Limited Impact of Treatment and Re-treatment with Artemether-Lumefantrine and Artesunate-Amodiaquine on the Selection of Plasmodium Falciparum Multidrug Resistance-1 Alleles

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Background The emergence of resistance against artemisinin combination treatment (ACTs) is a major concern for malaria control. ACTs are recommended as rescue treatment; however, there is limited evidence on the impact of treatment and re-treatment with ACTs on selection for drug-resistant parasites. We aimed to investigate the impact of treatment and re-treatment using artesunate-amodiaquine (ASAQ) and artemether-lumefantrine (AL) on the selection of Plasmodium falciparum multidrug resistance-1 (Pfmdr1) alleles.

Methods A total of 776 isolates were collected in 28-days follow-up involving children aged 0–59 months in a clinical trial in the Democratic Republic of Congo and Uganda. Nested PCR and RPFL was used to detect Pfmdr1 single-nucleotide polymorphisms at codons N86Y, F184Y, and D1246Y. The analysis compared Pfmdr1 alleles in the pre-randomisation (pre-RCT), randomisation (RCT) and post-randomisation (post-RCT) phases of the trial.

Results The pre-treatment prevalence of Pfmdr1 (N86 and D1246Y) in the RCT phase varied significantly between the sites. Pfmdr1 NYD haplotype was significantly higher in Uganda while haplotype YYD was higher in the Democratic Republic of Congo, (p<0.001). Comparison between pre-treatment and post-treatment adequate clinical and parasitological response (ACPR) or PCR-adjusted treatment failure did not indicate increased selection of Pfmdr1 N86, D1246 and Y184 in either AL or ASAQ arm in the pre-RCT, RCT and post-RCT phases. The relative risk (RR) of treatment failure (TF) in patients harbouring Pfmdr1 N86 did not significantly increase in patients treated with AL (RR=0.2, 95% CI: 0.11–1.05, p=0.061) or ASAQ (RR=1.03, 95% CI: 0.47–2.26, p=0.94). 

Conclusions Our findings suggest the limited impact of treatment and re-treatment with AL or ASAQ on selection for Pfmdr1 variants and haplotypes associated with resistance to partner drugs. These findings support the recent WHO recommendation to use ACTs as alternative rescue therapy for P. falciparum malaria. However, enhanced resistance monitoring is warranted to maintain the drug's effectiveness in endemic settings.