Targeted Therapies for Specific Asthma Phenotypes

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Objectives

• Discuss strategies to optimize treatment for asthma including the role of precision medicine
• Discuss patient-specific features that can influence the therapeutic benefits of specific therapies for asthma

Disclosure

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

<table>
<thead>
<tr>
<th>Type</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment full time / part time</td>
<td>None</td>
</tr>
<tr>
<td>Research Grant (P.I., collaborator or consultant; pending and received grants)</td>
<td>Novartis, Genentech, Sanofi, Regeneron</td>
</tr>
<tr>
<td>Other research support</td>
<td>None</td>
</tr>
<tr>
<td>Speakers Bureau / Honoraria</td>
<td>Genentech and Sanofi</td>
</tr>
<tr>
<td>Ownership interest (stock, stock-options, patent or intellectual property)</td>
<td>None</td>
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<tr>
<td>Consultant / advisory board</td>
<td>Novartis, Genentech, Sanofi, Regeneron, GSK and AstraZeneca</td>
</tr>
</tbody>
</table>
Phenotype vs. Endotype

Pathways Leading to Non-Eosinophilic Inflammation in T2-low Asthma
Therapeutic Agents Targeting Th17 Cell Responses

Non-Eosinophilic Asthma

- Lack of good biomarkers
- AIT: Not appropriate
- No specific T2lo biologics approved, and concern for AEs
- T2hi biologics:
  - Omalizumab: small case series of nonallergic asthma and ACO
  - Dupilumab: works poorly in eosinophil and/or FeNO low patients
  - IL-5 blockers: work poorly in eosinophil low patients
- Alarmin blockers:
  - Tezepelumab
  - Astegolimab (anti-ST2)
Box 3-5A
Adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Asthma medication options:
Adjust treatment up and down for individual patient needs

Preferred controller to prevent exacerbations and control symptoms

Other controller options

Preferred reliever

Other reliever option

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adult dose in mg)
Education & self-management

Step 2
As-needed low dose ICS-formoterol *

Step 3
Low dose ICS-LABA

Medium dose ICS-LABA

High dose ICS, add-on ICS, or LABA

Add low dose OCS, but consider side-effects

Step 4
As-needed low dose ICS-formoterol *

As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy

As-needed short-acting β₂-agonist (SABA)

* Data only with budesonide-formoterol (budesonide)
† Separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever only for patients prescribed budesonide or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted
Analysis of Inhaled Corticosteroid Partial- and Non-Responders

Patients (%)

<table>
<thead>
<tr>
<th>FEV₁ % Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>-40</td>
</tr>
</tbody>
</table>

Malmstrom et al (n = 895)
Adult Study (n = 470)
CAMP (n = 311)
ACRN (n = 336)


A New AIT Paradigm: True Personalized Medicine
1 wk after administration, immunologic changes occurred that typically take 1 year of traditional AIT.

What We Need to Avoid

“OUR NEW MULTI-SYRINGE WILL TAKE CARE OF ALL YOUR ALLERGIES IN ONE FELL SWOOP.”
Novel Therapies Targeting T2 High Asthma

Approved

Eosinophilic asthma: any of the following:
- sputum eosinophil count of ≥1%
- blood eosinophil count of ≥150 cells/uL
- FeNO of ≥20 ppb

Allergic asthma:
- asthma symptoms due to exposure to a perennial aeroallergen
- IgE 30-1300 IU/mL

Type 2 asthma: any of the following
- blood eosinophil count of ≥150 cells/uL
- FeNO of ≥20 ppb
Which T<sub>2</sub> Biologic is Best?
An Expert Scientific Panel Consensus

Caveats on Choosing a Biologic for Asthma:
Role of Allergy

- **Allergic asthma:**
  - Most data with omalizumab
    - comparable improvements regardless of number and type of allergen sensitizations*
  - Positive data with dupilumab, mepolizumab and benralizumab

*Ann Allergy, 4/21
IL-5 Blockers & Dupi Work Really Well with Elevated Blood EOS

Relative Change in Exacerbation Rate By Blood EOS

- Blood eosinophils/μL
  - ≥ 200: P = 0.002, n = 664
  - ≥ 300: P = 0.001, n = 442
  - ≥ 400: P = 0.001, n = 260

Mean Exacerbation Rate by T2 Biomarker Status

- Eosinophils <300 cells/μL
  - n = 459
  - Mean (SD) Exacerbation Rate: 3.0
- Eosinophils 300-399 cells/μL
  - n = 454
  - Mean (SD) Exacerbation Rate: 3.2
- Eosinophils ≥400 cells/μL
  - n = 249
  - Mean (SD) Exacerbation Rate: 2.8
- FeNO <30 ppb
  - n = 402
  - Mean (SD) Exacerbation Rate: 0.7
- FeNO ≥30 ppb
  - n = 398
  - Mean (SD) Exacerbation Rate: 0.8

