Clinical investigation of *in-vivo* susceptibility of *P. falciparum* to artesunate in Phuoc Long, Binh Phuoc Province, Vietnam

Tran Tinh Hien, Nguyen Hoan Phu, Le Thanh Dong, Nguyen Thi Thuy Nhien, Nguyen Thi Nha Ca, Le Hong Thai, Cao Quang Thai, Phung Duc Thuan, Vu Ngoc Tam, Le Thanh Long, Tran Van Chung, Pham Van Toi, Marcel Wolber, Nicholas J White, Pascal Ringwald, Jeremy Farrar

Oxford University Clinical Research Unit, WHO, Hospital for Tropical Diseases HCM City, Institute of Malariology-Parasitology- Entomology of HCM, City, Malaria Control Center of Binh Phuoc, Phuoc Long Hospital, Bu Gia Map Health Commune Station

* Correspondent author: Dr. Tran Tinh Hien

E-mail: hientt@oucru.org

There are worrying signs from Western Cambodia that parasitological responses to artesunate containing treatment regimens for uncomplicated falciparum malaria are slower than elsewhere in the world. In order to assess the need for treatment policy changes we proceeded quickly to investigate whether there is any evidence of resistance to artemisinin derivatives in southern provinces of Vietnam.

Method and materials:

We conducted a randomized clinical descriptive study in uncomplicated falciparum malaria, comparing the slope of the decline in the log parasitemia-time curve, PCT, and efficacy of artesunate 2mg/kg/day, artesunate 4mg/kg/day or dihydroartemisinin-piperaquine once daily to establish the current efficacy of the drugs and the sensitivity of the parasite in southern Vietnam. This surveillance study was a three-arm prospective evaluation of the efficacy of artesunate and dihydroartemisinin-piperaquine in acute uncomplicated falciparum malaria (WHO 2003, 2009). This was an evaluation of the slope of the decline in the log parasitemia-time curve, parasite reduction ratio (PRR), parasite clearance times (PCT) in patients randomized to one of two different doses of oral artesunate or dihydroartemisinin-piperaquine. The artesunate arms will immediately follow with dihydroartemisinin-piperaquine therapy for 3 days (study days 3 – 6) at the dose defined by national guidelines. Patients on all three arms will be monitored for 42 days. The follow-up will consist of a fixed schedule of check-up visits and corresponding clinical and laboratory examinations. PCR analysis will be used to distinguish between true recrudescence due to treatment failure and re-infection.

Result:

From 11 Aug 2010 to 16 May 2011 there were 6903 febrile patients having been screened for malaria at out-patient clinics in Phuoc Long area (324 *P.falciparum*; 159 *P.vivax* and 32 mixed infections). There were only 166 *P. falciparum* were eligible for study. Most of patients (155/166 = 93%) were adults. On admission 153/166 (92%) patients were febrile and the other ones had symptoms as headache or fatigue but had also a history of fever; the proportions of patients with fever on admission were comparable in 3 groups of treatment. Therefore 49, 46 and 52 patients in those 3 groups fulfilled the study follow up schedule. The characteristics of all 3 treatment groups on enrollment to the trial were similar.

Fever clearance times (median) were similar in 3 groups (30, 24, 24 hours in artesunate 2mg/kg, 4mg/kg and DHA-PPQ respectively). The parasite clearance times expressed as median parasite clearance times (PCT; 60,42, 48 hours respectively), parasite reduction ratios (PRR. 0.04, 0, 0 % respectively), median clearance constant rates (slopes; 0.19, 0.25, 0.23 respectively) were also comparable in 3 treatment groups; except patients receiving AS 2mg/kg tended to have slightly worse outcomes with respect to all endpoints but the comparison only reached conventional significance for the secondary endpoints of parasite-reduction ratios at 24 hours and the risk of failure (WHO definition, PCR-corrected, Kaplan-Meier analysis). However the proportions of patients who still had positive blood smear after 72 hours were 29%, 26% 22% and that seems higher than ones of previous years in the same areas. There were 3 early treatment failures (ETF) and 1 late treatment failure (LTF) in the 2 mg/kg artesunate group and the APCR rates of 3 treatment groups were 94%, 100%, 100% respectively in per protocol analysis (p=002).

Conclusion:

Artsunate is becoming less effective in patients with falciparum malaria in Southern provinces of Vietnam but dihydroartemisinin + piperaquine is still a powerful antimalarial drug combination with APCR over than 95%.