**Immunomodulators: Anti-IgE mAb**

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**Objectives**
- To explain the rationale behind IgE blockade
- To discuss which patients might benefit from omalizumab
- To explain dosing issues for omalizumab
- To address potential adverse effects of omalizumab
- To compare to immunotherapy

**Omalizumab Indications**
- **(Moderate) to severe persistent asthma in** patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS +/- LABA.
- Step 5/6 care (NHLBI) or 4/5 (GINA)

**What Is the Role of IgE in Severe Asthma?**

**IgE-Mediated Allergic Reactions**

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

![Graph showing longitudinal association between IgE and lung function in adult asthmatic non-smokers.](image)
Mechanisms Of Action of Omalizumab

- eNO
- Lung Ag Challenge
- Increased airway eosinophils, mast cells, basophils, T + B lymphocytes
- Increased IgE+, FcεRI+, IL-4+ cells in bronchial epithelium
- Increased free IgE bound to FcεRI
- Increased expression on mast cells, basophils, dendrites, CD3+

Mechanisms Of Action of Omalizumab

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

- Impacts that IgE plays an important role in airway inflammation in asthma
  - Djukanovic, et al, AJRCCM, 170:583, 2004

Effects Of Omalizumab On Eos & FEV1 In Severe (Step 4/5) Asthma

- Before Rx
- After Rx
- Omal
- Placebo
- FEV1

Changes In Airway Measurements After 16 Weeks Of Treatment

- Hoshino & Ohtawa, Respiration: 01/12

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 (40-50%)
  - 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

Asthma Exacerbations Over 48 Weeks In EPR3 Step 5/6

Omalizumab effect appears independent of:

- Duration of treatment
- Age
- Severity of asthma

Why Not For Acute Bronchospasm Or Status Asthmaticus?

Omalizumab Onset Of Action In Asthma: Pivotal Trials: While 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%

Respiratory data suggest that down regulation of FcεRI expression on effector cells is required for clinical inhibition of allergic respiratory responses.

Omalizumab Not Indicated

- Acute bronchospasm or status asthmaticus
- Pediatric patients less than 12 years of age
- Nonallergic asthma
- Other allergic conditions

Why Not Nonallergic Asthma? The Case For Entopy

- Nasal mucosa: allergic & “nonallergic” rhinitis & CFS
  - Nasal Polyps (also can involve Staph)
- Bronchial mucosa: Predominately in asthma
  - Regardless of atopic status
  - Possibly due to superantigens (Staph enterotoxins)
  - Related to asthma severity
- Clinical implications: Strategies aimed at blocking IgE locally could be fruitful

### Mean Change From Baseline In AQLQ After 16 Weeks Of Omalizumab In Asthmatics with Nasal Polyps

![Graph showing mean change from baseline in AQLQ after 16 weeks of Omalizumab in asthmatics with nasal polyps.](image)

Gevaert, JACI, 2012

### 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.
- Possible reasons:
  1. Relationship between free IgE levels and FcεRI expression
  2. Ratio of specific IgE to total IgE
  3. Intrinsic cellular sensitivity.
- Recent data indicate that response at 16 wks is highly predictive of persistent response at 32 wks.


### Dosing Table: 0.016 mg/kg/IU/mL every 4 weeks

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<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Monthly Dosing</th>
<th>Biweekly Dosing</th>
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<tr>
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<td>300</td>
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<tr>
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<td>&gt;900-1500</td>
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### Multiplicity of Antigenic Specificity as a Predictor of Therapeutic Success

- Low specific IgE/total IgE
- High specific IgE/total IgE

### 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, Darks=Omal, Light=Pl

![Graph showing 28-week Omalizumab treatment and 16-week follow-up.](image)
**Effects Of Omalizumab On Asthma Control 3 Years After 6 Years Treatment**

- 1 year
- 3 year

**Potential Clinical Uses of Omalizumab**
- SAR and PAR
- Atopic Dermatitis
- Food Allergy
- Insect Allergy
- Chronic Urticaria with and w/o Autoantibodies
- Adjuvant to Immunotherapy:
  - Increased Efficacy As Add On
  - Improved Safety As Pretreatment for SCIT and food SLIT

**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

**Treatment of Chronic Antihistamine-Resistant Urticaria with Omalizumab**

**What About Pretreatment In Patients With Asthma?**

A 26-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the effect of Xolair® (omalizumab) on improving the tolerability of specific immunotherapy in patients with at least moderate persistent allergic asthma* inadequately controlled with inhaled corticosteroids

- FEV1 ≥ 75%
- + ST to HDM, cat or dog

**Omalizumab and Immunotherapy: Study Design**

150 Patients per arm, Randomized 1:1

- Screening
- Visit 0
- Visit 1
- Visit 5
- Visit 11
- Visit 14
- Visit 19
- Visit 24

**Omalizumab Cluster IT**
**Maintenance IT**

**Omalizumab and Immunotherapy: Placebo Cluster IT**
**Maintenance IT**

**Sarbjit Saini et al. JACI, 2011**

**Massarani et al, JACI 2010**
**Proportion of Patients Who Experienced A Systemic Allergic Reaction: Primary Endpoint**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Omalizumab</th>
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<tr>
<td>26.2%</td>
<td>13.5%</td>
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<td>N = 122</td>
<td>N = 126</td>
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</table>

*P = 0.017*

**Additional Potential Uses Of Omalizumab**
- ABPA
- AERD with NSAID tolerance
- Latex allergy
- Chronic hyperplastic sinusitis
- Recurrent nasal polyposis
- Non-allergic asthma
- Drug Allergy
- Idiopathic anaphylaxis
- Others

**Omalizumab Warnings & Precautions:**

- **Safety Issues**
  - Anaphylaxis (Incidence ~0.1 to 0.2%)
  - Cancer...NO
  - Serum Sickness...Rare
  - Churg-Strauss Syndrome....?
  - Cardiovascular......NO/?
  - Other......?

**Omalizumab vs. Immunotherapy**

- Cost
- Safety
- Efficacy
- Ease of Use
- Severe asthma
- Scope of diseases
- Duration of effects
  - Immunomodulation

**Proportion Of Patients With Reported Anaphylaxis Due To Omalizumab During Recommended Observation Times**

- 1-3 Doses, <2Hrs: 1%
- >3 Doses, <30 Min: 1%
- 1 Dose, <2Hrs: 3Doses, <2Hrs: 3Doses, <30 Min: 3Doses, <30 Min