Effects of Omalizumab in Prospero:

48-wk, Prospective, Single-arm, Open-label Study Of Omalizumab For Allergic Asthma Based On Physician Assessment Of Need

Mean Exacerbation Rate by T2 Biomarker Status

- Eosinophils <300 cells/μL
  - n = 320
  - Mean (SD) Exacerbation Rate: 3.3
- Eosinophils 300-399 cells/μL
  - n = 316
  - Mean (SD) Exacerbation Rate: 0.8
- FeNO <30 ppb
  - n = 402
  - Mean (SD) Exacerbation Rate: 2.8
- FeNO ≥30 ppb
  - n = 398
  - Mean (SD) Exacerbation Rate: 0.7

Casale et al, JACI:Practice; May 2018

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Casale et al, JACI:Practice; May 2018
The "Placebo" Effect

Summary of Findings of Biologics Compared to Standard of Care for Eosinophilic Asthma

<table>
<thead>
<tr>
<th></th>
<th>Benralizumab</th>
<th>Mepolizumab</th>
<th>Reslizumab</th>
<th>Dupilumab</th>
<th>Omalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GRADE</strong></td>
<td>HIGH</td>
<td>MOD</td>
<td>HIGH</td>
<td>HIGH</td>
<td>MOD</td>
</tr>
<tr>
<td><strong>RISK DIFF</strong></td>
<td>0.53</td>
<td>0.49</td>
<td>0.46</td>
<td>0.44</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td>HIGH</td>
<td>MOD</td>
<td>HIGH</td>
<td>MOD</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>HIGH</td>
<td>MOD</td>
<td>HIGH</td>
<td>MOD</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>QOL</strong></td>
<td>HIGH</td>
<td>MOD</td>
<td>HIGH</td>
<td>MOD</td>
<td>MOD</td>
</tr>
<tr>
<td><strong>AEs</strong></td>
<td>MOD</td>
<td>HIGH</td>
<td>MOD</td>
<td>MOD</td>
<td>MOD</td>
</tr>
<tr>
<td><strong>Decr OCS</strong></td>
<td>HIGH</td>
<td></td>
<td>HIGH</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td><strong>FEV1 (mL Incr)</strong></td>
<td>MOD</td>
<td>140 mL</td>
<td>MOD</td>
<td>High</td>
<td>MOD</td>
</tr>
<tr>
<td><strong>Rescue med use (p/d Decr)</strong></td>
<td>NA</td>
<td>HIGH</td>
<td>HIGH</td>
<td>MOD</td>
<td>MOD</td>
</tr>
</tbody>
</table>

Agache et al, Allergy, 2020
Caveats on Choosing a Biologic: 
*Role of FeNO*

**Dupilumab Efficacy As a Function of FeNO**

![Graph showing Dupilumab Efficacy As a Function of FeNO](image)

*Pavord et al, Submitted*

---

Caveats on Choosing a Biologic: 
*Role of FeNO + Eosinophils*

![Graph showing Caveats on Choosing a Biologic: Role of FeNO + Eosinophils](image)

*Pavord et al, Submitted*
Which to Choose When the 3 Biomarkers Are Not Helpful

- Patient preferences (shared decision making)
- What is the end game for the patient?
  - Data-driven choices
- Co-morbidities
- Exacerbation Triggers
- Insurance coverage!

Effect of Biologics on Asthma Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Omalizumab</th>
<th>Mepolizumab</th>
<th>Reslizumab</th>
<th>Benralizumab</th>
<th>Dupilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic dermatitis</td>
<td>+/-</td>
<td>-</td>
<td>No data</td>
<td>No data</td>
<td>Indicated</td>
</tr>
<tr>
<td>CRSwNP (nasal polyposis)</td>
<td>Indicated</td>
<td>Indicated</td>
<td>+</td>
<td>+</td>
<td>Indicated</td>
</tr>
<tr>
<td>Food allergy</td>
<td>++</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>+</td>
</tr>
<tr>
<td>Allergic rhinoconjunctivitis/allergic rhinitis</td>
<td>++</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>+</td>
</tr>
<tr>
<td>ABPA</td>
<td>+</td>
<td>+</td>
<td>No data</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>EGPA</td>
<td>+</td>
<td>Indicated</td>
<td>No data</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>ACO/COPD</td>
<td>+</td>
<td>++</td>
<td>No data</td>
<td>+</td>
<td>No data</td>
</tr>
<tr>
<td>AERD</td>
<td>++</td>
<td>++</td>
<td>No data</td>
<td>No data</td>
<td>++</td>
</tr>
</tbody>
</table>
Picking a Biologic Based on Exacerbation Etiology

