Refractory Asthma: The Heterogenous Disease

Rohit Katial, MD, FAAAAAI, FACP
Professor of Medicine
Program Director, Allergy & Immunology
Director, Weinberg Clinical Research Unit
Director, A/I Clinical Services
Obstructive Airway Diseases

Refractory Asthma

- Patents remain difficult to control despite extensive evaluation and treatment

In the literature terms used
- “difficult to treat asthma”
- Therapy resistant asthma
- Steroid dependent asthma
- Brittle asthma
Definition: ATS workshop

- **Major criteria (must have one):**
  - Oral steroids for >50% of past year
  - Continuous high dose inhaled steroids
    - >880 µg FP

- **Two of 7 minor criteria:**
  - Concurrent use of at least 1 other controller medications
  - Daily symptoms requiring a short acting β-agonist
  - FEV1<80% predicted
  - One or more urgent care visits in last year
  - ≥3 oral steroid bursts in last year
  - Deterioration with decrease in steroid dose of 25%
  - History of near-fatal event

Questions

- What is the actual prevalence of severe asthma and its various phenotypes?
- Will phenotypic markers for severe asthma (biomarkers of airway inflammation) or tests for small airways allow better characterization of subgroups?
- Can complex statistical modelling be used to improve our ability to characterize patients?
- What else should be considered in these patients?
- What are therapeutic options?
Epidemiology

- Severe asthma associated with increased hospitalization and death
- Limited data on prevalence
- Estimated to be 5-10% of asthmatics
- Group accounts for 50% of total health care costs
- Although, risk factor for hospitalization and death how much due to inadequate treatment vs refractoriness?

What factors contribute to poor asthma control?
Risk Factors for Poor Asthma Control and Severity

- Technique
- Adherence
- Comorbidities
- Type of Inflammation
- Location of inflammation
- Misdiagnosis
- Genetics
Risk Factors for Poor Asthma Control and Severity

- Environmental exposure
  - ETS
  - Allergen

- Comorbidities
  - Sinusitis
  - GERD
  - Obesity
  - AERD
  - OSA
  - Influence of menstruation
  - Psychiatric disease
  - Role of Infection
Asthma is a chronic inflammatory disease of the airway with:

- Airway obstruction that may or may not be reversible, either spontaneously or with medication
- Airway inflammation caused by many cellular components
- Increased airway hyperresponsiveness
Asthma, COPD (Chronic bronchitis), categorize a clinical presentation which appeared to be distinct

Improved diagnostics, objective measures attempted to fit into this paradigm

Need to start with objective measure as the basis of classification
Airway Compartment

Asthma Phenotypes

- Variability in airflow obstruction
- Inflammatory eosinophilic
- FAO
- Non-eosinophilic
- Asthmatic smoker
- Eosinophilic bronchiectasis
Factors limiting airflow in acute and persistent asthma

Environmental factors

Th2/Th1 cytokines (e.g., IL-13, TNF-α)

Environmental factors and inflammatory products

Dendritic cell

B lymphocyte → T lymphocyte

IL-3, IL-4, IL-13, IL-9

Mast cell

IL-3, IL-5, GM-CSF

Neutrophil

Eosinophil

TNF-α

Airway microenvironment

AIRWAY EFFECTS

Bronchospasm
Acute inflammation
Persistent inflammation
Remodeling

Mucus

Initiation

Amplification

Propagation

Smooth muscle

Blood vessels

(myo) fibroblasts

Pro-inflammatory mediators

Persistent inflammation and development of remodeling

Asthma Phenotypes

Discordant Symptoms

EARLY SYMPTOM PREDOMINANT
Early onset, atopic.
Normal BMI.
High symptom expression.

OBSESE NON-EOSINOPHILIC
Later onset, female preponderance.
High symptom expression.

BENIGN ASTHMA
Mixed middle-aged cohort
Well controlled symptoms and inflammation. Benign prognosis.

Monitoring inflammation allows down-titration of corticosteroids.

Primary Care Asthma
Secondary Care Asthma

Concordant Disease

Symptom-based approach to therapy titration may be sufficient.

