Asthma update 2016

37th Pulmonary Winter Course
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Disclosures

- I have no financial or other conflicts of interest to report
Overview

- There are actually new treatments in asthma this year!
- This talk will cover the new developments over the past few years with a focus on the latest FDA approvals for asthma
Overview

- Mepolizumab (Nucala)
- Reslizumab
- Tiotropium (Spiriva)
- Bronchial thermoplasty
- Azithromycin (Zithromax)
Phenotyping

- A fertile area of research
- Multiple phenotypes have been proposed
- Most asthma therapies are nonspecific so clinical applications are limited at the present time
Phenotyping

- The only significant exception is the broad division of patients based on the presence or absence of significant eosinophilia.
- The currently available novel/targeted therapies are essentially all directed at the eosinophilic phenotype.
Table 1  Asthma phenotypes in relation to characteristics

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Natural history</th>
<th>Clinical and physiological features</th>
<th>Pathobiology and biomarkers</th>
<th>Genetics</th>
<th>Response to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset allergic</td>
<td>Early onset; mild to severe</td>
<td>Allergic symptoms and other diseases</td>
<td>Specific IgE; T&lt;sub&gt;H&lt;/sub&gt;2 cytokines; thick SBM</td>
<td>17q12; T&lt;sub&gt;H&lt;/sub&gt;2-related genes</td>
<td>Corticosteroid-responsive; T&lt;sub&gt;H&lt;/sub&gt;2-targeted</td>
</tr>
<tr>
<td>Late-onset eosinophilic</td>
<td>Adult onset; often severe</td>
<td>Sinusitis; less allergic</td>
<td>Corticosteroid-refractory eosinophilia; IL-5</td>
<td></td>
<td>Responsive to antibody to IL-5 and cysteiny leukotriene modifiers; corticosteroid-refractory</td>
</tr>
<tr>
<td>Exercise-induced</td>
<td>Mild; intermittent with exercise</td>
<td></td>
<td>Mast-cell activation; T&lt;sub&gt;H&lt;/sub&gt;2 cytokines; cysteiny leukotrienes</td>
<td></td>
<td>Responsive to cysteiny leukotriene modifiers, beta agonists and antibody to IL-9</td>
</tr>
<tr>
<td>Obesity-related</td>
<td>Adult onset</td>
<td>Women are primarily affected; very symptomatic; airway hyporesponsiveness less clear</td>
<td>Lack of T&lt;sub&gt;H&lt;/sub&gt;2 biomarkers; oxidative stress</td>
<td></td>
<td>Responsive to weight loss, antioxidants and possibly to hormonal therapy</td>
</tr>
<tr>
<td>Neutrophilic</td>
<td>Low FEV1; more air trapping</td>
<td></td>
<td>Sputum neutrophilia; T&lt;sub&gt;H&lt;/sub&gt;17 pathways; IL-8</td>
<td></td>
<td>Possibly responsive to macrolide antibiotics</td>
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A Th-2 (or Th-2 high) phenotype characterizes what is likely a slight majority of asthmatics. This group is characterized by eosinophilia and is the best understood group in terms of pathogenesis.
The Th-1 (or Th-2 low) phenotype is quite poorly understood by comparison.

- Characterized by a neutrophilic response and relative steroid insensitivity.
- Typically older and obese.
TH2 asthma consists of both early- and later-onset disease over a range of severities. It is likely that the majority of early-onset allergic asthma is mild but that an increasing complexity of immune processes leads to greater severity. Later-onset eosinophilic asthma without traditional allergic elements is more likely to be severe, whereas EIA is a milder form of TH2 asthma. Non-TH2 asthma includes very late-onset, obesity-associated asthma as well as smoking-related and neutrophilic asthma, and asthma in which affected individuals show little inflammation. The intensity of the colors represents the range of severity; the relative sizes of the subcircles suggest relative proportions of affected individuals.

New/emerging treatments

- 2 new approvals by the FDA in 2015 (mepolizumab, tiotropium)
- 1 expected in early 2016 (reslizumab)
Mepolizumab (Nucala)

