Chapter 1

Pathophysiology, identification, diagnosis, biomarkers and subtypes
Learning Objectives

1. Describe the role of eosinophils and type 2 inflammation in severe asthma and eosinophil-associated diseases.

2. Identify the mechanisms of action of biologic therapies for severe asthma and eosinophil-associated diseases.

3. Distinguish severe asthma and related eosinophilic diseases from one another using clinical presentation, diagnostic test results, and input from subspecialty consultants.

4. Apply the results of clinical studies that examine the tolerability, efficacy, and safety of approved agents when selecting and monitoring therapy for severe asthma and associated eosinophilic diseases.

Epidemiology of Severe Asthma

- About 5-15% of asthma patients have severe disease, not controlled by available therapies.

- This group accounts for > 50% of health care utilization related to asthma and is at increased risk of asthma-related death.

Chambers et al. JACI 2015;136: 628-3
Jarjour et al. AJRCCM 2012;185: 356-62
Severe Asthma and Related Eosinophilic Diseases: The Role of IL-5 in Diagnosis and Treatment

"Severe" Asthma

**Difficult-to-treat asthma**
Lack of asthma control is due to factors other than asthma itself (non-adherence, incorrect inhalation technique, comorbidities)

**True refractory asthma**
Causes of difficult asthma addressed or excluded, but still have poor asthma control or > 2 exacerbations/year despite high-intensity treatment & verified adherence


Severe Asthma and Related Eosinophilic Diseases: The Role of IL-5 in Diagnosis and Treatment

**Asthma Pathophysiology**

Smooth muscle dysfunction
Airway inflammation
Airway remodeling

Peripheral Eosinophilia: Differential diagnosis

- Allergy/Asthma
- Drug allergy
- Eosinophilic esophagitis/eosinophilic gastrointestinal disease
- Some connective tissue/rheumatologic disorders
- Parasitic infections
- Some cancers
- Acute or chronic eosinophilic pneumonia
- **Hypereosinophilic syndrome**
- **Chronic sinusitis with nasal polyposis**
- **Eosinophilic granulomatosis polyangiitis (EGPA)**
- Other conditions (HIV, hypoadrenalism, Loeffler’s syndrome)

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**Severe Asthma and Related Eosinophilic Diseases:**
The Role of IL-5 in Diagnosis and Treatment

<table>
<thead>
<tr>
<th>Thoracic and extrathoracic manifestations of Churg-Strauss syndrome</th>
<th>Anatomic location</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Pulmonary vasculitis, pleural effusions, hilar lymphadenopathy, cavitary lesion</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Acute pericarditis, constrictive pericarditis, cardiac failure, myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Mononeuritis complex</td>
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<td></td>
</tr>
</tbody>
</table>
Eosinophilic Granulomatosis with Polyangiitis

- Respiratory tract
- Nervous system
- Heart
- Kidney
- GI tract
- Vascular system
- Skin

Morbidity

- Those with higher FeNO and/or AEC compared to those without had worsened airflow obstruction, increased bronchial hyperresponsiveness, worsened asthma control, increased frequency of asthma exacerbations

When to Refer to Specialist

Stepwise Approach for Managing Asthma in Patients >12 Years of Age

Intermittent Asthma

STEP 1
PREFERRED
SABA PRN

STEP 2
PREFERRED
Low-dose ICS
ALTERNATIVE
Cromolyn, Nedocromil, LTRA or Theophylline

STEP 3
PREFERRED
Low-dose ICS + LABA
ALTERNATIVE
Low-dose ICS + either LTRA, Theophylline or Zileuton

STEP 4
PREFERRED
Medium-dose ICS + LABA
ALTERNATIVE
Medium-dose ICS + either LTRA, Theophylline or Zileuton

STEP 5
PREFERRED
High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

STEP 6
PREFERRED
High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Patient Education and Environmental Control at Each Step

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 systemic oral corticosteroids may be needed.
- Caution: Increasing of β2-agonist or use >2x/week for symptoms control indicates inadequate control and the need to step up treatment.


Refer to an asthma specialist for consultation or comanagement if there are difficulties achieving or maintaining control; step 4 care or higher is required (step 3 care or higher for children 0–4 years of age); immunotherapy or omalizumab is considered; or additional testing is indicated; or if the patient required 2 bursts of oral systemic corticosteroids in the past year or a hospitalization. Consider referral to an asthma specialist if signs and symptoms are atypical, if there are problems with a differential diagnosis, or if additional testing is indicated.

