Dr. Castro received his medical degree from the University of Missouri in 1988 and his Masters in Public Health from the St. Louis University School of Public Health in 1998. He is the Alan A. and Edith L. Professor of Pulmonary and Critical Care Medicine, Professor of Medicine, Pediatrics, and Radiology at the Washington University School of Medicine in St. Louis, Missouri and also serves as an Adjunct Associate Professor of Community Health at the St. Louis University School of Public Health. He is the Director of the Asthma and Airway Translational Research Unit (AATRU) at Washington University School of Medicine.

Dr. Castro has served as President of the ALA of Missouri Board, is current Board member of national ALA Board, and is Chair of the ALA Scientific Advisory Committee. Dr. Castro is Chair of the Board of the International Medical Assistance Foundation and past Chair of the St. Louis Regional Asthma Consortium and the Allergy Immunology Inflammation Program Committee for the American Thoracic Society. He also served on the National Asthma Educator Certification Board from 2000-2005.

Dr. Castro is following children from very early in life and looking at how their genetic, biologic and immune responses as well as their environment are coming together to cause some of them to develop asthma (NIH RSV Bronchiolitis in Early Life (RBEL) study). Dr. Castro is the lead investigator for two major asthma networks - the NIH AsthmaNet and the ALA Asthma Clinical Research Center (ACRC) network – which are studying better ways to treat asthma. He chairs the Protocol Committee for ACRC. He is also studying what causes asthma through the NIH Asthma and Allergic Disease Clinical Research Center (AADCRC) grant and what makes severe asthma different from milder forms (Severe Asthma Research Program (SARP)). Dr. Castro’s translational work has been complimented by multiple clinical trials evaluating new and existing therapies in the treatment of asthma, especially severe asthma. His major contribution to the treatment of severe asthma has been in the development of bronchial thermoplasty, a novel therapy to reduce airway smooth muscle, and anti-IL5 therapy for severe eosinophilic asthma.

OBJECTIVES:
Participants should be better able to:

1. Discuss current unmet medical needs in patients with severe asthma;
2. Understand new approaches to phenotyping/endotyping in asthma patients;
3. Review evidence for efficacy and safety with currently available and future biologic therapy for asthma.

THURSDAY, MARCH 23, 2017  10:30 AM
DISCLOSURE

Dr. Castro has received grant/research support from Sanofi-Aventis, Boehringer-Ingelheim, Gilead, Invion; serves as a consultant for Aviragen, Genentech, Holaira, Teva, Therabron, Sanofi-Aventis and serves on the speakers’ bureau at Boston Scientific, Genentech, Teva, Boehringer-Ingelheim; receives royalties from Elsevier, but these do not create a conflict related to his presentation.

NAMDRC Educational Conference: Biological Therapy in Asthma

Mario Castro MD, MPH
Asthma & Airway Translational Research Unit
Washington University School of Medicine
St. Louis, Missouri, USA
Disclosures

- Principal Investigator (University Grant Funding): AsthmaNet, American Lung Association, Severe Asthma Research Program
- Principal Investigator (Pharmaceutical Grant Funding): Amgen, Boeringer Ingelheim, Genentech, Gilead, GSK, Invion, Johnson&Johnson, Medimmune/AstraZeneca, Novartis, Pfizer, Sanofi Aventis, Teva, Vectura
- Consultant: AstraZeneca, Boston Scientific, Holaira, NeoStem, Neutronic, Novartis, Roche, Sanofi Aventis, Teva, Therabron
- Speaker: Boeringer Ingelheim, Boston Scientific, Genentech, Teva
- Royalties: Elsevier
- Stock Options: Sparo Inc.

