Artemether-Lumefantrine Trial with Increased Treatment Duration

DR. SARAH NANZIGU;

MBCHB, PHD-PHARMACOLOGY

LECTURER, DEPT. PHARMACOLOGY, MAKERERE UNIVERSITY COLLEGE OF HEALTH SCIENCES

NURTURE FELLOW; APR 2016

NURTURE THEMATIC AREA: INFECTIOUS DISEASES INCLUDING MALARIA

MENTORS: 1. PROF MOSES KAMYA

2. PROF. MOSES JOLOBA

NURTURE | MESAU CONSORTIUM UGANDA

WE BUILD FOR THE FUTURE

Background

Treatment of Uncomplicated malaria with AL: Threats and possible transitions

AL still has good efficacy in E. African region (~90%)

But higher rates of clinical & parasitological failure among

- HIV treated and non-treated patients
- Children showing higher recrudescence rates
- Patients with high initial parasite densities
- Spreading K13 – resistance mutations
- Treatment compliance issues

Among underlying pathological interpretations are

- HIV/Malaria: Immunological interaction between HIV & Malaria
- HIV/Malaria/other chemotherapies: Drug-drug interactions; ACTs with ARVs, AntiTB, AEDs
- High proportion of residual parasite left for Lum
- Delayed parasite clearance with K13 mutations

Treatment of Uncomplicated malaria with AL: Threats and possible transitions

Alternatives to enzyme inducing ARVs (NNRTIs-Efv)

- Ongoing trials with Pis (r-LPV):
  - To address: drug interactions & partly immunological contribution

Alternatives to AL

- Data comparing AL and DHA/PQ
  - This may address drug interactions and recrudescence issues

Approaches to improve compliance

- Proposed changes to DHA/PQ;
  - Approaches to reduce pill burden

Possible approach thru dosage optimization? Current research

Would address issues with:

- Recrudescence, Hypeparasitemia
- HIV/ART interactions,
- ?Drug resistance
- **But could worsen adherence**

AL-Pharmacokinetics

AL-Antimalaria treatment outcomes are driven by plasma exposure of the drugs

ARTETHER- Very high parasite killing rates, quickly reduces parasite biomass

Antimalarial outcomes driven by **AUC/ C_{max}**

But short T1/2 ; current course clears up to 2 asexual cycles

LUMEFANTRINE- Long T1/2 slowly clears residual parasites after ART

Antimalarial outcomes driven by **Time to MIC and D7 concentrations**

Post treatment prophylaxis- Reduces risk of recrudesce/ new infection

All these PK parameters can be altered thru dosage modification

Relevant history in Malaria Treatment

Drug	Discovery/ Dvt	Dosing
Quinine	**1820;** Isolated and standardized by French chemis	May differ with P. F sensitivity, Safety Quinine 10mg/kg 7-10 days Q + Doxy Q +Clindamycin
Chloroquine	**1932;** CQ syn Anderson 1946; Scienti	ince 1946; **CQ stable** 25mg/kg over 3 /7 1990's Resistance to CQ – spreading from Thai-Cambodia ➢ Later CQ + SP
Artemesinins	**1960's to 1970** Pharmacologist Tu **1985;** Zhou successfully combined A (coartem)	**Artemether;** •Mono max 7days •ACTS for 3 days •Studies up to 5 days •ACT-Resistance in SE Asia- spreading - ? Way forward?

Summation_ It is not impossible to alter AL dosing

Hypothesis and Objectives

Preliminary study with no atrisk persons

Hypothesis: AL longer treatment durations, improve efficacy-predicting PK parameters and heighten treatment outcomes among risky patients

Main Objective

To study the **pharmacokinetics**, **safety** and **efficacy** of AL among adult Ugandans with uncomplicated P. F malaria, who are treated with a max total daily dose of (A160mg: L960mg) for max period of 7days.

Specific Objectives

1) To compare **AL plasma exposures** among patients who are treated for different durations (3, 5, 7 days);

2) To compare **AL efficacy** (parasite clearance and clinical cure) between patients who are treated for different durations (3,5, 7days);

3) To compare the **safety of AL** among patients with uncomplicated P. F. malaria, who are treated for different durations (3, 5, 7 days).