Severe Asthma and Related Eosinophilic Diseases:
The Role of IL-5 in Diagnosis and Treatment

Differential diagnosis of Severe Asthma and associated Eosinophilic diseases

Chapter 2
Differential Diagnosis of Severe Asthma and associated Eosinophilic Diseases

- Clinical Evaluation of Severe Asthma
- Differentiating Severe Asthma from other Eosinophilic Conditions
  - Chronic rhinosinusitis and nasal polyposis
  - Allergic bronchopulmonary Aspergillosis
  - Eosinophilic granulomatosis and polyangiitis
  - Hypereosinophilic syndrome

Assessment of Severe Asthma

- Confirm Asthma Diagnosis
  - Symptoms
  - Review medications
  - PFT's
  - ± Methacholine challenge?
  - ± Bronchoscopy
- Assess Severity
  - Inhaler technique
  - Adherence
  - Adequate trial of ICS (low, medium, high)
  - Leukotriene receptor antagonists
  - Theophylline
  - LAMA
  - Oral corticosteroids
  - Previous biologics
- Optimize inhaled Therapy
  - Inhaler technique
  - Adherence interventions
  - Step up or Down??
  - Specialist referral??
- Assess Control
  - Asthma Control test
  - Asthma control questionnaire
Assessment of Asthma Control

Confirm Asthma Diagnosis
Phenotype/endotype

Assess Exacerbation
frequency in past 12 months
≥ 2 requiring systemic
Steroids ≥ 3 days
≥ hospitalization, ICU,
intubation
Post bronchodilator FEV1 < 80%
predicted

Uncontrolled:
• Asthma Control test < 20
• Asthma control
questionnaire ≥ 1.5

Assess Severity

Assess Control

Endotype/Phenotype

Identify Comorbid Conditions

Rule out other Eosinophilic Conditions

Confirm Asthma Diagnosis
Phenotype/endotype

Phenotype/Endotype

Assess Severity

Assess Control

Endotype/Phenotype

Identify Comorbid Conditions

Rule out other Eosinophilic Conditions

T2-High
Blood eos > 150-400
cells/µL
Sputum eos >3%
Increased IgE and
specific IgE
ENO >50 ppb

Non-T2
Neutrophilic
- Sputum neutrophils >40-60%
Paucigranulocytic (normal
neutrophils and eosinophils)
Identify Comorbid conditions

- Gastro-esophageal reflux disease/Aspiration
- Dysbiosis/chronic infection
- Obesity
- Asthma/COPD Overlap
- Paradoxical Vocal Fold Motion Disorder
- Bronchiolitis
- Tracheobronchomalacia

Rule out other Eosinophilic Conditions

Identify Comorbid Conditions

Rule out other Eosinophilic Conditions
**Rule Out Other Eosinophilic Conditions**

- **CRSwNP**
- **(ABPM)**
- **EGPA**
- **HES**

**Ruling out Other Eosinophilic Lung Diseases**

- **History and physical**
  - **History of asthma**
    - EGPA
    - Allergic bronchopulmonary mycosis
    - Bronchogenic granulomatosis
    - Hypereosinophilic syndrome
  - **Travel history**
    - Parasitic infections
  - **Multiorgan involvement**
    - EGPA
    - HES

- **Clinical Lab evaluation**
  - CBC eosinophils, ANCA, MPO, PR3, ABPM Screen, urinalysis
  - Stool and serological testing for parasites

- **Bone Marrow biopsy and karyotyping (HES)**

- **Pulmonary function test**
  - Restrictive pattern
    - Acute eosinophilic pneumonia, chronic eosinophilic pneumonia, tropical pulmonary eosinophilia
  - Obstructive pattern
    - Asthma, allergic bronchopulmonary mycosis, EGPA

- **CT Scan, Echo**
- **Bronchoscopy**
Ruling out Other Eosinophilic Lung Disease:
Allergic Bronchopulmonary Aspergillosis/Mycosis

• **Clinical features**
  1. History of asthma, C.F. Rarely have neither
  2. Systemic and airway eosinophilia
  3. Elevated IgE Levels
  4. Lung infiltration
  5. Bronchiectasis
  6. Mucoid impaction
  7. Lung Fibrosis