EARLY ONSET ATOPIC ASTHMA
Concurrent symptoms, inflammation & airway dysfunction.

MONITORING INFLAMMATION
Allows targeted corticosteroids to lower exacerbation frequency.

INFLAMMATION PREDOMINANT
Late onset, greater proportion of males.
Few daily symptoms but active eosinophilic inflammation.

Discordant Inflammation

Eosinophilic Inflammation

Haldar et al, Am J Respir Crit Care 2008;178:218
Early onset severe asthma more allergic

- **Hx eczema** (p=0.0007)
  - Early 40%  Late 4%

- **Serum IgE** (p=0.12)
  - Early 108  Late 56

- **Family hx of asthma**
  - Early>late

Allergic Symptoms (most or all of time)

- House Dust
- Furred Animals
- Seasonal Pollen
- Atopy

Miranda, JACI 2004
Pulmonary Function: Late onset slightly worse

<table>
<thead>
<tr>
<th>Group</th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEV₁/FVC</th>
<th>% change post bronchodilator</th>
<th>PC20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>56±3</td>
<td>76±3</td>
<td>60±2</td>
<td>27±4</td>
<td>0.39(0.30-0.49)</td>
</tr>
<tr>
<td>Late</td>
<td>48±4</td>
<td>66±4</td>
<td>55±2</td>
<td>31±4</td>
<td>0.39(0.28-0.55)</td>
</tr>
</tbody>
</table>

p-value 0.07 0.05 0.11

Late Onset disease with lower lung function despite shorter duration of disease
Eosinophils associated with increased symptoms*, near fatal events

*Symptoms “most or all of the time”

Early onset eosinophilic asthma: Higher % intubated (56% vs 22%)
SBM thickness associated with eosinophilic phenotype

Wenzel, AJRCCM, 1999
$\text{FE}_{\text{NO}}$ identifies persistent eosinophilia in severe asthma

Effect of Oral CS

No Tissue Eosinophilia

N=12 no cs  N=11 on cs
Effect of Oral CS

Tissue Eosinophilia

N=9 no cs     N=6 on cs
Risk Factors for Poor Asthma Control and Severity

- Technique
- Adherence
- Comorbidities
- Type of Inflammation
- Location of inflammation
- Misdiagnosis
- Genetics
Non-eosinophilic Severe Asthma

- Not all refractory asthma eosinophilic
- Very little inflammation and/or neutrophils also seen
- Neutrophil prominence--different disease? (i.e., bronchiolitis obliterans)
Neutrophils increase in sputum as asthma severity increases.
## Sputum cell counts

*Average cell counts (partial data – subset of baseline samples from each group):*

<table>
<thead>
<tr>
<th></th>
<th>Total cell counts (million)</th>
<th>Eo percent</th>
<th>Neut percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-asthmatic controls</td>
<td>4.63</td>
<td>2.4%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Well-controlled asthmatics</td>
<td>2.75</td>
<td>0.9%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Not well-controlled asthmatics</td>
<td>4.08</td>
<td>1.7%</td>
<td>40.8%</td>
</tr>
<tr>
<td>Poorly controlled asthmatics</td>
<td>4.43</td>
<td>2.5%</td>
<td>74.8%</td>
</tr>
</tbody>
</table>
Risk Factors for Poor Asthma Control and Severity

- Technique
- Adherence
- Comorbidities
- Type of Inflammation
- Location of inflammation
- Misdiagnosis
- Genetics
The disease process in asthma is located in all parts of the bronchial tree, including small and large airways.
Small airway walls thickened in severe asthma

Normal

Acute Fatal

Chronic Severe

Courtesy Sally Wenzel
Pattern of inflammatory cells also differs by lung region

Balzar, Am J Respir Crit Care Med. 2005 Mar 1;171(5):431-9
Different distribution of inflammatory cells: Mast cells

Courtesy Sally Wenzel
Small Airway Wall Thickness Increased in Cases of Both Fatal and Non-fatal Asthma

