Managing Severe Asthma in 2022 and Beyond

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Disclosures

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- Consultant/Honoraria: AstraZeneca, Sanofi, Genzyme, Regeneron, Teva, Novartis, Genentech, GlaxoSmithKline, Restorbio, Equillium
Lecture Objectives

1. Explain asthma heterogeneity and endotypes.
2. Review new 2021 NAEPP Guidelines
3. Define current and future approaches to asthma management
4. Explain the mechanisms of action of biologic therapies and the targets for treatment in severe asthma.
Evolution of Asthma Classification and Management

1960’s-1970’s
Bronchoconstriction

1980’s-1990’s
Inflammation

Early 2000’s
Identification of phenotypes and clusters

Late 2000’s
Precision medicine: identification of endotypes and mechanisms of disease including T2 vs. non-T2

Present
Precision therapy by endotype

Asthma Phenotype vs Endotype

**Phenotype**
The set of observable characteristics of an individual resulting from the interaction of its genotype with the environment

**Endotype**
A specific biologic mechanism that explains observable properties of an organism

Different asthma phenotypes and endotypes may respond differently to targeted therapies
Why Endotype?

To personalize therapy and maximize drug response
How do we Endotype?

Biomarkers!
Biomarkers to Identify Asthma Endotype

Current
- Sputum eosinophils
- Circulating blood eosinophils
- Exhaled nitric oxide
- IgE
- Allergen skin testing

Future
- Periostin
- Dipeptidyl peptidase-4 (DPP-4)
- Eosinophil peroxidase
- Urinary bromotyrosine

IgE = Immunoglobulin E.
Asthma Endotypes

- **Type 2 asthma**
  - Eosinophilic
  - High nitric oxide
  - High IgE
  - Mediated by IL-4, IL-5, and IL-13
  - Associated with atopic dermatitis, chronic rhinosinusitis

- **Non-type 2 asthma**
  - Neutrophilic
  - Mediated by IL-1, IL-6, IL-17, and TNF
  - Associated with smoking, obesity

IL, interleukin; TNF, tumor necrosis factor.
Inflammatory, Immunologic, and Pathobiologic Features Leading to Severe Asthma

Inflammatory mechanisms and pathobiologic features leading to severe asthma

Inflammatory mechanisms associated with granulocytic inflammation

Type 2 inflammation
- Antigens
- CRTH2
- TSLP
- IL-25
- IL-33
- IL-C2
- GATA3
- IL-13
- IL-4, 5, and 13

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

Th2 cell
- GATA3
- IL-4

Neutrophil
- Leukotriene B4
- Lipoxin
- ALX
- BLT2

Eosinophil
- Leukotrienes
- PGD2
- Histamine
- IL-3, 4, 5, and 9

Mast cell
- Leukotrienes
- Histamine
- IL-3, 4, 5, and 9

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

New Asthma Guidelines
GINA 2021 Guidelines Recommend Add-on Type 2-targeted Biologic Therapy at Step 5

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

**STEP 1**
Daily low-dose inhaled corticosteroid (ICS), or as-needed low-dose ICS-formoterol

**STEP 2**
Leukotriene receptor antagonist (LTRA), or low-dose ICS taken whenever SABA is taken

**STEP 3**
Low-dose ICS-LABA

**STEP 4**
Medium-dose ICS-LABA

**STEP 5**
High-dose ICS-LABA

Refer for phenotypic assessment ± add-on therapy, e.g., tiotropium, anti-IgE, anti-IL-5/-5R, anti-IL-4R

1. GINA. Pocket Guide for Asthma Management and Prevention, 2019; 2. GINA. Diagnosis and management of difficult-to-treat and severe asthma in adolescent and adult patients. 2019
What is my approach to treating patients with severe asthma?

