Anti-IgE Treatment In Severe Asthma

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Relevant Disclosures

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  Amgen, Novartis, Genentech, NIH, State Of Nebraska

• Legal Consult/Expert Witness: None

• Organizational: EVP of AAAAI and BOD WAO

• Gifts: None

• Other: N/A
Objectives

- To explain the rationale behind IgE blockade
- To consider which patients benefit
- To address how to assess response to treatment
The First Question

• What is severe asthma?

• Answer:
  – Depends upon who is asking and why
WHO Definition Of Severe Asthma

- Defined by the level of current clinical control and risks which can result in frequent severe exacerbations and/or adverse reactions to medications and/or chronic morbidity.

- 3 groups, each carrying different public health messages and challenges.
  - Untreated severe asthma
  - Difficult to treat asthma
  - Treatment resistant severe asthma
    - Controlled on high dose medication
    - Not controlled on high dose medication

Bousquet et al, JACI 2010
2009 ATS/ERS Task Force On Severe Asthma Definition

• Asthma which requires treatment with high dose ICS (fluticasone $\geq$ 1000 mcg/d or equivalent) plus a 2nd controller (and/or systemic CS) to prevent a patient from becoming “uncontrolled” or which, despite high dose therapy, remains “uncontrolled“.
Uncontrolled Asthma

– Any one of the following:

• **Poor symptom control:** ACQ consistently >1.5 (or “not well controlled” by NAEPP guidelines)

• **Frequent exacerbations:** 2 or more bursts of systemic CSs (>3 days each) in previous year

• **Severe exacerbations:** at least 1 hospitalization, ICU stay or mechanical ventilation in previous yr

• **Persistent airflow limitation:** pre-short and long acting bronchodilator FEV1< 80% predicted (in the face of reduced FEV1/FVC)
Second Question

What Is the Role of IgE in Severe Asthma?
Prevalence of Asthma Related to Serum IgE Level Standardized for Age and Gender

Ranges of serum IgE Z score

Prevalence of Asthma (%)

- Age 6 to <35 years
- Age 35 to <55 years
- Age 55+ years

Longitudinal Association Between IgE & Lung Function in Adult Asthmatic Non-Smokers

The Relationship between IgE and FcεRI Expression

Fractional increase over Day 21

Incubation time (days)

Atopic asthmatics
Non-atopic asthmatics
Atopic controls
Non-atopic controls

FcεRI Expression Upregulated in Asthma

Expression of High-Affinity IgE Receptor Increased in Fatal Asthma

FCεRI receptor expression in lamina propria (+ cells/mm²)

<p>| | | | | | | | |</p>
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</thead>
<tbody>
<tr>
<td></td>
<td>Non-Pulmonary Deaths (n=9)</td>
<td>Mild Intermittent Asthma† (n=16)</td>
<td>Fatal Asthma (n=10)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>328</td>
<td>302</td>
<td>1085*</td>
<td></td>
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</tr>
</tbody>
</table>

*P<0.05 vs other groups.
†Biopsy

Mechanisms Of Action of Omalizumab

- ↓ airway eosinophils, mast cells, basophils, T + B lymphocytes
- ↓ IgE+, FcεRI+, IL-4+ cells in bronchial epithelium
- ↓ free IgE, IgE bound to FcεRI, and FcεRI expression on mast cells, basophils, dendritic cells, monocytes
- ↓ response to allergen skin test
- ↓ eNO
- ↓ Lung Ag Challenge
Omalizumab Down-Regulates FcεRI Expression on Dendritic Cells in SAR


*p<0.05; **p<0.01; ***p<0.001 vs Day 0
Effects Of Omalizumab On Airway Inflammation In Mild Atopic Asthmatics

- 5-center, double blind, placebo-controlled, parallel-group, 16-week study (n=44):
  - Reduction in submucosal eos: 8.0 to 1.5
  - 10-fold reduction in IgE+cells
    - Decreases in FCεRI cells
  - Decreases in B cells, and CD3+, CD4+, and CD8+ cells ....
    - Implies that IgE plays an important role in airway inflammation in asthma

