Karolinska Institutet

Department of Medicine, Solna

The role of molecular markers in emerging artemether-lumefantrine resistant *Plasmodium falciparum*

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Hillarpsalen, Retzius väg 8, Karolinska Institutet

Fredagen den 18:e januari, 2013, kl 13.00

av

Maja Malmberg
MSc, Civilingenjör i bioteknik

Huvudhandledare:
Dr José Pedro Gil
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi

Bihandledare:
Dr Pedro Eduardo Ferreira
Nagasaki University
Institute of Tropical Medicine

Professor Anders Björkman
Karolinska Institutet
Institutionen för Medicin, Solna

Docent Andreas Mårtensson
Karolinska Institutet
Institutionen för Medicin, Solna

Fakultetsopponent:
Professor Harald Noedl
Medical University of Vienna
Institute of Specific Prophylaxis and Tropical Medicine

Betygsnämnd:
Professor Elias Arnér
Karolinska Institutet
Institutionen för Medicinsk Biokemi och Biofysik

Professor Dan Andersson
Uppsala Universitet
Institutionen för Medicinsk Biokemi och Mikrobiologi

Dr Kristina Persson
Karolinska Institutet
Institutionen för Mikrobiologi, Tumör- och Cellbiologi

Stockholm 2013

Abstract

Malaria is a devastating disease which kills ~1 million people yearly. The vast majority of lives lost due to malaria are children and pregnant women in sub-Saharan Africa. Although malaria is a treatable disease it continues to be one of the major causes of death, especially in poor settings. Chemotherapy is the key to control the disease, decrease the burden of malaria and save lives. The malaria parasites ability to develop resistance towards antimalarial drugs is therefore a major concern. Artemether-lumefantrine (Coartem®, Novartis) is currently the most used treatment for uncomplicated *Plasmodium falciparum* malaria. The aim of this thesis was to contribute to the understanding of the role of molecular markers in emerging artemether-lumefantrine resistant *P. falciparum*.

This thesis is based on artemether-lumefantrine clinical trials designed to evaluate the efficacy and effectiveness of artemether-lumefantrine for treatment of uncomplicated *P. falciparum* malaria in children in Tanzania. We measured lumefantrine concentrations and investigated their correlation with cure rates and with tolerance/resistance associated markers within the parasite. Our focus was primarily on polymorphisms within *P. falciparum* multidrug resistance gene 1 (*pfmdr1*) and *P. falciparum* chloroquine transporter gene (*pfcrt*).

One major finding is that lumefantrine blood drug concentrations in combination with pharmacokinetic parameters can be used to assess the relative importance of different single nucleotide polymorphisms for lumefantrine drug susceptibility *in vivo*. Lumefantrine blood drug concentrations after artemether-lumefantrine treatment were correlated with selection of recurrent infections with specific *pfmdr1* N86, 184F and D1246 single nucleotide polymorphisms.

Although artemether-lumefantrine was found to have excellent efficacy and effectiveness according to PCR adjusted cure rates, the number of recurrent infections were high and we observed an up to three week difference in post-treatment prophylactic effect depending on the *pfmdr1* polymorphisms among recurrent infections. Since the introduction of artemether-lumefantrine as first line treatment for uncomplicated malaria in Tanzania in 2006, the prevalence of *pfmdr1* N86, 184F and D1246 have increased significantly up to 2011.

Overall, the results indicate that *pfmdr1* is involved in the mechanism of resistance to lumefantrine. The increased prevalence of parasites carrying the *pfmdr1* NFD haplotype could be an early warning of reduced artemether-lumefantrine efficacy.

ISBN 978-91-7457-998-7