- Treat with personalized approach
- Identify asthma type by phenotype or endotype
- Treat with the most appropriate therapeutic strategy based on underlying asthmatic mechanism of inflammation
- Evaluate for comorbidities and optimize adherence
Novel Asthma Therapies

- Anti IgE- Omalizumab
- Anti IL5: mepolizumab, reslizumab, benralizumab
- Anti IL4- R alpha/Anti IL13: dupilumab
- Anti TSLP: Tezepelumab
- Other Novel therapies:
  - Anti IL33
  - Anti IL17
  - Anti IL6
  - Anti M1’
  - Anti Gata3 DNAzyme
  - TLR9 agonists
  - Antibiotics
  - CRTH2 Antagonists- Fevipiprant failed Phase 3
  - Anti IL13 lebrikizumab, tralokinumab- failed phase 3
What can we achieve with biologics?

- Reduced exacerbations
- Reduced steroid dose and side effects
- Improved symptoms and quality of life
- Disease modification to prevent asthma over long term
Which therapy is best for a specific patient?
How do you choose between biologics?

Which therapy is best for a specific patient? How do you choose between biologics?

- Biomarkers help predict therapeutic responses
  - Phenotype patients and choose most appropriate therapy
  - Goal of personalized or “precision medicine”
  - Potential need to measure different biomarkers to determine endotype/phenotype

BLOCKING EOSINOPHILS WITH ANTI IL5
The targets: IL-5 or eosinophils (IL-5Rα)

Eosinophil

Benralizumab

Mepolizumab
Reslizumab

IL-5

IL, interleukin
Reslizumab Effects on Exacerbations and Lung Function

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

Probability of not having CAE (%)

0 10 20 30 40 50 60 70 80 90 100
Placebo
Reslizumab

Number at risk
Placebo 244 169 138 112 107 97 0 0 0
Reslizumab 245 207 177 158 146 136 1 0 0

LS mean change from baseline in FEV₁ (L)

0 0.10 0.20 0.30 0.40
Visit (week)

Placebo
Reslizumab 3.0 mg/kg

Castro et al. Lancet Respir Med 2015; Epub ahead of print
Benralizumab Reduces Exacerbation

**Eosinophils ≥300 cells per μL**

**Percentage reduction relative to placebo**

-45%  
-51%

**Annual asthma exacerbation rate ratio (95% CI)**

**Bleecker ER, et al.**


**FitzGerald JM, et al.**

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma
Anti IL4/13 and Asthma

Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.
Dupilumab in Asthma

**Time to Exacerbation**

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

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

**Exacerbations — Primary End Point**

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

87% reduction

P<0.001
Improvement in Lung Function, On Top of Combination Rx

![Graph showing improvement in lung function with combination therapy](image)

- **Stable ICS/LABA**
- **LABA discontinuation**
- **ICS taper**
- **Dupilumab or placebo monotherapy**

**Mean Change ± SE**

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>52</td>
<td>52</td>
<td>51</td>
<td>51</td>
<td>50</td>
<td>49</td>
<td>47</td>
<td>46</td>
<td>45</td>
<td>43</td>
<td>41</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>52</td>
<td>51</td>
<td>52</td>
<td>52</td>
<td>50</td>
<td>49</td>
<td>52</td>
<td>52</td>
<td>47</td>
<td>46</td>
<td>46</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>

*P < 0.001*
Dupilumab Significantly Lowers Rates of Severe Exacerbation in a Phase 3 Trial

- Phase 3, randomized, double-blind, placebo-controlled trial
- n=1902 patients ≥12 years of age with uncontrolled asthma stratified by baseline blood eosinophil level
- Randomized to receive add-on SC dupilumab at a dose of 200 or 300 mg every 2 weeks or placebo for 52 weeks
- Primary outcomes: Annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in FEV₁ before bronchodilator use

Dupilumab Significantly Improved Lung Function

Change in the Prebronchodilator FEV₁ from Baseline over 52-Weeks

The benefit of dupilumab on FEV₁ was greatest among patients with a blood eosinophil count of ≥300 eos/cc at baseline

TRAVERSE:
LONG term benefits of 300mg Dupilumab up to 96 weeks

Improvement in FEV1 observed in the parent studies were sustained during open label treatment period

PSBL = parent study baseline
Asthma 2022 and Beyond:
Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.
Tezepelumab treatment reduced the annualised AER vs placebo at Week 52

- Significant reduction in annualised AER for all tezepelumab treatment groups compared with placebo; $P<0.001$

