diflavin reductase enzymes, which are upregulated in gametocytes and liver stages. The spontaneous oxidation of metabolites also generates hydrogen peroxide and hydroxyl radicals. It is hypothesized that the reactive oxygen species generated through *P. falciparum* ferredoxin-NADP⁺ reductase and diflavin reductase enzymes leads to parasite kill.⁸¹ The upregulation of these enzymes in TQ-sensitive stages of the parasite supports the hypothesis.

Similar to the blood schizonticide CQ, TQ inhibits heme polymerase in blood stage of the parasites.⁷⁸ This may explain the reason why TQ has activity against asexual blood stage of parasites, unlike PQ that does not inhibit the polymerization of hemozoin.

Clinical development of TQ

TQ, an investigational 8-aminoquinoline derivative for the treatment and relapse prevention of *P. vivax* malaria, has been granted a breakthrough therapy designation by the US Food and Drug Administration.⁸² Breakthrough therapy designation is the US Food and Drug Administration's program aimed at accelerating the development and review times of drugs for serious or life-threatening conditions. The designation was granted since preliminary clinical evidence indicated that TQ has substantial improvement over the existing therapy.⁸³

Efficacy of TQ in radical cure

There were six controlled trials published, out of which three were randomized controlled dose selection trials. Subsequently, out of the three randomized trials, only one trial was a double-blind study.^{84–87} High-quality evidence on the efficacy of TQ for radical cure is obtained from this double-blind study, which was also a multicenter, randomized, placebo-controlled Phase IIb study (the Dose and Efficacy Trial Evaluating Chloroquine and Tafenoquine In Vivax Elimination [DETECTIVE] trial). The trial evaluated efficacy of TQ in a range of doses in preventing relapse within 6 months. Single dose of TQ at 600 mg, following the standard CQ therapy for clinical cure, prevented relapse of vivax malaria by 91.9%, whereas 15 mg PQ administered for 14 days prevented relapse only by 77.3%.⁸⁵ The same study reevaluated the efficacy of TQ in homologous vivax strain. The recurrence rate was 3.5% and 1.8% at 300 mg and 600 mg single doses of TQ, respectively. At a dose of 300 mg TQ, there was a ninefold reduction in homologous recurrence compared with CQ alone. At the same dose of 300 mg, heterologous recurrences also reduced by threefold.⁸⁴ The DETECTIVE trial concluded that 50 mg and 100 mg of TQ do not provide a satisfactory prevention of relapse (Table 1).

Table 1 Efficacy of TQ in radical cure

Serial no	Study design	Study site	Study participants	Intervention arms	Relapse rate (95% CI), n	Outcome measure	References
1	Double-blind, randomized, placebo-controlled Phase IIb study (DETECTIVE trial) ^a	Peru, India, Thailand, and Brazil	329 vivax malaria cases	CQ + TQ 50 mg single dose CQ + TQ 100 mg single dose CQ + TQ 300 mg single dose CQ + TQ 600 mg single dose CQ + PQ 15 mg/d for 14 d CQ alone CQ + TQ 50 mg single dose CQ + TQ 100 mg single dose CQ + TQ 300 mg single dose CQ + TQ 600 mg single dose CQ + PQ 15 mg/d for 14 d CQ alone	29.1% (17.1–41.1), 55 28.1% (16.4–39.8), 57 3.5% (0–8.3), 57 1.8% (0–5.3), 56 10% (1.7–18.3), 50 31.5% (19.1–43.9), 54 42.3% (29.2–55.3), 55 45.9% (32.9–58.9), 57 10.1% (2.3–18), 57 8.1% (0.95–15.2), 56 22.7% (11.1–34.3), 50 62.5% (49.6–75.4), 54	Recurrence rate in 6 months for homologous <i>P. vivax</i>	84
2	Double-blind, randomized, placebo-controlled Phase IIb study (DETECTIVE trial)	Peru, India, Thailand, and Brazil	329 vivax malaria cases	TQ 3-d course PQ 14-d course CQ + TQ 200 mg/d for 3 d and then 200 mg weekly for 8 wks	3.48% (0.95–6.0), 201 3.3% (0.9–5.7), 210 3.7% (–3.4–10.8), 27	Relapse rate	88
3	Controlled trial ^b	Bougainville	411 vivax malaria cases			Relapse rate with 6 months of therapy	97
4	Single-arm study	Australia	27 patients relapse after PQ therapy				
5	Randomized, open-label, controlled trial	Thailand	44 vivax malaria cases	CQ + TQ 300 mg/d for 7 d CQ + TQ 500 mg/d for 3 d and repeat 1 wk after CQ + TQ 500 mg single dose CQ alone	0%, 15 9.1% (0–26.1), 11 11.1% (0–31.6), 9 44.4% (11.9–76.9), 9	Positive blood smears in 2–6 months study period	86
6	Randomized, open-label, controlled trial	Thailand	80 vivax malaria cases	CQ + TQ 300 mg/d for 7 d CQ + TQ 600 mg/d for 3 d CQ + TQ 600 mg single dose CQ + PQ 15 mg/d for 14 d CQ alone	0%, 18 0%, 19 5.6% (0–16.2), 18 25% (0.5–49.5), 12 61.5% (35–88.0), 13	Positive blood smears in 6 months study period	87

