What’s New in Allergy and Immunology

Samuel Gubernick, DO, FAAAAI, FACAAI, FAAP
Interpretation of Laboratory Tests

• Positive skin prick test or food-specific IgE
  • Indicates presence of IgE antibody and not clinical allergy
  • ~90% sensitivity; ~50% specificity
  • ~50% asymptomatic sensitization
  • Larger skin tests or higher sIgE levels correlate with increased likelihood of allergy but not the severity

• Negative skin prick test or food-specific IgE
  • Essentially excludes IgE antibody (>95% specific)

Sampson and Ho. JACI 1997;100:444-51.
Sampson HA, JACI 2001; 891-96.
Predictive value of food-specific IgE testing in positive and negative OFC

<table>
<thead>
<tr>
<th>Food</th>
<th>&gt;95% Positive</th>
<th>~50% Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>slgE, kIU/L</td>
<td>SPT, mm</td>
</tr>
<tr>
<td>Peanut</td>
<td>&gt;14</td>
<td>&gt;8</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Milk (&lt;2 yr)</td>
<td>&gt;5</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Milk</td>
<td>&gt;15</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Egg (&lt;2 yr)</td>
<td>&gt;2</td>
<td>&gt;7</td>
</tr>
<tr>
<td>Egg</td>
<td>&gt;7</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Fish</td>
<td>&gt;20</td>
<td>?</td>
</tr>
</tbody>
</table>

Molecular Diagnosis of Food Allergy

• Major allergens identified in many foods
• For example birch cross-reactive allergens:
  • Ara h 8 in peanut and Cor a 1 in hazelnut are associated with mild oral symptoms or no symptoms at all upon ingestion.
• Storage seed proteins:
  • Ara h 1, 2, 3 in peanut and Cor a 9 and 14 in hazelnut are associated with systemic reactions.

<table>
<thead>
<tr>
<th>Allergen Component</th>
<th>Severity Markers</th>
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</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Ara h 1, 2 and 3</td>
</tr>
<tr>
<td>Soy</td>
<td>Gly m 5 and 6</td>
</tr>
<tr>
<td>Wheat</td>
<td>Omega-5-gliadin</td>
</tr>
<tr>
<td>Milk</td>
<td>Bos d 8 (casein)</td>
</tr>
<tr>
<td>Egg</td>
<td>Gal d 1 (ovomucoid)</td>
</tr>
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</table>
**Egg**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gal d</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovomucoid</td>
<td>Gal d 1</td>
<td><strong>Heat-stable and highly allergenic</strong>&lt;br&gt;Risk for reaction to all forms of egg&lt;br&gt;High levels indicate persistent allergy</td>
</tr>
<tr>
<td>Ovalbumin</td>
<td>Gal d 2</td>
<td><strong>Heat-labile</strong>&lt;br&gt;Most abundant egg white protein&lt;br&gt;Risk for clinical reaction to raw or slightly heated egg</td>
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<tr>
<td>Conalbumin</td>
<td>Gal d 3</td>
<td><strong>Heat-labile</strong>&lt;br&gt;Risk for clinical reaction to raw or slightly heated egg</td>
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<tr>
<td>Lysozyme</td>
<td>Gal d 4</td>
<td>Risk for clinical reaction to raw or slightly heated egg&lt;br&gt;Lysozyme is used as an additive in certain pharmaceutical products and foods</td>
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</tbody>
</table>
# Peanut

