Asthma 2020 and Beyond: Endotypes, Phenotypes and Choosing the Right Treatment

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Disclosures

Michael Wechsler, M.D., MMSc.

- Consultant/Honoraria: AstraZeneca, Sanofi, Genzyme, Regeneron, Teva, Novartis, Genentech, GlaxoSmithKline, Restorbio, Equillium
Unlabeled/Unapproved Use

• Anti TSLP  tezepelumab.
• Anti CRTH2  fevipiprant
Lecture Objectives

1. Explain asthma heterogeneity.
2. Describe asthma phenotypes and endotypes.
3. Define current and future approaches to asthma management.
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

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
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.
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

**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

Global Initiative for Asthma GINA Recommends Add-on Type 2-targeted Biologic Therapy at Step 5

GINA Stepwise Approach to Asthma Treatment¹ (adults and adolescents ≥12 years)

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

**PREFERRED RELIEVER** to relieve symptoms

**STEP 1**
- As-needed low-dose ICS-formoterol

**STEP 2**
- Daily low-dose inhaled corticosteroid (ICS), or as-needed low-dose ICS-formoterol

**STEP 3**
- Low-dose ICS-LABA
  - Leukotriene receptor antagonist (LTRA), or low-dose ICS taken whenever SABA is taken

**STEP 4**
- Medium-dose ICS-LABA
  - Medium-dose ICS, or low-dose ICS + LTRA

**STEP 5**
- High-dose ICS-LABA
  - High-dose ICS, add-on tiotropium, or add-on LTRA
  - Add low-dose OCS, but consider side effects

Assess the **severe asthma phenotype** and factors contributing to symptoms, QoL, and exacerbations

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¹Off-label; data only with budesonide-formoterol (bud-form). ²Off-label; separate or combination ICS and SABA inhalers.

³Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted.

⁴Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy.
Approach to Asthma Management

1. Make sure it’s asthma
2. Evaluate comorbidities
3. Assess adherence
4. Characterize the asthma—what type of asthma is it?
5. 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

Severe Asthma Phenotype and Endotype

- Environment: Allergies
- Environment: Infections/Irritants
- Meds/Adherence
- Patient factors
- Comorbid disease
- Airway epithelium, smooth muscle
- Gene expression
- Cytokines
- Immune cells

Genes

# Asthma Phenotypes

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

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
- Gender
- Age
- Obesity
- Ethnicity/Race
- Smoking Hx
- Early vs. Late Onset
- IgE
- Eosinophils
- Periostin
- Cytokines

Sputum biomarkers
- Eosinophils
- Neutrophils
- Cytokines

Other
- FeNO

Genotype

TAILORED THERAPY

Dunn and Wechsler 2015
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

Inflammatory mechanisms and pathobiologic features leading to severe asthma

Inflammatory mechanisms associated with granulocytic inflammation

Type 2 inflammation
- Antigens
  - CRTH2
  - TSLP
  - IL-25
- IL-13
- IL-4, 5, and 13
- ILC2
  - GATA3

Non-type 2 inflammation
- Irritants, pollutants, microbes, and viruses
  - CXCL8
  - GM-CSF
- IL-6
- TGF-β
- IL-23

B cell
- IL-4
- IgE
- KIT
- GM-CSF
- Leukotrienes
  - PGD2
  - Histamine
  - IL-3, 4, 5, and 9

Mast cell

Th2 cell
- GATA3

ILC2
- CRTH2
- IL-13

Eosinophil

Th17 cell
- IL-6
- IL-17
- IL-8

Neutrophil
- CXCR2
- Lipoxin
- ALX
- BLT2

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

Inflammation, Endotypes, and Phenotypes in Severe Asthma are Heterogeneous

**Endotype**
- **Type 2-high**
  - IL-4, IL-13, IL-5-mediated
- **Type 2-low**
  - IL-6, IL-17, TNF mediated

**Biomarker**
- Eosinophilia (eosinophilic asthma)
- Elevated IgE
- Elevated FeNO
- Neutrophilia
- Paucigranulocytic

**Phenotype**
- Early age of onset
- Allergic sensitization
- Later age of onset
- Obesity, infections, smokers

**Comorbidities**
- Chronic rhinosinusitis ± nasal polyps
- Atopic dermatitis

**Type 2 inflammation is prevalent in patients with uncontrolled persistent asthma, and these patients have the highest disease burden**