Educational Objectives

- Discuss current unmet medical needs in patients with severe asthma
- Understand new approaches to phenotyping/endotyping in asthma patients
- Review evidence for efficacy and safety with currently available and future biologic therapy for asthma
Unmet Need in Severe Persistent Asthma

- Prevalence of severe asthma 5-20% (NAEPP/NHLBI)
- Many patients remain symptomatic despite standard of care medications
- Treatments are limited, require adherence, and may have serious side effects
- New options are needed

Higher Cost of Severe Asthma

Increased healthcare utilization
ER visits
Hospitalizations

Patients with exacerbations have higher healthcare costs than patients without exacerbations

Est. $56B total cost of asthma

$12,800

$4,800

$2,200

Mild Moderate Severe

Cost/Patient/Year

Asthma is a Complex Heterogeneous Disease

• Asthma likely encompasses many different disease variants with different etiologies and pathophysologies
  – Many phenotypes exist and are determined by clinical characteristics, physiology, triggers, and inflammatory parameters
  – Multiple environmental and genetic factors contribute to the disease

“Old School”

Categorizing Asthma by Endotype

Phenotype:
• Observable properties of an organism that are produced by the interactions of the genotype and the environment
• Encompasses the heterogeneity of clinical presentations but do not provide insight into the underlying pathophysiology

Endotype:
• A specific biologic pathway that explains the observable properties of a phenotype
• A subtype of a condition, which is defined by a distinct functional or pathophysiological mechanism

Classification by Endotype May Identify Appropriately Targeted Treatment Approaches

- One of the major unmet needs in asthma lies with delivering mechanism-specific treatments that are highly effective in specific endotypes of asthma.
- Understanding endotypes can identify those patients most likely to benefit from a particular type of therapy.
  - This strategy can be advantageous both in clinical study design and for the development of future targeted therapies.


Phenotypes based on TH2 vs non-TH2

Biomarkers Play an Important Role in Patient Diagnosis and Management

- Biomarkers provide objective evidence for patient diagnosis and management in many disease states
  - Diagnose patients, assess disease severity, identify if additional treatment is required and/or what treatments patients will optimally respond to
- Examples of commonly used biomarkers
  - Diabetes: A1C
  - Dyslipidemia: LDL, HDL, TG
  - Cardiac disorders: troponin, CK-MB
  - Hepatic disorders: AST, ALT
- Biomarkers may also be used to help assess and manage patients with asthma

ALT = alanine transaminase; AST = aspartate transaminase; CK-MB = creatine kinase myocardial band; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride.


Potential Biomarkers for Asthma Assessment and Management

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Sputum EOS | • Severe allergic and eosinophilic asthma  
• Increased exacerbations and poor lung function |
| Blood EOS | • Severe allergic and eosinophilic asthma  
• Increased exacerbations and poor lung function |
| IgE | • Severe allergic asthma |
| FeNO | • Indicator of oxidative and nitritative stress  
• Severe allergic and eosinophilic asthma |
| Periostin | • Potentially allergic and eosinophilic asthma |

EOS = eosinophil; FeNO = exhaled nitric oxide fraction; Ig = immunoglobulin.
Question 1

40 Year Old African American Male was diagnosed with asthma shortly after birth. He has history of allergic rhinitis. Hospitalized 15 times with one additional burst of steroids in the last year. During one hospitalization for asthma was in the ICU, but never intubated. Medications albuterol PRN and fluticasone/salmeterol (Advair) 500/50 1 puff BID. ACQ score today was 2.0. FEV1 1.93 L 50% predicted; post bronchodilator FEV1 increased to 2.50L 64% predicted (29% reversibility). 0.408 K/cu mm absolute blood eosinophils and total serum IgE 66 IU/ml.

The best predictor of a subsequent exacerbation of asthma in this patient is:

A. Bronchodilator reversibility
B. Blood eosinophils
C. African American race
D. ACQ score
E. Atopic history

40 Year Old African American Male was diagnosed with asthma shortly after birth. He has history of allergic rhinitis. Hospitalized 15 times with one additional burst of steroids in the last year. During one hospitalization for asthma was in the ICU, but never intubated. Medications albuterol PRN and fluticasone/salmeterol (Advair) 500/50 1 puff BID. ACQ score today was 2.0. FEV1 1.93 L 50% predicted; post bronchodilator FEV1 increased to 2.50L 64% predicted (29% reversibility). 0.408 K/cu mm absolute blood eosinophils and total serum IgE 66 IU/ml.

