JOURNAL CLUB

Artemisinin-Based Combination Therapy for Malaria

In the last year, results have been published from clinical trials evaluating the efficacy of artemisinin-based combination therapy for malaria. Artemisinin-based drugs were paired with other compounds, including lumefantrine, sulfamethoxypyrazine-pyrimethamine, sulphadoxine-pyrimethamine, or amodiaquine. Results from 6 of these clinical trials are summarized below.

PEDIATRIC FORMULATION OF ARTEMETHER-LUMEFANTRINE

Chanda P, Hawela M, Kango M, Sipilanyambe N. Assessment of the therapeutic efficacy of a paediatric formulation of artemether-lumefantrine (Coartesiane) for the treatment of uncomplicated Plasmodium falciparum in children in Zambia. Malar J. 2006,5:75.

The National Malaria Control Centre recently completed a 1-arm, prospective trial assessing the efficacy of the pediatric formulation of artemether-lumefantrine (Coartesiane). They evaluated clinical and parasitological responses to directly observed treatment for uncomplicated malaria.

Patients were enrolled at 2 sentinel sites, using the WHO standardized protocol for the assessment of therapeutic efficacy of antimalarial drugs in children under 5 years of age, weighing under 10kg. During the 28-day follow-up period blood was PCR genotyped for MSP1 and MSP2 to differentiate recrudescence from re-infections for parasites appearing after 14 days.

Of 111 children enrolled in the study, 91 were successfully followed up. Artemether-lumefantrine significantly reduced gametocytes. The Adequate Clinical and Parasitological Response (ACPR) was 100% (95% CI: 96.0 to 100). Coartesiane effectively treated uncomplicated malaria in Zambian children weighing under 10kg, an age group normally excluded from taking the tablet formulation of artemether-lumefantrine (Coartem).

ARTESUNATE + SULFAMETHOXYPYRAZINE-PYRIMETHAMINE

Adam I, Magzoub M, Osman ME, Khalil IF, Alifrangis M, Elmardi KA. A fixed-dose 24-hour regimen of artesunate plus sulfamethoxypyrazine-pyrimethamine for the treatment of uncomplicated Plasmodium falciparum malaria in eastern Sudan. Ann Clin Microbiol Antimicrob. 2006 .26;5:18.

The University of Khartoum reported results of a clinical trial assessing the efficacy of artesunate plus sulfamethoxypyrazine-pyrimethamine to treat uncomplicated Plasmodium falciparum malaria in eastern Sudan.

The efficacy of fixed co-formulated (f) artesunate-sulfamethoxypyrazine-pyrimethamine (AS+SMP f) given at 12-hour intervals for a 24-hour therapy was compared with the efficacy of a loose combination of the same drug (AS+SMP l) at 24-hour intervals for 3 days. 73 patients (39 and 34 in the fixed and the loose regimen of AS+SMP respectively) completed the 28-days of follow-up.

On day 3, all patients in both groups were aparasitemic but 1 patient in the fixed group of AS+SMP f was still febrile. Polymerase chain reaction (PCR) genotyping adjusted cure rates on day 28 were 92.3% and 97.1% ($P > 0.05$) for the fixed and loose combination of AS+SMP respectively. 3 (4.1%) patients (1 in the fixed and 2 patients in the loose group of AS+SMP) experienced drug-related adverse events. Gametocytemia was not detected during follow-up in any of the patients. Both regimens were effective and safe for treating uncomplicated P falciparum malaria. The fixed-dose 1-day treatment regimen was the preferred choice.

SULFADOXINE-PYRIMETHAMINE MONOTHERAPY VS SULFADOXINE-PYRIMETHAMINE + AMODIAQUINE VS SULFADOXINE-PYRIMETHAMINE + ARTESUNATE VS ARTEMETHER-LUMEFANTRINE

Bousema JT, Schneider P, Gouagna LC, Drakeley CJ, Tostmann A, Houben R, Githure JI, Ord R, Sutherland CJ, Omar SA, Sauerwein RW. Moderate effect of artemisinin-based combination therapy on transmission of Plasmodium falciparum. J Infect Dis. 2006. 15;193:1151-9.

Artemisinin-based combination therapy reduces microscopically confirmed gametocytemia and mosquito infection. However, molecular techniques have recently revealed high prevalences of submicroscopic gametocytemia. The trial objective was to determine the effect of sulfadoxine-pyrimethamine (SP) monotherapy and treatment with SP + amodiaquine (AQ), SP + artesunate (AS), and artemether-lumefantrine (AL; Coartem) on submicroscopic gametocytemia and infectiousness.

Kenyan children (n = 528) 6 months to 10 years of age were randomized to 4 treatment arms. Gametocytemia was determined by both microscopy and Pfs25 RNA-based quantitative nucleic acid sequence-based amplification (Pfs25 QT-NASBA). Transmission was determined by membrane-feeding assays.

Gametocyte prevalence was 89.4% (219/245) at enrollment and decreased after treatment with SP + AS, SP + AQ, and AL. Membrane-feeding assays for a group of randomly selected children revealed that the proportion of infectious children was as much as 4-fold higher than expected when based on microscopy. Artemisinin-based combination therapy did not significantly reduce the proportion of infectious children but did reduce the proportion of

infected mosquitoes. Submicroscopic gametocytemia is common after treatment and contributes considerably to mosquito infection.

