Alternative malaria medicines

Dr Isabelle Borghini-Fuhrer and Medicines for Malaria Venture’s partners are working to develop Pyramax®, a combination treatment of two antimalarial drugs that is soon to be launched in several malaria-endemic countries as a new therapy.
The spread and growing drug resistance of malaria is rapidly undermining currently available treatments. Fortunately, researchers from Medicines for Malaria Venture have recently seen a novel therapy approved for use which promises to make a real impact on malaria treatment in endemic countries.

PREVALENT IN SOUTHEAST ASIA. South America and some African regions, the malaria parasite *Plasmodium vivax* has historically been considered relatively benign compared to the deadly *P. falciparum*. However, this species is becoming increasingly resistant to the antimalarial drugs currently on the market and certainly represents a major threat to global public health. *P. vivax* can cause hypersplenism – an enlargement of the spleen which results in accelerated and premature destruction of blood cells. It can also assume the form of dormant hypnozoites in the liver, which recrudesce weeks, months, or even years later, causing the victim to experience bouts of sickness long after the initial mosquito bite.

Treatments capable of suppressing these resurgent malaria attacks in patients infected by *P. vivax* are available, but, owing to genetic incompatibilities, current medicines are not suitable for every affected individual. Dr Isabelle Borghini-Fuhrer, Clinical Development Director at the Medicines for Malaria Venture (MMV), voices the urgent need to develop new medications for malaria in general. “Resistance is a reality and we must anticipate the possibility of its spread; hence the need for continued research into new drugs with new modes of actions, as well as new combinations of antimalarials,” she emphasises.

ADAPTING A SOLUTION

One drug that has proven useful and holds potential for development is pyronaridine. Since its synthesis at the National Institute of Parasitic Diseases, Shanghai, China, in 1970, this benzonaphthyridine has shown itself to be a highly effective antimalarial. Once inside infected blood cells, the malaria parasite starts to digest haemoglobin in order to nourish itself. Pyronaridine is capable of intercepting this process, eliminating parasitic food vacuoles, toxic residues and, ultimately, the parasites themselves. Pyronaridine also has the benefit of a long half-life, meaning that it remains in the blood and protects patients against reinfection.

Derivatives of artemisinin, such as artesunate, are also effective in antimalarial therapy, but for different reasons. They promote the production of intensely reactive oxygen species within the malaria parasites, destroying these parasitic cells. Close analysis of both these drugs has prompted researchers to consider a possible artemisinin-based combination therapy (ACT) for malaria which incorporates the two. A key agent in this new development has been MMV – a Swiss organisation established in 1999 to ease the global burden of malaria. The foundation has formed a partnership with Shin Poong Pharmaceutical Co Ltd, which holds sway in over 50 countries and produces both pyronaridine and artesunate at a specialist manufacturing plant in Korea. The academic backbone behind this venture has been the University of Iowa, USA, where dedicated researchers, under the leadership of Professor Lawrence Fleckenstein, analyse the blood levels of clinical subjects and are well versed in pharmacokinetics, pharmacodynamics and bespoke modelling methods.

INTERNATIONAL TRIALS

The high efficacy of pyronaridine and its suitability for combination therapy has been demonstrated in a number of studies. Researchers have not only witnessed its superiority to chloroquine for treating different stages of erythrocytic malarial strain *P. falciparum*, but also its capacity to combat other resistant malarial varieties.
INTELLIGENCE

PYRONARIDINE ARTESUNATE VERSUS CHLOROQUINE IN PATIENTS WITH ACUTE PLASMODIUM VIVAX MALARIA: A RANDOMISED, DOUBLE-BLIND, NON-INFERIORITY TRIAL

OBJECTIVES

To develop and promote the use of pyronaridine-artesunate (Pyramax®) as a valuable artemisinin combination therapy to tackle malaria, including the increasingly dangerous Plasmodium vivax strain.

KEY COLLABORATORS

Shin Poong Pharmaceutical Company Ltd, Seoul, Korea • Professor Lawrence Fleckenstein, University of Iowa, USA • Dr YI Poravuth, National Malaria Center, Cambodia • Dr Ronnatriai Rueangweerayut, Mae Sot General Hospital, Thailand • Dr Chirapong Uthaisin, Mae Ramat Hospital, Thailand • Dr Aung Pyae Phyo, Shoklo Malaria Research Unit, Mae Sot, Thailand • Dr Neena Valecha, National Institute of Malaria Research, India • Dr B H Krishnamoorthy Rao, Wenlock District Hospital, Kasturba Medical College, Mangalore, India • Dr Emiliana Tjitra, National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia • Dr Asep Purnama, TC Hillers General Hospital, Maunere, Indonesia.