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**Asthma exacerbation rate (per patient-year)**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>Placebo (N=148)</th>
<th>Tezepelumab 70 mg Q4W (low dose) (N=145)</th>
<th>Tezepelumab 210 mg Q4W (medium dose) (N=145)</th>
<th>Tezepelumab 280 mg Q2W (high dose) (N=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.67</td>
<td>0.26**</td>
<td>0.19**</td>
<td>0.22**</td>
</tr>
</tbody>
</table>

Percentage AER reduction vs placebo

- Placebo: 61%
- Tezepelumab 70 mg Q4W (low dose): 71%
- Tezepelumab 210 mg Q4W (medium dose): 66%
Anti TSLP in Asthma (Corren 2017)
- NAVIGATOR: tezepelumab reduced the annualized asthma exacerbation rate over 52 weeks (primary endpoint)

**NAVIGATOR Results Summary**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Percentage reduction in AAER vs placebo</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>56%***</td>
<td>47, 63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Patients with baseline blood eosinophil counts &lt; 300 cells/μL</td>
<td>41%***</td>
<td>25, 54</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**AAER**, annualized asthma exacerbation rate; **CI**, confidence interval; **Q4W**, every 4 weeks
### NAVIGATOR: tezepelumab reduced exacerbations in patients with a broad range of inflammatory profiles

<table>
<thead>
<tr>
<th></th>
<th>Tezepelumab 210 mg Q4W, n/estimate</th>
<th>Placebo, n/estimate</th>
<th>Favors tezepelumab</th>
<th>Favors placebo</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>528/0.93</td>
<td>531/2.10</td>
<td></td>
<td></td>
<td>0.44 (0.37, 0.53)</td>
</tr>
<tr>
<td><strong>EOS at baseline (cells/µL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 300</td>
<td>219/0.79</td>
<td>222/2.66</td>
<td></td>
<td></td>
<td>0.30 (0.22, 0.40)</td>
</tr>
<tr>
<td>&lt; 300</td>
<td>309/1.02</td>
<td>309/1.73</td>
<td></td>
<td></td>
<td>0.59 (0.46, 0.75)</td>
</tr>
<tr>
<td><strong>EOS at baseline (cells/µL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 150</td>
<td>390/0.89</td>
<td>393/2.24</td>
<td></td>
<td></td>
<td>0.39 (0.32, 0.49)</td>
</tr>
<tr>
<td>&lt; 150</td>
<td>138/1.04</td>
<td>138/1.70</td>
<td></td>
<td></td>
<td>0.61 (0.42, 0.88)</td>
</tr>
<tr>
<td><strong>EOS at baseline (cells/µL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 450</td>
<td>120/0.68</td>
<td>127/3.00</td>
<td></td>
<td></td>
<td>0.23 (0.15, 0.34)</td>
</tr>
<tr>
<td>300–&lt; 450</td>
<td>99/0.92</td>
<td>95/2.22</td>
<td></td>
<td></td>
<td>0.41 (0.27, 0.64)</td>
</tr>
<tr>
<td>150–&lt; 300</td>
<td>171/1.00</td>
<td>171/1.75</td>
<td></td>
<td></td>
<td>0.57 (0.41, 0.79)</td>
</tr>
<tr>
<td>&lt; 150</td>
<td>138/1.04</td>
<td>138/1.70</td>
<td></td>
<td></td>
<td>0.61 (0.42, 0.88)</td>
</tr>
<tr>
<td><strong>FeNO at baseline (ppb)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 25</td>
<td>309/0.82</td>
<td>307/2.52</td>
<td></td>
<td></td>
<td>0.32 (0.25, 0.42)</td>
</tr>
<tr>
<td>&lt; 25</td>
<td>213/1.07</td>
<td>220/1.57</td>
<td></td>
<td></td>
<td>0.68 (0.51, 0.92)</td>
</tr>
<tr>
<td><strong>FeNO at baseline (ppb)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>151/0.75</td>
<td>156/2.83</td>
<td></td>
<td></td>
<td>0.27 (0.19, 0.38)</td>
</tr>
<tr>
<td>25–&lt; 50</td>
<td>158/0.87</td>
<td>151/2.20</td>
<td></td>
<td></td>
<td>0.40 (0.28, 0.56)</td>
</tr>
<tr>
<td>&lt; 25</td>
<td>213/1.07</td>
<td>220/1.56</td>
<td></td>
<td></td>
<td>0.68 (0.51, 0.92)</td>
</tr>
<tr>
<td><strong>Baseline perennial-specific IgE status (FEIA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any positive</td>
<td>339/0.85</td>
<td>341/2.03</td>
<td></td>
<td></td>
<td>0.42 (0.33, 0.53)</td>
</tr>
<tr>
<td>All negative</td>
<td>184/1.09</td>
<td>177/2.21</td>
<td></td>
<td></td>
<td>0.49 (0.36, 0.67)</td>
</tr>
</tbody>
</table>

