Evaluation of 4 artemisinin-based combinations for treating uncomplicated malaria in African children

Preliminary results

Umberto D’Alessandro and the 4ABC study group
Objectives

• Main
  – To compare the safety and efficacy of 4 ACT, i.e. AQ+AS, AL, DHAPQ, CDA, for single and repeat treatments of uncomplicated malaria

• Specific
  – To evaluate the efficacy of the 4 ACTs for the treatment of children with uncomplicated *P. falciparum* malaria (first active follow-up);
  – To determine after the first active follow-up the incidence rate of a second clinical episode of uncomplicated *P. falciparum* malaria
Objectives

• Specific
  – To evaluate the efficacy of treating the II clinical episode of uncomplicated *P. falciparum* malaria with the same ACT used for the first one (second active follow-up);
  – To evaluate *safety* of the 4 ACTs for the treatment of children with uncomplicated *P. falciparum* malaria;
Study design

- 3-arm multicentre, randomised, open label;
- First follow up of 28 days;
- Beyond 28 days: Passive follow-up for detection of a second clinical episode within 6 months; -> re-treatment;
- Second follow-up of 28 days;
- 510 patients per site/ 170 per arm
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<thead>
<tr>
<th>Country</th>
<th>N. sites</th>
<th>Study treatments</th>
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<tbody>
<tr>
<td>Burkina Faso</td>
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End points

• **Primary**
  – TF PCR adjusted and unadjusted up to day 28

• **Secondary**
  – TF up to day 63 (unadjusted and for the whole period of passive surveillance)
  – TF second clinical episode (D28 and D63);
  – Fever & parasite clearance time.
  – Gametocytaemia
  – Hb changes
Inclusion criteria

- Age 6 months and 59 months inclusive
- Body weight \( \geq 5 \) Kg
- Monoinfection of *Plasmodium falciparum* (parasitaemia \( \geq 1,000/\mu L \) to \( 200,000/\mu L \)).
- Fever/history of fever
- Haemoglobin value \( \geq 7.0 \) g/dl
- Signed informed consent
Exclusion criteria

- Participation in any investigational drug study during the previous 30 days.
- Known hypersensitivity to the study drugs.
- Severe malaria or danger signs
- Presence of intercurrent illness
- Severe malnutrition
- Ongoing prophylaxis with drugs having antimalarial activity
Passive follow up

• Parents/guardians asked to attend for any illness;
• Monthly visits at home to keep contact without collecting blood samples unless sick;
• When attending HC, blood slides, BT and Hb/PCV collected systematically;
• If inclusion criteria included in the second follow up;
• If malaria not fulfilling criteria, treated with I line treatment;
Amendements

- First (February 2007)
  - Some adjustments to the protocol

- Second (February 2008)
  - Stop of the CDA arm
  - Re-distribution of patients between sites: ↑ patients in Nanoro (BF) and Tororo (Uganda)

- Third (October 2008)
  - Discontinuation of DHA-PQ arm as product not available
Number of patients by site and treatment

Nanoro (BF) Lambarene (GB) Manhiça (MZ) Calabar (NG) Mashesha (RWA) Rukara (RWA) Jinja (UG) Mbarara (UG) Tororo (UG) Ndola (ZM)

Sites

AL DHAPQ ASAQ CDA

12-14/10/2009 EDCTP Forum, Arusha
Number of patients by treatment and site

- AL
- DHAPQ
- ASAQ
- CDA

Locations:
- Ndola (ZM)
- Tororo (UG)
- Mbarara (UG)
- Jinja (UG)
- Rukara (RWA)
- Mashesha (RWA)
- Calabar (NG)
- Manhiça (MZ)
- Lambarene (GB)
- Nanoro (BF)
Patients’ age group distribution

- 6-11m
- 12-23m: 1200
- 24-35m: 1000
- 36-47m: 800
- 48-59m: 600
ACPR D28 (uncorrected) by treatment

- AL
- DHAPQ
- ASAQ
- CDA
Treatment failure D28 (uncorrected) by treatment

%
Treatment failure D28 (uncorrected) by site

12-14/10/2009

EDCTP Forum, Arusha
Failure by treatment

Nanoro (BF)
Lambarene (GB)
Manhiça (MZ)
Calabar (NG)
Mashesha (RWA)
Rukara (RWA)
Jinja (UG)
Mbarara (UG)
Tororo (UG)
Ndola (ZM)
Number of patients in II active FU by site

- Nanoro (BF)
- Lambarene (GB)
- Manhiça (MZ)
- Calabar (NG)
- Mashesha (RWA)
- Rukara (RWA)
- Jinja (UG)
- Mbarara (UG)
- Tororo (UG)
- Ndola (ZM)

Number of patients:
- AL
- DHAPQ
- ASAQ
- CDA
Number of patients in II active FU by treat

- Nanoro (BF)
- Lambarene (GB)
- Manhiça (MZ)
- Calabar (NG)
- Mashesha (RWA)
- Rukara (RWA)
- Jinja (UG)
- Mbarara (UG)
- Tororo (UG)
- Ndola (ZM)
SAE and deaths (13) by treatment
Ongoing activities

• Genotyping: about 2000 samples to process

• Lock database by the end of December 2009

• Clinical study report by June 2010
Institutions involved

- Institute of Tropical Medicine, Antwerp, Belgium
- Liverpool School of Tropical Medicine and Centre for Medical Statistics and Health Evaluation, University of Liverpool, UK
- East African Network for Monitoring Antimalarial Treatment (EANMAT).
- Centre Muraz, Bobo Dioulasso, Burkina Faso.
- Department of Paediatrics, University of Calabar, Cross River State, Nigeria.
- Tropical Diseases Research Centre, Ndola, Zambia
- Institute of Tropical Medicine, Department of Parasitology, University of Tuebingen, Germany and Medical Research Unit,
- Albert Schweitzer Hospital, Lambaréné, Gabon.
- Uganda Malaria Surveillance Project (UMSP), Kampala, Uganda.
- Epicentre, Paris, France and Mbarara University of Science and Technology, Faculty of Medicine, Mbarara, Uganda
- Programme National de Lutte contre le Paludisme, Kigali, Rwanda.
- Fundacio Clinic per a la Recerca Biomèdica/Centre for International Health, University of Barcelona, Spain and Manhiça Health Research Center, Mozambique.