<table>
<thead>
<tr>
<th>Inner Wall Area (per mm Pbm)</th>
<th>&lt; 2 mm</th>
<th>2-4 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td><img src="#" alt="Control Bar" /></td>
<td><img src="#" alt="Control Bar" /></td>
</tr>
<tr>
<td>Non-fatal</td>
<td><img src="#" alt="Non-fatal Bar" /></td>
<td><img src="#" alt="Non-fatal Bar" /></td>
</tr>
<tr>
<td>Fatal</td>
<td><img src="#" alt="Fatal Bar" /></td>
<td><img src="#" alt="Fatal Bar" /></td>
</tr>
</tbody>
</table>

* P<0.05

Pbm = mm$^2$ per mm of basement membrane perimeter

Inflammation of Small Airways in Asthma

Q Hamid et al. J Allergy Clin Immunol 1997;100:44-51

Surgical lung specimens from 6 patients with asthma and 10 controls were examined. There was a similar inflammatory process present in the peripheral (< 2mm diameter) compared with the central airways.
Immunohistochemical Markers in the Large & Small Airways

Positive cells/mm²

Airways < 2 mm

Airways > 2 mm

A = asthmatics
C = controls

Hamid
JACI 1997
Risk Factors for Poor Asthma Control and Severity

- Technique
- Adherence
- Comorbidities
- Lack of eosinophilic inflammation
- Location of inflammation
- Misdiagnosis
- Genetics
Differential Dx Of Wheezing

* “Asthma”
* VCD
* ABPA
* Chronic Eosinophilic Pneumonia
* Airway Tumors
* Bronchostenosis/TBM/DAC
* CHF
* Infection
* TB
* Tonsils
* Foreign body
* Goiter
* Post polio syndrome
* COPD
* PE
* Fixes lesions
"I'm not really sure what it is but five or six thousand dollars of tests should help me figure it out."
Asthma (< -856 HU)

Pre-Bronchodilator - 56.6%

Post – Bronchodilator - 14.28%
Presented for Lidocaine Allergy

Alpha 1 AT Deficiency
Chlamydia + in BAL
Dyspnea at Rest and with Exertion/ “Severe Asthma”

End-Inspiratory

Dynamic Expiratory CT Severe Tracheomalacia
## Case Series of TM

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Smoking History</th>
<th>Clinical Symptoms</th>
<th>FEV1</th>
<th>Degree Of Collapse</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>JR</td>
<td>64</td>
<td>M</td>
<td>Asthma</td>
<td>40-pk-yr</td>
<td>cough wheeze</td>
<td>2.3L</td>
<td>70%: trachea 100% bronchi</td>
<td>stent placement</td>
</tr>
<tr>
<td>AW</td>
<td>78</td>
<td>M</td>
<td>COPD</td>
<td>30-pk-yr</td>
<td>SOB DOE</td>
<td>1.2 L</td>
<td>100% trachea 100% bronchi</td>
<td>stent placement</td>
</tr>
<tr>
<td>DD</td>
<td>29</td>
<td>F</td>
<td>Asthma</td>
<td>5-pk-yr</td>
<td>SOB steroid dependence</td>
<td>1.2 L</td>
<td>50% trachea 50% bronchi</td>
<td>conservative</td>
</tr>
<tr>
<td>JK</td>
<td>54</td>
<td>M</td>
<td>Asthma</td>
<td>minimal</td>
<td>SOB cough</td>
<td>2.5 L</td>
<td>50% trachea 50% bronchi</td>
<td>conservative</td>
</tr>
<tr>
<td>CK</td>
<td>50</td>
<td>M</td>
<td>COPD</td>
<td>nonsmoker</td>
<td>SOB/DOE intubated</td>
<td>1.1 L</td>
<td>80 -90% trachea and carnina</td>
<td>Pt defered further evaluation</td>
</tr>
</tbody>
</table>
Without Use of PEEP Valve

With Use of PEEP Valve
CT Densitometry in Asthma

- Computer analyses of CT images obtained at FRC can determine distribution of lung density
- Lung voxels with a density less than -850 HU are displayed in the images on the right as yellow
- Computer analyses of an entire contiguous set of lung CT images can provide useful information on air trapping in asthma
- Note: Airway geometry and histograms were also evaluated from a matched TLC scan (data not presented here).
Therapy: Where are We?