R Djukanovic, et al, AJRCCM, 170:583, 2004
Omalizumab Decreases FcεRI in Bronchial Biopsies

Omalizumab Significantly Reduces Submucosal Eosinophils

Clinical Effects Of Omalizumab: Pooled data from 7 trials

- In patients on ICS alone, or in combination with other agents, addition of omalizumab:
  - Reduced number of exacerbations
  - Reduced symptom scores
  - Reduced need for inhaled corticosteroids
  - Reduced use of rescue medication
  - Improved asthma-related quality of life

- Consider using in patients with poor control despite optimal care

### Effects Of Omalizumab On Exacerbations

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Omalizumab</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Busse 2001</td>
<td>39</td>
<td>268</td>
<td>60</td>
<td>257</td>
</tr>
<tr>
<td>Holgate 2004</td>
<td>13</td>
<td>126</td>
<td>15</td>
<td>120</td>
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<tr>
<td>Humbert 2005</td>
<td>35</td>
<td>246</td>
<td>55</td>
<td>236</td>
</tr>
<tr>
<td>Lanier 2009</td>
<td>56</td>
<td>384</td>
<td>59</td>
<td>192</td>
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<tr>
<td>Milgrom 2001</td>
<td>35</td>
<td>225</td>
<td>25</td>
<td>109</td>
</tr>
<tr>
<td>Ohta 2009</td>
<td>6</td>
<td>151</td>
<td>18</td>
<td>164</td>
</tr>
<tr>
<td>Soler 2001</td>
<td>35</td>
<td>274</td>
<td>83</td>
<td>272</td>
</tr>
<tr>
<td>Vignola 2004</td>
<td>43</td>
<td>209</td>
<td>59</td>
<td>198</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1883</strong></td>
<td><strong>1546</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>202</strong></td>
<td><strong>274</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.01; \quad \chi^2 = 8.15, \quad df = 7 (P = 0.32); \quad I^2 = 14\%$

Test for overall effect: $Z = 7.06 (P < 0.00001)$

G Rodrigo et al, Chest, 2010
<table>
<thead>
<tr>
<th>Outcome</th>
<th>References</th>
<th>N</th>
<th>Omalizumab vs. placebo</th>
<th>Measure 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean rescue medication (puffs/day) (Stable phase)</td>
<td>11,23,25-27</td>
<td>2285</td>
<td>*2.27 vs.2.76</td>
<td>WMD = -0.52 (-0.79,-0.25)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Final pulmonary function (FEV$_1$ or PEF) (Stable phase)</td>
<td>23-26</td>
<td>1651</td>
<td>*†3.82 vs. 3.63</td>
<td>*†SMD = 0.07 (-0.03,017)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean change from baseline in morning PEF (L/m) (Stable phase)</td>
<td>12,23,27</td>
<td>1245</td>
<td>*15.0 vs.3.05</td>
<td>WMD = 11.8 (8.1,15.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asthma symptom score (Stable phase)</td>
<td>11,23,25-27</td>
<td>1893</td>
<td>*1.53 vs.1.71</td>
<td>WMD = -0.30 (-0.40,-0.20)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean change in AQLQ score (Stable phase)</td>
<td>23,25-28</td>
<td>2131</td>
<td>*0.37 vs.0.06</td>
<td>WMD = 0.33 (0.28,0.37)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean rescue medication (puffs/day) (Steroid reduction phase)</td>
<td>23,25-26</td>
<td>1291</td>
<td>*2.27 vs.2.76</td>
<td>WMD = -0.73 (-1.04,-0.42)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

G Rodrigo et al, Chest, 2010
Omalizumab effect was independent of:

- Duration of treatment
- Age
- Severity of asthma
Omalizumab In Children 6 - 11

Avg FP dose 515 mcg
2/3 on LABA
1/3 on LTRA

Lanier et al. JACI.2009;124:1210-6
Effects Of Omalizumab In Elderly

All on high dose ICS & 50% on OCS

Steps of Therapy: Age ≥12 Years

**Step 1**
Preferred: SABA PRN

**Step 2**
Preferred: Low-dose ICS
Alternative: Cromolyn, LTAB, Nedocromil, or Theophylline

**Step 3**
Preferred: Medium-dose ICS
Alternative: Low-dose ICS + either LTAB, Theophylline, or Zileuton

**Step 4**
Preferred: High-dose ICS + LABA
Alternative: Medium-dose ICS + either LTAB, Theophylline, or Zileuton

**Step 5**
Consider Omalizumab for patients who have allergies

**Persistent Asthma: Daily Medication**
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

**Quick-Relief Medication for All Patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Step up if needed (first, check adherence, environmental control, and comorbid conditions)
Assess control
Step down if possible (and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
Steps ≥4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes)
Steps of Therapy: Age ≥12 Years

**Steps of Therapy:**

**Intermittent Asthma**
- Consult with asthma specialist if step 4 care or higher is required.
- Consider consultation at step 3.

**Step 1**
- **Preferred:** Low-dose ICS
- **Alternative:** Cromolyn, LTRA, Nedocromil, or Theophylline
- SABA PRN

**Step 2**
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 3**
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 4**
- **Preferred:** High-dose ICS + LABA
- **Alternative:** Low-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 5**
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Medium-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 6**
- **Preferred:** High-dose ICS + LABA + oral corticosteroid
- Consider Omalizumab for patients with allergies

*Step up if needed (first, check adherence, environmental control, and comorbid conditions)*

*Step down if possible (and asthma is well controlled at least 3 months)*

**Quick-Relief Medication for All Patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

**Assess control**

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).
# Dosing Table:
0.016 mg/kg/IU/mL every 4 weeks

<table>
<thead>
<tr>
<th>Monthly Dosing</th>
<th>Body Weight (kg)</th>
<th>30-60</th>
<th>&gt; 60-70</th>
<th>&gt; 70-80</th>
<th>&gt; 80-90</th>
<th>&gt; 90-150</th>
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<tr>
<td>Baseline IgE</td>
<td>IU/mL</td>
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<td></td>
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<tr>
<td>30-100</td>
<td></td>
<td>150</td>
<td>150</td>
<td>150</td>
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<td>300</td>
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<tr>
<td>&gt;100-200</td>
<td></td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
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<tr>
<td>&gt; 200-300</td>
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</table>

<table>
<thead>
<tr>
<th>Biweekly Dosing</th>
<th>450</th>
<th>450</th>
<th>450</th>
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<th>600</th>
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<tbody>
<tr>
<td>&gt; 100-200</td>
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<td>&gt; 200-300</td>
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<td>&gt; 300-400</td>
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<td>&gt; 400-500</td>
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<td>&gt; 500-600</td>
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<td>&gt; 600-700</td>
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Omalizumab Onset Of Action In Asthma

Asthma trials suggest that 8 to 16 weeks of treatment might be a reasonable therapeutic trial:

- While the onset of response was measurable at 4 weeks, the proportion of responders continued to increase throughout the 16 week period:
  - 4 wks: 61%
  - 8 wks: 78%
  - 12 wks: 87%
Factors Predictive of Response to Omalizumab

*Relative Rate (Confidence Interval)

BDP dose $\geq 800 \, \mu g/day$

$1.87^*$

(0.88 – 3.99)$^\circ$

N = 120

2.25

(1.02 – 4.97)

N = 103

3.54

(1.69 – 7.43)

N = 124

1.15

(0.54 – 2.44)

N = 114

4.20

(1.69 – 10.45)

N = 85

1.60

(0.75 – 3.42)

N = 119

3.38

(1.32 – 8.66)

N = 77

FEV$_1 \leq 65\%$ predicted

History of emergency asthma treatment in past year

Adequate IgE Suppression is Needed to Demonstrate Clinical Response

Serum free IgE (ng/mL)

Average nasal severity scores

**p<0.002 vs placebo

Casale, JAMA ‘01
Factors Predictive Of Clinical Response

- Reasons for omalizumab being ineffective for some (~40%) patients are unknown.
- Improvements correlate with IgE reductions, BUT free IgE levels in nonresponders are similar to those found in responders\(^1\)
- Possible reasons:\(^2\)
  1. Relationship between free IgE levels and Fc\(\varepsilon\)R1 expression
  2. Ratio of specific IgE to total IgE
  3. Intrinsic cellular sensitivity.

