Options for treating multidrug resistant falciparum malaria

Elizabeth Ashley, Myanmar Oxford Clinical Research Unit

March 2018
Overview

1. Status of drug resistance in *Plasmodium falciparum*

2. Treatment options
   a) New drugs?
   b) Longer courses?
   c) Triple combinations?

*Artemisia annua*
1. Current status of Artemisinin and partner drug resistance
Evidence of Artemisinin-Resistant Malaria in Western Cambodia

- 2008: Noedl et al. for the ARC1 Consortium; NEJM

- 2009: Dondorp et al.; NEJM
A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria

Frédéric AriéY1,2†, Benoit Witkowski3, Chanaki Amaratunga4, Johann Beghain1,2†, Anne-Claire Langlois1,2, Nimol Khim3, Saorin Kim3, Valentine Duru3, Christiane Bouchier5, Laurence Ma5, Pharath Lim3,4,6, Rithea Leang6, Socheat Duong6, Sokunthea Sreng6, Seila Suon6, Char Meng Chuar6, Denis Mey Bout7, Sandie Ménard8†, William O. Rogers9, Blaise Genton10, Thierry Fandeur1,3, Olivo Miotto11,12,13, Pascal Ringwald14, Jacques Le Bras15, Antoine Berry8†, Jean-Christophe Barale1,2†, Rick M. Fairhurst4†, Françoise Benoit-Vical16,17*, Odile Mercereau-Puijalon1,2* & Didier Ménard3*
A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria

Frédéric Ariey\(^1,2\), Benoit Witkowski\(^3\), Chanaki Amaratunga\(^4\), Johann Beghain\(^{1,2}\), Anne-Claire Langlois\(^{1,2}\), Nimol Khim\(^3\), Saorin Kim\(^3\), Valentine Duru\(^3\), Christiane Bouchier\(^5\), Laurence Ma\(^5\), Pharath Lim\(^{3,4,6}\), Rithea Leang\(^6\), Socheat Duong\(^6\), Sokunthea Sreng\(^6\), Seila Suon\(^6\), Char Meng Chuar\(^6\), Denis Mey Bout\(^7\), Sandie Ménard\(^8\), William O. Rogers\(^9\), Blaise Genton\(^10\), Thierry Fandeur\(^1,3\), Olivo Miotto\(^{11,12,13}\), Pascal Ringwald\(^{14}\), Jacques Le Bras\(^{15}\), Antoine Berry\(^8\), Jean-Christophe Barale\(^{1,2}\), Rick M. Fairhurst\(^{4\ast}\), Françoise Benoit-Vical\(^{16,17\ast}\), Odile Mercereau-Puijalon\(^{1,2\ast}\) & Didier Ménard\(^3\)\^\(\ast\)

*kelch13*

e.g. C580Y
Partner drug resistance (ACT failures)

- DHA-piperaquine failure rates of ~ 50% in Cambodia and Viet Nam
- AS-MQ failure rates of ~ 20% on the Thai-Myanmar border
Can it be stopped?

THE PATH OF CHLOROQUINE RESISTANCE

Malaria parasites resistant to chloroquine swept out of the Mekong region and spread around the world. So far, artemisinin hasn’t followed that path, and researchers are debating the likelihood it will.
Can it be stopped?

THE PATH OF CHLOROQUINE RESISTANCE

Malaria parasites resistant to chloroquine swept out of the Mekong region and spread around the world. So far, artemisinin hasn't followed that path, and researchers are debating the likelihood it will.
“Popping” or spread?

- Haplotype analysis has shown **independent emergence** of the same artemisinin-resistance mutations in different geographical areas in Southeast Asia,
  - e.g. C580Y emerged once in the east (Cambodia/Vietnam) and once in the West (Myanmar)

Takala-Harrison, JID 2015
Super-malaria?

- Transnational spread of multidrug resistant *P. falciparum kelchC580Y* lineage
  - Detected first in Pailin in 2008
  - It later acquired **piperaquine resistance** and spread east.
  - Now found in Cambodia, Thailand, Laos, Vietnam

2017

Imwong et al. Spread of a single multidrug resistant malaria parasite lineage (PfPailin) to Vietnam; LID, 2017
2. Options for treatment (endemic countries)

a. New drugs?
b. Recycle old drugs
c. Longer ACT courses
d. Triple ACTs
a. New antimalarial drugs

• Success rates for drugs in Phase 2 are 34-60%
• Success rates for drugs in preclinical phase are 8%

(Burrows et al. Malaria Journal 2017)
Leading candidates in clinical development

• Artefenomel+ferroquine
• Lumefantrine + KAF-156
• Cipargamin
Artefenomel+ferroquine

- Artefenomel (previously OZ439) a long-acting synthetic ozonide
- Ferroquine (FQ)- long-acting aminoquinoline (half-life 16 days)
- Targeting single dose treatment
- Multicentre dose-finding phase 2b study (NCT02497612) is underway
Artefenomel+ferroquine

