Asthma Heterogeneity: Endotypes, Phenotypes and Choosing the Right Treatment

Michael Wechsler, MD MMSc
Director, NJH Cohen Family Asthma Institute
Professor of Medicine
National Jewish Health
WechslerM@NJHealth.org
Disclosures

Dr. Wechsler has received consulting honoraria from AstraZeneca, Boehringer Ingelheim, Glaxosmithkline, Novartis, Regeneron, Sanofi, Teva
Asthma Defined

- Asthma is a heterogeneous disease, characterized by chronic airway inflammation and history of respiratory symptoms such as
  - Wheeze
  - Shortness of breath
  - Chest tightness
  - Cough that varies over time and in intensity
  - Variable airflow limitation

Global strategy for asthma management and prevention. Global Initiative for Asthma website. 
Heterogeneity in Asthma—Not a New Concept

The heterogeneity of asthmatic patients—an individualized approach to diagnosis and treatment

Sheldon L. Spector, M.D., and Richard S. Farr, M.D. Denver, Colo.
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
Basis for Disease is Present Early and Evolves Throughout Life

Genetics, environment

Proteins, biochemical pathways, cells

Physiology, symptoms
Factors That Can Contribute to Uncontrolled Asthma

Uncontrolled Asthma

**Environmental Factors**
- Passive smoking
- Frequent exposure to traffic or air pollution
- Outdoor and indoor allergens

**Disease-Related Factors**
- Cyclical nature of disease
- Increased disease severity
- Differing asthma phenotypes

**Physician-Related Factors**
- Medication under-prescribing
- Failure to assess adherence
- Failure to assess inhaler technique
- Misdiagnosis
- Lack of asthma action plan
- Absence of specialty care

**Patient-Related Factors**
- Comorbidities (eg, GERD, rhinosinusitis, depression)
- Smoking
- Obesity
- Age
- Psychosocial issues (eg, lower income, poor health literacy)
- Poor treatment adherence
- Inadequate inhaler technique
- Heterogeneity of treatment response
- Failure to follow self-management plan
- Side effects of other medications (eg, NSAIDs)
The Asthma Patient Population is Segmented

Asthma Patient Population

- Intermittent
- Mild
- Moderate
- Severe

Persistent Asthma

Evolution of Asthma Classification

1960’s-1970’s: Bronchoconstriction

1980’s-1990’s: Inflammation

Early 2000’s: Identification of phenotypes and clusters

Late 2000’s: Precision medicine: identification of endotypes and mechanisms of disease including T2 vs. non-T2

Present: Precision therapy by endotype

1. Assess adherence and make sure it’s asthma

2. Characterize the asthma-what type of asthma is it?

3. Treat the Asthma
**Asthma Phenotype vs Endotype**

**Phenotype**
The set of observable characteristics of an individual resulting from the interaction of its genotype with the environment.

**Endotype**
A specific biologic mechanism that explains observable properties of an organism.

Different asthma phenotypes and endotypes may respond differently to targeted therapies.
Understanding Severe Asthma Heterogeneity Through Phenotyping and Endotyping

# Asthma Phenotypes

<table>
<thead>
<tr>
<th>Category</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trigger-induced asthma</strong></td>
<td>• Allergic</td>
</tr>
<tr>
<td></td>
<td>• Non-allergic</td>
</tr>
<tr>
<td></td>
<td>• Aspirin-exacerbated respiratory disease (AERD)</td>
</tr>
<tr>
<td></td>
<td>• Infection</td>
</tr>
<tr>
<td></td>
<td>• Exercise-induced</td>
</tr>
<tr>
<td></td>
<td>• Occupational</td>
</tr>
<tr>
<td><strong>Asthma patient characteristics</strong></td>
<td>• Smoking</td>
</tr>
<tr>
<td></td>
<td>• Obesity</td>
</tr>
<tr>
<td></td>
<td>• Elderly</td>
</tr>
<tr>
<td></td>
<td>• Black</td>
</tr>
<tr>
<td><strong>Clinical presentation of asthma</strong></td>
<td>• Pre-asthma wheezing in infants</td>
</tr>
<tr>
<td></td>
<td>− Episodic (viral wheeze)</td>
</tr>
<tr>
<td></td>
<td>− Multi-trigger wheezing</td>
</tr>
<tr>
<td></td>
<td>• Exacerbation-prone asthma</td>
</tr>
<tr>
<td></td>
<td>• Asthma associated with apparent irreversible airflow limitation</td>
</tr>
</tbody>
</table>