The best predictor of a subsequent exacerbation of asthma in this patient is:

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D. ACQ score
E. Atopic history
Severe Exacerbations are Associated with High EOS Levels

- Medical record data to identify primary care patients with asthma aged 12–80 years with 2 years of continuous records, including 1 year before (baseline) and 1 year after – 20,929 (16%) of 130,248 had blood eos >400/μL.

<table>
<thead>
<tr>
<th>Severe exacerbations</th>
<th>Acute respiratory events</th>
<th>Risk-domain asthma control</th>
<th>Overall asthma control</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 1.42 (1.36–1.47)*</td>
<td>RR 1.28 (1.24–1.33)*</td>
<td>OR 0.79 (0.73–0.86)*</td>
<td>OR 0.74 (0.72–0.77)*</td>
</tr>
</tbody>
</table>

Adjusted rate ratios (RRs) for severe exacerbations and acute respiratory events, and odds ratios (ORs) for asthma control, for patients with peripheral blood eosinophil count greater than 400 cells per μL (vs 400 cells per μL or less) during 1 outcome year.

1Price DB et al Lancet Respiratory Medicine, Volume 3, Issue 11, 2015, 849–858

Question 2

40 Year Old African American Male was diagnosed with asthma shortly after birth. He has history of allergic rhinitis. Hospitalized 15 times with one additional burst of steroids in the last year. During one hospitalization for asthma was in the ICU, but never intubated. Medications albuterol PRN and fluticasone/salmeterol (Advair) 500/50 1 puff BID. ACQ score today was 2.0. FEV1 1.93 L 50% predicted; post bronchodilator FEV1 increased to 2.50L 64% predicted (29% reversibility). 0.408 K/cu mm absolute blood eosinophils and total serum IgE 66 IU/ml.

The best description of this patient’s asthma phenotype is:

A. Severe eosinophilic asthma
B. Severe neutrophilic asthma
C. Chronic airflow obstruction asthma
D. Severe allergic asthma
40 Year Old African American Male was diagnosed with asthma shortly after birth. He has history of allergic rhinitis. Hospitalized 15 times with one additional burst of steroids in the last year. During one hospitalization for asthma was in the ICU, but never intubated. Medications albuterol PRN and fluticasone/salmeterol (Advair) 500/50 1 puff BID. ACQ score today was 2.0. FEV1 1.93 L 50% predicted; post bronchodilator FEV1 increased to 2.50L 64% predicted (29% reversibility). 0.408 K/cu mm absolute blood eosinophils and total serum IgE 66 IU/ml.

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### Potential phenotype-targeted therapies in severe asthma

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<th>Characteristic</th>
<th>Associations</th>
<th>Specifically-targeted treatments</th>
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<tr>
<td>Severe allergic asthma</td>
<td>High eosinophil</td>
<td>Anti-IgE (adults and children)</td>
</tr>
<tr>
<td></td>
<td>High serum IgE</td>
<td>Anti-IL-4/IL-13</td>
</tr>
<tr>
<td></td>
<td>High FeNO</td>
<td>IL-4/R</td>
</tr>
<tr>
<td>Eosinophilic asthma</td>
<td>High serum IgE</td>
<td>Anti-IL-5</td>
</tr>
<tr>
<td></td>
<td>Recurrent exacerbations</td>
<td>Anti-IL-4/-13</td>
</tr>
<tr>
<td></td>
<td>High FeNO</td>
<td>IL-4/R</td>
</tr>
<tr>
<td>Non-eosinophilic, neutrophilic asthma</td>
<td>Corticosteroid insensitivity</td>
<td>Anti-IL-8</td>
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<tr>
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<td>Bacterial infections</td>
<td>CXCR2 antagonists</td>
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<td></td>
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<td>Macrolides (adults and children)</td>
</tr>
<tr>
<td>Chronic airflow obstruction</td>
<td>Airway wall remodelling as increased airway wall thickness</td>
<td>Anti-IL-13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchial thermoplasty</td>
</tr>
<tr>
<td>Recurrent exacerbations</td>
<td>Eosinophils in sputum</td>
<td>Anti-IL-5</td>
</tr>
<tr>
<td></td>
<td>Reduced response to ICS ± OCS</td>
<td>Anti-IgE (adults and children)</td>
</tr>
<tr>
<td>Corticosteroid insensitivity</td>
<td>High neutrophils in sputum</td>
<td>p38 MAPK inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macrolides (adults and children)</td>
</tr>
</tbody>
</table>
Role of Eosinophils in Severe Asthma

