A Breath of Fresh Air: Novel Biologic Agents for the Treatment of Eosinophilic Asthma

Amanda Schroeder
PGY-1 Pharmacy Resident
Mayo Clinic Health System – Eau Claire, WI
Learning Objectives

• Explain the pathophysiology and epidemiology of eosinophilic asthma
• Review recommendations for management of eosinophilic asthma
• Discuss available evidence for biologic agents approved for treatment of eosinophilic asthma
Definitions

ICS: Inhaled corticosteroid
IL: interleukin
IL-4Rα: interleukin-4 receptor alpha
IL-5Rα: interleukin-5 receptor alpha
ILC2: Innate lymphoid cell
LABA: Long-acting β agonist
Th: T helper cell
Th0: Naïve T helper cell
Th1: Type I T helper cell
Th2: Type II T helper cell
TSLP: Thymic stromal lymphopoietin
Asthma Phenotypes

- **Allergic Asthma**
  - IgE, mostly atopic
  - Corticosteroids; Th2-targeted therapy
  - (anti-IgE Ab, IL-4Ra/IL-13Rα2 blockers, anti-IL-13 Ab, anti-TSLP Ab, CysLT modifiers)

- **Exercise-induced Asthma**
  - CysLT modifiers

- **Eosinophilic Asthma**
  - Anti-IL-5 Ab, CysLT modifiers
  - Aspirin-exacerbated respiratory disease

- **Obesity-associated Asthma**
  - Eosinophils, oxidative stress
  - Weight loss, antioxidant (?)

- **Neutrophilic Asthma**
  - Th17, ILC3
  - Poorly responsive to corticosteroids

- **Infection-related Asthma, Th1**
  - Corticosteroids, interferons, CysLT modifiers

Influence of genetic background

Severity:
- Low-Th2
  - ↓IgE

Severity (symptoms, exacerbations):
- Early
  - Non-Th2
- Late
  - Th2

Age of onset:
- Early
  - Late

FEV₁

Severe Asthma

- Asthma that requires treatment with:
  - High dose ICS
  - A second controller medication
  - Oral corticosteroids

- Asthma is uncontrolled with the above regimen or worsens when treatment stepped down

Eosinophilic Asthma

• A phenotype of severe asthma characterized by elevated sputum and tissue eosinophils
  • Often measured by blood eosinophils $\geq 300$ cells/mcL
Epidemiology

- 8% of the population has asthma
- Severe asthma accounts for 10% of these cases
- $\geq 60\%$ of asthma costs can be attributed to severe asthma
- Per person cost of severe asthma $\geq 2x$ that of moderate asthma

Pathophysiology
Pathophysiology

[Diagram showing immune cell interactions, allergens, and cytokines involved in allergic and nonallergic eosinophilic airway inflammation.]
Pathophysiology

[Diagram of allergic and nonallergic eosinophilic airway inflammation]

References:
Pathophysiology
Targets for Drug Therapy

- **IL-4**: IgE, Th2 phenotype, Allergic sensitization
- **IL-5**: Eosinophil growth factor, Promotes eosinophil survival
- **IL-13**: Airway hyperresponsiveness, Airway remodeling

Th0 cell → Th2 cell → IL-4 → IL-5 → IL-13
Question 1

Which inflammatory cytokine is an eosinophil growth factor and promoter of eosinophil survival?

A. IgE
B. IL-4
C. IL-5
D. IL-13
Question 1

Which inflammatory cytokine is an eosinophil growth factor and promoter of eosinophil survival?

A. IgE  
B. IL-4  
C. IL-5  
D. IL-13
2018 GINA Guidelines for the Treatment of Type 2 Inflammation

Non-Biologic Options:

• Assess adherence

• Consider Type 2 phenotypes with available non-biologic treatment

• Increase ICS dose & reassess in 3-6 months
2018 GINA Guidelines for the Treatment of Type 2 Inflammation

Add-On Biologic Options:

• Patients with exacerbations and eosinophilic and/or allergic biomarkers despite high-dose ICS-LABA therapy

• Biologic therapy considerations:
  • cost
  • predictors of response
  • dosing frequency
  • route of administration
  • patient preference
2018 GINA Guidelines for the Treatment of Type 2 Inflammation

Monitoring:

• Assess response at 3-4 months and every 3-6 months thereafter
  • Re-evaluate the need for each medication
  • Continue at least medium-dose ICS
2018 GINA Guidelines for the Treatment of Type 2 Inflammation