Separation of Asthma Into Clinical Phenotypes

- Unbiased hierarchical cluster analysis
  - Clinical characteristics (gender, age of onset, severity)
  - Physiology (lung function, airway hyperresponsiveness)
  - Triggers (allergens, tobacco, occupation)
  - Sputum inflammatory cells (eosinophils, neutrophils)

- Sum total of characteristics are segregated into groups, with no single feature playing a predominant role in the classification
Asthma Cluster Approaches and Eosinophilic Inflammation


Discordant Symptoms

- Early Symptom Predominant
  - Early onset, atopic; normal BMI; high symptom expression

- Obese Noneosinophilic
  - Later onset, female preponderance; high symptom expression

- Benign Asthma
  - Mixed middle-aged cohort; well-controlled symptoms and inflammation; benign prognosis

Concordant Disease

- Early-Onset Atopic Asthma
  - Concordant symptoms, inflammation and airway dysfunction
  - Monitoring inflammation allows down-titration of CS
  - Symptom-based approach to therapy titration may be sufficient

- Inflammation Predominant
  - Late onset, greater proportion of males; few daily symptoms but active eosinophilic inflammation
  - Monitoring inflammation allows targeted CS to lower exacerbation frequency

Monitoring inflammation allows targeted CS to lower exacerbation frequency

Primary Care Asthma

Secondary Care Asthma

Eosinophilic Inflammation
The Transition from Phenotyping and Endotyping to Genotyping

Personalized approach to asthma

Diagnosis

Refractory asthma?

Characterize subtype

Phenotype/Cluster approach

Endotypes (Th2 high vs. low)

Blood biomarkers
- IgE
- Eosinophils
- Periostin
- Cytokines

Sputum biomarkers
- Eosinophils
- Neutrophils
- Cytokines

Other
- FeNO

Genotype

TAILORED THERAPY

Dunn and Wechsler 2015
Asthma is Not Just One Disease

Asthma Syndrome
Symptoms of asthma, variable airflow obstruction

Asthma Phenotype Characteristics
Based on observable features with no direct relationship to a disease process (e.g., gender, age, obesity, ethnicity, smoking history, early vs. late onset, etc.)

Asthma Endotypes
Distinct functional or pathophysiologic mechanisms that may be present in clusters of phenotypes; identified by biomarkers (e.g., blood, sputum, urine, FeNO, exhaled breath)

Why Endotype?

To personalize therapy and maximize drug response
Biomarkers to Identify Asthma Phenotype

**Current**
- Sputum eosinophils
- Circulating blood eosinophils
- Exhaled nitric oxide
- IgE
- Allergen skin testing

**Future**
- Periostin
- Dipeptidyl peptidase-4 (DPP-4)
- Eosinophil peroxidase
- Urinary bromotyrosine

IgE = Immunoglobulin E.
Asthma Endotypes

- **Type 2 asthma**
  - Eosinophilic
  - High nitric oxide
  - High IgE
  - Mediated by IL-4, IL-5, and IL-13

- **Non-type 2 asthma**
  - Neutrophilic
  - Mediated by IL-1, IL-6, IL-17, and TNF

IL, interleukin; TNF, tumor necrosis factor.
Inflammatory, Immunologic, and Pathobiologic Features Leading to Severe Asthma

Inflammation, Endotypes, and Phenotypes in Severe Asthma are Heterogeneous

## Targeted Pathways for Biologic Therapies

### Targeted Pathways

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>Inhaled allergens stimulate production of IgE by B lymphocytes and bind to mast cells → degranulation</td>
</tr>
<tr>
<td>IL-5</td>
<td>Pro-eosinophilic cytokine; cytokine that regulates proliferation, maturation, migration, and effector functions of eosinophils</td>
</tr>
<tr>
<td>IL-4</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>IL-13</td>
<td>Cytokine associated with eosinophil trafficking and production of eNO from epithelial cells</td>
</tr>
<tr>
<td>TSLP</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

