Discordant MIC Analysis: Testing for Superiority within a Non-inferiority Trial

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November 19, 2014
Current Anti-infective Drug Landscape

- Efficacy typically demonstrated with non-inferiority trial: comparing new Drug B to control Drug A

- CI of difference in success rates needs to exceed some *margin* $M$

```
Favors A  Favors B

-M  0

B unacceptably worse  B not unacceptably worse
```
Dual Goal

• Goal 1: Demonstrate Drug B is active (better than placebo)
  – Established indirectly: must know magnitude of A’s benefit over placebo, $M_1$. B must then be within $M_1$ of A

• Goal 2: Demonstrate that Drug B is similar to Drug A
  – By showing difference is less than $M_2$, which is \textit{clinical-judgment} based acceptable loss in efficacy

• To satisfy both goals: $M = \min(M_1, M_2)$
• With current approach: if no historic data sufficient to set $M_1$, no way forward
A Pharmacometric-based Approach to Estimate $M_1$

- Ambrose et al (2012)

- Using a one arm sample of patients treated with Drug A: model and estimate success rates as function of AUC:MIC
  - Estimate success at very high AUC:MIC value
  - Estimate success at very low AUC:MIC (proxy placebo)
  - Difference is considered the treatment effect of A vs placebo

- Lower bound of a 95% CI of this synthetic treatment effect can serve as an estimate of $M_1$
More on One Sample Approach

• But, not a randomized comparison
  – High AUC:MIC patients may be healthier.
  – Low AUC:MIC may identify pathogens that are harder for natural immunity to defeat
  – Crux: we do NOT know how these same patients would do with placebo

<table>
<thead>
<tr>
<th>Drug</th>
<th>Success Rate with Very High AUC:MIC</th>
<th>Success Rate with Very Low AUC:MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>90%</td>
<td>60%</td>
</tr>
<tr>
<td>Placebo</td>
<td>?</td>
<td>?</td>
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</tbody>
</table>
Can We Improve This Strategy with Randomization?

• Hidden within an ordinary non-inferiority anti-infective trial are precious sub-trials well placed to show superiority
Consider Four Interesting Subgroups: Where Overall Success Rates are 80% in Both Arms

MIC Drug A

<table>
<thead>
<tr>
<th>Low MIC Drug A</th>
<th>High MIC Drug A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug B 70%</td>
<td>Drug B 70%</td>
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<tr>
<td>Drug A 90%</td>
<td>Drug A 70%</td>
</tr>
<tr>
<td>Drug B 90%</td>
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<td>Drug A 70%</td>
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</tbody>
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Key Idea: Test for Superiority of B to A Where Most Likely to Find it

• Potentially get evidence of B’s activity DIRECTLY within the trial!
  – Test **superiority** of Drug B to Drug A in the discordant MIC subgroup of patients – who are highly susceptible to B and not so susceptible to A
  – Then, conclude B is active – one of our dual goals

  – Don’t need that hard-to-get historic evidence about the magnitude of A’s benefit over placebo, M₁!

  – Required assumption: A is not worse than placebo in subgroup
    • remember A is approved

• (Focus now on MIC as our marker of success prediction
  – AUC:MIC is trickier – more on this later)
Proposed Demonstration of Efficacy when $M_1$ Unknown

• Recall dual goal:
  – B has activity and B is similar in overall efficacy to A

• Decide on a clinically acceptable margin $M_2$ e.g. 10%.

• Efficacy supported if
  – Overall NI margin of 10% ($M_2$) is met AND
  – Good outcome on pre-specified test of superiority of B over A shown in patients for whom it is a priori most likely
    • High MIC-A/low MIC-B subgroup
    • The patient in the `sweet spot’’ (using Discordant MIC model)
    • Patients with high MIC-A (e.g., Advisory Committee 2012: Televancin vs Vancomycin results in s. aureus and MIC-V>1; p<.05)
Discordant Regression Method

• Only analyzing patients in the Low MIC-B/High MIC-A subgroup is likely to be statistically inefficient
• So, use all data with logistic regression to estimate response surface
• Log odds of success on B to success on A:

\[
\beta_0 + \beta_1 Z + \beta_2 \text{MIC-A} + \beta_3 \text{MIC-B} + \beta_4 Z \text{MIC-A} + \beta_5 Z \text{MIC-B}
\]

  – Z= 1 drug B (0 Drug A)

• Test \( H_0: \beta_1 + \beta_4 a_0 + \beta_5 b_0 = 0 \)
  – Procedure is point-wise, so need to pre-specify a single “sweet spot” (MIC-A=a_0, MIC-B=b_0) to have correct Type I error rate

• Simulations done with 200/arm, range of correlations between MIC-A and MIC-B, range of relationships between MIC & outcome
Patient Got Drug B and had Success

Patient got Drug A and Failed

Sweet Spot B beats A

p = .01
Simulation Study Results Suggest Method Will Have Reasonable Power When:

• Clear relationship *in the trial*:
  – Between MIC-A and success on Drug A, and
  – Between MIC-B and success on Drug B

• Little relationship between response and MIC to *other* drug

• MIC-A and MIC-B are not highly correlated

• Selected sweet spot is a powerful spot to test
Advantages

• Encourages sponsors to design for superiority
  – So that rigor is rewarded instead of punished
  – Try to avoid patients who cure spontaneously or who do not have bacterial disease

• Get *direct* evidence that B has activity, instead of relying on external data
  – External data might not be relevant

• But, challenges remain...
Challenge 1: How to use AUC:MIC ratio?

• AUC: MIC has (much?) stronger relationship to success than MIC
  – Much greater variability within a trial
    • (Side Question: are patients with high MIC to his/her randomized drug tossed out? If yes, is it compatible with ITT?)

• Problems with using AUC:MIC
  – AUC is a post-baseline covariate
  – AUC to A inherently missing in those randomized to Drug B, and vice versa
  – Currently only measured in subset of B – and none in A
Challenge 1: Using AUC:MIC

• Solutions?

• Augmentation:
  – Crossover patients twice to get their AUC to each drug at end of regular follow-up
    • but this requires (strong & untestable) assumptions

• Baseline models (More promising?):
  – Could use baseline characteristics to predict AUC
    • Prediction models exist, but how relevant?
    • If AUC were measured in both arms, could develop within-trial predictions of AUC using baseline data (age, gender, weight,...)
Challenge 2: Selection of Sweet Spot

• The discordant MIC regression analysis is point-wise, and thus to protect Type I error rate, we need to pick a single point *a priori*

• Could use a simultaneous approach to testing, but this is non-targeted and thus much more conservative

• Simple approach: pick observed value that is closest in Euclidean distance to (Max observed MIC-A, 0) point
  – But depending on the true model, this may not be optimal point

• Alternative: adaptive selection of sweet spot, using (half) blinded mixture models looks very promising
Challenge 3: Feasibility

- Enhance power by pooling multiple studies
  - Should not increase usual sample size requirement

- Feasibility probably highly dependent on the context of each given study setting. Evaluate power in Phase 2:
  - Relationship between MIC and outcome within arm
  - Also explore viability of using AUC:MIC
Summary

• New paradigm for demonstrating efficacy if inadequate historic data to know treatment effect of control drug A
  – Pick a clinically acceptable margin for total sample PLUS
  – Test for superiority where it’s most likely to be present

• Encourages a careful design/conduct to show superiority

• Current work:
  – Extension to AUC:MIC
  – Better procedures / sweet spot
  – Consideration of real world feasibility