AAER, annualized asthma exacerbation rate; CI, confidence interval; EOS, blood eosinophils; FEIA, fluorescence enzyme immunoassay; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ppb, parts per billion; Q4W, every 4 weeks
NAVIGATOR: tezepelumab reduced Type 2 Biomarkers

Blood eosinophil count (cells/µL)

FeNO level (ppb)

Serum total IgE level (IU/mL)

Data are LS means and 95% CIs.
CI, confidence interval; FeNO, fractional exhaled nitric oxide; Ig, immunoglobulin; LS, least-squares; ppb, parts per billion; Q4W, every 4 weeks.
### AntITSLP and OCS: SOURCE

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Tezepelumab 210 mg Q4W</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction from baseline in final daily OCS dose, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 90% to 100% reduction</td>
<td>40 (54.1)</td>
<td>35 (46.1)</td>
</tr>
<tr>
<td>≥ 75% to &lt; 90% reduction</td>
<td>5 (6.8)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>≥ 50% to &lt; 75% reduction</td>
<td>10 (13.5)</td>
<td>14 (18.4)</td>
</tr>
<tr>
<td>&gt; 0% to &lt; 50% reduction</td>
<td>5 (6.8)</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>No change or any increase</td>
<td>14 (18.9)</td>
<td>14 (18.4)</td>
</tr>
<tr>
<td>Comparison between treatment groups Cumulative odds ratio (95% CI)</td>
<td></td>
<td>1.28 (0.69, 2.35)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.434</td>
</tr>
</tbody>
</table>

- **Lack of difference may be due in part to the large placebo effect resulting from the long duration of the OCS reduction phase and multiple attempts to reduce OCS dose**
- **A greater reduction in OCS dose was seen with tezepelumab versus placebo in patients with baseline EOS ≥ 150 cells/µL and ≥ 300 cells/µL. Point estimates in the < 150 and < 300 cells/µL subgroups favored placebo**

CI, confidence interval; EOS, blood eosinophils; OCS, oral corticosteroid; Q4W, every 4 weeks
At week 48, improvements were greater with tezepelumab than with placebo for:

- **ACQ-6 score:** $-0.87$ vs $-0.51$; **LS mean difference, $-0.37$ (95% CI: $-0.71$, $-0.02$)**
- **AQLQ(S)+12 overall score:** $0.94$ vs $0.58$; **LS mean difference, $0.36$ (95% CI: $0.01$, $0.70$)**
- **Asthma Symptom Diary score:** $-0.36$ vs $-0.26$; **LS mean difference, $-0.10$ (95% CI: $-0.29$, $0.09$)**

**AAER over 48 weeks**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AAER (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 76)</td>
<td>2.00</td>
</tr>
<tr>
<td>Tezepelumab 210 mg Q4W (n = 74)</td>
<td>1.38</td>
</tr>
</tbody>
</table>

**31% reduction**

(95% CI: $-9$, $56$)

**Pre-BD FEV₁**

<table>
<thead>
<tr>
<th>LS mean change at week 48, L</th>
<th>Placebo (n = 76)</th>
<th>Tezepelumab 210 mg Q4W (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$-0.04$</td>
<td>$0.21$</td>
</tr>
</tbody>
</table>

**0.26**

(95% CI: $0.13$, $0.39$)

