Journal of Travel Medicine

International Society of Travel Medicine
Established 1991
Promoting healthy travel worldwide

Journal of Travel Medicine, 2018, 1–13
doi: 10.1093/jtm/tay110
Review

Review

Tafenoquine for travelers' malaria: evidence, rationale and recommendations

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Submitted 25 September 2018; Revised 17 October 2018; Editorial decision 21 October 2018; Accepted 30 October 2018

Abstract

Background: Endemic malaria occurring across much of the globe threatens millions of exposed travelers. While unknown numbers of them suffer acute attacks while traveling, each year thousands return from travel and become stricken in the weeks and months following exposure. This represents perhaps the most serious, prevalent and complex problem faced by providers of travel medicine services. Since before World War II, travel medicine practice has relied on synthetic suppressive blood schizontocidal drugs to prevent malaria during exposure, and has applied primaquine for presumptive anti-relapse therapy (post-travel or post-diagnosis of *Plasmodium vivax*) since 1952. In 2018, the US Food and Drug Administration approved the uses of a new hepatic schizontocidal and hypnozoitocidal 8-aminoquinoline called tafenoquine for the respective prevention of all malarias and for the treatment of those that relapse (*P. vivax* and *Plasmodium ovale*).
Methods: The evidence and rationale for tafenoquine for the prevention and treatment of malaria was gathered by means of a standard search of the medical literature along with the package inserts for the tafenoquine products Arakoda™ and Krintafel™ for the prevention of all malarias and the treatment of relapsing malarias, respectively.
Results: The development of tafenoquine—an endeavor of 40 years—at last brings two powerful advantages to travel medicine practice against the malaria threat: (i) a weekly regimen of causal prophylaxis; and (ii) a single-dose radical cure for patients infected by vivax or ovale malarias.
Conclusions: Although broad clinical experience remains to be gathered, tafenoquine appears to promise more practical and effective prevention and treatment of malaria. Tafenoquine thus applied includes important biological and clinical complexities explained in this review, with particular regard to the problem of hemolytic toxicity in G6PD-deficient patients.

Key words: Malaria, prevention, treatment, travelers, primaquine, tafenoquine, G6PD deficiency

Introduction

Each of the five species of malaria-causing plasmodial parasites naturally infecting humans often progress to threatening clinical syndromes in malaria-naïve patients unless prompt diagnosis and appropriate therapy first occurs. Death as an outcome of infection is confirmed in all of these species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium knowlesi*.[1–5] Infections by some species may more rapidly and frequently progress to serious illness than others, but malaria in all its forms provokes a debilitating febrile illness posing a potentially mortal threat in non-immune patients.[6] The notion of intrinsically benign or malignant species of the plasmodia should be acknowledged as dangerous dogma and the diagnosis of any malaria managed as a clinical emergency.[7] Successfully preventing such emergencies in travelers merits the relatively complex and difficult clinical task of doing so practically and effectively.

Naturally acquired immunity, community-based measures of prevention and control, along with local access to competent healthcare provided by malaria—aware governments, together

greatly mitigate the harm caused by these parasites in endemic areas.[8–10] In contrast, protection of relatively vulnerable travelers almost wholly depends on the recommendations and practices of travel medicine providers—local protections for them effectively do not exist beyond the passive benefit of reduced transmission and risk. Among the agencies and experts offering the distinct advice to travelers and residents alike, strategic thinking has historically been focused on the species once known as 'malignant tertian malaria', *P. falciparum*. In contrast, 'benign tertian malaria', *P. vivax*, was deeply neglected, and the tools and advice for its prevention, treatment or control were inadequate.[11–14] In 2015, the World Health Organization (WHO) acknowledged the mortal risk of vivax malaria and the neglect of it in public health and clinical medicine.[15]

A great deal of recent work and progress begins to correct the problem of neglect of vivax malaria in endemic communities,[16] but travel medicine strategy and practices remain aimed principally at falciparum malaria.[17–19] Up to the present day, suppressive chemoprophylaxis applying blood schizontocidal drugs dominates travel medicine practice.[20] A fundamental biological distinction between falciparum and vivax malarias-dormant liver stages called hypnozoites present in the latter and absent in the former—explains the inadequacy of suppressive chemoprophylaxis alone against the malarias.[21–23] Latent malaria and the threat of relapse require additional (post-travel presumptive anti-relapse therapy (PART)) or alternative (causal prophylaxis) approaches to chemoprevention.

Two regulatory events in the USA in 2018 offer potentially transformative changes in how travel medicine deals with the malaria threat.[24] The Food and Drug Administration (FDA) approved a new 8-aminoquinoline drug called tafenoquine for uses in the treatment or prevention of malaria: Krintafel™ (GlaxoSmithKline®, USA) or Arakoda™ (60 Degrees Pharmaceuticals® LLC, USA), respectively (Figure 1). The US Army discovered tafenoquine in 1978 during an era of historic neglect of antimalarial drug development[25,26] relative to the comparatively vigorous current efforts.[27] Tafenoquine thus lingered through fits and starts of clinical development in the three decades that followed.[28] Approximately 10 years ago, dawning realization of the clinical and public health importance of vivax malaria helped spur commitment to making tafenoquine available for use (Bill and Melinda Gates Foundation, Medicines for Malaria Venture and GSK).[29,30]

Complex biology governs the rationale underpinning safe and appropriate use of tafenoquine in travel medicine. The class effect of hemolytic toxicity in patients having the X-linked trait of glucose-6-phosphate dehydrogenase (G6PD) deficiency substantially deepens the complexity of its use. This review aims to explain these complexities along with the evidence and rationale for potential roles of tafenoquine for the prevention or treatment of malaria.