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17</td>
<td>Cytokine produced by Th17 cells; plays important role in the immunologic responses seen in asthma</td>
</tr>
<tr>
<td>CXCR2</td>
<td>Potent chemoattractant for neutrophils; under investigation in asthma and COPD</td>
</tr>
</tbody>
</table>


*CXCR2, Chemokine receptor 2; IgE, Immunoglobulin E; Th2, T helper 2 cells; TSLP, Thymic stromal lymphopoietin*
Novel Asthma Therapies

- Anti IL5: mepolizumab, reslizumab, benralizumab
- Anti IL4- R alpha/Anti IL13: dupilumab
- Anti IL13 lebrikizumab, tralokinumab
- Other Novel therapies:
  - Anti TSLP
  - Anti IL33
  - Anti IL17
  - Anti IL6
  - Anti M1’
  - Anti Gata3 DNAzyme
  - TLR9 agonists
  - CRTH2 Antagonists
  - Antibiotics
  - Vitamin D
What is your approach to treating patients with severe asthma?

- Treat with personalized approach
- Identify asthma type by phenotype or endotype
- Treat with the most appropriate therapeutic strategy based on underlying asthmatic mechanism of inflammation
What can we achieve with biologics?
What can we achieve with biologics?

- Reduced exacerbation
- Reduced steroid dose and side effects
- Improved symptoms and quality of life
- Disease modification to prevent asthma over long term
Which therapy is best for a specific patient?
How do you choose between biologics?

Which therapy is best for a specific patient? How do you choose between biologics?

- Biomarkers help predict therapeutic responses
  - Phenotype patients and choose most appropriate therapy
  - Goal of personalized or “precision medicine”
  - Potential need to measure different biomarkers to determine endotype/phenotype

BLOCKING EOSINOPHILS WITH ANTI IL5
Eosinophilic asthma

• Asthma can be classified phenotypically as eosinophilic (40–60% of cases) or non-eosinophilic

• Symptom severity is increased in eosinophilic asthma

• Interleukin-5 (IL-5) regulates proliferation, maturation, migration and effector functions of eosinophils

• IL-5 mRNA is increased in patients with asthma, correlates with asthma severity, and is inducible by allergen exposure

Wenzel SE. Lancet 2006;368:804–13
Eosinophilic cytokines contribute to the chronic inflammatory process.

- **Allergen/Irritant**
  - Epithelial cell
  - Basophil
  - Neutrophil

-**Cytokines**
  - IL-3, IL-6
  - IL-8, ECP
  - RANTES
  - MBP

-**Eosinophil**
  - IL-4
  - TNF-α

-**Endothelial cell**
  - IL-8
  - GM-CSF
  - IL-3

-**Mast cell**
  - IL-4
  - IL-5

-**Smooth muscle cell**
  - IL-6
  - IL-8
  - LT
  - ECP

-**Monocyte**
  - T_H0
  - T_H1
  - T_H2

-**Macrophage**
  - RANTES
  - IL-3
  - IL-5
  - GM-CSF

-**Dendritic cell**
  - IL-1
  - IL-2
  - IL-4
  - IL-10
  - IL-16

-**T Helper Cells**
  - TH2
  - TH1

Eosinophilic cytokines contribute to the chronic inflammatory process.
The targets: IL-5 or eosinophils (IL-5Rα)

- Benralizumab
- Mepolizumab
- Reslizumab

Eosinophil → IL-5

IL, interleukin
Total exacerbations over time are reduced with mepolizumab vs. placebo

Inclusion criteria

- sputum eos >3%,
- FeNO>50,
- blood eos >300,
- deterioration of asthma after <25% reduction in ICS or OCS

