ZIBI Graduate School

Project description

Project Title: Reduced susceptibility to and resistance selection against artemisinin and quinolone derivatives in alpha-thalassaemia

Research Group: Institute of Tropical Medicine and International Health
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Project Description:

One likely reason for the emergence of artemisinin-resistant malaria parasites in SE Asia lies in the abundance of haemoglobinopathies, which influence pharmacokinetics and pharmacodynamics of several antimalarials. Globally, the most common haemoglobinopathy is alpha-thalassaemia.

In severe alpha-thalassemia, artesunate (and chloroquine) show reduced *in vitro* efficacy due to low intra-erythrocytic drug concentration in infected RBCs competing with un-infected RBCs. Also, binding of artemisinin to pathogenic cell components inactivates the drug. Whereas these findings are seen with severe alpha-thalassaemia, less if anything is known for the very common but mild form of heterozygous alpha+-thalassaemia in Africa. Notably, we found evidence for reduced chloroquine efficacy in alpha-thalassaemic African children. Considering its abundance, the actual epidemiological relevance for impaired treatment efficacy may be substantial. Also, reduced intra-erythrocytic drug accumulation due to alpha+-thalassaemia likely favours the selection of resistant parasites in persisting infections but this has not yet been investigated.

We hypothesize that common mild alpha+-thalassaemia affects susceptibility and resistance formation towards artemisinins as well as towards amodiaquine and lumefantrine, i.e., components of first-line antimalarial drugs. We will examine this by i) assessing *in vitro* drug susceptibility using alpha-thalassaemic and normal RBCs as host cells, ii) determining the pace (and markers) of resistance formation when *P. falciparum* is cultured under drug pressure in alpha-thalassaemic vs. normal RBCs, and iii) by comparing treatment outcomes in individuals with and without alpha-thalassaemia. i) Alpha+-thalassaemic RBCs will be obtained from a population with respectively high frequencies (Ghanaian participants of another study in Berlin) or at cooperating sites in Ghana or Rwanda. Alpha+-thalassaemia will be typed by PCR. *P. falciparum* microcultures using alpha-thalassaemic and normal donor RBCs will be set up (each 10-20 donors) and used for the determination of IC50s and MICs, monitoring parasite growth by microscopy and FACS. RBC drug concentrations will be measured in collaborating laboratories. ii) Long-term *P. falciparum in vitro* cultures (3-6 months) will be established using alpha-thalassaemic and normal RBCs. Resistant parasites will be selected by incrementing or intermittent exposure to the target drug. During that, molecular markers of resistance will be monitored by PCR. Read-outs will be the time to resistance formation, stability and degree of resistance as well as accompanying molecular markers. iii) Available (African cohorts) samples of patients treated for malaria will be genotyped for alpha+-thalassaemia, and treatment outcome will be related to genotype. In addition, patients treated for malaria will be followed-up in observational studies and genotyped for alpha-thalassaemia.