Methodological Challenges in PreclSE

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• PrecISE (Precision Interventions for SEvere asthma)
• Collaborative Studies Coordinating Center (CSCC) at the Department of Biostatistics UNC at Chapel Hill was awarded $61 million by the National Heart, Lung and Blood Institute in September 2017

NHLBI stated the following objectives for PrecISE
1. Run a controlled clinical trial to evaluate efficacy of several novel interventions in severe asthma patients
2. Use precision medicine approaches
3. Trial design needs to be adaptive
Precision medicine approaches in severe asthma

Several asthma treatment recently approved by the FDA:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FDA approval</th>
<th>Approved for</th>
</tr>
</thead>
<tbody>
<tr>
<td>FASENRA (benralizumab)</td>
<td>2017</td>
<td>Eosinophilic phenotype, blood eosinophils ≥300 cells/μl</td>
</tr>
<tr>
<td>DUPIXENT (dupilumab)</td>
<td>2018</td>
<td>Eosinophilic phenotype, blood eosinophils ≥300 cells/μl</td>
</tr>
<tr>
<td>Tezspire (tezepelumab)</td>
<td>2021</td>
<td>Unselected population, but better treatment effect was seen in patients with blood eosinophils ≥300 cells/μl</td>
</tr>
</tbody>
</table>
Interventions that are being evaluated in PrecISE in patients with severe asthma

- **Imatinib** (brand name Gleevec) is an oral chemotherapy to treat patients with cancer
- **Clazakizumab**, a novel therapy currently being investigated in psoriatic arthritis. Not yet approved for any indication
- **Cavosonstat**, a novel treatment, was investigated in cystic fibrosis but did not demonstrate benefit
- **Broncho-Vaxom** is known to support respiratory tract resistance to bacterial infections, has been used in Europe for the last two decades
- **Medium chain triglycerides** (MCT), a food supplement
## Biomarker positive subgroups

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Subgroup</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Eos &lt; 300</td>
<td>62%</td>
</tr>
<tr>
<td>Clazakizumab</td>
<td>IL-6 &gt; 3.1</td>
<td>33%</td>
</tr>
<tr>
<td>Cavosonstat</td>
<td>Genotypes</td>
<td>64%</td>
</tr>
<tr>
<td>Broncho-Vaxom</td>
<td>Eos ≥ 300</td>
<td>38%</td>
</tr>
<tr>
<td>MCT</td>
<td>FeNO ≥ 15 ppb</td>
<td>64%</td>
</tr>
</tbody>
</table>

Eos = blood eosinophils count  
IL-6 = interleukin 6  
FeNO = fractional exhaled nitric oxide
PrecISE is a multi-period crossover trial

Option 1: N of 1

Option 2: a sequence of 2-period crossovers

Option 3: one random placebo

16-week long periods with 4-week washouts
2 - 6 treatment periods for each participant depending on the time of entry to the study.
PrecISE is a multi-period crossover trial

Option 1: N of 1

Option 2: a sequence of 2-period crossovers

Option 3: one random placebo

PrecISE: 2-period crossover followed by a sequence of active treatments with possibly 1 more placebo
### Other design decisions

- An inclusion of active control
  - Decided not to include
- Number of primary endpoints
  - 3
- Uncertainty about the value of within subject correlation
  - Interim analysis to estimate correlation

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Placebo</td>
<td>Placebo</td>
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<td>Placebo</td>
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<table>
<thead>
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<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
<th>Period 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the first two periods, patients receive the same intervention in active and placebo forms (random sequence).</td>
<td>In subsequent treatment periods, patients will be randomized to different interventions. Participants may also be randomized to receive placebo in periods 3-6, such that on average, 20% of participants will receive a 2nd placebo.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study design in each arm

- Proportion of biomarker positive (A+) and negative participants (A-)
- Test in A+ only? in A-? in unselected?

