Biologic Therapy in the Management of Asthma

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Disclosures

• None
Objectives

• Define severe asthma phenotypes and endotypes
• Describe the role of biologics in asthma management
• Review pivotal trials for mepolizumab and reslizumab (anti-IL5 monoclonal antibodies)
• Discuss the role of biomarkers in identifying appropriate patients for targeted therapy
Asthma Statistics in the U.S.

24 million
People with primary diagnosis of asthma

10.5 million
Physician office visits

1.8 million
Emergency department visits

439,000
Hospitalizations

3,630
Asthma-related deaths
Healthcare Costs Associated with Asthma

Higher healthcare costs with asthma severity\(^2\)

**Est. $56B total cost of asthma**\(^1\)

- **$12,800**
  - Increased healthcare utilization
  - Emergency Room (ER) visits
  - Hospitalizations

- **$4,800**
  - Patients with exacerbations have higher health care costs than patients without exacerbations\(^3\)

- **$2,200**

Severe Asthma

European Respiratory Society/American Thoracic Society definition of severe asthma for patients aged ≥6 years*

The definition of severe asthma requires that one or both of the following levels of treatment for the previous year has been needed to prevent asthma from becoming uncontrolled or asthma that remains uncontrolled despite this level of treatment:

- Treatment with guidelines suggested medications for GINA steps 4-5 asthma (high dose inhaled glucocorticoid and long-acting beta agonist [LABA] or leukotriene modifier/theophylline) for the previous year
- Treatment with systemic glucocorticoid for ≥50% of the year

Uncontrolled asthma is defined as at least one of the following:

- Poor symptom control: ACQ consistently >1.5, ACT <20 (or “not well controlled” by NAEPF/GINA guidelines)
- Frequent severe exacerbations: two or more bursts of systemic glucocorticoids (more than three days each) in the previous year
- History of serious exacerbation: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year
- Airflow limitation: after appropriate bronchodilator withhold FEV₁ <80% predicted (in the face of reduced FEV₁/FVC defined as less than the lower limit of normal)

The ERS/ATS definition of high doses of various inhaled glucocorticoids in relation to patient age (in mcg/day):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age 6 to 12 years</th>
<th>Age &gt;12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>≥320 (HFA MDI)</td>
<td>≥1000 (HFA MDI)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>≥800° (MDI or DPI)</td>
<td>≥1600° (MDI or DPI)</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>≥160 (HFA MDI)</td>
<td>≥320 (HFA MDI)</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>≥500° (HFA MDI or DPI)</td>
<td>≥1000° (HFA MDI or DPI)</td>
</tr>
<tr>
<td>Mometasone</td>
<td>≥500° (DPI)</td>
<td>≥800° (DPI)</td>
</tr>
</tbody>
</table>

*Note: The definition of severe asthma may vary based on regional and national guidelines.

UpToDate Online https://www.uptodate.com
Severe Asthma Subtypes

• Untreated severe asthma
• Difficult-to-treat severe asthma
• Treatment-resistant severe asthma

Asthma Heterogeneity

• Growing evidence that asthma is not a single disease process

• Patients with severe asthma present with a variety of clinical features and physiological characteristics

• Patients do not respond uniformly to asthma medications, particularly glucocorticoids
Asthma Phenotypes and Endotypes

- **Phenotype**: observable properties (clinical characteristics) produced by the interaction of the genotype and the environment
- **Endotype**: underlying pathological mechanisms
- A well-defined endotype should link the key pathogenic mechanism with a clinical phenotype of asthma thru biomarkers
Eosinophilic Asthma Phenotype

- **Asthma with elevated eosinophils** – bronchial biopsy, induced sputum, peripheral blood
- **Allergic phenotype** – young age of onset, adaptive Th2 driven, atopic, steroid responsive
- **Non-allergic phenotype** – innate/lymphoid cells, later onset, non-atopic, steroid resistant
- Both types do produce IL-5
Treatment Options for the “Unresponsive” Patient with Asthma
# Biologics Currently in Use or Under Investigation