Methods

Study Setting: Recruiting at Iganga hospital in Central-Eastern Uganda, the 2nd highest malaria burdened region in the country

Eligibility criteria:

Adults 18 years and above with uncomplicated malaria

Parasite reading 2000-200,000/µl

No malaria treatment during past two weeks

Hb = 9 and above

Not using enzyme modifying therapies

HCG negative (where applicable)

Methods

Study Design

Randomised open label trial with three treatment arms

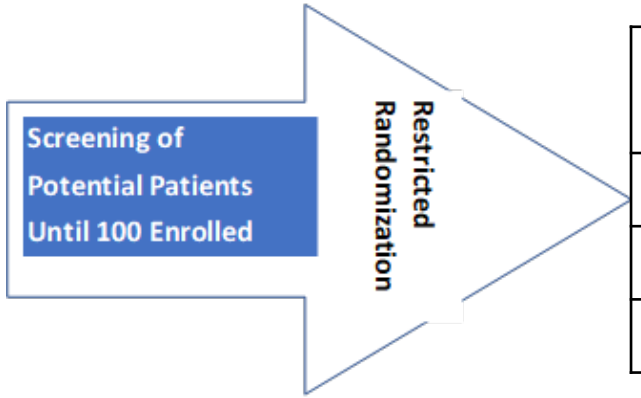
ARM1 (n=20)	AL	AL	AL	Standard Coartem Treatment				
ARM2 (n=40)	AL	AL	AL	AL	AL			
ARM3 (n=40)	AL	AL	AL	AL	AL	AL	AL	
Day of Treatment	**1**	**2**	**3**	**4**	**5**	**6**	**7**	

Randomization into :

- ✓ Treatment arms
- ✓ PPK bleeding schedules

Randomization Procedures

- **Block randomisation done ahead of time and site informed at each enrolment**
  - **To fulfil treatment ratio 1:2:2, then to PPK bleeding schedules (A at 0, 2, 4 AD; B at 6,8&12h AD)**



Treatment Arms	PK Group A Blood Drawn 0, 2 & 4h AD	PK Group B Blood Drawn 6, 8 & 12h AD
ARM 1	10	10
ARM 2	20	20
ARM 3	20	20

Targeting n=100;
So far 28 enrolled

  - **Consequently; six strata (1A, 1B, 2A, 2B, 3A, 3B).**

- **Patients are admitted through out treatment duration for : -**

  Patients are admitted through out treatment duration for : -

  DOTs + Clinical evaluations (Efficacy and Safety based on WHO toxicity table)

  To study autoinduction of artemether; therefore, repeated at D2 (all), D4 (Arms 2 and 3) and D6 (Arm 3 alone)

  Then followed with evaluations at scheduled visits on Days 7, 14, 28 & 42

  Parasitological evaluations at enrolment and all review points

Targeted Study Endpoints

Primary

- Time to levels <MIC for lumefantrine
- Day 7 lumefatrine levels
- Reinfection rate by day 42 (non-PCR adjusted)
- Grade 3/ 4 adverse events

Secondary

- Time to parasite clearance
- Total number of AES by day 42

- **<u>Indications for expanding study</u>**
- Longer period to MIC with longer treatment
- No expected significant differences in adverse drug event
- Any trend towards fewer reinfections

RESULTS

Treatment ARM	n	Baseline Characteristics			F/UP MPS/µl		
		Sex = F	Mean Age (SD)	Mean MPS/µl	D2	D7	D42
ARM 1	5	3	35.4 (14.4)	6501 (6624)	0	0	0
ARM 2	10	10	34.3 (9.0)	8161 (7153)	0	0	0
ARM 3	11	6	29.6 (8.7)	6061 (3340)	0	0	0
ALL	**25**		**32.5 (10)**	**7039 (5557)**	0	0	0

RESULTS- some safety indicators

	Hb (Ref: 12-16g/dl)			WBC (Ref: 5-10 (*10^3 cells/ul)			PLt (150-400 (*10^3/ul))			SAE/ G3/4 AEs	LOST	
	D0	D7	D42	D0	D7	D42	D0	D7	D42	0	D7	42
ARM 1	13.5	13.5	13.2	4.5	3.9	5.3	213	300	410	0	0	1
ARM 2	11.7	12.9	11.4	3.9	4.19	4.3	189	238	328	0	1	1
ARM 3	14.0	12.8	14.9	4.7	4.8	3.8	191	253	220	0	0	1

CONCLUSIONS and WAY FORWARD

- Debate on effect of increasing duration in endemic areas
- To modify bleeding schedule to reduce no of samples to improve consent rate hence improve enrolment rate
- Organizing for PK analysis by LCMS

For your attention and guidance

Acknowledgements

- Grant Number D43TW010132 supported by:
  - Office Of The Director
  - National Institutes Of Health (OD)
  - National Institute Of Dental & Craniofacial Research (NIDCR)
  - National Institute Of Neurological Disorders And Stroke (NINDS), National Heart, Lung, And Blood Institute (NHLBI)
  - Fogarty International Center (FIC)
  - National Institute On Minority Health And Health Disparities (NIMHD).

NURTURE partner institutions: Makerere University, JHU, CWRU

NURTURE PIs, mentors