Difficult Asthma II
Cased-based discussion
Focus on Advanced Therapies

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Sandy Khurana, MD, FCCP
Disclosures

Cowl:
None

Khurana:
Grant support – GSK, Sanofi

We will not be discussing off-label use for any drugs or devices
Learning Objectives

• Review heterogeneity in asthma and understand the concept of cluster analysis

• Review the pathophysiologic mechanisms that form the basis for biologics in asthma

• Describe how phenotypes and endotypes can be used to choose targeted therapy in asthma

• Discuss the approach to the patient with severe asthma and choosing the appropriate advanced therapy
Outline

Cowl
  • Case
  • Overview of pathophysiology, phenotypes and biomarkers

Khurana
  • Case
  • Selection and efficacy of advanced therapies
Jim: A 38-year-old man with asthma

- Jim is a never-smoker
- Diagnosed with asthma at age 3
- Asthma was mild during childhood and teenage years; worsened in his 20s, following an episode of pneumonia
- Recent 5 ED visits and 2 hospitalizations over past 2 years. Intubated twice in his lifetime.
- He reports daily cough, wheeze and shortness of breath. Asthma control test score is 11.

- Current medications include: Inhaled corticosteroid + long-acting β-agonist (ICS/LABA), long-acting muscarinic antagonist (LAMA), leukotriene modifier (LTM), antihistamine, intranasal corticosteroids, and proton pump inhibitor. He is also currently completing a prednisone taper for acute asthma.
Jim: A 38-year-old man with asthma

- Moved in with his parents two years ago after his first intubation/ICU admission
- His parents own a cat. The entire house is carpeted.
- Allergy skin testing during childhood was positive for multiple environmental allergens. He tried allergy shots (immunotherapy) for 2 years with some improvement.

- Physical Exam:
  - Normal vital signs. BMI 26.
  - Erythematous nasal mucosa, no polyps or exudate
  - No stridor
  - Good air movement b/l, clear to auscultation
What will be your next step in evaluating Jim’s asthma?

A. Pre- and Post- bronchodilator spirometry
B. Methacholine challenge test
C. High resolution CT chest
D. FeNO
What will be your next step in evaluating Jim’s asthma?

A. Pre- and Post- bronchodilator spirometry  
B. Methacholine challenge test  
C. High resolution CT chest  
D. FeNO
Case continued

<table>
<thead>
<tr>
<th>Spirometry (BTPS)</th>
<th>AT Actual</th>
<th>Predicted</th>
<th>% Pred</th>
<th>CI Range</th>
<th>Pre Bronchodilator</th>
<th>Post Bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Actual</td>
<td>% Pred</td>
</tr>
<tr>
<td>FEV₁</td>
<td>L 1.88</td>
<td>3.86</td>
<td>49</td>
<td>3.14</td>
<td>4.58</td>
<td>A</td>
</tr>
<tr>
<td>FVC</td>
<td>L 2.97</td>
<td>4.81</td>
<td>62</td>
<td>3.96</td>
<td>5.66</td>
<td>A</td>
</tr>
<tr>
<td>FEV₁ / FVC</td>
<td>% 63</td>
<td>80</td>
<td>79</td>
<td>70</td>
<td>90</td>
<td>A</td>
</tr>
<tr>
<td>FEF25-75</td>
<td>L/s 1.06</td>
<td>3.74</td>
<td>28</td>
<td>2.28</td>
<td>5.20</td>
<td></td>
</tr>
<tr>
<td>PEF₁</td>
<td>L/s 5.67</td>
<td>9.51</td>
<td>60</td>
<td>7.40</td>
<td>11.62</td>
<td></td>
</tr>
<tr>
<td>FIF50</td>
<td>L/s 1.52</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>MVV</td>
<td>L/m -----</td>
<td>157.3</td>
<td>-----</td>
<td>100.5</td>
<td>214.1</td>
<td></td>
</tr>
</tbody>
</table>

