Chlorproguanil Hydrochloride-Dapsone-Artesunate

Citation

. *Chlorproguanil Hydrochloride-Dapsone-Artesunate*. The Internet Journal of Infectious Diseases. 2004 Volume 4 Number 2.

Abstract

Figure 1

THE NEED

Worldwide, the World Health Organisation (WHO) estimates that there are 300 million malaria cases annually, directly causing over one million deaths.[1] Parasite resistance to anti-malarial treatments is increasing in malaria endemic countries, particularly in Africa. The most frequently used treatments for malaria, such as chloroquine and sulphadoxine/pyrimethamine (S/P), are becoming less and less effective. To tackle drug-resistant malaria, new treatments are urgently needed for the millions affected.

THE TREATMENT

CDA is a new artemisinin-based combination therapy (ACT) of chlorproguanil hydrochloride-dapsone-artesunate under development for the treatment of P. falciparum malaria.

The World Health Organisation's (WHO) Roll Back Malaria group has made the recommendation that National Malaria Control Programmes (NMCP) use ACT in treatment of uncomplicated malaria in the public sector.

Artemisinin and its derivatives, artemether and artesunate, are plant-derived compounds extracted from Artemisia annua (sweet wormwood). This plant has been used for centuries in traditional Chinese medicine to cure fevers. Artemisinin, first isolated by Chinese chemists in 1971, rapidly clears malarial parasites in the blood. When used in combination therapy, it allows short-course treatment which greatly reduces the potential for resistance induction.

RESULTS OF PHASE II TRIAL

TRIAL DESIGN

The phase II trial for CDA was designed to determine the optimum dose of artesunate to be used in combination with LAPDAP. This open-label study of a fixed-dose of LAPDAP alone plus 1, 2 or 4 mg/kg of artesunate was conducted in Malawi and the Gambia. The trial recruited 116 adults and 107 children with uncomplicated malaria. Patients were randomised into one of four treatment groups and received treatment for three days.

PRIMARY EFFICACY OUTCOME

The primary efficacy outcome for the trial was time to reduce baseline parasite levels in the blood by 90 percent. Treatment with CDA, at three doses of artesunate (1, 2 and 4mg/kg) in adults and at two doses (2 and 4mg/kg) in children, led to faster time to reduce parasite levels in the blood by 90 percent when compared to treatment with LAPDAP alone.[1]

SECONDARY EFFICACY OUTCOMES

Treatment with CDA versus LAPDAP alone also demonstrated reductions in the following:

Parasite viability – In adults, there was a statistically significant decrease in parasite viability observed in the 2mg/kg and 4mg/kg artesunate treatment groups versus LAPDAP alone. In children, all artesunate doses significantly reduced the number of viable parasites at 12 hours.

Potential parasite reproductive ability – A dose response effect was noted in the artesunate treatment groups (adults and children) with 2mg/kg and 4mg/kg doses stopping parasite reproductive activity all together.

SAFETY

All treatment doses were generally well tolerated, and the nature and incidence of adverse events were similar across

treatment groups.

PHASE III CDA TRIALS

TRIAL DESIGN

The phase III programme for CDA consists of two studies which will be conducted across sub-Saharan Africa. The studies will be multi-centre, randomised, double-blind trials utilizing the 4mg/kg artesunate dose. The safety and tolerability of CDA will also be further investigated in the phase III programme, which is expected to begin soon.

CDA VS. LAPDAP STUDY

This study is expected to enrol 900 subjects aged three months or older with acute uncomplicated P. falciparum malaria. Subjects will be randomised to receive CDA or LAPDAP in a ratio of 2:1 and will receive treatment for three successive days. The study is designed to demonstrate the efficacy of CDA compared to LAPDAP, measured by clearance of the initial malaria infection by Day 7 and remaining free of infection to Day 28. The secondary objective is to demonstrate an advantage of CDA over LAPDAP alone in terms of the proportion of subjects with parasites at 24 hours following the first dose.

CDA VS. COARTEM® (ARTEMETHER–LUMEFANTRINE) STUDY

This study will compare the efficacy of CDA to Coartem, measured by clearance of the initial malaria infection in 1,395 subjects at least three months of age and up to 14 years of age with acute uncomplicated P. falciparum malaria. Subjects will be randomised to receive CDA or Coartem in a ratio of 2:1 and will receive treatment for three successive days. Coartem is the only fixed-dose ACT currently available for malaria treatment and is therefore considered the standard for comparison. The study is designed to demonstrate the efficacy of CDA compared to Coartem, measured by clearance of the initial malaria infection by Day 7 and remaining free of infection to Day 28. The secondary objectives will compare parasite clearance times and fever reduction times between CDA and Coartem.

THE PARTNERSHIP

CDA is being developed by a public-private partnership (PPP) between GlaxoSmithKline (GSK), WHO/TDR (Tropical Disease Research Programme of the World Health Organization) and the Medicines for Malaria Venture (MMV). Academic partners in its development are the University of Liverpool, Liverpool School of Tropical Medicine and the London School of Hygiene and Tropical Medicine. If the development of CDA is successful, it will be supplied at sustainable, preferential prices to the public sector in malaria-endemic countries in Africa to maximise availability to those in need. CDA is expected to be available in 2008 as a convenient once-daily dose.

The partnership has already successfully developed LAPDAP, a combination therapy containing two well established antimalarial agents, chlorproguanil and dapsone, which act synergistically.

GSK is committed to PPPs which offer an innovative approach to creating safe, effective and affordable medicines for the developing world. GSK plays a leading role in the research and development of these medicines. CDA is part of GSK's sustained and long-term commitment to fighting malaria.

References

1. World Health Organisation Roll Back Malaria. What is Malaria? Infosheet 1. http://www.who.int. (Accessed Apr 2005)

Author Information