Evaluation and Treatment of Severe Asthma: The Role of Biologic and Directed Therapies

A free CME/CPE interactive, case-based activity with dinner and syllabus provided.

Mount Sinai - National Jewish Health
Respiratory Institute

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Evaluation and Treatment of Severe Asthma: The Role of Biologic and Directed Therapies

Learning Objectives:

- Recognize the epidemiology and distinguishing characteristics of “difficult to treat” versus severe asthma
- Explain the role of the Th2 pathway in severe asthma
- Distinguish the treatment approaches that are effective in patients with Th2-high versus Th2-low asthma
- Assess recent clinical data on the efficacy, safety, and mechanisms of action of biological drugs in asthma
Case #1

- 55 yo never smoker, NYPD officer who worked at the WTC site in rescue and recovery
- New onset asthma in 2002
- Persistent symptoms despite prescription of high dose ICS, LABA
- Methacholine challenge shows $PC_{20} = 1 \text{ mg/ml}$

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
The term ‘severe refractory asthma’ should be reserved for patients with asthma in whom alternative diagnoses have been excluded, comorbidities have been treated, trigger factors have been removed (if possible) and compliance with treatment has been checked, but still have poor asthma control or frequent severe exacerbations per year despite the prescription of high-intensity treatment or can only maintain adequate control when taking systemic corticosteroids and are thereby at risk of serious adverse effects of treatment.

Difficult to Control Asthma

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

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

Epidemiology of difficult to control asthma therapy
Standard of care guidelines
Asthma is treated empirically according to clinical severity and response to treatment, not according to underlying molecular mechanism

US pop (M)
High-Need (severe) (~2M)

NHLBI Guidelines for the Diagnosis and Management of Asthma, Oct 2007
Prevalence of True Refractory Asthma

- 3.6% of adults (10 in 10,000) had true refractory asthma
- Majority of difficult to control asthma is related to non-adherence and incorrect inhaler technique

Hekking et al JACI 2015
**Take home:**

- Most disease that is difficult to control is **NOT** true refractory asthma

- Most is due to poor adherence and technique, misdiagnosis and comorbidities

- Although 5-15% are difficult to control, probably < 5% true refractory

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**Evaluation of Difficult to Control Asthma**
Systematic Evaluation of Difficult to Control Asthma

Is the diagnosis correct?

Yes
1. Assess adherence
2. Assess environment
3. Assess comorbid conditions

No
- Address adherence and environmental factors.
- Targeted workup and treatment of comorbid disease

Yes
- Diagnose and treat upper airway issues, psychiatric issues, speech therapy for VCD etc. or other diagnosis (CHF, bronchiectasis)
- Consider advanced therapies depending on phenotype

Confirm variable airflow limitation

- Bronchodilator reversibility (FEV₁ > 12% & > 200 ml)
- Variability in 2x daily PEF over 2 weeks (> 10%)
- Increase in lung function after 2 weeks of ICS
- + Exercise challenge test (fall > 10% & 200 ml)
- + Bronchial challenge test fall > 20%
What if you are not sure of the diagnosis of someone on controller therapy?

- Repeat PFTS withholding bronchodilators or when patient is symptomatic
- If FEV > 70% consider challenge testing
- If FEV1 < 70% consider stepping down therapy and repeating testing
- If no change on the lowest dose of controller, stop controller, consider methacholine challenge

Global Initiative for Asthma (GINA) 2014

Non-adherence is the most common cause of difficult to control asthma

Intentional poor adherence (20-73%)
- take < daily prescribed dose
- therapeutic gaps of variable duration
- fail to refill after initial adherence (non-persistence) (50%)
- fail to fill 1st rx (primary poor adherence) (8%)

Unintentional poor adherence
- taking < prescribed dose (forgetfulness)
- misconception of how to use medication
- poor inhaler technique (46-59%)
- inability to afford medication (rationing)

As reviewed in Boulet Clinics of Chest Medicine 2012
Factors contributing to poor adherence

- Difficulty using inhaler device
- Burdensome regimen (multiple inhalers/multiple techniques)
- Misunderstanding instructions
- Forgetfulness
- Absence of a daily routine
- Cost/formularies
- Denial
- Perception that treatment is not necessary
- Concerns about side effects (real or perceived)

