Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated Plasmodium falciparum malaria: a randomised non-inferiority trial.

Abstract

BACKGROUND:

There is a need for new artemisinin-based combination therapies that are convenient, effective, and safe. We compared the efficacy and safety of pyronaridine-artesunate with that of artemether-lumefantrine for treatment of uncomplicated P falciparum malaria.

METHODS:

This phase 3, parallel-group, double-blind, randomised, non-inferiority trial was undertaken in seven sites in Africa and three sites in southeast Asia. In a double-dummy design, patients aged 3-60 years with uncomplicated P falciparum malaria were randomly assigned in a 2:1 ratio to receive pyronaridine-artesunate once a day or artemether-lumefantrine twice a day, orally for 3 days, plus respective placebo. Randomisation was done by computer-generated randomisation sequence in blocks of nine by study centre. 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 was PCR-corrected adequate clinical and parasitological response (ACPR) rate at day 28 in the per-protocol population. Non-inferiority was shown if the lower limit of the two-sided 95% CI for the difference between groups was greater than -5%. This study is registered with ClinicalTrials.gov, number NCT00422084.

FINDINGS:

1272 patients were randomly assigned to treatment (pyronaridine-artesunate, n=849; artemether-lumefantrine, n=423). The per-protocol population consisted of 784 patients in the pyronaridine-artesunate group and 386 patients in the artemether-lumefantrine group. PCR-corrected ACPR rate at day 28 was 99.5% (780 patients; 95% CI 98.7-99.9) in the pyronaridine-artesunate group and 99.2% (383 patients; 95% CI 97.7-99.8) in the artemether-lumefantrine group (treatment difference 0.3%, 95% CI -0.7 to 1.8; p=0.578). There were 509 (60.0%) adverse events in 849 patients assigned to pyronaridine-artesunate and 241 (57.0%) in 423 patients assigned to artemether-lumefantrine. The most frequent drug-related adverse event was eosinophilia (pyronaridine-artesunate, 53 events [6.2%]; artemether-lumefantrine 24 events [5.7%]). 21 (2.5%) patients in the pyronaridine-artesunate group and seven (1.7%) in the artemether-lumefantrine group discontinued study drugs or were withdrawn from the study. Mild and transient increases in alanine aminotransferase and aspartate aminotransferase concentrations were seen in the pyronaridine-artesunate group but not in the artemether-lumefantrine group.

INTERPRETATION:

Efficacy of pyronaridine-artesunate was non-inferior to that of artemether-lumefantrine for treatment of uncomplicated falciparum malaria. Pyronaridine-artesunate should be considered for inclusion in malaria treatment programmes.

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