Essential Biology

The life cycles of the plasmodia guide chemotherapeutic and chemopreventive strategies. The many stages of them are variably susceptible to antimalarial classes of drugs (Figure 2), most having class-specific therapeutic effects. Clinically applied blood schizontocidal drugs, for example, have no hypnozoitocidal activity. Nonetheless, cross-class effects among antimalarials occur, sometimes species-specific in manner; e.g. the blood schizontocide chloroquine also exerts gametocytocidal activity in *P. vivax* but not *P. falciparum*.[31] Tafenoquine may be unique among registered antimalarial compounds in having demonstrable activity among all classes of antimalarials.[32,33]

All malarias derive from the bite of infectious anopheline mosquitos (excepting congenital or transfusion/transplant malarias). Injected plasmodial tachysporozoites invade hepatic cells, multiply as hepatic schizonts and after a week or more

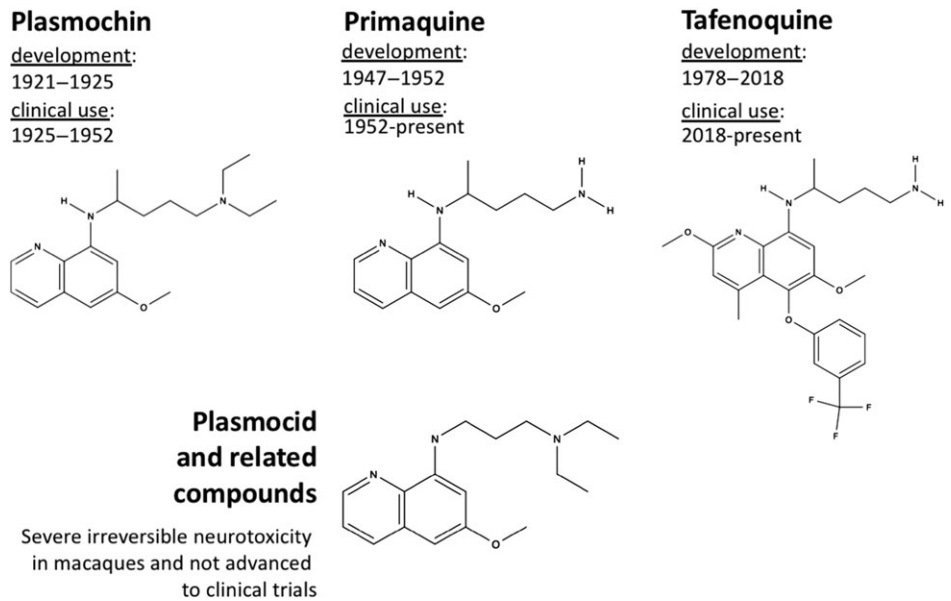

Figure 1. Evolution of the 8-aminoquinoline hypnozoitocides, including the winnowing out of irreversible severe neurotoxicity of plasmocid and related compounds distinguished by fewer than four methylene groups separating the amino groups of the alkyl chain at the defining 8-amino position. Plasmochin and others (including primaquine) having at least four methylene groups exhibited no such neurotoxicity but instead reversible toxicity at sub-lethal doses involving principally hepatic, hematological and gastrointestinal systems

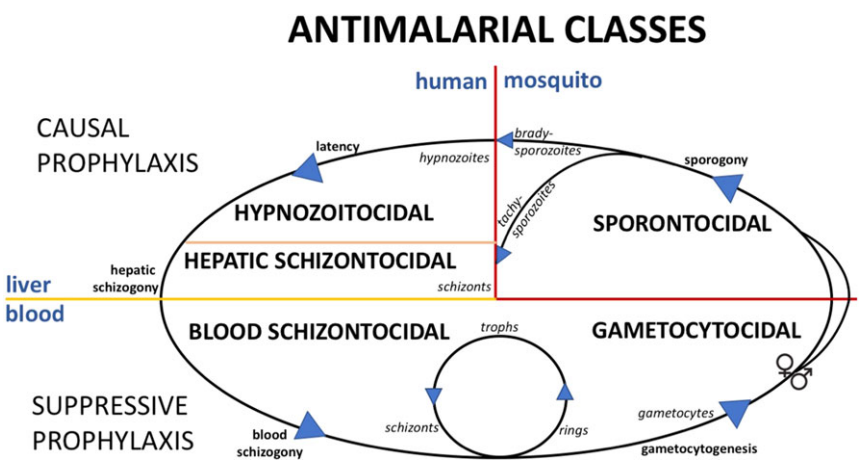

Figure 2. Antimalarial classes as guided by life cycle of the plasmodia

Table 1. Characteristics of relapsing and non-relapsing malarias

	Relapsing	Non-relapsing
Species	*P. vivax, P. ovale, P. cynomolgi*[a]	*P. falciparum, P. malariae, P. knowlesi*[b]
Hypnozoites	Present	Absent
Clinical attacks/infection	Variable, typically >3	1
Curative therapy	Blood schizontocidal, Hypnozoitocidal	Blood schizontocidal Gametocytocidal[c]
Suppressive chemoprophylaxis	Ineffective against relapses occurring post-chemoprophyaxis	Effective
Post-travel presumptive anti-relapse therapy	Not indicated after causal prophylaxis but necessary after suppressive prophylaxis	Not indicated
Causal chemoprophylaxis	Effective	Effective

[a]A natural zoonosis of Southeast Asian macaques confirmed in only a single patient but perhaps more common than now appreciated.
[b]A natural zoonosis of Southeast Asian macaques confirmed in thousands of patients.
[c]A single dose of 0.25 mg/kg primaquine to prevent onward transmission. Not recommended in relapsing malarias because hypnozoitocidal therapy also gametocytocidal.

emerge as infectious merozoites into the bloodstream where they again multiply asexually (schizogony) in red blood cells. Repeated cycles of that reproduction provoke the non-specific cyclic symptoms of acute malaria; typically daily bouts of spiking fever and shaking chills, often accompanied by headache, nausea, vomiting and myalgia. Some of those parasites become circulating sexual forms called gametocytes that may infect feeding anophelines but provoke no illness.

The infective bite of the relapsing malarias, *P. vivax* and *P. ovale*, includes bradysporozoites that become latent hepatic hypnozoites. The timing of their activation to hepatic schizogony and subsequent clinical attacks varies greatly, between a month and several years after infection. In general, attacks occurring less than a month after infection derive from tachysporozoite-borne active hepatic schizonts, whereas after 1 month attacks probably derive from the delayed hepatic schizogony of bradysporozoite-borne activated hypnozoites. These clinical events are called primary attacks and relapses.