Cardet and Casale, JACI 2019

Approach to Using a Biologic

Initial Evaluation

Patient Characteristics
- BMI
- Smoking History
- Exacerbation History
- Comorbidities
- Lung Functions

Biomarker Phenotyping
- Blood/Sputum Eosinophils
- Total and Ag-specific IgE

Goals Of Therapy
- Exacerbation Reduction
- Decreased Symptoms
- Improved Quality of Life
- Improved Lung Functions
- Reduction of Glucocorticoids
- Improved Comorbidities

Start Optimal Assessed Treatment Using Shared Decision Making
Approach to Using a Biologic

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- Exacerbation History
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**Goals of Therapy**
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- Improved Lung Functions
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- Improved Comorbidities

**Reassessment At 4 to 6 Mos**

**Goals of Therapy Met**
- Continue Prescribed Biologic

**Goals of Therapy Unmet**
- Reassess doing and compliance
- Reassess Biomarker Phenotyping:
  - If T2lo Consider Alternative Treatments
  - If T2hi Switch Class of Biologics

---

Approach to Using a Biologic

**Initial Evaluation**

**Patient Characteristics**
- BMI
- Smoking History
- Exacerbation History
- Comorbidities
- Lung Functions

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- FeNO
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- Reduction of Glucocorticoids
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**Reassessment At 4 to 6 Mos**

**Goals of Therapy Met**
- Continue Prescribed Biologic

**Follow Patient Monitoring Safety and Efficacy**

**Goals of Therapy Unmet**
- Reassess doing and compliance
- Reassess Biomarker Phenotyping:
  - If T2lo Consider Alternative Treatments
  - If T2hi Switch Class of Biologics

**Continue Treatment if Remains Safe and Effective**

---
What else is out there?

• **TSLP blockers**
• IL-33/ST2 blockers
• Second generation IL-5 Blockers
• Second generation IgE Blockers
• Biosimilars

### Annualized Rate of Exacerbations Over 52 Weeks By Biomarker: Tezepelumab NAVIGATOR Phase 3

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Tezepelumab</th>
<th>Placebo</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>59/4.93</td>
<td>53/2.10</td>
<td>0.44 (0.37-0.53)</td>
</tr>
<tr>
<td>Eosinophil count at baseline (cells/µL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300</td>
<td>309/1.02</td>
<td>309/1.73</td>
<td>0.59 (0.46-0.75)</td>
</tr>
<tr>
<td>&gt;300</td>
<td>219/0.79</td>
<td>221/2.66</td>
<td>0.30 (0.22-0.40)</td>
</tr>
<tr>
<td>Eosinophil count at baseline (cells/µL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>138/1.04</td>
<td>138/1.70</td>
<td>0.61 (0.42-0.88)</td>
</tr>
<tr>
<td>150 to &lt;300</td>
<td>171/1.00</td>
<td>171/1.75</td>
<td>0.57 (0.41-0.79)</td>
</tr>
<tr>
<td>300 to &lt;450</td>
<td>99/0.92</td>
<td>93/2.22</td>
<td>0.41 (0.27-0.64)</td>
</tr>
<tr>
<td>≥450</td>
<td>120/0.68</td>
<td>127/3.00</td>
<td>0.23 (0.15-0.34)</td>
</tr>
<tr>
<td>Eosinophil count at baseline (cells/µL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>138/1.04</td>
<td>138/1.70</td>
<td>0.61 (0.42-0.88)</td>
</tr>
<tr>
<td>≥150</td>
<td>390/0.89</td>
<td>393/2.24</td>
<td>0.39 (0.32-0.49)</td>
</tr>
<tr>
<td>FEV1 at baseline (ppb)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>213/1.07</td>
<td>220/1.57</td>
<td>0.68 (0.51-0.92)</td>
</tr>
<tr>
<td>≥25</td>
<td>309/0.82</td>
<td>307/2.52</td>
<td>0.32 (0.25-0.42)</td>
</tr>
<tr>
<td>FEV1 at baseline (ppb)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>213/1.07</td>
<td>220/1.56</td>
<td>0.68 (0.51-0.92)</td>
</tr>
<tr>
<td>≥25</td>
<td>158/0.87</td>
<td>151/2.20</td>
<td>0.40 (0.28-0.56)</td>
</tr>
<tr>
<td>≥50</td>
<td>151/0.75</td>
<td>154/2.83</td>
<td>0.27 (0.19-0.38)</td>
</tr>
<tr>
<td>Allergic status at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive for any perennial allergens</td>
<td>339/0.85</td>
<td>341/2.03</td>
<td>0.42 (0.33-0.53)</td>
</tr>
<tr>
<td>Negative for all perennial allergens</td>
<td>184/1.09</td>
<td>177/2.21</td>
<td>0.49 (0.36-0.67)</td>
</tr>
</tbody>
</table>

