Perspective Piece

Approval of Tafenoquine for Malaria Chemoprophylaxis

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Abstract. Malaria chemoprophylaxis has become increasingly prominent now that it is used for vulnerable populations in endemic regions in addition to nonimmune travelers to those regions. The objective would be a drug with > 95% efficacy and that is easily tolerated, including in children and pregnant women. For individuals who prefer weekly rather than daily drug administration, a further objective is a product that is administered weekly. The deficiencies of present agents are parasite resistance to chloroquine, neuropsychiatric liability of mefloquine, the need for daily dosing for atovaquone–proguanil, and daily dosing plus adverse reactions for doxycycline. A primaquine analogue, tafenoquine, has a 17-day half-life and was approved for weekly prophylaxis in the United States and in Australia in 2018. Weekly tafenoquine was equal to mefloquine in efficacy in nonimmunes. The tafenoquine label contains a contraindication for preexisting psychosis, but not for the broad number of other neuropsychiatric disorders which are listed as contraindications in the mefloquine label. As an 8-aminoquinoline, tafenoquine is contraindicated for glucose-6-phosphate dehydrogenase (G6PD)-deficient persons or in pregnancy if the fetus might be G6PD deficient. Other possible significant adverse reactions for tafenoquine are declines in hemoglobin levels reported in some G6PD-normal patients, asymptomatic elevations in methemoglobin, and minor psychiatric events. The lack of broad neuropsychiatric adverse reactions suggests that tafenoquine may have a role as the weekly prophylactic of choice for G6PD-normal persons.

Malaria chemoprophylaxis has become more prominent as the populations for which chemoprophylaxis is recommended have expanded. Prophylaxis has classically been recommended for travelers to malaria-endemic regions from non-malarious regions, a population that has now enlarged to include individuals from newly malaria-free regions. In addition, infants, young children, and pregnant women within malaria-endemic regions have a higher risk of poor outcomes, leading to recommendations for intermittent preventive treatment for these populations. Although one purpose of intermittent preventive treatment is to eliminate parasites present at the time of treatment, long half-life drugs are used to prevent future infection for as long as possible; thus, intermittent preventive treatment combines treatment with prophylaxis.¹

HISTORICAL DEVELOPMENT OF PRESENTLY APPROVED AGENTS

Malaria chemoprophylactic drugs approved in the United States include chloroquine, doxycycline, mefloquine, and atovaquone–proguanil. Chloroquine was introduced by the Allies during World War II,² was used for both treatment and prophylaxis in the late 1940s,³ and was the mainstay of prophylaxis in the Korean War.⁴ Chloroquine-resistant *Plasmodium falciparum* became apparent beginning in the mid 1960s,² and daily doxycycline was labeled for antimalarial prophylaxis in 1987.⁵ Mefloquine and atovaquone–proguanil were approved for both treatment and prophylaxis in 1989 and 2002, respectively.²

PARAMETERS BY WHICH TO EVALUATE MALARIA CHEMOPROPHYLACTIC AGENTS

The aforementioned summary shows that there are no malaria chemoprophylactic agents that have specifically been developed for prophylaxis. Rather, approved treatment agents have been used at a small fraction of their treatment

dose, because the parasite burden seen in prophylaxis is low compared with that encountered in treatment, and taken at a frequency appropriate to half-life. Atovaquone–proguanil and doxycycline are taken daily. The original mefloquine prophylactic regimen was 250 mg every 2 weeks⁶ (the half-life of mefloquine is approximately 3 weeks⁷), but the lack of efficacy (14 infections per month per 1,000 travelers) caused the change to the present regimen of 250 mg weekly (two infections per month per 1,000 travelers).⁶

Present antimalarial prophylactic regimens are extremely effective when studied under clinical trial conditions. Ninety-eight percent efficacy rates recorded during development for atovaquone–proguanil⁸ and mefloquine⁹ create a high bar for a new agent to equal, although with treatment use, resistance to mefloquine has been recognized in Southeast Asia¹⁰ and resistance to atovaquone has been uncommonly seen.¹¹ One strategy for a new prophylactic drug is to develop an agent that does not have a treatment indication, thus obviating this route to resistance.¹² A pathophysiologically appropriate way of implementing this strategy is to develop a drug effective against the asymptomatic initial liver stages rather than against the subsequent blood stages that give rise to clinical malaria. Because the liver stages are asymptomatic, the drug would not be used for treatment.

