PK/PD versus frequentist approaches for drug development

Dean Follmann
National Institutes of Health
Bethesda USA
Three Points

• PK/PD methods good to predict response to drug. RCTs good to assess causal effect of the drug.
• PK/PD methods can be used with RCT data to rigorously assess a causal drug effect where PK/PD predicts one should occur.
• Bayesian Methods good to leverage information. Frequentist methods good to objectively assess evidence.
Cardiovascular World

- Cardiac Arrhythmia Suppression Trial (CAST)
- At baseline, identified patients whose arrhythmias were suppressible by AAD.
- NIH: **Randomize** the suppressible.
  (some felt trial was immoral)

<table>
<thead>
<tr>
<th></th>
<th>Not suppressible resistant to AAD</th>
<th>Suppressible susceptible to AAD</th>
</tr>
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<tbody>
<tr>
<td>AAD</td>
<td><strong>Registry</strong></td>
<td>Randomize</td>
</tr>
<tr>
<td>Placebo</td>
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### CAST Trial & Registry
#### Death Rates

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<td>AAD</td>
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*Based on a plausible range of assumptions about who got AADs*

Nonrandomized study: Looks like drug works!
CAST Trial & Registry
Death Rates

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RCT: AADs *increased* the death rate in patients with suppressible arrhythmias.

* Based on a plausible range of assumptions about who got AADs
Current Anti-infective Drug Landscape

- Non-inferiority (NI) Trial: New Drug B versus comparator Drug A
- Confidence interval (CI) of difference in success rates needs to exceed a margin based on historical data

\[ CI_{B-A} \]

- \( M \)  
  - Favoring A: Drug B is not unacceptably worse  
  - Favoring B: Drug B is not unacceptably worse
PK/PD modeling for Margin

• In this talk focus on the AUC:MIC ratio
• MIC- minimum inhibitory concentration of drug to kill the bug
• AUC—area under the curve of drug concentration
• Idea
  – Lower MIC --- easier to kill bug with drug
  – Higher AUC --- more drug to better kill bug
• Use AUC:MIC ratio --- bigger is better

Use PK/PD to set a margin?
Log(AUC/MIC) can provide a good prediction of response but drug causality unclear.
Holmes et al JID 2011

- Patients with *Staphylococcus aureus* bacteremia treated with vancomycin or flucloxacillin
- Vancomycin MIC predicts death for both vancomycin & flucloxacillin treated patient
- MIC-Vanco correlated with pt health, immunity?
Randomizing to dose allows for a causal conclusion about drug effect

Mix of sick and healthy patients
mix of good and bad bugs
Causal drug conclusion from observational data?

- Make an observational study more like a trial
- Statistically adjust for patient characteristics
  - Comorbidities, age, health, nursing home/hospital
- Statistically adjust for bug characteristics
  - Susceptibility to human immunity
- Hard to know if adjustment creates a valid pseudo-trial
Blending PK/PD with Trial Data

• Do a NI randomized trial of old Drug A versus new Drug B
• Measure MIC-A
• Predict AUC-A based on patient characteristics
  – Form log (pAUC-A/MIC-A)
• See if Drug B beats Drug A in patients with large MIC-A, small pAUC-A
  – RCT quality causal evidence
Randomization Creates Similar Groups

Drug A Group

Drug B Group

Total consented

Randomization

A Good AUC-A/MIC-A

A Bad AUC-A/MIC-A
Look for Drug B Effect in Obvious Subgroup

Success Rates by AUC-A/MIC-A ratio

<table>
<thead>
<tr>
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<th>Bad AUC-A/MIC-A</th>
<th>Good AUC-A/MIC-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug B</td>
<td>.93</td>
<td>.98</td>
</tr>
<tr>
<td>Drug A</td>
<td>.52</td>
<td>.98</td>
</tr>
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</table>

B beats A! B has a causal effect!
Analysis of NI UTI trial

• Got data from FDA under a MOU
• NI trial, N=429 patients in UTI subset with complete data & *e. coli* sole pathogen
  – can’t say much else
• Success rates
  – 92.8% Comparator Drug A
  – 97.1% New Drug B
• p-value .072, not significant for superiority
pAUC-A:MIC-A ratio