<table>
<thead>
<tr>
<th>Predictive biomarker</th>
<th>Drug</th>
<th>Target</th>
<th>Effects</th>
<th>Regulatory status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood eosinophils</td>
<td>Omalizumab</td>
<td>IgE</td>
<td>Reduces exacerbations</td>
<td>FDA and EMA approved</td>
</tr>
<tr>
<td>Periostin</td>
<td></td>
<td></td>
<td>Improves symptoms and quality of life</td>
<td></td>
</tr>
<tr>
<td>FENO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood/sputum eosinophils</td>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Reduces eosinophil counts, exacerbations, and OCS</td>
<td>FDA approved</td>
</tr>
<tr>
<td>FENO</td>
<td></td>
<td></td>
<td>Improves FEV₁</td>
<td>EMA under consideration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tested for CRSwNP</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Reduces eosinophil counts, exacerbations</td>
<td>FDA under consideration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improves FEV₁</td>
<td></td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>Benralizumab</td>
<td>IL-5Rα</td>
<td>Reduces eosinophil and basophil counts, exacerbations</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improves FEV₁</td>
<td></td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>Dupilumab</td>
<td>IL-4Rα</td>
<td>Reduces exacerbations</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improves FEV₁</td>
<td>Tested for CRSwNP, AD, and EoE</td>
</tr>
<tr>
<td>Periostin</td>
<td>Tralokinumab</td>
<td>IL-13</td>
<td>Reduces eosinophil counts and exacerbations</td>
<td>Phase II</td>
</tr>
<tr>
<td>DPP-4</td>
<td></td>
<td></td>
<td>Improves FEV₁</td>
<td></td>
</tr>
<tr>
<td>Periostin</td>
<td>Lebrikizumab</td>
<td>IL-13</td>
<td>Reduces exacerbations</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improves FEV₁</td>
<td></td>
</tr>
</tbody>
</table>

Anti-IL5 Therapies
Initial Mepolizumab Studies

• Did not show clinical efficacy (FEV1, peak flow, airway hyper-responsiveness), despite being effective at lowering blood and airway eosinophils

• Brought into question the actual role of eosinophils in the pathophysiology of asthma

Mepolizumab use in Eosinophilic Asthma

• **Nair P, et al. NEJM 2009**
  - 9 pts mepolizumab vs 11 placebo
  - Significant reduction in exacerbations and steroid sparing effects in treatment arm
  - No improvement in daily symptoms or FEV1

• **Haldar P, et al. NEJM 2009**
  - 61 patient with eosinophilic asthma
  - Reduced exacerbations in treatment group
  - QoL scores improved in mepolizumab group
  - No change in FEV1, BHR

Dose Ranging Efficacy And safety with Mepolizumab (DREAM) Trial

• International, multicenter, double-blind, placebo-controlled trial (2009-2011)
• **Primary endpoint:** reduction in frequency of exacerbations
• **Secondary endpoints:** assess the effects of treatment on blood and sputum eosinophil counts, asthma control, asthma-related quality of life, and FEV1

DREAM Trial: Methods

• Inclusion Criteria:
  • ATS criteria for severe asthma
  • Documented airway reversibility
  • 2 or more exacerbations in the past year
  • Sputum eos > 3% or FeNO > 50ppb or blood eos > 500 cells/uL
• 621 patients randomized to receive 75mg, 250mg, or 750mg IV infusions (13 in total) every 4 weeks
DREAM Trial: Primary Outcome

- Decreased number of clinically significant exacerbations per patient per year:
  - 75 mg mepolizumab by 48% (95% CI 31–61%; p<0·0001)
  - 250 mg mepolizumab by 39% (19–54%; p=0·0005)
  - 750 mg mepolizumab by 52% (36–64%; p<0·0001)
- Similar clinical efficacy between the three doses
DREAM Trial: Secondary Outcomes

Blood Eos significantly reduced at all doses

Sputum Eos significantly reduced only at 750 mg
DREAM Trial: Secondary Outcomes

No statistical improvement in asthma control, quality of life, or FEV1
Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA)

• Placebo controlled comparison of subcutaneous and intravenous administration of mepolizumab
• Inclusion Criteria:
  • Severe asthma with reversibility
  • At least 2 exacerbations in past year requiring steroids
  • High-dose ICS + other
  • Blood Eos > 150 cells/μL or 300 cells/μL within past yr
• 576 patients divided into 75mg IV vs 100mg SQ every 4 weeks for 32wks
• **Primary Outcome**: frequency of clinically significant exacerbations

MENSA Trial Results

- Rate of exacerbations was reduced in both groups:
  - Mepolizumab 75mg IV: 47% (95% CI, 28-60; p<0.001)
  - Mepolizumab 100mg SQ: 53% (95% CI, 36-65; p<0.001)