Tolerance is an important consideration for prophylactic agents. Once its psychiatric liability was recognized, mefloquine's prophylactic use markedly diminished for the U.S. military (23% of prescriptions to 4%) and somewhat diminished for civilians (13–8%),¹³ even though the rate of major psychiatric events and seizures was low: 1.9 per 100,000 prophylactic users.¹⁴ (The rate of major psychiatric events associated with the treatment regimen with its higher dose was much higher—4.2 per 1,000 treatments.¹⁴)

The third clinical parameter on which prophylactic regimens are judged is compliance. Although it is difficult to prove that compliance to weekly regimens is greater than that to daily regimens, support for this proposition comes from a recent report of long-term antimalarial chemoprophylaxis in American soldiers in Afghanistan: “Compliance with daily doxycycline was

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poor (60%) compared with 80% with weekly mefloquine,” although the effect of adverse events on compliance was reasonably controlled because “adverse events were reported by approximately 30% with both mefloquine and doxycycline.”¹⁵ A further theoretical advantage of weekly regimens is conveyed by the CDC statement that “drugs with longer half-lives... offer the advantage of a wider margin of error if the traveler is late with a dose. For example, if a traveler is 1–2 days late with a weekly drug, prophylactic blood levels can remain adequate; if the traveler is 1–2 days late with a daily drug, protective blood levels are less likely to be maintained.”¹⁶

Until 2018, the unmet medical need for approved products was for an effective, well-tolerated, weekly drug: a “chloroquine” with unimpaired efficacy, a “mefloquine” without the neuropsychiatric liability, or a “malarone” that could be dosed weekly.

PRIMAQUINE

Primaquine is labeled for presumptive anti-relapse therapy of *Plasmodium vivax* but is also recommended by the U.S. CDC for off-label use as antimalarial prophylaxis.¹⁷ As the prototypic 8-aminoquinoline from which tafenoquine (Figure 1) is derived, efficacy and adverse reactions for primaquine may constitute a rough guide to tafenoquine pharmacodynamics. The comprehensive review by Hill et al.¹⁷ summarizes that for prophylaxis, “clinical trials indicate > 85% protective efficacy against *P. falciparum* and primary *P. vivax* infections at a dose of 30 mg daily.” Key contraindications are G6PD deficiency and pregnancy (“even if a pregnant woman is G6PD normal, the fetus may not be”). Gastrointestinal effects are the most common adverse drug reactions; “neuropsychiatric changes seem to be rare, with only a single case report of depression and psychosis after primaquine use.”

TAFENOQUINE

Tafenoquine has substitutions on the quinoline ring (Figure 1), which have resulted in a half-life of 17 days¹⁸ compared with 4–7 hours for primaquine.¹⁷ The recommended regimen is 200 mg on each of 3 days as a loading dose, then 200 mg weekly (half of a half-life) while in the endemic region, and then one dose of 200 mg in the week postexposure to kill late-arriving parasites.¹⁸ When the loading-and-in-country regimen was evaluated in nonimmune Australian troops on patrol in East Timor, tafenoquine was

100% effective, as was weekly mefloquine used as a comparator.¹⁹ Historic controls indicated a 6.8% *P. vivax* attack rate and 1.0% *P. falciparum* attack rate in this region.²⁰

As an 8-aminoquinoline, tafenoquine is primarily active against initial liver stages,²¹ but tafenoquine is also effective against small inocula of *P. falciparum* blood stages.²² Because tafenoquine is active against multiple parasite stages and there are multiple populations for which prophylaxis might be used, the likelihood of resistance generation is difficult to predict. Classic prophylaxis of travelers, no matter what parasite stage is targeted, is unlikely to generate resistance because the number of persons receiving prophylaxis and particularly who fail prophylaxis in the endemic region is far less than the number of persons in the parasite reservoir.

Tafenoquine’s blood stage activity should be sufficient to kill parasites that escape being killed in the liver during prophylaxis, but insufficient for the drug to be used as sole treatment in acute malaria. This latter characteristic may overall be an advantage because the lack of sole blood stage treatment use will avoid resistance generation by this route. Intermittent preventive treatment, on the other hand, could lead to resistance if the population receiving intermittent preventive treatment is large. Tafenoquine is also approved to treat *P. vivax* hypnozoites.²³ Because approximately 33% of individuals infected by *P. vivax* have recurrence of *P. vivax* parasitemia despite tafenoquine therapy,²⁴ it is possible that hypnozoites not killed by tafenoquine treatment would ultimately lead to gametocytes acquired by mosquitoes and a tafenoquine-resistant initial liver infection in a new host. This chain of events, however, is based on transmission of resistance from hypnozoites to initial liver stages, something unclear given our present lack of knowledge of these various parasite stages.

