Pharmacology Considerations for Combination Malaria Treatment

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What are our challenges?

Case Study OZ439 and DSM265

Contribution for selection of doses

Impact
Challenges

• Combinations required
• How to get the right dose of both compounds
• Operational and ethical obstacles to conduct full factorial design studies
• Large monotherapy study in clinically infected patients are not advisable
• MIC studies are necessary but very difficult to implement in the field
• How to utilise the challenge studies
• Extrapolate to doses in patients with higher baseline parasitemia
Recently published CHMI studies in antimalarial drug development

• McCarthy et al.  

• McCarthy et al.  

• Pasay et al.  
  Piperaquine monotherapy of drug sensitive *P. falciparum* infection results in rapid clearance of parasitemia but is followed by the appearance of gametocytemia (J Infect Dis. (2016) doi: 10.1093/infdis/jiw128)

• Krause et al.  
  Pharmacokinetic/pharmacodynamic modelling of the antimalarial effect of Actelion-4 51840 in an induced blood stage malaria study in healthy subjects (Br J Clin Pharmacol (2016) )
Case Study OZ439 and DSM265

- **OZ439**
  - PoC study in the field
  - Challenge Study

- **DSM265**
  - Phase I and Challenge Study

- **OZ439/DSM265**
  - Combination Challenge Study
OZ439 PoC

- PoC in patients after SAD/MAD/Food Effect Study
- Phase II a study in patients
- 4 cohorts (200, 400, 800, 1200 mg)
- Standard of care at 36h post OZ439
- Output: PRR, parasite clearance t$_{1/2}$, PCT, FCT

- Oct 2010 – May 2012

Phyo et al. LID, 2015 Volume 16, No. 1,
Measuring the MIC clinically

\[ P_t = \int_0^t P \cdot \left[ G - D_0 \cdot \left( \frac{C_t^H}{C_t^H + IC_{50}^H} \right) \right] dt \]
OZ439 Challenge Study

• Single dose 100, 200 and 500 mg
• Follow up to SD16
• At 500 mg,
  • PRR48 >4
  • parasite t1/2 3.6h
  • MIC: 4.1 ng/ml
• Sep 2012 – Feb 2013

McCarthy et al 2016
DSM265

- Phase I: SAD & challenge cohort (150 mg)
  - 4/7 recrudescence
  - PRR approx. 2
  - MPC 954 – 1400 ng/ml
  - HED~320 mg
  - 6 month after FiH

- PoC study*
  - *P. falciparum 2 cohorts (400, 250 mg)
  - Follow up 28 days
  - PRR, lag, MIC,
  - Feb 2015 – Oct 2015
OZ439 – DSM265 combination Challenge study: design

• Selected single dose of each drug which will not eliminate all parasites
  • DSM265: 150 mg 4/7 recrudescence
  • OZ439: 200 mg, 8/8 recrudescence

• Following preliminary modelling work dose:
  • 200 mg OZ439 & 100 mg DSM265: 40% success
  • 200 mg OZ439 & 50 mg DSM265: < 5% success
Based on daily qPCR data

OZ439 PK
DSM265 PK
Parasites

4/8 subjects recrudesce

### Individual parasitemia profiles: Cohort 200/100

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time MIC (hr)</th>
<th>MIC OZ ng/mL</th>
<th>MIC DSM ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>S017</td>
<td>168</td>
<td>0.3</td>
<td>815</td>
</tr>
<tr>
<td>S018</td>
<td>216</td>
<td>0.2</td>
<td>846</td>
</tr>
<tr>
<td>S020</td>
<td>216</td>
<td>0.3</td>
<td>521</td>
</tr>
<tr>
<td>S021</td>
<td>516</td>
<td>0.4</td>
<td>111</td>
</tr>
<tr>
<td>Mean</td>
<td>279</td>
<td>0.3</td>
<td>573</td>
</tr>
</tbody>
</table>
Individual parasitemia profiles: Cohort 200/50

