Synthetic Peroxides:
A Viable Alternative to Artemisinins

Jörg Möhrle
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Curing Malaria Together
www.mmv.org
Role of Artemisinins in the Treatment of Malaria

• Artemisinin derivatives are now the mainstay of treatment for malaria

• Since WHO endorsement of Artemisinin-based Combination Therapy (ACT) as 1st or 2nd line therapy for uncomplicated *P. falciparum* malaria:

  • Heavy reliance on the artemisinin component:
    • fast acting, highly effective against both *P. falciparum* and *P. vivax*
    • rapidly cleared; used in combination with a longer-acting partner drug

• But there are issues...
  • supply, cost, natural source
  • any clinical resistance to artemisinin will jeopardize ACT strategies
  • concerns regarding use in some special populations (infants, pregnancy)
Known Artemisinin Programmes

- Alternative Sources of Artemisinin / plant derived peroxides
  - One World Health, Amyris, Berkeley (yeast)
  - Dafra / Bouwmester (chicory)
  - Plant cell culture system (Russia, Japan and others)
  - Tobacco (Swiss)
  - Cameroon (Plant families)

- Fully Synthetics
  - Arterolane (OZ277/RBx11160), Ranbaxy (phase III)
  - University of Liverpool, (ANTIMAL programme) (candidate)
  - Ozonides OZ439 (MMV) (phase I)
MMV peroxide portfolio

- One ACT submitted for registration
- Two ACT and one mono-therapy currently in clinical trials
- Artemisinin Resistance Network
  - Testing our endoperoxide collections (8) against primary parasites from resistance areas (Laos, Cambodia, Thailand, Senegal) (ex vivo)
  - Clinical testing of novel endoperoxides in patients where PCT is increased: Artemifone
- Ozonides
Objectives: Synthetic Peroxides (OZ) Project

• **First Generation OZ project aimed to:**
  
  – identify a new class of peroxides
  
  – more potent than the currently available semi-synthetic artemisinin derivatives in reducing parasite burden
  
  – fully synthetic
  
  – low cost (< $1 USD per treatment when used in combination)
  
  – 3 day treatment regimen when used in combination

• **Next Generation OZ project extends these goals to also include:**
  
  – provision in combination of a single-dose oral cure for patients with uncomplicated *P. falciparum* malaria (and possibly *P. vivax*)
  
  – potential for prophylactic treatment and intermittent preventative treatment in pregnant women and infants (IPTp and IPTi)
First Generation of Synthetic Peroxides

OZ277 or RBx11160
What do we know about RBx11160?

• More active than chloroquine, mefloquine, and artemisinin derivatives against *P. falciparum in vitro*, and *P. berghei* in mice

• Good physicochemical and metabolic profile; good PK and oral bioavailability in rats and dogs; short half-life

• Excellent safety profile in rats, dogs and humans after single and repeat administration

• Similar exposure after single and repeat administration in humans; minimal food effects
Phase 1 Plasma Concentrations of RBx11160

Plasma concentrations after a single oral dose to healthy volunteers

- Excellent exposure at doses of 100 mg or above...
- Highly consistent with predictions based on animal data, but …
“Issues” that Arose with RBx11160 in Phase 2

- Significant reduction in drug plasma concentrations in malaria patients...
- Reduced exposure meant that it was unlikely to meet 3-day treatment regimen
- Phase II: Approx 70% efficacy (28 ACPR) with 7 days treatment
In Vitro Degradation in Infected Blood

- Rapid *in vitro* degradation of RBx11160 in infected blood
Second Generation of Synthetic Peroxides
Clearance in Red Blood Cells

- Fe(II)-mediated cleavage likely to be a significant contributor to the *in vivo* clearance of RBx11160

- Can we modify the ozonide structure to reduce the rate of cleavage without compromising biological activity?

- The answer is... **Yes**
Ozonide Clearance in Red Blood Cells

- Next Generation OZ are significantly more stable in whole blood *in vitro* than First Generation OZ
Key Pharmacology for OZ439: *Plasmodium berghei* Mouse Model (p.o.)

Single oral dose: 1x 30 mg/kg p.o.

