Treatment of Uncomplicated Malaria in the wake of Multi-drug Resistant Falciparum Malaria

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Outline

• Introduction
• Malaria drug resistance – current status
• Strategies to delay emergence of resistance
Introduction

• The World Health Organization (WHO) recommends artemisinin-based combination therapies (ACTs) for treating uncomplicated Plasmodium falciparum malaria
• The increasing availability of ACTs and long-lasting insecticidal nets (LLINs) over the last decade has contributed to a substantial reduction in malaria morbidity and mortality in Sub-Saharan Africa
• However, the reduced efficacy of artemisinin against Plasmodium falciparum malaria in the Greater Mekong region threatens to jeopardize the recent gains in malaria control and elimination
• For combination therapies, the early parasitological response is determined largely by the artemisinin component.
• To prevent recrudescence, the malaria parasites that remain after exposure to the artemisinin component for two 48-hr asexual cycles must be cleared by the slowly eliminated partner drug
• Therapeutic responses are mainly determined by density and susceptibility of the infecting malaria parasites and drug exposure, although acquired host immunity can compensate for failing treatments.
Therapeutic response vs. drug resistance

\[ y = a + bx + e \]

\[ y = a + b_1x_1 + b_2x_2 + b_3x_3 + e \]

- Therapeutic response
- Patient factors
- Drug factors
- Parasite factors
- Other factors
- Drug resistance
Drug resistance – evolving definition

• The ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject (WHO 1967)

• The drug must “gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action” (Bruce-Chwatt et al, 1986)

• Artemisinin resistance is defined as delayed parasite clearance following treatment with an artesunate monotherapy, or after treatment with an artemisinin-based combination therapy (ACT). Such resistance represents partial resistance (WHO 2015)
  • suspected artemisinin resistance – defined as a high prevalence of the delayed parasite clearance phenotype, or high prevalence of K13 mutants;
  • confirmed artemisinin resistance – defined as a combination of delayed parasite clearance and K13 resistance-associated mutations in a single patient.
Drug resistance – evolving definition

**RESULT ->**
- Stepniewska et al. (2010) analysis of recrudescence probability leads to the WHO definition of potential artemisinin resistance if >10% of patients are still parasitaemic by microscopy on day-3.

**CAVEAT ->**
- This definition may not be suitable for populations with high or low parasitaemia on admission.

**2010**

**2011**
- Flegg et al. (2011) propose the peripheral blood parasite half-life derived from the log-linear parasite clearance curve which is robust to initial parasitaemia and lag-phase.

**2015**
- White et al. (2014) propose a population-level definition of resistance which is robust to uncertainty of resistance status of individual infections.

This definition leads to distributions of half-lives which appear to overlap.

Generalisation to a high transmission setting as in regions of Sub-Saharan Africa will need additional evaluation.

White et al. PLOS Medicine | DOI:10.1371/journal.pmed.1001823
Biochemical mechanism of resistance

- Chloroquine inhibits the polymerization of haem, a toxic by-product of HgB digestion.
  - It is believed that resistance of *P. falciparum* to chloroquine is related to an increased capacity for the parasite to expel chloroquine at a rate that does not allow chloroquine to reach levels required for inhibition of haem polymerization
  - PfCRT mutation is the genetic signature
- Pyrimethamine and related compounds inhibit the folate synthesis step mediated by dihydrofolate reductase (DHFR) while sulfones and sulfonamides inhibit the step mediated by dihydropteroate synthase (DHPS)).
  - Specific gene mutations encoding for resistance to both DHPS and DHFR
- Atovaquone acts through inhibition of electron transport at the cytochrome *bc1* complex.
  - Although resistance to atovaquone develops very rapidly when used alone, when combined with a second drug, such as proguanil (the combination used in MalaroneTM) or tetracycline, resistance develops more slowly.
  - Resistance is conferred by single-point mutations in the cytochrome-b gene
- Genome wide association studies (GWAS) have revealed parasite genetic loci associated with artemisinin resistance (K13). However, there is no consensus on biochemical targets of artemisinin.
Emergence and spread of resistance

• Phase I: An initial genetic event produces a resistant mutant (de novo mutation); the new genetic trait gives the parasite a survival advantage against the drug

• Phase II: The resistant parasites are selected for and begin to multiply, eventually resulting in a parasite population that is no longer susceptible to treatment

• The propagation of newly emerged resistance depends on the recrudescence and subsequent transmission of an infection that has generated a de novo resistant malaria parasite.