<table>
<thead>
<tr>
<th>Storage proteins:</th>
<th>Ara h 1</th>
<th>Ara h 2</th>
<th>Ara h 3</th>
<th><strong>Associated with severe reactions  Stable to heat and digestion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PR-10 protein:</td>
<td>Ara h 8</td>
<td></td>
<td></td>
<td><strong>Associated with local reactions (e.g. OAS)</strong>&lt;br&gt;<strong>Labile to heat and digestion</strong>&lt;br&gt;Associated with allergy to birch and birch related tree pollens</td>
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<tr>
<td>LTP:</td>
<td>Ara h 9</td>
<td></td>
<td></td>
<td><strong>Associated with both severe and local reactions</strong>&lt;br&gt;<strong>Stable to heat and digestion</strong>&lt;br&gt;Associated with allergy to peach and peach related fruits</td>
</tr>
<tr>
<td>Protein</td>
<td>Allergen Code</td>
<td>Reactivity</td>
<td>Description</td>
<td></td>
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<td>---------------------------------</td>
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<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Alpha-lactoglobulin</td>
<td>Bos d4</td>
<td>Heat labile</td>
<td>Risk for reaction to fresh milk. IgE levels fall as tolerance develops.</td>
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<tr>
<td>Beta-lactoglobulin</td>
<td>Bos d5</td>
<td>Heat labile</td>
<td>Risk for reaction to fresh milk. IgE levels fall as tolerance develops.</td>
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<tr>
<td>Bovine serum albumin</td>
<td>Bos d6</td>
<td>Heat labile</td>
<td>Risk for reaction to fresh milk. The main allergen in beef.</td>
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<tr>
<td>Casein</td>
<td>Bos d8</td>
<td>Stable to heat</td>
<td>Risk for reaction to all forms of milk.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>High levels are connected with persistent milk allergy.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IgE levels fall as tolerance develops.</td>
<td></td>
</tr>
<tr>
<td>Bos d lactoferrin</td>
<td>Bos d lactoferrin</td>
<td>Heat labile</td>
<td>Risk for reactions to all fresh milk.</td>
<td></td>
</tr>
</tbody>
</table>
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team

NEJM 2015; 372:803-813 February 26, 2015
Learning Early About Peanut Allergy (LEAP)

• Prevalence of peanut allergy has doubled in last 10 years from 1.4 to 3 %.

• In Israel, peanut containing foods are given to infants starting about 7 months of age.

• In the United Kingdom children are not given peanut containing foods during their first year of life.

• Observation that the prevalence of peanut allergy was 10 times higher among Jewish children in the UK compared to Israeli children of similar ancestry.

• Purpose of LEAP trial was to determine if early introduction of dietary peanut could serve as an effective primary and secondary strategy for the prevention of peanut allergy.
LEAP trial

- 640 infants 4 to 11 months old with severe eczema, egg allergy or both
- Skin prick test to peanut
- Excluded infants with large positive skin prick tests
- Participants were stratified into 2 cohorts based on SPT:
  - Group 1: No measurable wheal after testing
  - Group 2: Wheal measuring 1 to 4 mm in diameter
- Groups were then randomized to either consuming or avoiding peanuts
- Peanut consumption group had an open-label peanut challenge
- Those who did not react on oral challenge received at least 6 g of peanut protein per week, distributed in 3 or more meals per week, until they reached 60 months of age.
- Evaluated for peanut allergy at 60 months of age
LEAP trial definitions

• Severe eczema defined as persistent or frequently recurring eczema covering ≥10% BSA with typical morphology and distribution as assessed by a health care provider and requiring frequent need for prescription-strength topical corticosteroids, calcineurin inhibitors or other anti-inflammatory agents despite appropriate use of emollients.

• Egg allergy is defined as a skin prick test wheal diameter of 3 mm or greater with egg white extract in an infant with a history of an allergic reaction to egg or who has failed an egg oral food challenge.

• FYI - 2000mg of peanut protein is about 9 peanuts
LEAP trial primary outcome

• 530 of 542 children in the negative SPT group were able to be evaluated. Prevalence of peanut allergy at age 5 was 13.7% in the avoidance group and 1.9% in the consumption group.  p<0.001, 86.1% relative risk reduction.

• All 98 children in the group with 1-4mm wheals on the initial SPT were evaluated. Prevalence of peanut allergy at age 5 was 35.3% in the avoidance group and 10.6% in the consumption group.  p<0.004, 70% relative risk reduction.
Primary prevention targets persons who are not sensitized to peanuts and secondary prevention targets those who are sensitized.

In this study, the intervention was effective in reducing the prevalence of peanut allergy in terms of both primary prevention (prevalence of 6.0% in the avoidance group vs. 1.0% in the consumption group, \( P=0.008 \)) and secondary prevention (33.1% vs. 6.8%, \( P<0.001 \)).
Effect of Avoidance on Peanut Allergy after Early Peanut Consumption


LEAP-ON

• LEAP-ON evaluated whether participants who had consumed peanut for more than four years were protected long-term against peanut allergy when they stopped eating peanut.