### Effects OF Tezepelumab on FEV1

![Graph showing the effects of Tezepelumab on FEV1 over 52 weeks](image-url)
Critical Issues /Questions for Biologics

- Many options for similar patient populations with T2hi asthma.
  - Phenotype/Endotype (Biomarker) driven choices overlap:
    - No specific biomarkers, except FeNO and dupi

- Little to no options for T2lo asthma
  - ?Tezepelumab?

- Optimal treatment goals have not yet been met:
  - True Immunomodulation: prevent/alter disease course

- T2hi blockers likely have favorable risk/benefit ratio.....too little info
  - On T2lo blockers

\[ \text{Too Powerful Broad-spectrum} \]
\[ \text{Too Weak Very Specific} \]
WHEN WE TESTED THIS DRUG ON MICE, NOBODY NOTICED ANY SIDE EFFECTS.
Economic Outlook for Biologics in Asthma – Are They Cost-Effective?

John Oppenheimer MD
UDMNJ-Rutgers

Potential Conflicts of Interest

• Consultant/Advisor: GlaxoSmithKline, Aquestive, Amgen, DBV
• Adjudication/DSMB: AZ, Novartis, GSK, Sanofi and Abbvie
• Research: NIH - Investigating Dupilumab’s Effect in Asthma by genotype- IDEA
Prevalence of Uncontrolled Asthma

• Previous studies have reported a prevalence of uncontrolled asthma ranging from 40–60%, depending on the population studied and the definition of asthma control.

  Price NPJ primary care respiratory medicine 2014; 24: 14009.

  • In patients attending 12 pulmonary and 12 allergy clinics, 53% were not well controlled (mean [SD] Asthma Control Test, 14.3 [3.6] vs 22.4 [1.6] in well-controlled patients).
  • Among ICS/LABA users, 56% were not well controlled, which increased with increasing ICS dose:
    • low-dose ICS 45.7%
    • high-dose ICS 59.7%.

  Oppenheimer Ann All Asthma Immunol 2021; 126:385-393

Consequences of Uncontrolled Asthma

• Poor asthma control is associated with increased:
  • exacerbation risk,
  • poor health-related quality of life (HRQoL),
  • increased health care utilization (HRU) and costs.

  Sullivan Annals of allergy, asthma & immunology 2016; 117(3): 251-7

• The 20-year cost of asthma in the U.S. is estimated to exceed $963 billion

Asthma is a Syndrome

- Evidence indicates asthma is a heterogeneous disorder.\(^1,2,3\)
  - Allergic vs nonallergic asthma
  - Severity
  - Age of Onset
  - Chronic Airway Obstruction
  - Triggers
    - Viral, Exercise, Occupational Allergens, Irritants
  - Pathobiology
    - Eosinophilic, Neutrophilic and paucigranulocytic asthma
  - Course
    - Early transient, persistent, late onset wheeze

1) Kontstantelou. Respiratory Medicine. 2015
2) Wenzel SE. Lancet 2006;368 (9537) 804-813
3) Zedan Pediatrics. 2013; 824

Figure 1d: Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

<table>
<thead>
<tr>
<th>Intermittent Asthma</th>
<th>Management of Persistent Asthma in Individuals Ages 12+ Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>STEP 1</strong></td>
</tr>
<tr>
<td><strong>Preferred</strong></td>
<td>DEXA, INH,</td>
</tr>
<tr>
<td></td>
<td>INH, ICS,</td>
</tr>
<tr>
<td></td>
<td>LABA, or</td>
</tr>
<tr>
<td></td>
<td>concomitant</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>DEXA, INH,</td>
</tr>
<tr>
<td></td>
<td>INH, ICS,</td>
</tr>
<tr>
<td></td>
<td>LABA, or</td>
</tr>
<tr>
<td></td>
<td>concomitant</td>
</tr>
</tbody>
</table>

Assess Control

- First check adherence, inhaler technique, environmental factors, & co-morbid conditions.
- Step 4 if control remains poor, or DEXA, INH, ICS, LABA, or concomitant medication.
- Consult with asthma specialist if Step 4 is needed. Consider consultation at Step 3.