• Duration:
  • Withdrawal of biologic may be trialed at 12 months if:
    • Symptoms well-controlled on medium-dose ICS; and
    • No exposure to a well-documented allergic trigger
Patient Case

RT is a 20-year-old female who presents for follow-up after an ED visit for asthma exacerbation. This is her third exacerbation in 12 months. She reports using her rescue inhaler at least 6 days/week for the past 2 weeks. You have confirmed her adherence and her inhaler technique.
Patient Case

Current Medications

- Fluticasone propionate/salmeterol HFA 230/21 mcg; 2 puffs BID
- Montelukast 10 mg po qHS
- Fluticasone propionate 50 mcg/spray; 2 sprays in each nostril daily
- Cetirizine 10 mg po daily
- Albuterol HFA 90 mcg; 2 puffs q4h prn for wheezing & SOB
- Prednisone 50 mg daily x7 days (increased from 5 mg daily)

PMH

- Asthma
- Allergic rhinitis

Medication Allergies

- Penicillin (rash)

Labs

- $FEV_1$: 70% of predicted
- Blood eosinophils: 452 cells/mcL
Question 2

Which of the following is the most reasonable treatment option for RT’s severe asthma?

A. Increase ICS dose
B. Increase albuterol frequency
C. Continue prednisone 50 mg daily long-term
D. Add a trial of a biologic therapy
Question 2

Which of the following is the most reasonable treatment option for RT’s severe asthma?

A. Increase ICS dose
B. Increase albuterol frequency
C. Continue prednisone 50 mg daily long-term
D. Add a trial of a biologic therapy
Evolution of Biologics for Asthma

- Omalizumab (2003)
- Benralizumab (2017)
- Dupilumab (2018)
- Reslizumab (2016)
- Mepolizumab (2015)
Novel Biologic Agents

Mepolizumab

- Monoclonal antibody to IL-5
- Add-on treatment of severe asthma for patients ≥ 12 years old with an eosinophilic phenotype
- Dose: 100 mg SQ every 4 weeks
- Herpes zoster vaccine for ≥ 50 years of age
Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM)

Population

- 621 patients with severe asthma, 12-74 years old
- ≥ 2 exacerbations requiring systemic corticosteroids in the past year
- Evidence of eosinophilic inflammation
  - Sputum eosinophil count ≥ 3%,
  - Blood eosinophil count ≥ 300 cells/mcL

DREAM Trial Design

Methods:
• Randomization to mepolizumab IV 75 mg, 250 mg, or 750 mg or placebo
• q4wks for a total of 13 infusions

Primary outcome:
• Clinically significant exacerbation
  • Oral corticosteroids for ≥ 3 days, admission, or ED visit

DREAM Trial Results

Asthma Exacerbations*

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

*per person per year

Ratio to placebo (95% CI)

Placebo: 2.4
Mepolizumab 75 mg: 1.24 (0.39-0.69)
Mepolizumab 250 mg: 1.46 (0.46-0.81)
Mepolizumab 750 mg: 1.15 (0.36-0.64)

MEpolizumab as adjunctive therapy in patients with Severe Asthma (MENSA)

Population

• 576 patients with severe asthma, 12-82 years old

• $\geq$ 2 exacerbations in the past year requiring oral corticosteroid treatment

• Evidence of eosinophilic airway inflammation
  • Peripheral blood eosinophil count of 150 cells/mcL at screening or
  • 300 cells/mcL in the previous year

Ortega et al. NEJM. 2014;371:1198-1207.
MENSA Trial Design

Methods

• Randomization to mepolizumab 75 mg IV, 100 mg SQ, or placebo
• 1 administration every 4 weeks for 32 weeks

Primary Outcome:

• Clinically significant exacerbations
  • Treatment with oral corticosteroids for ≥ 3 days, admission, or ED visit

Ortega et al. NEJM. 2014;371:1198-1207.
MENSA Trial Results

Asthma Exacerbations*

- Placebo (n=191)
- Mepolizumab IV (n=191)
- Mepolizumab SQ (n=194)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Exacerbations</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=191)</td>
<td>1.74</td>
<td>1.37-2.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mepolizumab IV (n=191)</td>
<td>0.93</td>
<td>0.75-1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mepolizumab SQ (n=194)</td>
<td>0.83</td>
<td>0.66-1.00</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*per person per year