• Followed 556 of the original 640 children in LEAP (both consumers and avoiders) for a one-year period of peanut avoidance.

• This cohort included 274 previous peanut consumers and 282 previous peanut avoiders.
LEAP-ON

• After 12 months of peanut avoidance, 4.8% of the original peanut consumers were found to be allergic, compared to 18.6% of the original peanut avoiders.

• LEAP-ON demonstrates that peanut allergy prevention achieved from early peanut consumption in at-risk infants persists after a one-year period of avoiding peanut.
Addendum Guideline 1

Severe eczema
or
Egg allergy
or
Both

Peanut sIgE*

- <0.35
  - Risk of reaction low. Over 90% will have (-) SPT to peanut.
  - Options:
    a) Introduce peanut at home
    b) Supervised feeding in the office (based on provider/parental preference)
  - Refer to specialist for consultation/SPT protocol

- ≥0.35

Peanut Skin Prick Test

- 0-2 mm
  - Risk of reaction varies from moderate to high.
  - Options:
    a) Supervised feeding in office
    b) Graded OFC in a specialized facility

- 3-7 mm

- ≥8 mm
  - Infant probably allergic to peanut. Continue evaluation and management by a specialist

* To minimize a delay in peanut introduction for children who may test negative, testing for peanut-specific IgE may be the preferred initial approach in certain health care settings. Food allergen panel testing or the addition of sIgE testing for foods other than peanut is not recommended due to poor positive predictive value.
Addendum Guideline 2

• The EP suggests that infants with mild to moderate eczema should have introduction of age-appropriate peanut-containing food as early as 4-6 months of age, in accordance with family preferences and cultural practices, to reduce the risk of peanut allergy.

• Peanut should not be the initial solid food introduced into an infant’s diet. Other solid food should be tried first to show the infant is developmentally ready.

• The EP recommends that infants in this category may have dietary peanut introduced at home without an in-office evaluation. However, the EP recognizes that some caregivers and health care providers may desire an in-office evaluation, in which case the decision points shown in Figure 1 should apply.
Addendum Guideline 3:

• The EP recommends that infants without eczema or any food allergy have age-appropriate peanut-containing foods freely introduced in the diet, together with other solid foods, and in accordance with family preferences and cultural practices.

•
The Global Burden of Asthma

- 334 million people have asthma
- Annual worldwide deaths due to asthma have been estimated at 250,000
- 14% of world’s children experience asthma symptoms
- 8.6% of young adults (18 to 45 years of age) experience asthma symptoms
- 4.5% of young adults have been diagnosed with asthma and/or are taking treatment for asthma
- The burden of asthma is greatest for children 10 to 14 years of age and the elderly 75 to 79 years of age
- Asthma is the 14th most important disorder in the world in terms of the extent and duration of disability

GINA
Asthma Definition GINA 2016

• “Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.”

• Clinical definition that does not take into account the clinical presentation or the individual response to treatment
The new paradigm

• Asthma is a heterogeneous disease with multiple phenotypes that have variable risk factors and responses to treatment.

• While mild-to-moderate asthma usually responds to traditional medications, severe asthma is often refractory to ICSs, LABAs, and LRAs.

• Phenotyping of asthma patients now part of the diagnostic workup of all patients not responding to standard therapy.

• Biomarkers help define the specific pathophysiology of different asthma phenotypes and identify potential therapeutic targets.

• An understanding of patient phenotypes and endotypes and the biologicals used to target specific classes of asthma allows for personalized care to asthmatic patients.
Phenotype

• Phenotype is an organism's expressed physical traits.
• Phenotype is determined by an individual's genotype and expressed genes, random genetic variation, and environmental influences.
• Examples of an individual's phenotype include traits such as color, height, size, shape, and behavior.
• Phenotypes also include observable characteristics that can be measured in the laboratory, such as levels of enzymes, hormones, blood cells, and inflammatory mediators.
The Asthma Syndrome
Symptoms of asthma, variable airflow obstruction

Asthma phenotype characteristics
Observable characteristic with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

Asthma Endotypes
Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Endotype 1  Endotype 2  Endotype 3  Endotype 4  Endotype 5
Endotypes

• New approach to asthma classification based on endotypes that represent specific cellular patterns along with clinical characteristics within each patient subgroup.

