Conducting Clinical Studies in Low Incidence/Rare Conditions: Scientific Challenges and Study Design Considerations

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Disclosure

• I am a full time employee of CTI Clinical Trial and Consulting Services, an international contract research organization that delivers a full spectrum of clinical trial and consulting services to the pharmaceutical and biotechnology industry.
"In other words, statistics prove that statisticians aren’t always right."
Scientific Challenges

• Very few epidemiologic studies have been performed describing the occurrence of AMR

• Reported incidence varies depending on:
  • Type of organ transplanted
  • Local practice
    • diagnostic criteria & clinical protocol
  • Period studied
  • Patient population/Geographic region
  • Clinical follow-up and management
Scientific Challenges (cont’d)

- Requires multi-center, multi-country participation
  - Inherently different healthcare systems, treatment options, and management approaches
- Study design and analysis complexity
- Prevention versus treatment
  - What defines success?
  - What defines enrollment criteria?
Regulatory Challenges

- No special methods for designing, carrying out or analyzing clinical trials in low incidence/rare conditions
  - Guidelines relating to common diseases are also applicable to rare conditions
- **Choice of endpoints**
  - Reliable & assessed consistently
  - Surrogate endpoints may be applicable but need to be fully justified
- **Choice of comparator group**
  - Ethics of randomization (Clinical equipoise/Uncertainty principle)
  - Historical controls
- **Sufficient sample size**
  - Minimize noise-to-effect ratio
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Location/setting</th>
<th>Number/Type of Patients</th>
<th>AMR Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marlo et al., 2011</td>
<td>Multicenter systematic review, 2000-2010 studies</td>
<td>725 patients in 21 studies</td>
<td>AMR 28% at 2-year median follow-up</td>
</tr>
<tr>
<td>Naesens et al., 2012</td>
<td>RCT Multicenter (US)</td>
<td>130 pediatric KTx</td>
<td>AMR 6.8% at 3-years post-transplant</td>
</tr>
<tr>
<td>Lefaucheur et al., 2013</td>
<td>Cohort (consecutive patients) Paris, FR 1998-2008</td>
<td>2,079 All ABOc and XM-Biopsies for indication in course of clinical care</td>
<td>Acute AMR 6.6%, occurring at median of 3.1 months post-transplant</td>
</tr>
<tr>
<td>Djamali et al., 2013</td>
<td>Cohort (consecutive patients) Madison, WI 2009-2011</td>
<td>146 “Moderately sensitized” (XM-, undergoing desensitization)</td>
<td>AMR 12% and mixed rejection 6% at mean follow-up 18 months</td>
</tr>
<tr>
<td>Malheiro et al., 2015</td>
<td>Cohort (consecutive patients) Single-center (Portugal)</td>
<td>462 (40 DSA+)</td>
<td>AMR 4% at 1-year post-transplant AMR in DSA+ KTx=35%</td>
</tr>
<tr>
<td>Vo et al., 2015</td>
<td>Cohort Single-center (US)</td>
<td>226 highly sensitized; desensitization with IVIG + rituximab</td>
<td>AMR 20% at mean follow-up 36 months</td>
</tr>
<tr>
<td>Burkhalter et al., 2016</td>
<td>RCT Single-center</td>
<td>35 patients DSA+, XM-</td>
<td>AMR (clinical/subclinical) 27% at 1-year post-transplant</td>
</tr>
<tr>
<td>Ferrandiz et al., 2016</td>
<td>Cohort Multicenter (France)</td>
<td>390 Non-HLA-sensitized, ABOc</td>
<td>AMR 4.4% at 1-year post-transplant</td>
</tr>
<tr>
<td>Calp-Inal et al., 2016</td>
<td>Cohort (consecutive patients) Single-center (US)</td>
<td>284, DSA-</td>
<td>AMR 45% at median follow-up of 2.5 years</td>
</tr>
</tbody>
</table>
Conventional Phase III Trial
Fixed Design

Anticipated proportion of first occurrence of AMR at one-year post-KTx in Control: 9.0%; 95% CI=4.7%,16.5%
Anticipated proportion of first occurrence of AMR at one-year post-KTx in Experimental: 1% to 8.0%
Power=80%
Type I error=0.05 (two-sided)
Test statistic: Chi-square

