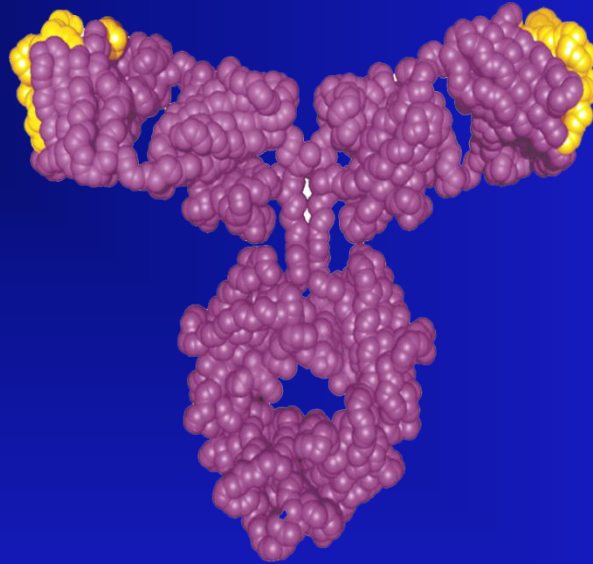


Immunomodulators: Anti-IgE mAb



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Omaha, NE

Objectives

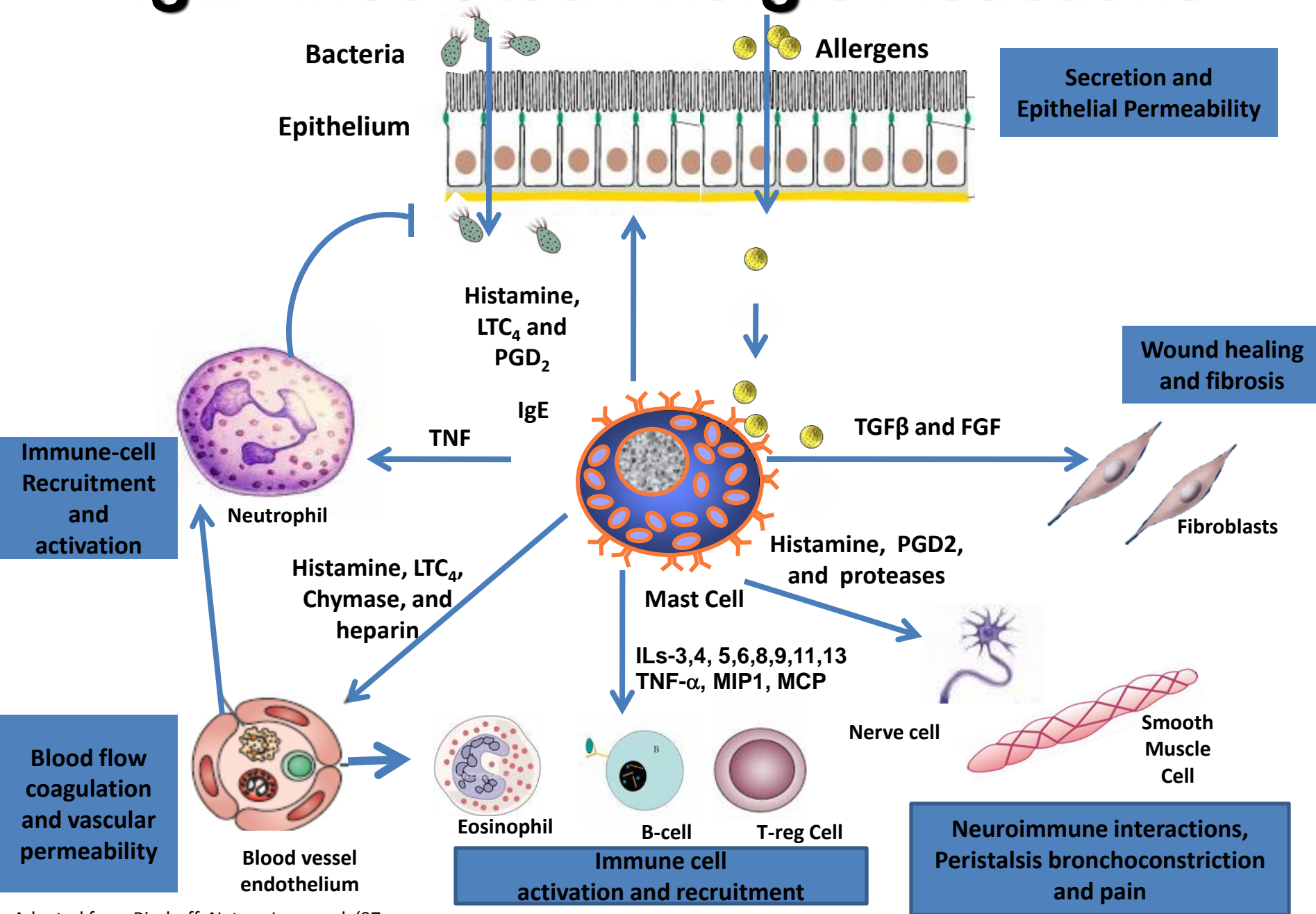
- To explain the rationale behind IgE blockade
- To discuss which patients might benefit from omalizumab
- To explain dosing issues for omalizumab
- To address potential adverse effects of omalizumab
- To compare to immunotherapy

Omalizumab Indications

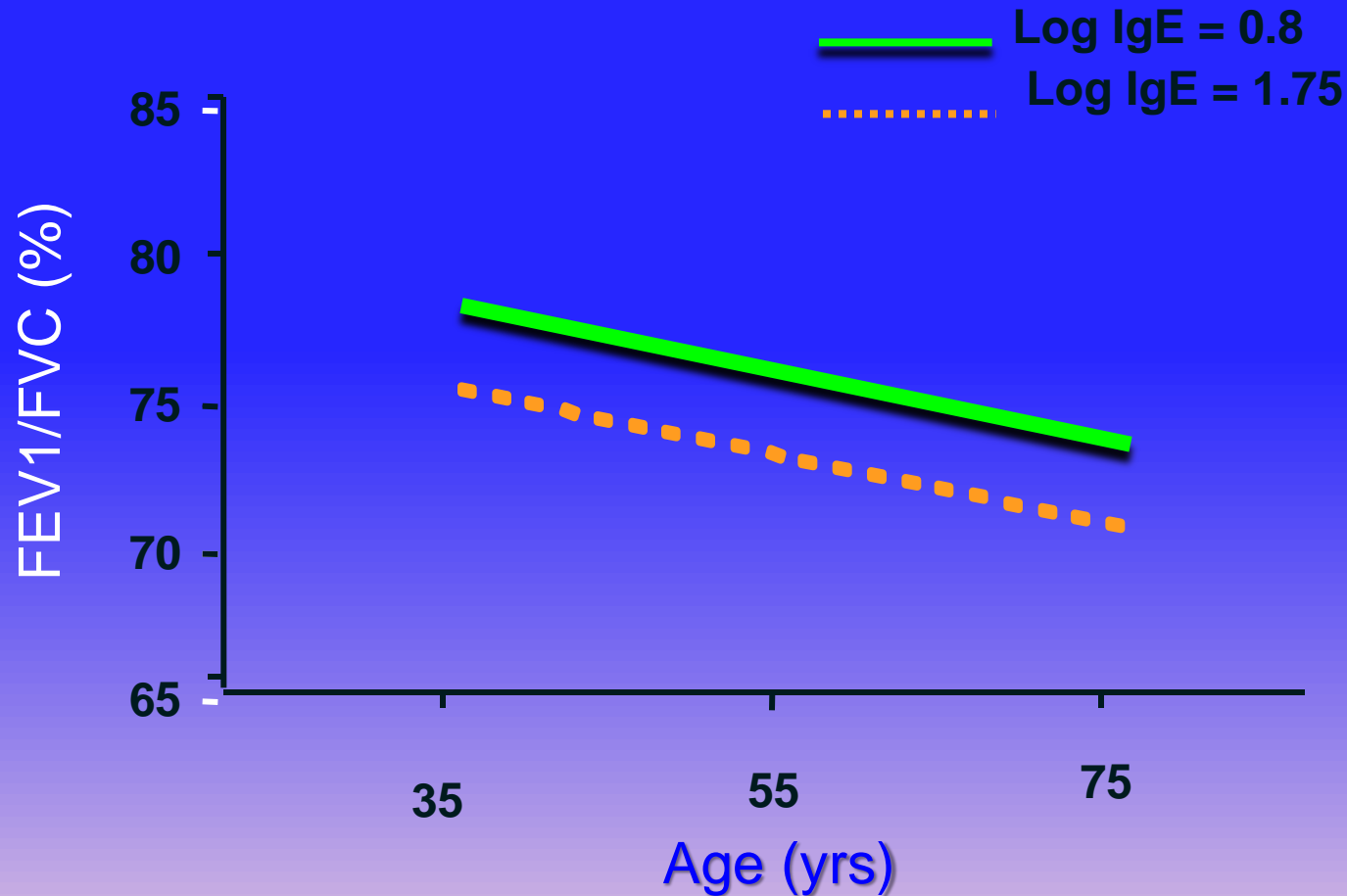
- (Moderate) to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS.
- Step 5/6 care (NHLBI) or 4/5 (GINA)

What Is the Role of IgE in Severe Asthma?

