Biologics in Asthma: Present and Future

Flavia Hoyte, MD
Associate Professor of Medicine
Fellowship Training Program Director
Division of Allergy and Immunology
National Jewish Health and University of Colorado
Disclosures

Clinical investigator for GSK, TEVA, and Astra-Zeneca.
Learning objectives

1. Discuss current approaches to the management of moderate to severe asthma in adult patients.

2. Describe new and emerging biologics for the management of moderate to severe asthma.
Asthma: A Highly Prevalent and Often Inadequately Controlled Disease

24+ million people in the US have asthma.¹

17.72 million adults have asthma.¹

8.86 million adults have inadequately controlled asthma.²

39% of adults with active asthma use long-term control medications.³

1.33 million adults have inadequately controlled asthma with eosinophilia.⁴

Paradigm Shift to a More Personalized Approach to Asthma Therapy

Immunopathology of Asthma

FIGURE 2. Important type 2-inflammation targets for biologic therapies. *TSLP*, Thymic stromal lymphopoietin. Adapted with permission from Mitchell et al. 

Katial et al.
Currently available biologic agents

- **Targeting IgE**
  - Omalizumab (approved 2003)

- **Targeting eosinophils**
  - Monoclonal antibody against IL-5
    - Mepolizumab (approved 2015)
    - Reslizumab (approved 2016)
  - Monoclonal antibody against IL-5R
    - Benralizumab (approved 2017)
Anti-IgE

Omalizumab
Omalizumab may be more effective in reducing exacerbations for high type 2 biomarker groups.

Hanania et al. 2013
Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma

T. B. Casale | B. E. Chipps | K. Rosén | B. Trzaskoma | T. Haselkorn
T. A. Omachi | S. Greenberg | N. A. Hanania

FIGURE 2 Relative percentage change in exacerbation rate by blood eosinophil levels
Anti IL-5

Mepolizumab (IL-5)
Reslizumab (IL-5)
Benralizumab (IL-5R)
**Mepolizumab: DREAM trial**

**Inclusion criteria**
One of the following:
- sputum eos >3%,
- FeNO>50,
- blood eos >300,
- deterioration of asthma after <25% reduction in ICS or OCS
AND
- >2 asthma exacerbations in previous year

Mepolizumab: Reduction of exacerbations & OCS

**MENSA:** Exacerbation-reduction Study

**SIRIUS:** Oral Steroid-reduction Study

Ortega NEJM 2014

Bel NEJM 2014
DREAM and MENSA: *Post-hoc* Analysis

Exacerbation Rate Reduction Correlates With Baseline Blood Eosinophil Levels

All mepolizumab doses (75 mg, 250 mg, 750 mg IV: and 100mg SQ) combined for analysis

Intention-to-treat population, n = 344 placebo, n = 841 mepolizumab)

**Mepolizumab Response Inversely Correlates with Bronchodilator Reversibility**

<table>
<thead>
<tr>
<th>Exacerbation no/patient/50 weeks</th>
<th>Mepolizumab</th>
<th>Placebo</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in FEV(_1) after prednisolone (ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; -50</td>
<td>2.4</td>
<td>2.0</td>
<td>0.63</td>
</tr>
<tr>
<td>-50 to 220</td>
<td>2.1</td>
<td>5.0</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;220</td>
<td>0.8</td>
<td>2.9</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Change in FEV(_1) after salbutamol (ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>1.3</td>
<td>3.8</td>
<td>0.02</td>
</tr>
<tr>
<td>50 to 150</td>
<td>1.7</td>
<td>3.6</td>
<td>0.11</td>
</tr>
<tr>
<td>&gt;150</td>
<td>2.6</td>
<td>2.4</td>
<td>0.85</td>
</tr>
</tbody>
</table>

FEV\(_1\), forced expiratory volume in 1 s.

Exacerbation numbers per patient per 50 weeks in patients treated with mepolizumab (n=29) and placebo (n=32) for 50 weeks by tertile of response to prednisolone 0.5 mg/kg up to maximum of 40 mg/day given for 14 days and by tertile of response to inhaled salbutamol 200 µg. The response to prednisolone represents the change in post-bronchodilator FEV\(_1\) measured at the same time of day before and 1–2 h after the last dose of prednisolone. FEV\(_1\) was measured before and 20 min after inhaled salbutamol. The values in the table represent the improvement in FEV\(_1\) before prednisolone and before randomisation to mepolizumab or placebo.

MUSCA: Mepolizumab Improves QOL

SGRQ = St. George’s Respiratory Questionnaire

Figure 3: St George’s Respiratory Questionnaire (SGRQ) scores at each visit
Figure shows adjusted mean changes (95% CI) from baseline in (A) total SGRQ score, (B) symptom domain SGRQ score, (C) activity domain SGRQ score, and (D) impacts domain SGRQ score.

