Non-Inferiority (NI) Clinical Trials: Some Key Considerations in Antibacterial Drug Studies

May 9, 2012

Thomas R. Fleming, Ph.D.

Professor of Biostatistics

University of Washington

Fleming TR. Statistics in Medicine, 27: 317-332, 2008
Fleming TR et al. Clinical Trials 8:432-439, 2011
Some Important Issues

• Many antibiotics provide major clinical benefit in settings such as Pneumonia

• Serious issue if meaningfully less effective antibiotics were used instead

• There can be differences between antibiotics in either “on target” or “off target” effects
There can be Differences between Antibiotics in either “on target” or “off target” effects

- Telithromycin in bronchitis and sinusitis
  ... *liver failure* & *unclear efficacy*

- Daptomycin in CABP
  ... *Pertel: “…not effective for Rx of CABP…”*

- Tigecycline in multiple types of infections
  ... *1/3 increase in mortality rate* (FDA: 9/1/10)

- Iseganan in VAP
  ... *increased trend in mortality*

- Doripenem in VAP
  ... *increased pneumonia deaths*
Doripenem in VAP:  
...Increased Rate of Pneumonia Deaths...

7/16/08 Anti-Infective Drug Advisory Committee Meeting

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Mortality During IV</th>
<th>Pneumonia Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doripenem</td>
<td>223</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>221</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

\[ p = 0.03 \quad \text{and} \quad p = 0.01 \]
Some Important Issues

- Many antibiotics provide *major* clinical benefit in settings such as Pneumonia.
- Serious issue if meaningfully less effective antibiotics were used instead.
- There can be differences between antibiotics in either “on target” or “off target” effects.

⇒ Reliable evaluation of benefit-to-risk profile of new antibiotics is necessary.
Dual Goals of Non-Inferiority Trials

• To enable a direct evaluation of the clinical efficacy/safety of EXP relative to STD

• To contribute evidence to the evaluation of efficacy/safety of EXP relative to PLA

E.g.: Doripenem (EXP) vs. Pip/Tazo (STD)
ICH E9: STD should have clinical efficacy

- that is of **substantial magnitude**
- that is **precisely estimated**
- with estimates that are **relevant** to the setting in which the non-inferiority trial is being conducted
Factors invalidating Constancy Assumption (EXP vs. STD NI Trial vs. Trials evaluating STD)

- patient characteristics
e.g., Disease caused by pathogens resistant to STD in NI Trial

- use of supportive care
e.g., Enhanced concomitant Rx attenuates effect of STD in NI Trial

- dose, schedule, level of adherence
e.g., Lower adherence to STD in NI trial

- efficacy and safety endpoints
  ~ well-defined & reliable ~ clinically meaningful ~ sensitive
Factors invalidating Constancy Assumption

use of supportive care

7/16/08 AIDAC

DORI - 09

Doripenem Adjunctive pseudomonal Rx: ≈ 80%
Pip / Tazo Adjunctive anti-MRSA Rx: ≈ 15%
45% of Dori pts received i.v. & oral therapy

…..FDA: “The evaluation of clinical response for most patients is confounded by the prolonged use of adjunctive amikacin therapy”

...among 109 clinically evaluable cures on Doripenem,

≥ 39 rec’d single agent Doripenem ≤ 2 days...

…FDA: “discuss how the treatment effect of study drug will be determined in patients administered combination antibacterial therapy”
Factors invalidating Constancy Assumption

- use of supportive care

Daptomycin vs. Ceftriaxone in CABP
Clinical Cure Rate in Clinically Evaluable Population

Pertel et al
*CID* 46: 1142-1151, 2008

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>C.R.</td>
<td>n</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>369</td>
<td>79.4%</td>
<td>97</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>371</td>
<td>87.9%</td>
<td>92</td>
</tr>
<tr>
<td>(95% C.I.)</td>
<td>(-13.8, -3.2)</td>
<td>(-6.1, 11.5)</td>
<td>(-18.8, -6.0)</td>
</tr>
</tbody>
</table>

“Daptomycin is not effective for the Rx of CAP…trials to evaluate CAP Rx may need to exclude patients who have rec’d any potentially effective prior Rx …”
Determining the **Margin** in NI Trials

**Goal in NI trials**: Ruling out the new intervention (EXP) is unacceptably worse than a standard (STD) regimen having *reliable* evidence of *substantial* effects…

⇒ Need an ‘evidence based’ NI **Margin**

**Determining the NI margin: Two Key considerations**

- The NI margin should be formulated using adjustments to account for bias or *inherent unreliability* in the estimate of the effect of STD in the non-inferiority trial setting.  
  
  (…*as in superiority trials that are not randomized*…)

- The NI margin should be formulated to preserve an appropriate percentage of the effect of STD.
Community Acquired Pneumonia: Mortality (Non-bacteremic patients, Age > 50)

* Sulfonamide derivatives & penicillin. (Fleming, Powers. CID, 2008)

21-day Mortality

- Antibiotics* 16.1%
- No Specific Rx 49.4%

Consider an EXP in patients who are candidates for Antibiotics:

21-day Mortality

- Experimental Rx 37%
- No Specific Rx 49%

Is a statistically significant, but clinically modest, ↓ in mortality acceptable in patients who are candidates for Antibiotics?
“it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing when:

1. the disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack); or

2. the disease to be treated is a contagious illness that poses serious consequences to the health of others (e.g., sexually transmitted disease).”
ICH E10: “The determination of the margin in a non-inferiority trial is based on both statistical reasoning & clinical judgment, and should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative.”

Some state: ‘We need to streamline the scientific process to reduce the burden on clinical development’
“Opportunity is missed by most people because it is dressed in overalls and looks like work”

Thomas Edison

‘The Good’ should be the enemy of ‘The Unreliable’

When considering the ‘public need’, we should keep in mind: …Not simply “a choice”, rather “an informed choice”…

* Emerson SS, Fleming TR. 2010; Journal of Biopharm Statistics
Probability of a Positive Trial
as a function of true EXP – STD Failure Rate

Scenario #1 (Superiority)  2N = 340 Evaluable pts

\[ \begin{array}{cccccc}
 \text{EXP} & -12 & -10 & -7.3 & -5 & 0 \\
 \text{STD} & .90 & .025 & .025 & .025 & .025 \\
 \end{array} \]

Scenario #2 (Non-Inferiority)  2N = 300 Evaluable pts

\[ \begin{array}{cccccc}
 \text{EXP} & -10 & -5 & 0 & 5.9 & 15 \\
 \text{STD} & .90 & .58 & .18 & .025 & .025 \\
 \end{array} \]

Scenario #3 (Non-Inferiority)  2N = 672 Evaluable pts

\[ \begin{array}{cccccc}
 \text{EXP} & -10 & -5 & 0 & 3.9 & 10 \\
 \text{STD} & .90 & .367 & .025 & .025 & .025 \\
 \end{array} \]

Scenario #4 (Non-Inferiority)  2N = 374 Evaluable pts

\[ \begin{array}{cccccc}
 \text{EXP} & -10 & -5 & -3 & 0 & 2.1 \\
 \text{STD} & .90 & .703 & .238 & .025 & .025 \\
 \end{array} \]