ANTIBIOTIC DEVELOPMENT FOR RESISTANT BACTERIA

A Pharmacometric-Based Solution

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• My primary scientific interest is PK-PD and furthering this science as a platform for the proper use and development of medicines

• I am President of the Institute for Clinical Pharmacodynamics, which receives monies supporting PK-PD research from government and industry sources
• The challenge is to find a regulatory pathway that balances unmet medical need with data quality and quantity

• PK-PD has long served as a tool for pre-clinical drug evaluation and dose regimen selection for early-stage clinical development\(^1\)
  
  o However, PK-PD is currently underutilized and could be further leveraged to:
    
    ▪ Identify the magnitude of antibiotic treatment effect, which is a critical element of non-inferiority study design\(^2\)
    
    ▪ Provide a paradigm for evaluating limited-sized clinical data in the context of other information to support regulatory decisions

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ONE PATH FORWARD
Single Randomized Clinical Trial Plus Supporting Clinical and Non-Clinical Data

• Reasonable in the circumstance where:
  o Appropriate preclinical models exist;
  o It is relatively easy to enroll patients with infection associated with wild-type or antibiotic-susceptible pathogens;
  o It is difficult to enroll patients with infection associated with antibiotic-resistant pathogens; and
  o Folks are willing and able to collect blood specimens from the majority of patients for drug assay

• Represents an intermediate regulatory path between one that requires two randomized controlled clinical trials and the animal rule, which requires none
HOW MIGHT THIS WORK?
One Randomized Clinical Trial Plus Supporting Clinical and Non-Clinical Data

• Pre-clinical infection model(s)
  o Demonstrate the impact of resistance determinant presence on the magnitude of the PK-PD index required for efficacy

• Single randomized comparative trial
  o Will enroll patients infected with wild-type pathogens
  o Sparse PK collection from all patients will allow for the construct of efficacy exposure-response relationship
  o Will contribute significantly to a drug’s safety database

• Smaller non-comparative trial
  o Will enroll mostly patients infected with resistant pathogens
  o Sparse PK collection from all patients allows for the integration of results across the program
Let’s pretend we are developing an intravenous cephalosporin for the treatment of wild-type and ESBL-producing Enterobacteriaceae.

In this example, we are going to synthesize data from 3 sources:
- Pre-clinical infection model
- Phase 3 randomized controlled clinical trial
- A non-comparative study
Minimum inhibitory concentration (MIC) distribution for cefepime against 1723 K. pneumoniae N. American clinical isolates collected during 2005-2007 by the SENTRY Surveillance Program. Data provided as a courtesy by Ronald N. Jones.

Key Question: What drives response? Is it the reason an MIC is elevated or drug exposure?
The Answer: It is not the presence or absence of particular resistance determinants that predict outcome, but rather the drug exposure indexed to MIC.
PK-PD INFECTION MODELS

What Do We Do with the Data?

- Pharmaceutical companies use animal-derived exposure-response relationships to select dose and dosing interval for study in Phase 2 and Phase 3 clinical trials.
- Regulatory agencies (FDA, EMA) and consensus bodies (CLSI) use such animal-derived exposure-response relationships as decision support for in vitro susceptibility interpretive criteria.

Key Question: Do pre-clinical PK-PD infection models forecast regulatory approval?
PK-PD INFECTION MODELS
Do They Forecast Regulatory Approval?

• We looked at the relationship between the regulatory approval and the probability of pre-clinical PK-PD target attainment
  o The study period was December 1996 through 2011
• Indications included community- and hospital-acquired pneumonia
  o For CAP, S. pneumoniae was the index pathogen
  o For HAP, the index pathogen was antibiotic spectrum dependent
  o We identified 14 antibiotics that gained regulatory approval and 6 that failed to gain approval

  ▪ Cefditoren
  ▪ Ceftaroline
  ▪ Ceftobiprole
  ▪ Daptomycin
  ▪ Doripenem
  ▪ Ertapenem
  ▪ Faropenem
  ▪ Garenoxacin
  ▪ Gatifloxacin
  ▪ Gemifloxacin
  ▪ Levofloxacin
  ▪ Linezolid
  ▪ Moxifloxacin
  ▪ Televancin
  ▪ Teilithromycin
  ▪ Tigecycline
  ▪ Trovaflloxacin
The Answer: Yes! The probability of regulatory approval increases with the probability of PK-PD target attainment

Note: PK-PD target was net-bacterial stasis in neutropenic mice for CAP agents and 1-2 log₁₀ unit reduction in bacterial burden for HAP agents
Data from a randomized, double-blind phase 3 clinical trial (NCT-00210964)

- Study compared ceftazidime versus ceftobiprole in patients with hospital-acquired pneumonia
- Ceftazidime regimen: 2 grams infused over 2 hrs. every 8 hrs.
- Blood specimens for drug assay were collected from nearly all (circa 90%) patients

• Data from a retrospective analysis evaluating the relationship between cephalosporin MIC and clinical outcome\(^1\)
  
  - 35 patients with bacteremia associated with ESBL-producing Enterobacteriaceae
  
  - Patients treated with mono-therapy with either cefepime, ceftrixone, cefotaxime or ceftazidime

• Now, I realize this is not an ideal dataset, but I think it will be instructive
Key Question: In patients, can one overcome the presence of resistance determinants with adequate drug exposure?

The Answer: Yes! Just like in animal infection models, drug exposure indexed to MIC predicts outcome.

![Graph showing the relationship between free-drug % time > MIC and probability of clinical response.](chart.png)
• What did the 3 distinct data sets teach us?
  o The pre-clinical infection model demonstrated:
    ▪ Response to cephalosporin therapy was related to %T>MIC
    ▪ The MIC is key—The relationship between %T>MIC and response was not different for wild-type, ESBL-elaborating isolates, or isolates having a high MIC for other reasons
  o The single randomized clinical trial demonstrated:
    ▪ Response to cephalosporin therapy was related to %T>MIC in patients infected with predominantly wild-type isolates
  o The small non-comparative study demonstrated:
    ▪ Response to cephalosporin therapy was related to %T>MIC in patients infected with ESBL-elaborating isolates

• A pharmacologically-based data package balances unmet medical need with data quality and quantity

1: All for one, one for all. The Three Musketeers, Alexandre Dumas, 1844.

ONE MORE THING
Concordance Between HAP Analyses

**CEFTAZIDIME**

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P = 0.001
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**TIGECYCLINE**

\[
P = 0.03
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THANK YOU FOR YOUR ATTENTION
Questions, Comments or Wise Remarks?