- FEV1 improved at wk 32 from baseline:
  - 100 mL greater increase in IV group (p=0.02)
  - 98 mL greater increase in SQ group (p=0.03)
Steroid Reduction with Mepolizumab Study (SIRIUS)

## SIRIUS Trial Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N=66)</th>
<th>Mepolizumab (N=69)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in oral glucocorticoid dose at 20 to 24 wk:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary outcome — no. (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 to 100%</td>
<td>7 (11)</td>
<td>16 (23)</td>
<td>2.39 (1.25–4.56)</td>
<td>0.008</td>
</tr>
<tr>
<td>75 to &lt;90%</td>
<td>5 (8)</td>
<td>12 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 to &lt;75%</td>
<td>10 (15)</td>
<td>9 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0 to &lt;50%</td>
<td>7 (11)</td>
<td>7 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No decrease in oral glucocorticoid dose, a lack of asthma control, or</td>
<td>37 (56)</td>
<td>25 (36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>withdrawal from treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in daily oral glucocorticoid dose of ≥50% — no. (%)‡</td>
<td>22 (33)</td>
<td>37 (54)</td>
<td>2.26 (1.10–4.65)</td>
<td>0.03</td>
</tr>
<tr>
<td>Reduction in daily oral glucocorticoid dose to a level ≤5 mg — no. (%)‡</td>
<td>21 (32)</td>
<td>37 (54)</td>
<td>2.45 (1.12–5.37)</td>
<td>0.02</td>
</tr>
<tr>
<td>Reduction of 100% in oral glucocorticoid dose — no. (%)‡</td>
<td>5 (8)</td>
<td>10 (14)</td>
<td>1.67 (0.49–5.75)</td>
<td>0.41</td>
</tr>
<tr>
<td>Median percent reduction from baseline in daily oral glucocorticoid</td>
<td>0.0 (–20.0 to 33.3)</td>
<td>50.0 (20.0 to 75.0)</td>
<td>NA</td>
<td>0.007</td>
</tr>
<tr>
<td>dose (95% CI)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SIRIUS Trial Results
Reslizumab – Phase III Trials

• Inclusion Criteria:
  • At least med dose ICS
  • Blood eos > 400 cells/uL during 2-4 week screening period
  • At least one exacerbation within past year
• Primary outcome:
  • Clinical exacerbations during 52 wk treatment period
• Secondary outcomes:
  • Change in FEV1, ACQ-7 score, ASUI score, SABA use, blood eos count
• 106 patients randomized into treatment (3.0mg/kg IV q4wk) vs placebo

Reslizumab Trial Results

- Significantly reduced annual rate of clinical exacerbations by 50-59%
- Time to first exacerbation increased
Reslizumab Trial Results

A

- Reslizumab 3.0 mg/kg
- Placebo

Visit (week) 0 4 8 12 16 20 24 28 32 36 40 44 48 52

LS mean change from baseline in FEV1 (L)

B

Visit (week) 0 4 8 12 16 20 24 28 32 36 40 44 48 52

Endpoint
IgE as Treatment Target in Asthma

- Allergic sensitization present in majority of patients with asthma
- Omalizumab – humanized monoclonal antibody directed against IgE → prevents interaction with FcERI on mast cells, basophils and eosinophils
- Efficacy: reduced asthma symptoms, prevented exacerbations, allowed for reduction in ICS use

Patient Selection for Omalizumab

Asthma Biomarkers: FeNO

- Good correlation with sputum eosinophilia
- Suggests responsiveness to corticosteroids
- No correlation between anti-IL5 therapy and reductions of eos and FeNO levels (suggests the two are unrelated) – Haldar NEJM 2009 and DREAM Trial
- Appears to be closer related to Th2-driven (allergic) inflammation, as FeNO decreases with use of anti-IL4 (pitrakinra) and anti-IL13 (lebrikizumab) therapy
**Asthma Biomarkers: Periostin**

- Extracellular matrix protein induced by IL-4 and IL-13 in airway epithelial cells and lung fibroblasts – proposed as eos asthma marker
- Has successfully identified Th-2 high and Th-2 low phenotypes, based on total IgE and blood Eos
- Useful biomarker for anti-IL13 therapy
- Association of periostin with airway eos induced by allergen-independent pathways remains to be confirmed
Thank you!

Questions?