Type 2 Inflammation in Asthma
New Insights and Treatment Options
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Disclosures

Dr. Williams reports that his spouse is an employee of GlaxoSmithKline and owns stock in that company.

The clinical reviewer, Matthew Casciano, PharmD, BCPS, has no actual or potential conflict of interest in relation to this program.

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Credits: 1.0 hour (0.10 CEU)
Type of Activity: Application
Learning Objectives

- **Discuss** the pathophysiology of type 2 inflammation in asthma and how it relates to severe asthma
- **Analyze** new agents and agents in clinical trials for asthma with unique targets in the inflammatory pathway
- **Evaluate** product-specific information for biologics in order to recommend optimal therapies for patients with uncontrolled asthma
- **Illustrate** the role of the pharmacist in various healthcare settings (community, hospital, managed care, specialty) in educating patients about the underlying mechanisms of asthma and making treatment recommendations
Asthma in the United States

• Epidemiology
  • Estimated to affect 24.6 million people, including 6.1 million children
  • Nearly half experience at least 1 acute asthma episode annually

• Impact
  • 9.8 million medical clinic visits annually
  • 1.8 million emergency department (ED) visits annually
  • Annual economic cost: $81.9 billion (data through 2013)

• Mortality
  • 3564 deaths (2017)

Asthma is Not a Clinically Homogeneous Condition

• Multiple areas of difference
  • Clinical presentations
  • Physiological characteristics
  • Responses to therapy

• Time of asthma development is a key factor
  • Children—relatively homogeneous with a strong personal and family allergic history of atopy
  • Adults—very mixed group of patients

Traditional Approach to Asthma Management

• Directed by guidelines and evidence
• Employs a stepwise approach
• Achieves outcomes for 90%+ of patients
• Does not address heterogeneous nature of disease

NAEPP 2007 Guidelines for Asthma Treatment

Intermittent asthma

Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

Step 1
Preferred: SABA PRN

Alternative: Cromolyn, LTRA, or theophylline

Step 2
Preferred: Low-dose ICS

Alternative: Medium-dose ICS

Step 3
Preferred: Medium-dose ICS + LABA

Alternative: Low-dose ICS + either LTRA, theophylline, or zileuton

Step 4
Preferred: High-dose ICS + LABA

AND

Consider omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA + oral systemic glucocorticoids

AND

Consider omalizumab for patients who have allergies

Step 6
Preferred: High-dose ICS + LABA + oral systemic glucocorticoids

AND

Consider omalizumab for patients who have allergies

Step up if needed
First, check adherence, environmental control, and comorbid conditions

ASSESS CONTROL

Step down if possible
and asthma is well controlled for 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

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-min intervals as needed. Short course of oral systemic glucocorticoids may be needed.
- Use of SABA >2 days/week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

EIB, exercise-induced bronchoconstriction; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; NAEPP, National Asthma Education and Prevention Program; PRN, as needed; SABA, short-acting beta agonist.

NAEPP. Guidelines for the Diagnosis and Management of Asthma (EPR-3).
Global Initiative for Asthma Recommendations

Adults & adolescents 12+ years

**Personalized asthma management:**
Assess, Adjust, Review response

**Asthma medication options:**
Adjust treatment up and down for individual patient needs

**PREFERRED CONTROLLER**
to prevent exacerbations and control symptoms

- As-needed low-dose ICS-formoterol*
- Low-dose ICS taken whenever SABA is taken†

**PREFERRED RELIEVER**
Other reliever option

- As-needed low-dose ICS-formoterol*

**STEP 1**
Daily low-dose ICS, or as-needed low-dose ICS-formoterol*

**STEP 2**
LTRA, or low-dose ICS taken whenever SABA is taken†

**STEP 3**
Low-dose ICS-LABA

**STEP 4**
Medium-dose ICS-LABA

**STEP 5**
High-dose ICS-LABA
Refer for phenotypic assessment ± add-on therapy (e.g., tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R)

