FACT Project AS-MQ

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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

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

Day 63 PCR adjusted cure rate:

95.3 %  [95% CI 93.0-97.7]
2. Population PK model for MQ 8mg/kg/d (AS-MQ loose)
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>
</tr>
</tbody>
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- Rescue therapy: 2 patients (Loose group)

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
Results: Serious Adverse Events

• 12 patients had seizures or other neuropsychiatric adverse event
  – Incidence rate 2 per 1000 (CI\textsuperscript{95} 1.3-4.0 per 1000)

• 4 deaths (unrelated)
Results - Early vomiting

- 30% lower risk if mefloquine dose is split (CI\textsuperscript{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
Acknowledgements

- **DNDi**
  - Dr JR Kiechel

- **WHO/TDR**
  - Bob Taylor
  - SCRIHS

- **Faculty of Tropical Medicine, Mahidol University BKK**
  - Ethical Committee
  - Dr N Lindegårdh and Pharmacology Dept.
  - Dr Wattana
  - Dr K Stepniewska (PK model)

- **SMRU**
  - Patients and Staff
  - Julien Zwang
    (MAS3 AE IPMA)

- **Julie Simpson**

- **FarManguinhos**
  - Solange Wardell

- **OXTREC**

- **Quintiles**

- **The Wellcome Trust of Great Britain**