## 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

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

- **Epithelial cell**: IL-3, IL-6, IL-8, ECP, RANTES, MBP
- **Basophil**: IL-6, IL-8, LT, ECP
- **Neutrophil**: IL-8, GM-CSF
- **Endothelial cell**: IL-3, IL-4, GM-CSF, TNF-α
- **Mast cell**: IL-4, IL-5
- **Dendritic cell**: IL-4, TNF-α
- **Macrophage**: IL-3, IL-5, GM-CSF
- **Dendritic cell**: RANTES
- **Eosinophil**: IL-1, IL-2, IL-4, IL-10, IL-16
- **B cell**: RANTES
- **Monocyte**: IL-4
- **Neuron**: RANTES
- **Myofibroblast**: IL-3, IL-5, GM-CSF

**Eosinophilic cytokines contribute to the chronic inflammatory process**

- **Allergen/irritant**
- **Smooth muscle cell**

**Illustrations**:
- **Epithelial cell**
- **Basophil**
- **Neutrophil**
- **Endothelial cell**
- **Mast cell**
- **Dendritic cell**
- **Macrophage**
- **Eosinophil**
- **B cell**
- **Monocyte**
- **Neuron**
- **Myofibroblast**
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

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 (%)
0 10 20 30 40 50 60 70 80 90 100
0 1 2 3 4 5 6 7 8 9 10
Probability of not having CAE (%)

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

LS mean change from baseline in FEV1 (L)
0 0.10 0.20 0.30 0.40
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Visit (week)

Placebo
Reslizumab 3.0 mg/kg

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 Chaney, 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
Benralizumab 30 mg, every 4 wk  72  70  70  69  69  68  66  68
Benralizumab 30 mg, every 8 wk  70  72  67  69  69  66  69  68
Placebo  74  75  73  74  73  73  73  72

B  Time to First Asthma Exacerbation

No. at Risk
Benralizumab 30 mg, every 4 wk  72  69  67  62  61  56  51  45
Benralizumab 30 mg, every 8 wk  73  68  66  60  58  56  55  51
Placebo  75  68  64  56  45  40  37  31
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
Anti IL4/13 and Asthma

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

- Stable background therapy
- Tapering of inhaled glucocorticoid
- Dupilumab or placebo monotherapy

Exacerbations — Primary End Point

- Placebo (N=52)
  - 44%
  - 87% reduction
  - P<0.001

- Dupilumab (N=52)
  - 6%

No. at Risk

- Dupilumab: 52 51 51 51 50 50 50 47 45 44 43 42
- Placebo: 52 52 50 50 48 44 43 41 37 35 32 28 24
Improvement in Lung Function, On Top of Combination Rx

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The NEW ENGLAND JOURNAL of MEDICINE

![Graph showing mean change ± SE over weeks for placebo and Dupilumab treatments.](#)

**No. patients**

<table>
<thead>
<tr>
<th></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>
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<tbody>
<tr>
<td><strong>Placebo</strong></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>36</td>
</tr>
<tr>
<td><strong>Dupilumab</strong></td>
<td>52</td>
<td>51</td>
<td>52</td>
<td>52</td>
<td>50</td>
<td>49</td>
<td>52</td>
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<td>46</td>
<td>46</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>
• 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

Change in the Prebronchodilator FEV<sub>1</sub> from Baseline over 52-Weeks

The benefit of dupilumab on FEV<sub>1</sub> 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 Mechanism of Action

- **B lymphocyte**
  - e-switch

- **Plasma cell**
  - Release of IgE

- **Omalizumab**
  - Binds to free IgE, reducing cell-bound IgE

- **Mast cells**
  - Basophils

- **Allergens**

- **Allergic mediators**
  - eosinophils and lymphocytes

- **Reduces mediator release**
  - Allergic inflammation

- **Reduces high-affinity receptors**

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

Stable Steroid Phase 16 weeks

Study 1: Omalizumab 0.2, Placebo 0.3
Study 2: Omalizumab 0.1, Placebo 0.4

Steroid Reduction Phase 12 weeks

Study 1: Omalizumab 0.2, Placebo 0.4
Study 2: Omalizumab 0.2, Placebo 0.3

P = 0.005, P < 0.001, P = 0.004, P < 0.001

Mean exacerbations per patient

Omalizumab
Placebo
Different biomarkers and omalizumab response

Effect of omalizumab based on Th2 biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Threshold 1</th>
<th>Threshold 2</th>
<th>Reduction in protocol-defined Asthma exacerbation rate (Mean %, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeNO</td>
<td>&lt;19.5 ppb</td>
<td>≥19.5 ppb</td>
<td>-16</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>&lt;260/µL</td>
<td>≥260/µL</td>
<td>-53</td>
</tr>
<tr>
<td>Periostin</td>
<td>&lt;50 ng/mL</td>
<td>≥50 ng/mL</td>
<td>-32</td>
</tr>
</tbody>
</table>

n = 193, P = 0.45*  
n = 201, P = 0.001*  
n = 383, P = 0.54*  
n = 414, P = 0.005*  
n = 279, P = 0.94*  
n = 255, P = 0.07*