The malarias infecting humans may be divided into relapsing and non-relapsing species, i.e. *P. vivax* and *P. ovale*, and *P. falciparum*, *P. malariae*, and *P. knowlesi*, respectively (Table 1). This fundamental distinction defines essential features of the treatment of the malarias; therapy of non-relapsing acute malarias involves only blood schizontocidal drugs (and gametocytocidal single-dose primaquine not considered here), whereas that of the relapsing malarias includes a hypnozoitocide. Strategy for the prevention of the malarias also invokes non-relapsing and relapsing biology and antimalarial drug classes; suppressive chemoprophylaxis employs blood schizontocides against asexual reproduction in blood, whereas causal chemoprophylaxis applies hepatic schizontocides or hypnozoitocides in killing parasites before they mature to either hepatic schizonts or hypnozoites (Figure 2). Widely used suppressive chemoprophylactic drugs do not interfere with hepatic development, with the exception of the causal activity of atovaquone against hepatic schizonts of *P. falciparum*[34,35] but not against hypnozoites of *P. vivax*[36,37] or those of *Plasmodium cynomolgi* in rhesus macaques.[38]

This review specifically considers the role of the new 8-aminoquinoline called tafenoquine in travel medicine practice. In terms of chemotherapy, only the relapsing malarias and hypnozoitocidal activity are relevant here. On the other hand, chemoprevention engages all malarias and activity against the hepatic stages of any plasmodial species, be those active schizonts, latent hypnozoites, or, more probably, their respective earliest (<48 h) post-invasion forms.[39] The broad spectrum activity of tafenoquine includes relatively potent blood schizontocidal effects,[40] but its clinical use as such is not recommended.

Rationale for prioritized causal prophylaxis

Suppressive chemoprophylaxis of malaria with blood schizontocides like quinine, atabrine, chloroquine, doxycycline, mefloquine and atovaquone–proguanil has successively dominated practice in travel medicine for over a century.[41,42] This strategy served the intended purpose of effectively preventing attacks by what had been considered the only intrinsically dangerous species, *P. falciparum*. The inadequacy of chemoprophylactic suppression alone against the delayed attacks of the relapsing malarias has long been understood and thoroughly demonstrated.[43–46] Though not always prescribed or even recommended,[20] post-travel PART using hypnozoitocidal primaquine addressed that inherent inadequacy. However, that practice also imposed G6PD-deficiency risk management, along with the inconvenience and adherence issues of 14 daily doses. Some authorities and experts have recommended daily primaquine (0.5 mg/kg) during exposure under some circumstances as safe, well-tolerated and effective causal prophylaxis (in non-pregnant, G6PD-normal travelers),[47] but with the important drawback of off-label use. Further, primaquine having poor activity against the asexual blood stages of *P. falciparum*[48] raises the specter of unmitigated prophylaxis breakthroughs. Primaquine as primary causal prophylaxis has thus not been widely adopted in travel medicine.

While chemoprophylaxis of any sort against significant risk of malaria imposes some obstacles and pitfalls, it is certainly preferred over no protection and may be less problematic than standby emergency self-treatment practices.[49–51] Figure 3 illustrates the practical protections and pitfalls of suppressive prophylaxis against non-relapsing (upper panel) and relapsing malarias (lower panel) relative to those of causal prophylaxis. The failure to properly load suppressive dosing before travel or to continue dosing sufficiently long after travel results in attacks during and after travel in both types of malarias. Fully compliant loading and post-exposure suppressive dosing successfully prevents non-relapsing but not relapsing malaria attacks delayed after travel. Causal prophylaxis during exposure (loading or post-exposure dosing is minimal), in contrast, effectively prevents both types of malarias. Causal prophylaxis exceeds suppressive approaches in terms of simplicity of use and thoroughness of protection, but the good efficacy of fully compliant suppressive prophylaxis against *P. falciparum* has been broadly accepted as the standard-of-care in travel medicine.

Acute falciparum malaria is unquestionably a dangerous infection that may rapidly progress to complicated and severe disease syndromes in malaria-naïve patients. It does so in travelers more often than the other plasmodia,[52] with the possible exception of *P. knowlesi*.[53] However, the notion of *P. falciparum* as the only species capable of such harm has been discredited with evidence, much of it only recently gathered.[2–5,54–59] When the malarias are allowed to progress to severe and complicated disease in travelers, the frequency of death among them appears essentially equal, ~5–10%.[52] All of the plasmodia are intrinsically dangerous and potentially lethal. Chemoprophylaxis strategy aimed at some species but not others, unless absolutely necessary, fails reason and many patients. Broad spectrum chemoprophylaxis against attacks by any plasmodial species, be those primary or relapsing, would potentially offer a conspicuously superior option.

The fact that *P. falciparum* acquired in Africa indeed causes most (~70%) malaria in travelers[19,60,61]—a problem solved by appropriate suppressive chemoprophylaxis—tends to obscure the broader geographic dominance of *P. vivax*. Excepting relatively few and minor geographic areas (e.g. Haiti), endemic transmission of *P. vivax* occurs wherever *P. falciparum* occurs, including much of malarious Africa.[62–64] Endemic transmission of *P. vivax* extends well beyond the tropical range of *P. falciparum* (e.g. to the Korean Peninsula).[65] Once travelers are deemed to be in need of chemoprevention against malaria by estimated weight of risk of exposure,[66,67] most of them will be at risk of infection by the hypnozoites of *P. vivax*, *P. ovale* or both (Figure 4). There may thus be few travelers not benefiting from an approach to chemoprophylaxis that prevents the formation of latent hypnozoites and post-travel attacks.

The availability of tafenoquine offers the critical strategic advantages of causal prophylaxis, along with practical advantages over primaquine for that indication. Tafenoquine overcomes three of the four key disadvantages of primaquine in comparison to most suppressive prophylaxis options: (i) chemoprophylaxis is an approved indication; (ii) dosing is weekly rather than daily; and (iii) blood schizontocidal activity may mitigate prophylaxis breakthroughs. The relatively very long plasma half-life of tafenoquine relative to primaquine (~15 days vs 6 h) confers many of its advantages. The key disadvantage is the 8-aminoquinoline liability of hemolytic toxicity in G6PD-deficient patients, and that problem is deepened by slow excretion. The safe use of tafenoquine or primaquine is nonetheless manageable by understanding G6PD deficiency and its diagnosis.

G6PD deficiency

The inherited X chromosome-linked G6PD deficiency trait is the most common human genetic abnormality and its genotypes and frequencies vary tremendously.[68] It tends to be absent in Native Americans, present at low frequencies (<1%) among most Caucasians and prevalent among people residing in malaria-endemic nations (averaging 8%).[69] The extent of harm caused by daily primaquine as hypnozoitocide depends on dose, the variant of G6PD deficiency involved, and whether hemi-, homo- or heterozygous.[70] Effects range from relatively mild and self-limiting to life-threatening. Caucasian, Middle Eastern and Asian peoples tend to have the most severely impaired G6PD deficiency variants.[71] In moderately deficient (40–60% of normal activity) G6PD-deficient heterozygous females having the moderately impaired Asian Mahidol variant, a single 300-mg dose of tafenoquine proved slightly more hemolytic (nadir of ~23% Hb drop) than a 14-day daily regimen of 15-mg primaquine in that trial (~16% drop)[72] or others (~13% Hb drop).[73] Prescribing tafenoquine for any indication requires ruling out any G6PD deficiency, excepting female heterozygotes having >70% of normal activity.

