Understanding Therapeutic Heterogeneity and Responsiveness in Asthma

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Stephen P. Peters, MD, PhD Disclosure

- **Basic and Clinical Research**
  - NHLBI (ACRN, AsthmaNet SARP, SPIROMICS)
  - ALA (ACRC)
- **Pharmaceutical Trials**
  - Actelion, Amgen, Astra-Zeneca, Boehringer-Ingelheim, Centocor, Cephalon, Genentech, GlaxoSmithKline, Medimmune, Sanofi-aventis
- **Advisory Boards**
  - AstraZeneca, Aerocrine, Airsonett AB, Delmedica, GlaxoSmithKline, Merck, TEVA
- **Speakers' Bureaus**
  - Integrity CME, Merck
- **Editorial Boards**
  - Resp Med, Assoc Editor,
  - Resp Research, Assoc Ed
  - J Allergy
  - Case Reports in Medicine

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

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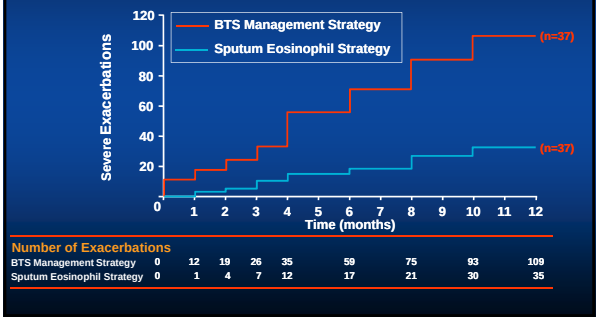
Th2 High
Eosinophils
Periostin

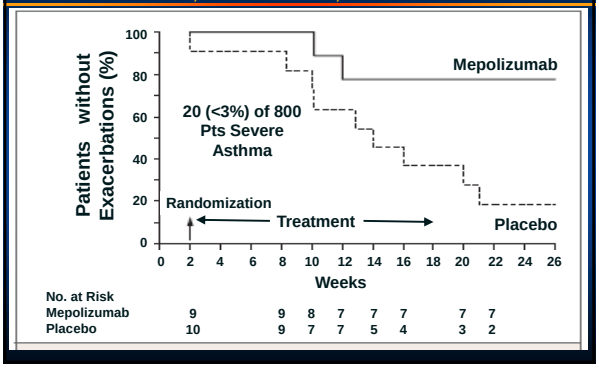
Phenotype: Sputum Eosinophils

Green. Lancet 2002; 360:17151721



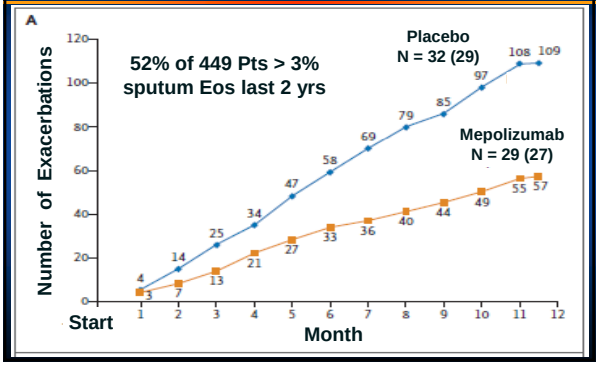
Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

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 FEV_1 Response to ICS

Tantisira, et al. NEJM 2011

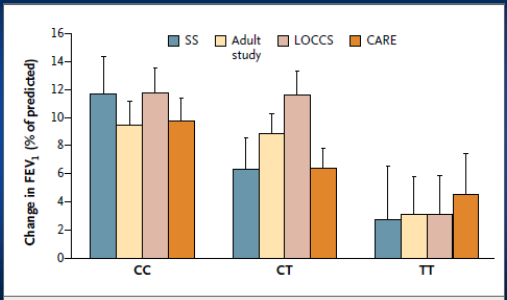
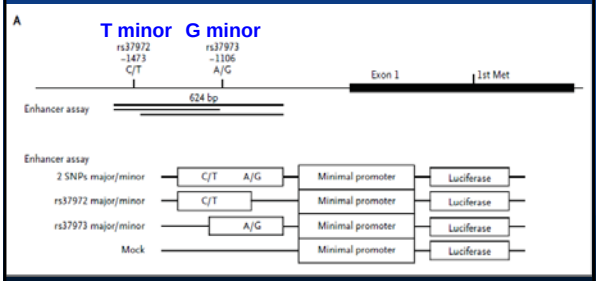


Figure 2. Changes in Lung Function with Therapy According to rs37972 Genotype.

Alterations in Glucocorticoid-Induced Transcript 1 Gene (*GLCCI1*) and FEV_1 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

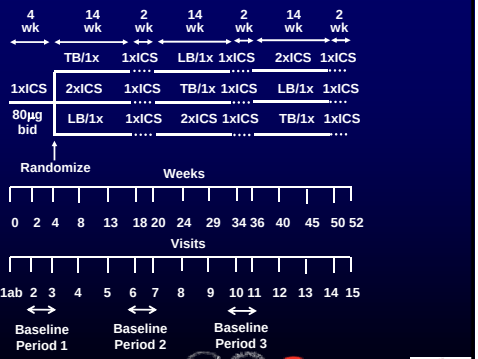
N Engl J Med 2010; 363:1715-1726

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

TALC Protocol



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 FEV_1 (0.10 L)**
- **Proportion of Asthma Control Days (0.079)**
- **Daily Symptoms (-0.11)**
- **ACQ score (-0.18)**
- **FEV_1 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 FEV_1 (0.11 L)
- FEV_1 after 4 puffs Albuterol (0.07 L)

Approaches to Personalizing Asthma Therapies

Demographic Characteristics

Inflammatory Characteristics

Th2 High Eosinophils Periostin → Defined by Clusters

Non-Eosinophilic → Defined by Genetics

Approaches to Personalizing Asthma Therapies

Inflammatory Characteristics

Th2 High Eosinophils Periostin → Defined by Clusters

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; 53% 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); 63% female; Less atopic; Severely decreased FEV1, more fixed, less reversibility; On OCS; higher BMI; more GERD.HTN; high HCU, BAG & GSS (increased PMN, EOS)

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

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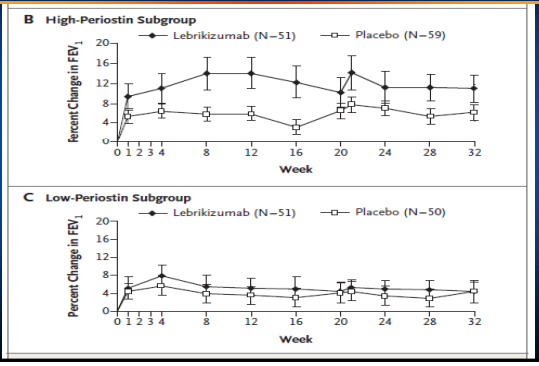
Moore et al. AJRCCM 2010; 181:315-323

Lebrikizumab (anti-IL-13) and Periostin

Corren et al . NEJM August 3, 2011 (10.1056/NEJMoa1106469)



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