As-needed low-dose ICS-formoterol*
As-needed SABA

*Off-label; data only with budesonide-formoterol (bud-form)
†Off-label; separate or combination ICS and SABA inhalers

Other controller options

Confirmation of diagnosis, if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

**STEP 5**
Add low-dose OCS, but consider side-effects

High-dose ICS, add-on tiotropium, or add-on LTRA

Low-dose ICS-formoterol is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

#Consider adding house dust mite sublingual immunotherapy for sensitized patients with allergic rhinitis and FEV >70% predicted

Source: © Global Initiative for Asthma, www.ginasthma.org
Controlling Asthma

• With good adherence, approximately 90% of patients with asthma can be well controlled by guideline-directed medical therapy
  • National Institutes of Health Expert Panel Report 3 (NIH EPR-3)
  • Global Initiative for Asthma (GINA)
• The remaining 5% to 10% remain uncontrolled despite therapy with multiple therapies, including ICS and OCS

Economic Burden of Severe Uncontrolled Asthma

Blue: Persistent asthma (n=63,597)
Gray: Severe uncontrolled asthma (n=1762)

P<0.001 for each comparison

Mean Costs ($)

- Total costs
- Asthma medication
- Total medical
- Hospitalization
- Office visits
- Outpatient services
- ED services

Evolving Definition of Severe vs. Uncontrolled Asthma

• Severity and control are linked and sometimes used interchangeably
  • NAEPP guidelines
    • Severity assessment is in patients who are not currently using long-term control therapies
    • Severity and control have similar definitions → contributes to confusion about how to accurately differentiate severe from uncontrolled asthma
  • GINA guidelines
    • Severity assessment is in patients who have been using regular control medication for several months

• Severity and control are separate aspects of asthma
  • Severity
    • Intrinsic to the disease state and molecular mechanism of disease
    • Related to the pathophysiology driving observable symptoms
    • Defines treatment aggressiveness in order to control symptoms
  • Control
    • Extrinsic to the disease (independent of disease severity)
    • Related to the frequency and impact of symptoms
    • Impacted by external factors, including inhaler technique and adherence, and environmental triggers

After confirmation of asthma diagnosis and management of comorbidities, severe asthma is defined as:

“Asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.”

ATS, American Thoracic Society; ERS, European Respiratory Society.

Severe Asthma: Unmet Needs

- Current guideline management strategies do not address all needs
- Asthma exhibits heterogeneity
- Patients with severe asthma represent disproportionate costs for asthma care
  - Individualized/personalized/precision approach is warranted for optimal management
# Phenotypic Classification by SARP

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Onset</th>
<th>Lung Function</th>
<th>Atopy</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>Early</td>
<td>Normal spirometry</td>
<td>Present</td>
<td>Controlled with 1 or 2 medications</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>Early</td>
<td>Preserved spirometry</td>
<td>Present</td>
<td>Increased medication use and healthcare utilization compared to above</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>Late</td>
<td>Moderate reduction</td>
<td>Absent</td>
<td>Often obese and female; requires OCS often for exacerbations</td>
</tr>
<tr>
<td>Clusters 4 and 5</td>
<td>Variable</td>
<td>Severe obstruction and persistently reduced</td>
<td>Variable</td>
<td>Significant variability in age of onset and medication/healthcare requirements</td>
</tr>
</tbody>
</table>

SARP, Severe Asthma Research Program.

Emerging Asthma Phenotypes

- Allergic asthma
  - Exercise-induced asthma
  - Late-onset eosinophilic asthma
  - Aspirin-exacerbated respiratory disease
- Childhood-onset asthma
- T2-type asthma
- Non-T2-type asthma
  - Very late-onset asthma (women)
  - Obesity-associated asthma
  - Smooth-muscle-mediated paucigranulocytic asthma
  - Smoking-related neutrophilic asthma
- Adult-onset asthma

Asthma pathophysiology can be classified as Th2 High or Th2 Low phenotypes
  - Refers to the degree of airway inflammation mediated by Th2 lymphocytes
  - Classification may be useful in predicting response to various therapies

Th2 cells secrete IL-4, IL-5, and IL-13, which promote processing of B cells to produce IgE and also recruit eosinophils

Resultant effects of cells and mediators include mucus production, airway obstruction and hyperreactivity, smooth muscle hypertrophy, and airway remodeling

Focus is Shifting Toward the Identification of Disease Mechanisms

What can be observed and measured clinically?

