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▣ BRIEF COMMUNICATION

Primaquine Administration after Falciparum Malaria Treatment in Malaria Hypoendemic Areas with High Incidence of Falciparum and Vivax Mixed Infection: Pros and Cons

Polrat Wilairatana[1,*], Noppadon Tangpukdee[1], Shigeyuki Kano[2] and Srivicha Krudsood[3]

[1]Department of Clinical Tropical Medicine and [3]Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, 10400, Thailand; [2]Department of Tropical Medicine and Malaria Research Institute, National Center for Global Health and Medicine (NCGM), Tokyo, 162-8655, Japan

Abstract: Mixed infections of *Plasmodium falciparum* and *Plasmodium vivax* is high (~ 30%) in some malaria hypoendemic areas where the patients present with *P. falciparum* malaria diagnosed by microscopy. Conventional treatment of *P. falciparum* with concurrent chloroquine and 14 days of primaquine for all falciparum malaria patients may be useful in areas where mixed falciparum and vivax infections are high and common and also with mild or moderate G6PD deficiency in the population even with or without subpatent vivax mixed infection. It will be possibly cost-effective to reduce subsequent vivax illness if the patients have mixed vivax infection. Further study to prove this hypothesis may be warranted.

Key words: *Plasmodium falciparum, Plasmodium vivax,* mixed infection, primaquine

In malaria endemic areas, e.g. Thailand, where both *Plasmodium falciparum* and *Plasmodium vivax* [1] have caused approximately equal numbers of malaria cases for many years until recently, the prevalence of both species are nearly up to 50% each [2]. Both diseases may cause severe and fatal diseases. *P. vivax* relapses after curative treatment of *P. falciparum*, or subsequent appearance of *P. vivax* after *P. falciparum* clearance, occurs in up to 30% of cases during 2 months follow-up in hospitals [3], and approximately 10% with vivax malaria during 28 days in hospital have developed subsequent falciparum malaria [4-7]. Re-infection by other *Plasmodium* species after admission with initial falciparum or vivax malaria presentations in those studies was not possible since all patients were monitored in hospitals in Bangkok where no malaria transmission occurs and none of them received blood transfusion during hospitalization.

The diagnosis of mixed infections even by expert microscopists is rather difficult since *P. falciparum* suppresses *P. vivax* [8] and the converse may also occur [9]. Drug treatment of *P. vivax* also suppresses *P. falciparum* parasitemia. Mixed infections with *P. falciparum* and *P. vivax* are clinically unpredictable. Vivax patients with cryptic *P. falciparum* infection had a significantly lower mean hematocrit than those with *P. vivax* alone [7]. In many malaria endemic areas, *P. falciparum* is highly chloroquine-resistant and not suppressed by conventional vivax treatment. The conventional *P. falciparum* treatment, e.g. artemisinin combination therapy (ACT) or quinine plus doxycycline or clindamycin, with or without single dose of primaquine (30-45 mg base for adults and 0.5-0.75 mg base/kg in children to kill *P. falciparum* gametocytes) can kill both asexual forms of *P. falciparum* and *P. vivax* but can not eradicate *P. vivax* hypnozoites, if the patients have.

With microscopy, it has been hardly possible to identify mixed infections with submicroscopic *P. falciparum* in patients diagnosed with acute vivax malaria. However, PfHRP-2 test was sensitive and 99% specific in predicting mixed infections with subpatent *P. falciparum* parasitemia at presentation since asexual and immature sexual *P. falciparum* secrete PfHRP-2 in the patient's circulation for 3-4 weeks. Pf HRP-2 may be useful adjunct to microscopy in areas where mixed infections are common. However, PfHRP-2 has limitation to detect *P. falciparum* in mixed infections if *P. falciparum* parasitemia is too low. If subpatent *P. falciaprum* in patients who present with vivax malaria can be

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* Corresponding author (tmpwl@mahidol.ac.th)

screened it may be useful.

Nested PCR and real-time PCR could detect mixed infections of *P. falciparum* and *P. vivax*. PCR assay surpass microscopy and also offer clear advantage in detection of mixed infections [10, 11]. PCR is more sensitive to detect both malaria species than PfHRP-2 for detection of *P. falciparum*. However, there is no study using pLDH adjunct to microscopy to detect *P. falciparum* and *P. vivax* mixed infections.

It was suggested by Mayxay et al. [7] that screening of every patient with vivax malaria at presentation with both microscopy and PfHRP-2 in areas where mixed infections were high should be weighted with the cost of the test, the risks, and cost of managing the subsequent falciparum malaria. However, in many endemic areas, PfHRP-2 or other rapid diagnostic test or PCR are not available or affordable. The cost of PfHRP-2 test with good quality is high (~US$3.00) and the cost of microscopic diagnosis of malaria is low (~US$0.50). Adjunct using PfHRP-2 and microscopy (which costs ~US$3.50) is rather expensive in many endemic countries and may not be practical.