As an 8-aminoquinoline, tafenoquine is contraindicated in G6PD-deficient individuals who comprise perhaps 10%²⁵ of the human population. The need to have G6PD testing before accessing tafenoquine is an inconvenience for subjects and a disadvantage for the drug. The label also contains a contraindication for history of psychosis and warnings concerning pregnancy, hemolytic anemia, methemoglobinemia, and rare hypersensitivity reactions.¹⁸

The history of psychosis contraindication is based on three incidents of psychosis in subjects who had a history of psychosis before tafenoquine administration.¹⁸ The psychiatric contraindication for tafenoquine can be compared with the broader psychiatric contraindication for mefloquine: “Mefloquine... should not be prescribed for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders, or with a history of convulsions,”⁷ which, as mentioned previously, has limited the population who receive the drug. For tafenoquine, other “psychiatric adverse reactions included sleep disturbances (2.5%), depression/depressed mood (0.3%), and anxiety (0.2%).”¹⁸ In placebo-controlled trials, the rates of dizziness were 5% of tafenoquine subjects versus 3% of placebo subjects, sleep disorders in 1% versus 1%, and depression in 1% versus 0%.¹⁸ This compilation of adverse neuropsychiatric reactions may be compared with the warnings for mefloquine: “Psychiatric symptoms ranging from anxiety, paranoia, and depression to hallucinations and psychotic behavior can occur with mefloquine use... During prophylactic use, the occurrence of psychiatric symptoms, such as acute anxiety, depression, restlessness, or confusion, suggests a risk for more

FIGURE 1. Structure of primaquine (left) and tafenoquine (right).

serious psychiatric disturbances or neurologic adverse reactions. . . Neurologic symptoms, such as dizziness or vertigo, tinnitus, and loss of balance, have been reported.”²⁷ The differences in neuropsychiatric adverse reactions in the clinical labels are supported by functional observational battery evaluations in rats. No histopathological changes were seen in tafenoquine animals at 10 times the clinical prophylactic exposure,²⁶ whereas neurodegeneration was seen in mefloquine animals at four times the clinical prophylactic exposure.²⁷ The TQ contraindication for history of psychosis should not materially limit the population that can be administered with this drug. A more precise understanding of whether tafenoquine prophylaxis results in psychiatric adverse reactions will derive from a post-marketing study.²⁸

The pregnancy warning is based on potential harm to a G6PD-deficient fetus. “Even if a pregnant woman has normal levels of G6PD, the fetus could be G6PD deficient.” A similar warning is in the primaquine label,²⁹ from which the tafenoquine warning derives. Although at present tafenoquine is only approved for prophylaxis in adults, another post-marketing requirement is to conduct a study in children, including infants;²⁸ thus, use in the pediatric population will soon be clarified. Vortex keratopathy (manifesting as benign corneal deposits) was seen in 15 (21.4%) tafenoquine subjects and in four (15%) placebo subjects in a placebo-controlled trial. These corneal changes did not impact vision, and resolved in 1 year in all tafenoquine patients.³⁰ Other possible adverse reactions are declines in hemoglobin levels which were reported in some G6PD-normal patients and asymptomatic elevations in methemoglobin.

POTENTIAL OF TAFENOQUINE FOR MALARIA PROPHYLAXIS

When tafenoquine was compared with a standard of care in clinical trials, the chosen comparator was weekly mefloquine. Both tafenoquine and mefloquine were found to be highly effective with weekly dosing in nonimmunes. Tafenoquine’s additional anti-hypnozoite treatment use, and possible future use in intermittent preventive treatment, could however lead to resistance generation. The improved neuropsychiatric adverse reaction profile of tafenoquine versus mefloquine suggests that it may replace mefloquine as the weekly antimalarial prophylactic of choice, except in G6PD-deficient persons or pregnant women who might be deficient. It is ironic that development of tafenoquine for antimalarial prophylaxis started at least 30 years ago³¹ was almost abandoned several times, yet at present, tafenoquine seems poised to be an important advance for this indication.

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