ALA-ACRC Overview and Ongoing Studies

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AAAAAI Annual Meeting
February 24, 2013
Mission of the ACRC

• To conduct clinical trials in diverse populations of people with asthma that will improve asthma care.
Strategic Goal of the ACRC

• To conduct straightforward clinical trials that will have an impact on clinical decision making and have an impact on clinical guidelines
ACRC Centers
Organization of the ALA-ACRC

- 18 Centers with 24 sites
- Coordinating center
- Core support by American Lung Association
- Support for clinical trials from investigator-initiated grant applications to NIH, Industry
Organization of the ACRC

- American Lung Association
  - Research Advisory Committee
    - ALA-ACRC Steering Committee
      - Data Coordinating Center
      - Clinical Centers
    - Data and Safety Monitoring Board
      - Executive Committee
Ongoing Trials

- **SOYA** - Soy genistein in poorly controlled asthma
- **STAN** – Nasal steroids for poorly controlled asthma in pts with perennial rhinosinusitis
- **CPAP** – CPAP to reduce airways reactivity in asthma
- **LASST** – Optimal stepdown therapy on pts well-controlled on LABA/ICS
SOYA (Soy Isoflavones in Asthma)

• Background
  – Intake of soy associated with better lung function and improved asthma control among asthmatics
  – Lower incidence of asthma in countries with high soy intake
  – Reduction in allergic inflammation in animal models with soy isoflavone genistein via tyrosine-kinase inhibition
  – Human asthmatics show reduced LT synthesis by eosinophils after ingestion of soy isoflavones
ACRC SIIVA Study: Association Between Soy Genistein Intake and Lung Function

No soy genistein intake vs. 1-249 µg/1000 Kcal vs. >250 µg/1000 Kcal

P<0.006

P<0.009
Soy Isoflavone Consumption Reduced *Ex Vivo* LTC₄ Synthesis by Blood Eosinophils

Decreased 33%
p = 0.02
FENO Decreased After 4 Weeks of Soy Isoflavone Supplementation

Decrease 17%
p = 0.03
SOYA

- Question: Does ingestion of 100 mg of Soy isoflavones improve FEV1 and other measures of asthma control in patients with poorly controlled asthma?
- Design: Parallel double-masked RCT, n=380
- Treatments: Soy Isoflavones (Novasoy®) 100 mg vs. placebo. 6 month f/u
- Primary outcome: FEV1
- Secondary outcomes: FeNO, Asthma control, methacholine reactivity, inflammatory biomarkers
- Status: Final Data Cleaning, Data presentation May 2013
SOYA Study Design

Screen

Soy Isoflavone

Placebo

Randomize

Follow-up Visits

V1 V2 V3 V4 V5 V6 V7 V8 V9

24 weeks
Nasal Steroids in Asthma (STAN)  
Background  
• 40-70% of asthmatics have either rhinitis or sinusitis or both  
• Nasal allergen challenge induces inflammatory changes in lower airway  
• Treatment with nasal steroids decreases expired NO  
• Small studies have suggested benefit of treating rhinitis, but results are inconclusive
STAN

• **Question:** Does treatment of perennial rhinosinusitis with nasal topical steroid (mometasone) improve asthma control in patients with inadequately controlled asthma?

• **Design:** Parallel double-masked RCT, n = 380, 50% adults, 50% children, 6 month f/u

• **Primary outcome:** Asthma Control (ACT, cACT)

• **Secondary outcomes:** Asthma diaries, FeNO, FEV1, Methacholine reactivity

• **Status:** Completing Follow-up April 2013
STAN – Study Schema

V1, V1a (-2 to -1 wks)  V2 (0 wk)  V3 (4 wks)  P1 (8 wks)  V4 (12 wks)  P2 (16 wks)  P3 (20 wks)  V5, 5a (24 wks)

Screen  RZ  Nasal Steroid  Placebo

6 months

V1-V5: Clinic visits
P1-P3: Phone Visits
V1a, V5a: Methacholine testing
SNQ for diagnosis of perennial rhinosinusitis

Over the last 3 months how often, on average, did you have the following symptoms?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>1 - 4 times per month</th>
<th>2 - 6 times per week</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Runny Nose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post nasal drip</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need to blow your nose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial pain/pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nasal obstruction</td>
<td></td>
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</tbody>
</table>

Scoring: Never (0), 1-4 times per month (1), 2- 6 times per week (2), and daily (3).