• Artefenomel (previously OZ439) a long-acting synthetic ozonide
• Ferroquine (FQ) - long-acting aminoquinoline (half-life 16 days)
• Targeting single dose treatment
• Multicentre dose-finding phase 2b study (NCT02497612) is underway

How much cross-resistance is there between artefenomel and artemisinin derivatives?
Lumefantrine-KAF156

• KAF156: highly potent imidazolopiperazine which has **multistage activity**
• Lumefantrine: an arylaminoalcohol already in widespread use combined with artemether
• Phase 3 dose-finding study ongoing in West Africa (NCT03167242)
• Targeting single dose treatment/radical cure
Cipargamin

• Spiroindolone
• PfATP4 inhibitor
• Potent, long-acting blood schizonticide
• Dose-escalation safety study is recruiting in Mali (NCT03334747) with a special focus on hepatotoxicity after signals in earlier studies
b. Prolonged ACT courses

• Artemisinin derivatives still work—just much less well
  – Non-response to treatment not described

• Giving longer courses can improve efficacy

TRAC study; NEJM 2014
## Day 42 Efficacy of 6 day treatments

<table>
<thead>
<tr>
<th>Site</th>
<th>Treatment</th>
<th>Duration (days)</th>
<th>N recurrences/ N patients</th>
<th>PCR-corrected efficacy [95% CI] @ D42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia-Pailin</td>
<td>AS4 + DP</td>
<td>6</td>
<td>2/100</td>
<td>97.7 [90.9-99.4]</td>
</tr>
<tr>
<td>Viet Nam-Binh Phuoc</td>
<td>AS2+DP</td>
<td>6</td>
<td>0/60</td>
<td>100 [93.2-100]</td>
</tr>
<tr>
<td>Viet Nam-Binh Phuoc</td>
<td>AS4+DP</td>
<td>6</td>
<td>0/60</td>
<td>100 [93.0-100]</td>
</tr>
<tr>
<td>Laos-Attapeu</td>
<td>AS4+AL</td>
<td>6</td>
<td>2/60</td>
<td>100 [93.5-100]</td>
</tr>
<tr>
<td>Myanmar-Shwe Kyin</td>
<td>AS4+AL</td>
<td>6</td>
<td>0/40</td>
<td>100 [87.9-100]</td>
</tr>
</tbody>
</table>
b. Triple Artemisinin-based combinations

DHA-piperaquine and mefloquine

Artemether-lumefantrine and amodiaquine

- Fairly well matched elimination kinetics
- Opposing resistance selection effects?
TRAC 2 study: RCT (120 patients/site)

19 sites  8 countries

DHA-PPQ vs DHA-PPQ+MQ
AM-LUM vs AM-LUM+AQ
ART-MQ vs DHA-PPQ+MQ
Aims

1. Update on status of artemisinin and partner drug resistance
   i. Phenotypic (parasite clearance half-life > 5h)
   ii. Genotypic (\textit{kelch13}, plasmepsin, pfmdr1)

2. Efficacy of ACTs and triple-ACTs

3. Safety and tolerability of triple ACTs
Key inclusion & exclusion criteria

Inclusion criteria
• Male or female, aged from 6 months to 65 years old.
• Symptomatic acute uncomplicated *P. falciparum* malaria, with asexual parasite density of 5,000 to 200,000/µL
• Written informed consent

Exclusion criteria
• Severe/complicated malaria
• Haematocrit < 25% or Hb < 8 g/dL
• For females: pregnancy, breast feeding
• ACT treatment within the previous 7 days or mefloquine within 2 months
• History of cardiac disease
Recruitment halted - January 2018

Total Enrolled (n=1109)
Preliminary conclusions

• Poor efficacy of DHA-piperaquine in Northeastern Thailand, Cambodia and Southwest Vietnam

• Good efficacy of the two Triple ACTs in sites with failing DHA-piperaquine

• Reassuring tolerability and safety so far but more data needed
But.........
Is it already too late?

Emergence of *Plasmodium falciparum* triple mutant in Cambodia

- Kelch13 C580Y (artemisinin)
- Pfmdr copy no. (mefloquine)
- Plasmepsin2 copy no. (piperaquine)

Rossi et al.; Lancet Infectious Diseases, December 2017
Next steps

• Evaluation of artemether-lumefantrine+amodiaquine in Vietnam/Cambodia
• Development co-blistered triple ACTs
• Large trial focused on safety and tolerability in Africa and Asia
• Development fixed dose TACTs
  – with existing drugs?
  – with new compounds?
Acknowledgements

• Rob van der Pluijm (TRAC 2 coordinator)
• Arjen Dondorp (TRAC2 PI)
• All TRAC2 management team, collaborators and participants
• TRAC 2 was funded by UK DFID
• ISID