• Analysis of induced sputum samples allows for determination of inflammatory endotypes according to granulocytic composition - eosinophilic, neutrophilic, mixed granulocytic, or paucigranulocytic.

• Patients with severe adult-onset asthma can be divided into a neutrophilic inflammatory phenotype or have eosinophilic inflammation that is unresponsive to high-dose steroids.
T-helper type 2-driven inflammation defines major subphenotypes of asthma.

Woodruff PG, Modrek B, Choy DF, Abbas AR, Koth LL, Arron JR, Fahy JV

Am J Respir Crit Care Med. 2009 Sep 1;180(5):388-95
• T2 asthma mediated by IL-4, IL-5 and IL-13.
• Half of patients with persistent asthma have T2 inflammation.
• Microarray and PCFR analyses of airway epithelial brushings from 42 patients with mild-to-moderate asthma and 28 healthy controls.
• Classified subjects with asthma based on high or low expression of IL-13-inducible genes.
• Analyzed cytokine expression in bronchial biopsies, markers of inflammation and remodeling, and responsiveness to ICSs.
• FEV1 measured at baseline, after 4 and 8 weeks of daily fluticasone (500 mg twice daily), and 1 week after the stopping fluticasone.
• FEV1 response to ICS is greater in Type 2 asthma and little/none occurs in Type 1 asthma
Biomarkers in Asthma

• FeNO values, peripheral blood eosinophil counts, and periostin levels reflect a T2 inflammatory response.
• Obvious overlap between these individual biomarkers.
• In studies to evaluate mepolizumab and lebrikizumab, for example, there were increases in FeNO, eosinophil counts and periostin levels.
• These markers have a general absence of specificity for components of T2 inflammation and are not precise in defining which treatment choice will be most effective.
FeNO

• Nitric oxide is generated by airway epithelium and is a marker of T2 inflammation.

• Fractional exhaled nitric oxide (FeNO) measured during exhalation can aid the diagnosis and monitoring of T2 asthma, differential diagnosis of eosinophilic asthma, prediction of responsiveness to ICS therapy, and differentiating nonadherence from poor responders.

• Approximately 50% of asthma attributed to eosinophilic inflammation.

• This type of asthma is sensitive to treatment with corticosteroids and is most strongly associated with elevated levels of NO.

• In contrast, inflammation associated with neutrophils is relatively resistant to corticosteroids and is not associated with elevated levels of NO.
FeNO

- FeNO has many confounding factors.
- Tobacco smoke decreases FeNO values.
- FeNO generally higher in in atopic disease with or without asthma.
- Obese have lower FeNO, and weight loss can increase FeNO.
- Demographic variations in FeNO.
- Children have lower FeNO values than adults.
- Males have 25% higher FeNO than females.
- The use of FeNO as a biomarker in asthma is still being evaluated.
Periostin

- Periostin involved in many aspects of allergic inflammation, such as eosinophil recruitment, airway remodeling, development of T2 phenotype, and increased expression of inflammatory mediators.
- Periostin is induced by IL-13, a T2 cytokine.
- Serum periostin levels significantly higher in asthmatic patients with evidence of eosinophilic airway inflammation compared to those with minimal eosinophilic airway inflammation.
- Subsets of asthmatic patients have increased IL-13 levels in their airways and periostin can be used to define T2 phenotypes.
- Lebrikizumab, a mAb against IL-13 demonstrated significant improvement in FEV1 in patients with increased periostin levels and minimal improvement in those with low periostin levels.
Allergic Asthma

- Most common phenotype
- 45-88% of asthmatic patients in recent studies
- Younger patients and onset at earlier age than non-allergic
- Higher prevalence in children, but 60-75% prevalence in elderly in two recent studies
- Defined based on sensitization and clinical correlation
- More common in males
- Family history of allergies common
- Seasonal variation more common than non-allergic asthma
- Exercise-symptoms more frequent/severe than non-allergic
Persistent Severe Asthma ≥ 6 y/o

Asthma requiring treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids for at least 50% of the previous year to prevent it from becoming uncontrollable or asthma that remains uncontrollable despite this therapy.

