New once-a-day antimalarial combination therapy as effective as the twice-a-day gold standard regimen

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The new antimalarial combination therapy pyronaridine-artesunate is as effective as the gold standard treatment of artemether-lumefantrine. Furthermore, the new therapy only needs to be taken once daily, compared to twice daily for the gold standard regimen. The findings are reported in an Article in this week's *Lancet*, written by Dr Isabelle Borghini-Fuhrer, Medicines for Malaria Venture, Geneva, Switzerland, and colleagues.

Artemether-lumefantrine is regarded as the gold standard for treatment of malaria, with good safety and generally more than 90% efficacy. However, it needs to be taken twice a day, requires a fatty diet for optimum absorption, and the fairly short time taken to metabolise the treatment exposes patients to the risk of early reinfection. Scientists are trying to develop new artemisinin-based combination therapies that are equally convenient, effective, and safe, such as pyronaridine-artesunate, to allow health policy makers and care givers in malaria endemic countries more choice of effective medicines for their patients.

This phase 3 randomised trial was undertaken in seven sites in Africa and three sites in southeast Asia. Patients aged 3? years with uncomplicated Plasmodium falciparum malaria (the most common form) were randomly assigned in a 2:1 ratio to receive pyronaridine-artesunate once a day or artemether-lumefantrine twice a day, orally for three days, plus respective placebo. Intervention tablets contained 180 mg pyronaridine and 60 mg artesunate; control tablets contained 20 mg artemether and 120 mg lumefantrine. Both treatments were given according to bodyweight. The primary efficacy outcome treatment response rate at day 28 judged by analysis of patients' blood for presence of malaria parasites.

The final efficacy analysis consisted of 784 patients in the pyronaridine-artesunate group and 386 patients in the artemether-lumefantrine group.Treatment response occurred in 99•5% in the pyronaridine-artesunate group and 99•2% in the artemether-lumefantrine group. Analysis* showed a lower rate of reinfection and a longer time to reinfection (Day 28 vs Day 21) in the pyronaridine-artesunate group than in the artemether-lumefantrine group. The percentage of adverse events was similar in the two treatment arms and most of the adverse events were related to malaria itself. There were 509 (60%) adverse events in 849 patients given pyronaridine-artesunate and 241 (57%) in 423 patients given artemether-lumefantrine. Mild and transient increases in liver enzymes were a side effect experienced in the pyronaridine-artesunate group but not in the artemether-lumefantrine group.

The authors conclude: "Fixed-dose pyronaridine-artesunate, given once a day for 3 days, showed high clinical and parasitological response rates and rapid parasite clearance, and was well tolerated in the treatment of uncomplicated P falciparum malaria. The efficacy of pyronaridine-artesunate still has to be assessed in a real-life setting across the wider population of patients who need antimalarial treatment, including those who are malnourished or have anaemia. However, in view of the results of this study and with a purchase price for pyronaridine-artesunate in the range of less than US$1 for adults and less than $0•50 for children, this drug combination should be considered for inclusion in malaria treatment programmes."

In an accompanying Comment, Dr Francois Henri Nosten. Mahidol Oxford University Tropical Medicine Research Programme, Shoklo Malaria Research Unit, Thailand, says that a serious limitation of the study is that consisted mainly of older children and adults in African countries. He

says: "These patients would have been expected to have acquired significant antimalarial immunity, which would improve treatment outcomes, particularly with partly effective drugs. What we really need to know is whether this new drug is effective in patients with no significant immunity, such as young children." He also voices his concerns regarding the patients who received pyronaridine-artesunate having raised liver enzymes, and says future studies will need to investigate the risk of toxicity to the liver.

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