Conventional qualitative screening for G6PD deficiency prior to tafenoquine use may not suffice and quantitative testing is indicated by standard laboratory spectrophotometric assay. Patients having <70% of normal G6PD activity may not receive tafenoquine.[74] Qualitative screening, for example by the NADPH fluorescent spot test (FST) or newly available point-of-care rapid diagnostic tests for G6PD deficiency (RDT), lack sensitivity to deficiency above 30% of normal activity.[75–77] Although qualitative screening offers nearly 100% sensitivity and specificity for male hemizygotes, female

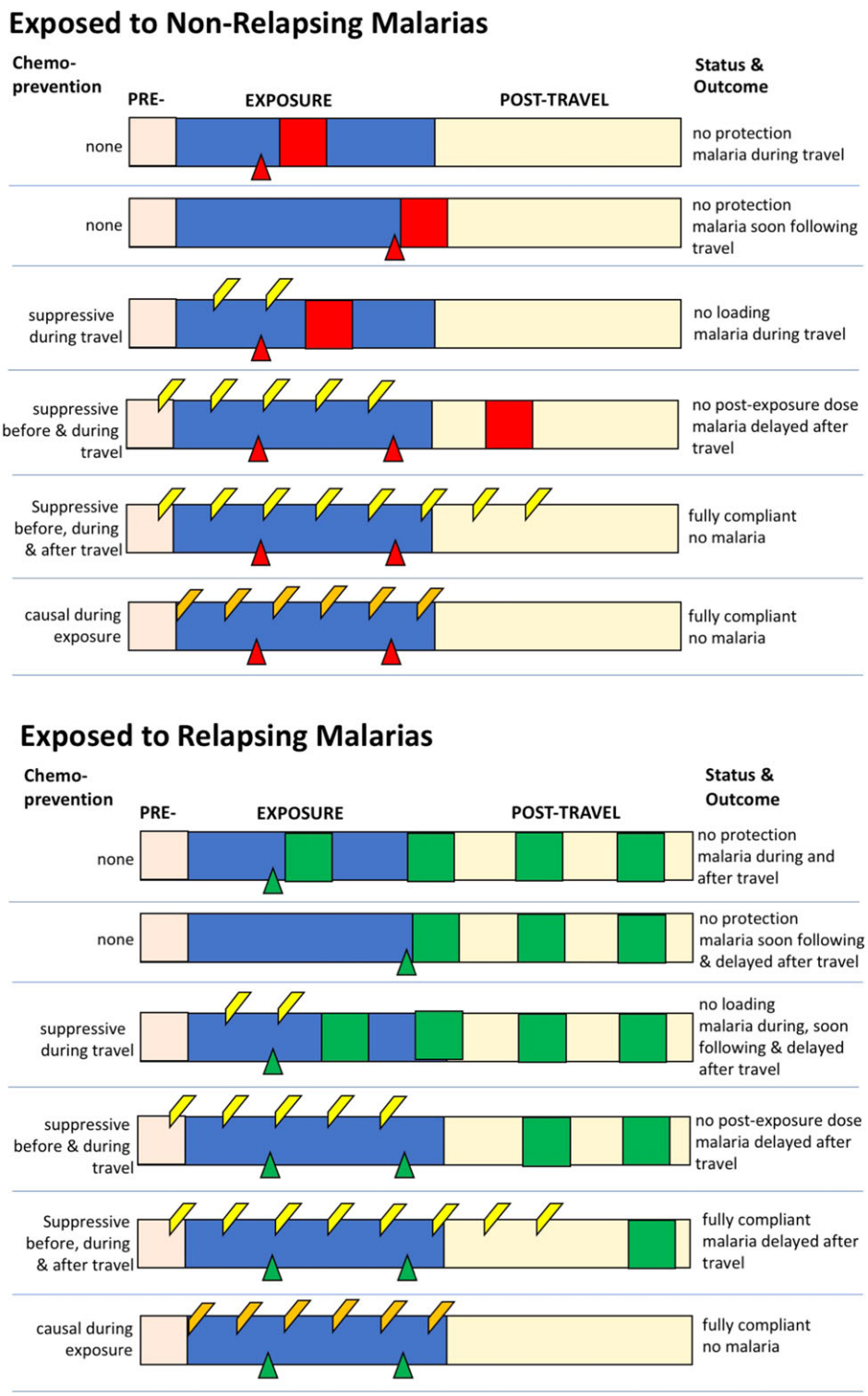

Figure 3. Schematic illustrating pitfalls and protections of suppressive (yellow dose indicators) or causal (orange dose indicators) chemoprevention of non-relapsing malaria like *P. falciparum* (top panel; red triangles and squares for inoculation and attack, respectively) or relapsing species like *P. vivax* (bottom panel; green triangles and squares)

homozygotes and female heterozygotes having <30% of normal activity,[78,79] the latter having 30–70% of normal G6PD activity will often screen as normal.[80] The basis of this problem lies in the phenomenon of lyonization during embryonic development of female heterozygotes resulting in apparently random frequencies of active/inactive normal vs abnormal X-chromosomes and red blood cell mosaicism for G6PD deficiency.[76] Recent efforts to develop simple and practical quantitative point-of-care test technologies may soon bear devices that greatly increase access to such testing and safe use of 8-aminoquinolines.[81]