Eur Resp J 2014; 43-343-73
Eosinophilic Asthma

- Pathologic studies led to the description of subgroups of severe asthmatics based on the presence or absence of eosinophils.
- Majority of severe asthmatics had elevated airway eosinophils despite chronic use of high-dose oral steroids.
- Far fewer patients who developed asthma early in life demonstrated tissue eosinophilia, as compared with those with late-onset asthma (36% versus 63%)
- Induced sputum eosinophils are higher in patients with more severe airflow obstruction and methacholine reactivity.
Severe Eosinophilic asthma

• Associated with increased severity, lower lung function, poor asthma control, late-onset disease, exacerbations in ICS and steroid refractoriness.
• Often associated with sinusitis, nasal polyps and sometimes AERD,
• Often lack of clinical allergy despite positive skin tests in ~75%.
• “Fixed” airflow obstruction, reduced FVC and increased RV.
• Induced sputum cell count (1% to 3% in various studies) is the gold standard for identifying eosinophilic inflammation.
• Several noninvasive biomarkers, including peripheral blood eosinophils, FeNO, and periositin, are potential surrogates.
• Normalization of induced sputum eosinophil counts is an effective strategy for preventing severe asthma exacerbations and hospitalizations.
Diagnostic evaluation of eosinophilic asthma – Peripheral blood eosinophils

• Peripheral blood eosinophil counts are easily obtained and widely available, but lack both specificity and sensitivity.

• In asthmatics with peripheral eosinophilia, there is a suggested correlation with severity of asthma symptoms and an inverse correlation in pulmonary function as measured by FEV₁.

• Hastie evaluated multiple variables including FeNO, FEV₁, IgE, and blood eosinophil counts in predicting asthma phenotype.

• Peripheral blood eosinophils >300/μL had a poor positive predictive value in identifying an eosinophilic asthma phenotype based on sputum eosinophils of >2%.

• Peripheral blood eosinophilia may be a marker of disease severity in asthma, but does not correlate consistently with sputum eosinophilia.

Hastie AT et al. JACI, 2013 Jul;132(1):72-80
Diagnostic evaluation of eosinophilic asthma - IgE

• Eosinophilic asthma can be associated with T2-mediated allergic disease and allergen sensitization, especially in earlier onset disease.

• Lack of correlation between total IgE levels and the presence of eosinophils in BAL fluid or biopsy specimens.

• Total IgE has little utility in evaluation of most patients with asthma.
Diagnostic evaluation of eosinophilic asthma

• Using a logistic regression model including age, sex, body mass index, IgE levels, blood eosinophils, FeNO levels, and serum periostin levels in 59 patients with severe asthma, Jia et al found serum periostin was the best predictor of airway eosinophilia.

• A serum periostin level >25 ng/mL had a positive predictive value of 93% and a negative predictive value of 37% for sputum eosinophils (>3%) or tissue eosinophilia.

Omalizumab

• Recombinant Chinese hamster ovary cell-derived humanized IgG1κ monoclonal antibody.

• Binds circulating IgE regardless of IgE specificity.

• Prevents binding of IgE to FcεRI, the high affinity IgE receptor on mast cells and basophils.

• Does not bind cell-bound IgE and therefore should not activate mast cells or basophils.

• Given SQ, dose by weight, every 2 or 4 weeks
Omalizumab

- Efficacy in moderate-severe asthma
  - Reduction in symptom scores
  - Reduction in rescue albuterol
  - Reduction in oral corticosteroid bursts
  - Reduction in # exacerbations
  - Improved AM PEFR
Appropriate Candidates for Anti-IgE Therapy

• Adults and adolescents 6 years and above
• Moderate to severe asthma
• Positive skin test or sIgE to a perennial aeroallergen
• IgE between 30-700 IU/mL
• Symptoms are inadequately controlled with inhaled corticosteroids
Table 1. Subcutaneous Omalizumab Dosing Every 4 Weeks for Patients 12 Years of Age and Older with Asthma