NAEPP 2021
Our Approach to the Severe Uncontrolled Asthmatic:

Step-up Therapy for Children with Uncontrolled Asthma Receiving ICS (BADGER STUDY)

Methods

- randomly assigned 182 children (6 to 17 years of age), who had uncontrolled asthma while receiving 100 μg of fluticasone BID, to receive each of three blinded step-up therapies in random order for 16 weeks:
  - 250 μg of fluticasone twice daily (ICS step-up),
  - 100 μg of fluticasone plus 50 μg of a long-acting beta-agonist twice daily (LABA step-up),
  - 100 μg of fluticasone twice daily plus 5 or 10 mg of Montelukast (LTRA step-up).
- used a triple-crossover design and a composite of three outcomes
  - exacerbations,
  - asthma-control days,
  - FEV1

Lemanske NEJM 2010;362:975-85.
A differential response occurred in 161 of 165 patients who were evaluated (P<0.001).

The response to LABA step-up therapy was most likely to be the best response.

Higher baseline ACT scores predicted a better response to LABA step-up (P=0.009).

White race predicted a better response to LABA step-up,

African American patients were least likely to have a best response to LTRA step-up (P=0.005).

Increased Neutrophilic Inflammation in Severe Steroid-Dependent Asthmatics

BAL Cell Differentials

Statistical difference among the 3 groups for neutrophils and eosinophils were p=0.032 and p<0.007, respectively.

**Biologic Agents**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>Reduces circulating IgE by binding to the constant region of the human immunoglobulin E molecule</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Binds free IL-5 which mediates airway and systemic eosinophilia.</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Binds IL-5 receptor-alpha on eosinophils and basophils.</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>Binds IL-5 receptor-alpha on eosinophils and basophils.</td>
</tr>
<tr>
<td>Cedirizumab</td>
<td>Binds to circulating IL-5 reducing airway permnin</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Blocks both IL-4 and IL-13 signaling pathways by binding to IL-4 receptor-alpha.</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>Anti-IL17 receptor A which blocks IL-17 and IL-25</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Reduces and neutralizes soluble TNF-a, a key regulator of innate immunity and the T helper response</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Reduces circulating IgE by binding to the constant region of the human immunoglobulin E molecule</td>
</tr>
</tbody>
</table>

Draikwicz + Oppenheimer Immunology and Allergy Clinics 2017
We have to balance Rx costs with outcomes

Cost-effectiveness and comparative effectiveness of biologic therapy for asthma: To biologic or not to biologic?

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Target</th>
<th>Annual WAC, $</th>
<th>Base-case incremental cost-effectiveness ratio, $</th>
<th>Discount from WAC required to achieve cost-effectiveness threshold price, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>Anti-IgE</td>
<td>39,048</td>
<td>325,000</td>
<td>66-77</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Anti-IL-5</td>
<td>37,293</td>
<td>344,000</td>
<td>64-75</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Anti-IL-5</td>
<td>31,637</td>
<td>391,000</td>
<td>67-80</td>
</tr>
<tr>
<td>Brolucizumab</td>
<td>Anti-IL-5</td>
<td>30,880</td>
<td>373,000</td>
<td>62-73</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Anti-IL-4</td>
<td>38,110</td>
<td>351,000</td>
<td>62-73</td>
</tr>
</tbody>
</table>

Wholesale Acquisition Cost (WAC)

Anderson and Szefler Ann Allergy Asthma Immunol 2019;122:367-72
Cost-effectiveness and comparative effectiveness of biologic therapy for asthma: To biologic or not to biologic?

- Current pricing for all biologics exceeds measures of cost-effectiveness.
- To meet available measures indicating cost-effectiveness, prices would have to be reduced by a minimum of approximately 60%.

Conclusion:
Cost effectiveness could be significantly improved if we better understood indicators of those likely to respond to therapy before its initiation, or had knowledge of some early sign of those responding to therapy.

Anderson and Szefler Ann Allergy Asthma Immunol 2019;122:367-72
Improving our Precision in Medicine
We are Going to Have to!

Can we improve our choice of patients/Improve the CEA?
Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies

Mepolizumab significantly reduces the rate of exacerbations in patients with severe eosinophilic asthma.

Methods
- Post-hoc analysis of data from two randomized, double-blind, placebo-controlled studies of at least 32 weeks duration DREAM and MENSA done between 2009 and 2014.
- The primary endpoint in both studies was the annual rate of clinically significant exacerbations—defined as worsening of asthma that required the use of systemic corticosteroids, or admission to hospital, or an emergency-room visit, or a combination of these occurrences.
- Subjects were stratified by baseline eo count

Findings
- The overall rate of mean exacerbations per person per year was reduced by 47% on mepo (vs pbo p<0·0001).
- The exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52% in patients with a baseline blood eosinophil count of at least 150 cells per μL to 70% with a baseline count of at least 500 cells per μL.
- A baseline count less than 150 cells per μL, predicted efficacy of mepolizumab was reduced.