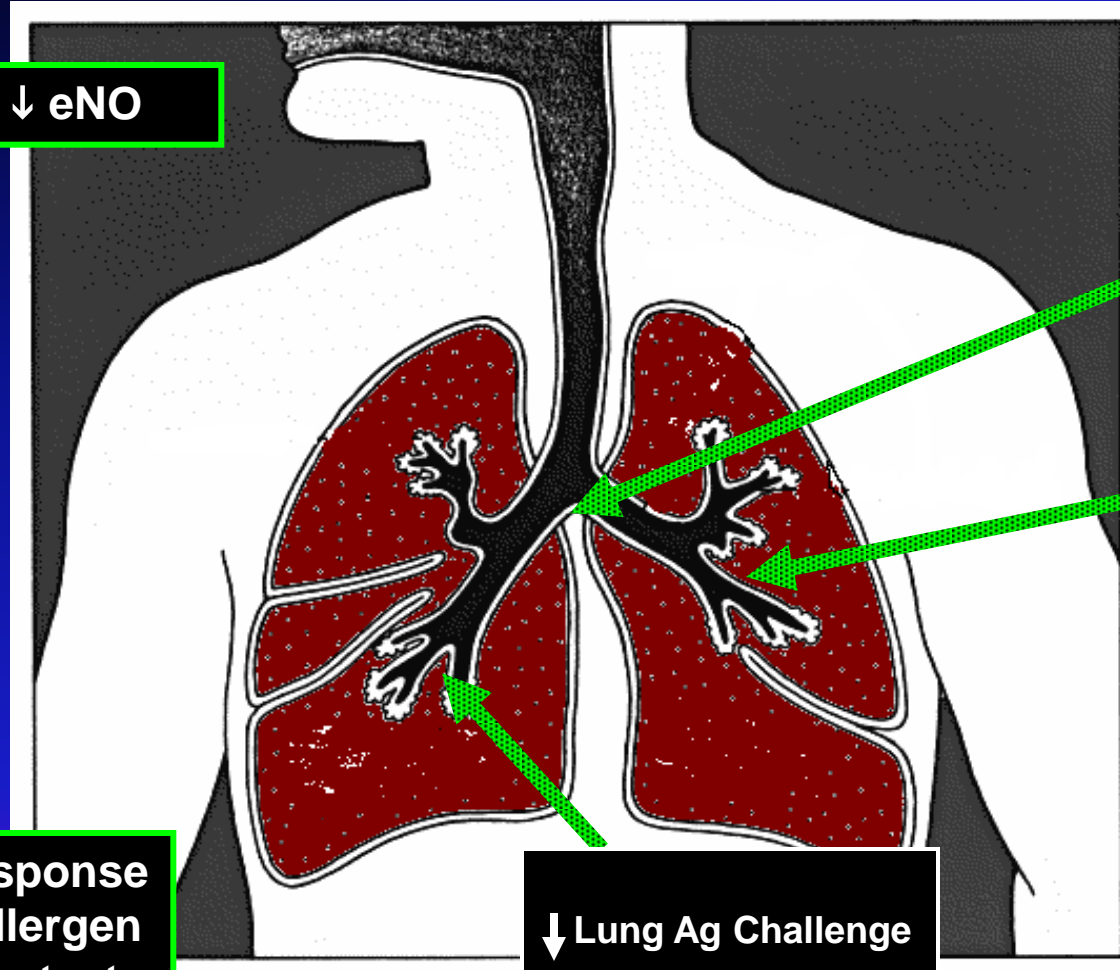
IgE- Mediated Allergic Reactions



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



Mechanisms Of Action of Omalizumab



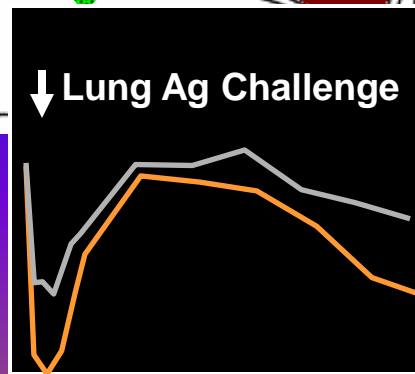
↓ eNO

↓ airway eosinophils,
mast cells, basophils,
T + B lymphocytes

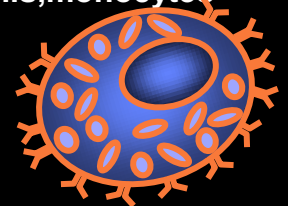
↓ IgE+, FcεRI+,
IL-4+ cells in
bronchial
epithelium

↓ response
to allergen
skin test

↓ Lung Ag Challenge



↓ free IgE, IgE bound to
FcεRI, and FcεRI expression
on mast cells, basophils,
dendritic cells, monocytes

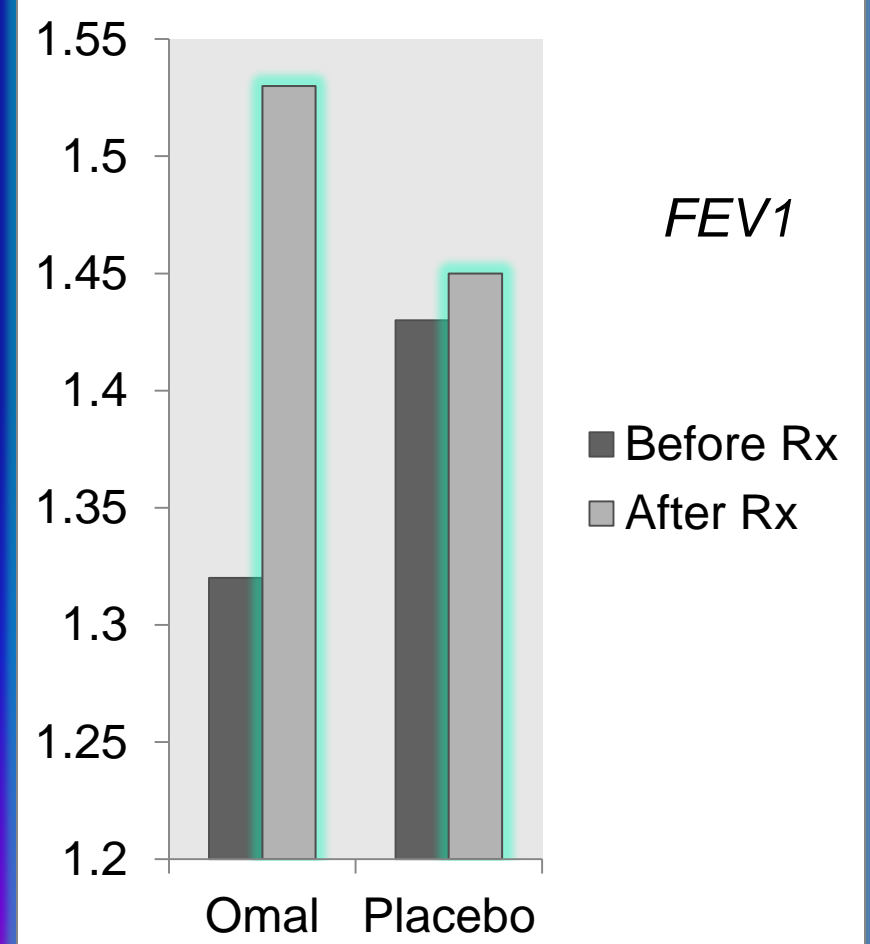
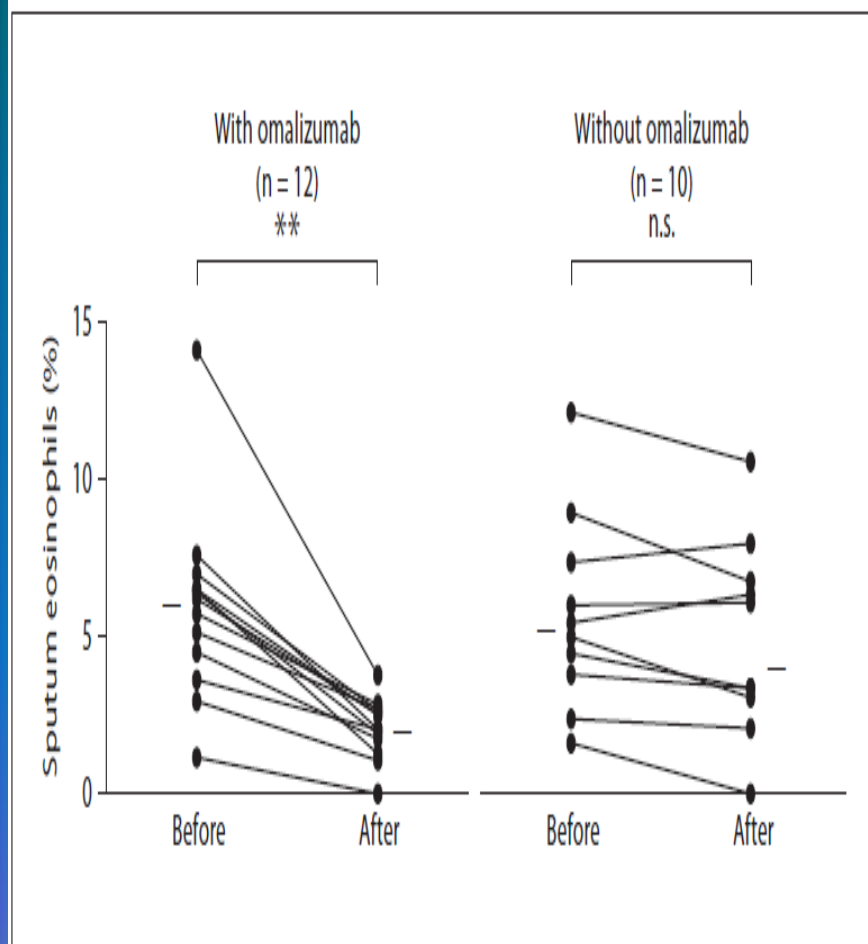