Several (interdependent) determinants of anti-IL-5 clinical response in asthma

- Exposure to drug
  - Individual IL-5 drive
  - Burden of disease in the airway
- Blood eosinophil level
  - OR
  - Demonstrable airway eosinophilia
- Disease severity
  - Based on background medication level
- Level of baseline control
  - Exacerbation history
- Other patient factors
  - e.g. Associated comorbidities (e.g. nasal polyps/sinus disease), allergy etc

- Treating currently active tissue eosinophilia AND/OR
- Preventing the influx associated with a future exacerbation
Mepolizumab: DREAM trial

**Primary endpoint**

- Placebo (exac=2.40/year, n=159)
- Mepolizumab 75 mg (exac=1.24/year, n=154)
- Mepolizumab 250 mg (exac=1.46/year, n=152)
- Mepolizumab 750 mg (exac=1.15/year, n=156)

Mepolizumab is not currently licensed for the treatment of asthma

Exac, exacerbation rate


---

**Secondary endpoints**

- Placebo
- Mepolizumab 75 mg
- Mepolizumab 250 mg
- Mepolizumab 750 mg

Change in blood eosinophil count

- All mepolizumab doses P<.001 vs placebo at 52 weeks

Change in sputum eosinophil count

p=0.0082 for mepolizumab 750 mg vs placebo at 52 weeks

Change in pre BD FEV1

Mepolizumab is not currently licensed for the treatment of asthma

Mepolizumab: MENSA study

Primary endpoint - asthma exacerbations

![Graph showing cumulative asthma exacerbations over weeks for Placebo, Mepolizumab 75 mg IV, and Mepolizumab 100 mg SC.]

Mepolizumab 100 mg SC is licensed for the treatment of severe eosinophilic asthma.


Changes in SGRQ

![Bar chart showing changes in St. George's Respiratory Questionnaire (SGRQ) scores for Placebo, 75 mg IV, and 100 mg SC.]

6.4 points difference *
7.0 points difference **

* p<0.001

IV, intravenous; SC, subcutaneous; SGRQ, St. George's Respiratory Questionnaire.
Mepolizumab: Oral Steroid Sparing

Mepolizumab summary

- Mepolizumab significantly reduces the number of asthma exacerbations in patients with severe eosinophilic asthma compared with placebo
- Treatment lowers blood and sputum eosinophil counts (750 mg IV) but SC 100 mg Q4wks variable effects
- There were small effects of mepolizumab on FEV₁, QOL and ACQ scores, which generally did not differ significantly from those reported with placebo
- Safety and tolerability profile for mepolizumab comparable to that for placebo
Reslizumab 3 mg/kg q 4 weeks over 52 weeks in exacerbation-prone, uncontrolled asthmatics with elevated blood eosinophils

<table>
<thead>
<tr>
<th></th>
<th>Pooled results (Studies 3082/3083)</th>
<th>Reslizumab 3 mg/kg n=477</th>
<th>RR (95% CI)</th>
<th>% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAE*</td>
<td>1.81</td>
<td>0.84</td>
<td>0.46 (0.37, 0.58)</td>
<td>54%</td>
</tr>
<tr>
<td>CAE requiring systemic corticosteroid</td>
<td>1.54</td>
<td>0.66</td>
<td>0.42 (0.33, 0.55)</td>
<td>58%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from baseline over 52 weeks</th>
<th>ΔResl-PBO (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td>0.12</td>
</tr>
<tr>
<td>AQLQ</td>
<td>0.81</td>
</tr>
<tr>
<td>ACQ</td>
<td>−0.77</td>
</tr>
<tr>
<td>ASUI</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*CAE defined as a worsening requiring additional corticosteroid and/or other urgent treatment including ER/hospital