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

Asthma 2020 and Beyond:
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)

- Placebo
- Low-dose tezepelumab (70 mg every 4 wk)
- Medium-dose tezepelumab (210 mg every 4 wk)
- High-dose tezepelumab (280 mg every 2 wk)

P-values:
- Placebo vs. Low-dose: P=0.03
- Placebo vs. Medium-dose: P=0.001
- Placebo vs. High-dose: P=0.001
- Low-dose vs. Medium-dose: P<0.001
- Low-dose vs. High-dose: P=0.008
- Medium-dose vs. High-dose: P=0.005

Annualized Rate of Asthma Exacerbations (events per patient-yr)

Blood Eosinophil Count (cells/µl)

- <250
- ≥250

Feno (ppb)

- <24
- ≥24

Th2 Status

- Low
- High
Other new therapies

- Anti CRTH2-
  - Fevipiprant Phase 3 failed to improve FEV1
  - GB001
- Anti IL33
  - Reduced exacerbations
  - Less effective with dupilumab
PrecISE: Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network
PrecISE DESIGN OBJECTIVES

Adaptive Platform Trial with Placebo Control to Quickly Identify Novel Asthma Treatments and Bring Them to the Right Patients

Co-Primary Objectives

1. Use an adaptive design to identify treatments that work in biomarker-defined subgroups of severe asthmatic patients

2. Optimize the subgroup targeted for treatment by refining the biomarker definition and assay cut-point via adaptive design
DENVER PRECISE TEAM=
NJH Adults/Peds: Wechsler, Alam, Guntur, Covar
UCH: Holguin
CO Children’s: Szefler, Liu
PrecISE MASTER PROTOCOL
Adaptive Platform Trial with Placebo Control

2 month Run-in

4 month Treatment

1-2 month Wash-out

Re-randomization based on biomarkers to another treatment, or placebo control

Placebo Wash-out

Treatment Wash-out

Re-randomization based on biomarkers to another treatment
PrecISE SUBJECTS

Enrollment

- We anticipate 18.5 months for total enrollment

- 600 adults
- 200 adolescents
## Planned PrecISE INTERVENTIONS

<table>
<thead>
<tr>
<th>Intervention</th>
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<tbody>
<tr>
<td>Imatinib (Kit R inhibitor)</td>
</tr>
<tr>
<td>Anti IL-6</td>
</tr>
<tr>
<td>Cavosonstat (GSNOR inhibitor)</td>
</tr>
<tr>
<td>Jak inhibitors</td>
</tr>
<tr>
<td>BronchoVaxom (bacterial vaccine)</td>
</tr>
<tr>
<td>Medium Chain Triglycerides</td>
</tr>
</tbody>
</table>
PrecISE TIMELINE

- PrecISE began
- Protocol Development Begins
- Protocol Synopsis Done
- Finalize Interventions
- Begin Enrollment

September 2017
November 2017
June 2018
July 2018
September 2018
November 2018
February 2020

- Share PrecISE with Industry
- Share Master Protocol with Industry
- Done

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

Head-to-head studies are needed

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

- Allergist
- Pediatrician
- Immunologist
- Pulmonologist
- Otolaryngologist
- Pulmonary Rehabilitation Specialist
- Nurse APN
- Nurse Practitioner
- Case Manager
- School personnel
- Primary care physician
- Pharmacist

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>
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<tr>
<td>Mepolizumab Anti IL5</td>
<td>Approved asthma 2015;</td>
<td>100 mg</td>
<td>Q4W</td>
<td>Sub-Q</td>
<td>53%</td>
<td>98 ml</td>
</tr>
<tr>
<td></td>
<td>Phase 3 COPD</td>
<td></td>
<td></td>
<td></td>
<td>53%</td>
<td>98 ml</td>
</tr>
<tr>
<td>Benralizumab Anti IL5 Receptor</td>
<td>Approved asthma 2017;</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></td>
<td>Phase 3 COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Omalizumab Anti IgE</td>
<td>Approved asthma 2003;</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></td>
<td>Approved urticaria</td>
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</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