

Clinical Studies: AS-MQ in Africa

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Indications for use

- ***First line indication: Fixed-dose combination for the treatment of uncomplicated falciparum malaria in children, adults and 2nd and 3rd trimester pregnant women***
- **AS/MQ: Has a role to play in all endemic regions, including Africa and areas with multi-drug resistance. Increases the number of options, thus allowing better access and decreasing risk of resistance.**

Mefloquine use in Africa

- Evidence on MQ monotherapy raised concerns of tolerability:
 - Increased incidence of vomiting (Slutsker et al, 1990)
 - 29% of children within 30 minutes of drug administration
 - 13% unable to tolerate a second treatment dose
 - Neuropsychiatric symptoms
 - Phillips-Howard PA, ter Kuile FO, 1995: 1 in 10 000 travellers on prophylaxis, 1 in 1000 patients treated in Asia, 1 in 200 patients treated in Africa, and 1 in 20 patients following severe malaria
 - Sowunmi et al, 1993 (15 or 25 mg/kg, case series): 2/303 children symptoms; 7/14 adults in Ibadan, Nigeria.

AS +MQ Combination in Africa

- Limited data of AS-MQ in Africa
- Different routes of administration of artesunate: rectal and oral
- Different dosing and schedules of mefloquine: single, 3-doses concomitant with AS, sequential dosing
- Reassuring safety data in recent studies Adam 2005, Bhatt 2006

AS + MQ Combination in Africa

Adam 2005

- Study conducted October-November 2003, Sudan
- MQ vs. AS-MQ (15 mg/kg) used sequentially
- 92 patients, 78 complete the 28 days follow-up
- Vomiting: 10 patients on MQ, 1 patient on AS-MQ
- No other safety outcomes described

AS + MQ Combination in Africa

Bhatt 2006

- Study conducted between January 2004 and April 2004, Kenya
- 203 patients with uncomplicated plasmodium falciparum malaria weighing 35kg and above were recruited in the study
- Artequin (AS-MQ co-blister)
- Cure rate d28 98.4%; day 14 and 7 cure rates were 98.4% and 99.2% respectively
- Well tolerated
 - Vomiting: 2/100 children, 16/103 adults
- No significant abnormalities in the haematological, biochemical and ECG parameters

WHO Treatment Guidelines 2006

Interventions: oral AL, AS+AQ, AS+MQ, AS+SP

Summary of RCTs: AL 6-dose regimen compared with 4-dose regimen; 6 doses resulted in higher cure rate in 1 trial in Thailand (RR: 0.19; 95% CI: 0.06–0.62).

AS+MQ compared with AL 6-dose regimen; systematic review including 2 small RCTs from Thailand. Higher proportion of patients with parasitaemia at day 28 with AL but difference not statistically significant. One additional RCT in Lao People’s Democratic Republic also reported higher proportions of patients with parasitaemia at day 42 with AL but also not statistically significant.

AS+AQ compared with AL 6-dose regimen; 1 trial in Tanzania found a significantly higher proportion of parasitological failures on day 28 with AS+AQ.

No trials of AL compared with AS+SP.

Expert comment: the efficacy of ACTs with AQ or SP as partner medicines is insufficient where cure rates with these medicines as monotherapies is less than 80%. The efficacy of AL and AS+MQ generally exceeds 90% except at the Thai-Cambodian border, where AL failure rate was 15%.

Basis of decision: expert opinion.

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- : the following ACTs: AL (6-dose regimen), AS+AQ, AS+MQ, AS+SP.
- : areas with AQ and SP resistance exceeding 20% (PCR-corrected at day 28 of follow-up), use AS+MQ or AL.

WHO Treatment Guidelines 2006

- Current data with AS + MQ shows superiority in efficacy to any of the combinations of AS with SP or AM+Lumefantrine, but the studies were small.
- Therefore, there is a need for a study with greater power to confirm or ascertain both safety and efficacy of the AS + MQ.

WHO Treatment Guidelines 2006

Rationale for study in Africa

- The need for a robust study is supported by the fact that there is currently insufficient safety and tolerability data on AS+MQ at the recommended dose of 25 mg per kg in African children.
- This study is mandatory to provide a suitable choice for African children

Planned Study in Africa

- General Objective:
- To evaluate and compare the efficacy and safety of the fixed-dose combination of AS-MQ with first line treatment (ALU) for uncomplicated falciparum malaria in Tanzania children.

Planned Study in Africa

- Primary Objective:
- To determine the clinical and parasitological efficacy of Artesunate-Mefloquine fixed-dose combination in children patients with uncomplicated falciparum malaria, by determining the proportion of patients achieving a negative parasitemia without recrudescence by 42 days (cure rate).
- To compare safety and efficacy of AS + MQ against ALU

- Secondary Objectives:
- To measure the parasite reduction ration at 48 hours, fever clearance time, gametocyte carriage
- To evaluate cure rate at 28 days
- To evaluate the incidence of adverse events

Study Design

- Open-label, prospective, randomised, controlled, non-inferiority design clinical trial of AS + MQ vs ALU
- Sample size: 362 patients
 - 157 patients in each group, 90% power at 5% significance level using a two-sided equivalence test of proportions
 - PCR-adjusted 42-day cure rate in either group is 99%
 - Clinically relevant difference is 0.05.
 - Adjustment for 15% loss of follow-up

Study Design

Inclusion Criteria :

- Age between 1-5 years.
- Acute uncomplicated *P. falciparum* mono-infection confirmed by:
 - Axillary temperature $\geq 37.5^{\circ}$ C **and**,
Positive microscopy of *P. falciparum* with parasite density between 2,000 and 200,000 asexual parasites/ μ l
- Consent from parent/guardian

Study Design

Exclusion Criteria :

- Severe/complicated malaria, requiring parenteral treatment according to the World Health Organization Criteria 2000
- Inability to tolerate oral medication
- Mixed Plasmodium infection.
- Presence of febrile conditions caused by diseases other than malaria.
- Known history of hypersensitivity, allergic or serious adverse reactions to Mefloquine, Quinine, Quinidine, Artesunate or other Artemisinins.
- History of use of any other anti-malarial agent within 2 weeks prior to start of the study.

Study Site

- National Institute of Medical Research Unit – Kilosa District, Tanzania
- Kilosa District population is 440,000 of whom 15 to 20 % are underfives children.
- Malaria commonest cause of OPD attendances, morbidity 30-42%
- Malaria Contributes 25 % of hospital mortality

Necessary requirements

- **Provision of full, supervised treatment**
- **Patients will remain hospitalised for at least 3 days**
- **Study microscopist(s) will remain blinded**
- **Anti-malarials and antibiotics with anti-malarial activity including macrolides and cyclins are not allowed during the study**

Necessary requirements

- All instruments should be of quality and calibrated prior to study commencement and at regular intervals during study
- Specimens will be labelled anonymously (screening number or study number, day of follow-up, visit date).
- Patients are encouraged to return on their own for scheduled follow-up visits(patients costs).
- Establishments of DSMB

Study Team

- Principal Investigator: Dr. Zakayo Mrango
- Co-Investigators:
 - Dr. Andrew Kitua
 - Dr. Marian Warsame
 - Dr. Charles Makasi
 - Dr. Omari Kimbute
- Opportunity for greater collaboration with Brazil and DNDi