Identifying Poor Adherence

- Acknowledge likelihood of incomplete adherence (no judgments!)
- Check medication use (dates, counters), EMR rx fills, call pharmacies
- Assess asthma knowledge
- Assess attitudes about medications
  - Do they have a routine?
  - What do friends/family tell them about their medications?
  - Are they having/are they worried about adverse effects?
- Ask about obstacles (formulary, can they afford their medications)
- Check technique (then check again.... and again....)
Few interventions found effective for improving adherence

- Shared decision-making
- Simplifying the medication regimen (1x vs. 2x-daily)
- Comprehensive asthma education with nurse home visits
- Inhaler reminders for missed doses
- Reviewing patients’ detailed dispensing records

Poor Inhaler Technique is Common

- Prevalence of correct technique was 31%, acceptable, 41%, and poor 31%
- No significant differences over 20-year period
- The most frequent MDI errors were in coordination, speed and/or depth of inspiration, and no post-inhalation breath-hold
- Frequent DPI errors were incorrect preparation in 29%, no full expiration before inhalation in 46%, and no post-inhalation breath-hold in 37%

Sanchis CHEST 2016; 150(2):394-406
Differential diagnosis, misdiagnosis & comorbidities

- COPD
- ABPA
- Bronchiectasis/NTM
- Laryngeal hypersensitivity (PVCM, “vocal cord dysfunction”)
- GER
- Rhinosinusitis
- Obesity
- Sleep apnea
- Medication associated symptoms (BB, ACE, NSAIDS)

- CHF
- Sarcoidosis
- Foreign body
- Vascular ring
- Laryngeal web
- Airway malacia
- Tracheal/bronchial stenosis
- Obliterative bronchiolitis
- Hyperventilation/panic

As many as 25-35% patients with a diagnosis of asthma in primary care cannot be confirmed as having asthma.

Case # 2

- 66 year old RN with dyspnea for 1 year
- Steroids for control, unable to taper below 10 mg
- Adherence and inhaler technique are verified as adequate
- Evaluation for comorbidities negative

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>No oral steroids</th>
<th>40 mg prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (%)</td>
<td>1.19 (49%)</td>
<td>1.87 (80%)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.59</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Spirometry on high dose ICS, LABA

The Asthma Syndrome

Phenotypes of Severe Asthma Using Cluster Analysis in SARP

Age of onset, lung function, reversibility are key characteristics

Moore et al. AJRCCM 2010; 181 :315-23.

SARP Phenotypes With Addition of Sputum Induction

A - B: Mild-mod, early onset allergic asthma with paucigranulocytic or eosinophilic-predominant patterns
C - D: Mod-severe, frequent health care utilization in spite of high dose ICS or po steroids; reduced lung function, sputum neutrophilia

Moore et al. JACI 2013.
Asthma Phenotypes Using Inflammatory Cellular Subtypes in Induced Sputum


Phenotype using clinical and sputum characteristics

Characteristics of the Th2 High vs. Th2 Low Severe Asthma Phenotypes


Molecular Phenotypes of Severe Asthma

Gene signature for Th2-driven inflammation is prominent in only half of patients with mild asthma

Molecular Phenotypes of Severe Asthma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Th2-High</th>
<th>Th2-Low</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PC_{20} Mch</strong></td>
<td>0.27</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>IgE, IU/ml</strong></td>
<td>244</td>
<td>125</td>
</tr>
<tr>
<td><strong>Blood eos, x10^9/L</strong></td>
<td>0.37±0.22</td>
<td>0.23±0.21</td>
</tr>
<tr>
<td><strong>BAL eos %</strong></td>
<td>1.9±1.9</td>
<td>0.42±0.46</td>
</tr>
<tr>
<td><strong>RBM thickness, μm</strong></td>
<td>5.91±1.72</td>
<td>4.67±0.99</td>
</tr>
<tr>
<td><strong>ΔFEV₁, L, fluticasone, 4 wks</strong></td>
<td>0.35±0.2</td>
<td>0.03±0.12</td>
</tr>
</tbody>
</table>