Notes: ^aAt the 300 mg TQ, a ninefold reduction in homologous recurrence compared with CQ alone. Heterologous recurrences reduced by threefold. ^bDosage regimen of TQ was not accessed.

Abbreviations: TQ, tafenoquine; 95% CI, 95% confidence interval; CQ, chloroquine; PQ, primaquine; d, day; *P. vivax*, *Plasmodium vivax*; wk, week.

Two open-label controlled trials showed that a single dose of 500 mg or 600 mg of TQ added to the standard dose of CQ reduced the recurrence rate of vivax infection by 75% and 91.1%, respectively, compared with the control arm treated with CQ alone.^{86,87} Although these studies involved few study participants, the findings were somewhat in agreement with those of the DETECTIVE trial (Table 1).

Trials investigating the effect of repeated doses of TQ to prevent relapse of vivax malaria were also conducted. A 3-day course of TQ was found to be noninferior to a 14-day course of PQ treatment with a relapse rate of 3.48% and 3.3%, respectively.⁸⁸ Two randomized open-label controlled trials from Thailand also revealed that a 7-day course of TQ after the standard dose of CQ prevented relapse completely (Table 1).^{86,87}

Chemoprophylactic efficacy of TQ

In a human challenge study, administration of TQ (600 mg single dose) 1 day prior to mosquito challenge prevented falciparum infection in three of the four volunteers included in the study. In this study, the volunteer who got infected had a low plasma TQ concentration.⁸⁹ A study on protective efficacy of TQ against falciparum malaria in Ghana revealed that the drug's efficacy ranges from 84.4% to 87.2% using a regimen of 50–200 mg/d for 3 days as loading followed by weekly maintenance doses. Shanks et al support the idea of adding weekly maintenance dose of TQ in the regimen in order to achieve a better efficacy.^{90,91} Another study in Gabon confirms the prophylactic efficacy of TQ at 250 mg for 3 days to be 100% during a 2-month study period.⁹² Another study in East Timor comparing the chemoprophylactic efficacy of TQ and mefloquine against vivax infection showed that TQ's prophylactic efficacy of 99.1% was not inferior to that of mefloquine's, which was 99.3% as shown in Table 2.⁹³

Efficacy of TQ for terminal prophylaxis

Randomized controlled trials evaluated the terminal prophylactic efficacy of TQ in Australian defense force personnel returning from Bougainville and East Timor.⁹⁴ The relapse rate was higher in study participants returning from East Timor than in those returning from Bougainville even though the treatment did not differ in the two locations. This study revealed TQ to be a good drug for PART. TQ administered with a twice daily (bid) dose of 200 mg for 3 days had a similar efficacy to 400 mg of the drug administered once daily for 3 days (Table 3). The pooled relapse rate in treatment

arms getting the divided dose of 200 mg TQ bid (3.1%; 85% confidence interval [CI]: 1–7.1) was not significantly different from that getting the single dose of 400 mg daily (7.9%; 95% CI: 4.8–12).⁹⁴

Another trial compared the terminal prophylactic efficacy of 400 mg TQ for 3 days (divided and undivided dose) with PQ (7.5 mg tid for 14 days) in study participants returning from Bougainville.⁹⁵ The relapse rate in the TQ arm was 1.9% (95% CI: 0.5–3.3), whereas that in the PQ arm was 2.8% (95% CI: 0.6–5; Table 3).