Observable characteristics (Phenotype)

What are the potential drivers of disease?

Pathophysiologival mechanism (Endotype)

**Key Mechanisms in Airway Inflammation**

**Type 2 Asthma**
- Allergens
- CRTH2
- Th2 Cell (GATA3)
- B cell (IgE, KIT)
- Mast cell (KIT)

**Non-Type 2 Asthma**
- Irritants/pollutants/microbes/viruses
- Th 17 Cell
- Th 1 Cell

- **Airway Epithelium**
  - TSLP
  - IL-25

- **ILC2** (GATA3)
  - IL-4, 5, and 13
  - GM-CSF
  - Leukotrienes
  - IL-4 and-5
  - PGD₂
  - Histamine
  - IL-3 and -9

- **Eosinophil** (CRTH2)
  - IL-5
  - IL-13

- **Neutrophil**
  - IL-6
  - IL-8
  - Lipoxin

- **Hyperresponsiveness, remodeling, mucus production, and smooth-muscle constriction and hypertrophy**

# Characterization of Inflammatory Pathways and Biomarkers

<table>
<thead>
<tr>
<th>Type 2 — 50% to 70%</th>
<th>Non-Type 2 — 30% to 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main cytokines = IL-4, IL-5, IL-13</td>
<td>Cytokines and cells not well characterized; may involve IL-17, GM-CSF</td>
</tr>
<tr>
<td>Cell sources = Th2 cells, IL-C2 cells, mast cells</td>
<td>Frequently related to bronchial infection</td>
</tr>
<tr>
<td>Variable airway, tissue and blood eosinophilia and eNO; leukotrienes in AERD</td>
<td>No increase in eosinophils, eNO; may have increase in sputum PMNs</td>
</tr>
<tr>
<td>Large portion have elevated total IgE and specific IgE</td>
<td>Typically do not have elevated IgE or relevant specific IgE</td>
</tr>
</tbody>
</table>

AERD, aspirin-exacerbated respiratory disease; eNO, exhaled nitric oxide; GM-CSF, granulocyte-macrophage colony-stimulating factor; PMN, polymorphonuclear; Th2, T-helper 2.

Personalized Approach to Asthma: Utility of Biomarkers

Diagnosis

Severe asthma

Characterize subtype

Phenotype
Gender
Age
Obesity
Ethnicity
Smoking history

Endotype

Blood biomarkers
IgE
Eosinophils
Periostin
DPP-4

Sputum biomarkers
Eosinophils
Neutrophils

Exhaled biomarkers
FeNO

Genotype

Tailored therapy


DPP-4, dipeptidyl peptidase 4.
## Comparison of Asthma Biomarkers

<table>
<thead>
<tr>
<th>Test</th>
<th>Suggested Cut-Off Values for Asthma</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IgE</td>
<td>&gt;150 IU/mL</td>
<td>Consistent with atopic phenotype</td>
<td>Treatment with anti-IgE begins at 30 IU/mL when combined with documented sensitivity</td>
</tr>
<tr>
<td>FeNO</td>
<td>&gt;50 ppb</td>
<td>Simple, noninvasive test</td>
<td>Affected by age, gender, height, smoking, and respiratory infections</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>&gt;150 vs. 300-400 cells/µL</td>
<td>Simple blood test</td>
<td>Affected by allergen exposure, steroids, and infections</td>
</tr>
<tr>
<td>Sputum eosinophils</td>
<td>&gt;3%</td>
<td>Good correlation with Th2 asthma</td>
<td>Semi-invasive; not widely available outside of research settings</td>
</tr>
<tr>
<td>Serum periostin</td>
<td>&gt;50 ng/mL (some sources state &gt;95)</td>
<td>Simple blood test</td>
<td>Primarily evaluated with anti-IL-13 and anti-IgE</td>
</tr>
</tbody>
</table>