Artemether-lumefantrine vs Artesunate + Amodiaquine

Guthmann JP, Cohuet S, Rigutto C, Fortes F, Saraiva N, Kiguli J, Kyomuhendo J, Francis M, Noel F, Mulemba M, Balkan S. High efficacy of two artemisinin-based combinations (artesunate + amodiaquine and artemether + lumefantrine) in Caala, Central Angola. Am J Trop Med Hyg. 2006;75:143-5.

Researchers from Doctors without Borders recently completed a clinical trial comparing 2 artemisinin-based combination pharmacological treatments for the treatment of P falciparum malaria. The trial was conducted in 2004 in Caala, central Angola, and enrolled 137 children between the ages of 6 and 59 months with uncomplicated P falciparum malaria. Children were randomized to receive either artemether-lumefantrine (Coartem) or artesunate + amodiaquine (ASAQ).

At 28-day follow-up, 2 of 61 (3.2%) patients given artemether-lumefantrine and 4 of 64 (6.2%) patients in the ASAQ group had recurrent parasitemias (P = 0.72). These recurrent parasitemias were classified as re-infections after PCR genotyping (cure rate = 100% [95% CI: 94 to 100] in both groups. Only 1 patient (given artesunate + amodiaquine) had gametocytes on day 28; 3 patients administered artesunate + amodiaquine compared with 5 patients given artemether-lumefantrine at baseline.

Anemia was significantly improved after 28-day follow-up in both groups (artemether-lumefantrine: from 54.1% to 13.4%; artesunate + amodiaquine: from 53.1% to 15.9%), compared with baseline.

Artesunate-sulfamethoxypyrazine-pyrimethanmine vs Artemether-lumefantrine

Sagara I, Dicko A, Djimde A, Guindo O, Kone M, Tolo Y, Thera MA, Sogoba M, Fofana M, Ouattara A, Sissoko M, Jansen HF, Doumbo OK. A randomized trial of artesunate-sulfamethoxypyrazine-pyrimethanmine versus artemether-lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Mali. Am J Trop Med Hyg. 2006 75(4);630-636.

Researchers from the University of Bamako reported results from a clinical trial comparing 2 artemisinin-based combination pharmacological treatments for the treatment of Plasmodium falciparum malaria.

The trial was run during 2 transmissions seasons (2003 and 2004) in Sotuba, Mali and enrolled 606 patients at least 6 months of age with uncomplicated P. falciparum malaria. Patients were randomly treated with artesunate-sulfamethoxypyrazine-pyrimethanmine or artemether-lumefantrine.

At 28-day follow-up, more patients had been cured by artesunate-sulfamethoxypyrazine-pyrimethanmine therapy than by artemether-lumefantrine therapy (98.7% vs. 89.6%; P < 0.001). After correcting for cases of re-infection, the cure rates were 100% and 99.0%, respectively (P = 0.08).

Artesunate + amodiaquine vs Artesunate + sulphadoxine-pyrimethamine

Swarthout TD, van den Broek IV, Kayembe G, Montgomery J, Pota H, Roper C. Artesunate + amodiaquine and artesunate + sulphadoxine-pyrimethamine for treatment of uncomplicated malaria in Democratic Republic of Congo: a clinical trial with determination of sulphadoxine and pyrimethamine-resistant haplotypes. Trop Med Int Health. 2006 11:1503-11.

Researchers from Doctors without Borders reported results from a clinical trial comparing 2 artemisinin-based combination treatments for P falciparum malaria. This 2004 trial, in the Democratic Republic of Congo, enrolled 180 children between 6 and 59 months. All had been diagnosed with uncomplicated P falciparum malaria.

Children randomly received either artesunate + amodiaquine or artesunate + sulphadoxine-pyrimethamine for 3 days.

At 28-day follow-up, the parasite recurrence rates were 16.9% (14/83; 95% CI: 9.5 to 26.7) in the artesunate + amodiaquine group compared with 34.6% (28/81; 95% CI: 24.3 to 46.0) in the artesunate + sulphadoxine-pyrimethamine group (P = 0.009). After PCR correction, recrudescence rates were 6.7% (5/74; 95% CI: 2.2 to 15.1) for artesunate + amodiaquine compared with 19.7% (13/66; 95% CI: 10.9 to 31.3) for artesunate + sulphadoxine-pyrimethamine (P = 0.02).

The 2 groups had equivalent time to parasite clearance, fever clearance, and gametocyte clearance. Parasite genotyping had high frequencies of dihydrofolate reductase and dihydropteroate synthase molecular sulphadoxine-pyrimethamine-resistance markers, with 57% of the samples having over 3 mutations linked to sulphadoxine-pyrimethamine resistance, and 27% with triple-dihydrofolate reductase/double-dihydropteroate synthase haplotype. Thus, sulphadoxine-pyrimethamine treatment failure rates are likely to be high.

The final conclusion: artesunate + amodiaquine therapy was significantly more effective than artesunate + sulphadoxine-pyrimethamine therapy.

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