Curative efficacy of TQ

In vitro experiments showed that TQ has antimalarial effect on the blood stage of *P. falciparum* isolates. The IC₅₀ of TQ against falciparum isolates ranges from 59 nM to 9.7 μM from different studies.^{78,79} Evidences support the effect of TQ to be related with the inhibition of heme polymerase.⁷⁸ The reported IC₅₀ of TQ against falciparum isolates were higher than the artesunate IC₅₀ (range, 1.85–2.42 nM) and lower than the CQ IC₅₀ (range, 104–334 nM). This is explained by the fact that the isolates used for test were resistant to CQ.⁷⁹

An exploratory study investigated the curative efficacy of TQ (400 mg single dose followed by 200 mg bid for 2 days) in two vivax malaria patients after their return from Papua New Guinea. The patients had no positive blood smears during the 2-year follow-up period. The investigators observed that malaria parasites were cleared rapidly. These findings, however, need to be supported by randomized controlled trial(s) before TQ is used for curative purpose.⁹⁶

Safety of TQ

A study investigating the safety of 200 mg weekly dose of TQ for 6 months in 492 participants showed that 13% of the participants encountered at least one adverse event. The most frequent complaint was gastrointestinal abnormalities (nausea and abdominal pain). Treatment-related mild vortex keratopathy, corneal deposits, was also detected in 93% (69 of 74) of subjects taking TQ. The vortex keratopathy was not associated with any effect on visual acuity and was fully resolved in all subjects by 1 year.⁹³

Another study assessed possible adverse effects of TQ in 369 participants with a dose range of 25 mg to 200 mg in a weekly prophylactic therapy. Gastrointestinal abnormalities (diarrhea, dysentery, and abdominal pain) were the most common reported adverse events with a frequency ranging from 13% to 18%. The study also confirmed that there is no evidence of a relationship between TQ dosage and reports of physical complaints or the occurrence of abnormal laboratory

Table 2 Chemoprophylactic efficacy of TQ

Serial no	Study design	Study site	Study participant	Outcome measure	Intervention arms	Efficacy/relapse rate (95% CI), n	References
1	Randomized, placebo-controlled, double-blind ^a human challenge model	Experimental study: USA	Six normal volunteers	Rate of positive blood smears in 65 d (<i>P. falciparum</i>)	TQ 600 mg single dose Placebo	25% (0–67.4), 4 100%, 2	89
2	Randomized, double-blind, placebo-controlled chemoprophylaxis trial	Ghana	509 health volunteers	Protective efficacy relative to placebo in 16 wks (4 wks after the last dose; <i>P. falciparum</i>)	TQ 200 mg/d for 3 d + weekly TQ 100 mg/d for 3 d + weekly TQ 50 mg/d for 3 d + weekly TQ 25 mg/d for 3 d + weekly MQ 250 mg weekly Placebo	85.6% (76.2–91.6), 91 87.2% (78.3–92.7), 94 84.4% (74.8–90.7), 91 31.8% (20.2–43.4), 93 85.7% (71.9–93.3), 46	90
3	Double-blind, placebo-controlled, randomized study	Kenya	225 health volunteers	Protective efficacy relative to placebo in 13 wks (1 wk after the last dose; <i>P. falciparum</i>)	TQ 400 mg/d for 3 d + weekly TQ 400 mg/d for 3 d TQ 200 mg for 3 d + weekly Placebo	89% (77–95), 57 68% (53–79), 54 86% (73–93), 53	91
4	Randomized, double-blind, placebo-controlled study	Thailand	205 participants	Rate of positive blood smears during 6 months (<i>P. vivax</i> and <i>P. falciparum</i>)	TQ 400 mg/d for 3 d +400 mg monthly Placebo	1% (0–3.0), 96 ^b 32.6% (23–42.2), 92 ^c	98
5	Randomized, placebo-controlled study	Gabon	410 Gabonians	Rate of positive blood smears by day 77 (<i>P. falciparum</i>)	TQ 250 mg/d for 3 d TQ 125 mg/d for 3 d TQ 62.5 mg/d for 3 d TQ 31.3 mg/d for 3 d Placebo	0%, 84 1.3% (0–3.8), 79 3.5% (0–7.4), 86 20.3% (11.4–29.2), 79 17.1% (8.9–25.2), 82 0.9% (0.07–1.7), 492 0.7% (0–1.98), 162	92
6	Randomized, double-blind, controlled Phase III study	East Timor	654 Australian soldiers	Rate of positive vivax blood smears in 6 months	TQ 200 mg/d for 3 d + weekly MQ 250 mg/d for 3 d + weekly		93

Notes: ^aTQ concentration in the oligosymptomatic case was one half of that in the protected individuals. ^bOne vivax case. ^c30 cases, 21 vivax and eight falciparum cases and one mixed infection.

