Case studies in the design, analysis and interpretation of non-inferiority trials

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Outline

- Introduction & Background
- Case Studies
  - Altabax – a topical antibiotic
  - Arixtra – an anticoagulant
  - Taxus Liberté – a medical device
- Summary
US Congressional Investigation

- September 2006: US Congressional Committee questions the FDA for use of non-inferiority trials as proof of efficacy for antibiotics due to concerns about
  - design and limitations of non-inferiority trials
  - difficulties in interpreting NI trials due to lack of internal validity in contrast to superiority trials
- Investigation triggered by post-marketing hepatic and cardiovascular adverse events observed with telithromycin
  - FDA withdraws approval for ABS and AECB
- Use of NI trials questionable for indications with high rate of self resolution
- No issues with use of NI trials for serious diseases such as CAP or complicated skin infections
Impact on Sponsors of New Drugs

- Increased scrutiny in the application of non-inferiority designs
- Protocol, study design and analysis plans previously reviewed and agreed by the FDA no longer acceptable
- Sponsors asked to provide rationale for non-inferiority trial and re-justification of margin
- Additional/adequate and well controlled trial(s) requested to support approval of new drugs
Key Statistical Issues in the Design of NI Trials

- Choice of control group
- Constancy of control treatment effect
- Estimation and variability of control treatment effect
- Assay Sensitivity
- Selection of non-inferiority margin
History of ∆ Selection

FDA AI Division 1992 Points to Consider - Step Function Approach

<table>
<thead>
<tr>
<th>Success Rate</th>
<th>∆</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 - 100%</td>
<td>10%</td>
</tr>
<tr>
<td>80 - 89%</td>
<td>15%</td>
</tr>
<tr>
<td>70 - 79%</td>
<td>20%</td>
</tr>
</tbody>
</table>

1998 FDA Advisory Committee proposed:
- ∆ must be clinically relevant and indication specific
- discuss with agency during protocol development
- provide rationale for selection of control arm

In 2001, the FDA adds disclaimer that PTC approach (step function) will be phased out
1997 CPMP “Guidance on evaluation of AI products”

- $\Delta = 10\%$ for “common non-serious infections”
- Smaller $\Delta$ for very high cure rates
- Based on minimum clinically relevant difference
A new class of antibiotic for uncomplicated skin and soft tissue infections: SITL, SID & Impetigo

- 2 SITL and 1 SID NI trials, each against cephalexin ($\Delta = 10\%$, event rate 90%)
- Impetigo: one NI trial against fucidin ($\Delta = 10\%$, event rate 90%) and one placebo controlled trial

2004: SITL & SID protocols reviewed and agreed by the FDA including the non-inferiority margin

Jun-06: FDA asks the sponsor to justify the non-inferiority margin

FDA uses a 1984 mupirocin study to derive the treatment effect and concludes 10% $\Delta$ not justifiable
## Results

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>Population</th>
<th>T-C (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITL</td>
<td>I</td>
<td>PPC</td>
<td>-3.2</td>
<td>(-7.4, 0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ITTC</td>
<td>1.1</td>
<td>(-3.9, 6.0)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>PPC</td>
<td>-1.6</td>
<td>(-5.8, 2.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ITTC</td>
<td>0.0</td>
<td>(-4.5, 4.6)</td>
</tr>
<tr>
<td>SID</td>
<td>III</td>
<td>PPC</td>
<td>-3.8</td>
<td>(-9.9, 2.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ITTC</td>
<td>-3.4</td>
<td>(-9.7, 2.9)</td>
</tr>
</tbody>
</table>

- All three studies met the protocol defined objective (10% margin)
- SITL approvable - additional adequate and well controlled trial needed, implying need a placebo-controlled trial
- SID not approved
Issues

- \( \Delta \) chosen based upon step function approach – guidance in force at the time
- No historical placebo controlled trials against cephalexin
- Unable to establish cephalexin effect and hence the non-inferiority margin
- Conclusion: must conduct a placebo controlled trial to support approval in SITL
- Problem/challenge: investigators not willing to participate in a placebo trial for ethical reasons
  - highly effective antibiotic with >90% success rate
  - not willing to expose patients to placebo
- Changes in study design issues under consideration for a placebo controlled study in order to meet regulatory acceptance and investigators’ compliance
ARIXTRA®, an anti-coagulant already approved for a variety of indications

Currently pursuing a new indication for the treatment of unstable angina/non ST-segment elevation (UA/NSTEMI)

OASIS-5 - study supporting this new indication:
- 20,000 patient, non-inferiority study comparing ARIXTRA to Lovenox; primary endpoint composite of death/myocardial infarction/refractory ischemia
At End of Phase 2 meeting, FDA reviewed and provided feedback on study design and statistical methods:

- patient population and sample size adequate
- no comments on the non-inferiority margin
- “for a non-inferiority...one trial is not sufficient to determine safety and efficacy…”

Sponsor’s Understanding:

- agency agreed with the non-inferiority margin
- no mention if one non-inferiority study would not be sufficient
To clarify the discrepancy, “Type A” meeting:
- a single non-inferiority study could be adequate to support a new indication if issues such as choice of non-inferiority margin, possibility of changes in medical practice, comparability of patient populations, assay sensitivity are adequately addressed

Sponsor confident that the chosen margin was conservative, and proceeded with OASIS-5
Supplement Submitted

- Supplemental NDA submitted included detailed justification for the margin and addressed complications noted earlier by the FDA.

