ABSTRACT

Artemisinin-based combination therapy (ACT) is recommended first-line treatment for malaria in a number of Sub-Saharan African (SSA) countries. Recent reports of decline in efficacy of ACT and emergence of ACT resistant *Plasmodium falciparum* isolates has raised global health concern. The underlying mechanisms for the development of resistance to ACT is however, not fully understood. Naturally acquired immunity to *P. falciparum* is associated with clinical protection against malaria and has been shown to influence efficacy of antimalarial drugs. To what extent pre-existing naturally acquired immunity to malaria affects efficacy of ACT remains to be established. The present study hypothesize that soluble immune factors present in sera of malaria-exposed (immune) individuals enhance the efficacy of ACT for treatment of uncomplicated *P. falciparum* malaria. Therefore, the study aims to determine the effect of serum-derived immune factors on *in vitro* growth of *P. falciparum* by serum from malaria immune and non-immune participants then correlate the effect of serum-derived immune factors on *in vitro* growth of *P. falciparum* in immune participants and ACT efficacy for uncomplicated malaria. To test the hypothesis, sera from participants (n=118) (i.e. immune sera) previously enrolled in a two-arm (i.e. artesunate-mefloquine or artemether-lumefantrine), randomized open-label trial conducted in Kisumu Country, western Kenya, were assessed for *in vitro* growth inhibitory activity (GIA) of 3D7 *P. falciparum* strain, then compared with pooled sera from malaria naïve volunteers (n=6) (i.e. non-immune sera). Each sample was divided into two portions from which one was heat inactivated, and GIA was performed at 10% and 1% serum concentration. Continuous variables were compared using Mann Whitney test and One-way analysis of variance with Tukey's post hoc. Spearman correlation coefficient test was used to correlate GIA and parasite clearance rate. Median parasite clearance rate was used as cut-off to assess treatment outcome, where fast clearers (n=80) had parasite clearance slope half-life ($PCt_{1/2)}$ above the median parasite clearance rate while faster clearers (n=25) had $PCt_{1/2}$ below the median parasite clearance rate. Serum from immune participants significantly inhibited *P. falciparum* growth compared to non-immune ($p < 0.0001$). Heat inactivation further diminished growth inhibitory activity of immune sera ($p = 0.009$). There was age-independent inhibitory activity ($p > 0.05$). In addition, GIA correlated with parasite clearance rate after adjusting with age (< 5years vs > 5years ($p < 0.0001$). Further analysis showed significant positive correlation between GIA and faster parasite clearance in participants aged > 5years ($p = 0.02$). The results of this study suggest that serum-derived immune factors affect the efficacy of ACT for treatment of uncomplicated *P. falciparum* malaria. These findings will provide insight into improving on effective use of ACT drugs (dosage) in area where malaria is endemic.

CHRISTINE N.L. WANJALA (PG/MSC/00087/2012)