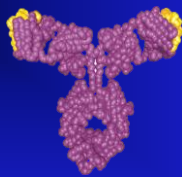


Immunomodulators: Anti-IgE mAb



Thomas B. Casale, MD
Professor of Medicine
Chief, Allergy/Immunology
Creighton University
Omaha, NE

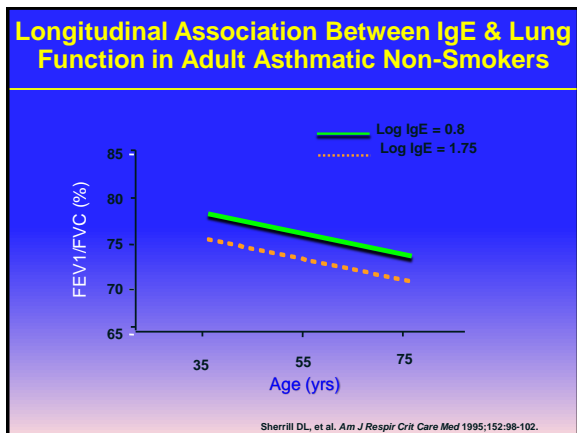
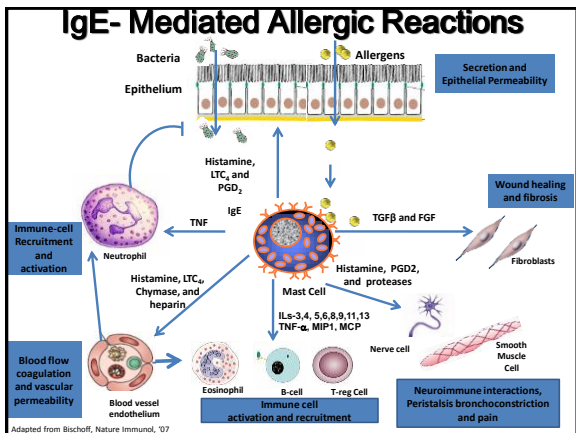
Objectives

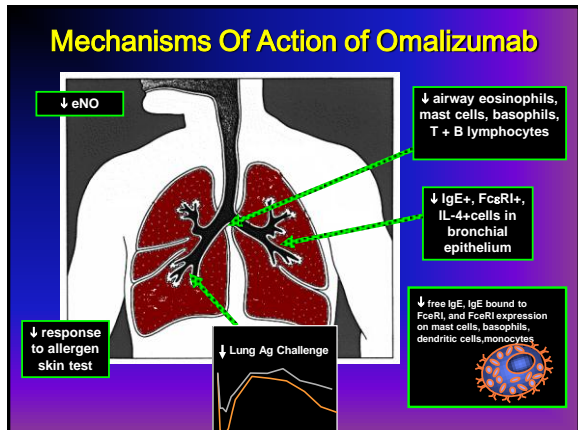
- To explain the rationale behind IgE blockade
- To discuss which patients might benefit from omalizumab
- To explain dosing issues for omalizumab
- To address potential adverse effects of omalizumab
- To compare to immunotherapy

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?



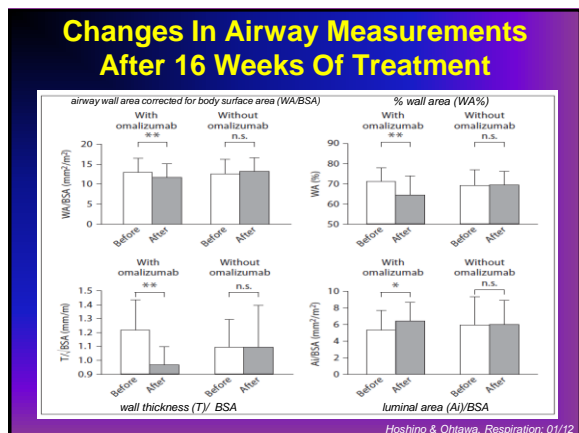
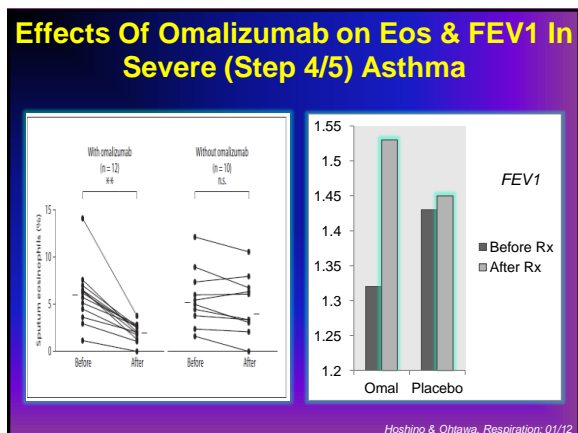