Asthma Therapy - Omalizumab EXTRA Study

- Patients 12-75 years of age with uncontrolled severe persistent asthma were enrolled
  - Need history of severe persistent asthma > 1 year before screening.
  - Uncontrolled despite being on high dose ICS and LABA
- Randomized 1:1 to receive omalizumab or placebo for 48 weeks.
- 850 patients enrolled:
  - FENO
  - blood eosinophils
  - serum periostin
- Primary endpoint was number of observed protocol-defined exacerbations over 48 week trial period
  - Worsening asthma symptoms requiring systemic corticosteroids for >=3 days.


Asthma Therapy - Omalizumab

<table>
<thead>
<tr>
<th>Exacerbation rates</th>
<th>Low FEVI at baseline</th>
<th>High FEVI at baseline</th>
<th>Low eosinophils at baseline</th>
<th>High eosinophils at baseline</th>
<th>Low periostin at baseline</th>
<th>High periostin at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>0.85</td>
<td>0.59</td>
<td>0.85</td>
<td>0.79</td>
<td>0.79</td>
<td>0.66</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.71</td>
<td>1.67</td>
<td>0.72</td>
<td>1.63</td>
<td>0.72</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Cluster Analysis of Inflammatory Biomarker Expression in the International Severe Asthma Registry

Goal:
• characterize biomarker expression in adults with severe asthma.

METHODS:
• Within the International Severe Asthma Registry analyzed data with prespecified thresholds for biomarker positivity and with hierarchical cluster analysis using biomarkers as continuous variables.
  – serum IgE ≥ 75 kU/L
  – blood eosinophils ≥ 300 cells/mL
  – FeNO ≥ 25 ppb

CONCLUSIONS:
• There is significant overlap of biomarker positivity in severe asthma.
• Distinct clusters according to biomarker expression exhibit unique clinical characteristics, suggesting the occurrence of discrete patterns of underlying inflammatory pathway activation and providing pathogenic insights relevant to the era of monoclonal biologics.
  – Some patients may respond better than others to a specific biologic agent

FIGURE 3. Graphical representation of the clinical characteristics of the 5 severe asthma clusters relating to biomarkers

Biomarkers: blood eosinophils ≥ 300 cells/mL, FeNO ≥ 25 ppb, total IgE ≥ 75 kU/L
Gene-environment interaction between an IL4R variant and school endotoxin exposure contributes to asthma symptoms in inner-city children

Xia JACI 2015; 136:441-53.

Pharmacogenomics and Dupilumab

In a humanized mouse model of the IL4Ra-R576 variant, exposure of the mice to fine/ultrafine particles from vehicular exhaust exacerbated allergic inflammation in association with augmented mixed TH2/TH17 airway cell responses, demonstrating the plausibility that interactions between this allele and environmental exposures contribute to asthma morbidity.

Xia JACI 2015; 136:441-53.

Gene-environment interaction between an IL4R variant and school endotoxin exposure contributes to asthma symptoms in inner-city children

Lai JACI 2018;141:794-6
Effect of IL-4RαR576 polymorphism on response to Dupilumab in Asthma, a Genotype stratified, randomized-placebo controlled trial
Investigating Dupilumab’s Effect in Asthma by genotype- IDEA

• double-blind, randomized, placebo-controlled parallel-group phase 2 clinical trial.
• Patients will be genotyped and categorized and stratified:
  – 1) the wild type allele (Q576/Q576),
  – 2) heterozygous allele (Q576/R576),
  – 3) homozygous mutant allele (R576/R576); the genotype associated with more severe disease.
• This study addresses fundamental mechanisms by which the IL-4Rα-R576 variant drives the TH2/TH17 disease endotype and the influence of this variant on response to Dupilumab therapy.
• Asthmatics bearing this endotype will be particularly likely to favorably respond to Dupilumab

Can we improve our timing of therapy?
FIG 1. Number of hospitalizations of children age 5 to 15 years by week of the year in Ontario from 1990 to 2000.

Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations

Hypothesis:
• Short-term targeted treatment can potentially prevent fall asthma exacerbations while limiting therapy exposure.

Objective:
• Compared (1) omalizumab with placebo and (2) omalizumab with an inhaled corticosteroid (ICS) boost with regard to fall exacerbation rates when initiated 4 to 6 weeks before return to school.