Based on daily qPCR data

OZ439 PK
DSM265 PK
Parasites

5/5 subjects recrudesce

- Below LOQ (=64 /uL)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time MIC Hr</th>
<th>MIC OZ ng/mL</th>
<th>MIC DSM ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>S022</td>
<td>108</td>
<td>1.2</td>
<td>987</td>
</tr>
<tr>
<td>S026</td>
<td>200</td>
<td>0.5</td>
<td>520</td>
</tr>
<tr>
<td>S028</td>
<td>216</td>
<td>2.7</td>
<td>523</td>
</tr>
<tr>
<td>S029</td>
<td>100</td>
<td>0.9</td>
<td>896</td>
</tr>
<tr>
<td>S030</td>
<td>120</td>
<td>0.8</td>
<td>709</td>
</tr>
<tr>
<td>Mean</td>
<td>149</td>
<td>1.2</td>
<td>727</td>
</tr>
</tbody>
</table>
### Parasite killing and MIC

<table>
<thead>
<tr>
<th>Drug</th>
<th>OZ439 200mg</th>
<th>DSM265 150 mg</th>
<th>OZ/DSM Combo 200 / 100 mg</th>
<th>OZ/DSM Combo 200 / 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Log$_{10}$ PRR</strong></td>
<td>2.2</td>
<td>1.5</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>(2.1–2.3)</td>
<td>(1.4–1.7)</td>
<td>(2.6–3.0)</td>
<td>(2.6–2.8)</td>
</tr>
<tr>
<td><strong>OZ439 MIC (ng/ml)</strong></td>
<td>4.1</td>
<td>0.3</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td><strong>DSM265 MIC (ng/ml)</strong></td>
<td>954–1400</td>
<td>573</td>
<td>709</td>
<td></td>
</tr>
</tbody>
</table>

The model shows the contribution of both drugs on Parasite Reduction Rate and apparent MIC.
PD Model

\[
\frac{dP}{dt} = P \left( G - D \frac{c^\gamma}{c^\gamma + IC_{50}^\gamma} \right)
\]

P: parasite concentration
T: time in hour,
G: the first order parasite growth rate in absence of drug
D: the maximum drug-specific parasite reduction rate
C: the drug concentration
IC_{50} the drug concentration required to achieve half the maximum parasite reduction rate
\gamma: an optional nonlinearity parameter defining the steepness of the concentration-effect curve

INT: The potential PD interaction of the two drugs. If INT is significantly greater than 0 then the two drugs are deemed to be **synergetic**, and if not, **antagonistic**.

For OZ439: (E_{max} model)

For DSM265: (E_{max} model)

For Combo:

\[
D_{OZ} \frac{C_{OZ}^{\gamma_{OZ}}}{C_{OZ}^{\gamma_{OZ}} + IC_{50,OZ}^{\gamma_{OZ}}}
\]

\[
+ D_{DSM} \frac{C_{DSM}^{\gamma_{DSM}}}{C_{DSM}^{\gamma_{DSM}} + IC_{50,DSM}^{\gamma_{DSM}}}
\]

\[
+ INT \times E_{max} \text{ model for OZ and DSM}
\]
In Preparation: Phase IIa

- Low, non-therapeutic doses are not acceptable
- 2 cohort study in patients
- Two dose combinations will be investigated that predict treatment success based on PK/PD M&S of the CHMI study and higher parasitemia in the field
Data generation for PKPD modelling

Compound A and B
PKPD model assuming no interaction
Advise doses

SCID mouse
Characterize compound PD interaction

Human challenge
Advise doses to be tested in patients to confirm PKPD relationship

Phase 2a
Estimate PK and PD parameters in patients

Phase 2b
Advise doses for Phase 2b including adjustment for children.

Phase 3
Advise doses for Phase 3 including adjustment for subpopulation

Drug-Drug Interaction

Paediatric PK
Conclusions

CHMI, Modelling and Simulation have been successfully applied

• Generate in phase I PD Information
• Reduce size of first in patient study
• Generate more data (28 f/u)
• Reduce overall time lines
• Show the contribution of each compounds on parasite reduction rate, apparent MIC and probability of success
Acknowledgements

• Our patients, their caregivers and volunteers

• Our R&D partners from across academia and industry

• Our ESAC and colleagues

• Our funding partners without whom we couldn’t do any of this work