<table>
<thead>
<tr>
<th>Pre-treatment Serum IgE</th>
<th>Body Weight</th>
<th>30−60 kg</th>
<th>&gt; 60−70 kg</th>
<th>&gt; 70−90 kg</th>
<th>&gt; 90−150 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30−100 IU/mL</td>
<td>150 mg</td>
<td>150 mg</td>
<td>150 mg</td>
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<tr>
<td>&gt; 100−200 IU/mL</td>
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<tr>
<td>&gt; 200−300 IU/mL</td>
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<td>&gt; 400−500 IU/mL</td>
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<tr>
<td>&gt; 500−600 IU/mL</td>
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</table>

See Table 2
Table 2. Subcutaneous Omalizumab Dosing Every 2 Weeks for Patients 12 Years of Age and Older with Asthma

<table>
<thead>
<tr>
<th>Pre-treatment Serum IgE</th>
<th>Body Weight</th>
<th>30−60 kg</th>
<th>&gt; 60−70 kg</th>
<th>&gt; 70−90 kg</th>
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<td>≥ 30−100 IU/mL</td>
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<tr>
<td>&gt; 100−200 IU/mL</td>
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<td>&gt; 200−300 IU/mL</td>
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<tr>
<td>&gt; 300−400 IU/mL</td>
<td>225 mg</td>
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<td>300 mg</td>
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<tr>
<td>&gt; 400−500 IU/mL</td>
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<td>375 mg</td>
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<tr>
<td>&gt; 500−600 IU/mL</td>
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<td>375 mg</td>
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<tr>
<td>&gt; 600−700 IU/mL</td>
<td>375 mg</td>
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</table>

DO NOT DOSE
## Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Pediatric Patients With Asthma Who Begin XOLAIR Between the Ages of 6 to <12 Years

<table>
<thead>
<tr>
<th>Pretreatment serum IgE (IU/mL)</th>
<th>Dosing Freq.</th>
<th>Body weight</th>
<th>Dose (mg)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Pounds</td>
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<td></td>
<td>&gt;176-198 lbs</td>
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<td>&gt;800-900</td>
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<td>&gt;198-276 lbs</td>
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<tr>
<td>&gt;900-1000</td>
<td></td>
<td>&gt;276-330 lbs</td>
<td>&gt;125-150 kg</td>
</tr>
</tbody>
</table>

*Subcutaneous doses to be administered every 4 weeks

*Subcutaneous doses to be administered every 2 weeks

*DO NOT DOSE

*Dosing frequency:
Warnings

• Anaphylaxis estimated to be 0.1% and at least 0.2%.
• Anaphylaxis occurred with the first dose of XOLAIR in 2 patients and with the fourth dose in 1 patient.
• The time to onset of anaphylaxis was 90 minutes after administration in 2 patients and 2 hours after administration in 1 patient.
• Malignant neoplasms were observed in 20 of 4127 (0.5%) XOLAIR-treated patients compared with 5 of 2236 (0.2%) control patients in initial studies.
• A subsequent 5-year observational study of 5007 XOLAIR-treated and 2829 non-XOLAIR-treated adolescent and adult patients found that the incidence rates of primary malignancies (per 1000 patient years) were similar in both groups (12.3 vs 13.0).
Xolair Adverse reactions

• In patients ≥12 years of age, the most commonly observed adverse reactions were: arthralgia (8%), pain (general) (7%), leg pain (4%), fatigue (3%), dizziness (3%), fracture (2%), arm pain (2%), pruritus (2%), dermatitis (2%), and earache (2%).

• In pediatric patients 6 to <12 years of age, the most commonly observed adverse reactions were: nasopharyngitis, headache, fever, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bite, and epistaxis.
IL-5

• Recruitment, granule maturation, and survival of eosinophils in the airways are promoted by IL-3, GM-CSF, and especially IL-5.

• IL-5 is produced by CD4+ Th2 cells, mast cells, eosinophils, and basophils.

• Main biological role of IL-5 is to control proliferation, differentiation, and activation of eosinophils.

• It also stimulates the final differentiation of activated B cells into antibody-forming cells.