Methods:
• A 3-arm, randomized, double-blind, double placebo controlled, multicenter clinical trial was conducted among inner-city asthmatic children aged 6 to 17 years with 1 or more recent exacerbations.
• Guidelines-based therapy was continued over a 4- to 9-month run-in phase and a 4-month intervention phase.
Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations

Results:
• The fall exacerbation rate was significantly lower in the omalizumab versus placebo arm (11.3% vs 21.0%; OR, 0.48; 95% CI, 0.25-0.92)
• In a pre-specified subgroup analysis, among participants with an exacerbation during the run-in phase, omalizumab was significantly more efficacious than both placebo (6.4% vs 36.3%; OR, 0.12; 95% CI, 0.02-0.64)

Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations

• Cost of omalizumab is a limitation, but their findings help identify populations most likely to respond to pre-seasonal treatment.
• For those patients, the reduced cost of treatment for only the fall season to prevent an exacerbation compared with a full year of treatment might be justifiable.
• This suggests a paradigm shift for managing high-risk patients.

Teach JACI 2015:136:1476-85
Comorbidities

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

• I. Executive Summary
• II. Scope and purpose
• III. Introduction
• IV. Methods
• V. How to use these guidelines
• VI. Definition of Severe Asthma
  – Stage 1: Confirm asthma diagnosis and identify difficult-to-treat asthma *
  – Stage 2: Differentiate severe asthma from milder asthma *
  – Stage 3: Determine whether severe asthma is controlled or uncontrolled

Chung ERJ 2014;43:343-73
International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

• I. Executive Summary
• II. Scope and purpose
• III. Introduction

**consider comorbidities, poor inhaler technique and adherence to rx**

IV. Definition of Severe Asthma

– Stage 1: Confirm asthma diagnosis and identify difficult-to-treat asthma *
– Stage 2: Differentiate severe asthma from milder asthma*
– Stage 3: Determine whether severe asthma is controlled or uncontrolled

Chung ERJ 2014;43:343-73

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**TABLE 7 Comorbidities and contributory factors**

<table>
<thead>
<tr>
<th>Comorbidities and contributory factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Rhinosinusitis (adults) nasal polyps</td>
</tr>
<tr>
<td>2) Psychological factors: personality trait, symptom perception, anxiety, depression</td>
</tr>
<tr>
<td>3) Vocal cord dysfunction</td>
</tr>
<tr>
<td>4) Obesity</td>
</tr>
<tr>
<td>5) Smoking/smoking related disease</td>
</tr>
<tr>
<td>6) Obstructive sleep apnoea</td>
</tr>
<tr>
<td>7) Hyperventilation syndrome</td>
</tr>
<tr>
<td>8) Hormonal influences: premenstrual, menarche, menopause, thyroid disorders</td>
</tr>
<tr>
<td>9) Gastro-oesophageal reflux disease (symptomatic)</td>
</tr>
<tr>
<td>10) Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), β-adrenergic blockers, angiotensin-converting enzyme inhibitors</td>
</tr>
</tbody>
</table>

Chung ERJ 2014;43:343-73
Chronic Rhinosinusitis (CRS)

- Inflammatory disorder of the nasal mucosa and paranasal sinuses, characterized by at least 12 weeks of symptoms
- US prevalence: 3.0% to 6.4%


- With significant downstream issues
  - More asthma and allergic rhinitis diagnoses
  - Greater utilization of OCS and macrolides
  - More office and ambulatory care visits
  - Overall healthcare cost burden in the US: $5.7 billion


Dupilumab

**LIBERTY NP SINUS-24**

![Graph showing the effect of Dupilumab on nasal polyp score and nasal congestion or obstruction.](image-url)

Phase 3 Investigations of Biologics for CRSwNP (*ClinicalTrials.gov*)

- **Omalizumab**
  - Phase 3 [NCT03280550, NCT03280537]
  - Open-label extension study ongoing [NCT03478930]
- **Benralizumab**
  - (ORCHID) [NCT04157335]
- **Mepolizumab**
  - Phase 3 SYNAPS, [NCT03085797]

Nonadherence: Intentional and Unintentional

*Biologic therapy is not a replacement for adherence*

*Barnes PJ. Chest 2017; 151: 17–20*
Adherence to Asthma Controller Therapies

• Overall adherence is ≤70%
  – 6%–44% rate of failure to fill initial prescription\(^1\)
  – ICS used as directed <50% of the time, with range of 0%–98%\(^2\)
  – Reported adherence to LTRAs ranges from 18%–68%\(^3,4\)
• In treatment failures, nonadherence should be considered a possible cause


Adherence - Decline in Corticosteroid Use in Adults After Hospital Discharge

• ICS and OCS use fell to ≈50% by day 7
• Poor ICS adherence in 40.8% of patients 14 days after discharge
• Poor OCS adherence in 27.1% of patients over 7 days

ICS = inhaled corticosteroid; OCS = oral corticosteroid.