• **Diagnostic Criteria**
  1. Asthma or C.F. Aspergillus skin test positive or Specific IgE (>35 kU/L)
  2. IgE typically > 1000 (can be less if meets other criteria)
  3. At least 2 of the following:
     1. Precipitating Antibodies to A fumigatus or other fungi
     2. Radiographic pulmonary opacities c/w ABPA,
     3. Total eosinophil count > 500 in steroid naïve patients

---

Eosinophilic Granulomatosis with Polyangiitis
Multiorgan Eosinophilic Vasculitis

**Associations**
- Adult onset Asthma (90%)
- Allergic Sinus disease
- Nasal polyps
- Multi-organ involvement

**Signs and Symptoms**
- Prodrome: asthma, allergies, sinus disease
- 2\textsuperscript{nd} phase: high eos in blood and tissue, eosinophilic pneumonia, GI
- 3\textsuperscript{rd} life threatening vasculitis
  - Renal, Cardiac, GI, Neuro

**Testig:**
- CT Chest: Lung opacities, Nodular disease, pleural effusions
- Peripheral blood eosinophilia
  - >1500 eos/µL (5k to 9K)
- ANCA ANCA +ve (30-60%): MPO (P-ANCA)(70-75%) of +ve ANCA
- BAL lavage eos > 33%
- Sputum cultures
- Surgical lung biopsy (skin, kidney, lung or peripheral nerve)
- Urinalysis
- Echocardiogram
Diagnostic Criteria (American College of Rheumatology):

Must have 4/6 criteria
1. History of asthma
2. > 10% eosinophils on differential Leukocyte count
3. Migratory/transient lung opacities
4. Mononeuropathy or polyneuropathy
5. Paranasal sinus abnormality
6. Biopsy containing a blood vessel showing an accumulation of eosinophils in extravascular areas

Eosinophilic Granulomatosis with Polyangiitis
Multiorgan Eosinophilic Vasculitis

Thoracic and Extrathoracic manifestations of Eosinophilic Granulomatosis with Polyangiitis

<table>
<thead>
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<th>Anatomic location</th>
<th>Manifestations</th>
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</tbody>
</table>
## Hypereosinophilic Syndrome

**Hypereosinophilia**
- Peripheral blood (> 1500 cell/μL)
  - On at least 2 occasions
  - At least month apart
- Pathologic Confirmation of tissue hypereosinophilia
  - Bone marrow
    - > 20% of all nucleated cells
    - Extensive eosinophilic infiltration in Pathologist opinion
    - Marked deposition of eosinophilic granule proteins in tissue

### Eosinophilic infiltration, degranulation and mediator release

### Multiorgan damage

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## Severe Asthma and Related Eosinophilic Diseases:
The Role of IL-5 in Diagnosis and Treatment

### Thoracic and extrathoracic manifestations of Hypereosinophilic Syndrome

<table>
<thead>
<tr>
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<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung</strong></td>
<td>Pulmonary infiltrates, pleural effusions, Asthma, Sinus disease, cough, recurrent infections</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td>Cardiomyopathy, pericardial effusion, cardiac failure, <strong>myocarditis</strong>, Valvular disease</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td>Vertigo, paresthesia, <strong>change in mentation</strong>, aphasia, visual changes</td>
</tr>
<tr>
<td><strong>Gastrointestinal tract</strong></td>
<td>Abdominal pain, vomiting and diarrhea</td>
</tr>
<tr>
<td><strong>Constitutional</strong></td>
<td>Fever, weight loss, malaise, fatigue, night sweats, flulike illness</td>
</tr>
<tr>
<td><strong>Rheumatologic</strong></td>
<td>Myalgia, joint pain, myositis</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Urticaria, angioedema, dermatitis, eosinophilic vasculitis, bullous lesions</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td><strong>Deep venous thrombosis</strong>, anemia, superficial thrombophlebitis</td>
</tr>
</tbody>
</table>
**Hypereosinophilic Syndrome**

Hypereosinophilia (> 1500 cell/μL)

**History:** symptoms, Drugs, Travel, Exposure

**Physical:** skin, pulmonary, heart, nasal neurological signs

Screen for Secondary causes
- Parasites, Allergic, Pulmonary, Connective Tissue,

Reactive Eosinophilia

**Myeloproliferative**
- Clonal eosinophilia
- Chronic eosinophilic Leukemia (CEL)

Clonal cytogenetic abnormality or increase in Marrow blasts (CEL NOS)

Screen for FIP121-PDGFRA gene mutation

Positive

Negative

Familial: Mutation not identified as yet

Lymphocytic HES
- Abnormal T-cell associated HES
- Increased IL-5 production?