AAER, annualized asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire – 6; AQLQ(S)+12, Asthma Quality of Life Questionnaire (standardized) for patients 12 years and older; BD, bronchodilator; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LS, least-squares; Q4W, every 4 weeks
CASCADE: change from baseline in airway submucosal inflammatory cells in bronchoscopic biopsies (primary endpoint)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Tezepelumab 210 mg Q4W, n/geometric LS mean</th>
<th>Placebo, n/geometric LS mean</th>
<th>Favors tezepelumab</th>
<th>Favors placebo</th>
<th>Ratio of geometric LS means (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils (cells/mm²)</td>
<td>48/0.11</td>
<td>51/0.75</td>
<td></td>
<td></td>
<td>0.15 (0.06, 0.35)</td>
</tr>
<tr>
<td>Neutrophils (cells/mm²)</td>
<td>48/1.11</td>
<td>51/0.81</td>
<td></td>
<td></td>
<td>1.36 (0.99, 1.86)</td>
</tr>
<tr>
<td>T cells – CD3⁺ (cells/mm²)</td>
<td>48/0.91</td>
<td>51/0.81</td>
<td></td>
<td></td>
<td>1.12 (0.90, 1.40)</td>
</tr>
<tr>
<td>T cells – CD4⁺ (cells/mm²)</td>
<td>48/0.96</td>
<td>51/0.81</td>
<td></td>
<td></td>
<td>1.18 (0.94, 1.48)</td>
</tr>
<tr>
<td>Mast cells tryptase⁺ (cells/mm²)</td>
<td>48/0.84</td>
<td>51/1.01</td>
<td></td>
<td></td>
<td>0.83 (0.64, 1.09)</td>
</tr>
<tr>
<td>Mast cells chymase⁺ (cells/mm²)</td>
<td>48/1.07</td>
<td>51/0.90</td>
<td></td>
<td></td>
<td>1.19 (0.74, 1.92)</td>
</tr>
</tbody>
</table>

Analyses were performed using an ANCOVA model with log-transformed data

ANCOVA, analysis of covariance; CD, cluster of differentiation; CI, confidence interval; LS, least-squares; Q4W, every 4 weeks
CASCADE: change from baseline or screening in airway submucosal eosinophils by subgroups (pre-specified exploratory endpoint)

<table>
<thead>
<tr>
<th>Baseline blood EOS count (cells/µL)</th>
<th>Tezepelumab 210 mg Q4W, n/geometric LS mean</th>
<th>Placebo, n/geometric LS mean</th>
<th>Favors tezepelumab</th>
<th>Favors placebo</th>
<th>Ratio of geometric LS means (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>48/0.11</td>
<td>51/0.75</td>
<td></td>
<td></td>
<td>0.15 (0.06, 0.35)</td>
</tr>
<tr>
<td><strong>Baseline blood EOS count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 150</td>
<td>12/0.13</td>
<td>14/0.85</td>
<td></td>
<td></td>
<td>0.15 (0.03, 0.86)</td>
</tr>
<tr>
<td>150–&lt; 300</td>
<td>19/0.09</td>
<td>16/0.89</td>
<td></td>
<td></td>
<td>0.10 (0.02, 0.45)</td>
</tr>
<tr>
<td>≥ 300</td>
<td>17/0.18</td>
<td>21/0.70</td>
<td></td>
<td></td>
<td>0.25 (0.06, 1.07)</td>
</tr>
<tr>
<td><strong>Baseline FeNO (ppb)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 25</td>
<td>26/0.10</td>
<td>29/0.62</td>
<td></td>
<td></td>
<td>0.16 (0.05, 0.52)</td>
</tr>
<tr>
<td>≥ 25</td>
<td>19/0.12</td>
<td>21/0.93</td>
<td></td>
<td></td>
<td>0.13 (0.03, 0.53)</td>
</tr>
</tbody>
</table>

Analyses were performed using an ANCOVA model with log-transformed data

ANCOVA, analysis of covariance; CI, confidence interval; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; LS, least-squares; ppb, parts per billion; Q4W, every 4 weeks.
Other new therapies

- **Anti CRTH2-**
  - Fevipiprant Phase 3 failed to improve FEV1
  - GB001
- **Jak Inhibitors**
  - Downstream of most asthma related cytokines
  - In phase 2
Anti IL33

- Itepekimab
  - Reduced exacerbations vs. placebo
  - Comparable to dupilumab
  - Less effective in combination with dupilumab
Anti IL33 Itepekimab improved loss of asthma control vs. placebo

Why did addition of dupilumab to anti IL33 result in worse outcomes?