Importance of Blood and Sputum Eos

<table>
<thead>
<tr>
<th></th>
<th>Blood eosinophils &lt;400 cells per mm³, sputum eosinophils &lt;3%</th>
<th>Blood eosinophils &gt;400 cells per mm³, sputum eosinophils ≥3%</th>
<th>Blood eosinophils &gt;400 cells per mm³, sputum eosinophils ≥9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>Blood eosinophils &lt;400 cells per mm³</td>
<td>Blood eosinophils &gt;400 cells per mm³</td>
<td>Blood eosinophils &gt;400 cells per mm³</td>
</tr>
<tr>
<td>Males/females n</td>
<td>249 (49)</td>
<td>128 (25)</td>
<td>34 (7)</td>
</tr>
<tr>
<td>Age years</td>
<td>52 (21-86)</td>
<td>53 (21-86)</td>
<td>51 (21-45)</td>
</tr>
<tr>
<td>Age of onset</td>
<td>&lt;12 years: 22.4</td>
<td>27.6</td>
<td>28.5</td>
</tr>
<tr>
<td>12-40 years: 34.5</td>
<td>36.2</td>
<td>32.3</td>
<td>45.6</td>
</tr>
<tr>
<td>&gt;40 years: 43.9</td>
<td>43.2</td>
<td>41.2</td>
<td>31.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>146±19</td>
<td>146±19</td>
<td>149±9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73±15</td>
<td>74±15</td>
<td>78±17</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3±5</td>
<td>26.4±5</td>
<td>28.3±4.8</td>
</tr>
<tr>
<td>Asthma yes/no (%)</td>
<td>124/122 (51)</td>
<td>82/64 (64)</td>
<td>22/72 (45)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>54 (22)</td>
<td>29 (23)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Bronchiectasis*</td>
<td>19</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>77</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>Nasal polyps*</td>
<td>9</td>
<td>25***</td>
<td>37***</td>
</tr>
<tr>
<td>Sinusitis*</td>
<td>34</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>53</td>
<td>59</td>
<td>72</td>
</tr>
<tr>
<td>Exacerbations per patient per year</td>
<td>0.42±0.9</td>
<td>0.32±2.72*</td>
<td>0.59±0.8</td>
</tr>
</tbody>
</table>

Blood Eosinophils as a Risk Factor

- A high blood eosinophil count is a risk factor for increased future asthma exacerbations after adjustment of potential confounders
- Suggests a higher disease burden


Currently Available Biomarkers of Type 2 Inflammation

Biomarkers predict response & are modulated by asthma biologics

Traditional and Personalized Approach to Asthma Therapy

Dunn RM and Wechsler ME. Clinical Pharmacology and Therapeutics 2015; 97(1): 55-65
Advanced Therapies
Present and Future

Case # 2

- 66 year old RN with dyspnea for 1 year
- Steroids for control, unable to taper below 10 mg
- Adherence and inhaler technique are verified as adequate
- Evaluation for comorbidities negative
- Allergy testing IGE 200, + multiple perennial allergens, elevated FeNO 95 ppb and absolute eosinophil count 400/uL

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Spirometry on high dose ICS, LABA
Important Th2 Biologic Targets

Targeting the Th2 pathways-anti-IgE


Omalizumab (anti-IgE)

- Monoclonal IgE antibody
- Binds free IgE & inhibits its binding to mast cells
- Reduces early & late allergic responses
- Reduces exacerbations 50% (moderate and severe asthma)
- Expensive ($10-30K/year)
- Requires bimonthly or monthly visits
- Non-responders (40%+) - no clear way to distinguish responders and non-responders

Omalizumab in Severe Allergic Asthma Inadequately Controlled With Standard Therapy
A Randomized Trial

Nicola A. Hanania, MD, MS; Oral Alpan, MD; Daniel L. Hamilos, MD; John J. Cosimoni, MD; Imanie Reyes-Rivers, PhD; Jin Zhu, PhD; Karin E. Rosen, MD, PhD; Mark D. Eisner, MD, MPH; Dennis A. Wong, MD; and William Busse, MD

- Double-blind, placebo-controlled, randomized trial of 850 patients with inadequately controlled asthma despite treatment with high-dose ICS plus LABAs (48 weeks)
- 25% reduction in asthma exacerbation rate
- Reduced rescue inhaler use
- Improved symptoms and quality-of-life scores over 48 weeks
- No difference in the incidence of adverse events