Effects Of Omalizumab On Airway Inflammation In Mild Atopic Asthmatics

➤ 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 FcεR1 cells
- Decreases in B cells, and CD3+, CD4+, and CD8+ cells
- *implies that IgE plays an important role in airway inflammation in asthma*

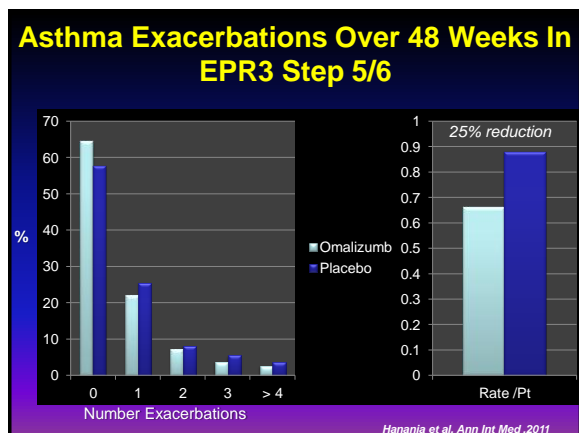
R Djukanovic, et al, AJRCCM, 170:583, 2004



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

¹Busse W et al. J Allergy Clin Immunol 2001;108:184-90.
²Soler M et al. Eur Respir J 2001;18:254-61.
³Humbert M, et al. Allergy 2005;60:209-16.



Omalizumab effect appears independent of:

- Duration of treatment
- Age
- Severity of asthma

Omalizumab Not Indicated

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

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 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

Omalizumab and Seasonal Asthma Exacerbations In 6 to 20 y/o

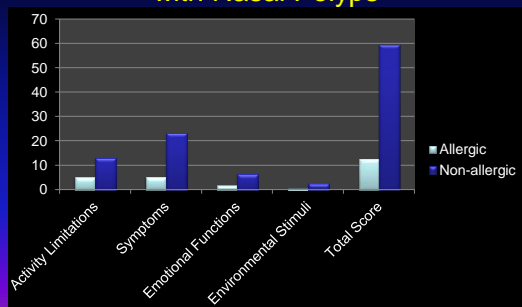
NEJM, 3/11

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

¹ Cameron et al, J Immunol, '03. ² Coker et al, J Immunol, '03 ³ Takhar et al, J Immunol, '05
⁴ Takhar et al, JACI, '07 ⁵ Shin et al, Ped Allergy Immunol, '09. ⁶ Suh et al, Clin Exp Allergy, '04

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



Gevaert, JACI, 2012

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

Monthly Dosing	Body Weight (kg)				
	Baseline IgE IU/mL	30-60	> 60-70	> 70-80	> 80-90
30-100	150	150	150	150	300
>100-200	300	300	300	300	
> 200-300	300				

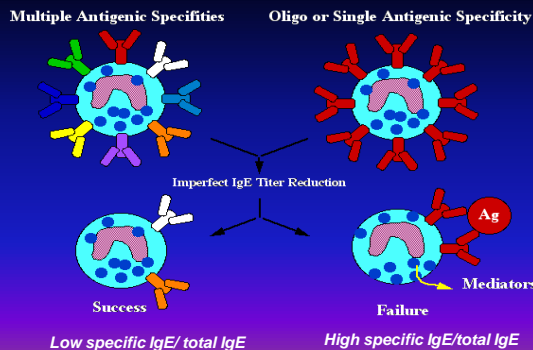
Biweekly Dosing	> 100-200				450	
	> 200-300		450	450	450	600
	> 300-400	450	450	600	600	
	> 400-500	600	600	750	750	
	> 500-600	600	750			
	> 600-700	750				

Factors Predictive Of Clinical Response

- Reasons for omalizumab being ineffective for some (~40%) patients are unknown.
- Improvements correlate w/ IgE reductions, BUT free IgE levels in nonresponders are similar to those found in responders¹
- Possible reasons:²
 - Relationship between free IgE levels and FcεR1 expression
 - Ratio of specific IgE to total IgE
 - Intrinsic cellular sensitivity.
- Recent data indicate that response at 16 wks is highly predictive of persistent response at 32 wks³

1. Slavin, et al. JACI, 2009; 2. MacGlashan, JACI 2009; 3. Bousquet et al. Allergy, 2011

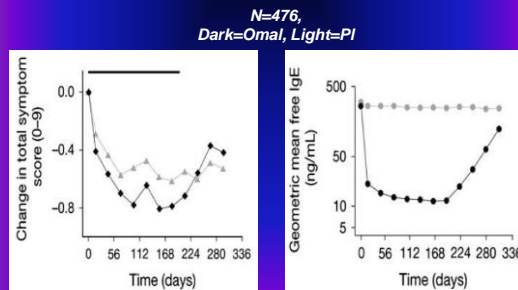
Multiplicity of Antigenic Specificity as a Predictor of Therapeutic Success



Do the Effects Of Omalizumab Continue After Treatment Is Stopped?