- AND

>2 asthma exacerbations in previous year

MEPOLIZUMAB NEJM 2014

Asthma Exacerbations

- Cumulative No.
  - Placebo
  - Mepolizumab 75 mg
  - Mepolizumab 100 mg
- Week

B FEV1

- Placebo
- Mepolizumab 75 mg
- Mepolizumab 100 mg
- Week

Change from Baseline in Glucocorticoid Dose

- Median Change (%)
  - Placebo (N=66)
  - Mepolizumab (N=69)
  - Optimized dose
  - Maintenance dose
- Week

Asthma Exacerbations

- Placebo
- Mepolizumab
- Week
Reslizumab Effects on Exacerbations and Lung Function

Placebo; n=244
Reslizumab 3.0 mg/kg; n=245
HR 0.575 (95% CI 0.440–0.750) p<0.0001

Probability of not having CAE (%)

Placebo Reslizumab
0 10 20 30 40 50 60 70 80 90 100

Number at risk

Placebo 244 169 138 112 107 97 0 0 0
Reslizumab 245 207 177 158 146 136 1 0 0

LS mean change from baseline in FEV₁ (L)

Placebo
Reslizumab 3.0 mg/kg
0 0.10 0.20 0.30 0.40
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Endpoint
Visit (week)

Castro et al. Lancet Respir Med 2015; Epub ahead of print
Benralizumab and Exacerbations

Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators*

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β₂-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

Eugene R Bleecker, J Mark FitzGerald, Pascal Chanéz, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Magnus Aurivillius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators*

Reduction in Exacerbation

Eosinophils ≥300 cells per μL


Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

P NAIR ET AL, NEJM MAY 2017
A  Change from Baseline in Oral Glucocorticoid Dose

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>02</th>
<th>04</th>
<th>08</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab 30 mg, every 4 wk</td>
<td>72</td>
<td>70</td>
<td>70</td>
<td>69</td>
<td>69</td>
<td>68</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>Benralizumab 30 mg, every 8 wk</td>
<td>70</td>
<td>72</td>
<td>67</td>
<td>69</td>
<td>69</td>
<td>66</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>Placebo</td>
<td>74</td>
<td>75</td>
<td>73</td>
<td>74</td>
<td>74</td>
<td>73</td>
<td>73</td>
<td>72</td>
</tr>
</tbody>
</table>

B  Time to First Asthma Exacerbation

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>04</th>
<th>08</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab 30 mg, every 4 wk</td>
<td>72</td>
<td>69</td>
<td>67</td>
<td>62</td>
<td>61</td>
<td>56</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>Benralizumab 30 mg, every 8 wk</td>
<td>73</td>
<td>68</td>
<td>66</td>
<td>60</td>
<td>58</td>
<td>56</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>Placebo</td>
<td>75</td>
<td>68</td>
<td>64</td>
<td>56</td>
<td>45</td>
<td>40</td>
<td>37</td>
<td>31</td>
</tr>
</tbody>
</table>
Does Broader Blockade of Type 2 Cytokines Improve Outcomes?

**Type I Receptor**
- B cells, T cells, Monocytes, Eosinophils, Fibroblasts

**Type II Receptor**
- Epithelial cells, Smooth muscle cells, Fibroblasts, Monocytes, Activated B cells

*IL-4* and *IL-13* binding to their respective receptors triggers JAK/STAT signaling pathways.

**Dupilumab**
- A monoclonal antibody directed against IL-4Rα, blocking IL-4 and IL-13 signaling.

Property of Presenter
Not for Reproduction
Anti IL4/13 and Asthma

The New England Journal of Medicine

Original Article

Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.
Dupilumab in Asthma

B Time to Exacerbation

Exacerbations — Primary End Point

Placebo (N=52) vs Dupilumab (N=52)

- 44% Placebo
- 6% Dupilumab

87% reduction
P<0.001
Improvement in Lung Function, On Top of Combination Rx

**Graph Description:**
- **Y-axis:** Mean Change ± SE
- **X-axis:** Week (0 to 12)
- **Legend:**
  - Stable ICS/LABA
  - LABA discontinuation
  - ICS taper
  - Dupilumab or placebo monotherapy
- **Comparative Treatments:**
  - Dupilumab
  - Placebo
- **Statistical Note:** P < 0.001