• Represent a functional link between T-cell activation and inflammatory responses mediated by eosinophils.
Eosinophil Functions

• Antiparasitic - especially against helminths in the larval stage
• Antiviral
• Antibacterial - acts as APC, generation of cytokines and chemokines and phagocytosis of intracellular bacteria such as mycobacterium
• Eosinophils can be efficient in host defense against gram-negative bacteria and oxygen-dependent killing, i.e., superoxide acting in conjunction with EPO, may be the most important bactericidal effector function of these cells. Important at mucosal interfaces and in the mucosa of, for example, the large intestine, where the conditions are aerobic.
• Staph aureus, E. coli, Pseudomonas
Mepolizumab

• Mepolizumab was the first anti-IL-5 molecule designed and tested in for eosinophilic asthma.

• Nucala (mepolizumab) is a humanized IgG1 kappa monoclonal antibody which binds to soluble interleukin-5 (IL-5), preventing its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface.
Mepolizumab

• Indication:
  • As add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller, and have a blood eosinophil count of ≥150 cells/μL at initiation of treatment with mepolizumab OR ≥300 cells/μL in the past 12 months.

• Dosage:
  • A fixed dose of 100 mg mepolizumab (Nucala™) by subcutaneous injection every 4 weeks.
Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez, M.D., Ph.D., for the MENSA Investigators

Clinical Trials: Exacerbation Study (MENSA)

• A 32-week, multicenter, randomized, DBPC parallel-group study evaluating the efficacy and safety of mepolizumab 100 mg SC and mepolizumab 75 mg IV vs placebo in the add-on treatment of severe eosinophilic asthma (N=576).

• Primary end point:
  • Annualized frequency of clinically significant exacerbations.

• Secondary end points:
  • Annualized frequency of exacerbations requiring hospitalization or ER visit
  • Change from baseline in lung function at week 32.
  • Change from baseline in health-related QOL at week 32.
MENSA

• Inclusion criteria:
  • History of $\geq 2$ asthma exacerbations in the past year
  • Peripheral blood eosinophils $\geq 150$ cells/$\mu$L within 6 weeks of first dose, or $\geq 300$ cells/$\mu$L within past year
  • Regular use of high-dose ICS plus an additional controller with or without OCS

• Background therapy:
  • All patients received maintenance therapy prior to and during the study, which consisted of high-dose ICS plus additional controller(s), with or without OCS
Results

• **Efficacy results: Exacerbations**
  
  • Mepolizumab 100 mg SC significantly reduced the frequency of clinically significant exacerbations vs. placebo.
  
  • Mepolizumab 100 mg SC also significantly reduced the frequency of clinically significant exacerbations requiring hospitalizations and/or ER visits by 61% vs. placebo.
  
  • The mean change from baseline in pre-bronchodilator FEV$_1$ was 183 mL with mepolizumab vs. 86 mL with placebo at week 32.

• **Results from cluster analysis**
  
  • Larger mepolizumab treatment response in clusters with blood eosinophil levels of 150 cells/µl or greater, with the largest treatment response seen in obese patients with more comorbidities and airway reversibility.
Cluster Analysis and Characterization of Response to Mepolizumab. A Step Closer to Personalized Medicine for Patients with Severe Asthma

Hector Ortega, Hao Li, Robert Suruki, Frank Albers, David Gordon and Steven Yancey

• Examined dataset from the Dose Ranging Efficacy And safety with Mepolizumab (DREAM) study with the specific objective of identifying clusters of data associated with exacerbation rates as obtained by mepolizumab treatment.

• Baseline covariates considered for inclusion were region, sex, age, weight, number of exacerbations in the year before the study, use of maintenance oral corticosteroids, percent predicted FEV$_1$, airway reversibility, blood eosinophil count, and IgE levels.
• Higher levels of blood eosinophils and greater number of previous exacerbations at baseline led to greater reduction in exacerbations with mepolizumab.

• For the majority of patients with elevated eosinophils, blood eosinophil count is the biomarker of choice for predicting treatment outcome with mepolizumab in severe asthma.

• There was a larger mepolizumab treatment response in clusters with blood eosinophil levels of 150 cells/μl or greater, with the largest treatment response seen in obese patients with more comorbidities and airway reversibility.
Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma

Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID; SIRIUS Investigators.

Clinical Trials: Oral Corticosteroid Reduction Study (SIRIUS)

• A 24-week, multicenter, randomized, DBPC parallel-group study that evaluated the efficacy and safety of mepolizumab vs. placebo on reducing the requirement for maintenance oral corticosteroids, while maintaining asthma control, in patients with severe eosinophilic asthma (N=135).