Critical Errors in Inhaler Technique among Children Hospitalized with Asthma

- Conducted a prospective cross-sectional study in a tertiary children's hospital for children 2-16 years of age admitted for an asthma exacerbation, and inhaler technique demonstrations were evaluated in attempt to identify risk factors of improper use.

- Of 113 participants enrolled, 55% had uncontrolled asthma, and 42% missed a critical step in inhaler technique.

- More patients missed a critical step when they:
  - used a spacer with mouthpiece instead of a spacer with mask (75% vs 36%)
  - were older (7.8 vs 5.8 years).

Samady JI of Hosp Med 2019

BACKGROUND:
- Biologic therapy is associated with concerns for therapy-associated anaphylaxis which may limit access to these therapies for patients unable to travel to medical clinics, especially with concerns regard CV19.

OBJECTIVE:
- To characterize the cost-effectiveness of in-clinic versus at-home biologic therapy with omalizumab and mepolizumab.

METHODS:
- Economic evaluation using microsimulations was performed from societal and health care sector perspectives for patients with asthma or chronic spontaneous urticaria receiving omalizumab or mepolizumab in an allergy clinic, primary care provider (PCP) office, or at home over a 1-year period.

Shaker JACI in Pract 2020;8:565-72
RESULTS:

- In the omalizumab societal analysis, annual PCP and allergy clinic administration cost $1369.14 (mean) +/− $51.33 (SD) and $1916.68 +/− $40.86, respectively.
- Small reductions in medication-related fatalities with in-clinic administration were offset by the potential increase in automobile fatalities resulting from traveling to the allergy clinic (14.6 – 15.0 per million person-years for this strategy).

- Routine mepolizumab clinic administration was dominated by at-home administration unless anaphylaxis rates or self-administration teaching costs were high.

CONCLUSIONS:

- For many patients, at-home administration of omalizumab or mepolizumab may be a cost-effective strategy.
Asthma Patients Who Stop Asthma Biologics Have a Similar Risk of Asthma Exacerbations as Those Who Continue Asthma Biologics

OBJECTIVE:
• There is limited information about outcomes associated with stopping asthma biologics.
• To compare outcomes in people who stopped or continued asthma biologics.

METHODS:
• Identified a cohort of people with asthma who stopped or continued asthma biologics exploring multiple potential confounders.
• Primary outcome used to assess failure of stopping was an increase of 50% or more in the asthma exacerbation rate in the 6 months after discontinuing the biologic compared with the 6-month period before biologic initiation.

RESULTS:
• Identified a matched cohort of 1247 stoppers and 1247 people who continued biologic use for at least 18 months.
• In the first 6 months after stopping, 10.2% of stoppers and 9.5% of continuers had an increase of 50% or more in asthma exacerbations.

CONCLUSIONS:
• An increase in asthma exacerbations is infrequently observed in people who stopped asthma biologics and was observed at similar rates as in matched controls who continued asthma biologics.
Asthma Patients Who Stop Asthma Biologics Have a Similar Risk of Asthma Exacerbations as Those Who Continue Asthma Biologics

Discussion:

- Previous randomized trials with omalizumab and mepolizumab in which a group had their biologic discontinued demonstrated a consistent pattern of a small but statistically significant increase in asthma exacerbations in people randomly assigned to stop the biologic agent.
  - Ledford JACI 2017;140:162-169
  - clinicaltrials.gov/ct2/show/NCT02555371.
- The findings of this suggest that patients and their doctors who choose to stop biologics appear to be making appropriate decisions.
- Furthermore:
  - this cohort had low estimated ICS/LABA treatment consistency before starting biologic treatment, with an average MPR below 40%*.
  - more than half of the cohort did not experience an exacerbation in the 6 months before index biologic use.

*The medication possession ratio = sum of days supplied for use during the period divided by the number of days in the period

Jeffery JACI in Pract 2021;9:2742-50
Putting All the Data Together in the Real World

• Severe asthma is very costly

• Before use of biologics consider:
  – Non-adherence
  – Treatment of comorbidities
  – Most likely phenotypes to respond
  – Most appropriate time and place to use
  – Appropriate patient selection with consideration of d/c

• Physicians must appropriately use of biologic agents in a personalized medicine approach, otherwise we will bankrupt the system