Reslizumab is not currently licensed for the treatment of asthma


Reslizumab effect on lung function

- Change from baseline to each visit in FEV₁ by treatment group: pooled results for studies 3082/3083

** p<0.01

Reslizumab is not currently licensed for the treatment of asthma

Influence of background therapy on asthma exacerbations with reslizumab

- Reslizumab was efficacious in reducing CAE regardless of the treatments patients were receiving at baseline

<table>
<thead>
<tr>
<th>Rate-Ratio*</th>
<th>Reslizumab Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>0.46 (0.37–0.58)</td>
<td>477 476</td>
</tr>
<tr>
<td>0.32 (0.18–0.55)</td>
<td>73 73</td>
</tr>
<tr>
<td>0.45 (0.35–0.58)</td>
<td>397 383</td>
</tr>
<tr>
<td>0.51 (0.29–0.89)</td>
<td>80 93</td>
</tr>
</tbody>
</table>

*Reslizumab relative to placebo

Reslizumab is not currently licensed for the treatment of asthma


Predicting response to reslizumab

Pooled studies 3082 and 3083: Percentage CAE reduction

**Reslizumab summary**

- Patients receiving reslizumab (3 mg/kg IV Q 4wks) showed significantly greater reductions in sputum eosinophils, asthma exacerbations, improvements in airway function, and greater asthma control than those receiving placebo.

- Reslizumab can be targeted to the patients most likely to benefit by applying fairly simple blood eosinophil, asthma control, lung function, and disease severity criteria.

- Reslizumab was generally well-tolerated.

---

**Benralizumab (anti-IL-5Rα)**

- A targeted, anti-eosinophil therapy under investigation for asthma.

- Benralizumab is a humanized, afucosylated monoclonal antibody (IgG1k) that binds with high affinity to IL-5Rα and efficiently depletes eosinophils through antibody-dependent cell-mediated cytotoxicity (ADCC).

- Eosinophils are thought to play a critical role in the pathogenesis and severity of asthma.
- ~40–60% of people with severe asthma have eosinophilic inflammation.
- Increased eosinophil count is associated with an increased frequency of exacerbations.
- IL-5R is important in mediating the differentiation, proliferation, and activation of eosinophils by IL-5.

---

References:
Benralizumab

**Eosinophilic phenotype**
- ELEN Index positive and/or
  - FeNO ≥50 ppb

**Non-eosinophilic phenotype**
- ELEN Index negative and
  - FeNO <50 ppb

ELEN Index: mathematical algorithm to predict sputum eosinophils from CBC data


Benralizumab is not currently licensed for the treatment of asthma

---

**Benralizumab: primary efficacy endpoint: AER (mITT)**

- Benralizumab 20 mg significantly reduced AER relative to placebo in patients with baseline blood eosinophils ≥300 cells/µL
- Benralizumab 100 mg significantly reduced AER relative to placebo in eosinophilic patients and in patients with baseline blood eosinophils ≥300 and ≥400 cells/µL

*Statistically significant (p<0.169)
†Data are expressed as mean (80% CI)

Benralizumab is not currently licensed for the treatment of asthma


ACQ-6; Asthma Control Questionnaire-6; AER, annual exacerbation rate (total observed exacerbations to week 52 divided by total duration of person-year follow-up); CBC, complete blood count with differential; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ppb, parts per billion
Benralizumab (anti-IL-5Rα)

Estimates calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use, and prior exacerbations.
Sirocco: *p <0·0001. †p =0·0471. Calima: *p=0·0018. ‡p=0·0150. §p=0·0048.
CI=confidence interval. Q4W=once every 4 weeks; Q8W=once every 8 weeks.

Benralizumab: conclusions

◆ In patients with uncontrolled asthma, benralizumab 30 mg SC Q 4 and 8 wks moderately reduced exacerbations
◆ In patients with high eosinophils (≥300/µL), benralizumab Q 8 wks improved lung function and asthma control compared with placebo
◆ Benralizumab had an acceptable safety profile at all doses
◆ Attractive every other month dosing option

Benralizumab is not currently licensed for the treatment of asthma
Question 3

- 42 Year old female (BMI 33), diagnosed asthma age 32, has severe uncontrolled persistent asthma despite high dose fluticasone (1,000 mcg/day), salmeterol, and tiotropium. She has had 4 courses of corticosteroids in the past year and one hospitalization for asthma resulting in BiPAP therapy. Baseline FEV1 of 1.60 L 65% of predicted, post-bronchodilator FEV1 increased to 2.02L. 0.440 K/cu mm absolute blood eosinophils and total serum IgE 660.

