Application of PK/PD in New Anti-Infective Drug Development: Current Challenges and Future Perspectives

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Outline

• Summarize PK/PD principles for anti-infective drugs: Current application

• Describe potential application of PK/PD in new anti-infective drug development

• Discuss current challenges and future perspectives
Why is PK/PD information important?

- Drug class/MOA
- PK characteristics
- PD behavior
- Dose and regimen

- Immunocompetence
- Comorbidities
- Previous treatment
- Colonization

- Susceptibility
- Resistance mechanisms
- MIC

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PK/PD index: Determinant of drug response
Identifying the PK/PD index that best correlates with efficacy

- In vitro hollow-fiber system
- Animal model of infection
Determination of PK/PD Target

PK/PD target: The magnitude of PK/PD index required for desired efficacy in animal models of infection

PK/PD target determined from animal models is used as the target for humans.
Current Utility of PK/PD target

Dose selection for clinical studies:

Target $AUC_{24}/MIC$ Ratio = 30

- **500 mg** ⇒ $AUC_{24} = 40 \, \mu g \cdot hr/\text{mL}$
- **200 mg** ⇒ $AUC_{24} = 15 \, \mu g \cdot hr/\text{mL}$
- **100 mg** ⇒ $AUC_{24} = 8 \, \mu g \cdot hr/\text{mL}$

$MIC = 0.5 \, \mu g/\text{mL}$
Current Utility of PK/PD target: Probability of Target Attainment (PTA)

PK/PD target & Human (Patients) PK

Target $\text{AUC}_{24}/\text{MIC}$ Ratio $= 5$  Dose: 100 mg QD

<table>
<thead>
<tr>
<th>AUC (n=1000)</th>
<th>AUC/MIC (n=1000)</th>
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<tbody>
<tr>
<td></td>
<td>MIC=1</td>
</tr>
<tr>
<td>10 (P1).....</td>
<td>10</td>
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<tr>
<td>20 (P10)....</td>
<td>20</td>
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<tr>
<td>30 (P25)....</td>
<td>30</td>
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<td>40 (P40)....</td>
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<tr>
<td>200 (P100)</td>
<td>200</td>
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<tr>
<td>% PTA</td>
<td>$\sim$100%</td>
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To determine susceptibility criteria
To evaluate the clinical dose proposed
Potential Application of PTA as an Evidence of Drug Efficacy

When a clinical efficacy trial is not feasible or is limited for infections or pathogens of low occurrence,

Quality of data for **PK/PD target** and **human PK simulation** are critical.
PTA as an Evidence of Drug Efficacy: Limitations and Challenges

PK/PD target determined in animal model

- PD endpoints vs. Clinical Response: stasis, 1-log kill, 2-log kill, or survival in animals
- Role of immune system: Immunocompromised animals
- Concentrations in infection sites: Animals ≤ Human

\[ \text{AUC}_{24} / \text{MIC (Free Drug)} \]

\[ R^2 = 76\% \]
PTA as an Evidence of Drug Efficacy: Limitations and Challenges

Human PK simulations

- Monte Carlo Simulation: Observed PK variability
- Different variability b/w healthy subjects vs. patients with infection

\[ 35 \pm 8.5 \text{ (HS)} \text{ vs. } 33 \pm 23 \text{ (Pts)} \]

- Covariates of Pop. PK: Comorbidities, Infection itself, and etc
PTA as an Evidence of Drug Efficacy: Future Perspective

- Intensive animal studies with better animal models
- PK/PD target using clinical exposure-response data
- PK, MIC, and clinical outcomes from Phase 2 dose-ranging studies
- PK, MIC, and clinical outcomes from Phase 3 studies:
  To apply to other infection sites

![Graph showing clinical response vs. AUC/MIC ratio]
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