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PERSPECTIVES

Safety and Efficacy of Tafenoquine for *Plasmodium vivax* Malaria Prophylaxis and Radical Cure: Overview and Perspectives

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Abstract: This article is inter alia a brief, first-stop guide to possible adverse events (AEs) associated with tafenoquine (TQ) intake. Safety and efficacy findings for TQ in *Plasmodium vivax* malaria prophylaxis and radical cure are summarized and some of the latest TQ-related studies (published in 2020 and 2021) are highlighted. In addition, little-known biological and other matters concerning malaria parasites and 8-aminoquinoline (8-AQ) drug action are discussed and some correct terminology pertinent to malaria is explained.

Keywords: chloroquine, G6PD, hypnozoite, primaquine, relapse, WR238605

Introduction

Tafenoquine (TQ) is an antimalarial drug of the 8-aminoquinoline (8-AQ) class.[1,2] A single oral dose is more often than not effective for the radical cure of *Plasmodium vivax* malaria. TQ is thought to prevent malarial recurrence by killing a dormant plasmodial stage in the liver, for which I coined the term "hypnozoite" more than four decades ago.[3–5] On the basis of my research at Imperial College London on an organism related to malaria parasites, I thought it likely[6] that a hypnozoite stage exists in the life cycle of *Plasmodium*, and this turned out to be the case.[7]

Ever since 1980, it has traditionally been stated by malariologists as a fact that hypnozoites are the source of relapse in *P. vivax* malaria. Despite this assumption, only recently have hypnozoites actually been shown to activate. The first researchers to demonstrate this were Voorberg-van der Wel et al,[8,9] using the primate model organism *P. cynomolgi*. The factors that account for hypnozoite formation and activation are unknown, giving rise to much speculation.[10] Whether *P. vivax* sporozoites can persist anywhere extra-hepatically (as hypnozoites do in the liver) and be a source of malarial recurrence is not known.[11,12] Like other aspects of early post-invasion plasmodial biology,[13] this theoretical possibility has been insufficiently investigated. Gametocytes of *Plasmodium* occur dermally in humans, although significant sequestration there has not been detected.[14] TQ will not necessarily eliminate *P. vivax* sporozoites or merozoites if they are present in human skin, extrapolating from what has been shown in rodent malaria for primaquine.[15–17]

The most widespread cause of human malaria globally is *P. vivax*,[18] the other common etiological agent being *P. falciparum*. One of the ways in which the

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biology of *P. vivax* differs[19–21] from that of *P. falciparum* is that the latter does not seem to occur in a hypnozoite form. *P. vivax*-like recurrences sometimes take place in humans infected with *P. ovale curtisi* and *P. ovale wallikeri*.[22] It has therefore been widely assumed that hypnozoites are the origin of such recurrences, but persisting hypnozoites have not (yet) been shown to exist in the life cycle of *P. o. curtisi* or *P. o. wallikeri*.[23–28] The effect of TQ in the prophylaxis and treatment of *P. o. curtisi* and *P. o. wallikeri* malaria is unknown (and evidence to support the use of its sister drug primaquine is limited[27,29]). Consequently, this article is only about TQ in relation to *P. vivax* malaria.

Terminology

The terms "recurrence", "recrudescence" and "relapse" are used here. A malarial recurrence is a re-infection, a recrudescence or a relapse. Thus, all three are covered by the word "recurrence". More specifically, a recrudescence has a merozoite origin and a relapse has a hypnozoite origin. The definition of "recrudescence" as renewed parasitemia or clinical manifestations resulting from the multiplication of bloodstream parasites following failed drug treatment is out of date, because extravascular and sequestered merozoites are probably also sources of *P. vivax* malarial recrudescences. I introduced this non-circulating parasite theory[30,31] regarding the source of *P. vivax* malarial recurrences ten years ago. Also, the implications of the presumed presence of these particular stages for the elimination of malaria were pointed out for the first time.[30] That introduction was the theory's sole origin (see Table 1 in Markus[31]) in the post-hypnozoite-discovery era. The theory was not reiterated by anyone else during the ensuing seven years. This bit of recent history has in the meantime been obfuscated in a few publications by other authors. In those articles, citations which would have been appropriate are conspicuous by their absence. That aside, it is important to be aware that amongst the published literature on malaria are numerous papers (both old and new) in which some recurrences interpreted as relapses of *P. vivax* malaria are likely to have been non-circulating merozoite-initiated recrudescences.