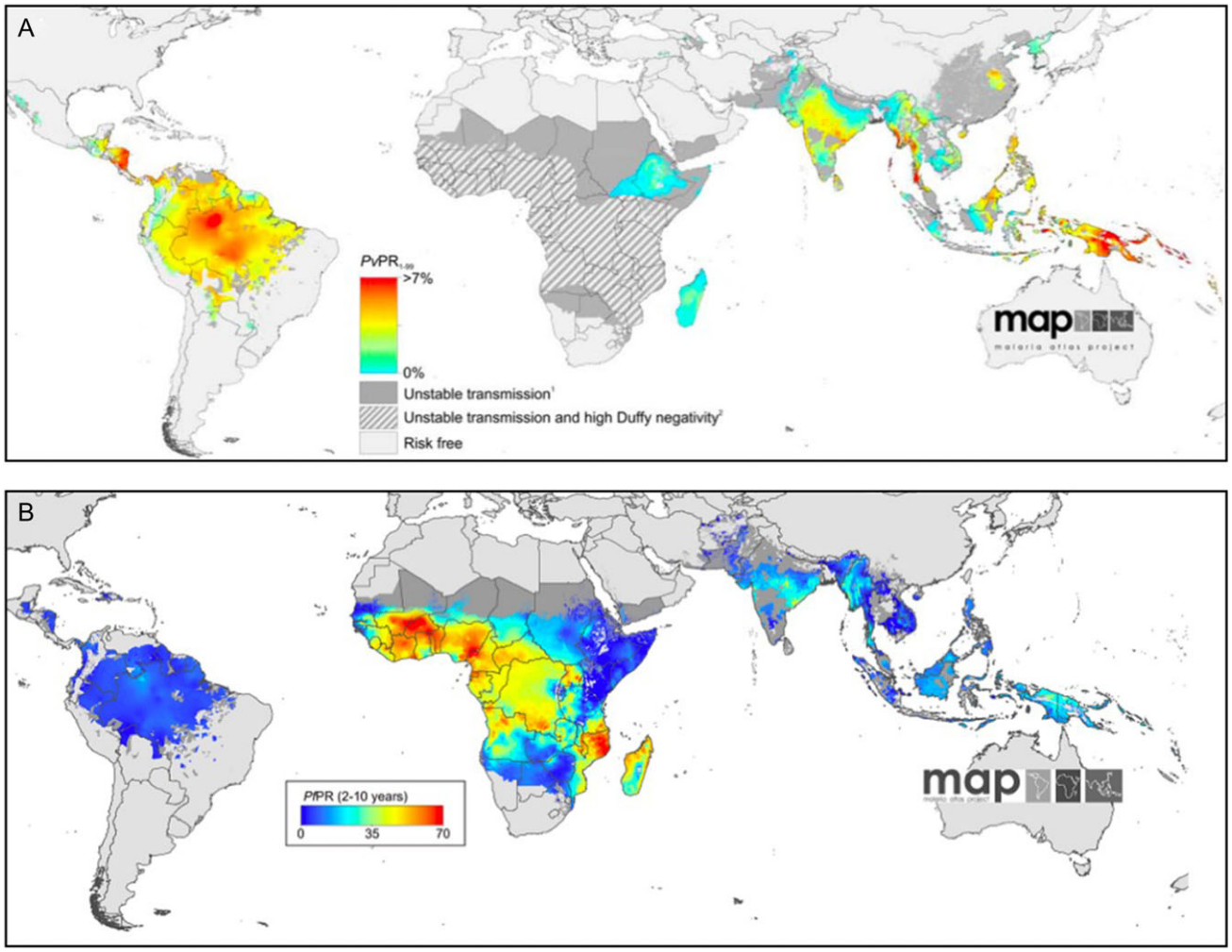

Figure 4. Geographic distribution and prevalence of *P. vivax* (A) and *P. falciparum* (B) in 2010[65,120] reproduced here under Creative Commons license

Impaired CYP2D6 metabolism

Clinical and laboratory evidence suggested that the efficacy of primaquine may depend on natural variation in cytochrome P-450 2D6 (CYP2D6) isotype activity.[82–84] In a trial of 177 Indonesian patients with vivax malaria given directly observed high-dose primaquine (0.5 mg/kg/day for 14 day) as PART in combination with artesunate, artesunate–pyronaridine or dihydroartemisinin–piperaquine, 26 (15%) experienced relapses during 1 year of follow-up free of reinfection risk.[85] Among the 21 relapsing subjects evaluated for CYP2D6 genotype and dextromethorphan metabolism phenotype, 20 exhibited significantly impaired CYP2D6 activity.[86] Relatively common impaired CYP2D6 alleles like *10 (in Asian people) coupled with other less frequent impaired alleles (e.g. *4, *5 or *41) appeared to explain most therapeutic failures despite otherwise adequate dosing.

Although tafenoquine activity against rodent hepatic schizonts seems to also depend on CYP2D6 activity,[87] one randomized multi-center trial did not detect an association of CYP2D6 genotypes with tafenoquine efficacy (but did with the primaquine comparator arm).[88] The efficacy of tafenoquine in humans is not known to require metabolism by CYP2D6 or any other cytochrome P-450 isotype or monoamine oxidase, but this body of evidence is as yet far from thorough or conclusive. Tafenoquine activity may or may not come with the liability of CYP2D6 dependency—decisive studies are needed to inform this important question.

Weekly tafenoquine for causal prophylaxis

Tafenoquine was registered with the US FDA under the tradename Arakoda™ by 60 Degrees Pharmaceuticals® (USA) in 2018 with a labeled indication for chemoprevention of malaria in adult patients (≥18 year) confirmed to be G6PD-normal (>70% of normal activity) and not pregnant, lactating or having a history of psychoses.[74] The drug is available as tablets containing 100 mg base. A loading dose of 200 mg tafenoquine daily for 3 days during the week before travel is recommended, followed by weekly maintenance doses of 200 mg commencing 7 days after the last loading dose. Upon return from travel, the final dose should occur 7 days after the last maintenance dose taken in the malarious area.[74]

The label for Arakoda™ includes an indication for 'terminal prophylaxis', an antiquated term for post-travel PART in connection with suppressive prophylaxis during travel.[89] The term is not particularly apt for tafenoquine as Arakoda™ because it

is no more than a final weekly dose after travel rather than the distinct dosing for PART with tafenoquine (i.e. 300 mg rather than 200 mg). Post-travel PART, i.e. terminal prophylaxis, is not necessary with tafenoquine (or primaquine) causal prophylaxis. On the other hand, when suppressive chemoprophylaxis is used and post-travel PART is indicated, tafenoquine as a single 300-mg dose may suffice in lieu of 14 days of primaquine (Table 2).