Flow Volume
- Pre Rₓ
- Post Rₓ
- Predicted

Volume (L)

Volume Time
- FVC = 2.97
- FEF25-75 = 2.59
- PEF₁ = 2.23

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Jim: A 38-year-old man with asthma

- You confirm adherence and inhaler technique
- You identify and mitigate triggers
- You optimize management of comorbidities: GERD and CRS

- Asthma remains uncontrolled on current asthma regimen:
  - Inhaled corticosteroid
  - Long-acting beta agonist
  - Long-acting muscarinic antagonist
  - Leukotriene modifier (LTM)
  - Antihistamine
  - Nasal steroids
  - Proton pump inhibitor
What is true regarding the definition of phenotype vs endotype?

A. A phenotype is the inflammatory pathway producing the endotype
B. A phenotype is a collection of clinical characteristics; the endotype is the mechanism producing the phenotype
C. There is one endotype for every phenotype
D. Multiple phenotypes are associated with an endotype
What is true regarding the definition of phenotype vs endotype?

A. A phenotype is the inflammatory pathway producing the endotype
B. A phenotype is a collection of clinical characteristics; the endotype is the mechanism producing the phenotype
C. There is one endotype for every phenotype
D. Multiple phenotypes are associated with an endotype
Terminology & Definitions

**Phenotype:** Observable characteristic/traits

**Endotype:** Distinct pathophysiology that provides insight into mechanism

**Biomarker:** Measurable indicator of biologic state
Selected asthma sub-phenotypes

- T2-type asthma
  - Allergic asthma
  - Late-onset eosinophilic asthma
  - Very late-onset asthma (women)

- Non-T2-type asthma
  - Obesity-associated asthma
  - Smooth-muscle-mediated paucigranulocytic asthma
  - Smoking-related neutrophilic asthma

Childhood-onset asthma

Adult-onset asthma

Nature Reviews | Disease Primers

Wenzel Nature Medicine 2012
Holgate Nat. Rev. Dis. Primers 2015
Severe Asthma Research Program (SARP) clusters

726 subjects in Severe Asthma Research Program

628 total variables reduced to 34 core variables

Unsupervised hierarchical cluster analysis

Five major phenotypes emerged

1. Younger, mild childhood onset, atopic
2. Older, childhood onset, atopic, moderate severity
3. Older women, high BMI, late-onset, non-atopic
4. Severe, earlier onset, reversible obstruction
5. Severe, later onset, fixed obstruction

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Moore et al. AJRCCM 2010
What additional information will help guide further treatment for your patient?

A. Allergy testing & IgE level
B. Blood eosinophil count
C. Serum periostin level
D. A and B
What additional information will help guide further treatment for your patient?

A. Allergy testing & IgE level
B. Blood eosinophil count
C. Serum periostin level
D. A and B
Other controller options

RELIEVER

PREFERRED CONTROLLER CHOICE

Low dose ICS

Consider low dose ICS

Leukotriene receptor antagonists (LTRA)
Low dose theophylline*

As-needed short-acting beta₂-agonist (SABA)

Med/high dose ICS
Low dose ICS/LABA**

Add tiotropium*

Med/high dose ICS/LABA (or + theoph*)
Add low dose OCS

As-needed SABA or low dose ICS/formoterol#

Add-on treatment

STEP 5

Source: ginaasthma.org
Personalized approach to asthma


BIOMARKERS
Type 2 inflammation in asthma

Robinson et al. Clinical & Experimental Allergy
2017
Biomarkers in T2 asthma

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Eos</td>
<td>Allergic &amp; Eosinophilic Asthma Increased exacerbations and poor lung function</td>
</tr>
<tr>
<td>Blood Eos</td>
<td>Allergic &amp; Eosinophilic asthma Increased exacerbations and poor lung function</td>
</tr>
<tr>
<td>IgE</td>
<td>Allergic asthma</td>
</tr>
<tr>
<td>FeNO</td>
<td>Indicator of oxidative and nitrative stress</td>
</tr>
<tr>
<td></td>
<td>Allergic &amp; eosinophilic asthma</td>
</tr>
<tr>
<td>Periostin</td>
<td>Potentially allergic &amp; eosinophilic asthma</td>
</tr>
</tbody>
</table>