Wechsler NEJM 2021
Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: A randomized clinical trial

Steven G. Kelsen, MD, a Ioana O. Agache, MD, PhD, b Weily Soong, MD, c Elliot Israel, MD, d Geoffrey L. Chupp, MD, e Dorothy S. Cheung, MD, f Wiebke Theess, PhD, f Xiaoying Yang, PhD, f Tracy L. Staton, PhD, f David F. Choy, BS, f Alice Fong, PharmD, f Ajit Dash, MD, PhD, f Michael Dolton, PhD, f Rajita Pappu, PhD, f and Christopher E. Brightling, FMedSci, PhD g Philadelphia, Pa; Brasov, Romania; Birmingham, Ala; Boston, Mass; New Haven, Conn; South San Francisco, Calif; and Leicestershire, United Kingdom

![Graph showing annualized AERs in the overall population and patients stratified by baseline eosinophil levels (Eos; cells/μL). Bars show unadjusted rates by treatment groups. Gray arrows indicate unadjusted percentage rate reductions.](image)
Blocking IL-25 with a murine anti-IL-25 mAb prevents airway type-2 inflammation in allergic asthma model in mice (e.g., less IL-5 and IL-13 production).

Source: Ballantyne, McKenzie JACI 2007
Long Acting Anti-IL5

- Depemokimab
- Administered q 6 months
- In phase 3
Dexpramipexole

- Oral therapy
- Developed for ALS
- Uncertain mechanism
- Reduces eosinophils
- Improves lung function (Siddiqui ERS 2021)
PrecISE: Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network
## Planned PRECISE INTERVENTIONS

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

- IL4, IL13 and TSLP act through JAK (Janus Activated Kinase) signaling following binding of cytokine receptors → activate STAT proteins that in turn directly bind DNA and regulate gene expression

- JAK activation associated with:
  - TH2 differentiation, eosinophilic inflammation, airway hyperresponsiveness, matrix deposition, mucus metaplasia, leading to Type 2 asthma phenotypes

- Recent animal models of allergic pulmonary inflammation:
  - JAK inhibitor tofacitinib diminished BALF eosinophilia, IL-13, and eotaxin suggesting potential for the treatment of T2 asthma
  - JAK1 inhibitor (Jak-381) suppressed STAT6 activation by IL-13 and ovalbumin-induced lung inflammation while improving allergen-induced airway hyperresponsiveness and airway lung pathology

- Could JAK inhibition improve asthma outcomes in patients with Type 2 severe asthma (eos, eNO) or nonType 2 Asthma
Individualizing Asthma Therapy: Conclusions

• Response to asthma therapies is variable
• Need to understand who responds to what
• We now have multiple novel biologic therapies that may treat patients with severe eosinophilic asthma
• How will we decide which therapies work best in which patients?
Treating Severe Asthmatics Now

- Do extensive workup
- Endotype your patients
Asthma Biomarkers

- IGE
- FENO
- EOS
  - Sputum
  - Blood
- Periostin
- DPP4 (Dipeptidyl Peptidase 4 / CD26; an adipokine)
Selecting Treatment for Severe Asthma: Anti-IgE Versus Anti–IL-5

- Patients with allergic eosinophilic asthma
  - Anti-IgE or Anti–IL-5 or Anti IL4/13
- Patients with allergic noneosinophilic asthma
  - Anti-IgE or Anti IL4/13 if eNO high
- Patients with eosinophilic asthma who:
  - Are nonallergic
  - Do not respond to anti-IgE treatment
  - Are out of range of dosing for anti-IgE treatment
  - Anti–IL-5 or Anti IL4/13

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

Head-to-head studies are needed

What about non type 2 asthma?

- Azithromycin
- Bronchial Thermoplasty
- ? tezepelumab
What about targeting IL23?