Imprecise language should be avoided when discussing the drug treatment of malaria.[32] For example, hypnozoites do not relapse – they activate. It is the infection that relapses (the patient suffers a relapse). However, we should not refer to a "relapse infection", since it is still the same infection. "Relapse infection" means a new infection. So instead, say "relapsed infection" or "relapsing infection". We do not "treat" or "cure" hypnozoites with TQ – they are destroyed, eliminated, inactivated or killed. We treat or cure the patient who has malaria, not the hypnozoites. Likewise, we do not "treat *P. vivax*" or "cure *P. vivax*", those being the expressions which are sometimes used. In the therapeutic sense of "treat" (unlike "treating" cell cultures or mosquito nets, for instance), it is not the parasite that is treated but the disease or the patient. Thus, we "treat *P. vivax* malaria" or "cure *P. vivax* malaria". The term "malaria(s)" should not be used to refer to one or more species of *Plasmodium*, only to the disease (malaria). For example, it is seriously incorrect to call a species of *Plasmodium* "a malaria"[32] or to talk about the "malaria life cycle". And note that *Plasmodium* does not have a plural "Plasmodia".[33] For the plural, we must write "*Plasmodium* species"; or "*Plasmodium* spp."; or "species of *Plasmodium*"; or "plasmodial species". The adjective "plasmodial" is correct. Mistakes like those mentioned above are common in the literature[32,33] but the repetition does not make them correct.

Attention needs to be paid to all of this terminology if we are to avoid perpetuating technical errors in publications on antimalarial drugs.

Tafenoquine Action

TQ seems to have a marked hypnozoite-killing effect. We now need to ascertain the extent to which, if at all, this apparent anti-relapse activity of TQ (both alone and in combination with chloroquine) can be ascribed to elimination of non-circulating merozoites.[34] Asexual *P. vivax* stages that have not been phagocytosed occur in the human spleen in huge numbers,[35–37] something not previously known. As had been suspected,[30,38,39] they are also constantly present in the bone marrow of infected humans and non-human primates.[40–43] In comparison with the number of merozoites in the human spleen and also in bone marrow, the number of hypnozoites in the liver is very small. Non-circulating asexual parasites are likely to occur elsewhere too in chronic human *P. vivax* infections – their distribution not being restricted to just the spleen and bone marrow. To quote a decade-old, essentially predictive statement:

> Malariologists need to reassess the conventional view that plasmodial habitats in humans are only liver and blood and

Table 1 Common Adverse Events (Regardless of Causality) in Some Prophylaxis Studies, Correlated with Tafenoquine Dosage (Information from Papers Additional to Those Cited in the "Adverse Events" Section)

Adverse Event Details	Drug Dosage	Number of Individuals	Reference Number
AEs reported: abdominal pain; headache; fever; fatigue	250 mg/d for 3 d (highest dosage tested)	84	[100]
≥ 5% AEs (detailed breakdown given in the paper[101]): GI 46; respiratory 39; neurologic 25; dermatologic 22; MS 20	400 mg/d for 3 d + 400 mg/w for 13 w (highest dosage tested)	59	[101]
Only mild and transient AEs (diarrhea and headache) reported	400 mg/d for 3 d + 400 mg/m for 5 m	104	[102]
≥ 5% AEs: RTI 14.4; myalgia 13.4; diarrhea 12.4; back pain 6.2; arthralgia 5.1; gastritis 5.1	200 mg/w for 12 w (highest dosage tested)	93	[103]
AEs: mild 13.7; moderate 1.0; severe 0.2	200 mg/d for 3 d + 200 mg/w for 6 m	490	[104]
≥ 5% AEs: URTI 21; diarrhea 16; back pain 15; rash 14; headache 12; arthralgia 11; fungal dermatitis 9; viral infection 8; nausea 6; abdominal pain 5; pharyngitis 5	200 mg/w for 6 m	492	[105]

Notes: The figures for adverse events (AEs) are percentages. AEs that have frequently been recorded are shown. For the full range of possible AEs, see the paper concerned.