**Patient Data:**

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
<th>Week 9</th>
<th>Week 10</th>
<th>Week 11</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>52</td>
<td>52</td>
<td>51</td>
<td>51</td>
<td>50</td>
<td>49</td>
<td>47</td>
<td>46</td>
<td>45</td>
<td>43</td>
<td>41</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>52</td>
<td>51</td>
<td>52</td>
<td>52</td>
<td>50</td>
<td>49</td>
<td>52</td>
<td>52</td>
<td>47</td>
<td>46</td>
<td>46</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>
Dupilumab Significantly Lowers Rates of Severe Exacerbation in a Phase 3 Trial

- Phase 3, randomized, double-blind, placebo-controlled trial
- n=1902 patients ≥12 years of age with uncontrolled asthma stratified by baseline blood eosinophil level
- Randomized to receive add-on SC dupilumab at a dose of 200 or 300 mg every 2 weeks or placebo for 52 weeks
- Primary outcomes: Annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in FEV$_1$ before bronchodilator use

Dupilumab Significantly Improved Lung Function

The benefit of dupilumab on FEV₁ was greatest among patients with a blood eosinophil count of ≥300 eos/cc at baseline.

BLOCKING IGE WITH OMALIZUMAB
Omalizumab Blocks IgE Binding to Mast Cells

IgE molecule

Omalizumab → FcεRI receptor → Mast cell

Omalizumab → FcεRI receptor → Mast cell

Omalizumab
Omalizumab Mechanism of Action

- **B lymphocyte**
- **Plasma cell**
- **Omalizumab**
- **Mast cells**

- **Release of IgE**
- **Reduces high-affinity receptors**
- **Binds to free IgE, reducing cell-bound IgE**

**Allergens**
- **Reduces mediator release**
- **Allergic mediators**
- **Allergic inflammation: eosinophils and lymphocytes**

**Reduces asthma exacerbations and symptoms**
Summary of Reduction in Asthma Exacerbations in Pivotal Studies 1 and 2

Stable Steroid Phase 16 weeks

- Study 1: Mean exacerbations per patient
  - Omalizumab: 0.2
  - Placebo: 0.3
  - P = 0.005
- Study 2: Mean exacerbations per patient
  - Omalizumab: 0.1
  - Placebo: 0.4
  - P < 0.001

Steroid Reduction Phase 12 weeks

- Study 1: Mean exacerbations per patient
  - Omalizumab: 0.2
  - Placebo: 0.4
  - P = 0.004
- Study 2: Mean exacerbations per patient
  - Omalizumab: 0.2
  - Placebo: 0.3
  - P < 0.001
Different biomarkers and omalizumab response

Effect of omalizumab based on Th2 biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Cutoff 1</th>
<th>Cutoff 2</th>
<th>Reduction</th>
<th>n</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeNO</td>
<td>&lt;19.5 ppb</td>
<td>≥19.5 ppb</td>
<td>−16</td>
<td>193</td>
<td>0.45*</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>&lt;260/µL</td>
<td>≥260/µL</td>
<td>−9</td>
<td>201</td>
<td>0.001*</td>
</tr>
<tr>
<td>Periostin</td>
<td>&lt;50 ng/mL</td>
<td>≥50 ng/mL</td>
<td>−32</td>
<td>383</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

*Exacerbation reduction P-values; omalizumab versus placebo in each biomarker subgroup.

Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.
Tezepelumab treatment reduced the annualised AER vs placebo at Week 52

- Significant reduction in annualised AER for all tezepelumab treatment groups compared with placebo; P<0.001
Anti TSLP in Asthma (Corren 2017)

![Graph showing the annualized rate of asthma exacerbations for different doses of tezepelumab and blood eosinophil counts.](image)
Individualizing Asthma Therapy: Conclusions

• Response to asthma therapies is variable
• Need to understand who responds to what
• We now have multiple novel biologic therapies that may treat patients with severe eosinophilic asthma
• How will we decide which therapies work best in which patients?
Treating Severe Asthmatics Now

- Do extensive workup
- Endotype your patients
Asthma Biomarkers

- IGE
- FENO
- EOS
  - Sputum
  - Blood
- Periostin
- DPP4 (Dipeptidyl Peptidase 4 / CD26; an adipokine)
Selecting Treatment for Severe Asthma: Anti-IgE Versus Anti–IL-5