Effects Of Omalizumab On Airway Inflammation In Mild Atopic Asthmatics

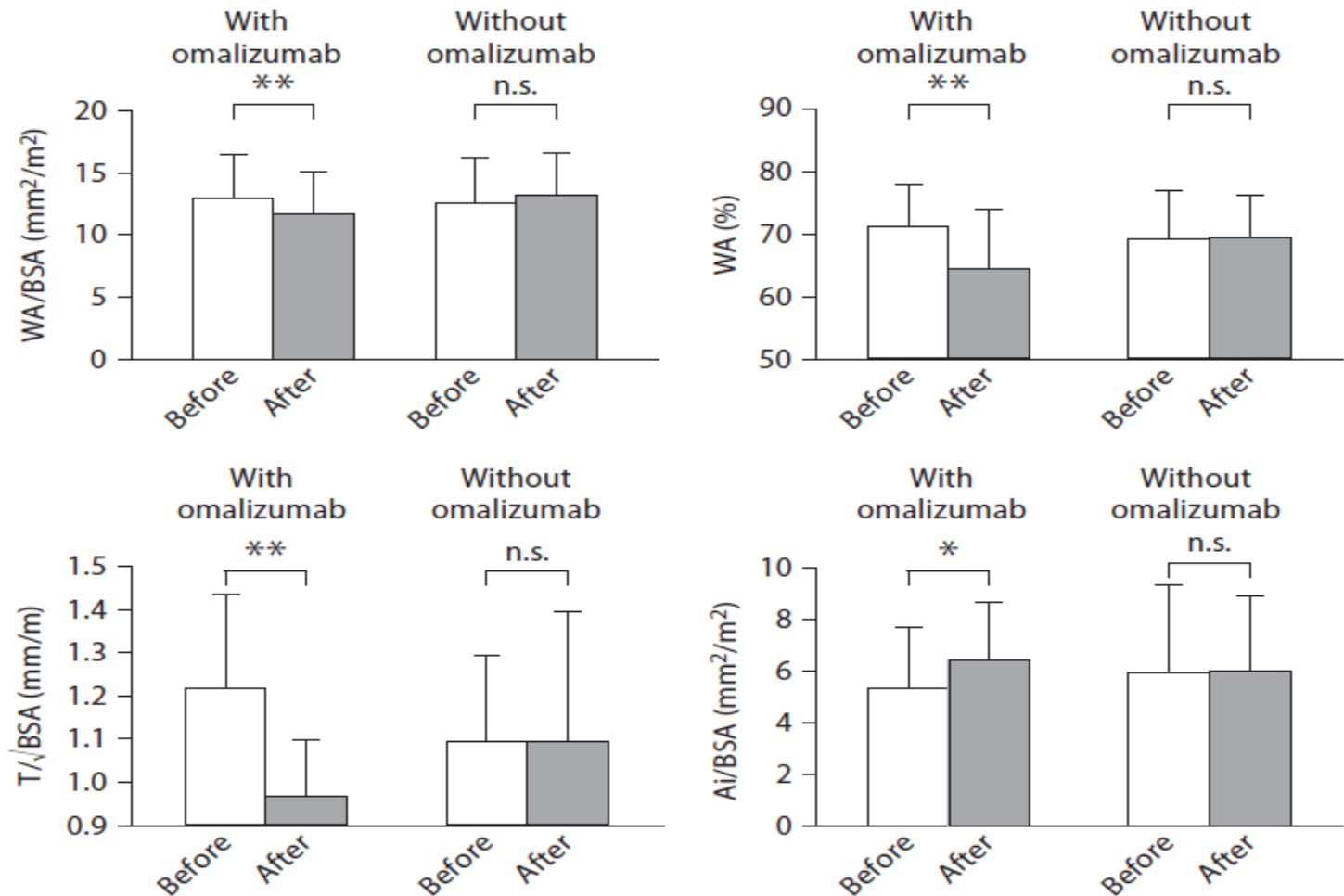
➤ *5-center, double blind , placebo-controlled, parallel-group, 16-week study (n=44) :*

- Reduction in submucosal eos: 8.0 to 1.5
- 10-fold reduction in IgE+cells
 - Decreases in FC ϵ RI cells
- Decreases in B cells, and CD3+, CD4+, and CD8+ cells
 - *implies that IgE plays an important role in airway inflammation in asthma*

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



Changes In Airway Measurements After 16 Weeks Of Treatment



Clinical Effects Of Omalizumab:

Pooled data from 7 trials

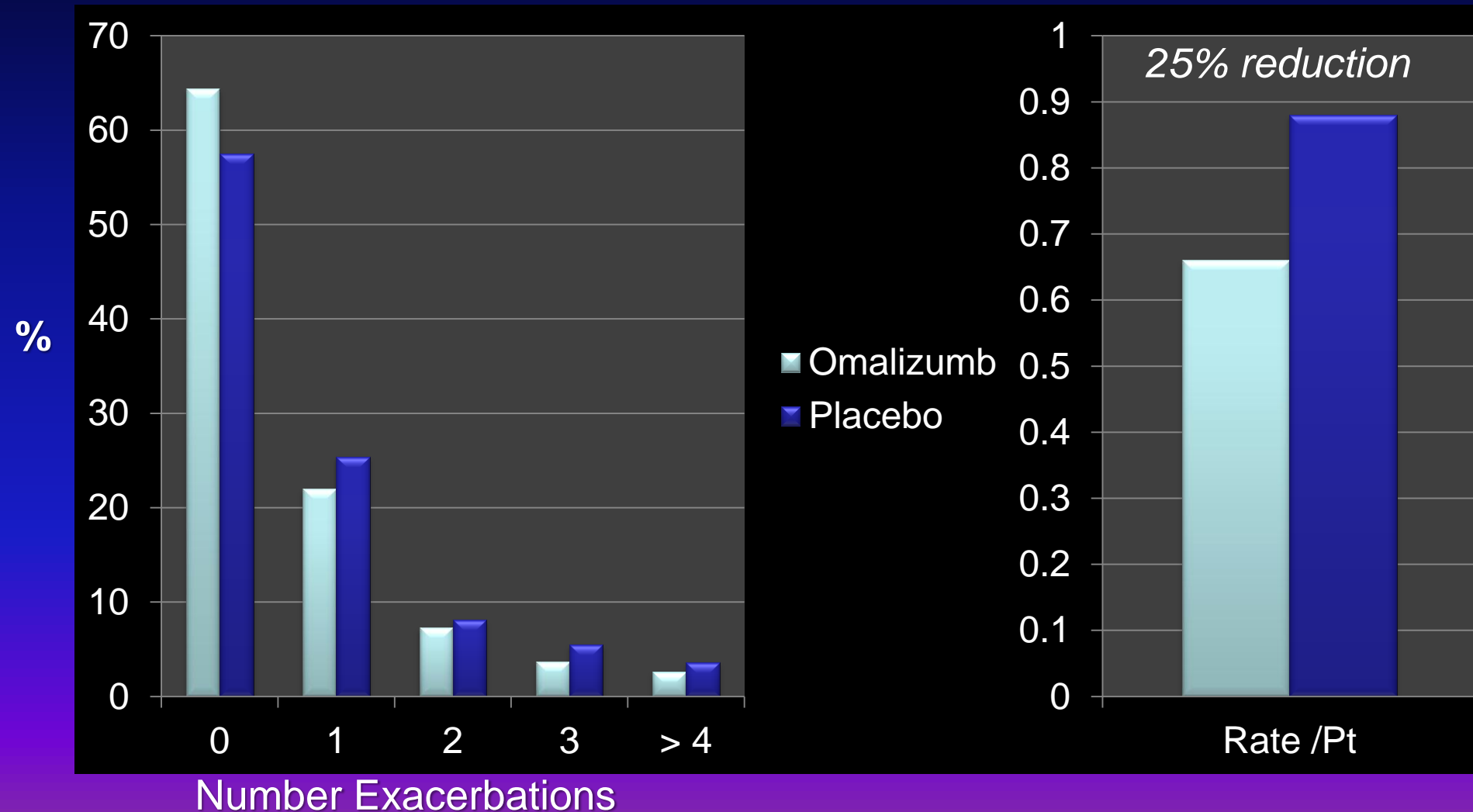
- In patients on ICS alone, or in combination with other agents, addition of omalizumab:
 - ✓ Reduced number of exacerbations (40-50%)
 - ✓ Reduced symptom scores
 - ✓ Reduced need for inhaled corticosteroids
 - ✓ Reduced use of rescue medication
 - ✓ Improved asthma-related quality of life
- Consider 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;60:309-16.

Asthma Exacerbations Over 48 Weeks In EPR3 Step 5/6



Omalizumab effect appears independent of:

- ☐ Duration of treatment
- ☐ Age
- ☐ Severity of asthma

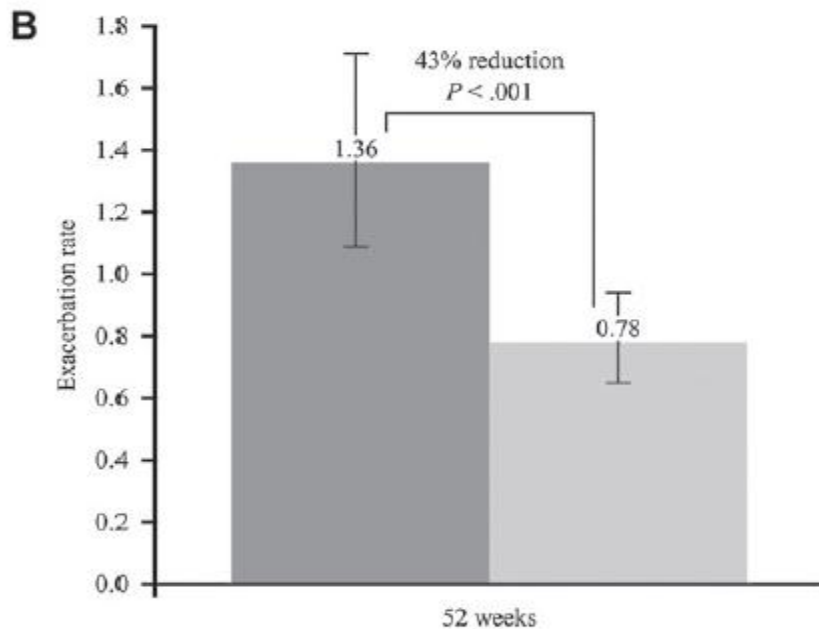
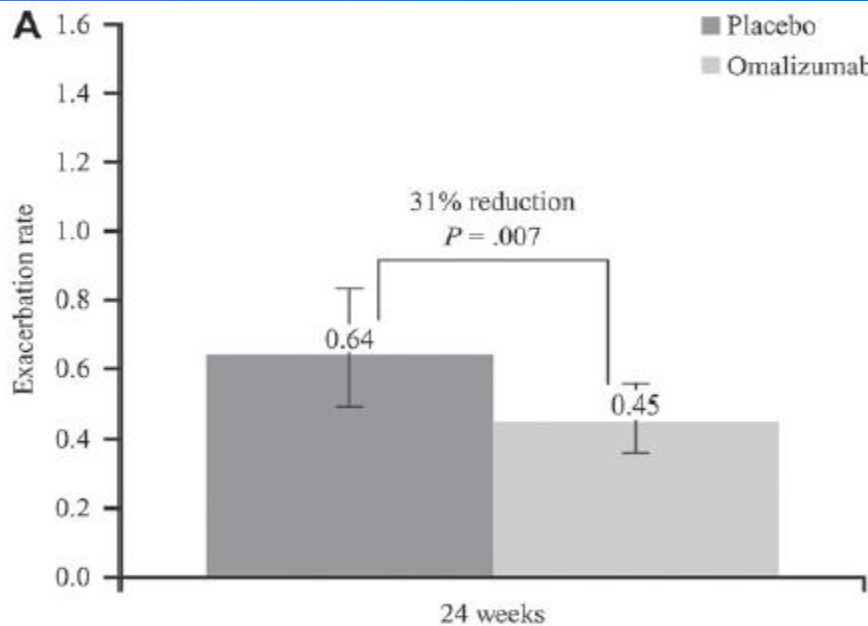
Omalizumab Not Indicated

- 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?

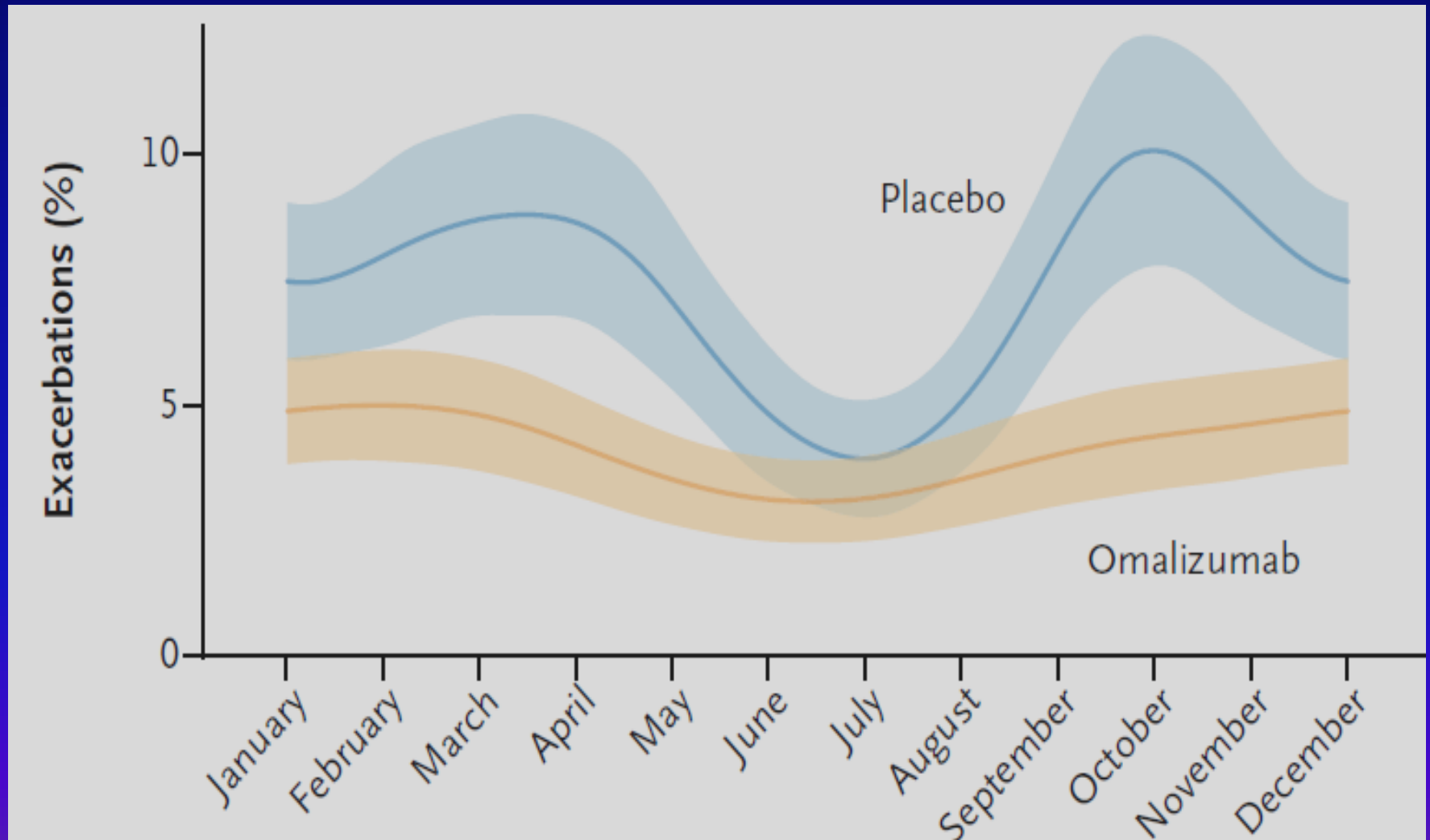
- ❑ *Omalizumab Onset Of Action In Asthma: Pivotal Trials* : While onset of response was measurable at 4 weeks, the proportion of responders continued to increase throughout the 16 week period:
 - 4 wks: 61%
 - 8 wks: 78%
 - 12 wks: 87%
- ❑ Respiratory data suggest that down regulation of Fc ϵ RI expression 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*

