Asthma Phenotypes, Immunology and Implications for Therapy

J R Hansbrough MD, Ph.D.
Graves Gilbert Clinic
Bowling Green, Kentucky

Definition of Asthma
A chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation.

Inflammatory disease of the airway
Reversibility of airway obstruction (with time and treatment)
Waxing and waning symptoms
Asthma
Prevalence, Morbidity and Mortality

- Approximately 11 People Die From Asthma Each Day in the US
- 13.6 Million Unscheduled Office Visits Annually
- 0.5 Million Hospitalizations Annually
- Approximately 4000 Asthma-Related Deaths
- 22.2 Million People Are Currently Diagnosed With Asthma

National Center for Health Statistics, CDC, 2005; http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.html

Mainstay of Asthma Therapy

- Inhaled steroids are by far the most effective therapy for chronic therapy.

- Should be utilized for anyone with chronic symptoms (use of rescue inhaler 2 or more times a week or evidence of chronic airflow obstruction).

- Long acting beta agonists (LABA) in combination with inhaled steroids improve control. Cardiovascular side effects have been of some concern.

Environmental Control

- Smoking history and exposure
- Pets, plants, basement, damp living spaces, carpet.
- Exposure to fumes or smoke (wood burning stoves)
- Known triggers to asthma symptoms
- Specific IgE sensitivity (RAST or ImmunoCAP prolifes)
Stepwise Approach for Managing Asthma

Step 1: Short-acting Beta-2-agonists

Step 2: Low-dose Inhaled Corticosteroids (ICS)

Step 3: Low-dose ICS + Long-acting Beta-2-agonists (LABA) or Medium-dose ICS

Step 4: Medium-dose ICS + LABA

Step 5: High-dose ICS + LABA and Consider Omalizumab

Step 6: High-dose ICS + LABA + Oral Corticosteroids and Consider Omalizumab

Phenotypes of Asthma

Extrinsic vs. Intrinsic

Allergic vs. Non Allergic

Thy-2 vs. Non Thy-2

IgE mediated

Eosinophilia Bronchitis

The more we know, the less we understand. Better characterization of asthma phenotypes, the more heterogeneous the disease appears

Immunology of WBCs

• Monocytes

• Granulocytes—Polymorphonuclear leukocytes
  – Neutrophils
  – Eosinophils
  – Basophils—Mast cells

• Lymphocytes
  – T cells—regulatory cells
  – B cells—Mature into immunoglobulin producing cells
Immunoglobulins

Infection fighting proteins produced by matured B cells (Plasma Cells)

- IgA
- IgG
- IgM
- IgE - anti parasitic and allergy mediators

Interleukins (IL)

- **Interleukin** are a group of cytokines (secreted proteins and signal molecules) that were first described as being expressed by white blood cells.
- The function of the immune system depends in large part on interleukins.
- Produced by a large number of cell types
- Local response to injury, inflammation or infection
- Maturation and development of different white cell types (esp. T/B cells)
- Most recent data describes 36 human interleukins
Interleukins of interest in asthma

- **IL-4**—Stimulates B cell maturation to IgE producing plasma cells and production of eosinophils

- **IL-5**—Maturation, production and stabilization of eosinophils

- **IL-13**—Stimulates B cell maturation to IgE producing plasma cells and production of eosinophils

**THIS IS A SIMPLIFICATION!!!!—**As with all interleukins, they can have multiple and wide ranging effects

Pathophysiology of asthma

- **Th2 pathways**—T cell subtype associated with classic allergic (IgE mediated) mechanisms
  - IL-4 and IL-13 mediated pathways
  - IL-5—Eosinophil maturation and survival

- **Non Th2 pathways**—Less well defined. Explains may of the non-allergic mediated asthma
  - Epithelial-extracellular matrix inflammation
  - Response to infectious agents
  - TGF-beta/Smad2 overexpression
  - Airway remodeling

Inflammatory Cascade
Humanized Monoclonal Antibodies

- Revolutionary advance in the use of antibodies as therapy
- Monoclonal antibodies produced in animals/non human cell cultures
- Genetic sequence for the binding sites is spliced out of non human source and inserted into a human gene for IgG production
- Identified by the -mab ending.

