Population pharmacokinetics of Murepavadin (POL7080) and Monte Carlo simulations to develop clinical dosing regimen, including the renally impaired.

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\textsuperscript{4}Polyphor Ltd, Allschwil, Switzerland
Indirect disclosures

- Wockhardt
- Basilea
- Eumedica
- Polyphor
- Nordic pharma
Background Murepavadin

• New peptidomimetic antibiotic
• Specifically aimed at *Pseudomonas aeruginosa*, including multidrug resistant strains
• Mechanism of action: interaction with LptD, a target critical in the outer membrane biogenesis.
• Indication pneumonia

• Aim study: describe the pharmacokinetics and perform MCS to design dosing regimen.
Data for population PK analysis

• 211 subjects
• 2656 concentration-time observations
• Doses ranged from 0.05 mg/kg up to 10 mg/kg

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Median</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (% of the group)</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44</td>
<td>18 – 81</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>79</td>
<td>39 – 110</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173</td>
<td>149 – 196</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>26</td>
<td>16 – 49</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.9</td>
<td>1.3 – 2.35</td>
</tr>
<tr>
<td>Creatinine concentration (umol/L)</td>
<td>82</td>
<td>34 - 368</td>
</tr>
<tr>
<td>Cleatinine clearance (mL/min)</td>
<td>112</td>
<td>15 – 244</td>
</tr>
<tr>
<td>VAP (number)</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>
Methods

- Population pharmacokinetic model
  - NONMEM
  - Rstudio, Xpose, Pirana
  - 1-, 2-, 3 compartment models
  - Covariate model
  - Validation of the final model: NPDE (normalised prediction distribution errors)

- Monte Carlo simulations
  - NONMEM
  - Used the popPK model without covariates (general) and with covariates for adjustments renal impairment
  - 1000 simulations per regimen
  - Total concentrations
  - PK/PD target: AUC/MIC >208
Results population PK

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Structural model Mean</th>
<th>Covariate model Mean (RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (L/h)</td>
<td>5.89</td>
<td>7.03 (2%)</td>
</tr>
<tr>
<td>TVCL (L/h)</td>
<td>40.2</td>
<td>0.714 (5%)</td>
</tr>
<tr>
<td>A (influence of CRCL)</td>
<td></td>
<td>1.71 (17%)</td>
</tr>
<tr>
<td>B (influence of height)</td>
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<td>21.4 (7%)</td>
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<tr>
<td>IPV (%)</td>
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<td>0.0.714 (5%)</td>
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<tr>
<td>Central volume of distribution (L)</td>
<td>13.6</td>
<td>21.5 (14%)</td>
</tr>
<tr>
<td>IPV (%)</td>
<td>21.1</td>
<td>21.5 (14%)</td>
</tr>
<tr>
<td>Intercompartmental clearance (L/h)</td>
<td>5.15</td>
<td>4.66 (3%)</td>
</tr>
<tr>
<td>TVQ</td>
<td>48.3</td>
<td>2.64 (12%)</td>
</tr>
<tr>
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<td>27.1 (14%)</td>
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</tr>
<tr>
<td>Peripheral volume of distribution (L)</td>
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<td>24.0 (3%)</td>
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<td>TVVp</td>
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<tr>
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</tr>
<tr>
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<td>24.0 (3%)</td>
</tr>
<tr>
<td>Residual error</td>
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Covariate model

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Results
Validation of the PK model

Results

Goodness-of-fit plots

No systematic errors indicating a good model fit

Normalised prediction distribution errors (npde)
Methods

• Population pharmacokinetic model
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  • Validation of the final model: NPDE (normalised prediction distribution errors)

• Monte Carlo simulations
  • NONMEM
  • Used the popPK model without covariates (general) and with covariates for adjustments renal impairment
  • 1000 simulations per regimen
  • Total concentrations
  • PK/PD target: AUC/MIC >208
  • Target MIC 0.25 mg/L
  • Duration of infusion 2hours
MCS

Results

Dose: 100 mg tid

Dose: 150 mg tid

Dose: 200 mg tid

Dose: 250 mg tid
Target attainment with normal renal function

<table>
<thead>
<tr>
<th>MIC</th>
<th>0.125 mg/mL</th>
<th>0.25 mg/mL</th>
<th>0.5 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>26</td>
<td>52</td>
<td>104</td>
</tr>
<tr>
<td>Target attainment for dose regimen:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100mg tid</td>
<td>95.5%</td>
<td>50.6%</td>
<td>3.1%</td>
</tr>
<tr>
<td>150mg tid</td>
<td>99.6%</td>
<td>81.0%</td>
<td>21.7%</td>
</tr>
<tr>
<td>200mg tid</td>
<td>100%</td>
<td>94.2%</td>
<td>50.6%</td>
</tr>
<tr>
<td>250mg tid</td>
<td>100%</td>
<td><strong>98.8%</strong></td>
<td>69.9%</td>
</tr>
</tbody>
</table>
Target attainment in renally impaired individuals

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>120 mL/min</th>
<th>70 mL/min</th>
<th>30 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MIC=0.25 mg/mL (AUC≥52)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100mg tid</td>
<td>18.9%</td>
<td>81.7%</td>
<td>100%</td>
</tr>
<tr>
<td>150mg tid</td>
<td>82.7%</td>
<td><strong>99.6%</strong></td>
<td>100%</td>
</tr>
<tr>
<td>200mg tid</td>
<td><strong>99.3%</strong></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>250mg tid</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>MIC=0.5 mg/mL (AUC≥104)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100mg tid</td>
<td>0%</td>
<td>0.9%</td>
<td>67.4%</td>
</tr>
<tr>
<td>150mg tid</td>
<td>1.4%</td>
<td>32.5%</td>
<td><strong>98.7%</strong></td>
</tr>
<tr>
<td>200mg tid</td>
<td>17.5%</td>
<td>79.8%</td>
<td>100%</td>
</tr>
<tr>
<td>250mg tid</td>
<td>53.9%</td>
<td><strong>97.2%</strong></td>
<td>100%</td>
</tr>
</tbody>
</table>
Conclusions

• Population pharmacokinetics can be described adequately
• Standard dosing regimen: 250 mg tid Murepavadin if ECOFF is 0.25 mg/L
• MCS indicates dosing regimen:
  • For an MIC of 0.25 mg/L and Target Attainment Rate of 99%
    • For a creatinine clearance of 120 ml/min: 200 mg tid
    • For a creatinine clearance of 70 ml/min: 150 mg tid
    • For a creatinine clearance of 30 ml/min: 100 mg tid
Acknowledgment

ErasmusMC, Rotterdam, the Netherlands:
• Brenda de Winter
• Johan Mouton

Polyphor Ltd, Allschwil, Switzerland
• Glenn Dale
• Achim Wach