Serum Eosinophils and Risk of Asthma Exacerbations

Claims database analysis examining eosinophil count and exacerbations requiring systemic corticosteroids or ED/hospital care

<table>
<thead>
<tr>
<th>Eosinophil Stratum</th>
<th>Severe Exacerbations Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>201–300 cells per µL (n=25,882)</td>
<td>0.94</td>
</tr>
<tr>
<td>301–400 cells per µL (n=15,030)</td>
<td>1.08</td>
</tr>
<tr>
<td>401–500 cells per µL (n=8659)</td>
<td>1.16</td>
</tr>
<tr>
<td>501–600 cells per µL (n=4928)</td>
<td>1.34</td>
</tr>
<tr>
<td>601–700 cells per µL (n=2726)</td>
<td>1.71</td>
</tr>
<tr>
<td>701–800 cells per µL (n=1631)</td>
<td>1.49</td>
</tr>
<tr>
<td>801–900 cells per µL (n=947)</td>
<td>1.58</td>
</tr>
<tr>
<td>901–1000 cells per µL (n=1019)</td>
<td>2.02</td>
</tr>
<tr>
<td>&gt;1000 cells per µL (n=1019)</td>
<td>2.32</td>
</tr>
</tbody>
</table>

# Targeted Pathways for Biologic Therapies

<table>
<thead>
<tr>
<th>Targeted Pathways</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgE</strong></td>
<td>Inhaled allergens stimulate production of IgE by B lymphocytes and bind to mast cells → degranulation</td>
</tr>
<tr>
<td><strong>IL-5</strong></td>
<td>Pro-eosinophilic cytokine; cytokine that regulates proliferation, maturation, migration, and effector functions of eosinophils</td>
</tr>
<tr>
<td><strong>IL-4</strong></td>
<td>Cytokine found in increased levels in airways and sputum of asthma patients and involved in eosinophil trafficking and B cell production of IgE</td>
</tr>
<tr>
<td><strong>IL-13</strong></td>
<td>Cytokine associated with eosinophil trafficking and production of eNO from epithelial cells</td>
</tr>
<tr>
<td><strong>TSLP</strong></td>
<td>Novel target; epithelial cell-derived cytokine; drives allergic inflammatory responses by activating dendritic cells and mast cells</td>
</tr>
</tbody>
</table>

## Non-Type 2 Inflammatory Pathways

| **IL-17** | Cytokine produced by Th17 cells; plays important role in the immunologic responses seen in asthma |
| **CXCR2** | Potent chemo-attractant for neutrophils; under investigation in asthma and COPD |

COPD, chronic obstructive pulmonary disease; CXCR2, chemokine receptor 2; TSLP, thymic stromal lymphopoietin. Wechsler ME. *Respir Care.* 2018;63(6):699-707.
## Development of Target-Specific Therapies for Severe Asthma

<table>
<thead>
<tr>
<th>Downstream mediators</th>
<th>Target Class</th>
<th>Target</th>
<th>Treatments</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immunoglobulins</td>
<td>IgE</td>
<td>Omalizumab</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td>Cytokines</td>
<td>IL-5</td>
<td>Benralizumab</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mepolizumab</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reslizumab</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td>IL-13</td>
<td></td>
<td>Tralokinumab</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td>IL-4 and IL-13</td>
<td></td>
<td>Dupilumab</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td>Receptor (antagonist)</td>
<td>DP₂/CRTTH2</td>
<td>Fevipiprant</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OC000459</td>
<td>Oral</td>
</tr>
<tr>
<td>Upstream mediators</td>
<td>Transcription factor</td>
<td>GATA-3</td>
<td>SB010 DNAzyme</td>
<td>Inhaled</td>
</tr>
<tr>
<td></td>
<td>Alarmin</td>
<td>TSLP</td>
<td>Tezepelumab</td>
<td>Injection</td>
</tr>
</tbody>
</table>
Active cell types of Th2 inflammation: B cells, mast cells, dendritic cells, CD8, CD4, NKT, eosinophils, basophils, Th2 lymphocytes