Life cycle vs resistance
Spread of resistance

Factors influencing the spread of resistance

• Biological
  • Host immunity
  • Characteristics of recrudescent infections
  • Vector-parasite combinations
  • Cross-resistance
  • Prolonged elimination periods

• Programmatic
  • Overall drug pressure
  • Inadequate drug intake
  • pK and pD properties

Bloland. WHO/CDS/CSR/DRS/2001.4
Detection of resistance

• *In vivo* tests
  • Reflect actual epidemiological situations
  • Affected by patient factors (host immunity, drug absorption), misclassification of reinfections as recrudescence

• *In vitro* tests
  • More accurately reflect pure resistance
  • Culture adaptation may result in different parasite population

• Molecular characterization
  • PCR techniques to detect genetic mutations

• Animal model studies
  • Essentially *in vivo* test in non-humans
Historical perspective – CQ and SP

http://www.wwarn.org
Artemisinin resistance distribution

www.yourgenome.org
K13 mutations, RSA findings

<table>
<thead>
<tr>
<th>K13 mutation</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>441L</td>
<td>Associated</td>
</tr>
<tr>
<td>446I</td>
<td>Associated</td>
</tr>
<tr>
<td>449A</td>
<td>Associated</td>
</tr>
<tr>
<td>458Y</td>
<td>Associated</td>
</tr>
<tr>
<td>493H</td>
<td>Confirmed</td>
</tr>
<tr>
<td>539T</td>
<td>Confirmed</td>
</tr>
<tr>
<td>543T</td>
<td>Confirmed</td>
</tr>
<tr>
<td>553L</td>
<td>Associated</td>
</tr>
<tr>
<td>561H</td>
<td>Associated</td>
</tr>
<tr>
<td>568G</td>
<td>Associated</td>
</tr>
<tr>
<td>574L</td>
<td>Associated</td>
</tr>
<tr>
<td>580Y</td>
<td>Confirmed</td>
</tr>
<tr>
<td>675V</td>
<td>Associated</td>
</tr>
</tbody>
</table>


WHO/HTM/GMP/2015.4
K13 polymorphisms in Africa

K13-Propeller Polymorphisms in Plasmodium falciparum Parasites From Sub-Saharan Africa

Anita Ghansah et al. Science 2014;345:1297-1298

The Journal of Infectious Diseases 2015;211:1352-5
### AL efficacy findings - Kisumu

**Drug**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Median IC50, nM (IQR)</th>
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<tbody>
<tr>
<td>Artemether</td>
<td>4.13 (1.68, 10.75)</td>
</tr>
<tr>
<td>Dihydroartemisinin</td>
<td>8.34 (1.84, 35.21)</td>
</tr>
<tr>
<td>Lumefantrine</td>
<td>31.69 (3.40, 111.49)</td>
</tr>
</tbody>
</table>

**Table 3:** Results from immediate ex vivo assay. Medians and interquartile range (IQR) of IC50s are presented.

**Treatment outcome**

<table>
<thead>
<tr>
<th>PC50</th>
<th>Range</th>
<th>ACPR Before PCR correction</th>
<th>ACPR After PCR correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4</td>
<td>(0.8, 15.5)</td>
<td>D28 32/51 (62.8%)</td>
<td>51/51 (100%)</td>
</tr>
<tr>
<td>12.7</td>
<td>(4.5, 21.7)</td>
<td>D42 21/48 (43.8%)</td>
<td>48/48 (100%)</td>
</tr>
<tr>
<td>15.2</td>
<td>(6.5, 24.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.2</td>
<td>(10.4, 32.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Distribution of slope half life**

Preliminary data, TES study. PI Andagalu, B
Hard facts

1. Antimalarial drugs will continue to be needed for the foreseeable future
2. As long as drugs are used, there is the chance that resistance will develop
3. Rate of development of resistance > rate of development of new drugs
4. Cost of strategies to counter drug resistance is an important factor to consider in Africa
5. Outside the Greater Mekong region, treatment failure with AL appears to be uncommon and is not necessarily due to drug resistance.
   • Other factors such as non-compliance with treatment schedule, poor drug quality, under dosing and drug–drug interactions contribute to treatment failure.
What needs to be done

• Rational use of malaria drugs
• Increased monitoring of antimalarial drug efficacy and resistance
• Use of molecular markers to identify genetic mutations related to antimalarial drug resistance in the parasite genome
• Use of gametocidal drugs for the reduction of malaria transmission
• Attainment of additional pharmaceuticals
• Use of multiple first line treatments
MFTs

- Multiple simulation models show that Multiple First Line Treatments (MFT) delays the emergence and spread of drug resistance
- MFT comes with higher program costs
- MFT could be socially beneficial but only for new products with unique dosing or adherence benefits
- Implementation can be a challenge
- MFT requires a balanced viewpoint from multi-stakeholders
- More studies that closely monitor the emergence and spread of resistance in countries that have recently started MFT are needed to strengthen the evidence base on MFT
Thank you