- Humanized monoclonal antibody against interleukin-5 (IL-5)
- IL-5 is felt to be the most specific cytokine in eosinophil regulatory pathways
The pathway begins with the development of TH2 cells and their production of the cytokines IL-4, IL-5 and IL-13. These cytokines stimulate allergic and eosinophilic inflammation as well as epithelial and smooth-muscle changes that contribute to asthma pathobiology. APC, antigen-presenting cell; CRTH2, chemoattractant receptor-homologous molecule expressed on TH2 cells; iNOS, induced nitric oxide synthase; PGD2, prostaglandin D2; TSLP, thymic stromal lymphoprotein.
In atopic asthma (left), eosinophilic airway inflammation and BHR are driven by adaptive $T_{H2}$ cells that are stimulated by DCs to produce IL-5, IL-13 and IL-4, the latter driving IgE synthesis. In nonatopic or intrinsic asthma (right), which is not dependent on adaptive immunity, ILC2 cells produce IL-5 and IL-13 and thus cause eosinophilia and BHR. As there is no specific allergen involved and as ILC2 cells produce little IL-4, there is no associated IgE response from B cells. Modified from ref. 185. MHCII, MHC class II; TSLPR, receptor for TSLP; NKT cells, natural killer T cells.

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Omalizumab (Xolair)

- Applies to a more discrete patient population
- Anti-IgE mAb
- Criteria:
  - Skin or serum allergen testing positive for a year-round allergen such as dust mites, molds, animal dander, et cetera
  - An elevation in total serum IgE
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MENSA trial

- 576 patients with history of frequent exacerbations (2+) randomized to mepolizumab or placebo
- Statistically significant:
  - Reduction in significant exacerbations (ED/hospitalization)
  - Increase in FEV1 (~100mL)
  - SGRQ and ACQ scores

SIRIUS trial

- 135 adults with severe eosinophilic asthma on oral glucocorticoids

- Compared to placebo:
  - Reduction in steroid dose (50%)
  - Reduced exacerbation rate (32%)
  - ACQ score improvement was both statistically and clinically significant

Patient selection

- FDA indication: Patients with severe asthma aged 12 years and older and with an eosinophilic phenotype
- Dose: 100mg every 4 weeks by subcutaneous injection
- No adjustment for age, weight, or renal/hepatic disease
### Omalizumab Doses (mgs) Administered SQ Injection Every 4 Weeks (≥12 Years of Age)

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<tr>
<th>Baseline IgE IU/mL</th>
<th>Body Weight (kg)</th>
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<tbody>
<tr>
<td></td>
<td>30-60</td>
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<tr>
<td>30-100</td>
<td>150</td>
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<td>&gt;100-200</td>
<td>300</td>
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<td>&gt;200-300</td>
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### Omalizumab Doses (mgs) Administered SQ Injection Every 2 Weeks (≥12 Years of Age)

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<td>&gt;300-400</td>
<td>225</td>
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<tr>
<td>&gt;400-500</td>
<td>300</td>
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<tr>
<td>&gt;500-600</td>
<td>300</td>
</tr>
<tr>
<td>&gt;600-700</td>
<td>375</td>
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</table>
Eosinophilia

- The phase 2 mepolizumab trial (DREAM) used sputum eosinophilia as a criteria but as this test is not widely available it was dropped

Pavord et al., Lancet 2012 Aug 18;380(9842):651-9
**Eosinophilia**

- Defined in the MENSA/SIRIUS trials as either:
  - Peripheral eosinophil count of 150/microliter or more during optimization phase
  - 300/microliter or more in the prior 12 months
Reslizumab

- Another anti-IL-5 monoclonal antibody
- Similar indication for eosinophilic asthma
- Used a higher eosinophil cut off (400) based on a greater predictive value for sputum eosinophilia

Reslizumab

- One major difference with mepolizumab: requires IV infusion instead of sc injection
- Recommended for approval for age 18 and above by FDA advisory committee in Dec 2015
- Expected final decision in March
Other noteworthy mAb

- Benralizumab: Also targets IL-5
- Dupilumab: Directed against the IL-4/IL-13 “complex”
  - Designated as a breakthrough drug by the FDA
  - Effective for eczema/atopic dermatitis as well
- Both entering phase III trials
In atopic asthma (left), eosinophilic airway inflammation and BHR are driven by adaptive T_{h2} cells that are stimulated by DCs to produce IL-5, IL-13 and IL-4, the latter driving IgE synthesis. In nonatopic or intrinsic asthma (right), which is not dependent on adaptive immunity, ILC2 cells produce IL-5 and IL-13 and thus cause eosinophilia and BHR. As there is no specific allergen involved and as ILC2 cells produce little IL-4, there is no associated IgE response from B cells. Modified from ref. 185. MHCII, MHC class II; TSLPR, receptor for TSLP; NKT cells, natural killer T cells.