- MIC to drug A from baseline sample
- Predicted AUC to drug A from an equation
  \[ B_0 + B_1 \text{CrCl} + B_2 \text{Age} + \text{Cl}_{\text{race}} \]
  \[ \text{Cl}_{\text{race}} = (D_1, D_2, D_3, D_4) \]
- Form \( LR = \log \{ \frac{\text{pAUC-A}}{\text{MIC-A}} \} \)

*All from baseline data*
pAUC:MIC predicts Drug A benefit

\[
\frac{12}{23} = 0.52 \\
\frac{195}{200} = 0.98
\]
Drug B beats Drug A in patients with bad AUC:MIC for Drug A.

\[
\frac{25}{27} = 0.93 \\
\frac{12}{23} = 0.52 \\
\frac{175}{179} = 0.98 \\
\frac{195}{200} = 0.98
\]

* \( p = 0.01 \)
Consequences

• Superiority in a region obviates need for historical evidence of a margin
  – Use modern endpoints---e.g. patient reported outcomes
• Superiority demonstrates the trial had assay sensitivity
• Targeting of proven drugs may be possible
  – Use Drug B in AUC:MIC region of proven superiority
  – Go beyond the overall NI pronouncement
  – Requires timely evaluation of pAUC/MIC
Bayesian Paradigm

• A philosophy of statistics different from the common *frequentist* view of statistics of p-values and confidence intervals
• Formally allows blending of knowledge or belief with objective collected data
• Requires specification of *intensity of belief* about prior knowledge: a lot, . . . , a little
• In simple cases, intensity of belief is equivalent to a hypothetical number of patients with data
**Frequentist Analysis of a Trial**

<table>
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<tr>
<td>Drug A</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Drug B</td>
<td>90</td>
<td>10</td>
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Data: 100 subjects per arm

80% probability of success on Drug A versus 90% probability of success rate on Drug B
‘Objective’ Bayesian Analysis of a Trial

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<tbody>
<tr>
<td>Drug A</td>
<td>80 + 1</td>
<td>20 + 1</td>
</tr>
<tr>
<td>Drug B</td>
<td>90 + 1</td>
<td>10 + 1</td>
</tr>
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Data 100 subjects per arm
Prior Belief 50% success rate on A 50% success on B, each worth 2 patients

79% probability of success on Drug A versus 89% probability of success rate on Drug B

Used in RCT to evaluate Zmapp in patients with Ebola Virus Disease
Adaptive trial with good frequentist statistical behavior
Subjective Bayesian Analysis of a Trial

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<tr>
<td>Drug A</td>
<td>80 + 50</td>
<td>20 + 50</td>
</tr>
<tr>
<td>Drug B</td>
<td>90 + 95</td>
<td>10 + 5</td>
</tr>
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</table>

Data 100 subjects per arm
Prior Belief 50% success rate on Drug A versus 95% success rate on Drug B, each worth 100 patients

65% probability of success on Drug A versus 93% probability of success rate on Drug B

Prior belief as important as the collected data
Bayesian Methods

• If prior beliefs are accurate, leads to better estimation & decisions
• If prior beliefs are not accurate, biased conclusions can be drawn
  – *Not great for objectively assessing evidence*
• Specifying intensity of belief is crucial and often unclear in complex settings.
Final Points

• Development of anti-microbial resistance is ceaseless
• PK/PD & Bayesian methods are essential for efficient drug discovery & development
• RCTs ideal way to prove drugs are clinically effective
Acknowledgements

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- Gyan Joshi  NIAID
- John Powers  NIAID
- Scott Evans  Harvard University
References


Total Randomized

Show Noninferiority

Promising Pre-specified Subgroup
Show Superiority

All Randomized Patients
Use AUC instead of pAUC?
Summary

• Tempting to use PK/PD data in patients who all get Drug A to propose a margin
• Hard to know if Drug A has a causal effect on success without a randomized evaluation.
  – Margin may be questionable
Randomizing to Dose allows a causal conclusion about drug effect

Causal effect of Drug

Mix of sick and healthy patients
mix of goodness and bad bugs
A New Path for Licensure

• Decide on a clinically acceptable margin e.g. 10%.

• Licensure supported if
  – NI margin of 10% met
  – Superiority of B over A shown in patients for whom it is a priori most likely

• Large MIC to drug A, Small AUC to drug A