Reslizumab BREATH Program

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

Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials

Mario Castro, James Zangrilli, Michael E Wechsler, Eric D Bateman, Guy G Brusselle, Philip Bardin, Kevin Murphy, Jorge F Maspero, Christopher O’Brien, Stephanie Korn

Reslizumab: Reduction in Exacerbations

A

B

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

Reslizumab 3.0 mg/kg; n=232
HR 0.486 (95% CI 0.353-0.672)
p=0.003

Placebo; n=244

Placebo; n=232

Number at risk

Number at risk

Probability of not having CAE (%)

Probability of not having CAE (%)

OCS at baseline
ICS plus LABA
ICS no LABA
All

0.32 (0.18-0.55)
0.45 (0.35-0.58)
0.51 (0.29-0.89)
0.46 (0.37-0.58)

Rate ratio (95% CI)
Benralizumab: Mechanism

Enhanced ADCC is being studied to determine a correlation with depletion in blood and airway eosinophils.
Benralizumab: Effect on 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 FitGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Kom, Ken Ohta, Mark Lommertsz, 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 FitGerald, Pascal Chanez, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Magnus Aurivillius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators*

Benralizumab: Reduction in Exacerbations

**SIROCCO**

- **A** Eosinophils ≤300 cells per μL
  - Percentage reduction relative to placebo
    - 45%
    - 51%
  - Annual asthma exacerbation rate ratio (95% CI)
    - Placebo (n=267)
    - Benralizumab 30 mg Q4W (n=275)
    - Benralizumab 30 mg Q8W (n=267)
  - Benralizumab 30 mg Q4W vs Placebo: p=0.0001 (0.60-0.89)
  - Benralizumab 30 mg Q8W vs Placebo: p=0.0001 (0.53-0.80)

- **B** Eosinophils ≤300 cells per μL
  - Percentage reduction relative to placebo
    - 30%
    - 17%
  - Annual asthma exacerbation rate ratio (95% CI)
    - Placebo (n=140)
    - Benralizumab 30 mg Q4W (n=124)
    - Benralizumab 30 mg Q8W (n=131)
  - Benralizumab 30 mg Q4W vs Placebo: p=0.047 (0.65-1.11)
  - Benralizumab 30 mg Q8W vs Placebo: p=0.0769 (0.78-1.28)

**CALIMA**

- **A** Eosinophils ≤300 cells per μL
  - Percentage reduction relative to placebo
    - 36%
    - 28%
  - Annual asthma exacerbation rate ratio (95% CI)
    - Placebo (n=248)
    - Benralizumab 30 mg Q4W (n=241)
    - Benralizumab 30 mg Q8W (n=239)
  - Benralizumab 30 mg Q4W vs Placebo: p=0.0018 (0.48-0.74)
  - Benralizumab 30 mg Q8W vs Placebo: p=0.0188 (0.54-0.82)

- **B** Eosinophils ≤300 cells per μL
  - Percentage reduction relative to placebo
    - 36%
    - 40%
  - Annual asthma exacerbation rate ratio (95% CI)
    - Placebo (n=122)
    - Benralizumab 30 mg Q4W (n=116)
    - Benralizumab 30 mg Q8W (n=125)
  - Benralizumab 30 mg Q4W vs Placebo: p=0.0150 (0.59-1.02)
  - Benralizumab 30 mg Q8W vs Placebo: p=0.0048 (0.55-0.95)


Benralizumab: Oral steroid dose & time to first exacerbation

**FIGURE 2.** Important type 2-inflammation targets for biologic therapies. *TSLP,* Thymic stromal lymphopoietin. Adapted with permission from Mitchell et al.\textsuperscript{57}
Biologic agents in the pipeline

• Targeting both IL-4 and IL-13 via IL-4Rα, a shared receptor component for both cytokines
  – Dupilumab
    • Approved for atopic dermatitis 3/2017
    • Phase 3 OCS reducing study, completed 11/2017
    • Phase 3 efficacy, safety, & tolerability in severe asthma, completed 11/2017 (primary outcome: exacerbation rate, pre-BD FEV1 change)
    • Phase 3 age 6-12, actively recruiting
Biologic agents in the pipeline

• Targeting IL-13 (phase 3 trials completed, mixed results)
  – Lebrikizumab
  – Tralokinumab

• Targeting TSLP (phase 2b results published, phase 3 trials starting up)
  – AMG157, tezepelumab
Anti IL-4Ra