Abbreviations: TQ, tafenoquine; 95% CI, 95% confidence interval; *P. falciparum*, *Plasmodium falciparum*; wk, week; d, day; MQ, mefloquine; *P. vivax*, *Plasmodium vivax*.

Table 3 Efficacy of TQ in terminal prophylaxis

Serial no	Study design	Study participants	Outcome measure	Intervention arm	Relapse rate (95% CI), n	References
1	Randomized, open-label controlled trial	348 Australian defense force personnel returning from Bougainville	Relapse rate after 12 months	TQ 200 mg bid for 3 d TQ 400 mg/d for 3 d PQ 7.5 mg tid + doxycycline 100 mg/d for 14 d	1.2% (0.03–6.3), 86 2.3% (0.3–8.1), 87 3.4% (1.3–7.3), 175	94
2	Randomized, open-label controlled trial	925 Australian defense force personnel returning from Timor-Leste	Relapse rate after 12 months	TQ 200 mg qd for 3 d TQ 200 mg bid for 3 d TQ 400 mg qd for 3 d PQ 7.5 mg tid + doxycycline 100/d for 14 d	4.9% (3–7.5), 406 5.3% (1.5–13.1), 75 11% (6.5–17), 155 10% (6.8–14.1), 289	94
3	Randomized, controlled trial	592 Australian defense personnel volunteers returning from Bougainville	Positive blood smear within 12 months	TQ 200 mg bid or 400 mg/d for 3 d PQ 22.5 mg for 14 d	1.9% (0.5–3.3), 378 2.8% (0.6–5), 214	95

Abbreviations: TQ, tafenoquine; 95% CI, 95% confidence interval; d, day; PQ, primaquine; bid, twice daily; tid, three times daily; qd, once daily.

parameters. The laboratory parameters assessed in the study were alanine aminotransferase, hemoglobin, white blood cell counts, platelet counts, and bilirubin levels.⁹⁰

Study participants included in the clinical trial of TQ are screened for normal level of G6PD activity. A single study reported hemolytic anemia in study participants with G6PD deficiency who were wrongly recruited in a TQ trial.⁹¹

Prolongation of the QT interval is also one of the concerns in patients treated with antimalarial drugs. In the DETECTIVE trial, QT prolongation occurred in 2% of patients taking TQ, while the phenomenon was observed in 8% and 4% of patients taking PQ and CQ, respectively.⁸⁵ In another study,⁷⁰ TQ did not cause prolongation of QT interval even at a dose of 1,200 mg. Hence, TQ could be taken as a safer drug in terms of QT prolongation compared with other quinoline antimalarial drugs probably due to short duration of treatment with TQ.⁷⁰

Conclusion

The conclusions of this review are as follows:

1. TQ is an efficacious drug for radical cure, terminal prophylaxis, and chemoprophylaxis of vivax malaria. TQ has at least similar efficacy to PQ for radical cure and terminal prophylaxis with the additional benefit of short treatment duration, which can significantly improve patient adherence. A weekly administration of TQ also demonstrated equivalent chemoprophylactic efficacy with that of mefloquine.
2. Most of TQ efficacy studies are conducted in individuals with normal G6PD activity. However, one clinical study reported severe hemolytic anemia in G6PD-deficient individuals who were wrongly included in the study. Data on the relative safety of TQ over PQ in patients with G6PD deficiency are lacking.

3. Though TQ has a better activity against clinical isolates of blood stage *P. vivax* parasite in vitro compared to PQ and CQ, there is not enough evidence supporting its use for clinical cure.

The authors recommend further multicenter clinical studies on TQ with appropriate sample size and considering special populations before labeling TQ as an alternative medication for radical cure, terminal prophylaxis, and chemoprophylaxis of vivax malaria. Additional studies might be also required to investigate possible drug interactions with TQ.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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