Idiopathic HES

**When to Refer**

Rule out other Eosinophilic Conditions

CRSwNP

(ABPM)

EGPA

HES

ENT: Surgery?

Allergist (AERD)

Allergist

Pulmonologist (Bronchoscopy)

Rheumatologist (Vasculitis)

Hematologist (Bone Marrow Bx)
Treatment Selection for the spectrum of Eosinophilic diseases

Chapter 3

### Inhaled Corticosteroids Adverse Effects

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Mechanism</th>
<th>Potential Minimizing Factors</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphonia</td>
<td>Local deposition leading to myopathy of laryngeal muscles, candidiasis, mucosal irritation</td>
<td>Spacer devices may help to reduce risk</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal candidiasis</td>
<td>Local deposition</td>
<td>Spacer devices may help to reduce risk</td>
<td></td>
</tr>
<tr>
<td>Contact hypersensitivity</td>
<td>Local deposition on skin. Most commonly budesonide</td>
<td>Confirm with patch testing then switch to ICS that does not cross-react with budesonide</td>
<td>ICS that do not cross-react with budesonide include: beclomethasone, mometasone, fluticasone</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Systemic absorption</td>
<td>Screen asymptomatic children at higher risk</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Systemic absorption</td>
<td>Possible avoidance of fluticasone propionate</td>
<td>Risk of mortality not increased</td>
</tr>
<tr>
<td>Growth deceleration</td>
<td>Systemic absorption</td>
<td>Further research needed to determine whether certain ICS have different effects</td>
<td>Effect on adult height appears small</td>
</tr>
</tbody>
</table>
### Systemic Corticosteroid Adverse Effects

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmologic</td>
<td>Cataracts, glaucoma, exophthalmos</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension, arteriosclerosis, arrhythmias</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Gastritis, peptic ulcer disease, steatohepatitis</td>
</tr>
<tr>
<td>Immune</td>
<td>Increased susceptibility to infections</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Leukocytosis</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Insomnia, mania, psychosis, dysphoria, depression, euphoria</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Osteopenia/osteoporosis, avascular necrosis, myopathy</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Acne, hirsutism, striae, skin thinning, purpura, ecchymosis</td>
</tr>
<tr>
<td>Endocrinologic</td>
<td>Diabetes mellitus/hyperglycemia, adrenal insufficiency, weight gain, cushingoid appearance, fluid retention</td>
</tr>
</tbody>
</table>

### Asthma Approved Biologic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Approval in US</th>
<th>Age</th>
<th>Dosing and Frequency</th>
<th>Route</th>
<th>Biomarker Criteria</th>
<th>Phase 3 Clinical Trial Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>2003 Asthma 2016 C.I.U.</td>
<td>≥ 6 y.o</td>
<td>75-575 mg (based upon weight, IgE level, age)</td>
<td>Q2W</td>
<td>s.q. office</td>
<td>IgE: 30-1300</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>2015 Asthma 2019 EGPA</td>
<td>≥ 12 6-11</td>
<td>100 mg 40 mg 100 mg x 3</td>
<td>Q4W</td>
<td>X3</td>
<td>Office/ Home-prefilled (&gt; 11 y.o.)</td>
</tr>
<tr>
<td>Resilizumab</td>
<td>IL-5</td>
<td>2016</td>
<td>≥ 12</td>
<td>3.0 mg/kg</td>
<td>Q4W</td>
<td>i.v. Clinic/ Infusion center</td>
<td>CBC eos &gt;400</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL-5Rα</td>
<td>2018</td>
<td>≥ 12</td>
<td>Q4W (x3) → Q8W</td>
<td>s.q. prefilled Office</td>
<td>CBC eos: All comers 300 for primary 150 for OCS rel.</td>
<td>✔</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4Rα (impacts IL-4 and IL-13)</td>
<td>2017 A.D. 2018: Mod Severe Asthma 2019 CRSwNP</td>
<td>≥ 12</td>
<td>200 mg or 300 mg 300 if O.C.D.</td>
<td>Q2W</td>
<td>s.q. prefilled Home office</td>
<td>No minimum eos</td>
</tr>
</tbody>
</table>
Newer Biologics Under Development

The Alarmins

- Anti- TSLP
- Anti-IL 33
- Anti-IL-25

Tezepelumab in Adults with Uncontrolled Asthma

- **Design:**
  - 52 weeks Phase II study RDBCT
  - Multicenter
  - 3 doses SQ vs placebo q 4 weeks
  - 137 patients each group on LABA and med/high dose ICS
  - Th2 high (IgE >100 Blood eos≥ 140 /mCL

