27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: OS123 Issues concerning treatment of malaria, echinococcosis and cryptosporidiosis

Category: 7c. Antiparasitic drugs & treatment

24 April 2017, 12:18 - 12:28
OS0596

Single dose treatment of malaria: A randomized-double blind clinical phase IIb study of artefenomel (OZ439) and piperaquine

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Background:

The development of an effective single dose treatment of malaria would constitute a breakthrough in the control and ultimate elimination of malaria. The novel antimalarial artefenomel (OZ439) currently holds the greatest potential for such a single dose treatment regimen when combined with a partner drug. This clinical phase IIb dose-ranging study was designed to assess the dose response relationship of artefenomel-piperaquine for day 28 PCR adjusted adequate clinical and parasitological response and to identify significant covariates influencing efficacy.

Material/methods:

Patients aged aged ≥6 months to <70 years, with uncomplicated *P. falciparum* malaria were randomized in a double-blind, single-dose study of artefenomel 800mg plus piperaquine phosphate at three different dose levels (640, 960, 1440mg). Patients were recruited in Benin, Burkina Faso, DR of Congo, Gabon, Mozambique & Uganda in Africa and 4 sites in Vietnam. Patients were followed up for 42-63 days for clinical signs of malaria, temperature, parasitemia (microscopy), ECGs, AEs & PK

Results:
437 patients were randomized with a median age of 3.8 years. Median baseline asexual parasitemia was 12,913.0/µL [range: 187/µL to 220,240/µL]. Efficacy was lower in Asian patients compared to African participants. None of the treatment arms reached the target efficacy of 95% ACPR 28. Median PCt1/2[9] was greater in Vietnam vs Africa (6.09 hours [IQR: 3.43–8.30] vs 3.47 hours [IQR: 2.53–4.12]). In Vietnam, high frequency of Kelch 13 mutation[10] observed (70.1%); most 'suspected' or 'confirmed' related to artemisinin resistance

Conclusions:

Artefenomel-piperaquine failed to demonstrate adequate ACPR28 in the investigated dose levels as single dose therapy. Future development of artefenomel for single dose therapy will be based on the addition of alternative combination partner drugs such as the second generation 4-aminoquinoline ferroquine.