Omalizumab in Allergic Asthma: An Analysis of Biomarkers in the Extra Study


Anti IL-5

Mepolizumab
Reslizumab
Benralizumab
Mepolizumab (anti-IL5) suppressed blood eosinophilia but did not improve FEV$_1$ in a general population of asthma (no eosinophilia)


Mepolizumab in Severe Eosinophilic Asthma

- Significant reduction in exacerbations ($P=0.002$)
- Significant reduction in steroid dose (84% in mepolizumab group vs. 48% in placebo, median 50%)
- Sustained benefit x 8 weeks
- Reduced eosinophils
- No serious adverse events

Kaplan-Meier analysis of the proportion of patients without an asthma exacerbation during the study

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Patients without Exacerbations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mepolizumab</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>26</td>
<td>0</td>
</tr>
</tbody>
</table>

No. at risk
- Mepolizumab
  - Randomization: 9
  - Weeks 2-26: 9, 8, 7, 7, 7, 7, 7
- Placebo
  - Randomization: 10
  - Weeks 2-26: 10, 9, 8, 7, 7, 5, 4, 3, 2


Mepolizumab and Asthma Exacerbations

Significant reduction in exacerbations

No effect on lung function, symptom scores, or NO


Mepolizumab for Severe Eosinophilic Asthma—The DREAM Study Design

Patients with severe refractory eosinophilic asthma sputum
- Sputum eosinophils >3%
- Exhale nitric oxide ≥50ppb
- Blood eosinophils ≥300/µL
- Deterioration of asthma after ≤25% reduction in ICS or OCS

Rate of clinically significant exacerbation is measured per patient per year.

OCS = oral corticosteroid

The DREAM Study: Dose-Ranging Efficacy of Mepolizumab in Reducing Exacerbation

![Graph showing the number of clinical exacerbations over time for different doses of Mepolizumab compared to placebo.](image)


Reslizumab BREATHE

**Eosinophil Inclusion Criteria**

- Asthma Eosinophils Level Unselected
- Asthma with Elevated Eosinophils (≥400)

**Study Design**

- 16-week FEV1 – study 3084
  - 3 mg/kg IV, ages 18-65, n = 496
- 16-week FEV1 – study 3081
  - 3 mg/kg IV and 0.3 mg/kg, ages 12-75, n = 315
- 52-week exacerbation and FEV1 – study 3082
  - 3 mg/kg IV, ages 12-75, n = 489
- 52-week exacerbation – study 3083
  - 3 mg/kg IV, ages 12-75, n = 464
- Open label safety extension – study 3085
  - Enrolled patients from 3081, 3082, 3083
  - 3 mg/kg IV, ages 12-75, n = 1051

**Key Objectives & Outcomes**

- Primary — lung function
- Primary — lung function
- Primary — exacerbation
- Primary — long-term safety

Study 3081: Inclusion Criteria and Study Design

Key Enrollment Criteria

<table>
<thead>
<tr>
<th>Key Enrollment Criteria</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>12-75 years</td>
</tr>
<tr>
<td>Background Medication Requirement</td>
<td>≥ 440µg fluticasone or equivalent ± another controller (moderate-to-severe asthma)</td>
</tr>
<tr>
<td>Asthma Control</td>
<td>ACQ ≥ 1.5 (inadequately controlled)</td>
</tr>
<tr>
<td>FEV₁ Reversibility</td>
<td>≥ 12%</td>
</tr>
<tr>
<td>Screening Blood Eosinophils</td>
<td>≥ 400 cells/µL</td>
</tr>
</tbody>
</table>

Randomization (1:1:1)

Reslizumab (n=103)
IV 0.3 mg/kg q4W (4 doses)

Reslizumab (n=103)
IV 3.0 mg/kg q4W (4 doses)

Placebo (n=105)
IV q4W (4 doses)

Follow-up (90 days) or option to continue into 3085 study

ACQ, Asthma Control Questionaire; FEV₁, Forced Expiratory Volume in 1 second; ICS, inhaled corticosteroid; IV, intravenous; q4W, every 4 weeks; SABA, short-acting beta agonist Study - 3081; Data on file

Reslizumab Reduced Blood Eosinophil Counts in a Dose-Dependent Manner

Blood Eosinophil Count Over Time, x10⁹/L

SEM, standard error of the mean. Data are actual mean ± SEM. Study 3081; Data on file
Reslizumab Significantly Improved Lung Function
(Primary Outcome)