Omalizumab

**Biological Characteristics**

- Humanized monoclonal antibody against IgE
- Binds circulating IgE regardless of specificity
- Forms small, biologically inert Xolair: IgE complexes
- Does not activate complement

---

In this simplistic model of asthma, specific antagonism of selected mediators could be a very effective treatment for asthma

<table>
<thead>
<tr>
<th>Specific targets</th>
<th>Specific Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td>Dupilumab</td>
</tr>
<tr>
<td>IL-5</td>
<td>Mepolizumab</td>
</tr>
<tr>
<td>IL-13</td>
<td>Dupilumab</td>
</tr>
<tr>
<td>IgE</td>
<td>Omalizumab*</td>
</tr>
</tbody>
</table>
Recent Classification of Asthma Phenotypes

Early onset atopic with stable asthma
Early onset atopic asthma with poor control
Late onset female predominant asthma associated with obesity
Late onset atopic asthma
Late onset with mixed inflammation

Am J Respir Crit Care Med Vol 181, pp 315–323, 2010

Theory: Response to treatment, especially treatment with biological modifiers can be predicted by clinical asthma phenotypes

Omalizumab—Anti IgE therapy
IgE mediated asthma with significant allergy triggers

Mepolizumab—Anti IL-5 therapy
Asthma with eosinophilia

Dupilumab—Anti IL-4 and Anti-13
Allergic asthma with eosinophilia

In actual practice, patient selection and response to treatment is much more complicated
Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response.
Biomarkers useful in directing asthma therapy

Blood eosinophil—IL-5 especially (IL-4 and IL-13)

Periostin—IL-13

FeNO—IL-4, IL-5, IL-13

IgE—Allergic mediated, IgE blocking agents

Biomarker based asthma therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>IgE, FeNO, atopy, eosinophil</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Blood Eosinophilia</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4/IL-13</td>
<td>FeNO, Periostin, Eosinophilia</td>
</tr>
</tbody>
</table>

Biological Modifiers in Asthma

• Omalizumab

• 1st Monoclonal antibody on market for asthma treatment

• Selective IgE Blocker
Overview of IgE-Mediated Inflammatory Cascade

Omalizumab Mechanism of Action (cont’d)

Omalizumab Mechanism of Action
**Relationship Between Asthma and Serum IgE Level**

The risk for allergic asthma starts with relatively low IgE levels. Data from several population-based studies indicate that the overall geometric mean levels of IgE in the general population range from 20 IU/mL to 40 IU/mL.\(^1\)*

*Results of a random, stratified cluster sample of 2657 patients that investigated the association of self-reported asthma with serum IgE levels and skin-test reactivity to allergens. Adapted from Burrows et al. *N Engl J Med*. 1989;320:271.


**Clinical Summary of Omalizumab Therapy**

- Clinical studies—50% reduction in asthma flares and significant improvement in symptoms and quality of life.
- Clinical experience—Outstanding drug for selected moderate to severe asthmatics.
- Cancer risk—most likely a statistical anomaly.
- Anaphylaxis risk. (25 patients out of 39,510 patients treated)
- Duration of Therapy—Of patients stopping drug after 5-7 years, 75% maintained asthma control

**Mepolizumab therapy in asthma (NEJM 2014)**
Biological Modifiers in Asthma--Summary

- Omalizumab reduces exacerbations, improves symptom control, reduces glucocorticoid and β2-agonist usage, improves patient quality of life, together with significant improvements in lung function and has a favorable risk–benefit profile.

- Mepolizumab is efficacious in patients with specific phenotypes of severe asthma characterized by persistent, glucocorticosteroid-resistant eosinophilia.

- Dual inhibition of IL-4 and IL-13 with dupilumab represents a very promising avenue for biologic-based asthma therapy, but further large-scale clinical trials on patients with day-to-day asthma are required to fully validate such an approach.
Bronchial Thermoplasty Rationale

Reduces Excessive Airway Smooth Muscle (ASM) →
Reduced Ability for Bronchoconstriction →
Reduced Asthma Symptoms and Exacerbations →
Improved Asthma Control and Quality of Life

Bronchial Thermoplasty

• If airway smooth muscle is reduced, airway bronchoconstriction can be reduced, and therefore asthma symptoms and quality of life will potentially improve.

• Bronchial Thermoplasty with the Alair® System reduces airway smooth muscle through controlled thermal treatment to the airway wall.

The Alair® System

• The Alair® Catheter is a flexible tube with an expandable wire array at the tip.

• The Alair® Radiofrequency Controller supplies energy via the Alair® Catheter to heat the airway wall.
Reduced Airway Smooth Muscle
3 Years Post-Treatment (Canine Model)

UNTREATED

TREATED

Masson’s Trichrome stain

Treatment Method

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

https://www.youtube.com/embed/el_bQPhH48
Bronchoscopic View of Local Methacholine Challenge

Treated airway on left


Treatment Effects of Bronchial Thermoplasty

- Reduces, but does not eliminate ASM.
- No clinical evidence of airway structure based on FEV₁ values in human studies.
- No clinical evidence of long-term (5 yr) bronchiectasis, decreased pulmonary function, or pneumonia based on CT scans.

Cox et al. AJRCCM. 2006; 173(9): 965-969

- Preclinical histology in canine model showed a reduction in ASM, persistent out to 3 years.


Summary

- Asthma is a complex disease.
- Newer therapies will be directed based on both clinical phenotypes and biomarkers.
- Biological modifiers have and should continue to have dramatic effects on the control of severe asthma.
- Bronchial Thermoplasty represents a promising, new, and novel treatment for asthma.