Score reported as average of 5 items: range of possible scores 0 - 3.
Diagnosis of Rhinosinusitis by SNQ

ROC Curves for 7 Measurements

<table>
<thead>
<tr>
<th>Measurement</th>
<th>AUC (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>SSS Score</td>
<td>0.82 (0.70, 0.92)</td>
</tr>
<tr>
<td>RQLQ</td>
<td>0.89 (0.80, 0.96)</td>
</tr>
<tr>
<td>SNOT20</td>
<td>0.84 (0.72, 0.94)</td>
</tr>
<tr>
<td>6-item</td>
<td>0.97 (0.92, 1.00)</td>
</tr>
<tr>
<td>SNQ</td>
<td>0.97 (0.93, 1.00)</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>0.71 (0.56, 0.83)</td>
</tr>
<tr>
<td>CT</td>
<td>0.78 (0.64, 0.89)</td>
</tr>
</tbody>
</table>
CPAP (Continuous Positive Airway Pressure for Asthma)

• Background
  – Mechanical stretch of airway smooth muscle increases $L_0$ and decreases airway reactivity
  – CPAP in animal models of asthma decreases airways reactivity
  – Nocturnal CPAP x 1 week in humans with asthma decreases airways reactivity
CPAP for 1 week decreases airways reactivity

CPAP

• Questions
  – Does nocturnal CPAP decrease airways reactivity?

• Study Design
  – Randomized Trial, n = 192, f/u = 3 months
  – Treatments: CPAP sham, 5, 10 cm H₂O

• Primary outcome: Methacholine PC_{20}

• Secondary outcomes: Adherence, tolerability

• Current Status: Actively enrolling
LASST (Long-acting beta agonist step-down trial)

• **Background**
  – Guidelines for stepping down ICS/LABA asthma therapy are conflicting
  – Previous studies have focused on lung function after decreasing LABA

• **Study Question**
  – What is the optimal approach to stepping down asthma combination therapy?
LASST

• Design: RCT enrolling well-controlled asthmatics on moderate dose ICS/LABA, n = 450
  - Treatment arms
    - ICS / LABA (Fluticasone-Salmeterol 250/50)
    - ICS/LABA (Fluticasone-Salmeterol 100/50)
    - ICS (Fluticasone 250)
  - Primary outcome: Treatment failure (fall in PEFR, FEV1, exacerbation requiring steroids)
  - Secondary outcomes: Asthma control, FEV1, symptom free days
  - Status: Actively Enrolling. Completion date Dec 2015
LASST Schema

Stable ICS/LABA (8 wks)

Continue same dose ICS/LABA

Reduce ICS 50% / continue LABA

Continue same dose ICS/discontinue LABA

-8 -4 0 3 6 12 18 24 30 36 42 48
V1 V2 V3 V4 V5 V6 V7 V8 V9 V10 V11 V12
Rz
LASST

- Sponsor: American Lung Association, GSK
- Research Network: ALA-ACRC
- Status: Enrollment in December 2011
- Completion date: December, 2015
Pilot Studies

• Smoking in asthma studies
  – Pilot trial of theophylline, anticholinergics, anti-leukotrienes (UCSD, PIs – Ramsdell / Wasserman)
  – Smoking Cohort Study to validate asthma outcome measures in smoking asthmatics (n = 150)
  – Registry of smoking asthmatics
Pilot Studies – Streamlining Clinical Trials

• Streamlined clinical trial methodology
  – Participant recruitment via electronic patient record
  – Multimedia Consent Procedures
  – Electronic remote data capture with tablets
  – Home spirometry with distant coaching

• Parallel protocol to LASST trial
  – Conducted at Nemours affiliated sites (PI – Blake)
  – Validation against traditional study methods
Thank you