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Asthma is a complex heterogeneous condition

Best understood in terms of underlying phenotypes (observable characteristics) and endotypes (specific biologic mechanisms)

Biomarkers can provide information about the disease as well as targeted therapy

Many biomarkers available for Type 2 asthma including sputum eosinophils, FeNO, blood eosinophils, IgE level

No biomarkers currently available for non-Type 2 asthma and this is an area of great need
Back to our patient…
Jim – A 38-year-old man with severe asthma

- Childhood asthma
- Uncontrolled on ICS, LABA, LAMA, LTM
- Frequent exacerbations
- Moderate airflow obstruction on spirometry with reversibility
- Adherence, triggers, comorbidities addressed and optimized

- Additional diagnostic tests performed
Scenario 1

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>WBCs</td>
<td>7.7 K/µL</td>
</tr>
<tr>
<td>Eos (%)</td>
<td>3.6</td>
</tr>
<tr>
<td>Absolute Eos</td>
<td>277 cells/µL</td>
</tr>
<tr>
<td>IgE</td>
<td>386 kU/L</td>
</tr>
<tr>
<td>FeNO</td>
<td>14 ppb</td>
</tr>
</tbody>
</table>

Multiple positives on blood test for allergies
- Dustmites
- Seasonal molds
- Trees
- Pollen
- Ragweed
- Cats
- Dogs
Which of the following therapies would you add to this patient’s current regimen?

A. Mepolizumab
B. Omalizumab
C. Dupilumab
D. Lebrikizumab
E. None of the above
Which of the following therapies would you add to this patient’s current regimen?

A. Mepolizumab
B. Omalizumab
C. Dupilumab
D. Lebrikizumab
E. None of the above
Allergic Asthma - Omalizumab

Robinson et al. Clinical & Experimental Allergy 2017
Omalizumab Decreases Asthma Exacerbations

Analysis 1.2. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid).
Outcome 2 Exacerbations requiring oral steroids.

Review: Omalizumab for asthma in adults and children.
Comparison: 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid)
Outcome: 2 Exacerbations requiring oral steroids

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log [Rate Ratio] (SE)</th>
<th>Rate Ratio</th>
<th>Weight</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IV/Fixed, 95% CI</td>
<td></td>
<td>IV/Fixed, 95% CI</td>
</tr>
<tr>
<td>Moderate to severe asthma (ICS + mixed treatments)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INNOVATE</td>
<td>-0.6931 (0.2225)</td>
<td>60.1 %</td>
<td>0.50 [0.32, 0.78]</td>
<td></td>
</tr>
<tr>
<td>Lanier 2009</td>
<td>-0.5978 (0.2763)</td>
<td>39.9 %</td>
<td>0.55 [0.32, 0.95]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0.00%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.75 (P = 0.0017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe asthma (ICS + LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanania 2011</td>
<td>-0.4155 (0.1965)</td>
<td>100.0 %</td>
<td>0.66 [0.45, 0.97]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.11 (P = 0.034)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe asthma (ICS + LABA + other treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanania 2011</td>
<td>-0.3285 (0.1573)</td>
<td>100.0 %</td>
<td>0.72 [0.53, 0.98]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>
Omalizumab Decreases Hospitalizations