Tiotropium (Spiriva)

- Long-acting muscarinic antagonist (LAMA)
- In use for over decade as one of the mainstays of COPD therapy
- Asthma recently approved as a second indication by the FDA
- Included in the most recent (2015) GINA guidelines as a possible add-on at step 4
GINA 2015 – changes to Steps 4 and 5

*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy
# Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years.
Tiotropium (Spiriva)

- TALC trial was a noninferiority study with 3 crossover arms (210 patients on low-dose beclomethasone at baseline)
  - Double dose of ICS
  - Add LABA to low-dose ICS
  - Add tiotropium to low-dose ICS

TALC trial

- Tiotropium was at least non-inferior to adding a LABA to low-dose ICS in all outcomes
- Tiotropium was superior to doubling the dose of ICS in almost all of the outcomes (so is LABA)
- So: Tiotropium = LABA

PrimoTinA asthma 1&2

- Addition of tiotropium to ICS+LABA increased time to first exacerbation (primary e.p.) and also pre-bronchodilator FEV1 compared to placebo

BELT trial

- Previously suggested that LABAs were less effective and possibly deleterious in African Americans
- Pragmatic trial of 1070 AA adults randomized to the addition of LABA or tiotropium to their existing dose of ICS

Wechsler, et al., JAMA 2015; 314(16):1720-1730
BELT trial

- No difference in time to first exacerbation, FEV1, or ACQ score between groups
- Not a prespecified outcome but hospitalizations were more frequent in the tiotropium group (p=0.02)

Wechsler, et al., JAMA 2015; 314(16):1720-1730
Bronchial thermoplasty

- Bronchoscopic procedure in which bronchial smooth muscle mass is reduced by (essentially) RF ablation
- Series of 3 procedures
- Not covered by most insurances
- Carries an increased risk of asthma exacerbation immediately after the procedure
BT is performed by a BT-certified pulmonologist in 3 outpatient visits, typically scheduled 3 weeks apart.
Bronchial thermoplasty

- The role of BT in asthma therapy is controversial
- Hotly debated in the literature as well as international conferences
AIR2 trial

- 288 patients randomized to thermoplasty or a sham procedure (control group)
- Main endpoint: AQLQ scores
  - Statistically significant increase compared to sham procedure
  - Not clinically significant (0.19)

AIR2 trial

- Both patient groups had a much larger improvement from baseline AQLQ (1.16 in control group)
- No difference in prespecified secondary endpoints (PEF, FEV1, rescue inhaler use)

AIR2 trial

- Significantly fewer ED visits and severe exacerbations were seen but were not part of the study design.
- This is one of the major sources of contention based on patient selection criteria, along with a lack of follow up of the control group.

The size of the increase in AQLQ scores from baseline were also more than 5x higher than the difference between groups.

This leads many to question whether simply educating and improving compliance is more effective than the procedure.

AIR2: 5 year follow up data

- 82% of the original treated patients (no control patients) completed 5 years of follow up
- Designed as a non-inferiority trial comparing each subsequent year of follow up to the first year after treatment

Reduction in ER Visits Maintained out to 5 years

- The reduction in ER visits for respiratory symptoms at Year 1 was maintained out to at least 5 years.

Compared with 1 year prior to BT treatment (baseline):
- **78%** average decrease in percentage of patients having ER visits
- **88%** average decrease in ER visit event rates

AIR2: 5 year follow up data

- Demonstrates persistence of benefit for 5 years post procedure
- Importantly, there was no decline in FEV1 or radiographic evidence of structural changes of the lung on HRCT

Bronchial thermoplasty

- FDA labeling is for “severe persistent asthma inadequately controlled on ICS + LABA”
- Many interventionalists use the AIR2 study inclusion criteria
Simplified AIR2 criteria

- High dose ICS + LABA
- Oral steroids OK if stable dose
- MTX and others excluded
- Less than 3 hospitalizations or 4 pulses of oral steroids in last year
- Stable meds for 4+ weeks
- Nonsmoker (less than 10 pack-year)
Azithromycin

- Aka statins for pulmonologists
- Little quality data concerning use for the treatment of asthma
- One recent RCT of note
AZISAST trial

- Randomized 109 patients on high-dose ICS/LABA (step 4 or 5 per GINA guidelines) to maintenance therapy with azithromycin or placebo
- Dose: 250mg PO 3x/week

Brusselle, et al., Thorax 2013; 88:322-329
Overall, there was no benefit seen with azithromycin therapy with regards to any of the outcomes tested.

However, subgroup analysis showed that patients with non-eosinophilic asthma had fewer exacerbations.

Brusselle, et al., Thorax 2013; 88:322-329
AZISAST trial

- Non-eosinophilic asthma was defined as a peripheral eosinophil count less than 200 cells/microliter.
- More data is needed but this result suggests azithromycin may be an effective option for the neutrophilic/Th-1 phenotype (COPD is also neutrophilic).

Thank you

- Questions?