"Toto, I've a feeling we're not in Alaska any more"
Asthma Therapy Through the Ages

- **G. Cardano**
  - Diet
  - Exercise
  - Sleep
  - No feathers

- **T. Willis**
  - Fetid gums
  - Musk
  - Vitrioloic ether

- **J. Floyer**
  - Gill
  - Hyssop
  - Syrup of sulphur
  - Bleeding

- **W. Osler**
  - Atropine
  - Morphine
  - Chloroform
  - Lobelia

1500s 1600s 1700s 1800s

- Amyl nitrate
- Asthma cigarettes
Asthma Therapy – 1800s
Asthma Therapy in the 1900s

- Adrenaline
- Methyl xanthines
- Oral steroids
- \( \beta \)-agonists
- Long-acting \( \beta_2 \)-agonists
- Leukotriene modifiers

1900-30s
- Systemic steroids (ACTH)

1940s
- Cromones
- Inhaled steroids
- \( \beta_2 \)-selective agonists
Management of Asthma
Pharmacologic Therapy

- Corticosteroids
- Anti-leukotrienes
- β₂-Agonists
- Anti-IgE
- Anti-Cholinergics
- Chromones Methylxanthines
Little evidence that using additional “standard” Rx helpful

<table>
<thead>
<tr>
<th>Condition</th>
<th>1 controller (n=338)</th>
<th>2 controllers (n=1649)</th>
<th>3 or more controllers (n=2679)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever intubated</td>
<td>10%</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>Overnight hospitalization in past 3 months</td>
<td>6%</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Emergency room visit in past 3 months</td>
<td>13%</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>Steroid burst in past 3 months</td>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Unscheduled office visit in past 3 months</td>
<td></td>
<td>41%</td>
<td>47%</td>
</tr>
<tr>
<td>Scheduled office visit in past 3 months</td>
<td></td>
<td>41%</td>
<td>49%</td>
</tr>
<tr>
<td>Missed at least 1 day of work/school in past 2 weeks</td>
<td>12%</td>
<td>21%</td>
<td>20%</td>
</tr>
</tbody>
</table>

TENOR data, ATS 2003
Asthma Exacerbations and Sputum Eosinophil Counts

Sputum EOS
- >3% increase iGC
- 1-3% no change
- <1% decrease iGC

Severe Exacerbations

Green et al., Lancet 2002;360:1715-1721
Sputum Neutrophilia and Poor Response to ICS

Neutrophils reduce response to ICS:

<table>
<thead>
<tr>
<th></th>
<th>Neuts.</th>
<th>Eos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms (analog)</td>
<td>- 5.5 mm</td>
<td>- 19.4 mm</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>- .08 L</td>
<td>+ .13L</td>
</tr>
<tr>
<td>PC$_{20}$ Methacholine</td>
<td>0.15 dd</td>
<td>1.29 dd</td>
</tr>
</tbody>
</table>

RH Green et al., Thorax 2002;57:875-9
Management of Asthma
Pharmacologic Therapy

- Corticosteroids
- Anti-leukotrienes
- Anti-Cholinergics
- Anti-IgE
- Chromones Methylxanthines
- $\beta_2$-Agonists
- Anti-IgE

Asthma
Management of Asthma
Pharmacologic Therapy

- Corticosteroids
- Anti-leukotrienes
- β₂-Agonists
- Anti-IgE
- Anti-Cholinergics
- Chromones
- Methylxanthines
Management Based on Phenotypes

- Non-eosinophilic
- Eosinophilic
- Fixed Airway Obstruction
- Asthmatic Smoker
- Similar to COPD
- Eosinophilic Bronchiectasis