- **Patients with allergic eosinophilic asthma**
  - **Anti-IgE or Anti–IL-5 or Anti IL4/13**

- **Patients with allergic noneosinophilic asthma**
  - **Anti-IgE or Anti IL4/13 if eNO high**

- **Patients with eosinophilic asthma who:**
  - Are nonallergic
  - Do not respond to anti-IgE treatment
  - Are out of range of dosing for anti-IgE treatment
  - **Anti–IL-5 or Anti iL4/13**

  - Other factors influencing the decision: patient comfort with a new agent vs older treatment with more experience

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 and endotypes in asthma is a young field, but it is making progress
• Tailoring treatment to phenotypes and endotypes is the ultimate goal
Conclusions

- Patients with severe asthma may require additional evaluation and referral
- Patients with **allergic** asthma not well controlled with high-dose ICS and an additional controller can be considered for treatment with omalizumab
- Patients with severe **eosinophilic** asthma not controlled with ICS/LABA may benefit from an inhibitor of IL-5 (mepolizumab, reslizumab, or benralizumab)
- Consider Dupilumab with **eosinophilic or type 2** moderate severe asthma or on systemic steroids
Understanding Disease Mechanisms May Guide Therapy to a More Personalized Approach

One Size Fits All
- Evidence-based
- One treatment for all

Stratified Medicine
- Evidence-based
- Different treatments for groups of patients

Personalized Medicine
- Evidence-based
- Individualized treatment for each patient

Providing Asthma Care is a Team Sport

FUTURE QUESTIONS

• How will clinicians and payers decide between different biologics based on existing biomarkers?
• Can we use combinations of biologics?
• Are there biomarkers that should be studied other than blood eosinophils, IgE, FeNO?
• What are best therapies for nontype 2 severe asthma?
• What about Asthma COPD overlap Syndrome???
<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Dosing</th>
<th>Frequency</th>
<th>Route</th>
<th>Exacerbation Reduction Rate (vs. Placebo)</th>
<th>Increased FEV₁ (vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reslizumab Anti IL5</td>
<td>Approve 2016</td>
<td>3.0 mg/kg</td>
<td>Q4W</td>
<td>IV</td>
<td>50-59%</td>
<td>110-126 ml</td>
</tr>
<tr>
<td>Mepolizumab Anti IL5</td>
<td>Approved asthma 2015; Phase 3 COPD</td>
<td>100 mg</td>
<td>Q4W</td>
<td>Sub-Q</td>
<td>53%</td>
<td>98 ml</td>
</tr>
<tr>
<td>Benralizumab Anti IL5 Receptor</td>
<td>Approved asthma 2017; Phase 3 COPD</td>
<td>30 mg</td>
<td>Q8W (first 3 doses every 4 weeks)</td>
<td>Sub-Q</td>
<td>36-55% (Q4W frequency) 28-70% (Q8W frequency)</td>
<td>0-125 ml</td>
</tr>
<tr>
<td>Omalizumab Anti IgE</td>
<td>Approved asthma 2003; Approved urticaria</td>
<td>125mg – 375mg (based on weight/ IgE level)</td>
<td>Q2W or Q4W (depending on weight/ IgE level)</td>
<td>Sub-Q</td>
<td>33-75%</td>
<td>NS</td>
</tr>
<tr>
<td>Dupilumab Anti IL4 Receptor</td>
<td>Approved 2017 for Atopic Dermatitis; 2018 for Asthma</td>
<td>200-300 mg</td>
<td>Q2W</td>
<td>Sub-Q</td>
<td>59.9-80.7%</td>
<td>390-430ml</td>
</tr>
<tr>
<td>Tezepelumab Anti TSLP</td>
<td>Phase III for asthma</td>
<td>70-280 mg</td>
<td>Q2-4 W</td>
<td>Sub-Q</td>
<td>61-71%</td>
<td>110-150 ml</td>
</tr>
</tbody>
</table>
Thank You!
WechslerM@NJHealth.org