Dose-ranging activity of rifampin and rifapentine in two pathologically distinct murine models of tuberculosis

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Background

• Animal models play a vital role in developing new TB drugs and regimens
• Mouse models are economical, highly tractable, and have a good track record in predicting the activity of existing TB drugs
• However, lack of caseating granulomas and cavitation in mice raises concerns about their ability to predict results in humans
Necrotizing granulomas in C3HeB/FeJ ("Kramnik") mice

- Susceptibility allele at *sst1*
- Candidate gene is *lpr1*
- The cell death pathway in *Mtb*-infected *lpr1*-negative macrophages is necrosis rather than apoptosis
- Mice are not otherwise immunodeficient
- Utility as a preclinical efficacy model requires further study

Pan et al, Nature 2005
Apt & Kramnik, Tuberculosis 2009

Davis et al, AAC 2010
Comparative activity of escalating doses of rifampin (R) and rifapentine (P) when combined with INH-PZA (HZ)

Drug regimen | Percentage (proportion) of mice with positive cultures 3 months after stopping treatment for: |
--------------|---------------------------------------------------------------------------------|
              | 8 weeks | 10 weeks | 12 weeks |
--------------|--------|----------|----------|
R₂₀HZ         | ND     | 100% (15/15) | 67% (10/15) |
P₅HZ          | ND     | 100% (15/15) | 67% (10/15) |
R₄₀HZ         | ND     | 27% (4/15) | 0% (0/15) |
P₁₀HZ         | 100% (15/15) | 33% (5/15) | 0% (0/15) |
Presented at the 4th International Workshop on Clinical Pharmacology of TB Drugs, 16 September 2011, Chicago, IL, USA

Schema of TBTC Study 29

Sputum smear (+) PTB suspect

Randomization

- **RIF 10 mg/kg**
  - INH+PZA+EMB
  - 5/7 for 8 weeks without food

- **RPT 10 mg/kg**
  - INH+PZA+EMB
  - 5/7 for 8 weeks without food

End of intensive phase (≈ wk 8): assess for primary endpoints

ATS/CDC/IDSA-recommended continuation phase regimen
## Efficacy: Primary Endpoints (TBTC Study 29)

% of subjects having negative sputum cultures at end of intensive phase in the **Protocol Correct** analysis group

<table>
<thead>
<tr>
<th>Culture Medium</th>
<th>Rifampin</th>
<th>Rifapentoin</th>
<th>p</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>liquid</td>
<td>128/179</td>
<td>152/202</td>
<td>0.48</td>
<td>3.7 (-5.7, 13.2)</td>
</tr>
<tr>
<td></td>
<td>71.5%</td>
<td>75.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>solid</td>
<td>152/171</td>
<td>182/198</td>
<td>0.42</td>
<td>3.0 (-3.6, 9.6)</td>
</tr>
<tr>
<td></td>
<td>88.9%</td>
<td>91.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Why was the efficacy of the RPT regimen not superior? (some possible explanations)

• PK/PD
  – RPT exposures were lower in TB pts compared to mice
    – but so were RIF exposures
  – Drug effect may be different in human vs. murine TB
    – Is protein binding greater in humans?
    – Does RPT penetrate poorly into necrotic lesions compared to RIF?
    – Does RPT’s superior accumulation intracellularly, where bacilli reside in mice, lead to overestimation of its effect in humans?
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  – May have suboptimal discriminatory power
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Comparison of rifamycin activity against intracellular and extracellular *M. tb*

Intracellular accumulation ratio is 5x greater for P vs. R

Extracellular bacilli: RPT 2x more potent than RMP
Intracellular bacilli: RPT 16x more potent than RMP

Mor et al, AAC 1995
Objective

• Compare the activity of R vs. P in BALB/c vs. C3HeB/FeJ mice, in terms of:
  – Dose-ranging activity when administered alone, and
  – Activity when administered at 10 mg/kg in combination with HZE
Experimental scheme*

