New Biologic Therapies For Severe Asthma

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Disclosures for Jonathan Corren, MD

For the 12 months preceding this CME activity, I or my spouse/partner disclose the following types of financial relationships:

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I will be discussing products that are investigational or not labeled for use under discussion.
Overview

- To understand the functions of select cytokines in asthma
- To review the efficacy of anti-cytokine inhibitors and inhibitors in poorly-controlled asthma
What is Severe Asthma?

- “Untreated severe asthma” - uncontrolled symptoms before starting treatment
- “Difficult-to-treat asthma” - uncontrolled asthma due to factors other than asthma
- “Severe refractory asthma” - uncontrolled asthma without other mitigating factors

10-15% of asthmatics are in one of the above categories

Moore, JACI, 2007
ATS Criteria for Severe Asthma

**Major criteria (need 1 or more)**

- 1. Treatment with continuous or near continuous OCS
- 2. Requirement for treatment with high-dose ICS

**Minor criteria (need 2 or more)**

- 1. Requirement for additional daily treatment with controller
- 2. Asthma symptoms requiring short-acting β-agonist daily
- 3. Persistent airway obstruction (FEV1 <80% predicted)
- 4. One or more urgent care visits for asthma per year
- 5. Three or more OCS bursts per year
- 6. Prompt deterioration with 25% reduction in OCS/ICS dose
- 7. Near-fatal asthma event in the past

Wenzel, Am J Respir Crit Care Med, 2000
General Observations Regarding Asthma Therapy

- Asthma medications are usually prescribed without consideration of markers of responsiveness to a specific therapy.

- Current treatment guidelines for severe asthma emphasize high-dose ICS + LABA.

- Data indicate only partial response rate of severe asthma to ICS, even at high doses or when combined with LABA.
## Control of Asthma with ICS and ICS/LABA Combination

<table>
<thead>
<tr>
<th>Stratum*</th>
<th>N</th>
<th>Well-controlled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - FP</td>
<td>544</td>
<td>65</td>
</tr>
<tr>
<td>1 - FP-S</td>
<td>539</td>
<td>71</td>
</tr>
<tr>
<td>2 - FP</td>
<td>577</td>
<td>52</td>
</tr>
<tr>
<td>2 - FP-S</td>
<td>583</td>
<td>69</td>
</tr>
<tr>
<td>3 - FP</td>
<td>567</td>
<td>33</td>
</tr>
<tr>
<td>3 - FP-S</td>
<td>568</td>
<td>52</td>
</tr>
</tbody>
</table>

*Stratum 1 = no ICS  
Stratum 2 = < 500 mcg ICS  
Stratum 3 = 500-1000 mcg ICS

Bateman, Am J Respir Crit Care Med, 2004
Important Factors in Poor Responses to Asthma Therapy

- Poor adherence
- Comorbid disease states
- Smoking
- Low vitamin D
- Unabated environmental trigger
- Poor delivery of ICS to small AW’s
- Poor response to existing agents
Important Factors in Poor Responses to Asthma Therapy

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- Smoking
- Low vitamin D
- Unabated environmental trigger
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- Poor response to existing agents
Need for Additional Treatments in Asthma

**Step 5**

*Preferred:*

- High-dose ICS + LABA
- Consider Omalizumab for patients who have allergies

**Step 6**

*Preferred:*

- High-dose ICS + LABA + oral corticosteroid
- Consider Omalizumab for patients who have allergies
Currently Available Biologic Therapy for Severe Asthma: Omalizumab

- Humanized monoclonal anti-IgE Ab

- Significant improvement of outcomes in patients receiving 3 controllers:
  - 25% less exacerbations in patient using maximal inhaled therapy
  - Improved asthma symptoms and AQLQ
  - Small improvements in lung function

- Overall response rate 50-60%
  - Absence of active inflammation
  - Insufficient dose of drug
  - Absence of relevant allergen exposure
  - Mechanisms other than IgE-mediated inflammation, e.g., infection, advanced remodeling
**Table 2. Protocol-Defined Asthma Exacerbations Over the 48-Week Treatment Period**

