Understanding Therapeutic Heterogeneity and Responsiveness in Asthma

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Therapeutic Heterogeneity and Responsiveness: Learning Objective

• To understand the heterogeneity of patient groups and their unique responses to different asthma therapies
Approaches to Personalizing Asthma Therapies

Demographic Characteristics

Phenotypes Descriptions Based on Defined Categories  
Task Force Consensus 1&2

- Clinical Presentation
  - Pre-Asthma in Infants
  - Irreversible Airflow Limitation
  - Exacerbation-Prone
- Inflammatory
  - Eosinophilic
  - Non-Eosinophilic
  - Expired Nitric Oxide
- Triggers
  - Allergic
  - Non-Allergic
  - Aspirin-Sensitive
  - Exercise-Induced
  - Infection-Induced

Approaches to Personalizing Asthma Therapies

Inflammatory Characteristics

- Th2 High Eosinophils Periostin
Phenotype: Sputum Eosinophils
Green, Lancet 2002; 360:1715-1721

Sputum Eosinophils and Incidence of Asthma Exacerbations (N=74)

BTS Management Strategy
Sputum Eosinophil Strategy

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia
Nair, et al. NEJM 2009; 360:985-993

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma
Haldar, et al. NEJM 2009; 360:973-984
Approaches to Personalizing Asthma Therapies

Inflammatory Characteristics

Th2 High Eosinophils Periostin

Defined by Genetics

Alterations in Glucocorticoid-Induced Transcript 1 Gene (GLCCI1) and FEV1 Response to ICS

Tantisira, et al. NEJM 2011

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Approaches to Personalizing Asthma Therapies

Demographic Characteristics

Inflammatory Characteristics

Non-Eosinophilic

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma: Main Study Outcomes and Predictors of Response


Stephen P Peters, MD, PhD, for the NHLBI's Asthma Clinical Research Network's (ACRN) TALC Investigators
TALC Hypotheses

• **Primary**: To demonstrate efficacy for tiotropium when added to ICS in patient with uncontrolled asthma on ICS alone

• **Secondary**: To demonstrate that tiotropium/ICS was not inferior to LABA (salmeterol)/ICS

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TALC Protocol

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**Randomize**

- Baseline Period 1
- Baseline Period 2
- Baseline Period 3

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TALC Summary

**Tiotropium/1x Beclomethasone Has Been Proven Superior to 2x Beclomethasone**

• AM PEF (25.8 L/min)
• PM PEF (35.3 L/min)
• PreBronch FEV₁ (0.10 L)
• Proportion of Asthma Control Days (0.079)
• Daily Symptoms (-0.11)
• ACQ score (-0.18)
• FEV₁ after 4 puffs Albuterol (0.04 L)
TALC Summary

Tiotropium/1x Beclomethasone Has Been Proven Noninferior to Salmeterol/1xBeclomethasone

- AM PEF (6.4 L/min)
- PM PEF (10.6 L/min)
- Proportion of Asthma Control Days (-0.009)
- Daily Symptoms (-0.04)
- ACQ score (0.09)
- Sputum Eosinophils (0.20%)

Superior with Respect to:
- PreBronch FEV1 (0.11 L)
- FEV1 after 4 puffs Albuterol (0.07 L)

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Demographic Characteristics

Inflammatory Characteristics

- Th2 High Eosinophils Periostin
- Defined by Clusters

- Non-Eosinophilic
- Defined by Genetics

Inflammatory Characteristics

- Th2 High Eosinophils Periostin
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Asthma Cluster Analysis: 5 Clusters

1. Mild Allergic Asthma
   - Early onset asthma (EOA); 80% female; Normal lung function <= 2 Controllers; Minimal Health Care Utilization (HCU) (decreased EOS)

2. Mild-Moderate Allergic Exacerbating Asthma
   - Most common cluster: EOA, 67% female; Borderline normal FEV1 but reverses to normal; <= 2 Controllers; Very low HCU, but some steroid bursts (decreased EOS)

3. Moderate-to-Severe Older Onset Asthma
   - Older; LOA: higher BMI; 71% female; Less atopic; Moderate decrease in FEV1, some reversibility; On higher ICS; > 3 Controllers, but despite this more OCS bursts (increased EOS)

4. Severe Variable Allergic Asthma
   - Young; EOA; 52% female; Severely decreased FEV1, but very reversible to near normal; OCS; "Variable" with need for frequent steroid bursts; High BAG & GSS (increased EOS)

5. Severe Fixed Airflow Asthma ("COPD similarities")
   - Older; LOA (longest duration); 65% female; Less atopic; Severely decreased FEV1, more fixed, less reversibility; On OCS; higher BMI; more GERD, HTN; high HCU, BAG & GSS (increased EOS)

Moore et al. AJRCCM 2010; 181:315-323

Lebrikizumab (anti-IL-13) and Periostin
Corren et al. NEJM August 3, 2011 (10.1056/NEJMoa1106469)