FACT Project AS-MQ

Francois NOSTEN, Shoklo Malaria Research Unit, Mahidol Oxford University, Tropical Medicine Research Unit, Thailand.
Standard treatment since 1994 =
Artesunate 4mg/kg x3d +
Mefloquine 25mg/kg
FACT AS-MQ

1. MQ 8mg/kg/d x3 regimen tested in 2 RCTs
2. Population PK study of MQ 8mg/kg/d
3. AS-MQ FIXED combination vs LOOSE drugs Phase III Clinical Trial
4. Population PK of new fixed combination
5. AS-MQ – 13 years of Adverse Events. Individual Patient Meta-Analysis
1. RCTs of Mefloquine 8mg/kg/d for 3 days with artesunate

2002-2003
A Randomized, Controlled Study of a Simple, Once-Daily Regimen of Dihydroartemisinin-Piperaquine for the Treatment of Uncomplicated, Multidrug-Resistant Falciparum Malaria

Elizabeth A. Ashley,1,2,3 Rose McGready,1,2,3 Robert Hutagalung,1 Lucy Phaiphun,1 Thra Slight,1 Stephane Proux,1 Kyaw Lay Thwai,1 Marion Barends,1 Sornchai Looareesuwan,2 Nicholas J. White,2,3 and François Nosten1,2,3

1Shoklo Malaria Research Unit, Mae Sot, and 2Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; and 3Center for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, United Kingdom

343/1029 pts treated with AS+MQ 8mg/kg/d

Day 63 PCR adjusted cure rate:

95.3 % \[95\% \text{ CI 93.0-97.7}\]
2. Population PK model for MQ
8mg/kg/d
(AS-MQ loose)
Pop PK of Mefloquine 8 mg/kg/d

AUC was 40% higher than previous estimates in patients treated with mefloquine (15+10 mg/kg)

Predicted population pharmacokinetic profile for mefloquine 8mg/kg/day for 3 days with artesunate.
3. Phase III trial of Fixed Combination
Fixed Combination vs Loose Drugs

- November 2004 – June 2005
- 500 patients
- Age: 6 months- 65 years
- 9 weeks follow up
Efficacy

PCR-adjusted cure rate at D63 [95% CI]

AS-MQ FIXED 92%
[87-95]

AS-MQ LOOSE 89%
[84-93]

P=0.4
Early vomiting

• < 1 h after dose.

<table>
<thead>
<tr>
<th></th>
<th>Fixed N%</th>
<th>Loose</th>
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<tbody>
<tr>
<td>Day 0</td>
<td>8 (3%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Day 1</td>
<td>0</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Day 2</td>
<td>0</td>
<td>2 (0.8%)</td>
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</tbody>
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• Rescue therapy: 2 patients (Loose group)

1 Fishers Exact Test
4. Individual Patient Meta Analysis of Adverse Events following mefloquine + artemisinin treatment in SMRU clinical trials
Population & Methods

• 5,277 patients enrolled in 18 clinical trials at SMRU between 1992 and 2005
• Mefloquine and artemisinin (artesunate or artemether) studied in 11 different regimens
• 25 different adverse events studied
• Frequency expressed as **Incidence density**
• 28 days follow up used
• 12 patients had seizures or other neuropsychiatric adverse event
  – Incidence rate 2 per 1000 (CI$^{95}$ 1.3-4.0 per 1000)

• 4 deaths (unrelated)
Results - Early vomiting

- 30% lower risk if mefloquine dose is split (CI\(^{95}\) 19-40)
- Risk factors: female, higher parasite count, fever, younger age
- (0-4 years: OR=6.84 P=0.001)
MQ 8mg/kg/d regimen (+AS) had the LOWEST incidence of AEs
AS-MQ Summary Points

✓ Efficacious
✓ Safe
✓ Well tolerated
✓ Favourable PK profile
✓ Simple regimen
✓ Competitively priced
✓ Convenient coformulation

X Not recommended in pregnancy or severe malaria
X Cumulative toxicity with repeated dosing

The evidence supports deployment of the fixed combination where AS-MQ is used
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