Treatment of *P. falciparum* with blood schizontocides and concurrent chloroquine (10 mg base/kg start followed by 5 mg base/kg at 12, 24, and 36 hr; or 10 mg base/kg at 24 hr, 5 mg base/kg at 48 hr) and primaquine 15-30 mg base (0.25-0.5 mg/kg base) for 14 days for eradication of hypnozoites may be justified and possibly cost-effective in mixed infections. The incidence of *P. vivax* reappearance after *P. falciparum* treatment is high (~30%) in Thailand where nearly equal incidence of both malaria species (~50%) occurs. A 14 day primaquine administration concurrently with treatment of asexual forms of *P. vivax* is recommended in hypoendemic areas, e.g. Thailand. Concurrent chloroquine and primaquine administration reduces the period that the patient is infective to mosquitoes by about 4 days. Chloroquine and primaquine concurrent treatment may enhance the activity of chloroquine against blood-stage parasites and enhance the primaquine effects against the liver stage of the parasite [12]. While this may not be significant in a hospital setting in non-transmission areas, e.g., Bangkok, where no anopheles mosquitoes are found due to polluted water, in rural areas where patients are released to bed rest at their home, they will continue to infect mosquitoes.

Since G6PD deficiency status in Thailand is mild to moderate and all malaria clinics of Ministry of Public Health of Thailand do not routinely screen G6PD status of the patients as the national antimalarial program. Therefore, this management may be useful and possibly cost-effective (without taking into account of supplemental therapy or hospitalization costs or opportunity loss of work during illness) to treat both *P. falciparum* and *P. vivax* mixed infections when the patients present with *P. falciparum* malaria at only one visit at the clinic or hospital. Moreover, the risk of hemolysis from 14 day primaquine administration for vivax infection is very low in Thailand. The patients with mixed infections will be ill or lose work again with *P. vivax* if they are treated with only conventional treatment of *P. falciparum* without concurrent chloroquine and 14 days of primaquine administration. The cost of chloroquine treatment for a 60 kg adult is US$0.10 [13] and the cost of primaquine is also very cheap (US$0.30-0.60 for 14 tablets of 15-30 mg base primaquine). In some countries, like Indonesia, where *P. vivax* is chloroquine-resistant, ACTs with the exception of combinations containing sulfadoxine-pyrimethamine are the first-line of *P. vivax* treatment which will be beneficial to kill asexual forms of both *P. vivax* and subpatent *P. falciparum* mixed infections. However, if the patients given primaquine develop black urine or anemia due to hemolysis, they are advised to go to hospitals for further G6PD test and the cost of the test (NADH+ Spot test) is low (< US$1.00 per test) [14]. In the patients with mild to moderate G6PD deficiency, primaquine 0.75 mg base/kg body weight once a week for 8 weeks may be given. The cost of weekly 45 mg base of primaquine for 8 weeks is US$0.50.

Major drug interactions of chloroquine are very unusual. Theoretically, the risk of convulsions may be increased with mefloquine. Primaquine should be given after meal to avoid abdominal pain (an adverse effect if administered to an empty stomach). The disadvantage of the concurrent administration of ACT with chloroquine and primaquine is the amount of drugs, since the patients have to take many tablets for completing the treatment course.

In contrast, the incidence of *P. falciparum* appearance after *P. vivax* presentation is not high (~10%). Chloroquine given concurrently with 14 days of primaquine, which is the conventional treatment of *P. vivax*, cannot kill chloroquine-resistant *P. falciparum*. Conventional non-chloroquine treatment of *P. falciparum*, e.g., ACT, and concurrent administration of chloroquine and primaquine 14 days when the patients present with vivax malaria from the areas with chloroquine-sensitive *P. vivax* is expensive, not justified, and possibly not cost-effective although the patients may have mixed infections since the incidence of subsequent *P. falciparum* after *P. vivax* presentation is lower (~10%) than incidence of subsequent *P. vivax* after *P. falciparum* presentation (~30%) in mixed infections. The costs of antimalarial treatment

for a 60 kg adult are US$2.50 for artesunate-mefloquine for 3 days, and US$2.00 for quinine plus doxycycline for 7 days [13]. Therefore, the cost of artesunate-mefloquine with concurrent chloroquine and 14 days of primaquine administration is US$2.90-3.20 which is not much higher than US$2.50 for the cost of artesunate-mefloquine alone. However, some clinicians do not prefer to treat malaria infection unless specific species is laboratory-confirmed, e.g., by microscopy. The national antimalarial program of many countries, including Thailand, recommended to treat certain malaria species according to laboratory confirmed diagnosis, even though the incidence of mixed *P. falciparum* and *P. vivax* infections is high and common when the patients present with *P. falciparum* malaria.