**Analysis 1.3. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 3 Hospitalisations.**

**Review:** Omalizumab for asthma in adults and children.

**Comparison:** Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid)

**Outcome:** 3 Hospitalisations

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Omalizumab</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H fixed 95% CI</td>
<td></td>
<td>M-H fixed 95% CI</td>
</tr>
<tr>
<td>Moderate to severe asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busse 2001</td>
<td>1/268</td>
<td>2/257</td>
<td></td>
<td>7.1%</td>
<td>0.48 [0.04, 5.30]</td>
</tr>
<tr>
<td>Busse 2011</td>
<td>3/208</td>
<td>13/211</td>
<td></td>
<td>44.4%</td>
<td>0.22 [0.06, 0.79]</td>
</tr>
<tr>
<td>Migrom 2001</td>
<td>0/225</td>
<td>5/109</td>
<td></td>
<td>25.8%</td>
<td>0.04 [0.00, 0.77]</td>
</tr>
<tr>
<td>Soler 2001</td>
<td>0/274</td>
<td>6/272</td>
<td></td>
<td>22.7%</td>
<td>0.07 [0.00, 1.33]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>975</td>
<td>849</td>
<td></td>
<td>100.0%</td>
<td>0.16 [0.06, 0.42]</td>
</tr>
</tbody>
</table>

Total events: 4 (Omalizumab), 26 (Placebo)
Heterogeneity: Chi² = 2.13, df = 3 (P = 0.55); I² = 0.0%
Test for overall effect: Z = 3.77 (P = 0.00017)

**Severe asthma**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Omalizumab</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H fixed 95% CI</td>
<td></td>
<td>M-H fixed 95% CI</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 0 (Omalizumab), 0 (Placebo)
Heterogeneity: not applicable

---

Biomarkers Predict Response to Omalizumab


<table>
<thead>
<tr>
<th></th>
<th>Low FeNO at baseline</th>
<th>High FeNO 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>0.60</td>
<td>0.50</td>
<td>0.65</td>
<td>0.70</td>
<td>0.73</td>
<td>0.66</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.71</td>
<td>1.07</td>
<td>0.72</td>
<td>1.03</td>
<td>0.72</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Exacerbation rates

- FeNO: <19.5 ppb vs. ≥19.5 ppb
- Eosinophils: <260/μL vs. ≥260/μL
- Periostin: <50 ng/mL vs. ≥50 ng/mL

Percent reduction in protocol-defined asthma exacerbation rate (mean, 95% CI):

- FeNO: -16 (n = 193, P = 0.45*)
- Eosinophils: -9 (n = 383, P = 0.54*)
- Periostin: -32 (n = 414, P = 0.005*)

- FeNO: -53 (n = 201, P = 0.001*)
- Eosinophils: -3 (n = 279, P = 0.94*)
- Periostin: -30 (n = 255, P = 0.07*)

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Omalizumab: Duration of Therapy

Time to first exacerbation

Change in symptoms

# Omalizumab: Safety

The table below presents the incidence of events during the study periods.

<table>
<thead>
<tr>
<th>Event</th>
<th>Core study (32 weeks)</th>
<th>Extension 1 (96 weeks)</th>
<th>Extension 2 (52 weeks)</th>
<th>Extension 3 (104 weeks)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Omalizumab (n = 174)</td>
<td>Omalizumab (n = 222)</td>
<td>Omalizumab (n = 178)</td>
<td>Omalizumab (n = 118)</td>
</tr>
<tr>
<td>Any AE</td>
<td>136 (78.2)</td>
<td>195 (87.8)</td>
<td>134 (75.3)</td>
<td>78 (66.1)</td>
</tr>
<tr>
<td>Mild or moderate</td>
<td>120 (69.0)</td>
<td>156 (70.3)</td>
<td>115 (64.6)</td>
<td>71 (60.2)</td>
</tr>
<tr>
<td>Severe</td>
<td>16 (9.2)</td>
<td>39 (17.6)</td>
<td>19 (10.7)</td>
<td>7 (5.9)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>11 (6.3)</td>
<td>27 (12.2)</td>
<td>8 (4.5)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>6 (3.4)</td>
<td>26 (11.7)</td>
<td>4 (2.2)</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>
### Scenario 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBCs</td>
<td>7.7 K/µL</td>
</tr>
<tr>
<td>Eos (%)</td>
<td>6.3</td>
</tr>
<tr>
<td>Absolute Eos</td>
<td>570 cells/µL</td>
</tr>
<tr>
<td>IgE</td>
<td>53 kU/L</td>
</tr>
<tr>
<td>FeNO</td>
<td>35 ppb</td>
</tr>
</tbody>
</table>