Resulting in production of antibodies and cytokines

**Biologic Targets**

**Actions**

- IgE
- IL-4
- IL-5
- IL-13

**(Examples)**

- Omalizumab and ligelizumab
- Dupilumab
- Benralizumab (IL-5Ra receptor), mepolizumab, and reslizumab
- Dupilumab, lebrikizumab, and tralokinumab

NKT, natural killer T cell.
Therapeutic Targets for Severe Asthma

## Available Targeted Therapies for Asthma Control

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Target</th>
<th>Age (years)</th>
<th>Route</th>
<th>Frequency</th>
<th>Single-dose vial</th>
<th>Prefilled syringe</th>
<th>Admin. by</th>
<th>Dose determined by</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>≥6</td>
<td>SC</td>
<td>Q2W Q4W</td>
<td>Powder for reconstitution</td>
<td>150 mg/mL 75 mg/0.5 mL</td>
<td>HCP only</td>
<td>Age Weight IgE</td>
<td></td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>≥12</td>
<td>SC</td>
<td>Q4W</td>
<td>Powder for reconstitution</td>
<td>100 mg/mL (also auto-injector)</td>
<td>HCP and patient</td>
<td>N/A (Fixed)</td>
<td></td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>≥18</td>
<td>IV</td>
<td>Q4W</td>
<td>Solution for infusion</td>
<td>No</td>
<td>HCP only</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL-5R</td>
<td>≥12</td>
<td>SC</td>
<td>Q4W Q8W</td>
<td>No</td>
<td>30 mg/mL Auto-injector in development</td>
<td>HCP only</td>
<td>N/A (Fixed)</td>
<td></td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4R†</td>
<td>≥12</td>
<td>SC</td>
<td>Q2W</td>
<td>No</td>
<td>300 mg/2 mL 200 mg/1.14 mL</td>
<td>HCP and patient</td>
<td>Age</td>
<td></td>
</tr>
</tbody>
</table>

†Inhibits IL-4 and IL-13 signaling pathways.

HCP, healthcare professional; IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

FDA. www.accessdata.fda.gov.
Relevant Outcomes from Biologic Therapies

- Reduced exacerbation risks
- Reduced steroid dose, side effects, and adverse effects
- Improved symptoms and quality of life
- Disease modifying effects?
# Biologic Therapies Available for Asthma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>FDA Label</th>
<th>Dosing</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab</td>
<td>IL-5 receptor</td>
<td>Patients ≥12 years with asthma poorly controlled on ICS/LABA/systemic steroids; &gt;2 exacerbations in past year; serum eosinophils &gt;300 cells/µL</td>
<td>30 mg SC every 8 weeks (initial: 30 mg SC every 4 weeks x 3 doses)</td>
<td>Reduces exacerbation rates by 28%-51%; improves FEV1 by 100-160 mL</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4 and IL-13</td>
<td>Patients ≥12 years with moderate to severe asthma with eosinophilic phenotype or with OCS-dependent asthma (also indicated for atopic dermatitis)</td>
<td>400-600 mg SC initially, then 200-300 mg SC every other week; can be self-administered</td>
<td>Reduces exacerbation rates by 60%-80%; reduces FeNO and IgE; improves spirometry and reduces oral steroid dosing</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Patients ≥12 years with severe asthma and eosinophilic phenotype; to be added to maintenance therapy</td>
<td>100 mg SC every 4 weeks (approved for self-administration June 2019)</td>
<td>Reduces exacerbation rates by 47%-53% overall; if serum eosinophils &gt;500 cells/µL, reduces exacerbation rates by 79% and improves FEV1 100-132 mL</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>Patients ≥6 years with moderate-severe persistent asthma poorly controlled despite ICS; positive skin test to perennial aeroallergen (or in vitro reactivity)</td>
<td>75-375 mg SC every 2-4 weeks, based on body weight and total serum IgE</td>
<td>Reduces exacerbation rates by 40% and improves QOL; if serum eosinophils &gt;300 cells/µL, reduces exacerbation rates by 60%</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Patients ≥18 years with severe asthma and eosinophilic phenotype; to be added to maintenance therapy</td>
<td>3 mg/kg IV every 4 weeks</td>
<td>Reduces exacerbation rates by 50%-60%; improves FEV1 100 to 160 mL</td>
</tr>
</tbody>
</table>