<table>
<thead>
<tr>
<th>Compound (30 mg/kg)</th>
<th>Activity (%)†</th>
<th>Survival (d), Cure (%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>92</td>
<td>9 d, 0%</td>
</tr>
<tr>
<td>AM</td>
<td>99.7</td>
<td>9 d, 0%</td>
</tr>
<tr>
<td>CQ</td>
<td>99.9</td>
<td>10 d, 0%</td>
</tr>
<tr>
<td>MEF</td>
<td>99.6</td>
<td>22 d, 0%</td>
</tr>
<tr>
<td>OZ277</td>
<td>99.9</td>
<td>11 d, 0%</td>
</tr>
<tr>
<td>OZ439</td>
<td>99.0</td>
<td>&gt;30 d, 100%</td>
</tr>
<tr>
<td>Control</td>
<td>--</td>
<td>6 d, 0%</td>
</tr>
</tbody>
</table>

† % parasitemia on day 3 post infection  
‡ % of mice that were parasite free on day 30

AS, AM, CQ and MEF do not cure in this model up to 200 mg/kg.

Onset & Recrudescence: 1x 100mg/kg p.o.
<table>
<thead>
<tr>
<th>Dose</th>
<th>Frequency</th>
<th>Avg Survival</th>
<th>Cures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 1 mg/kg</td>
<td>single dose</td>
<td>6</td>
<td>0/5</td>
</tr>
<tr>
<td>1 x 3 mg/kg</td>
<td>single dose</td>
<td>6</td>
<td>0/5</td>
</tr>
<tr>
<td>1 x 5 mg/kg</td>
<td>single dose</td>
<td>10.4</td>
<td>0/5</td>
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<tr>
<td>1 x 10 mg/kg</td>
<td>single dose</td>
<td>18.2</td>
<td>0/5</td>
</tr>
<tr>
<td>1 x 15 mg/kg</td>
<td>single dose</td>
<td>30</td>
<td>4/5</td>
</tr>
<tr>
<td>1 x 20 mg/kg</td>
<td>single dose</td>
<td>&gt;30</td>
<td>5/5</td>
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<tr>
<td>1 x 25 mg/kg</td>
<td>single dose</td>
<td>&gt;30</td>
<td>5/6</td>
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<tr>
<td>1 x 30 mg/kg</td>
<td>single dose</td>
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<td>5/7</td>
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<tr>
<td>3 x 1 mg/kg</td>
<td>every 24 h</td>
<td>6</td>
<td>0/5</td>
</tr>
<tr>
<td>3 x 3 mg/kg</td>
<td>every 24 h</td>
<td>15.2</td>
<td>0/5</td>
</tr>
<tr>
<td>2 x 5 mg/kg</td>
<td>every 24 h</td>
<td>14.6</td>
<td>0/5</td>
</tr>
<tr>
<td>3 x 5 mg/kg</td>
<td>every 24 h</td>
<td>&gt;30</td>
<td>5/5</td>
</tr>
<tr>
<td>2 x 10 mg/kg</td>
<td>every 24 h</td>
<td>&gt;30</td>
<td>5/5</td>
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<tr>
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</tr>
<tr>
<td>3 x 3 mg/kg</td>
<td>every 12 h</td>
<td>12.2</td>
<td>0/5</td>
</tr>
<tr>
<td>3 x 5 mg/kg</td>
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<td>28.2</td>
<td>4/5</td>
</tr>
<tr>
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In Vitro Degradation in Infected Blood

- Next Generation OZ significantly more stable in healthy and especially infected blood

![Graph showing degradation in healthy and infected blood](image-url)
OZ439 Exposure in Healthy and Infected *P. berghei* Mice

10 mg/kg po

Approximately 50% decrease in exposure in presence of infection

Half life still > 5-fold longer than that of OZ277 and Art derivatives at similar dose
Conclusions

• Fe(II)-mediated cleavage in RBCs contributes to the \textit{in vivo} clearance of RBx11160 (and possibly other peroxides)

• Structural modifications for Next Generation OZ have resulted in:
  – improved stability in blood
  – reduced \textit{in vivo} clearance, prolongation in half-life and increased exposure in rats
  – enhanced biological activity in well-established mouse model of malaria
  – excellent prophylactic activity in mice – exceeds that of the benchmark chemoprophylactic, mefloquine

• Potential for reduced treatment regimen
Timelines

Launch → Q4 2013
Partners

- **Medicinal and synthetic chemistry**
  University of Nebraska, USA

- *In vitro* activity and *in vivo* efficacy assessment
  Swiss Tropical Institute, Switzerland

- **ADME, lead optimisation and compound profiling**
  Monash University, Australia

- **Manufacturing and Formulation**
  Unimark Remedies, India, Wilmington Pharma, USA, Penn Pharmaceuticals UK

- **Project management and Consultants**
  Fulcrum, UK, Carl Craft and John Scott, USA

- **Medicines for Malaria Venture**
  Ian Bathurst and Jörg Möhrle
Thank you

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