2. MacGlashan. JACI 2009;23: 114
Do the Effects Of Omalizumab Continue After Treatment Is Stopped?

• Conflicting data, but may depend upon duration of treatment

• 2 different studies with 2 different answers:
  1. INvestigation of Omalizumab in seVere Asthma TrEatment (INNOVATE) study
  2. Nopp et al, 2010 Allergy
28-week Omalizumab Treatment And 16-week Follow-up

N=476,
Dark=Omal, Light=Pl

Effects Of Omalizumab On Asthma Control 3 Years After 6 Years Treatment

A Nopp et al, Allergy 2010
Omalizumab and Asthma Summary

- Omalizumab is effective in children and adults in reducing exacerbations and steroid requirements
  - Also positive effects on SABA use, QOL, Sxs and PFTs (minor)
- Omalizumab has anti-inflammatory effects
- If not effective by 4-6 months, probably will not be effective
  - Predictors of who will respond are unclear
- Whether omalizumab can be stopped with sustained clinical efficacy is unclear
  - May depend on duration of treatment
Other Potential Clinical Uses of Omalizumab In Asthma

- SAR and PAR +/- Asthma
- Non-allergic Asthma
- ABPA

- Adjuvant to Traditional Immunotherapy:
  - Increased Efficacy As Add On in SAR
  - Improved Safety As Pretreatment:
    - 80% Decr In RIT Assoc Anaphylaxis in SAR
    - 50% Decr In Cluster Assoc AEs in Asthma
Omalizumab and Immunotherapy: Study Design

150 Patients per arm, Randomized 1:1

Study Design

Omalizumab and Immunotherapy:

150 Patients per arm, Randomized 1:1

Visit 0: -2wks
Visit 1: 0
Visit 5: 13wks
Visit 11: 16wks
Visit 14: 17wks
Visit 19: 24wks

Persistent perennial allergic asthmatics requiring ICS & FEV1 ≥ 75%
Proportion of Patients Who Experienced A Systemic Allergic Reaction: Primary Endpoint

- Placebo: N = 122, 26.2% (P = 0.017)
- Omalizumab: N = 126, 13.5% (N = 32, N = 17)

M Massanari et al, JACI, 2010
Severity of First Systemic Allergic Reaction

<table>
<thead>
<tr>
<th>Grade</th>
<th>Placebo (n=32)</th>
<th>Omalizumab (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (Skin)</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Grade 2 (GI)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Grade 3 (Resp)</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Grade 4 (CV)</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

M Massanari et al, JACI, 2010
Omalizumab and IT Conclusions

• Pretreatment with omalizumab:
  • Added Efficacy to SCIT
  • Added Safety to SCIT
  • Allowed more patients to reach maintenance
    • 87 vs. 72% (p<0.01)

• Unanswered questions:
  • How long do you need to treat with both?
  • Can you stop the omalizumab after reaching maintenance IT?
Omalizumab Safety Issues

- Anaphylaxis
- Cancer
- Cardiovascular
- Other?
Major Unanswered Question

- If Anti-IgE Prevents Anaphylaxis By Decreasing Circulating and Bound IgE.....

- And IgE is essential for development of anaphylaxis........

How does it cause anaphylaxis?????
- Incidence ~0.1 to 0.2%
Conclusions

- Since IgE plays an important role in a number of diseases, strategies aimed at blocking the effects of it will likely prove important.....
  - Not just for asthma and rhinitis

- Omalizumab has many potential therapeutic applications
  - On going safety issues need to be monitored

- Small, easy to make and deliver antagonists should be pursued, especially those that....
  - Induce tolerance