Abbreviations: AE, adverse event; d, day(s); GI, gastrointestinal; m, month(s); mg, milligrams; MS, musculoskeletal; RTI, respiratory tract infection; URTI, upper respiratory tract infection; w, week(s).

> be more open to the concept of there perhaps being additional parasite reservoirs.[44]

Furthermore, "much remains to be learnt about clinically relevant aspects of the basic biology of human malaria parasites."[44]

Administration of primaquine for malaria produces hydrogen peroxide in the bone marrow.[45] This will presumably inactivate an unknown proportion of plasmodial stages there, including *P. falciparum* gametocytes. It has been suggested[34] that, by analogy, asexual parasites and gametocytes in bone marrow could conceivably also be killed when TQ is used for the radical cure of *P. vivax* malaria. The possibility has not been investigated, however. Another unanswered question is whether or not drug synergism[46–48] (especially TQ + chloroquine) intensifies the destruction of non-circulating merozoites anywhere in the body.[34] Interpretation of in vivo findings in this regard could be difficult, partly because it is often not clear to what extent malarial recurrences might be the result of drug-resistant *P. vivax*[49–51] (something that is better understood for *P. falciparum*, however[52,53]).

As mentioned above in the section on terminology, many of the recurrences in patients with *P. vivax* malaria are now believed to be recrudescences (as opposed to relapses) with an extravascular or sequestered merozoite origin.[30,31] Even some late (post-28-days) homologous recurrences are thought to be recrudescences.[30,31,51] This realization has called into question the rule of thumb that pre-28-day recurrences are more likely to be recrudescences and post-28-day recurrences are more likely to be relapses. That idea is based largely on information about drug levels in the bloodstream. Whereas many post-28-day recurrences will no doubt indeed be relapses, it is also possible, if not likely,[30] that some long-term recurrences of *P. vivax* malaria have the same presumed non-hypnozoite origin as long-term recurrences of *P. malariae* infection (*P. malariae* is not known to have a hypnozoite form), whatever the non-hypnozoite origin concerned may be.[30,54–56] For that matter, presumed non-hypnozoite *P. falciparum* and *P. ovale sensu lato* parasites can persist for long periods too.[54,57,58]

To summarize, the point being made above is that, as I recently hypothesized elsewhere,[34] TQ may help to prevent not only hypnozoite-derived relapses but possibly also recrudescences which have a splenic, bone marrow, or some other non-circulating merozoite origin. Besides its likely anti-relapse action, TQ is indeed known to eliminate parasite stages that are not hypnozoites.[59,60] When used

prophylactically, it might do so before schizogony can take place in the liver.

Tafenoquine and Glucose-6-Phosphate-Dehydrogenase Deficiency

A major obstacle to treating *P. vivax* malaria with TQ (and other 8-AQs like the related, older and ubiquitously used drug primaquine[61]) or using TQ for prophylaxis is the danger of severe and life-threatening hemolysis associated with glucose-6-phosphate-dehydrogenase (G6PD) deficiency. This is a chromosomally X-linked disorder and a fairly common inherited enzymopathy.[62] Testing for G6PD deficiency is required before TQ (or any other 8-AQ) can be taken. Accordingly, health care workers in *P. vivax*-endemic rural areas must be trained in G6PD testing.[63–65] The diagnosis of G6PD deficiency can be especially tricky in heterozygous women because of random X-chromosome inactivation.

A reliable quantitative G6PD deficiency-related cut-off point is required in order to decide whether TQ can be used safely.[66–68] Calvaresi and Genzen[69] propose that retrospective analysis of a laboratory's data set might help to evaluate eligibility for malaria prophylaxis or radical cure treatment with TQ. A 100% normal G6PD activity reference value would be determined and then the individual's activity result would be converted to a percentage of that laboratory-specific normal activity.[69] As the results of spectrophotometry to measure G6PD activity vary widely between laboratories, study findings are often not comparable. In considering this variability, Pfeffer et al[70] conclude that novel handheld quantitative G6PD diagnostics might facilitate future standardization.

Other laboratory matters require investigation too. One suggestion, by Boonyuen et al,[71] is that a newly developed and simplified high resolution melting curve assay, which has 100% specificity and 100% sensitivity, could be helpful as a supplementary approach to high-throughput screening, particularly for heterozygous females.