Recent clinical trials in severe asthma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Trials</th>
<th>Trial Design</th>
<th>Primary and Secondary Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FASENRA (benralizumab)</td>
<td>CALIMA, SIROCCO</td>
<td>66% with blood eos ≥300*</td>
<td>Primary analysis in blood eos ≥300</td>
</tr>
<tr>
<td>DUPIXENT (dupilumab)</td>
<td>LIBERTY ASTHMA QUEST</td>
<td>44% with blood eos ≥300*</td>
<td>Primary analysis in unselected Prespecified subgroup analyses in blood eos ≥300</td>
</tr>
<tr>
<td>Tezspire (tezepelumab)</td>
<td>NAVIGATOR</td>
<td>50% with blood eos ≥300*</td>
<td>Primary analysis in unselected Prespecified subgroup analyses in blood eos ≥300</td>
</tr>
</tbody>
</table>

*Population prevalence of eosinophilic phenotype (blood eos ≥300) in severe asthma is 38%
How to design a trial with a biomarker defined subgroup?

• Phase 2 approach to designing a trial with a subgroup:
  • The goal is to show that the treatment effect is significantly different from 0 in a biomarker negative subgroup (A-) and/or a biomarker positive (A+)
  • The easiest is to run 2 parallel trials: in A- and A+
  • More efficient options are available (Freidlin et al., 2013; Parashar et al., 2016)

• Phase 3 approach to designing a trial with a subgroup:
  • The goal is to show that the treatment effect is significantly different from 0 in unselected population (A- and A+ combined) and/or in A+
  • The most efficient way is run a trial in A+ only
  • However, it is often desirable to enroll participants according to population prevalence (Rosenblum and Qian, 2016; Rosenblum et al., 2016, Dmitrienko et al., 2017)
Phase 2 versus phase 3 approach

- Phase 2 enrolls to A- and A+ according to the required allocation proportion
- Phase 3 enrolls according to the population prevalence

- Phase 3 approach requires 20-50% less participants
  - even more participants need to be screened to find the required number of A- and A+ participants

- When A+ prevalence is high, Phase 3 approach is likely to conclude that the treatment is effective in unselected population when only A+ shows activity (Rothmann et al., 2012)
Approaches we considered to design PrecISE

• Enroll A+ only
  • Advantage: will be able to utilize study resources in the most efficient way
  • Disadvantage: This design is not responsive to the Request for Application (RFA) since there is no precision medicine component

• Enroll A- and A+ according to the population prevalence and test for treatment effect in unselected and in A+ (Phase 3 approach)
  • Advantage: responsive to the RFA since we can update the biomarker cut-off during the trial (if we can halt enrollment to an intervention) or in a post-hoc analysis
  • Disadvantage: Not enough power for interventions with small subgroup
PrecISE Study Design

• Test for efficacy in A+ only
  • No testing for treatment effect in A- or in unselected population

• Enroll more participants from A+ than A-, **2:1 ratio A+/A-**, this is to update the biomarker cut-off (precision medicine component)
  
  • If the biomarker cut-off is re-estimated during the trial, test for treatment effect in the combined sample of old A+ (before cut-off re-estimation) and a new A+ (after cut-off re-estimation)

• Imatinib, cavosonstat, and MCT have subgroup prevalence of 64%, enrolling according to population prevalence (as in LIBERTY ASTHMA QUEST trial)
• Clazakizumab and Broncho-Vaxom have subgroup prevalence of 38% and 33%, need to oversample A+ (as in CALIMA and SIROCCO trials)
How to define the best subgroup?

• Definition 1. The best subgroup is defined as the largest subgroup with a treatment effect of at least $\Delta$.

• Definition 2. The best subgroup is defined as the subgroup maximizing

$$U = \text{Treatment effect} \times \text{Prevalence}^\gamma$$

- When $\gamma = 0$, the treatment effect is maximized.
- When $\gamma = 0.5$, the power is maximized.

• In PrecISE, we use $\gamma = 0.5$ due to the new cut-off being applied prospectively to baseline data of participants already on the treatment.
How to update the cut-off at the interim and final analysis?

When updating a cut-off of a single biomarker, a non-parametric approach performed the best (Joshi et al., 2019)

**Non-parametric approach**: select the subgroup that maximizes

\[ U = \text{Treatment effect} \times \text{Prevalence}^\gamma \]

When \( \gamma = 0.5 \), select the subgroup with the largest test statistic
How to adjust for multiplicity in post-hoc subgroup analysis?

- Cross-validation and bootstrap (Simon, 2008; Zhang, et al., 2017)
- Bootstrap (Guo et al., 2020)
PrecISE

• First participant screened Dec 2019
• First participants randomized Aug 2020
• 136 participants have been randomized as of April 1, 2022
• Target sample size 500
References