The clinical experience with 200-mg weekly tafenoquine prophylaxis is now limited to trials conducted in 462 non-immune subjects naturally exposed to falciparum and vivax malaria in Southeast Asia[90]; 152 semi-immune subjects exposed to falciparum malaria in holoendemic sub-Saharan Africa[91,92] and 12 non-immune, malaria-naïve volunteers experimentally challenged with blood stages of *P. falciparum*.[74] Comparators in these trials included mefloquine (with or without post-travel PART with primaquine) or placebo (Table 3). There was no placebo control in Trial 1 (Australian soldiers in Timor Leste), but a comparator of weekly mefloquine followed by post-travel PART with primaquine; four post-exposure attacks occurred among subjects taking tafenoquine, and one also occurred in that period among mefloquine-treated subjects. Another analysis of this trial mathematically derived a hypothetical malaria attack rate (8%) and estimated 100% protective efficacies of tafenoquine or mefloquine against primary attacks.[93] The placebo-controlled trial of tafenoquine prophylaxis in Kenyan adults[91] showed 86% protective efficacy during 15 weeks of heavy exposure to risk of *P. falciparum* (Trial 2, Table 3). Another trial in Ghana also included a placebo control but with a mefloquine comparator (Trial 3, Table 3):[92] after 12 weeks the protective efficacy of tafenoquine or mefloquine was 87% for each for *P. falciparum*. A separate analysis of these African trials estimated 94% and 95% protective efficacies for tafenoquine and mefloquine, respectively.[94] The African studies did not assess efficacy against late attacks by relapsing malarias. Shanks[95] explained the limitations and obstacles to conducting chemoprophylaxis trials. While head-to-head trials of the chemoprophylactic options against primary and delayed attacks would be ideal, they are also unlikely to be possible.

No clinical trial of tafenoquine has definitively demonstrated a causal vs suppressive prophylaxis mechanism. An early human challenge trial demonstrated a single 600 mg dose of tafenoquine successfully prevented *P. falciparum* in three of four subjects challenged.[96] At such a dose, slowly eliminated tafenoquine would have exerted blood schizontocidal activity over the normal incubation period of *P. falciparum* (i.e. less than several weeks) if hepatic schizontocidal activity (causal) had been inadequate. Nonetheless, given the proven causal activity of primaquine against acute *P. falciparum* and acute or latent *P. vivax* malaria,[39] the structural relatedness of primaquine to tafenoquine (Figure 1), and evidence from an experiment in rhesus macaques challenged with *P. cynomolgi* sporozoites,[38] a causal mechanism of prophylaxis very likely pre-empts the suppressive activity of tafenoquine. Nonetheless, some workers argue that tafenoquine prophylaxis may include a significant suppressive activity component.[97] A randomized, placebo-controlled trial at Gabon measured the durability of post-treatment prophylaxis of tafenoquine at variable daily doses administered for only 3 days: after 77 days, 14 of 82 placebos experienced *P. falciparum*, whereas 16/79, 3/86, 1/79 and 0/84 subjects did with daily doses of 31.25, 62.5, 125 and 250 mg tafenoquine, respectively.[98] Such protection very long after dosing logically hints at suppressive prophylaxis, but this is not relevant with weekly tafenoquine dosing. Efficacious monthly dosing of tafenoquine during long-term travel, perhaps exploiting both causal and suppressive activities, may yet be demonstrated.

The label for Arakoda™ warns that adverse reactions may be delayed in onset or prolonged in duration due to the relatively very long plasma half-life of tafenoquine.[99] The listed warnings and precautions include hemolytic anemia, G6PD deficiency in pregnancy and lactation, methemoglobinemia, psychiatric effects and hypersensitivity reactions. An integrated safety analysis by the developers of Arakoda™ reported that diarrhea, nausea, vomiting, sinusitis, gastroenteritis and back/neck pain occurred at higher frequencies (≥1%) relative to placebo; only the latter two occurring at >5%.[100] Two trials followed up on the observed high rate (93%) of mild reversible vortex keratopathy and retinal abnormalities (39%) in the subjects of the trial in Southeast Asia and Australia[91] and reported no concerns with regard to functional visual impairment.[101,102] The 6-month limitation on tafenoquine prophylaxis in the Arakoda™ label stems from a lack of data rather than any indication of harm beyond that period. Necessity in practice with tafenoquine will likely extend that exposure period, and the reporting of adverse events in practice will later inform evidence-based limitations of use (https://www.fda.gov/safety/MedWatch/default.htm).

For most G6PD-normal, non-pregnant adult travelers at substantial risk of any malaria, weekly tafenoquine as causal prophylaxis provisionally (pending greater clinical experience with it) offers a superior option to either causal daily primaquine or any

Table 2. Chemoprophylactic strategies and agents

	Chemoprophylaxis strategy				
	Suppressive			Causal	
Agent	Mefloquine	Doxycycline	Atovaquone–proguanil	Primaquine	Tafenoquine
Dosing	Weekly	Daily	Daily	Daily	Weekly
Post-exposure PART required	Yes	Yes	Yes	No	No
Pregnancy	Yes	No	No	No	No
G6PD-deficient safety	Yes	Yes	Yes	No	No
Children	Yes	No	Yes	Yes	Insufficient evidence
Parasite resistance	Yes	Yes	Yes	No	Improbable
CYP-dependent	No evidence	No evidence	No evidence	Yes	Insufficient evidence

Table 3. Human trials of 200 mg weekly tafenoquine for prophylaxis against malaria

	Trial 1	Trial 2	Trial 3	Trial 4
Location	Timor Leste/Australia	Kenya	Ghana	Australia
Exposure	6mo meso-endemic *P. falciparum* and *P. vivax*; 6mo post-exposure	15 weeks exposure to holoendemic *P. falciparum*	12 weeks exposure to holoendemic *P. falciparum*	Experimental *P. falciparum* blood stages
Subjects	Australian soldiers	Resident adults	Resident adults (excluding reproductive age females)	Malaria-naïve adults
Number of subjects and arms[a]	TQ = 462 MQ + PQ = 153	TQ = 61 Placebo = 62	TQ = 91 MQ = 46 Placebo = 94	TQ = 12 Placebo: 4
Protective Efficacy	Not estimable without placebo; 5 attacks occurred, all post-exposure; 4 in TQ group	86%	TQ = 87% MQ = 87%	100%
Reference	87	88	89	71

[a]TQ, tafenoquine administered weekly 200 mg; MQ, mefloquine administered weekly 250 mg; PQ, primaquine administered daily 30 mg for 14 days immediately following travel.