Subjects did worse with Risankizumab vs. Placebo!!!
Questions to ask in Choosing whether to use Biologics

• Is the patient poorly controlled?
• Is the patient not adherent to therapy?
• Have comorbidities not been addressed?
• Is the patient on systemic corticosteroids?
Factors in Choosing Biologics

• Have biomarkers been assessed?
• What is the DOMINANT biomarker?
• Are there Type 2 comorbidities?
• Did the patient respond to initial biologic? If no, consider switching!!!
Understanding Disease Mechanisms May Guide Therapy to a More Personalized Approach

- **One Size Fits All**: Evidence-based, One treatment for all
- **Stratified Medicine**: Evidence-based, Different treatments for groups of patients
- **Personalized Medicine**: Evidence-based, Individualized treatment for each patient

Emerging Asthma Therapy: Conclusions

• Current biologics are effective but don’t completely eliminate exacerbations
• Our current understanding of asthma mechanisms remains rudimentary
• Novel therapies targeting upstream alarmins offer promise:
  • TSLP
  • IL33
  • IL25
  • How redundant are these pathways?
• We still need good therapies for Nontype 2 disease
• We still need to use biomarkers to identify dominant pathways
• Need to appreciate that asthma is dynamic
<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Dosing</th>
<th>Frequency</th>
<th>Route</th>
<th>Exacerbation Reduction Rate (vs. Placebo)</th>
<th>Increased FEV$_1$ (vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reslizumab Anti IL5</td>
<td>Approve 2016</td>
<td>3.0 mg/kg</td>
<td>Q4W</td>
<td>IV</td>
<td>50-59%</td>
<td>110-126 ml</td>
</tr>
<tr>
<td>Mepolizumab Anti IL5</td>
<td>Approved asthma 2015;</td>
<td>100 mg</td>
<td>Q4W</td>
<td>Sub-Q</td>
<td>53%</td>
<td>98 ml</td>
</tr>
<tr>
<td></td>
<td>Phase 3 COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benralizumab Anti IL5 Receptor</td>
<td>Approved asthma 2017;</td>
<td>30 mg</td>
<td>Q8W (first 3 doses every 4 weeks)</td>
<td>Sub-Q</td>
<td>36-55% (Q4W frequency) 28-70% (Q8W frequency)</td>
<td>0-125 ml</td>
</tr>
<tr>
<td></td>
<td>Phase 3 COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Omalizumab Anti IgE</td>
<td>Approved asthma 2003;</td>
<td>125mg – 375mg (based on weight/ IgE level)</td>
<td>Q2W or Q4W (depending on weight/ IgE level)</td>
<td>Sub-Q</td>
<td>33-75%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Approved urticaria</td>
<td></td>
<td></td>
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<tr>
<td>Dupilumab Anti IL4 Receptor</td>
<td>Approved 2017 for Atopic</td>
<td>200-300 mg</td>
<td>Q2W</td>
<td>Sub-Q</td>
<td>59.9-80.7%</td>
<td>390-430ml</td>
</tr>
<tr>
<td></td>
<td>Dermatitis; 2018 for Asthma</td>
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<tr>
<td>Tezepelumab Anti TSLP</td>
<td>Approved 2021 for asthma</td>
<td>210 mg</td>
<td>Q4 W</td>
<td>Sub-Q</td>
<td>61-71%</td>
<td>110-150 ml</td>
</tr>
</tbody>
</table>
Inflammatory, Immunologic, and Pathobiologic Features Leading to Severe Asthma

Inflammatory mechanisms and pathobiologic features leading to severe asthma

Type 2 inflammation
- Antigens
- IL-25
- IL-33
- IL-4, 5, and 13
- CRTH2
- TSLP

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

Th2 cell
- GATA3
- IL-13

ILC2
- GATA3
- IL-13

Th1 cell
- IL-17

Neutrophil
- CXCR2
- Neutrophil
- Leukotriene B4

Eosinophil
- Lipoxin
- ALX

Mast cell
- IgE
- Leukotrienes
- PGD2
- Histamine
- IL-3, 4, 5, and 9

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

Thanks!!
WechslerM@NJHealth.org