Dupilumab
Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

A Exacerbations — Primary End Point

- Placebo (N=52): 44%
- Dupilumab (N=52): 6%

87% reduction
P<0.001

B Time to Exacerbation

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

Hazard ratio, 0.10
(95% CI, 0.03–0.34)
P<0.001

Week
No. at Risk
- Dupilumab: 52, 51, 51, 50, 50, 50, 47, 44, 43, 37, 35, 32, 28, 24
- Placebo: 52, 52, 50, 50, 48, 44, 43, 41, 37, 35, 32, 28, 24

## Dupilumab & Annualized Severe Exacerbation Rate

### Overall population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (n = 158)</th>
<th>200 mg q4w (n = 150)</th>
<th>300 mg q4w (n = 157)</th>
<th>200 mg q2w (n = 148)</th>
<th>300 mg q2w (n = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted annualized severe exacerbation rate, estimate (95% CI)</td>
<td>95% CI 0.62, 1.30</td>
<td>95% CI 0.26, 0.66</td>
<td>95% CI 0.40, 0.91</td>
<td>95% CI 0.16, 0.46</td>
<td>95% CI 0.16, 0.45</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>-54%</td>
<td>-33%</td>
<td>-70%</td>
<td>-70%</td>
<td></td>
</tr>
</tbody>
</table>

### Eos ≥ 300 cells/µL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (n = 68)</th>
<th>200 mg q4w (n = 59)</th>
<th>300 mg q4w (n = 66)</th>
<th>200 mg q2w (n = 64)</th>
<th>300 mg q2w (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted annualized severe exacerbation rate, estimate (95% CI)</td>
<td>95% CI 0.57, 1.90</td>
<td>95% CI 0.16, 0.81</td>
<td>95% CI 0.36, 1.29</td>
<td>** 95% CI 0.13, 0.68</td>
<td>** 95% CI 0.08, 0.52</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>-66%</td>
<td>-35%</td>
<td>-71%</td>
<td>-81%</td>
<td></td>
</tr>
</tbody>
</table>

### Eos < 300 cells/µL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (n = 90)</th>
<th>200 mg q4w (n = 91)</th>
<th>300 mg q4w (n = 91)</th>
<th>200 mg q2w (n = 84)</th>
<th>300 mg q2w (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted annualized severe exacerbation rate, estimate (95% CI)</td>
<td>95% CI 0.49, 1.23</td>
<td>95% CI 0.25, 0.79</td>
<td>95% CI 0.29, 0.84</td>
<td>** 95% CI 0.12, 0.52</td>
<td>** 95% CI 0.17, 0.58</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>-43%</td>
<td>-37%</td>
<td>-68%</td>
<td>-60%</td>
<td></td>
</tr>
</tbody>
</table>

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

---

**Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β₂ agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial**


Anti IL-13

Lebrikizumab
Tralokinumab
Lebrikizumab: LAVOLTA I and LAVOLTA II

High-biomarker group: improved response to Lebrikizumab

Tralokinumab: Subset responses based on biomarkers

High vs. low Dpp4

High vs. low Periostin

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.


**Figure 1.** Annualized Rate of Asthma Exacerbations at Week 52, According to Baseline Biomarker Status, and Change from Baseline in the Fraction of Exhaled Nitric Oxide (FENO).
Asthma Biomarkers: Moving to endotype

- IgE
- FeNO
- EOS
  - Sputum
  - Blood
- Periostin
- DPP4 (Dipeptidyl Peptidase 4 / CD26; an adipokine)
Other possible immune targets

- IL-33R, ST2 receptor for IL-33 (GSK3772847)
- IL-17 (brodalumab)
- IL-6 (tocilizumab and others)
- TNF (golimumab)
- M1' segment of membrane-expressed IgE (quilizumab)
- CRTH2 (fevipiprant)
- TLR9
- IL-25
Future Questions

• Are there other biomarkers available for phenotyping and endotyping our patients and helping guide therapy?
• Is there a role for pharmacogenetics in helping to guide our use of biologic agents?
• Could certain biologic agents work better for specific racial or ethnic groups?
More questions ...

• Will patients develop resistance to some of these agents, as they do to some of the biologics currently used for autoimmune conditions?
• Is there a role for the concurrent use of several biologics at once?
• What do we do with non-Th2 asthmatics (40-45% of severe asthmatics)?
More questions ...

• Could biologics change the course of asthma progression? If so, should they be started early, prior to development of severe asthma with remodeling?

• Furthermore, could they impact the development of asthma ... in which case, should they be used in toddlers to help prevent asthma?

• Given their cost in healthcare dollars, who should be given these biologic agents?

Take-home points

• The introduction of biologics for asthma has been exciting, and the use of these biologics life-changing for many of our patients.
• There are several newer biologics in the pipeline that hold promise for our patients with severe asthma.
• Many questions remain about how best to decide about their use in clinical practice.
• There is an unmet need for biologics that can target non-Th2 asthma.
Questions?