Also important to take into account is the effect of different blood storage conditions on the results of post-storage screening for G6PD deficiency. It is obviously vital that the level of G6PD deficiency be accurately determined, safety being at stake if TQ is to be used. With this in mind, Chamchoy et al[72] used the WST-8 assay to evaluate the consequences of storage of blood samples. Their conclusions will probably be applicable to other G6PD tests as well, although this is subject to confirmation. They found that activity in G6PD-deficient specimens decreased markedly under all the storage conditions they studied, although G6PD classification was not affected. They offer advice about the storage of both dried blood spots and ethylenediaminetetraacetic acid (EDTA) whole blood specimens.

Contraindications, Precautions and Warnings

TQ for malaria prophylaxis or radical curative therapy should not be taken by anybody whose G6PD status is not known; or by a breastfeeding mother if the infant is G6PD-deficient or its G6PD status is unknown. Use of TQ in pregnancy is not recommended. TQ is contraindicated for individuals with known hypersensitivity to 8-AQs. Use of TQ by persons with a current psychiatric illness or a history of psychosis is potentially problematic, and caution is advised.[73,74] Lastly, medical treatment is required if signs or symptoms of methemoglobinemia occur.

Adverse Events

TQ is generally well tolerated but adverse events (AEs) can take place. As there is almost total overlap between the kinds of AEs that may follow prophylaxis and those that may follow radical curative treatment, they are first dealt with together here and then specific safety issues for each are covered separately in the next two sections of the article as well as in Tables 1–3.

TQ-related AEs are almost always mild and self-resolving. However, there can be severe reactions in cases of G6PD deficiency. In some studies, AEs occurred more often in people who received higher doses of TQ, as were given in some drug trials. In other studies, no correlation was found between dosages and the frequency of AEs.

Central Nervous System

Rodent, canine and non-human primate drug studies suggest that TQ is unlikely to cause serious central nervous system problems in humans.[75,76] TQ is not classed as neurotoxic in humans at prophylactic doses.[75] In patients with no mental disorder history, only self-limiting and mild-to-moderate central nervous system AEs have been observed after a single 300 mg radical cure dose of TQ combined with chloroquine.

Table 2 Common Adverse Events (Regardless of Causality) in Post-Exposure Prophylaxis Studies, Correlated with Tafenoquine Dosage and Gender (Information from Papers Additional to Those Cited in the "Adverse Events" Section)

Adverse Event Details	Drug Dosage	Number of Individuals	Reference Number
≥ 5% AEs: nausea 27; abdominal cramps 9; diarrhea 10; headache 5	400 mg/d (single dose) for 3 d	254 males	[106]
≥ 5% AEs: nausea 53; abdominal cramps 26; diarrhea 8; vomiting 16; headache 11; lethargy 5	400 mg/d (single dose) for 3 d	38 females	[106]
≥ 5% AEs: nausea 19; abdominal cramps 11; diarrhea 16	200 mg 2x/d for 3 d	73 males	[106]
≥ 5% AEs: nausea 38; abdominal cramps 23; diarrhea 8; headache 8; lethargy 15	200 mg 2x/d for 3 d	13 females	[106]
≥ 5% GI AEs: abdominal distress 13.2; diarrhea 14.5; nausea 31.6; reflux 15.8; vomiting 5.3	400 mg/d (single dose) for 3 d	76 males	[107]
≥ 5% GI AEs: abdominal distress 54.5; diarrhea 27.3; nausea 72.7; reflux 18.2; vomiting 9.1	400 mg/d (single dose) for 3 d	11 females	[107]
≥ 5% GI AEs: abdominal distress 6.8; diarrhea 21.9; nausea 21.9; reflux 5.5; vomiting 21.9	200 mg 2x/d for 3 d	73 males	[107]
≥ 5% GI AEs: abdominal distress 15.4; diarrhea 15.4; nausea 46.2; reflux 23.1	200 mg 2x/d for 3 d	13 females	[107]
≥ 5% AEs: nausea 25.6; abdominal distress 17.4; diarrhea 9.5; headache 7.4; reflux 5.8	400 mg/d (single dose) for 3 d (highest dosage tested)	242	[108]
≥ 5% AEs: nausea 19.3; diarrhea 14.9; abdominal distress 10.6; reflux 6.2	200 mg 2x/d for 3 d (highest dosage tested)	161	[108]

Notes: The figures for adverse events (AEs) are percentages (GI AEs are reported less often when TQ is taken after a meal). AEs that have frequently been recorded are shown. For the full range of possible AEs, see the paper concerned.
Abbreviations: AE, adverse event; d, day(s); GI, gastrointestinal; mg, milligrams.