<table>
<thead>
<tr>
<th>Analysis of Primary End Point</th>
<th>Omalizumab Group (n = 427)</th>
<th>Placebo Group (n = 421)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of protocol-defined asthma exacerbations, (n (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>275 (64.4)</td>
<td>242 (57.5)</td>
</tr>
<tr>
<td>1</td>
<td>94 (22.0)</td>
<td>107 (25.4)</td>
</tr>
<tr>
<td>2</td>
<td>31 (7.3)</td>
<td>34 (8.1)</td>
</tr>
<tr>
<td>3</td>
<td>16 (3.7)</td>
<td>23 (5.5)</td>
</tr>
<tr>
<td>(\geq 4)</td>
<td>11 (2.6)</td>
<td>15 (3.6)</td>
</tr>
<tr>
<td>Rate of protocol-defined asthma exacerbations per patient</td>
<td>0.66</td>
<td>0.88</td>
</tr>
<tr>
<td>Incidence rate ratio (95% CI); (P) value</td>
<td>0.75 (0.61–0.92); 0.006</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Hanania, Ann Intern Med, 2011
New Medications in Development for Severe Asthma

- CRTH2 inhibitors
- Tyrosine kinase inhibitors
- Toll-like receptor agonists
- Cytokine inhibitors
  - IL4/13
  - IL5
  - IL9
  - IL17
  - Thymic stromal lymphopoietin (TSLP)
New Medications in Development for Severe Asthma

- CRTH2 inhibitors
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  - IL4/13
  - IL5
  - IL9
  - IL17
  - Thymic stromal lymphopoietin (TSLP)
Overview of Asthma Pathophysiology
Lymphocyte Phenotypes in Asthmatics

- Lymphocyte phenotypes in bronchial tissue of asthmatics - approximately 60% of patients have TH2 predominance (IL-4,-5,-13)

- Airway eosinophils - associated with presence of TH2 phenotype
  - Bronchial tissue eosinophilia - 60%
  - Sputum eosinophils - 40-50%
  - Blood eosinophils - 40-50% (may not correlate with sputum)

- Airway neutrophils
  - Frequency unknown
  - May be linked to infection, tobacco, air pollution
Biomarkers of TH2 Phenotype

- **Exhaled nitric oxide**
  - NO is produced by respiratory epithelium under direct control of IL-13; correlates with amount of IL-13
  - Often but not always correlated with sputum/blood eosinophil numbers
  - Is a reproducible marker of TH2 phenotype (coefficient of variation 20%)
  - Predicts responsiveness to inhaled corticosteroids

- **Serum markers**
  - Periostin
  - Dipeptidyl peptidase-4
  - Both are produced by airway epithelium and are induced by IL-13
TH2 Cytokine Expression in Patients with Low and High TH2 Asthma

Woodruff, Am J Respir Crit Care Med, 2009
Actions of IL-13 in Asthma

- Produced by TH2 cells, mast cells, basophils, eosinophils, innate type 2 cells, natural killer T cells, and macrophages
- Increased adhesion of eosinophils to vascular endothelium
- Increased mast cell proliferation and activation
- Increased epithelial permeability
- Induction of goblet cell proliferation
- Transformation of fibroblasts into myofibroblasts and increased production of collagen
Actions of IL-13

- Reduced smooth muscle response to beta-agonists and enhanced response to acetylcholine
- B-cell class switching to IgE
- IL-4 shares all of the above activities and also promotes differentiation of TH0 cells → TH2 cells
IL-13 is a Central Mediator of Asthma

- Mouse studies revealed that administration of IL-13 to the airway resulted in most of the immunologic and inflammatory features of allergic asthma
- Bronchoalveolar lavage studies demonstrated the presence of IL-13 in patients with asthma
Differential Levels of IL-13 in Sputum of Asthmatics

Saha et al, J Allergy Clin Immunol, 2008
IL-13 Antagonists in Development

- Anti-IL-13 antibodies
  - Lebrikizumab (Genentech-Roche)
  - Tralokinumab (AZ)
  - GSK679586 (GSK)

- Anti-IL-4/-13 receptor antibody
  - Dupilumab (Sanofi)
Effect of Lebrikizumab on Bronchial Allergen Challenge

- RDBPC study of LEB (n=13) vs. placebo (n=16)
- LEB dose = 5 mg/kg given every 4 weeks x 4 doses

Scheerens et al, Clin Exp Allergy, 2014
Relationship of Biomarkers to Lebrikizumab Effects on LAR

Scheerens et al, Clin Exp Allergy, 2014
Effects of Lebrikizumab in Poorly-Controlled Asthma