- Reslizumab significantly improved lung function by the earliest evaluation (4 weeks) and maintained improved lung function throughout treatment (16 weeks)

Overall Change in FEV₁
From Baseline
Over 16 Weeks of Treatment

Change in FEV₁
From Baseline to Each Visit

Reslizumab Increased the Time to First Exacerbation

Study 3082

Study 3083

<table>
<thead>
<tr>
<th>Study</th>
<th>Probability of Not Having a CAE by Week 52, % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>44 (38-51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>61 (55-67)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Calculated by Kaplan-Meier estimate of probability.

CAE, clinical asthma exacerbation; 95% CI, 95% confidence interval; HR, hazard ratio.

## Mepolizumab vs. Reslizumab

<table>
<thead>
<tr>
<th>Study</th>
<th>CAE primary</th>
<th>CAE requiring</th>
<th>CAE ER or hospital</th>
<th>FEV1 change from baseline at time point (ml)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>primary</td>
<td>sys. cortico.</td>
<td>or hospital</td>
<td>16 wk</td>
</tr>
<tr>
<td>Study 3082</td>
<td>50% p &lt; .0001</td>
<td>55% p &lt; .0001</td>
<td>34% ns</td>
<td>72 p = 0.0483</td>
</tr>
<tr>
<td>Study 3083</td>
<td>60% p &lt; .0001</td>
<td>61% p &lt; .0001</td>
<td>31% ns</td>
<td>101 p&lt;0.010</td>
</tr>
<tr>
<td>Study MENSA</td>
<td>53% p&lt;.001</td>
<td>61% p=0.015</td>
<td>-</td>
<td>98 p=0.028</td>
</tr>
<tr>
<td>DREAM</td>
<td>47% p&lt;.001</td>
<td>32% ns</td>
<td>-</td>
<td>100 p=0.025</td>
</tr>
<tr>
<td>Study 3081</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>165 p= 0.018</td>
</tr>
</tbody>
</table>

## Benralizumab depletes eosinophils in a different way from anti-IL-5 ligand approaches

1. Binds with high specificity to IL-5Rα on eosinophils and basophils,
2. Binds with increased affinity to Fc receptors on immune effector cells through the afucosylated (lack of fucose sugar residues) Fc region of benralizumab
3. This results in increased ADCC and death of eosinophils and basophils via apoptosis (programmed cell death).

Fc = fragment, crystallizable (of immunoglobulin); ADCC = antibody-dependent cell-mediated cytotoxicity; IL-5Rα = interleukin-5 receptor α.

Clinical Studies with Benralizumab

### Table 3. Clinical trials of benralizumab in asthma (MEDI-563, Anti-interleukin-5a, IgG1 - Medimmune)

<table>
<thead>
<tr>
<th>First author/ref/year</th>
<th>Disease severity</th>
<th>No. of patients treated</th>
<th>Dosage/delivery</th>
<th>Outcome summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busse et al. [63], 2010</td>
<td>Mild atopic asthma</td>
<td>44</td>
<td>0.0003-3 mg/kg i.v. single dose</td>
<td>Blood Eos at dose 0.03-3 mg; Eosinophilia lasted 8-12 weeks; Transient, mild decrease in WBC; CRP increased ±5.5 fold; Interleukin-6 increased</td>
</tr>
<tr>
<td>Lavoie et al. [65], 2013</td>
<td>Eosinophilic asthma</td>
<td>26</td>
<td>1 mg/kg i.v.; 100 mg s.c. every month for 3 doses; 200 mg s.c. every month for 3 doses</td>
<td>Eosin in blood, sputum and bronchial mucosa; Basophilis; Nasopharyngitis 25%; Headache 25%; Nausea 22%</td>
</tr>
<tr>
<td>Castro et al. [64*], 2014</td>
<td>Eosinophilic asthma</td>
<td>384</td>
<td>2-20-200 mg s.c. every 4 weeks for the first 3 doses, then every 8 weeks for 1 year</td>
<td>20 mg and 100 mg asthma; Exacerbation = FEV1</td>
</tr>
<tr>
<td>Novak et al. [66], 2015</td>
<td>Asthma after acute attack</td>
<td>72</td>
<td>Single dose 0.3 mg/kg i.v.</td>
<td>Blood Eos; Exacerbations</td>
</tr>
</tbody>
</table>