Which of the following currently available biologic therapy would be most appropriate for this patient?

A. Omalizumab
B. Mepolizumab
C. Dupilumab
D. Reslizumab
E. Epinephrine pen
IL-4 and IL-13 share the same receptor subunit

Dupilumab, a fully human monoclonal antibody against the IL-4 receptor alpha subunit, inhibits IL-4 and IL-13 signaling

Multinational, 24-week, randomized, double-blind, placebo-controlled, dose-ranging study in patients with persistent, uncontrolled asthma despite use of medium-to-high dose ICS/LABA

To ensure a balanced distribution of blood eosinophil (Eos) counts in patients across treatment regimens, randomization was stratified by blood Eos count at screening: ≥ 300 cells/µL, 200–299 cells/µL, and < 200 cells/µL

Screening period (14–21 days)

Randomization (1:1:1:1)

Dupilumab or placebo was added on to therapy with ICS/LABA

n = 150 Dupilumab 300 mg q2w with loading dose (600 mg)
n = 150 Dupilumab 300 mg q4w with loading dose (600 mg)
n = 150 Dupilumab 200 mg q2w with loading dose (400 mg)
n = 150 Dupilumab 200 mg q4w with loading dose (400 mg)
n = 150 Placebo

24-week treatment period

## Dupilumab: Severe Exacerbation Rate

The annualized exacerbation rate was adjusted for treatment duration in patients who discontinued prematurely. Arrows represent percent change relative to placebo.

*P < 0.05, **P < 0.01, ***P < 0.001 vs placebo.

CI, confidence interval.

- At Week 24, the q2w regimens showed a significant decrease in severe asthma exacerbation rates in patients with Eos ≥ 300 cells/µL, patients with Eos < 300 cells/µL, and the overall population.


The annualized exacerbation rate was adjusted for treatment duration in patients who discontinued prematurely. Arrows represent percent change relative to placebo.

- *P < 0.05, **P < 0.01, ***P < 0.001 vs placebo.

CI, confidence interval.

## Anti-IL-13: lebrikizumab in moderate asthma

- IL-13 induces bronchial epithelial cells to secrete periostin<sup>1,2</sup>

- Patients with high pretreatment levels of serum periostin had greater improvement in lung function with anti-IL-13 therapy than patients with low periostin levels<sup>3</sup>

FEV<sub>1</sub>, forced expiratory volume in 1 second; IL, interleukin.


Lebrikizumab is not currently licensed for the treatment of asthma.
Anti-IL-13: lebrikizumab in severe asthma

**Anti-IL13: tralokinumab in severe asthma**

- RCT phase 2b study of 452 patients with severe asthma (2–6 exacerbations in previous year) treated with placebo or tralokinumab Q2W or Q2W for 12 weeks then Q4W
  - Neither tralokinumab regimens significantly reduced asthma exacerbation rates:
    - Annual asthma exacerbation rate at week 52 was similar with tralokinumab Q2W (0.91 per patient per year [0.76–1.08]), Q4W (0.97 [0.81–1.14]) and placebo (0.90 [0.75–1.08])

- In patients with high biomarkers (greater than the median):
  - Serum dipeptidyl peptidase-4 (DPP-4) - improvements in pre-bronchodilator FEV1, ACQ-6, and AQLQ(S)
  - Periostin concentrations - improvements in asthma exacerbation rate, pre-bronchodilator FEV1, and ACQ-6

---

**Question 4**

- 22 Year old female (BMI 33) diagnosed with asthma at age 2 has severe uncontrolled persistent asthma despite high dose fluticasone (1,000 mcg/day), salmeterol, and tiotropium with history of allergic rhinitis and urticaria. She has had 4 courses of corticosteroids in the past year and one hospitalization for asthma resulting in BiPAP therapy. Baseline FEV1 2.70 L 95% of predicted, post-bronchodilator FEV1 increased to 3.02L (107% predicted, 12% reversibility), 0.240 K/cu mm absolute blood eosinophils, FeNO 55 ppb and total serum IgE 660.