**BD Effective**

- Variability in airflow obstruction
- Inflammatory Eosinophilic

**GC Most Effective**

- ? Abx or overuse of GC
- Asthmatic Smoker
- Systemic steroids, anti-microbials

- ? Bronchial Thermoplasty

- Effective GC
- Most Effective BD

Systemic steroids, anti-microbials
New Steroids

Adcock et al. Lancet 2008;372:1073
New Drug Targets

Adcock et al. Lancet 2008;372:1073
# New Drug Targets

<table>
<thead>
<tr>
<th>Function</th>
<th>Drug and stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>β$_2$ adrenergic receptor</td>
<td>Ultra-long bronchodilation Indacaterol (phase II), carmoterol (phase II), GSK159797 (phase II)</td>
</tr>
<tr>
<td>Glucocorticoid receptor</td>
<td>Anti-inflammatory GSK588589 (phase II), GSK580086 (phase II), AII-428 (phase I), ZK 216348 (phase I)</td>
</tr>
<tr>
<td>PDE2/CXR2 inhibitors</td>
<td>Th2 cell recruitment and activation TM-30088, DCG9101 (phase II), AZD1981 (phase II), naronoban (phase II)</td>
</tr>
<tr>
<td>BLT1 antagonist</td>
<td>Mononuclear/granulocyte recruitment CP-305696 (phase I), LY293111 (phase II, no effect against allergen challenge)</td>
</tr>
<tr>
<td>CCL11</td>
<td>Blocks eosinophil recruitment/activation CAT-213 (preclinical)</td>
</tr>
<tr>
<td>CCR3</td>
<td>Blocks eosinophil recruitment/activation Met RANTES (phase II, moderate/Severe asthma)</td>
</tr>
<tr>
<td>OXCR1/2</td>
<td>Blocks Th2 activation AMD070, AMD3100, SPP1A (all preclinical for asthma, all phase II HIV, AMD3100 phase III for multiple myeloma)</td>
</tr>
<tr>
<td>OXCR1/2</td>
<td>Blocks neutrophil recruitment/activation Repertaxin (preclinical, phase II for graft-versus-host disease)</td>
</tr>
<tr>
<td>Interleukin 5</td>
<td>Blocks eosinophil recruitment/activation MEDI 563 (phase I, severe asthma), mepolizumab (phase II)</td>
</tr>
<tr>
<td>Interleukin 12</td>
<td>Interleukin 12 (phase II, no effect on lung function, adverse side-effects, not developed further)</td>
</tr>
<tr>
<td>Interleukin 10</td>
<td>Endogenous anti-inflammatory agent Interleukin 10 (preclinical for asthma, approved for psoriasis/Grhone’s disease, recruited in 1999 for asthma)</td>
</tr>
<tr>
<td>Interferon γ</td>
<td>Interferon γ (phase II, no effect on lung function in severe asthma, not developed further)</td>
</tr>
<tr>
<td>Interleukin 13</td>
<td>Key driver of asthmatic inflammation Pitrakima (interleukin-4/13 mutatin), CAT 354, IMAA-638 (both in phase II)</td>
</tr>
<tr>
<td>VLA4 antagonist</td>
<td>Adhesion molecule blocker GW-555909, NV745, CDP323 (CDP323 phase II, not developed)</td>
</tr>
<tr>
<td>PDE4</td>
<td>Anti-inflammatory GSK266666 (phase II)</td>
</tr>
<tr>
<td>p38 MAPK</td>
<td>Anti-inflammatory GSK581223, GSK65552, VX-745, BIRB-795, Ro-20-1195, Soo-450 (all in phase II), SB243906, RWJ-07557</td>
</tr>
<tr>
<td>JNK</td>
<td>Anti-inflammatory SP600125, CC-401, CNI-1493 (dual JNKp38 MAPK) (all in preclinical for asthma, CC-401 and CNI-1493 in phase II in rheumatoid arthritis and Grown’s disease)</td>
</tr>
<tr>
<td>SYK</td>
<td>Mast cell degranulation, T-cell and B-cell function Anti-Sense (preclinical), BAY51-3606 (preclinical), R443 (phase I)</td>
</tr>
<tr>
<td>IKK2</td>
<td>Anti-inflammatory A5206888, SC-514, BMS345541, TPCA-1 (all preclinical, MLN0415 (phase I))</td>
</tr>
<tr>
<td>CD23</td>
<td>Reduces IgE Lumiliximab (phase I)</td>
</tr>
<tr>
<td>Sphingosine-1 phosphate receptor</td>
<td>Prevents dendritic cell activity FFT720 (preclinical for asthma, Phase II for multiple sclerosis and transplant rejection)</td>
</tr>
<tr>
<td>DP1</td>
<td>Prevents dendritic cell activity BW245C (preclinical)</td>
</tr>
<tr>
<td>VDR</td>
<td>Increased interleukin-10 expression in Treg cells Vitamin D3 (phase II, steroid sparing)</td>
</tr>
</tbody>
</table>