FUNDING

Shin Poong Pharmaceutical Co Ltd, Seoul, Korea

Medicines for Malaria Venture, Geneva, Switzerland.

CONTACT

Dr Isabelle Borghini-Fuhrer
Director of Clinical Development
Route de Pré-Bois 20
PO Box 1826
ICC-Entrance G, 3rd Floor
1215 Geneva 15
Switzerland
E borghini@mmv.org
www.mmv.org
www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0014501

ISABELLE BORGHINI-FUHRER is Director of Clinical Development at Medicines for Malaria Venture, a not-for-profit research foundation committed to developing and delivering new, affordable and effective medicines for malaria. Prior to moving into the not-for-profit sector, Borghini-Fuhrer spent 10 years at Serono International in clinical development. She obtained a PhD in Biochemistry from the University of Geneva, where she also held two postdoctoral positions.

Having established the validity of pyronaridine as a useful treatment, it was proposed that this drug should be incorporated into a new ACT treatment. Shin Poong Pharmaceutical Co Ltd developed a fixed-dose combination therapy with pyronaridine tetrathosphate in a 3:1 ratio with artesunate for once-daily oral doses over a three day period. Once prepared, it was tested on over 3,500 malarial patients in 18 countries including Senegal, Mali, Ghana, Cambodia, Thailand, Tanzania, Burkina Faso, and Korea. This tablet formulation was shown to be effective against both P. falciparum and the blood stages of P. vivax.

ASSESSING SAFETY

When it came to testing the drug in patients, MMV researchers observed relatively few negative side-effects in clinical trials. The most regularly observed events were similar to malarial symptoms, such as headache, myalgia and an increased rate of mild, transient blood elevations in the hepatic enzymes alanine amino transferase (ALT) and aspartate aminotransferase (AST). Few serious clinical, vital sign or haematological alterations were observed in patients.

The optimistic conclusion extractable from this series of clinical trials, together with the already successful application of pyronaridine as a monotherapy, is that pyronaridine-artesunate – known commercially as Pyramax® – is a highly valuable ACT capable of countering a range of malaria parasites.

SAVING YOUNG LIVES

For researchers at MMV, children are a priority population, as infants younger than five years old are the demographic most vulnerable to the ravages of malaria. According to the World Health Organization (WHO), 86 per cent of the estimated 627,000 malaria fatalities in 2012 were children, a statistic which equates roughly to a child dying every minute.

WHO recommends treatment of P. falciparum with ACTs, but, as Borghini-Fuhrer explains, most current forms of these drugs are not easily administrable to children: “Currently, pyronaridine-artesunate only comes in a tablet form to treat patients from 20 kg of body weight and up”. To address this loophole in antimalarial treatment, MMV’s scientific partners are working to develop a bespoke alternative: a taste-masked granule formulation that is packaged in sachets and can disperse in liquid to prepare an oral suspension. As well as its suitability for infants with a low body weight, this formulation also makes it easier to deliver the medicine to sick children.

These dissolve granules have been tested in a clinical trial of 535 malaria-infected children from African and Asian countries, with highly encouraging results. In comparison with the widely used ACT artemether-lumefantrine (Coartem®) in a crushed tablet form, pyronaridine-artesunate granules showed non-inferiority in terms of efficacy for treating acute malaria attacks. Acceptable safety and tolerability profiles for this granule formulation were recorded, and Borghini-Fuhrer is pleased to announce that it is currently being investigated further in a large-scale West African trial, which aims to compare its safety and effectiveness to that of three other ACTs when used repeatedly over a two-year period.

LOOKING TO THE FUTURE

Borghini-Fuhrer and the Pyramax® team are delighted with the progress they have made towards this new medical innovation. In February 2012, pyronaridine-artesunate became the first antimalarial to receive positive scientific opinion under Article 58 from the European Medicines Agency for the treatment of both P. falciparum and P. vivax malaria. It also received Korean Food and Drug Administration approval in August 2011. The team has taken steps towards wider distribution of this drug by submitting marketing authorisation applications in a number of malaria-endemic countries. She expects the first approvals and, therefore, the first launches, in early 2014. “After years of shepherding this drug through a rigorous development and registration process it will finally be saving lives, and that is really exciting,” she enthuses.