- **Results:**
  - All 3 doses 70 mg, 210 mg were 62%, 71%, 66% lower than in the placebo arm.(p<0.001)
  - FEV1 higher in all groups 120,130,150 ml compared to placebo (p< 0.015)
  - Results not influenced by baseline eosinophil count, FeNO

From The New England Journal of Medicine, Corren et al. Tezepelumab in Adults with Uncontrolled Asthma, 377:936-946. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society."
## ALARMINS trials for Eosinophilic Diseases

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Mechanism/ Target</th>
<th>Biomarkers</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tezepelumab</td>
<td>antiTSLP</td>
<td>FeNO, serum periostin</td>
<td>SC</td>
<td>Phase III</td>
</tr>
<tr>
<td>AREGN3500 GSK 3772847 ANB020</td>
<td>Anti-IL-33</td>
<td>FeNO, serum periostin, Blood eos, Sputum inflammatory markers</td>
<td>SC</td>
<td>Phase II</td>
</tr>
<tr>
<td>Anti-IL25</td>
<td>IL-25 also known as IL-17E</td>
<td>Blood and Sp eos</td>
<td>SC</td>
<td>None to date</td>
</tr>
</tbody>
</table>

## Biologics that failed for Severe Asthma

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Mechanism</th>
<th>Biomarkers</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebrikizumab</td>
<td>IL-13</td>
<td>FeNO, serum periostin</td>
<td>SC</td>
<td>Failed</td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>IL-13</td>
<td>FeNO, serum periostin</td>
<td>SC</td>
<td>Failed</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>Anti-IL17</td>
<td>Blood and Sp eos</td>
<td>SC</td>
<td>Failed</td>
</tr>
</tbody>
</table>
Biologics Currently in Phase II or III Studies For Severe Asthma

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Mechanism</th>
<th>Biomarkers</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREGN3500 GSK 3772847</td>
<td>anti IL-33</td>
<td>Blood eos, FeNO, IgE</td>
<td>SC</td>
<td>ongoing</td>
</tr>
<tr>
<td>ANB020</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CJM112</td>
<td>Anti-IL-25</td>
<td>Blood eos, FeNO, IgE</td>
<td>SC</td>
<td>ongoing</td>
</tr>
<tr>
<td>Tezepelumab</td>
<td>Anti-TSLP</td>
<td>Blood Eos, IgE, FENO</td>
<td>SC</td>
<td>ongoing</td>
</tr>
<tr>
<td>Navarixin</td>
<td>CXCR2</td>
<td>Blood + sp neutrophils</td>
<td>oral</td>
<td>ongoing</td>
</tr>
<tr>
<td>Fevipiprant</td>
<td>DP2 receptor</td>
<td>Sp Eos</td>
<td>oral</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>KIT</td>
<td>Serum Tryptase</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Proposed Targets: IL-6, IL-9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Biologics in Chronic Rhinosinusitis with nasal polyposis show encouraging results

- Biologics in active trials at current time
  - Dupilumab (approved 2019)
  - Mepolizumab
  - Benralizumab
  - Omalizumab
  - Tezepelumab
  - Anti-IL33
  - CRTH2 Antagonists
  - TP antagonist Ifetroban
Biologics Currently in Phase II or III Studies For Other Eosinophilic Diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Studies</th>
</tr>
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<tbody>
<tr>
<td>EGPA</td>
<td>Mepolizumab (Approved 2017) Benralizumab</td>
<td>Clinical trials Clinical trials</td>
</tr>
<tr>
<td>Hyper-eosinophilic syndrome</td>
<td>Mepolizumab Benralizumab</td>
<td>Clinical trial Clinical trial</td>
</tr>
<tr>
<td>ABPA</td>
<td>Omalizumab Mepolizumab Benralizumab Dupilumab</td>
<td>RCT Case studies Case series Case series</td>
</tr>
</tbody>
</table>

Conclusions

- Asthma is a spectrum of diseases, with different pathologic and clinical phenotypes
- There has been an increased understanding of the immunology of asthma, leading to new therapeutic options
- Defining phenotypes/endotypes in asthma is a young field, but it is making progress.
- In the severe asthma population Investigating and managing comorbidities cannot be overemphasized
- Tailoring treatment to phenotypes/endotypes and/or treatable traits is the ultimate goal.