An Allergist’s Approach to Asthma

S. Shahzad Mustafa, MD, FAAAAI
Disclosures

- Consultant – Genentech, Teva
- Speaker’s Bureau – Genentech, Teva
Outline

- Case
- One airway hypothesis
- Diagnostic evaluation
- Therapeutic options
  - Immunotherapy
  - Biologic agents / monoclonal antibodies
- Case Revisited
Case

- 18 y/o adolescent African American boy with PMH of childhood eczema and seasonal allergies was diagnosed with asthma at age 4. Initially, he experienced difficulty with viral URIs, but then his asthma became more difficult to manage during the warmer months as well. Over the past two years, despite being on fluticasone/salmeterol 500/50, montelukast 10 mg, and albuterol as needed, he has required 3 inpatient hospitalizations for asthma (two in September), and has been treated with systemic steroids two additional times as an outpatient. In between the exacerbations, he feels perfectly well. The patient has no other medical problems, does not smoke cigarettes, and has a cat and a dog at home.
Asthma and Comorbid Conditions

One Airway Hypothesis

- Similar anatomy between upper and lower airway, along with similar pro-inflammatory infiltrate
- Significant epidemiologic relationship between asthma and rhinitis/sinusitis
- Numerous therapeutic studies have shown improvement in asthma with treatment of upper airway
One Airway Hypothesis

Intranasal steroids and the risk of emergency department visits for asthma

Robert J. Adams, MBBS, MD,a Anne L. Fuhlbrigge, MD, MS,b Jonathan A. Finkelstein, MD, MPH,c and Scott T. Weiss, MD, MSb Woodville, Australia, and Boston, Mass

- 13,844 patients, all 5+ years of age, mean age 26, followed for a mean of 3 years
- All patients with asthma and upper airway symptoms
- Primary outcome: ED visits for asthma

Numerous studies have demonstrated minimal deposition of intranasal steroids into the lungs. Suggests a key role for nasal inflammation in modulating lower airway inflammation.

NHLBI Asthma Guidelines

Step 1: Preferred: Low-dose ICS
   Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 2: Preferred: Either: Low-dose ICS + LABA
   Alternative: Medium-dose ICS + either LABA, LTRA, or Theophylline
   OR Medium-dose ICS + Theophylline

Step 3: Preferred: Medium-dose ICS + LABA
   Alternative: Medium-dose ICS + either LTRA or Theophylline

Step 4: Preferred: High-dose ICS + LABA
   Alternative: High-dose ICS + either LTRA or Theophylline

Step 5: Preferred: High-dose ICS + LABA + oral systemic corticosteroid
   Alternative: High-dose ICS + either LTRA or Theophylline + oral systemic corticosteroid

Step 6: Preferred: High-dose ICS + LABA + oral systemic corticosteroid
   Alternative: High-dose ICS + either LTRA or Theophylline + oral systemic corticosteroid

Step up if needed (first, check adherence, inhaler technique, environmental control, and comorbid conditions)

Step down if possible (and asthma is well controlled at least 3 months)

Each step: patient education, environmental control, and management of comorbidities.
Steps 2-4: consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see footnotes).

Quick-relief medication for all patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Caution: Increasing use of SABA or use > 2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines
Therapeutic Options

- SABA
- ICS
- ICS/LABA
- LTRA
- Theophylline
- Anticholinergic agents
- Macrolide antibiotics
- Biologic agents / monoclonal antibodies
- Immunotherapy
- Bronchial thermoplasty
Diagnostic Evaluation

- Eosinophilia (peripheral or sputum)
  - CBC with differential
- Total serum IgE
- Presence of bronchodilator response
- Exhaled nitric oxide (FeNO)
- Presence of allergic sensitizations
- Periostin
Aeroallergen Skin Testing
Common Aeroallergens
Allergen Immunotherapy

- Efficacious for naso-ocular symptoms in ~80% of individuals
- Decreases risk of future allergic sensitizations
- Decreases risk of developing asthma
- Augments asthma management

Allergen Immunotherapy

Subcutaneous (SCIT)  Sublingual (SLIT)

Images taken Google Images.
Prevention of Asthma (PAT Study)

Asthma, rhinitis, other respiratory diseases

Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-Study)

Christian Möller, MD, PhD, a Sten Dreborg, MD, PhD, b Hosne A. Ferdousi, MD, c Susanne Halken, MD, d Arne Høst, MD, PhD, e Lars Jacobsen, MSc, f Antti Koivikko, MD, PhD, g Dieter Y. Koller, MD, h Bodo Niggemann, MD, i Lene A. Norberg, MD, a Radvan Urbanek, MD, PhD, h Erkka Valovirta, MD, PhD, g and Ulrich Wahn, MD, PhD j Umeå and Linköping, Sweden, Oslo, Norway, Sønderborg, Odense, and Hørsholm, Denmark, Turku, Finland, Vienna, Austria, and Berlin, Germany