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



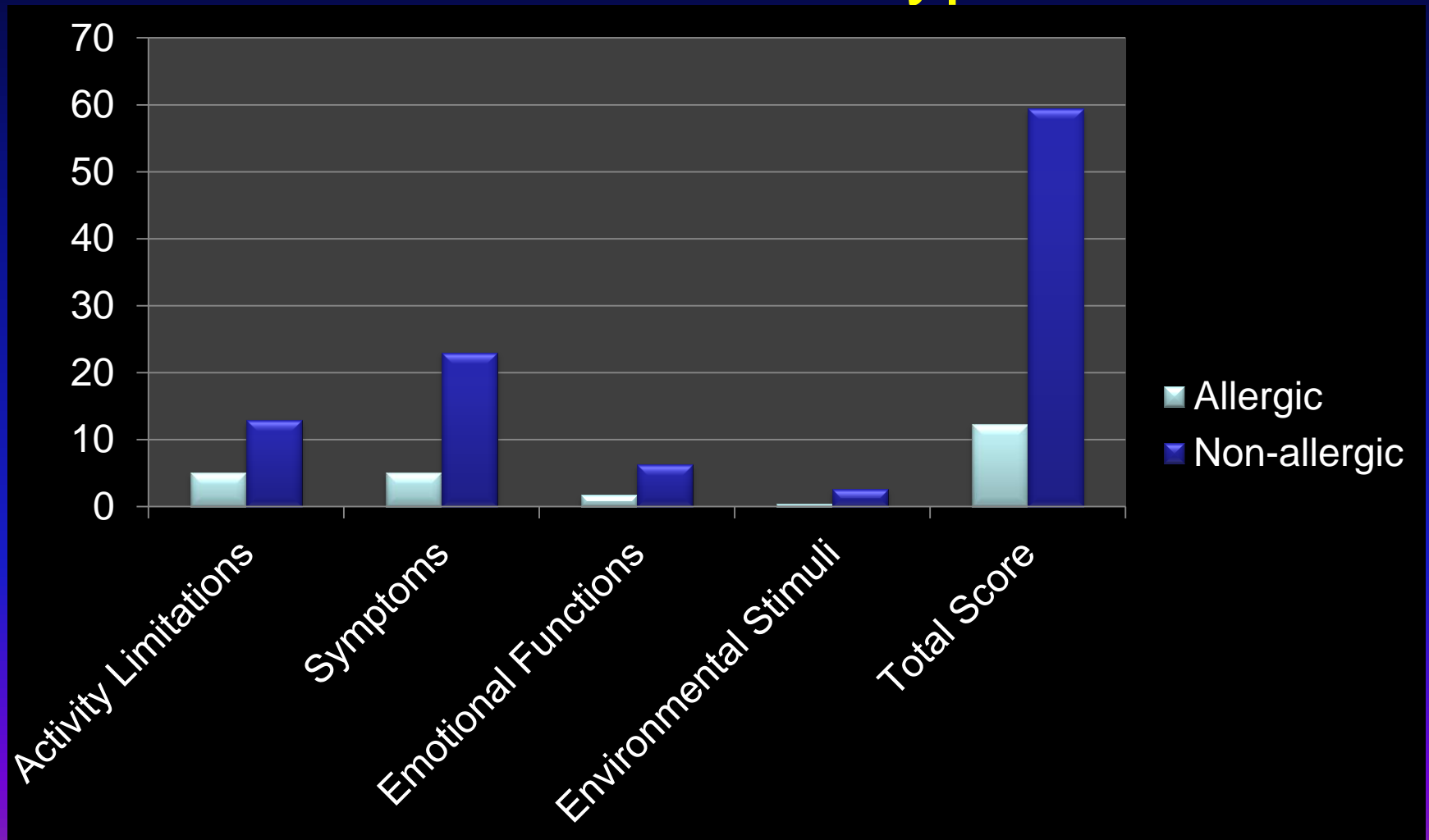
Why Not Nonallergic Asthma?

The Case For Entropy

- 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



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	> 90-150
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				

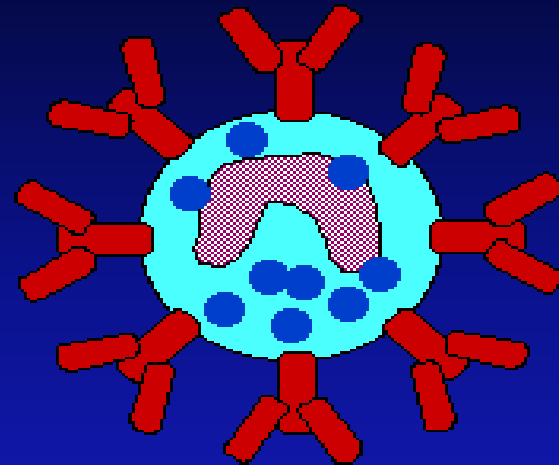
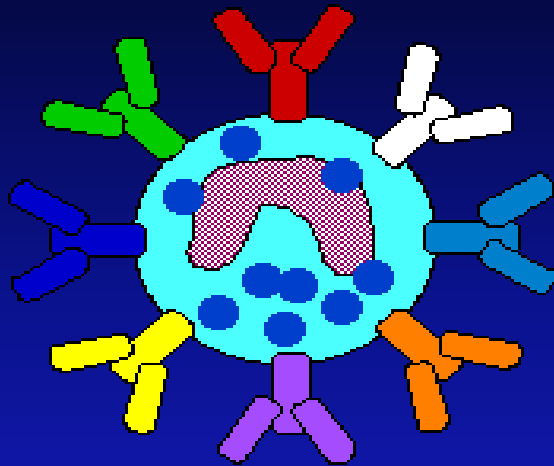
Factors Predictive Of Clinical Response

- 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
 - (1) Relationship between free IgE levels and FcεR1 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 wks³