50% relative reduction in AMR requires n=487 subjects per group
Key Considerations in Overcoming Challenges

• Goal: Design a trial with an acceptable compromise between (i) level of scientific evidence and (ii) feasibility in terms of trial size and duration

• Key considerations at the design stage:
  • Enrichment strategies
  • Adaptive Designs
  • Surrogate endpoints
  • Composite endpoints
  • Bayesian methods
Design Stage
Enrichment Strategies

*Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2016.101
Design Stage
Decrease Heterogeneity

• Include subjects that have certain characteristics that put them at risk
  • Example:
    • Class II HLA epitope mismatch
    • Patients likely to be medication compliant

• Characteristics need to be agreed to by the regulatory agency:
  • Example:
    • Quantitative measures of pre-transplant DSA levels
    • > pre-determined threshold value

• Limit the number of sites
Design Stage
Prognostic Enrichment

- Select subjects with a greater likelihood of occurrence of AMR (event-driven study) or a substantial worsening of renal function (for continuous measurement endpoints e.g., change in estimated GFR)
- Characteristic or measurement process needs to be validated and agreed to by the regulatory agency
Risk of Antibody Mediated Rejection Highly Sensitized Patient

Vo et al., Transplantation 2015; 99: 1423-1430
Risk of Antibody Mediated Rejection
Peak HLA DSA Risk Stratification

# Sample Size Under Prognostic Enrichment

<table>
<thead>
<tr>
<th>Background Rate AMR</th>
<th>Relative Reduction in AMR with Treatment</th>
<th>Sample Size per Group$^1$</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.09</td>
<td>50%</td>
<td>487</td>
<td>1</td>
</tr>
<tr>
<td>0.20</td>
<td>50%</td>
<td>200</td>
<td>0.41</td>
</tr>
<tr>
<td>0.30</td>
<td>50%</td>
<td>121</td>
<td>0.25</td>
</tr>
<tr>
<td>0.40</td>
<td>50%</td>
<td>82</td>
<td>0.17</td>
</tr>
<tr>
<td>0.50</td>
<td>50%</td>
<td>58</td>
<td>0.12</td>
</tr>
</tbody>
</table>

1. Test statistic=Chi square; Power=80%; type I error=0.025 (one-sided significance)
Sample Size Under Prognostic Enrichment Peak Pre-transplant HLA-DSA

Figure 1

Relevant Event Rate Among Biomarker-Positive Patients

![Graph showing event rate vs. percent of patients screened from trial.]

Figure 2

Clinical Trial Total Sample Size

![Graph showing total sample size vs. percent of patients screened from trial.]

<table>
<thead>
<tr>
<th>Input Name</th>
<th>Input Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background rate of any type of AMR</td>
<td>0.09</td>
</tr>
<tr>
<td>Percent reduction in AMR rate under treatment</td>
<td>50</td>
</tr>
<tr>
<td>Form of alternative hypothesis</td>
<td>one.sided</td>
</tr>
<tr>
<td>Type I error rate</td>
<td>0.025</td>
</tr>
<tr>
<td>Power</td>
<td>0.8</td>
</tr>
<tr>
<td>AUC</td>
<td>0.9</td>
</tr>
</tbody>
</table>

2. Package ‘BioPET’ in R
Choose people more likely to respond to treatment (probable responders)

Based on:

- Patient characteristics related to a study drug’s mechanism (pathophysiology, proteomic/genomic)
- Response of a biomarker
- Past response to the test drug (e.g., randomized withdrawal study)

### Design Stage

#### Predictive Enrichment

<table>
<thead>
<tr>
<th>Prevalence of Marker Positive Patients</th>
<th>Response in Marker-negative Patients (0% of marker positive response)</th>
<th>Sample Size Ratio</th>
<th>Sample Size Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0%</strong></td>
<td><strong>50%</strong></td>
<td><strong>1.0</strong></td>
<td><strong>1.0</strong></td>
</tr>
<tr>
<td><strong>75%</strong></td>
<td><strong>1.3</strong></td>
<td><strong>1.8</strong></td>
<td><strong>4</strong></td>
</tr>
<tr>
<td><strong>50%</strong></td>
<td><strong>1.8</strong></td>
<td><strong>2.6</strong></td>
<td><strong>16</strong></td>
</tr>
<tr>
<td><strong>25%</strong></td>
<td><strong>2.6</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Predictive Enrichment
Adaptive population-enrichment