Blood test for allergies negative
Which of the following therapies would you add to the patient’s current regimen?

A. Omalizumab
B. Mepolizumab
C. Dupilumab
D. Lebrikizumab
E. None of the above
Which of the following therapies would you add to the patient’s current regimen?

A. Omalizumab
B. Mepolizumab
C. Dupilumab
D. Lebrikizumab
E. None of the above
Eosinophilic Asthma: Anti-IL5 Therapy
(mepolizumab, benralizumab, reslizumab)

Robinson et al. Clinical & Experimental Allergy 2017
Mechanism of action of anti-IL5 therapies

Tan et al. Journal of Asthma and Allergy 2016:9 71–81
Mepolizumab decreases exacerbation rates in patients with severe eosinophilic asthma


Register now at congress.chestnet.org
Mepolizumab has a steroid-sparing effect in patients with asthma and blood eosinophilia

Reslizumab decreases exacerbations in patients with uncontrolled asthma and blood eosinophilia

Benralizumab reduces frequency of asthma exacerbations

Benralizumab reduces OCS dose in severe asthma

Scenario 3

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBCs</td>
<td>5.0 K/µL</td>
</tr>
<tr>
<td>Eos (%)</td>
<td>1.2</td>
</tr>
<tr>
<td>Absolute Eos</td>
<td>60 cells/µL</td>
</tr>
<tr>
<td>IgE</td>
<td>23 kU/L</td>
</tr>
<tr>
<td>FeNO</td>
<td>21 ppb</td>
</tr>
</tbody>
</table>

AND

OCS dependent
Which of the following therapies would you consider adding on in this patient?

A. Omalizumab
B. Lebrikizumab
C. Reslizumab
D. Dupilumab
E. None of the above
Which of the following therapies would you consider adding on in this patient?

A. Omalizumab
B. Lebrikizumab
C. Reslizumab
D. Dupilumab
E. None of the above
Dupilumab inhibits IL-4/IL-13

- IL-4 and IL-13 bind to a shared subunit, IL-4Rα.
- Dupilumab, a human monoclonal IgG4 antibody, binds to IL-4Rα, blocking both IL-4 and IL-13 signaling.
- IL-4 and IL-13 pathways have unique and overlapping functions.

*Illustration: Cytokine production, Signalling, Effects*

*Middleton’s allergy essentials*
*Robinson et al. Clinical & Experimental Allergy 2017*
Dupilumab reduces exacerbations in patients with uncontrolled asthma

Castro M. et al. NEJM 2018
Effect of dupilumab on exacerbation and lung function by baseline Eos and FeNO

Castro M. et al. NEJM 2018
Dupilumab reduced OCS use

Rabe KF. et al. NEJM 2018

Mean percent reduction in OCS dose at Week 24

Proportion of patients no longer requiring OCS at Week 24

Rabe KF. et al. NEJM 2018

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Summary

- Current biologics target patients with a T2 high phenotype
- Biomarkers of T2 inflammation can help to determine which therapies may be most efficacious
- Omalizumab treatment is effective in patients with atopic asthma
- Mepolizumab, benralizumab and reslizumab are effective in patients with eosinophilic asthma
- Dupilumab targets IL-4/IL-13 and is effective in patients with type 2 asthma
- Dupilumab, mepolizumab and benralizumab are effective in OCS-dependent asthma
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