Ortega et al. NEJM. 2014;371:1198-1207.
Reslizumab

- Anti-IL-5 monoclonal antibody
- Add-on, maintenance therapy of severe asthma in patients ≥ 18 years old
- Dose 3 mg/kg IV q4wks
- Must be administered in a setting to manage anaphylaxis (boxed warning)
Reslizumab Phase 3 Trials

• Duplicate randomized, controlled trials

Population

• 953 patients 12-75 years old with asthma
• Not controlled with medium-to-high-dose ICS
• ≥ 1 exacerbation in the past year requiring systemic corticosteroids
• Blood eosinophil count ≥ 400 cells/mcL

Reslizumab Phase 3 Trials Design

Methods:

• Randomization to reslizumab 3 mg/kg IV or placebo q4wks for 13 infusions

Primary Outcome:

• Frequency of clinical exacerbations
  • Systemic corticosteroid therapy, or
  • Doubling of ICS or systemic corticosteroid dose for $\geq$ 3 days, or
  • ED, hospital admission, or office visit for treatment

Reslizumab Phase 3 Trials Results

Asthma Exacerbations*

- Placebo (n=476)
- Reslizumab (n=477)

Rate ratio (95% CI)

0.46 (0.37-0.58); p<0.0001

*per person per year

Benralizumab

- Anti-IL-5Rα humanized monoclonal antibody
- Add-on therapy for patients ≥ 12 years old with severe asthma with an eosinophilic phenotype
- Dose: 30 mg SQ q4wks x3 doses, then q8wks
Benralizumab for severe asthma uncontrolled with high-dose ICS & LABA (SIROCCO)

Population:

• 1,205 patients with asthma age 12-75 years
• Therapy with medium-high dose ICS + LABA
• $\geq 2$ exacerbations requiring systemic corticosteroids in the past year, or
• Temporary increase in oral corticosteroid dose

SIROCCO Trial Design

Methods:
• Randomized to benralizumab 30 mg q4wks, q8wks, or matched placebo

Primary Outcome:
• Annual rate of exacerbations
  • Treatment with systemic corticosteroids, or
  • Temporary increase in oral corticosteroid dose, or
  • Hospital admission, ED, or urgent care visit

SIROCCO Results

Annual Exacerbation Rate

- **Placebo**
  - Ratio vs. placebo: 1.33
  - 0.55 (0.42-0.71) p<0.001

- **Benralizumab q4wks**
  - 0.73
  - 0.49 (0.37-0.64) p<0.001

- **Benralizumab q8wks**
  - 1.21
  - 0.70 (0.50-1.00) p=0.0471

Blood Eosinophils ≥ 300 cells/mcL

- **Placebo**
  - 1.33
  - 0.55 (0.42-0.71) p<0.001

- **Benralizumab q4wks**
  - 0.73
  - 0.49 (0.37-0.64) p<0.001

- **Benralizumab q8wks**
  - 1.21
  - 0.70 (0.50-1.00) p=0.0471

Blood Eosinophils < 300 cells/mcL

- **Placebo**
  - 1.00
  - 0.83 (0.59-1.16) p=0.2685

Dupilumab

- Anti-IL-4Rα monoclonal antibody
- Expressed by both eosinophils and mast cells
- Add-on therapy for patients ≥12 years with severe asthma with an eosinophilic phenotype
- Dose: 400 mg SQ x1, then 200 mg SQ q14days
- Treat preexisting parasitic infections
LIBERTY ASTHMA QUEST Trial

Population:

• 1,902 patients ≥ 12 years old with severe asthma
• Treatment with medium-high dose ICS
• Plus 1-2 additional controller medications
• ≥1 asthma exacerbation in the past year
  • Treatment with systemic corticosteroids 3 days, or
  • Hospitalization, ED, or urgent care visit

Castro et al. NEJM. 2018;378:2486-2496.
LIBERTY ASTHMA QUEST Design

Methods:

- Randomization to dupilumab 200 mg SQ, 300 mg SQ, or matched placebo
- Administered every 2 weeks for 52 weeks

Primary Outcome:

- Annual rate of severe exacerbations
  - Treatment with systemic corticosteroids 3 days, or
  - Hospitalization, ED, or urgent care visit

Castro et al. NEJM. 2018;378:2486-2496.
LIBERTY ASTHMA QUEST Results

Annual Exacerbation Rate

- Placebo: 0.87 (0.41-0.66)
- Dupilumab 200 mg: 0.52 (0.43-0.68)
- Dupilumab 300 mg: 1.08 (0.29-0.47)
- 1.24 (0.32-0.51)