Eyes

Reassuringly, no conclusive evidence of short-term ocular toxicity of clinical significance has been found in patients who received a single therapeutic dose of 300 mg of TQ,[77] nor in individuals who took 400 mg/day for three days.[78] Some minor and temporary ophthalmic changes were recorded,[77,78] as other authors have reported too.[73] In one study, no clinically significant ocular effects were detected at a dosing regimen of 200 mg of TQ daily for three consecutive days (this being a 600 mg loading dose), followed by 200 mg once weekly for 23 weeks.[79]

Heart

There is no convincing evidence for cardiac toxicity.[73,80,81]

Range of Adverse Effects

AEs described in this article are those which are encountered most frequently. However, the full range of AEs that have been detected in or described by persons who have taken TQ either for prophylaxis or for radical cure is covered by recent reviews.[82–89] Infrequent AEs are also specified in some of the other papers cited, particularly those referenced in Tables 1–3.

Safety for Prophylaxis

The most common AEs (≥ 1%) when TQ is used for malaria prophylaxis are headache, dizziness, nausea, vomiting, motion sickness, diarrhea, abnormal dreams, insomnia, anxiety, depression, back pain, and an increased alanine transaminase (ALT) level.[90]

AEs that were often recorded in clinical trials (trials not already mentioned in the "Adverse Events" section) for individuals who took TQ prophylactically are listed in Tables 1 and 2, together with associated dosages.

Safety for Radical Cure

The most common AEs (≥ 5%) when TQ is used for radical cure are headache, dizziness, nausea, vomiting, and a decreased hemoglobin level.[91]

Table 3 Common Adverse Events (Regardless of Causality) in Some Radical Cure Studies, Correlated with Tafenoquine Dosage (Information from Papers Additional to Those Cited in the "Adverse Events" Section)

Adverse Event Details	Drug Dosage	Number of Individuals	Reference Number
AEs (mild and infrequent): dizziness; headache; heartburn/gas; diarrhea; vomiting; eye irritation (once, perhaps TQ-unrelated)	Up to 600 mg	48	[109]
AEs occurred in a minority of patients in all treatment groups: mainly abdominal discomfort; diarrhea or loose stools; nausea; headache	A: 300 mg/d for 7 d; B: 500 mg/d for 3 d + 1 w after 1st dose, 500 mg/d for 3 more d; C: 500 mg (single dose)	A 15 + B 11 + C 9 = total 35	[110]
AEs (mild and transient): mainly abdominal discomfort; diarrhea or loose stools; nausea; dizziness; headache; weakness	A: 300 mg/d for 7 d; B: 600 mg/d for 3 d; C: 600 mg (single dose)	A 18 + B 19 + C 18 = total 55	[111]
≥ 5% AEs: headache 29; chills 16; diarrhea 16; pyrexia 13; upper abdominal pain 11; nausea 9; weakness 9; dizziness 7; parasitic gastroenteritis 7; back pain 7; arthralgia 5; insomnia 5; myalgia 5; vomiting 5; increased alanine transaminase level 5	600 mg (highest single dose tested) + CQ for 3 d	56	[112]
≥ 5% AEs: methemoglobinemia 47.8; keratopathy 31.8; headache 30.4; URTI 30.4; dizziness 26.1; retinopathy/retinal disorder 22.7; eosinophilia 17.4; abdominal pain 13.0; nausea 13.0; thrombocytopenia 13.0; pyrexia 10.9; asthenia 8.7; diarrhea 6.5; dyspepsia 6.5; hepatomegaly 6.5; hypokalemia 6.5; myalgia 6.5	400 mg/d for 3 d	46	[113]
≥ 5% AEs: pruritus 11.2; dizziness 8.5; nausea 6.2; vomiting 5.8; decreased hemoglobin level 5.4	300 mg (single dose) + CQ for 3 d	260	[114]
≥ 5% AEs: dizziness 16.3; pruritus 12.0; headache 11.4; nausea 9.6; vomiting 6.6	300 mg (single dose) + CQ for 3 d	166	[115]

Notes: The figures for adverse events (AEs) are percentages. AEs that have frequently been recorded are shown. For the full range of possible AEs, see the paper concerned.
Abbreviations: AE, adverse event; CQ, chloroquine; d, day(s); mg, milligrams; URTI, upper respiratory tract infection; w, week.