Design Stage
Randomized Withdrawal Study

- Subjects receiving a test treatment for a specified time are randomly assigned to continued treatment or to placebo (i.e., withdrawal of active therapy)
Design Stage
Three-stage Trial Design

Honkanen et al. Statist Med 2001; 20: 3009-3021
Biomarker/Surrogate Endpoints

- A biomarker intended to substitute for a clinical endpoint (patient and graft survival) and expected (is reasonably likely) to predict clinical benefit/outcome
- Easy to quantify and measure, reproducible, not subject to wide variation in the general population and unaffected by co-morbid factors
- Composite surrogate endpoints:
# Biomarker/Surrogate Endpoints

<table>
<thead>
<tr>
<th>Potential Surrogate Endpoints&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Change in GFR</td>
<td>- Timing? 1, month, 6 months or 1 year post-transplant</td>
</tr>
<tr>
<td>- GFR &lt; 30 ml/min</td>
<td>- Near term change may not be a good correlate with long-term allograft survival (5-, 10-years?)</td>
</tr>
<tr>
<td>- Post-transplant DSA</td>
<td>- Measurement - Reliability/Validity?</td>
</tr>
<tr>
<td>- Variable incidence</td>
<td>- Timing?</td>
</tr>
<tr>
<td>- Non-adherence potential confounder</td>
<td>- Variable incidence</td>
</tr>
<tr>
<td>- Cd4 positive stain plus TG+</td>
<td>- Non-adherence potential confounder</td>
</tr>
<tr>
<td>- Banff CG score</td>
<td>- May not correlate with long-term allograft survival</td>
</tr>
<tr>
<td></td>
<td>- Prognostic significance not clearly elucidated</td>
</tr>
</tbody>
</table>

What about a Composite Surrogate Endpoint?

- Assumptions:
  - Individual components of the composite are clinically meaningful and of similar importance to the patient
  - The expected effects on each component are similar, based on biological plausibility
  - The clinically more important components of composite endpoints should at least not be affected negatively

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Statistical precision and efficiency</td>
<td>– Individual components are not always clinically meaningful</td>
</tr>
<tr>
<td>– Trial are smaller and less costly</td>
<td>– Problems of non-validated surrogate endpoints</td>
</tr>
<tr>
<td>– Results of promising therapies could be available earlier</td>
<td>– Differential distribution of the individual components makes interpretation difficult</td>
</tr>
<tr>
<td></td>
<td>– Including a component that is insensitive to treatment increases variability</td>
</tr>
<tr>
<td></td>
<td>– Potential bias due to competing risks between endpoints</td>
</tr>
</tbody>
</table>

Kleist P. Applied Clinical Trials 2006
EXHIBIT 2
Additional Reasons For The Unreliability Of Proposed Surrogates: Disease Processes Having Multiple Causal Pathways And Interventions Having Mechanisms Of Action Independent Of The Disease Process


Summary

• Therapeutic development in AMR present many challenges:
  • Incomplete understanding of AMR to inform trial design
  • Need for alternatives to the traditional randomized controlled clinical trial
  • Requirement for more sensitive and creative outcome measures
    • Biomarkers/surrogate endpoints
    • Non-biologic measures such as time-off dialysis or Quality of Life
  • Difficulties of recruiting a small sample to participation:
    • Due to unpredictable occurrence of AMR
    • Recruiting a control group
Summary – cont’d

- **Solutions require:**
  - Multi-collaboration among stakeholders (Transplant community, Sponsors, Regulatory agency)
  - Regulatory acceptance of biomarkers
  - Creative or non-traditional endpoints
  - Alternative trial designs e.g., adaptive, withdrawal, historical controls
  - Leveraging existing resources (e.g., transplant registry, clinical trial data)