Multiplicity of Antigenic Specificity as a Predictor of Therapeutic Success

Multiple Antigenic Specificities

Oligo or Single Antigenic Specificity

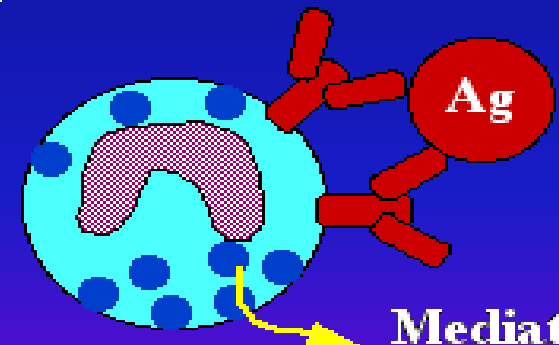


Imperfect IgE Titer Reduction



Success

Low specific IgE/ total IgE



Failure

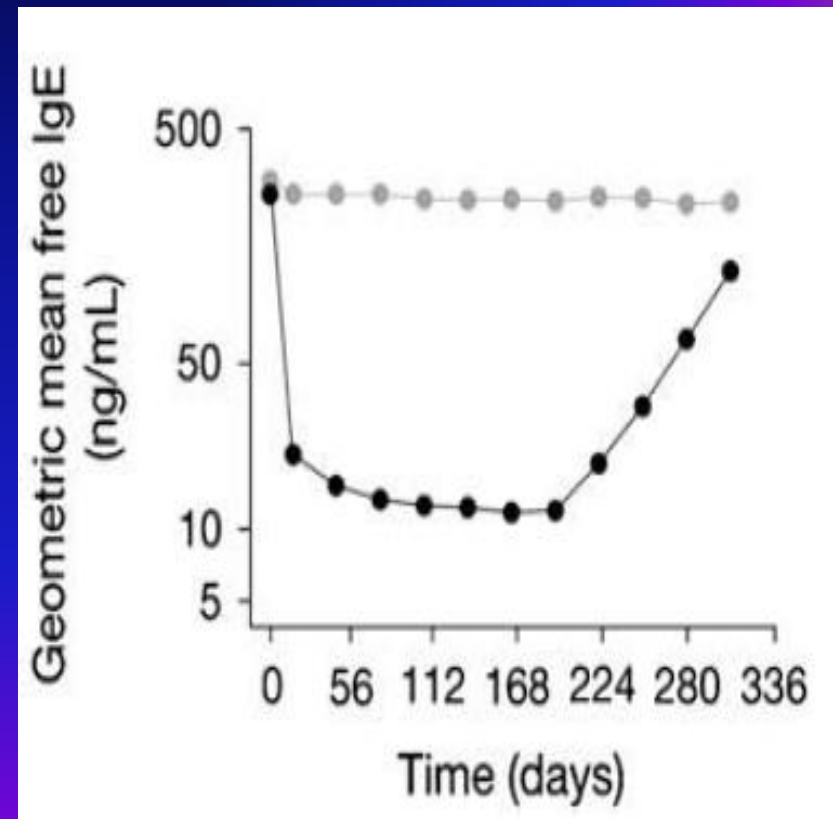
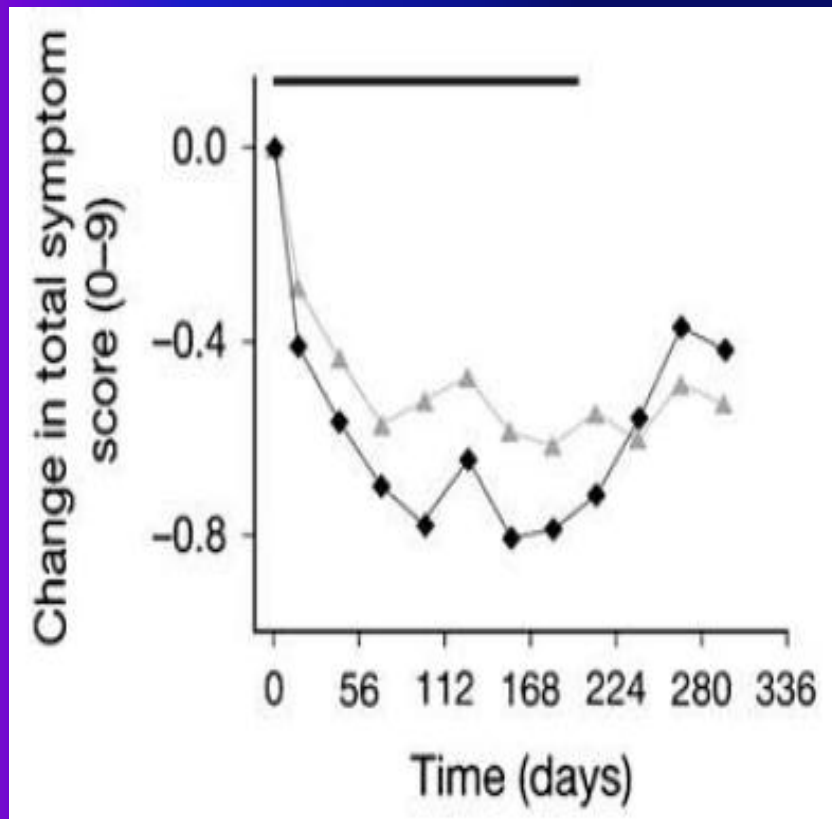
High specific IgE/total IgE

Do the Effects Of Omalizumab Continue After Treatment Is Stopped?

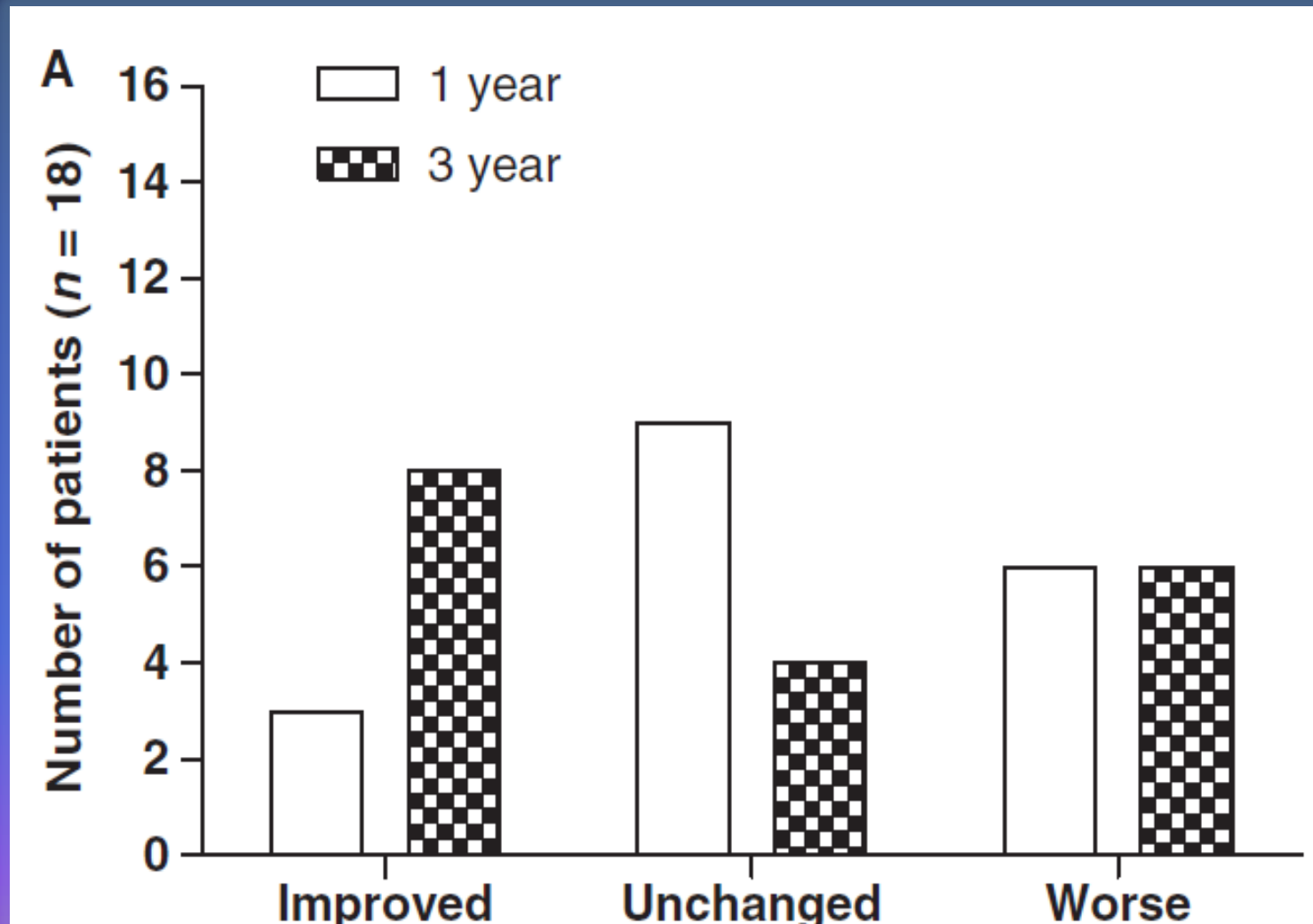
- **Conflicting data, but may depend upon duration of treatment**
- **2 different studies with 2 different answers:**
 - 1. INvestigation of Omalizumab in seVere Asthma TrEatment (INNOVATE) study**
 - 2. Nopp et al, 2010 Allergy**

