

ABSTRACT

Significant advancement achieved in the chemoprophylaxis and chemotherapy of malaria has been pivotal for eventual reduction of malaria prevalence. However, a major setback has been the emergence of resistance to antimalarial drugs. Towards the goal of curbing emergence of resistance, artemisinin-based combination therapies (ACT), is now adopted by many countries as the first-line treatment for malaria. The recently reported cases of resistance to ACT in South East Asia (SEA), have raised concerns on future of ACT. Therefore, an urgent need exists to fully understand the molecular determinants of ACT efficacy. This study aims to determine the baseline magnitude and breadth of antibody responses and also to associate the antibody responses to efficacy of ACT. We hypothesize that in Kombewa-western Kenya, a holoendemic region, pre-existing antibody responses to specific *P. falciparum* antigens is a predictive correlate of ACT efficacy in patients with uncomplicated malaria. There has been reported delay in parasite clearance following artemisinin treatment in Kenyan and resurgence of parasite prevalence and malaria vector in Kombewa recently. This sub-study was conducted as part of the larger two-arm (Artesunate-Mefloquine (ASMQ) and Artemether Lumefantrine (AL) randomized, open-label trial. Baseline sera from 82 patients (AL=40,ASMQ=42) enrolled in the arms of the trial were analyzed for total IgG against erythrocytic (Apical membrane Antigen-1 (HB3 and 3D7 strains), Merozoite surface protein -1(3D7 and FVO strains) and pre-erythrocytic stage (Liver Stage Antigen , Cell-traversal for Ookinetes and sporozoites and Circumsporozoite protein) *P. falciparum* antigens using Luminex. Since ACT efficacy can be assessed based on parasite clearance rate, patients were grouped into fast clearers and faster clearers, using parasite clearance half-life ($PC_{1/2}$). The threshold was fixed at the 25th percentile which was 2.02 hours. Variables were compared using Mann-whitney U test, χ^2 test and z test as appropriate to examine associations between immunological endpoints and clinical endpoints. Patients generally had high prevalence of IgG antibodies (91-100%) and those >5 years of age had significantly higher titers of anti-AMA1HB3-specific antibodies ($p=0.0316$) than those <5 years. Faster clearers had levels of AMA1HB3-specific antibodies significantly higher ($p=0.0065$) than fast clearers. This association was significant even when ASMQ subjects were analyzed ($p=0.0073$). However, in AL arm anti-LSA-1 antibodies were significantly higher in faster clearers. This finding suggests that specific IgG antibodies against AMA1-HB3 and LSA-1, observed in this setting, could be predictive of ACT efficacy and could therefore be used in surveillance for resistance (delayed clearance). This result should be confirmed in a large-scale study.