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**Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study** (Castro et al. Lancet Resp Med 2014; 2:879)

**Diagram:**
- **Non-eosinophilic**
- **Eosinophilic**

\[ D_1 \rightarrow \text{Day 1} \rightarrow \text{Week 0} \rightarrow \text{Treatment period} \rightarrow \text{Follow up} \rightarrow \text{Eosinophil recovery period} \]

- **Primary endpoint:** AER
- **Secondary endpoints:** FEV1, ACQ-6

---

*ASTHMA Control Questionnaire (6-10), AER, annual exacerbation rate (total observed exacerbations to week 53 divided by total duration of person-year follow-up); CRP, C-reactive protein with differential; FEV1, fraction of expired vital capacity; FEV1/FVC, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; pps, parts per billion; SC, subcutaneous.

Primary Endpoint: Exacerbation Rate

- Benralizumab 30 mg significantly reduced AER relative to placebo in subjects with baseline blood eosinophils ≥300 cells/µL.
- Benralizumab 100 mg significantly reduced AER relative to placebo in eosinophilic subjects and in subjects with baseline blood eosinophils ≥300 and ≤400 cells/µL.

*Statistically significant (p<0.001).
*Data are expressed as mean (95% confidence interval).
AER, annual exacerbation rate; AERR, annual exacerbation rate reduction; mITT, modified intent-to-treat; IR, inter-rater.


Secondary Endpoint: FEV₁

- Benralizumab (all doses) showed significant improvements in FEV₁ vs placebo in:
  - Eosinophilic and non-eosinophilic subjects
  - Subjects with baseline blood eosinophils ≥300 cells/µL

*Statistically significant (p<0.001).
Data are expressed as mean (standard error).
FEV₁, forced expiratory volume in 1 second; mITT, modified intent-to-treat.

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

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

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### Reduction in Exacerbation

**Eosinophils ≥300 cells per μL**

<table>
<thead>
<tr>
<th>Group</th>
<th>Annual asthma exacerbation rate ratio (95% CI)</th>
<th>Percentage reduction relative to placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=267)</td>
<td>1.12 (1.00-1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benralizumab 30 mg Q4W (n=275)</td>
<td>0.60 (0.53-0.68)</td>
<td>-51%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Benralizumab 30 mg Q8W (n=267)</td>
<td>0.77 (0.70-0.82)</td>
<td>-45%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Placebo (n=248)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Annual asthma exacerbation rate ratio (95% CI)</th>
<th>Percentage reduction relative to placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=248)</td>
<td>1.12 (1.00-1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benralizumab 30 mg Q4W (n=241)</td>
<td>0.60 (0.53-0.68)</td>
<td>-36%</td>
<td>0.0168</td>
</tr>
<tr>
<td>Benralizumab 30 mg Q8W (n=239)</td>
<td>0.54 (0.48-0.62)</td>
<td>-28%</td>
<td>0.0018</td>
</tr>
</tbody>
</table>

- **Bleecker ER, et al.**
- **FitzGerald JM, et al.**

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### Anti-IL5: Summary

- **Mepolizumab approved by FDA in November 2015**
- **Reslizumab approved by FDA in March 2016**
- **Benralizumab (IL5 receptor antagonist) in phase 3 program**
Blocking IL4/IL13 Axis in Asthma

Vatrella Journal of Asthma and Allergy 2014

Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

**Phase 2b Study Design**

Multinational, randomized, placebo-controlled study in patients with uncontrolled asthma despite background therapy with medium- to high-dose ICS and LABA

- Patients were stratified by blood eosinophil (Eos) count
- For this interim analysis, all patients had completed ≥ 12 weeks treatment; exacerbation data are based on all available treatment data (average exposure to treatment was 21.4 of 24 weeks)

**Randomization** (1:1:1:1)

- 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

**Screening period** (14–21 days)

**Dupilumab was used as add-on therapy to ICS and LABA**

**24-week treatment period**
Lung Function: % Change in \( \text{FEV}_1 \)

- **Placebo**
- **Dup 200 mg q4w**
- **Dup 300 mg q4w**
- **Dup 200 mg q2w**
- **Dup 300 mg q2w**

