Small Airways (SAW) Symposium: 
Asthma Treatment Issues

New Bronchodilator for Asthma:
A Patient-Centric Approach for Treating Asthma

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Disclosure

• Basic and Clinical Research
  – NHLBI (AsthmaNet, SARP, SPIROMICS)
• Book Chapters
  – UpToDate
• Pharmaceutical Trials
  – Actelion, Amgen, AstraZeneca, Boehringer-Ingelheim, Centocor, Cephalon, Genentech, GlaxoSmithKline, Forest, Medimmune, Sanofi-aventis

• Advisory Boards
  – Array Biopharma, AstraZeneca, Aerocrine, Aironett AB, Boehringer-Ingelheim, Experts in Asthma, Gilead, GlaxoSmithKline, Merck, Novartis, Ono Pharmaceuticals, Pfizer, PPD Development, Quintiles, Sunovion, Saaechi & Saechi, Targacept, TEVA, Theron
• Editorial Boards
  – Resp Med, Assoc Editor
  – Resp Research, Assoc Ed
  – J Allergy
  – Case Reports in Medicine
  – US Resp Disass
  – J Pulm Resp Medicine
  – Clin Exp Med Sciences
  – JACI: In Practice

Goals and Learning Objectives

• Discuss the use of Patient Characteristics to 
  Guide Asthma Treatment with respect to
  – Characteristics of Inflammation
  – Smoking
  – Hyperinflation
  – Airflow Limitation
  – N of 1 Approaches as an Adjunct
From Clinical to Molecular to Endotype

ACOS – Revised Taxonomy

Drugs for COPD and Asthma
Patient Characteristics to Guide Therapy

- Characteristics of Inflammation
- Smoking Without or With COPD
- Air Trapping
- Airflow Limitation
  - With Reversibility
  - Persistent Obstruction

Characteristics of Inflammation
"Th2 high"

Eosinophilic
- Steroids
- Anti-eosinophilics (Anti-IL-5)
- Anti-IL-5
- Anti-IL-13
- Anti-TSLP
- Anti-L-33
- CRTH2 antagonists

Targeting Sputum Eosinophils in Asthma

Inhaled Corticosteroids
Mepolizumab – Anti-IL-5

Characteristics of Inflammation

Barnes. J Allergy Clin Immunol 2015; 136:531-545

“Th2 low”

- Neutrophilic
  - Steroid-resistant
  - Anti-neutrophilics
  - Macrolides
- Paucigranulocytic
  - Steroid-resistant

- CXCR2 antagonists
- Anti-TNF
- Anti-IL-1
- Inflammasome inhibitors
- Anti-IL-17/23
- p38 MAPK inhibitors
- PDE4 Inhibitors

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Effect of Smoking on Response to ICS and LTRA in Asthma

Lazarus, et al. AJRCCM 2007; 175:783-90

Non-Smokers
Smokers

Δ FEV1 (L)

Δ PEF (L/M)

Beclo Montelukast

Tiotropium: COPD and Concomitant Asthma


Patient Characteristics to Guide Therapy

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Effect of Small Particle ICS on Exhaled Nitric Oxide (eNO)

Placebo  Ciclesonide

- P=0.006 from Mann-Whitney U test
- P=0.012 from Wilcoxon signed rank test


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NHLBI ACRN’s Tiotropium Add-on Therapy to ICS (TALC) Trial: Study Outcomes

Morning PEF

- p = 0.96

Trough FEV1

- p = 0.001

Asthma control days

- p = 0.78

Predictors of Response to Tiotropium: Summary

- Higher Cholinergic Tone (Lower Resting Heart Rate)
- Greater Airway Obstruction (Lower FEV1/FVC ratio)
- Positive Response to Short-Acting Bronchodilator (Albuterol > Ipratropium)
- Younger Age (Asthma Control Days)


Exploratory Predictors Not Associated with Response to Tiotropium

- Ethnicity
- Gender
- Atopy (skin test +)
- IgE Level (ln)
- Sputum Eosinophils
- FeNO (ln)
- Asthma Duration
- BMI


Combination Tiotropium & Olodaterol Therapy in COPD

Response of Persistent, Intermittent, and Non-Eosinophilic Asthmatics to Antiinflammatory Tx and β-Agonists

McGrath, et al. AJRCCM 2012;185:612–619

Lung Elastic Recoil in Asthma – Never Smokers
(52 ± 14 yrs, Persistent Airflow Obstruction)

Gelb et al. 2015; 148:313-320

Centrilobular Emphysema in Elderly Never Smoker Asthmatics

Gelb et al. 2015; 148:313-320
Time for one-person trials
Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says Nicholas J. Schork.

IMPRECISION MEDICINE
For every person they do help (trial), the ten highest-growing drugs in the United States fail to improve the conditions of between 3 and 24 people ( Crew ).

1. ARLUN (aripiprazole)
   Schizophrenia

2. NEXUM (oesoprase)
   Heartburn

3. JUMBA (celecoxib)
   Arthritis

4. CRESTOR (rosuvastatin)
   High cholesterol

Differential Response to Tiotropium vs Salmeterol: PEF_{am}

Better response to tiotropium (N = 78)

Better response to salmeterol (N = 20)

The N of 1 Clinical Trial: The Ultimate Strategy for Individualizing Medicine?

Do n-of-1 trials have a role in clinical science?
- N-of-1 trials that focus exclusively on the objective, empirically determined optimal intervention for a single patient are compatible with the ultimate end point of clinical practice: the care of individual patients.
- Meta-analyses of the outcomes of multiple n-of-1 trials could be compared with standard treatment regimens and help put into context the utility and practicality of n-of-1 trials.

Design issues in n-of-1 clinical trials
- Randomization of treatment order, carryover effects, washout periods and blinding are key design elements that need to be considered in n-of-1 trials.

The analysis of n-of-1 clinical trials
- Methods that account for serial correlation in comparing the response to two or more treatments, such as certain time-series analyses, are necessary.
- More research into how to identify and accommodate carryover effects in n-of-1 trials is clearly needed.

How Should Control of Asthma Be Assessed?

- Exacerbations
- Utilization of Healthcare Resources
- Inflammation: Direct or Indirect?
- Lung Function
- Missed Work and/or School
- Daytime Symptoms
- Nighttime Awakenings
- Use of a “Quick Relief” Inhaler and/or Nebulizer
- Patient Self-Report of Control

Adding N of 1 Trials to Genomics

Two Step Model for Asthma Initiation and Progression AND Eos Role in Exacerbation

Questions?