Blood Eosinophils ≥ 300 cells/mcL

Castro et al. NEJM. 2018;378:2486-2496.
## Summary of Results

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reduction in Exacerbations</th>
<th>Lung Function</th>
<th>Symptoms &amp; Quality of Life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab</td>
<td>~50%</td>
<td>Inconsistent</td>
<td>Improved AQLQ scores</td>
<td>Conflicting results with improvement in FEV1</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>~50%</td>
<td>Improved by week 4</td>
<td>Improved AQLQ, ACQ-7, &amp; ASUI scores</td>
<td>Did not significantly decrease exacerbations requiring ED visit or hospitalization</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>25-60%</td>
<td>Improved by week 4</td>
<td>q8wk regimen improved AQLQ &amp; ACQ-6 scores</td>
<td>Greater treatment effect with blood eosinophils ≥ 300 cells/mcL</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>50-70%</td>
<td>Improved by week 2</td>
<td>Improved AQLQ &amp; ACQ-5 scores</td>
<td>Greater treatment effect with blood eosinophils ≥ 300 cells/mcL</td>
</tr>
</tbody>
</table>
# Summary of Novel Biologics for Asthma

<table>
<thead>
<tr>
<th></th>
<th>Mepolizumab</th>
<th>Reslizumab</th>
<th>Benralizumab</th>
<th>Dupilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td>Anti-IL-5</td>
<td>Anti-IL-5</td>
<td>Anti-IL-5 receptor α</td>
<td>Anti-IL-4 receptor α</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥ 12 years</td>
<td>≥ 18 years</td>
<td>≥ 12 years</td>
<td>≥ 12 years</td>
</tr>
<tr>
<td><strong>Blood Eosinophils</strong></td>
<td>≥ 150-300 cells/mcL</td>
<td>≥ 400 cells/mcL</td>
<td>≥ 300 cells/mcL</td>
<td>≥ 150 cells/mcL</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>100 mg SQ</td>
<td>3 mg/kg IV</td>
<td>30 mg SC</td>
<td>200-300 mg SQ</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>q4weeks</td>
<td>q4weeks</td>
<td>q4weeks x3, Then q8weeks</td>
<td>q2weeks</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Clinic</td>
<td>Clinic</td>
<td>Clinic</td>
<td>Home</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Headache (10%) Injection site rxn (&lt;15%) Hypersensitivity rxn (&lt;4%) Herpes zoster activation</td>
<td>Anaphylaxis – black box warning (&lt;1%) Ab development (5%) Oropharyngeal pain (3%)</td>
<td>Ab development (13%) Headache (8%) Pharyngitis (5%) Hypersensitivity rxn (&lt;1%)</td>
<td>Injection site rxn (10-18%) Conjunctivitis (10%) Ab development (9%) Oral herpes simplex (4%) Eosinophilia (2%)</td>
</tr>
<tr>
<td><strong>Cost (AWP)</strong></td>
<td>$3,545.68</td>
<td>$107.52/mL</td>
<td>$5,788.07</td>
<td>$1,811.70</td>
</tr>
</tbody>
</table>
Patient Case

NB is a 55 year-old male with eosinophilic asthma and a blood eosinophil count of 408 cells/mcL. He is interested in starting biologic therapy but is concerned about frequent clinic visits as he relies on public transportation.
Question 3

What biologic agent would be most appropriate for NB?

A. Mepolizumab
B. Reslizumab
C. Benralizumab
D. Dupilumab
Question 3

What biologic agent would be most appropriate for NB?

A. Mepolizumab
B. Reslizumab
C. Benralizumab
D. Dupilumab
Summary

• Severe asthma accounts for <10% of cases, yet a majority of morbidity and costs
• New biologic therapies have been shown to reduce asthma exacerbations in these patients
• Head-to-head trials are needed to determine relative efficacy and safety
Questions?
References