Table: Summary of some of the compounds in development for asthma

Adcock et al. Lancet 2008;372:1073
# New Drug Targets

<table>
<thead>
<tr>
<th>Cytokine target</th>
<th>Cellular origin</th>
<th>Predicted effects</th>
<th>Nature of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-15</td>
<td>Leukocytes, including phagocytes. Also, neurons and muscle</td>
<td>Increases T&lt;sub&gt;H&lt;/sub&gt;2-cell, B-cell, NK-cell, macrophage and monocyte responses</td>
<td>Blocking antibody and soluble IL-15Rα</td>
</tr>
<tr>
<td>IL-17A</td>
<td>Subset of CD4+ T cells</td>
<td>Neutrophil influx</td>
<td>Blocking antibody</td>
</tr>
<tr>
<td>IL-17F</td>
<td>Subset of CD4+ T cells</td>
<td>Antagonizes the effects of IL-17A</td>
<td>Receptor agonist</td>
</tr>
<tr>
<td>IL-17E (IL-25)</td>
<td>Subset of CD4+ T cells</td>
<td>Increases the T&lt;sub&gt;H&lt;/sub&gt;2-cell response and BHR</td>
<td>Blocking antibody</td>
</tr>
<tr>
<td>IL-33 (IL-1F11) (IL-1/TLR superfamily)</td>
<td>Epithelium</td>
<td>Increases the mast-cell response and induces the production of T&lt;sub&gt;H&lt;/sub&gt;2-cell cytokines</td>
<td>Soluble receptor, ST2R</td>
</tr>
<tr>
<td>IL-31</td>
<td>T&lt;sub&gt;H&lt;/sub&gt;2 cells</td>
<td>Increases the T&lt;sub&gt;H&lt;/sub&gt;2-cell response, pruritis and dermatitis</td>
<td>None identified</td>
</tr>
<tr>
<td>IL-21 (homology with IL-2, IL-4 and IL-15)</td>
<td>CD4+ T cells</td>
<td>Augments CD4+ and CD8+ T cells, NK cells and B cells</td>
<td>None identified</td>
</tr>
<tr>
<td>TSLP (IL-7 superfamily)</td>
<td>Epithelium and mast cells</td>
<td>Augments co-stimulation by DCs to increase the T&lt;sub&gt;H&lt;/sub&gt;2-cell response and activates mast cells</td>
<td>Blocking antibody</td>
</tr>
<tr>
<td>IL-18 (IL-1 superfamily)</td>
<td>Macrophages and activated T cells</td>
<td>Increases IFNγ production by T cells. Additional targets are macrophages, neutrophils, DCs and endothelial cells</td>
<td>IL-18</td>
</tr>
</tbody>
</table>

BHR, bronchial hyper-responsiveness; DC, dendritic cell; IFNγ, interferon-γ; IL, interleukin; NK cell, natural killer cell; T<sub>H</sub>2 cell, T helper 2 cell; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin

Holgate, Nat Rev Imm 2008;8:218
**Role of Smooth Muscle in Health**
- Support
- Gas exchange
- Mucus clearance
- Defense
- Cough
- Vestigial

**Role of Smooth Muscle in Asthma**
- Bronchoconstriction
- Hyperresponsiveness
- Inflammation
- Remodeling
- Interactions with epithelium and nerves
Bronchial Thermoplasty

Reduction in Airway Smooth Muscle

↓

Reduced Ability for Bronchoconstriction

↓

Reduction in Frequency and Severity of Asthma Symptoms

↓

Improved Quality of Life

* Bronchial Thermoplasty reduces airway smooth muscle through controlled thermal treatment to the airway wall.
The Alair Catheter is a flexible tube with an expandable wire basket at the tip.