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

*N=476,
Dark=Omal, Light=PI*



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



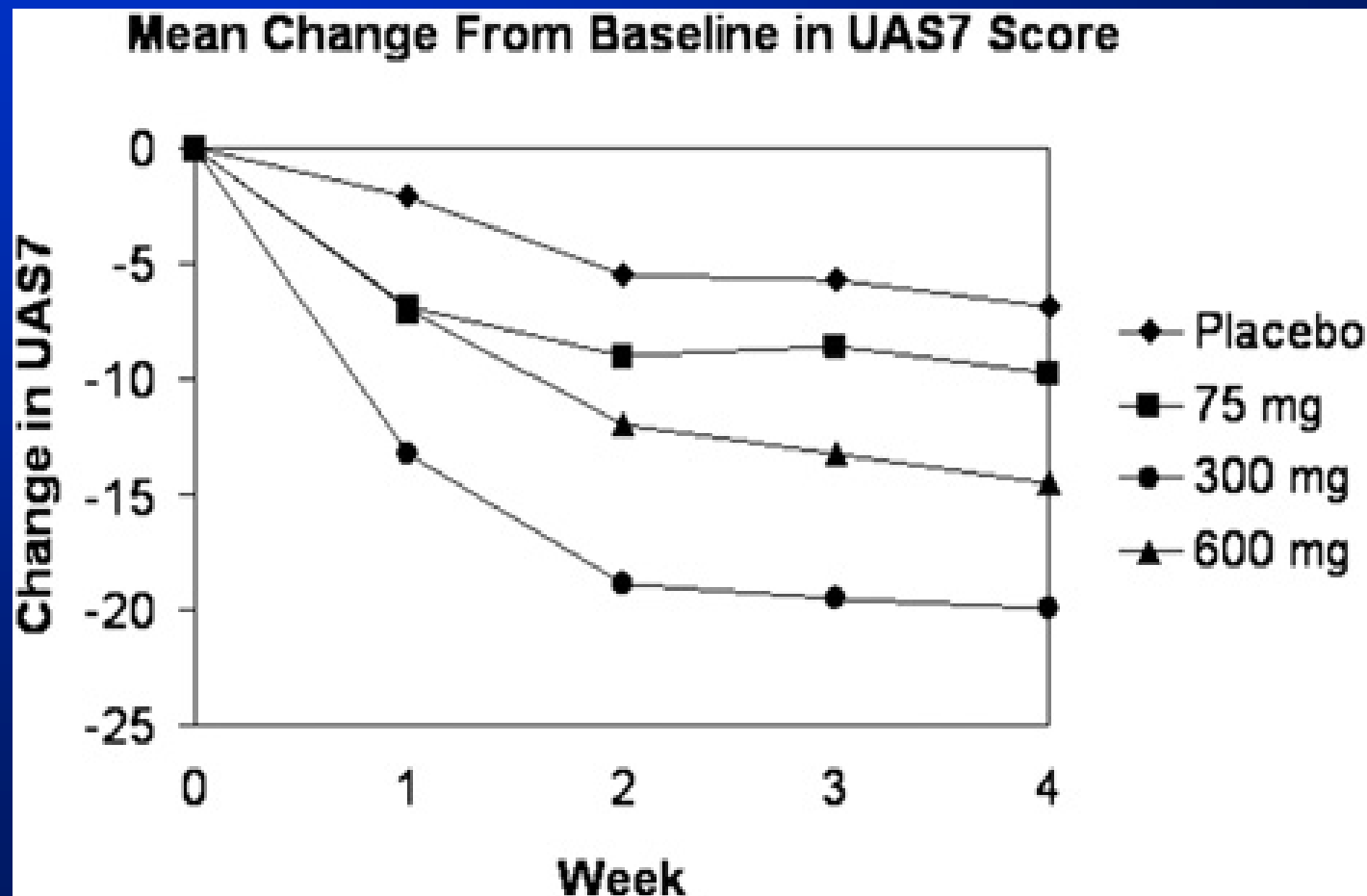
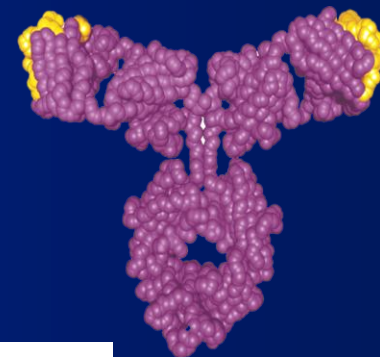
Omalizumab and Asthma Summary

- 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



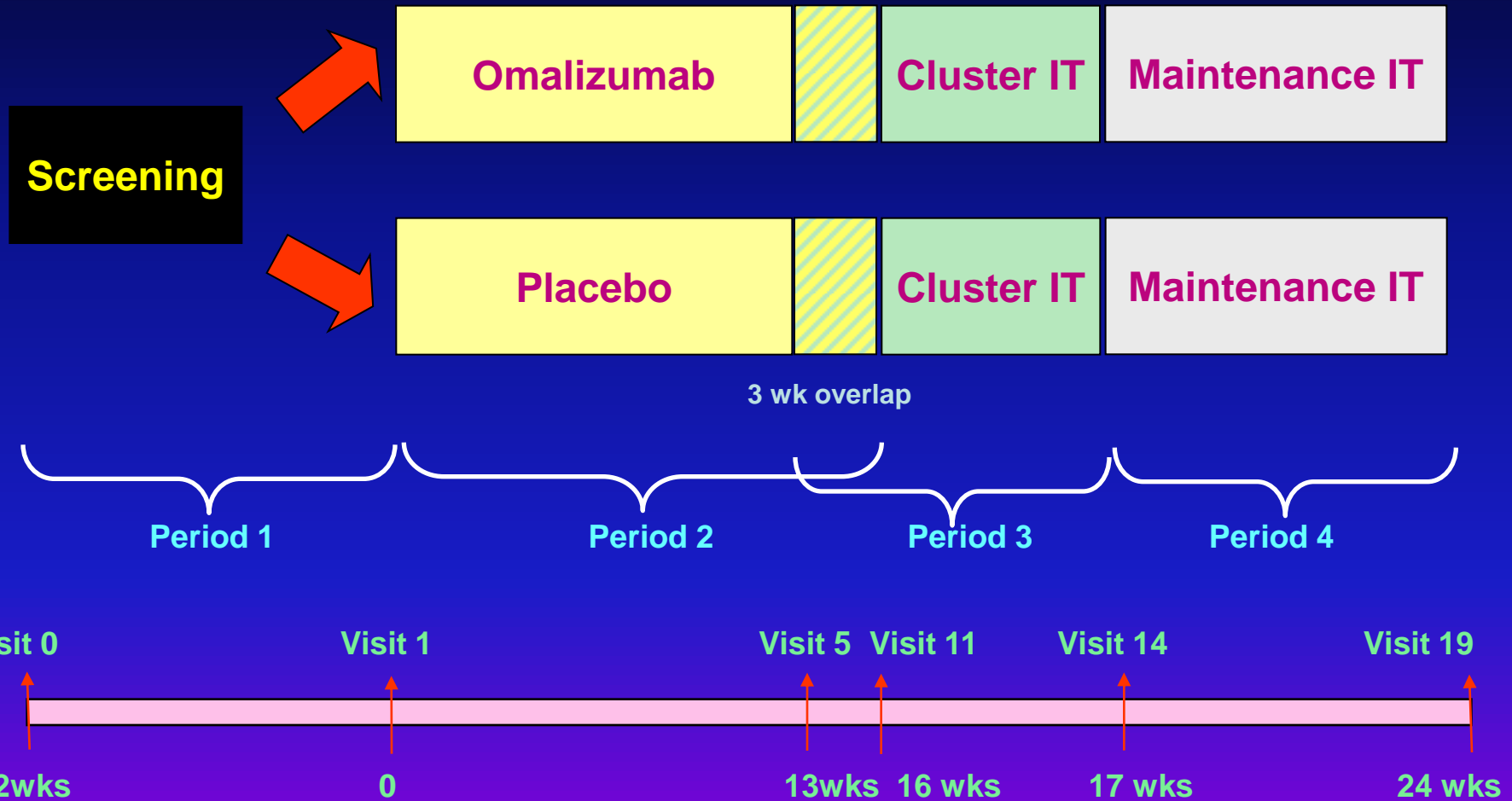
What About Pretreatment In Patients With Asthma?