<table>
<thead>
<tr>
<th>Group</th>
<th>W-6</th>
<th>D0</th>
<th>M1 (+3)</th>
<th>M2 (+3)</th>
<th>M3 (+3)</th>
<th>M4 (+3)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>R(_{10})</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>R(_{20})</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>R(_{40})</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>RZHE</td>
<td>5</td>
<td>5</td>
<td>5 (15)</td>
<td>(15)</td>
<td>(15)</td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>P(_{5})</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>P(_{10})</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>P(_{20})</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>PZHE</td>
<td>5 (15)</td>
<td>5 (15)</td>
<td>(15)</td>
<td></td>
<td></td>
<td></td>
<td>55</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4</td>
<td>4</td>
<td>34 (15)</td>
<td>34 (30)</td>
<td>(30)</td>
<td>(15)</td>
<td>186</td>
</tr>
</tbody>
</table>

*Scheme conducted simultaneously in BALB/c and C3HeB/FeJ mice

Presented at the 4th International Workshop on Clinical Pharmacology of TB Drugs, 16 September 2011, Chicago, IL, USA
R and P have similar activity in both strains.
Equipotent doses are similar in both mouse strains.
RHZE vs. PHZE in 2 mouse strains

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Relapse results*

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>Mouse strain</th>
<th>1 month</th>
<th>2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>R_{10}HZE</td>
<td>BALB/c</td>
<td>ND</td>
<td>100% (15/15)</td>
</tr>
<tr>
<td></td>
<td>C3HeB/FeJ</td>
<td>ND</td>
<td>100% (15/15)</td>
</tr>
<tr>
<td>P_{10}HZE</td>
<td>BALB/c</td>
<td>100% (14/14)</td>
<td>7% (1/15)</td>
</tr>
<tr>
<td></td>
<td>C3HeB/FeJ</td>
<td>100% (13/13)</td>
<td>21% (3/14)</td>
</tr>
</tbody>
</table>

*Relapse results after 3 and 4 months of treatment are pending*
Efficacy: Post-hoc analysis (TBTC Study 29)
% of subjects having negative sputum cultures at end of intensive phase in the **Protocol Correct** analysis group

<table>
<thead>
<tr>
<th></th>
<th>Rifampin</th>
<th>Rifapentine</th>
<th>$p$</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LIQUID</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cavitary</td>
<td>41/57 (71.9)</td>
<td>53/64 (82.8)</td>
<td>0.22</td>
<td>10.9 (-5.7, 27.4)</td>
</tr>
<tr>
<td>Cavitary</td>
<td>87/122 (71.3)</td>
<td>99/138 (71.7)</td>
<td>1.00</td>
<td>0.4 (-11.3, 12.2)</td>
</tr>
<tr>
<td><strong>SOLID</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cavitary</td>
<td>50/56 (89.3)</td>
<td>61/61 (100)</td>
<td>0.03</td>
<td>10.7 (0.9, 20.5)</td>
</tr>
<tr>
<td>Cavitary</td>
<td>102/115 (88.7)</td>
<td>121/137 (88.3)</td>
<td>1.00</td>
<td>-0.4 (-8.3, 9.1)</td>
</tr>
</tbody>
</table>


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Conclusions

• The presence/absence of necrotic granulomas:
  – did not affect the relative potency of RIF vs. RPT
  – did not affect the outcome of treatment in mice with the regimens evaluated in TBTC Study 29

• Potential explanations for the apparent discrepancy between mouse and human results still include:
  – reduced penetration of RPT relative to RIF into larger necrotic lesions or cavities
  – inadequacies of the surrogate endpoint of sputum culture conversion
Acknowledgments

• **Funding**: U18-FD004004, Global Alliance for TB Drug Development

• **Drug**: sanofi-aventis (RPT)

• **Assistance**: Sanjay Jain, Susan Dorman