Eos ≥ 300 cells/µL

- At Week 24, significant improvements were observed in all three populations for the q2w and q4w regimens versus placebo, except for the 200 mg q4w regimen in patients with Eos ≥ 300 cells/µL.
- Improvements in \( \text{FEV}_1 \) in the dupilumab 200 mg and 300 mg q2w regimens versus placebo, respectively, were:
  - Eos ≥ 300 cells/µL: 10.1% and 12.1%
  - Eos < 300 cells/µL: 8.8% and 7.9%
  - Overall: 9.6% and 10.3%

Eos < 300 cells/µL

- In the HEos and overall populations, significant decreases in severe asthma exacerbation rates were observed for all dupilumab regimens versus placebo, except the 300 mg q4w.
- In the LEos population, significant decreases in severe asthma exacerbation rates were observed for the dupilumab q2w regimens versus placebo.

Annualized Severe Exacerbation Rate

- In the HEos and overall populations, significant decreases in severe asthma exacerbation rates were observed for all dupilumab regimens versus placebo, except the 300 mg q4w.
- In the LEos population, significant decreases in severe asthma exacerbation rates were observed for the dupilumab q2w regimens versus placebo.

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
Tralokinumab

Targeting the Th2 pathways-anti-IL-13

**T\(_2\) asthma, IL-13 and periostin**

- Periostin, ligand for integrin receptors, supports adhesion & migration of epithelial cells
- IL13 increased in airways of asthma but is unstable, difficult to measure
- One of IL-13 induced genes in airway epithelia is periostin & is a surrogate for IL-13 measurable in blood
- Periostin may alter collagen fibrillogenesis or cross-linking and lead to stiffening of the matrix

Woodruff et al. AJRCCM 2009; Jia et al JACI 2012

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**Lebrikizumab Treatment in Asthma**

- **A Total Cohort**
  - Lebrikizumab (N=100) vs. Placebo (N=100)
  - 9.8±1.9% vs. 4.3±1.5%; p = 0.02

- **B High-Periostin Subgroup**
  - 14.0±3.1% vs. 5.8±2.1%; p = 0.03

- **C Low-Periostin Subgroup**
  - 5.1±2.4% vs. 3.5±2.1%; p = 0.61

# Lebrikizumab: LAVOLTA I and LAVOLTA II Trials

Rate of asthma exacerbations over 52 weeks for all patients

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Adjusted Exacerbation Rate</th>
<th>Rate Difference / Rate Reduction %</th>
<th>Rate Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAVOLTA I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>362</td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 37.5mg</td>
<td>360</td>
<td>0.42</td>
<td>-0.42 / 50%</td>
<td>0.50 (0.37-0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lebrikizumab 125mg</td>
<td>359</td>
<td>0.59</td>
<td>-0.25 / 30%</td>
<td>0.70 (0.54-0.91)</td>
<td>0.0078</td>
</tr>
<tr>
<td><strong>LAVOLTA II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>354</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 37.5mg</td>
<td>356</td>
<td>0.52</td>
<td>-0.09 / 14%</td>
<td>0.86 (0.66-1.12)</td>
<td>0.2607</td>
</tr>
<tr>
<td>Lebrikizumab 125mg</td>
<td>357</td>
<td>0.48</td>
<td>-0.13 / 21%</td>
<td>0.79 (0.61-1.04)</td>
<td>0.0920</td>
</tr>
</tbody>
</table>


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# Tralokinumab Anti IL-13 in patients with High DPP4

DPP4= Dipeptidyl Peptidase 4
IL13 Current Status

- Lebrikizumab for asthma program on hold after inconclusive phase 3 trials (one reduced exacerbations, other did not)
- Tralokinumab phase 2 b improved lung function, but did not reduce exacerbations. Still in development.

Summary:

- 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 in asthma is a young field, but making progress
- Tailoring treatment to phenotypes is the ultimate goal
Summary, Cont.:

• Severe asthma represents a major unmet need
• Asthma is a heterogeneous condition with diverse characteristics and biologic mechanisms
• Asthma phenotyping by increasingly sophisticated methods provides a way to increase insight into disease heterogeneity
• We are moving toward precision medicine in which therapy will be targeted toward specific asthma phenotypes and their biomarkers

Thank You!

Questions and Answers...