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

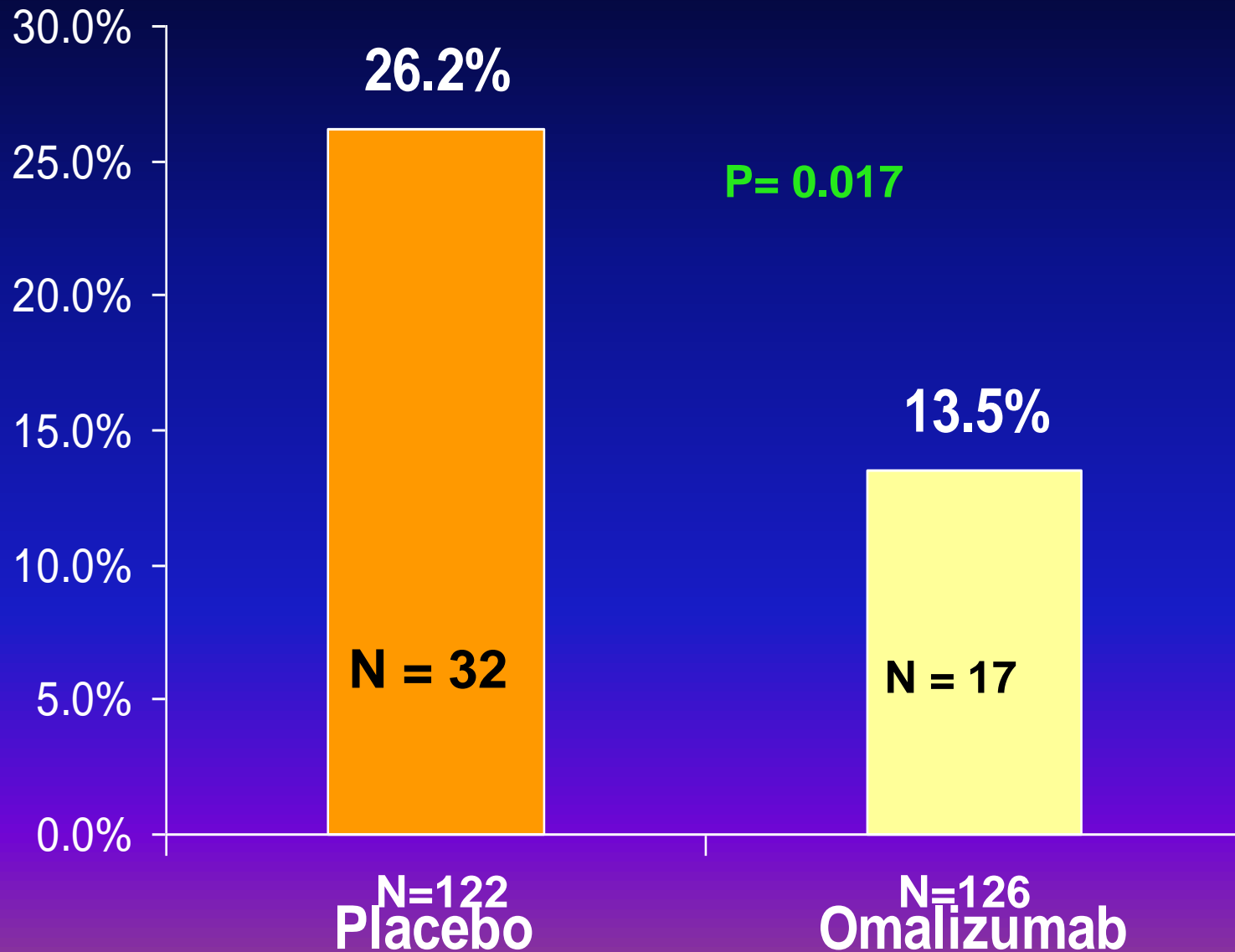
- FEV1 \geq 75%
- + ST to HDM, cat or dog^{*}

Omalizumab and Immunotherapy: Study Design

150 Patients per arm, Randomized 1:1



Proportion of Patients Who Experienced A Systemic Allergic Reaction: Primary Endpoint



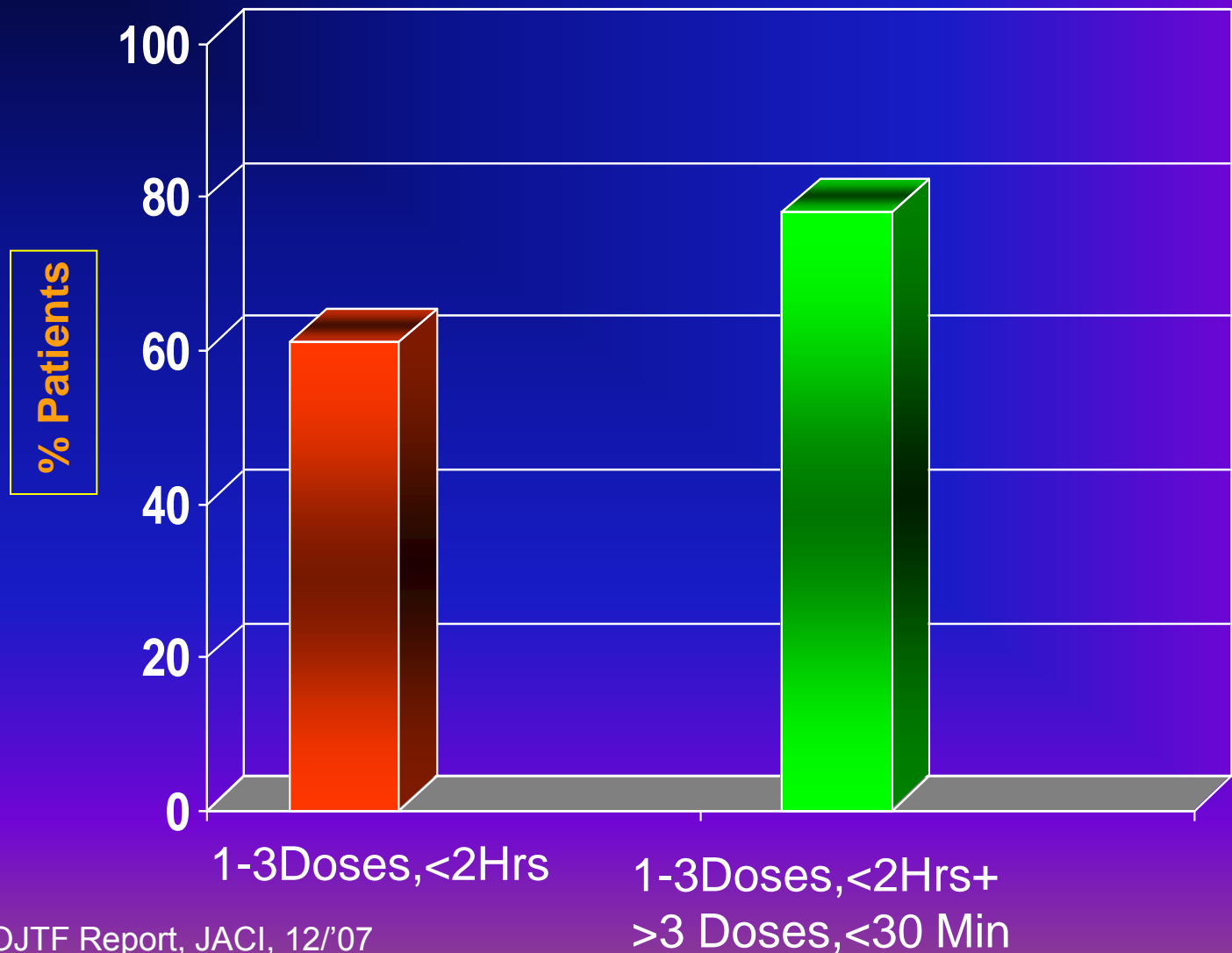
Additional Potential Uses Of Omalizumab

- 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.....?

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



Omalizumab vs. Immunotherapy

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