- FDA issues approvable letter
  - In establishing the effect of the active control based on historical studies, limited consideration given to accounting for between-study variability.
  - FDA recalculated the effect size accounting for variability to come up with a narrower margin (1.06 vs 1.185).
  - With an upper confidence interval of 1.13, study couldn’t be considered a positive study.
Sponsor response to the non-inferiority margin

- Margin chosen was strict yet clinically meaningful
- Approach used to define the pre-specified NI margin of 1.185 using fixed effects meta-analysis methodology is the most appropriate
  - FDA used random effects methodology which has limitations when applied to meta-analyses of small # of trials and trials with low event rates
- Across multiple efficacy endpoints and timepoints, the high degree of consistency further supports that there is no reason to suspect departure from non-inferior efficacy between the two drugs
- Concludes…margin was conservative and appropriate and the strength of the clinical data supports non-inferiority

FDA and sponsor discussion continues!
Key Learnings

- Importance of obtaining regulatory agency agreement upfront
- Justification of non-inferiority margin is crucial, including methodology used to compile historical trials and meta analysis used to derive the estimate of active control effect
- A single non-inferiority study to support a new indication or approval of a new drug carries significant risk
TAXUS® Liberté

- TAXUS® Liberté – a coronary stent (medical device) recently approved by the FDA in Oct 2008

- A paclitaxel-eluting stent system to improve luminal diameter for the treatment of *de novo* lesions in the native arteries

- TAXUS ATLAS: pivotal phase III study supporting this indication
  - 871 patient, single-arm, non-inferiority trial to compare TAXUS Liberté Stent to TAXUS Express Stent in subjects indicated for PCI or CABG
  - Objective is to demonstrate non-inferiority of TAXUS Liberté to TAXUS Express using case-matched historic control data derived from TAXUS IV (662 patients) and TAXUS V (329 patients) *de novo* studies
  - Primary endpoint for the study is 9-month target vessel revascularization (TVR) rate®
  - Non-inferiority margin is 3%
Results

<table>
<thead>
<tr>
<th></th>
<th>TAXUS Liberté</th>
<th>TAXUS Express</th>
<th>Difference (Upper 95% CI)</th>
<th>p-value</th>
<th>△</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>7.95% (68/855)</td>
<td>7.01% (67/956)</td>
<td>0.94 (2.98%)</td>
<td>0.0487</td>
<td>3%</td>
</tr>
<tr>
<td>ITT</td>
<td>8.03% (69/859)</td>
<td>7.14% (69/967)</td>
<td>0.90 (2.94%)</td>
<td>0.0454</td>
<td>3%</td>
</tr>
</tbody>
</table>

Since upper bound of the 95% CI < 3%, sponsors claims non-inferiority is demonstrated with p-value < 5%
- Wald’s method used to calculate the CI
- Methodology defined upfront in the protocol and agreed by FDA

WSJ reported, per several reputed academic statisticians, Wald method is flawed as it “overstates the certainty” of clinical results
- Variance must be estimated assuming true difference is 3%, not 1% as observed, which gives the upper bound of the 95% CI as 3.0183% (p-value = 0.0515) => non-inferiority can not be claimed
FDA’s medical device branch: WSJ analysis raises “good question” but declines to comment on the trial or the Liberté Stent, and calls the calculation approach “a standard methodology”

Studies designed to satisfy FDA’s medical device branch are generally much less rigorous than those for US approval of drugs – in part due to a 1997 federal law that requires device manufacturers for the “least burdensome appropriate means” of proving new device works

- Active control NI trials are required only for novel devices
- Non-inferiority margin based on consensus between the sponsor and the agency (objective performance criteria)
- For all other devices, single arm, case-matched historic control trials are acceptable
Selection of Δ

Information should be obtained from:
- preferably from multiple placebo controlled trials with same design, population etc as NI trial
- single placebo-controlled trial – may be acceptable
- single/multiple trials with different designs – questionable value
- no information to estimate Δ₁ – hard to justify NI trial

Precision and constancy of control effect is critical in defining Δ₁ and in turn Δ₂
Major Challenges

- What if no placebo controlled data exist?
- Indications where treatment effect is modest but not precisely known?
- Serious indications with low incidence?
Suggested Solutions

- Consider superiority trial design as an alternative to NI trial design – stronger evidence and potentially smaller sample size

- If no serious harm in delaying treatment, it may be possible to randomize patients to placebo with early escape/rescue
  - If no improvement at early blinded assessment, treat as treatment failure and switch to standard care

- Three arm design: test drug, active control and placebo
  - Not necessary to predefine margin
  - Built-in assay sensitivity
  - Tests both superiority and non-inferiority

- Compare Test drug (target dose) against Test Drug (low/ineffective dose) which could address ethical concerns
Summary

- Many issues in the design and interpretation of non-inferiority trials
- Choice of active control: to prevent potential “bio-creep”, active control should be consensus standard of care
- Selection of non-inferiority margin is critical: must be based on both clinical judgment and statistical consideration
- Selection of margin should reflect uncertainties in the evidence on which selection is based and should be conservative
- Consider alternate designs when historical information on control effect is of concern
References