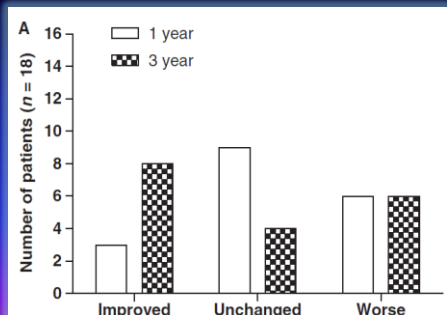
- Conflicting data, but may depend upon duration of treatment
- 2 different studies with 2 different answers:
 - Investigation of Omalizumab in seVere Asthma TrEatment (INNOVATE) study
 - Nopp et al, 2010 Allergy

28-week Omalizumab Treatment And 16-week Follow-up



Slavin, et al. JACI. 2009;123:107

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



A Nopp et al, Allergy 2010

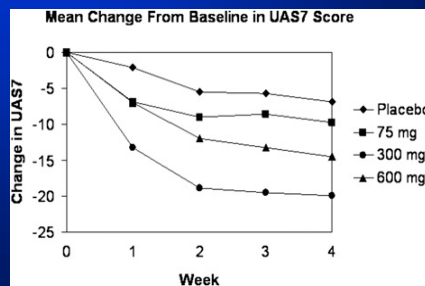
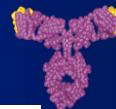
Omalizumab and Asthma Summary

- 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

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

Treatment of Chronic Antihistamine-Resistant Urticaria with Omalizumab



Sarbjit Saini et al, JACI, 2011

What About Pretreatment In Patients With Asthma?

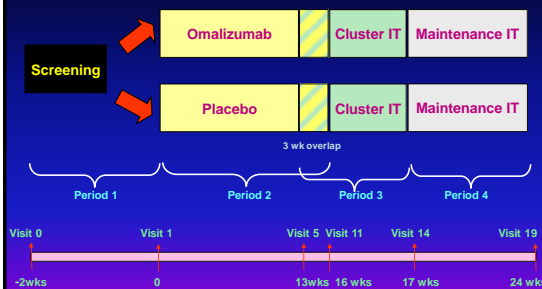
A 26-week, randomized, double-blind, parallel-group, placebo-controlled, multi-center study to evaluate the effect of Xolair® (omalizumab) on improving the tolerability of specific immunotherapy in patients with **at least moderate persistent allergic asthma* inadequately controlled with inhaled corticosteroids**

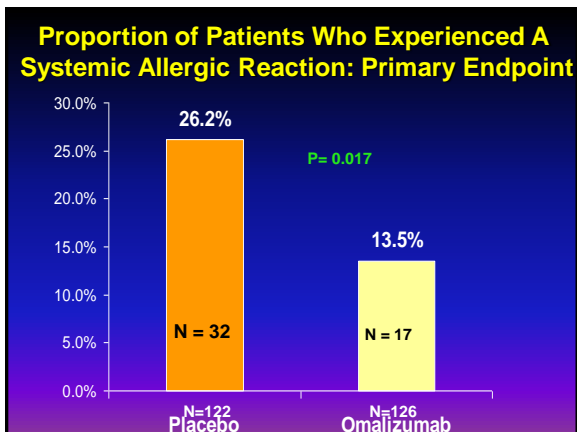
- FEV1 ≥ 75%
- + ST to HDM, cat or dog

Massanari et al, JACI 2010

Omalizumab and Immunotherapy: Study Design

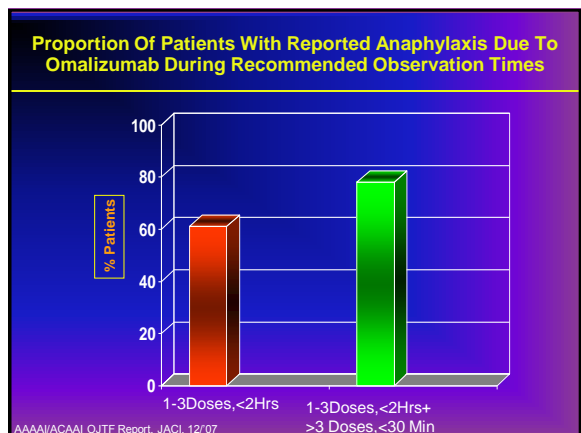
150 Patients per arm, Randomized 1:1





- ### 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