- Age 44 yr
- FEV1 65% of predicted
- Median ICS 500 mcg; LABA use in 80% of subjects
- Dosed 250 mg SC every 4 wks (n=102) or placebo (n=110) for 20 weeks
- Randomization based upon TH2 signature (TH2-high = IgE > 100 IU/ml + blood eosinophils > 140 cells/ml); primary analysis based upon periostin levels above and below median for study group

# Effects of Lebrikizumab on Secondary End-Points

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo Periostin High</th>
<th>Placebo Periostin Low</th>
<th>Lebrikizumab Periostin High</th>
<th>Lebrikizumab Periostin Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe exacerbations</td>
<td>0.27</td>
<td>0.25</td>
<td>0.08</td>
<td>0.24</td>
</tr>
<tr>
<td>ACQ-5</td>
<td>-0.98</td>
<td>-0.75</td>
<td>-1.02</td>
<td>-0.79</td>
</tr>
<tr>
<td>Asthma symptom score</td>
<td>-0.66</td>
<td>-0.57</td>
<td>-0.68</td>
<td>-0.50</td>
</tr>
</tbody>
</table>


P = NS for all comparisons
### Intra-subject Variability of Biomarkers During Run-In

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum periostin (n=201)</th>
<th>FeNO (n=212)</th>
<th>Blood eosinophils (n=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CV, %</td>
<td>5.0 (4.4, 5.6)</td>
<td>19.3 (17.4, 22.2)</td>
<td>21.3 (18.7, 24.)</td>
</tr>
</tbody>
</table>

### Effects of Lebrikizumab on Exacerbations in Poorly-Controlled Asthma

- **463 patients, equally divided between 4 groups**
- **Dosed with lebrikizumab - 37.5, 125 or 250 mg SC or placebo every 4 wk for 24 wk**

<table>
<thead>
<tr>
<th>Periostin status</th>
<th>Lebrikizumab 37.5 mg</th>
<th>Lebrikizumab 125 mg</th>
<th>Lebrikizumab 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>62%*</td>
<td>35%</td>
<td>11%</td>
</tr>
<tr>
<td>Periostin High</td>
<td>81%*</td>
<td>77%*</td>
<td>22%</td>
</tr>
</tbody>
</table>

*P<0.05

Hanania, AAAAI Annual Meeting, 2014
Effects of Tralokinumab in Patients with Detectable Sputum IL-13

- Age 47-50 yr
- FEV1 61% of predicted
- Median ICS 1000 mcg
- LABA use in 87% of subject
- Dosed 150, 300, or 600 mg or placebo SC for 20 weeks
- Randomization required that 50% of patients be skin test (+)
- Sputum IL-13 assay:
  - Placebo, n = 17
  - Sputum IL-13 (+), n = 11
  - Sputum IL-13 (-), n = 28

Piper et al, Eur Respir J, 2013
Tralokinumab in Poorly-Controlled Asthma

- 463 subjects
- Age 49-50 yr
- FEV1 68-69%
- Chronic OCS 16-18% of patients
- Dosed with tralokinumab 300 mg SC or placebo SC every 2 wk x 52 wk
AQLQ in Relation to Periostin and DPP-4 Status

Difference vs placebo at Week 52 (95% CI) = 0.22 (-0.15, 0.59); 0.21 (-0.16, 0.58); 0.69 (0.30, 1.08); -0.20 (-0.54, 0.15) for periostin-high, -low, DPP-4-high and -low, respectively.

*P<0.05

*Dipeptidyl peptidase-4
Effects of Dupilumab on Asthma with Eosinophils

- Age 37-50 yr
- FEV1 72% of predicted
- High-dose ICS + LABA (FP/S 500/50) use – 80%
- Dosed 300 mg IV weekly or placebo for 12 weeks
- Randomization required blood eosinophils greater than 300 cells/ml
- LABA stopped after 4 weeks; ICS tapered weekly for 4 weeks as tolerated

Functions of IL-5

- Primary cell sources: CD4 TH2 cells, innate lymphoid cells, mast cells

- Primary functions:
  - Eosinophil differentiation
  - Eosinophil migration
  - Eosinophil activation
  - Eosinophil survival
IL-5 Antagonists in Development

- Anti-IL5 antibodies
  - Mepolizumab
  - Reslizumab

- Anti-IL5 receptor antibodies
  - Benralizumab
Early studies of mepolizumab in mild-moderate asthmatics did not demonstrate any consistent significant benefits.

Given the relationship of sputum eosinophilia and exacerbations of asthma, investigators speculated that patients with high sputum eosinophil counts might benefit most from mepolizumab.