Which of the following currently available biologic therapy would be most appropriate for this patient?

A. Omalizumab  
B. Mepolizumab  
C. Dupilumab  
D. Reslizumab  
E. Epinephrine pen
22 Year old female (BMI 33) diagnosed with asthma at age 2 has severe uncontrolled persistent asthma despite high dose fluticasone (1,000 mcg/day), salmeterol, and tiotropium with history of allergic rhinitis and urticaria. She has had 4 courses of corticosteroids in the past year and one hospitalization for asthma resulting in BiPAP therapy. Baseline FEV1 2.70 L 95% of predicted, post-bronchodilator FEV1 increased to 3.02 L (107% predicted, 12% reversibility), 0.240 K/cu mm absolute blood eosinophils, FeNO 55 ppb and total serum IgE 660.

Which of the following currently available biologic therapy would be most appropriate for this patient?

A. Omalizumab
B. Mepolizumab
C. Dupilumab
D. Reslizumab
E. Epinephrine pen

Omalizumab: anti-IgE therapy for severe eosinophilic asthma?

EXTRA study: exacerbations reduced in severe asthma patients treated with high dose ICS+LABA: omalizumab vs. placebo RR 0.75 [0.61-0.92]1

- Exploratory analysis revealed greatest effect in high biomarker subsets (median FeNO, Blood EOS, Periostin)2

## Potential phenotype-targeted therapies in severe asthma

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<tr>
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<th>Specifically-targeted treatments</th>
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</tr>
<tr>
<td></td>
<td>High serum IgE</td>
<td>Anti-IL4/IL-13</td>
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<td></td>
<td>High FeNO</td>
<td>IL-4 Receptor</td>
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<tr>
<td>Eosinophilic asthma</td>
<td>High serum IgE</td>
<td>Anti-IL5</td>
</tr>
<tr>
<td></td>
<td>Recurrent exacerbations</td>
<td>Anti-IL4/IL-13</td>
</tr>
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<td></td>
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<td>IL-4R</td>
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<td>Recurrent exacerbations</td>
<td>Eosinophils in sputum</td>
<td>Anti-IL5 (adults and children)</td>
</tr>
<tr>
<td></td>
<td>Reduced response to ICS ±OCS</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid insensitivity</td>
<td>High neutrophils in sputum²</td>
<td>p38 MAPK inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Theophylline (adults and children)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macrolides (adults and children)</td>
</tr>
</tbody>
</table>

*International ERS/ATS GUIDELINES Eur Respir J, 2014; 43(2):343-373*

### Site of action of targeted therapies for severe asthma.

![Diagram of site of action of targeted therapies for severe asthma](image)

*Trivedi A et al Lancet Resp 2016 In press*
Phenotype-guided approach in severe asthma with biologics

- Many phenotypes exist in asthma though the biologic pathway (endotype) is unclear for most.
- Ongoing studies of large-scale, molecularly and genetically focused and extensively clinically characterized cohorts of asthma should enhance our ability to molecularly understand these phenotypes.
- Biologic therapy with anti-IL 5 for the eosinophilic uncontrolled asthma is a well established endotype but likely represents less 40% of uncontrolled asthma.
- Promising evidence for anti-IL4 R for uncontrolled asthma, especially the non-eosinophilic patient.

Phenotype-guided approach in severe asthma with biologics

- Targeted phenotype therapy can lead to personalized medical therapy for asthma.

- Many questions remain:
  - Are there better biomarkers than the blood EOS?
  - Is anti-IL-4/13 therapy as effective as anti-IL-5?
  - Will other biologic targets work?
    - Anti-IL-17, -23, -33, anti-TSLP, -CRTH2, and more
  - Is chronic airflow obstruction and airway remodeling responsive to biologics?