AEs that were often recorded in clinical trials (trials not already mentioned in the "Adverse Events" section) for individuals who took TQ for radical cure are listed in Table 3, together with associated dosages.

Efficacy for Prophylaxis

Leaving aside the different dosages used,[85] protective TQ efficacy percentages of between 85.6% and 100% have been calculated.[82,85]

In a recent paper on TQ usage for malaria prophylaxis, Islam et al[92] reported that a loading dose alone (200 mg daily for three days), in other words not followed by any additional doses, was effective in preventing malaria in short-term travelers (meaning a trip duration of less than 28 days). It may be that sporozoites inoculated by a mosquito[12] are inactivated by TQ before hepatic schizogony can commence. This lower intake of TQ may also have meant fewer AEs. Longer-term monitoring for at least six months is required to see whether these short-term travelers do indeed continue to remain malaria-free.[92]

Efficacy for Radical Cure

A single 300 mg dose of TQ for radical cure prevented recurrence of *P. vivax* malaria over a 6-month period in 62% to 89% of cases.[85] The efficacy profile of TQ is in general similar to that of primaquine, although some variability geographically has been detected. Also, there has been inconsistency in trial findings in South-East Asia (as discussed by Llanos-Cuentas et al in the last paper covered in Table 3). A possible future course of action might be to reassess the currently recommended 300 mg dose of TQ in respect of parts of Oceania, South America and South-East Asia[73] because so far, it seems that this TQ dose is not always sufficiently effective in those regions.

St Jean et al[93] have carried out initial research into the pharmacogenetics of TQ efficacy in treating *P. vivax*

malaria. TQ efficacy was found to be correlated with particular patient genotypes, although it is unclear at this stage whether these were spurious connections. Further study is needed.[93]

Recommended Partner Drug for Tafenoquine

It is at present recommended that TQ be administered together with chloroquine, specifically, as the partner drug.[74,94] This differs from previous advice.[74] The change is because of a low efficacy finding when patients in Indonesia were treated with a combination of TQ and dihydroartemisinin-piperaquine for the prevention of *P. vivax* malarial recurrences.[95] The reason(s) for the low efficacy is not readily apparent. An account of the study was given in 2020 at the 69th Annual Meeting of the American Society of Tropical Medicine and Hygiene but full details have not yet been published, so the matter cannot be discussed here. It has in the meantime been argued, in relation to the research, that the currently recommended dose of TQ might be too low.[96] Perhaps this hypothesis will be followed up in due course, depending partly upon what information becomes available in the meantime.

Tafenoquine in Children

TQ is not advised for prophylaxis in children under 18 or for radical cure in patients under 16. However, the safety and efficacy of TQ for children has been under investigation. On the basis of a pharmacokinetic bridging modeling study for the radical cure indication,[97] the Australian Therapeutic Goods Administration (TGA) has accepted a filing for the use of TQ for radical cure in children.[98] Further developments are awaited.

Tafenoquine in Pregnancy

As previously mentioned, TQ is not recommended for pregnant women.[90,91]

Drug Injection

To overcome or reduce the risk of hemolysis because of G6PD deficiency, Srinivasan et al[99] have given initial consideration to the idea of a non-oral route of drug administration, based on the assumption that TQ acts against hypnozoites. Murine experiments with *P. berghei* showed that there was reduced drug-associated hemotoxicity when compounds were not administered via the gastrointestinal tract. Outstanding bioavailability was achieved subcutaneously using liver-targeted TQ polymer prodrugs ("drugamers"). The ultimate goal of this ongoing research is to produce a single-dose subcutaneous therapeutic that eliminates hypnozoites but has minimal hemotoxicity in G6PD-deficient humans.[99]

Conclusion

This article is a synopsis of current knowledge about the safety and efficacy of TQ for *P. vivax* malaria prophylaxis and radical cure. It covers some new TQ-associated findings reported in papers published in 2020 and 2021. It also draws attention to relevant theoretical and terminological considerations that are often overlooked.

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