FDA, United States Food and Drug Administration; QOL, quality of life.
Ongoing Clinical Considerations

- Deciding between biologics that target same pathways
- Decisions when patients qualify for more than one class
- Duration of treatment
- Benefits of combinations
- Optimal time for initiation
- Long-term adverse effects
- Could other populations benefit?
Considerations for Formulary Assessment

- Efficacy and asthma control
- Safety profile
- Patient adherence and education
- Patient QOL and patient-reported outcomes
- FDA label
- Asthma guidelines
- Value-based assessment and payment models
- Cost and utilization management programs
Considerations for the Pharmacist

• Is the patient a candidate for the biologic?
  • Has appropriate step therapy been used?
  • Have adherence, inhaler technique, and trigger avoidance been assessed?
  • Has biomarker and other testing been performed?

• What is the patient’s immunization status?
  • Are vaccines indicated? If so, when should they be given?
Considerations for the Pharmacist (continued)

• What is the patient’s insurance coverage?
  • Will this be a pharmacy benefit or a medical benefit?
  • Does the medication require prior authorization?
  • Does the provider have any policies regarding receipt and administration?
    • Brown bagging versus white bagging

• Manufacturer considerations
  • How does medication get to the patient?
  • What is the previous experience with the company?
  • What patient assistance programs and other support are available?
Considerations for the Pharmacist (continued)

- Is the patient a better candidate for clinic administration or self-injection?
- What adverse reactions should be monitored for and counseled about?
- What teaching and counseling is required?
- What efficacy outcomes should be monitored?
- What are the storage requirements/considerations?
<table>
<thead>
<tr>
<th>Biologic</th>
<th>Target</th>
<th>Key Trials</th>
<th>Age (years)</th>
<th>Route</th>
<th>Frequency</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>Study 008/009/ALTO</td>
<td>≥6</td>
<td>SC</td>
<td>Q2W</td>
<td>• Powder in single-dose vial for reconstitution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q4W</td>
<td>• PFS available in two doses: 150 mg/mL and 75 mg/0.5 mL</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Dose determined by: age, weight, and baseline IgE levels</td>
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<td></td>
<td></td>
<td></td>
<td>• Administered by: HCP only</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>MENSA/SIRIUS</td>
<td>≥12</td>
<td>SC</td>
<td>Q4W</td>
<td>• Powder in single-dose vial for reconstitution</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Fixed dose for all patients: 100 mg/injection</td>
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<td></td>
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<td>• Administered by: HCP, patients (newly approved)</td>
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<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>BREATH trials</td>
<td>≥18</td>
<td>IV</td>
<td>Q4W</td>
<td>• Solution in single-dose vial for infusion</td>
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<td></td>
<td></td>
<td>• Dose determined by: weight (3 mg/kg)</td>
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<td>• Administered by: HCP only</td>
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<tr>
<td>Benralizumab</td>
<td>IL-5 receptor</td>
<td>SIROCCO/CALIMA/ZONDA</td>
<td>≥12</td>
<td>SC</td>
<td>Q4W</td>
<td>• PFS available for all patients: 30 mg/mL</td>
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<td>Q8W</td>
<td>• Administered by: HCP only</td>
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<tr>
<td>Dupilumab</td>
<td>IL-4 receptor – IL-13</td>
<td>VENTURE/LIBERTY/VOYAGE</td>
<td>≥12</td>
<td>SC</td>
<td>Q2W</td>
<td>• PFS available in two doses: 300 mg/2 mL and 200 mg/1.14 mL</td>
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<td></td>
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<td></td>
<td></td>
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<td>• Dose determined by: OCS use, underlying atopic dermatitis</td>
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<td></td>
<td>• Administered by: HCP, patients</td>
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<tr>
<td>Tezepelumab</td>
<td>TSLP</td>
<td>PATHWAY/NAVIGATOR/SOURCE</td>
<td>≥18</td>
<td>SC</td>
<td>Q2W</td>
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<td></td>
<td></td>
<td></td>
<td>Q4W</td>
<td></td>
</tr>
<tr>
<td>Fevipiprant</td>
<td>DP2 receptor</td>
<td>LUSTER</td>
<td>≥18</td>
<td>Oral</td>
<td>QD</td>
<td></td>
</tr>
</tbody>
</table>