## DREAM Trial Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n = 155)</th>
<th>Mepolizumab 75 mg (n=153)</th>
<th>Mepolizumab 250 mg (n=152)</th>
<th>Mepolizumab 750 mg (n=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations per patient/yr Ratio to placebo</td>
<td>2.40 (0.11)</td>
<td>1.24 (0.12)</td>
<td>1.46 (0.11)</td>
<td>1.15 (0.12)</td>
</tr>
<tr>
<td></td>
<td>0.52 (0.39-0.69)</td>
<td>0.61 (0.46-0.81)</td>
<td>0.48 (0.36-0.64)</td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring ED visit or admission per patient/yr Ratio to placebo</td>
<td>0.43 (0.24)</td>
<td>0.17 (0.30)</td>
<td>0.25 (0.26)</td>
<td>0.22 (0.26)</td>
</tr>
<tr>
<td></td>
<td>0.40 (0.19-0.81)</td>
<td>0.58 (0.30-1.12)</td>
<td>0.52 (0.27-1.02)</td>
<td></td>
</tr>
<tr>
<td>Change in FEV₁ in mL Difference from placebo</td>
<td>60 (38)</td>
<td>121 (38)</td>
<td>140 (37)</td>
<td>115 (37)</td>
</tr>
<tr>
<td></td>
<td>61 (-39-0.07)</td>
<td>81 (-19-180)</td>
<td>56 (-43-155)</td>
<td></td>
</tr>
<tr>
<td>Change in score on asthma control questionnaire Difference from placebo</td>
<td>-0.59 (0.09)</td>
<td>-0.75 (0.09)</td>
<td>-0.87 (0.09)</td>
<td>-0.80 (0.09)</td>
</tr>
<tr>
<td></td>
<td>-0.16 (-0.39-0.07)</td>
<td>-0.27 (-0.51-0.04)</td>
<td>-0.20 (-0.43-0.03)</td>
<td></td>
</tr>
<tr>
<td>Ratio of geometric mean FE_{NO} to baseline Ratio to placebo</td>
<td>1.01 (0.06)</td>
<td>0.99 (0.06)</td>
<td>0.91 (0.06)</td>
<td>0.97 (0.06)</td>
</tr>
<tr>
<td></td>
<td>0.97 (0.82-1.15)</td>
<td>0.90 (0.76-1.06)</td>
<td>0.96 (0.81-1.13)</td>
<td></td>
</tr>
</tbody>
</table>

MENSA Trial Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n = 191)</th>
<th>Mepolizumab IV (n=191)</th>
<th>P Value</th>
<th>Mepolizumab SQ (n=194)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean rate of exacerbations</td>
<td>1.74</td>
<td>0.93</td>
<td>&lt;0.001</td>
<td>0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>47 (28-60)</td>
<td></td>
<td></td>
<td>53 (36-35)</td>
<td></td>
</tr>
<tr>
<td>Mean rate of exacerbations requiring ED visit or admission</td>
<td>0.20</td>
<td>0.14</td>
<td>0.30</td>
<td>0.08</td>
<td>0.02</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>32 (-41-67)</td>
<td></td>
<td></td>
<td>61 (17-82)</td>
<td></td>
</tr>
<tr>
<td>Change in FEV&lt;sub&gt;1&lt;/sub&gt; in mL</td>
<td>Before bronchodilation</td>
<td>86 ±31</td>
<td>0.02</td>
<td>183 ±31</td>
<td>0.03</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>100 (13-87)</td>
<td></td>
<td></td>
<td>98 (11-184)</td>
<td></td>
</tr>
<tr>
<td>After bronchodilation</td>
<td>30 ±34</td>
<td>176 ±34</td>
<td>0.003</td>
<td>167 ±33</td>
<td>0.004</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>143 (50-242)</td>
<td></td>
<td></td>
<td>138 (43-242)</td>
<td></td>
</tr>
<tr>
<td>Change in score on asthma control questionnaire</td>
<td>Before bronchodilation</td>
<td>-0.50 ±0.07</td>
<td>&lt;0.001</td>
<td>-0.94 ±0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-0.42 (-0.61-0.23)</td>
<td></td>
<td></td>
<td>-0.44 (-0.63-0.25)</td>
<td></td>
</tr>
</tbody>
</table>

Ortega et al. NEJM. 2014;371:1198-1207.
### Reslizumab Phase 3 Trials Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Reslizumab</th>
<th>Rate Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All exacerbations</td>
<td>1.81</td>
<td>0.84</td>
<td>0.46 (0.37-0.58)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Exacerbations requiring corticosteroids ≥ 3 days</td>
<td>1.54</td>
<td>0.66</td>
<td>0.43 (0.33-0.55)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Exacerbations requiring admission or ED treatment</td>
<td>0.12</td>
<td>0.077</td>
<td>0.66 (0.38-1.16)</td>
<td>0.510</td>
</tr>
<tr>
<td>Change in FEV&lt;sub&gt;1&lt;/sub&gt; (L)</td>
<td>0.12</td>
<td>0.22</td>
<td>0.11 (0.067-0.15)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Change in ACQ-7 score</td>
<td>-0.77</td>
<td>-1.02</td>
<td>-0.25 (-0.343-0.156)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Change in SABA use (puffs/day)</td>
<td>-0.45</td>
<td>-0.61</td>
<td>-0.16 (-0.39-0.06)</td>
<td>0.1571</td>
</tr>
<tr>
<td>Change in blood eosinophil count</td>
<td>-101</td>
<td>-576</td>
<td>-475 (-501- -450)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