Two studies published in 2009 in patients with eosinophilic asthma and recurrent exacerbations (Nair, Haldar)
Mepolizumab in Refractory Eosinophilic Asthma

- 61 patients
- Age 44-50 yr
- FEV1 (post-BD) 78% of predicted
- ICS 1711-2038 mcg/day
- Regular use of oral CS in 53-57%
- Asthma exacerbations - 5-5.5 in past year
- Dosed 750 mg IV weekly or placebo for 50 weeks

Mepolizumab in Refractory Eosinophilic Asthma – Secondary Endpoints

Mepolizumab in Severe Eosinophilic Asthma

- 576 patients
- Required to have eosinophil count of 150 cells/mcl at screen or 300 cells/mcl in the past year
- Age 49-51yr
- FEV1 59-62% of predicted
- Regular use of oral CS in 23-27%
- Asthma exacerbations – 3.5-3.6 in past year
- Dosed with mepolizumab 75 or 100 mg SC or placebo every 4 weeks for 32 weeks

Effects of Benralizumab in Poorly Controlled Asthma

- Age 45-50 yr
- FEV1 65-69% of predicted
- Exacerbations in past year = 2.2-2.3
- Medium-high dose ICS + LABA use in 100% of subjects
- Dosed benralizumab 2, 20, or 100 mg or placebo SC at weeks 1, 4, 8, 16, 24, 32, and 40
- Primary endpoint = annual exacerbation rate

Castro et al, Annual ATS Meeting, 2014
Annual Exacerbation Rate

Castro et al, Annual ATS Meeting, 2014
Pulmonary Function Changes in Relation to Blood Eosinophils

Castro et al, Annual ATS Meeting, 2014
Functions of IL-9 in Asthma

- Produced by CD4 TH2 cells, TH9 cells, TH17 cells, Treg cells, and mast cells

Activities:
- Stimulation of mast cell growth
- Promotion of TH2 cytokine production
- Promotion of TH2, TH17, and B cell growth
- Upregulation of mucin expression
- Contribute to regulation of allergic inflammation
- Increase fibrosis in airways
Anti-IL-9 in Severe Asthma

- 367 patients
- Age 41-45 yr
- FEV1 70-72% of predicted
- 50% had eosinophils > 300 cells/ml, 50% < 300 cells/ml
- 50% on high-dose ICS/LABA, 50% on medium dose
- Exacerbation mean 2 in past yr
- Dosed with MEDI-528 - 30, 100, or 300 mg or placebo SC every 2 wk
- Steroids stable for 13 weeks, then reduced x 12 weeks

Oh et al, Respir Res, 2013
Functions of IL-17 is Asthma

- Primary sources = Th17 cells, CD8⁺T cells, γδ T cells, NKT cells.
- Other possible sources = eosinophils, neutrophils, macrophages

Biologic effects:
- Neutrophil maturation from CD34+ cells
- Stimulation of neutrophil-attracting chemokines (CXCL1, CXCL2, CXCL5, CXCL6, CXCL8, and CCL2)
- Increased expression of eosinophil-attracting chemokines (CCL5 [RANTES] and CCL11 [eotaxin])

Presence of IL-17 correlates with:
- Asthma severity
- Neutrophil percentage in BAL
- IL-5 concentration in BAL
Anti-IL-17RA (Brodalumab) in Moderate-Severe Asthma

- 302 patients with moderate-severe asthma
- Randomized to brodalumab 140 mg, 210 mg, or 280 mg or placebo SC every 2 weeks for 12 weeks
- Primary endpoint = ACQ
Functions of TLSP in Asthma

- Main source = epithelium

- Main functions
  - Polarizes macrophages, leading to shift in TH cell differentiation to TH2
  - Increases release of TH2 cytokine

- TSLP mRNA identified in lung epithelium in patients with asthma
Effect of Anti-TSLP (AMG 157) on Early and Late Asthmatic Responses

Scheerens et al, Clin Exp Allergy, 2014
Effect of Anti-TSLP on Eosinophils and Exhaled Nitric Oxide

Scheerens et al, Clin Exp Allergy, 2014
Conclusions

- Specific cytokine antagonism using monoclonal antibodies is a promising approach to the treatment of severe asthma.

- IL-5 and IL-13 (with or without IL-4) appear to be relevant targets and inhibition improves pulmonary function and reduces exacerbations.

- These drugs appear to be most effective when utilized in patients characterized as having “TH2” asthma.