PFS, prefilled syringe; QD, once a day.
Guideline-directed asthma therapy

Well controlled

Continue therapy with periodic monitoring; consider stepdown if well controlled x3 months

Well controlled

Assess adherence, access, avoidance of triggers, appropriate pharmacotherapy, technique

Assess endotype

Not well controlled

Not well controlled

IgE (allergic): anti-IgE biologic, 3-month trial

Eosinophilic: anti-IL-5 or 4/13 biologic, 3-month trial

Mixed IgE and eosinophilic: either biologic class

Consider emerging biologics, macrolides, or bronchial thermoplasty

Consider
Systematic Approach to Considering Biologic Therapies

1. Identify phenotypic and endotypic characteristics
2. Select biologic candidate therapies
3. Identify intermediate outcomes (e.g., ↓ exacerbations, ↑ spirometry, ↓ OCS)
4. Assess risks for harm (e.g., systemic and injection site reactions, SAEs and all AEs)
5. Evaluate
   - Healthcare utilization outcomes (e.g., ED visits or hospitalization; medication use; mortality)
   - Clinical and patient-centered outcomes (e.g., work or school absences, QOL, asthma symptom scores)

AEs, adverse events; SAEs, serious adverse events.
**Recommendations for Biologics Consideration-GINA**

Type 2 airway inflammation if:

- Meets ≥1 of the following criteria while on high-dose ICS (before OCS):
  - Blood eosinophils ≥150 cells/µL
  - FeNO ≥20 ppb
  - Sputum eosinophils ≥2%
  - Asthma is clinically allergen-driven

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### Start with anti-IgE therapy if:

- Age ≥6 years
- Severe allergic asthma
- Sensitization on skin prick testing or specific IgE
- Total serum IgE* and weight within dosage range
- Exacerbations in the last year

**Predictors of good response:**
- Blood eosinophils ≥260 cells/µL
- FeNO ≥20 ppb
- Allergen-driven symptoms
- Childhood-onset asthma

### Start with anti-IL5 or -IL5R therapy if:

- Age ≥12 or ≥18 years
- Severe eosinophilic asthma
- Exacerbations in the last year
- Blood eosinophils ≥300 cells/µL

**Predictors of good response:**
- Higher blood eosinophils
- More exacerbations in previous year
- Adult onset of asthma
- Nasal polyps

### †Start with anti-IL4/-13 if:

- Age ≥12 years
- Moderate-to-severe asthma
- Eosinophilic asthma
- Dependency on OCS

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*Baseline IgE levels do not predict likelihood of response; †Not included in the GINA guidelines, as indicated in the prescribing label.

Thank you!