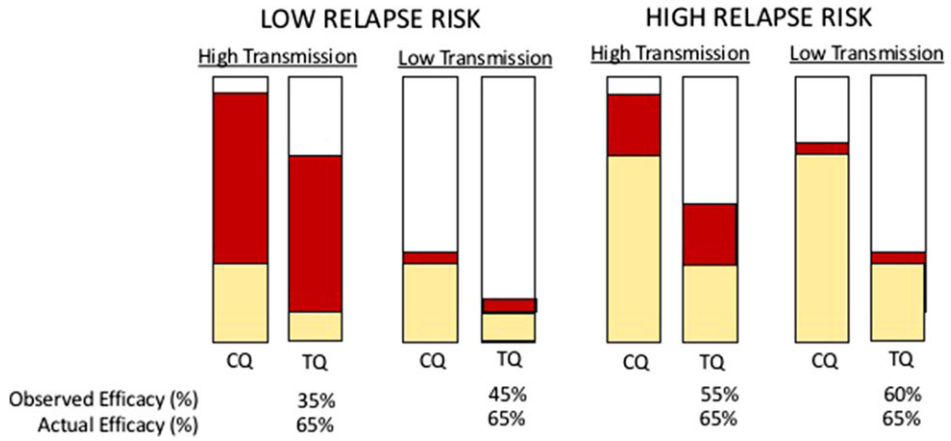

Figure 5. Hypothesized relative attack rates in the months following radical cure illustrate possible impacts of variable risks of relapse or reinfection on the estimation hypnozoitocidal efficacy of tafenoquine (TQ) fixed at a presumed 'actual' 95% rate compared to a chloroquine (CQ) arm without hypnozoitocidal therapy (relapse and reinfection attacks)

suppressive malaria prophylactic regimen (weekly or daily with or without post-travel PART). It is compatible with both short-notice or short-duration travel and particularly favored where endemic vivax or ovale malaria transmission occurs. Mainstream use of tafenoquine for the prevention of malaria in travelers offers a potential solution to the problem of delayed attacks by the relapsing malarias.

Single-dose tafenoquine for radical cure of relapsing malaria

The introduction of tafenoquine into practice as a hypnozoitocidal 8-aminoquinoline requires examination of the therapeutic principles at work. The primaquine standard-of-care, problematic as it may be, defines those with decades of experience and many millions of patients.[103–106] Primaquine nonethless imposes the

SUMMARY BOX 1. KEY POINTS ON TAFENOQUINE PROPHYLAXIS IN TRAVEL MEDICINE

- Suppressive malaria prophylaxis standard-of-care is not adequate to the threat of delayed attacks after travel by the relapsing malarias.
- Relapsing malarias occur wherever there is falciparum malaria, with few and minor exceptions.
- Causal prophylaxis is effective against all malarias and prevents delayed attacks after travel.
- Causal prophylaxis is suitable for both short-notice and short-duration travel.
- Tafenoquine is a new drug that offers the advantages of causal prophylaxis with a weekly dosing regimen.
- Tafenoquine is hemolytically toxic to patients having inherited G6PD deficiency, so is prohibited in those patients along with pregnant and lactating women. Safety in children is not yet established.

Table 4. Randomized clinical trials of tafenoquine for PART against vivax malaria

	Trial 1	Trial 2	Trial 3
Location	Multi-centers in Asia, Africa, and Americas	Multi-centers in Asia, Africa and Americas	Multi-centers in Asia, Africa and Americas
Subjects	Adult non-pregnant G6PD-normal residents with acute vivax malaria	Adult non-pregnant G6PD-normal residents with acute vivax malaria	Adult non-pregnant G6PD-normal residents with acute vivax malaria
Treatment arms, and numbers of subjects[a]	TQ + CQ = 57 PQ + CQ = 50 Placebo + CQ = 54	TQ + CQ = 260 PQ + CQ = 129 Placebo + CQ = 133	TQ + CQ = 166 PQ + CQ = 85
% Recurrence-free after 6 months	TQ + CQ = 89 PQ + CQ = 77 Placebo + CQ = 38	TQ + CQ = 62 PQ + CQ = 70 Placebo + CQ = 28	TQ + CQ = 73 PQ + CQ = 75
Reference	105	106	106

[a]TQ, 300 mg single dose tafenoquine; CQ, 1500 mg chloroquine in three daily doses; PQ, 15 mg primaquine daily for 14 days.

difficulties of unknown mechanism of therapeutic activity against a cryptic and highly nuanced stage of some plasmodia—the hypnozoite—coupled with a vitally important hemolytic toxicity problem also of unknown mechanism in patients having a highly prevalent and diverse genetic abnormality, G6PD deficiency. Estimates of primaquine efficacy as impacted by parasite biology, epidemiology and partner blood schizontocides imposes great complexity of interpretation.[107] These issues all also bear on tafenoquine and its use in radical cure of the relapsing malarias.

Estimates of the efficacy of hypnozoitocides like tafenoquine are subject to important confounding factors. The natural activation of hypnozoites typically occurs over months following infection.[108] When relapse occurs in the presence of risk of reinfection, these two sources of acute malaria temporally mingle and no molecular laboratory technology differentiates them. Post-hypnozoitocidal recurrences in endemic areas may thus be represented by both therapeutic failures (relapse) and the primary attacks of mosquito-borne reinfection—recrudescence with blood schizontocidal failure may also occur but is not considered here. The rates of both relapse and reinfection naturally vary widely across endemic zones and each may impact inherently variable estimates of hypnozoitocidal efficacy. Figure 5 presents hypothetical rates of each in high and low transmission settings in order to illustrate these potential impacts. High transmission with low relapse risk (e.g. <30%) may greatly underestimate efficacy (left panels), an effect mitigated by high relapse risk (e.g. >70%), especially where there is low risk of reinfection (right panels). Reported estimates of efficacy from endemic areas are thus not absolute but reported as the fraction of patients not experiencing a recurrent parasitemia during months of follow-up, often relative to a hypnozoitocidal comparator or placebo control group (also called a relapse control). Conducting treatment and follow-up where reinfection does not occur and with a relapse control arm largely resolves these ambiguities.[85,109] Such a trial for tafenoquine has yet to be completed, though one is in progress in Indonesia in 2018.

The two multi-center, double-blind and placebo-controlled randomized clinical trials estimating efficacy of tafenoquine at a single dose of 300 mg combined with standard chloroquine therapy (1500 mg base over 3 days) included 317 subjects thus dosed against naturally acquired *P. vivax* infections in Brazil, Peru, Ethiopia, Thailand, Cambodia and the Philippines (Trials 1 and 2, Table 4).[110,111] A total of 187 subjects in those trials received chloroquine and a placebo of tafenoquine. Subjects were followed for recurrent infections for six months. A total of 226 of 317 (71%) subjects did not experience recurrence within 6 months of tafenoquine and chloroquine therapy, whereas 79 of 187 (42%) subjects treated with chloroquine and placebo did so. In a third trial lacking a placebo control, tafenoquine (n = 166) or primaquine (n = 85) combined with chloroquine resulted in 73% and 75% remaining free of recurrence for 6 months (Trial 3, Table 4), consistent with non-inferiority of single-dose tafenoquine relative to daily 15 mg primaquine for 14 days.[110]