## SIROCCO Trial Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Blood eosinophils ≥ 300 cells/mcL</th>
<th>Blood eosinophils &lt; 300 cells/mcL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Benralizumab q4wks</td>
</tr>
<tr>
<td>Annual exacerbation rate (95% CI)</td>
<td>1.33 (1.12-1.58)</td>
<td>0.73 (0.60-0.89)</td>
</tr>
<tr>
<td>Ratio vs. placebo (95% CI)</td>
<td>0.55 (0.42-0.71) p&lt;0.0001</td>
<td>0.49 (0.37-0.64) p&lt;0.0001</td>
</tr>
<tr>
<td>Prebronchodilator FEV₁ LS mean change (n)</td>
<td>0.239 (233)</td>
<td>0.345 (236)</td>
</tr>
<tr>
<td>LS mean difference vs. placebo</td>
<td>0.106 (0.016-0.196) p=0.0215</td>
<td>0.159 (0.068-0.249) p=0.0006</td>
</tr>
<tr>
<td>Asthma symptom LS mean change</td>
<td>-1.04 (180)</td>
<td>-1.12 (197)</td>
</tr>
<tr>
<td>LS mean difference vs. placebo</td>
<td>-0.08 (-0.27-0.12) p=0.4420</td>
<td>-0.25 (-0.45- -0.06) p=0.0118</td>
</tr>
</tbody>
</table>

## LIBERTY ASTHMA QUEST Trial Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Dupilumab 200 mg</th>
<th>Placebo</th>
<th>Dupilumab 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual rate of exacerbations (95% CI)</td>
<td>0.87 (0.72-1.05)</td>
<td>0.46 (0.39-0.53)</td>
<td>0.97 (0.81-1.16)</td>
<td>0.52 (0.45-0.61)</td>
</tr>
<tr>
<td>RR vs. placebo (95% CI)</td>
<td>0.52 (0.41-0.66)</td>
<td>0.52 (0.41-0.66)</td>
<td>0.54 (0.43-0.68)</td>
<td></td>
</tr>
<tr>
<td>Mean change in FEV₁ (SE)</td>
<td>0.18 (0.02)</td>
<td>0.32 (0.02)</td>
<td>0.21 (0.02)</td>
<td>0.34 (0.02)</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>0.14 (0.08-0.19)</td>
<td>0.14 (0.08-0.19)</td>
<td>0.13 (0.08-0.18)</td>
<td></td>
</tr>
<tr>
<td>Mean change in ACQ-5 score (SE)</td>
<td>-1.15 (0.06)</td>
<td>-1.54 (0.04)</td>
<td>-1.30 (0.06)</td>
<td>-1.52 (0.04)</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-0.39 (-0.53- -0.25)</td>
<td>-0.39 (-0.53- -0.25)</td>
<td>-0.22 (-0.36-0.08)</td>
<td></td>
</tr>
</tbody>
</table>

### Eosinophil count ≥ 300 cells/mcL

<table>
<thead>
<tr>
<th>Outcome</th>
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<th>Placebo</th>
<th>Dupilumab 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual rate of exacerbations (95% CI)</td>
<td>1.08 (0.85-1.38)</td>
<td>0.37 (0.29-0.47)</td>
<td>1.24 (0.97-1.57)</td>
<td>0.40 (0.32-0.51)</td>
</tr>
<tr>
<td>RR vs. placebo (95% CI)</td>
<td>0.34 (0.24-0.48)</td>
<td>0.34 (0.24-0.48)</td>
<td>0.33 (0.23-0.45)</td>
<td></td>
</tr>
<tr>
<td>Mean change in FEV₁ (SE)</td>
<td>0.21 (0.03)</td>
<td>0.43 (0.03)</td>
<td>0.22 (0.03)</td>
<td>0.47 (0.02)</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>0.21 (0.13-0.29)</td>
<td>0.21 (0.13-0.29)</td>
<td>0.24 (0.16-0.32)</td>
<td></td>
</tr>
</tbody>
</table>

Castro et al. NEJM. 2018;378:2486-2496.