The Alair Radiofrequency Controller supplies energy via the Alair Catheter to heat the airway wall.
ALTERED AIRWAY SMOOTH MUSCLE
12 WEEKS POST-TREATMENT

UNTREATED:
Smooth muscle present

TREATED:
Smooth muscle absent
Treatment Method

- All visible and accessible airways (3-10mm) distal to mainstem bronchi are treated
- Series of contiguous activations
- 3 treatment sessions

Previous BT Studies in Asthma

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
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<td>n = 297</td>
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</table>
AIR2 Trial: Effectiveness Summary

- BT is superior to Sham at improving AQLQ
- BT Group - Mean change of 1.38 over Baseline
- 79% of BT patients are AQLQ Responders*
  - Significantly more BT patients are Responders
- 32% decrease in severe exacerbations compared to Sham*
- 66% decrease in days lost from work/school/activities compared to Sham*

* Statistically significant
AIR2 Trial: Safety

* Safety Timeframes
  - Short-term: Treatment Period
    - Beginning at First bronchoscopy till 6 weeks after 3rd bronchoscopy (approximately 12 week period)
  - Long-term: Post Treatment Period
    - >6 weeks till 12 Months (46 week period)

* Safety Data
  - Adverse Events
  - Unscheduled Physician Office Visits for respiratory symptoms
  - Emergency room visits for respiratory symptoms
  - Hospitalizations for respiratory symptoms
## AIR2 Respiratory Adverse Events

### Overall Adverse Events With > 3% Incidence

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment Period (~12 weeks)</th>
<th>Post-Treatment Period (~46 weeks)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>BT (N=190) %</td>
<td>Sham (N=98) %</td>
</tr>
<tr>
<td>Asthma (Multiple Symptom)</td>
<td>52.1</td>
<td>38.8 *</td>
</tr>
<tr>
<td>Wheezing</td>
<td>15.3</td>
<td>6.1 *</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>4.7</td>
<td>0 *</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>3.2</td>
<td>0 *</td>
</tr>
<tr>
<td>Lower Respiratory Tract Infection</td>
<td>7.9</td>
<td>2.0 *</td>
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<tr>
<td>Upper Respiratory Tract Infection</td>
<td>20.0</td>
<td>11.2 *</td>
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<tr>
<td>Nasopharyngitis</td>
<td>4.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>4.7*</td>
<td>12.2</td>
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</tbody>
</table>

* pp superiority >95.0%
AIR2 Trial: Safety Results

190 BT Subjects
(558 bronchoscopies)

* **Treatment Phase Respiratory Adverse Events** (Treatment 1 through 6 wks; 12 wks):
  - Majority occurred within 1 day of procedure and resolved within 7 days.
  - Most common were related to transient worsening of asthma symptoms
  - BT > Sham
  - No unanticipated device-related adverse events

* **Post-Treatment Phase** (6 wks – 12 months; 46 wks)
  - BT better than Sham
    - 36% reduction in % Subjects with Asthma (multiple symptoms) adverse event
    - 83% reduction in ER Visits due to respiratory symptoms
Clinical Benefits of BT

* **Short term risks:**
  - Treatment adverse events related to transient worsening of asthma
  - Typically occur within one day and resolve within one week with standard care

* **Long term benefits:**
  - Improved AQLQ
  - 32% decrease in severe exacerbations
  - 84% decrease in ER visits
  - 66% decrease in days lost from work/school/activities
  - 36% decrease in patients reporting asthma (multiple symptoms) adverse events

* Long term benefits outweigh short term risks
Summary

- Obstructive Lung Diseases need to be viewed broadly
- Asthma heterogeneity has to ultimately be based on objective classification
- This approach should lead to future clinical trials to define responders and tailored therapy
- Future drugs will be targeted therapy