An important factor regarding hypnozoitocidal therapy bearing upon both efficacy and safety is co-administration with varied blood schizontocidal therapies. Indeed, the discovery effort leading to primaquine stemmed from an unexpected drug–drug interaction (DDI) between atabrine (mepacrine) and plasmochin (pamaquine) disqualifying co-administration for radical cure.[112] The developers of plasmochin and primaquine each reported DDI phenomena with varied partner blood schizontocides impacting efficacy, safety or both. Tafenoquine has thus far been examined only in combination with chloroquine in vivax malaria patients. However, it was evaluated with several distinct partner blood schizontocides against *P. cynomolgi* relapses in rhesus macaques.[113] Those investigators reported a 10-fold increase in tafenoquine efficacy when administered with chloroquine, mefloquine or artemether–lumefantrine compared to tafenoquine alone. Over 60 years ago, Alving *et al.* reported essentially similar findings with primaquine given concurrent vs consecutive quinine or chloroquine.[114] How these purely blood schizontocidal drugs so dramatically impact the hypnozoitocidal efficacy of 8-aminoquinolines remains unknown.

While chloroquine or artemether–lumefantrine did not significantly impact tafenoquine pharmacokinetics in healthy subjects, dihydroartemisinin–piperaquine increased the C_{max} of tafenoquine by 38%, the area under the concentration (AUC) curve by 12%, and the plasma half-life by 29%.[115,116] Tafenoquine did not appear to impact the pharmacokinetics or dynamics of chloroquine, artemether–lumefantrine, or dihydroartemisinin–piperaquine. The FDA label for Krintafel™ cites chloroquine as an example of appropriate companion therapy,

implicitly allowing for other partner blood schizontocides for radical cure.[110] The data from *P. cynomolgi* in macaques seem to affirm that view so far as mefloquine and artemether–lumefantrine are concerned.[112]

The package insert for Krintafel™ expresses an indicated use in radical cure of *P. vivax* malaria in patients at least 16 years of age who are also receiving companion blood schizontocidal therapy.[111] The warnings and precautions expressed therein are essentially similar to those for Arakoda™ (see above). Both labels warn of serious psychotic adverse reactions having occurred at the indicated dose (for Krintafel™) or higher dosing (for Arakoda™) in patients with a history of psychoses, along with serious hypersensitivity events (e.g. angioedema).[74,111] Tafenoquine (as Arakoda™ or Krintafel™) may or may not be suited to patients with psychiatric histories; the evidence needed to definitively inform that question is lacking. In the instance of primaquine, there have been no significant clinical neurotoxicity signals after decades of use.[117,118] Indeed, in the defining neurotoxicological studies of 8-aminoquinolines in rhesus macaques, severe irreversible brainstem neuronal injury occurred only among compounds of the plasmocid (or Rhodoquine) subclass (Figure 1).[119] Among the plasmochin (or pamaquine) subclass of 8-aminoquinolines (all 8-aminoquinolines that advanced to human clinical trials, including primaquine and, later, tafenoquine), no such neurotoxicity occurred.

In summary, adult G6PD-normal non-pregnant or lactating patients diagnosed with acute *P. vivax* malaria, or those returning from travel of risk without causal prophylaxis, a single 300 mg dose of tafenoquine provides safe, well-tolerated, and efficacious PART. Post-diagnosis PART may be confidently combined with chloroquine, mefloquine, or artemether–lumefantrine. Post-travel PART should consider the apparently conspicuous dependency of tafenoquine efficacy on the presence of select blood schizontocides as convincingly demonstrated in the *P. cynomolgi* animal model. Tafenoquine without a companion blood schizontocide possibly not killing hypnozoites at prescribed dose merits clinical caution and scientific attention. More details are available in the FDA Advisory Committee Briefing Document for Krintafel™: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm612875.pdf

Conclusions

The availability of tafenoquine for the prevention and treatment of malaria appears to offer potentially transformative new options in the practice of travel medicine. These applications strictly require reliable screening for G6PD deficiency, like the current standard of responsible care involving primaquine for causal prophylaxis or for post-travel or post-diagnosis PART in travelers. Excepting travel to the very few malarious areas where infection by hypnozoites is highly improbable, G6PD screening should be acknowledged as indicated in any traveler taking any chemoprophylactic option. Avoidance of G6PD screening with non-hemolytic suppressive chemoprophylactics (without post-travel PART) invites risk of post-travel attacks. No species of plasmodia is intrinsically benign. They all merit the diligence and relative difficulty of preventing them. Tafenoquine offers G6PD-normal and non-pregnant adults a convenient, safe, well-tolerated and efficacious means of preventing all malarias during travel or treating those that relapse after travel. The important work needed to assure the safety of tafenoquine in children is in progress, along with appropriate formulation for them. Far broader clinical experience with tafenoquine will have to accrue before fully understanding both its advantages and limitations, but its promise certainly merits such accrual.

Conflict of interest: None declared.

Disclaimer

The author served as a paid consultant to GlaxoSmithKline® (GSK, UK) in support of the application of Krintafel™ for registration with the US FDA. His laboratory in Jakarta, Indonesia, today conducts a pivotal clinical trial of Krintafel™ for radical cure of vivax malaria for which GSK is the sponsor. He receives no personal financial incentive or award for that work from GSK or any other organization. The author holds no financial interest in GSK or any of its products. At the invitation of 60 Degrees Pharmaceuticals® (USA), the author provided testimony to the US FDA favorable to the registration of Arakoda™ for chemoprevention of malaria, for which he received no financial

SUMMARY BOX 2. KEY POINTS ON TAFENOQUINE RADICAL CURE IN TRAVEL MEDICINE

- Suppressive malaria prophylaxis standard-of-care requires post-travel presumptive anti-relapse therapy (PART) to destroy latent hypnozoites and prevent delayed attacks in the months following travel.
- A diagnosis of acute relapsing malaria (*P. vivax* or *P. ovale*) in any patient requires PART to destroy latent hypnozoites and prevent subsequent attacks by them.
- Primaquine has been the standard-of-care for PART as 14 daily doses of 0.5 mg/kg for the past 66 years.
- Tafenoquine is a new drug with an indication for post-travel or post-diagnosis PART against relapsing malarias as a single adult dose of 300 mg.
- Tafenoquine is, like primaquine, hemolytically toxic to patients having inherited G6PD deficiency, so is prohibited in those patients along with pregnant and lactating women. Safety in children is not yet established.

compensation or award. He holds no financial interest in that drug, its manufacturer or any of its products.

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