In conclusion, in malaria hypoendemic areas where mixed infections of *P. falciparum* and *P. vivax* is high when the patients present with *P. falciparum* malaria which is confirmed only by microscopy, conventional treatment of *P. falciparum* with concurrent chloroquine and 14 days of primaquine administration (for hypnozoite eradication, if there is subpatent *P. vivax* infection or even there is no mixed vivax infection at all) may be useful and possibly cost-effective. However, further studies to prove this hypothesis may be warranted in geographic regions where mixed infections are common and high and G6PD deficiency is mild or moderate. Whether the incidence of both falciparum and vivax malaria will decline in malaria endemic areas after this new treatment of falciparum malaria is interesting to follow.

REFERENCES

1. Luxemburger C, Ricci F, Nosten F, Raimond D, Bathet S, White NJ. The epidemiology of severe malaria in an area of low transmission in Thailand. Trans R Soc Trop Med Hyg 1997; 91: 256-262.
2. Ministry of Public Health, Thailand, 2009 (unpublished data).
3. Looareesuwan S, White NJ, Chittamas S, Bunnag D, Harinasuta T. High rate of *Plasmodium vivax* relapse following treatment of falciparum malaria in Thailand. Lancet 1987; 2: 1052-1055.
4. Krudsood S, Wilairatana P, Mason DP, Treeprasertsuk S, Singhasivanon P, Looareesuwan S. Hidden *Plasmodium falciparum* infections. Southeast Asian J Trop Med Public Health 1999; 30: 623-624.
5. Wilairatana P, Silachamroon U, Krudsood S, Singhasivanon P, Treeprasertsuk S, Bussaratid V, Phumratanaprapin W, Srivilirit S, Looareesuwan S. Efficacy of primaquine-resistant *Plamodium vivax* in Thailand. Am J Trop Med Hyg 1999; 61: 973-977.
6. Mason DP, Krudsood S, Wilairatana P, Viriyavejakul P, Silachamroon U, Chokejindachai W, Singhasivanon P, Supavej S, McKenzie FE, Looareesuwan S. Can treatment of *P. vivax* lead to an unexpected appearance of falciparum malaria? Southeast Asian J Trop Med Public Health 2001; 32: 57-63.
7. Mayxay M, Pukrittayakamee S, Chotivanich K, Imwong M, Looareesuwan S, White NJ. Identification of cryptic coinfection with *Plasmodium falciparum* in patients presenting with vivax malaria. Am J Trop Med Hyg 2001; 65: 588-592.
8. Maitland K, Williams TN, Bennett S, Newbold CI, Peto TE, Viji J, Timothy R, Clegg JB, Weatherall DJ, Bowden DK. The interaction between *Plasmodium falciparum* and *P. vivax* in children on Espiritu Santo Island, Vanuatu. Trans R Soc Trop Med Hyg 1996; 90: 614-620.
9. Takagi T, Kano S, Masuda G, Suzuki M. Submicroscopic double infection of *Plasmodium falciparum* in *P. vivax* malaria. Trans R Soc Trop Med Hyg 1988; 82: 384.
10. Siribal S, Nakasiri S, Looareesuwan S, Chavalitshewinkoon-Petmitr P. Identification of human malaria parasites and detection of mixed infection in Thai patients by nested PCR. Southeast Asian J Trop Med Public Health 2004; 35: 5-9.
11. Katakai Y, Chiabchalard R, Komaki-Yasuda K, Kawazu S, Singhasivanon P, Krudsood S, Looareesuwan S, Kano S. Application of real-time polymerase chain reaction (PCR) analysis for detection and discrimination of malaria parasite species in Thai patients. Southeast Asian J Trop Med Public Health 2004; 35: 10-14.
12. Baird JK, Schwartz E, Hoffman SL. Prevention and treatment of vivax malaria. Curr Inf Dis Rep 2007; 9: 39-46.
13. White NJ. Malaria. In Cook GC, Zumla AI, eds. Manson's Tropical Diseases. 22nd ed. China. Saunders. 2009, p 1274.
14. Bryan JP. Cost considerations of malaria chemoprophylaxis including use of primaquine for primary or terminal chemoprophylaxis. Am J Trop Med Hyg 2006; 75: 416-420.