- 205 patients, ages 6-14, mean age
- All patients with AR but no asthma
- Primary endpoint: development of asthma

PAT Study

SCIT for Asthma

- Included 88 trials
- SCIT directed at house dust mites, pollen, animal dander, mold, and cockroach
- Significant decrease in asthma symptoms
- Significant decrease in utilization of asthma medications
- Significant decrease in bronchial hyperreactivity
- Must account for risk of local or systemic reaction

Cochrane Collaboration 2010.
SLIT for Asthma

Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial

Holger Mosbech, MD, Regina Deckelmann, MD, Frédéric de Blay, MD, Elide Anna Pastorello, MD, Ewa Trebas-Pietras, MD, Luis Prieto Andres, MD, Inga Malcus, MD, Christian Ljørring, MSc, and Giorgio Walter Canonica, MD

Gentofte, Denmark, Leipzig, Germany, Strasbourg, France, Milan and Genoa, Italy, Lublin, Poland, Valencia, Spain, Malmö, Sweden, and Hørsholm, Denmark

- 604 patients, ages 14 years and over, mean age ~30 years
- All patient with AR and well controlled asthma on monotherapy with ICS
- Primary endpoint: reduction in ICS dose from baseline

SLIT for Asthma

SLIT for Asthma

SLIT for Asthma - Safety

# SCIT Versus SLIT

<table>
<thead>
<tr>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available for all aeroallergens</td>
<td>FDA approved for grass and ragweed only</td>
</tr>
<tr>
<td>0.1% risk of systemic reaction</td>
<td>Negligible risk of systemic reaction</td>
</tr>
<tr>
<td>Must be administered at a medical facility</td>
<td>Can be administered at home</td>
</tr>
<tr>
<td>Year round therapy</td>
<td>Co-seasonal therapy</td>
</tr>
</tbody>
</table>

**FIG 3.** SCIT versus SLIT: a balance of efficacy and safety.

Anti-IgE (omalizumab)

- Recombinant humanized IgG mAb

- Numerous studies have shown improvement in:
  - QoL
  - Exacerbations
  - ED visits
  - Hospitalizations
  - Requirement of systemic steroids
Anti-IgE (omalizumab)

Randomized Trial of Omalizumab (Anti-IgE) for Asthma in Inner-City Children


- 419 patients, age 6-20, mean age 11
- All patients with asthma, AR, elevated IgE, and uncontrolled asthma despite at least a daily ICS
- Primary endpoint: number of days with asthma symptoms

Busse W. NEJM 2011; 364: 1005.
Anti-IgE (omalizumab)

Busse W. NEJM 2011; 364: 1005.
Anti-IgE (omalizumab)

Busse W. NEJM 2011; 364: 1005.
Rates of Anaphylaxis

- **Anti-IgE (omalizumab)**
  - 0.1-0.2%
- **Subcutaneous immunotherapy**
  - 0.1%
  - 1 per 1 million doses result in grade 3/4 systemic reaction
  - 1 confirmed death since 2008
- **Sublingual immunotherapy**
  - Case reports only (~6)
  - No fatality reported despite more than 1 billion doses administered

Anti-IL 5

- mepolizumab, reslizumab, benralizumab
- Interleukin 5 and effects of eosinophils
  - Differentiation and maturation
  - Mobilization
  - Activation
  - Survival
- Many individuals with atopic conditions demonstrate local and peripheral eosinophilia
Anti-IL 5

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez

- 621 patients, age 12-74, mean age 48 years
- All patients with eosinophilic asthma uncontrolled on high dose ICS + additional controller medications
- Primary endpoint: clinically significant exacerbations

Anti-IL 5

## Case Revisited

### History
- 18 y/o AA boy
- Early onset of asthma
- Allergic rhinitis
- Infrequent symptoms
- Seasonal exacerbations
- Presence of pets

### Evaluation
- Total IgE = 473 kU/L
- CBC with 800 abs eos
- FEV1 = 86%, s/p BD = 99%
- FeNO = 54 ppb
- + SPT to cat, dust mite, ragweed, alternaria

### Additional Therapeutic Options
- Anti IgE (omalizumab)
- Anti IL 5 agents (mepolizumab, reslizumab)
- Allergen immunotherapy (SCIT or SLIT)
When to Refer

- Patients with moderate to severe asthma
- Patients requiring 2 or more courses of systemic steroids annually
- Patients with a history suggestive of allergic triggers
- Any patient who has been admitted to the hospital or with multiple urgent care visits
Summary

- Must evaluate and treat the upper airway when managing asthma
- For patients with moderate to severe asthma, must complete an appropriate diagnostic evaluation to phenotype the patient before pursuing additional therapies

Therapeutic options

- Allergen immunotherapy
- Biologic agents / monoclonal antibodies
  - Omalizumab
  - Anti IL 5 agents
Thank You

shahzad.mustafa@rochesterregional.org
syedshahzad_mustafa@urmc.rochester.edu