• Primary Endpoint
  • Percent reduction of OCS dose over Weeks 20-24 compared with the dose of OCS established during the run-in/optimization phase.
SIRIUS

• Select inclusion criteria:
  • Peripheral blood eosinophil ≥150 cells/uL in the 6 weeks prior to first dose, or ≥300 cells/uL in the previous 12 months
  • Regular use of high-dose ICS plus additional controller(s)
  • Regular maintenance treatment with OCS

• Background therapy:
  • Prior to the study, patients were on high-dose ICS plus an additional controller(s) with OCS (5-35 mg/day prednisone or equivalent)
  • During a 3- to 8-week run-in phase, the OCS dose was adjusted weekly to establish the lowest possible OCS dose required to maintain asthma control.
  • After randomization, the OCS dose was reduced every 4 weeks between Weeks 4-20 until zero, or the lowest dose required to maintain asthma control. No further OCS dose adjustments were made after Week 20.
At Week 20-24 (secondary endpoints):

• 54% (37/69) of mepolizumab patients achieved a ≥50% reduction in the daily OCS dose vs. 33% (22/66) on placebo.

• 54% (37/69) of mepolizumab patients achieved a reduction in the daily OCS dose to ≤5 mg vs. 32% (21/66) on placebo.

• 14% (10/69) of patients on mepolizumab 100 mg SC achieved a total (100%) reduction in daily OCS dose to 0 mg vs. 8% (5/66) on placebo.
Mepolizumab Adverse Reactions

• Headache, pharyngitis, lower respiratory tract infection, urinary tract infection, nasal congestion, upper abdominal pain, eczema, back pain, pyrexia and injection site reactions

• Acute and delayed systemic reactions, including hypersensitivity reactions

• Parasitic infections

• Herpes Zoster - consider varicella vaccination
Reslizumab

- Reslizumab (Cinqair) is an interleukin-5 antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.

- Reslizumab binds to IL-5 inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil surface.
Reslizumab Dosing

• Reslizumab (CINQAIR) is for intravenous infusion only.
• Reslizumab (CINQAIR) should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis
• Recommended dosage regimen is 3 mg/kg every 4 weeks by IV infusion over 20-50 minutes
Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study

Leif Bjерmer, Catherine Lemiere, Jorge Maspero, Sivan Weiss, James Zangrilli, Matthew Germinaro

Chest Volume 150, Issue 4, October 2016, Pages 789–798
Rezlizumab

• Patients aged 12 to 75 years with asthma inadequately controlled by at least a medium-dose ICS and with a blood eosinophil count $\geq 400$.

• Of 1,025 screened patients, 315 were randomly assigned to treatment and 265 completed the study.

• Randomized to receive reslizumab 0.3mg/kg or 3.0 mg/kg or placebo administered once every 4 weeks for 16 weeks.

• Primary end point was change from baseline in pre-bronchodilator FEV1 over 16 weeks.

• Secondary end points included FVC, FEF25%-75%, patient-reported control of asthma symptoms, SABA use, blood eosinophil levels, and safety.
• Reslizumab significantly improved \( \text{FEV}_1 \) in the treatment groups. 115 ml in the 0.3mg/kg group and 160ml in the 3.0mg/kg group.

• Increases in FVC (130 mL) and FEF25%-75% (233 mL/s) were observed with reslizumab 3.0 mg/kg.

• Reslizumab improved scores on the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) vs placebo.

• SABA use decreased with reslizumab.

• 3.0-mg/kg dose of reslizumab provided greater improvements in asthma outcomes vs the 0.3-mg/kg dose, with comparable safety.

• Most common adverse events were worsening of asthma, headache, and nasopharyngitis.
Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials.

Mario Castro, James Zangrill, Michael Wechsler, Eric D Bateman, Guy G Brusselle, Philip Barden, Kevin Murphy, Jorge F Maspero, Christopher O’Brien, Stephanie Korn

Reslizumab

• Of 2597 patients screened, 953 were randomly assigned to receive either reslizumab (n=477) or placebo (n=476).
• In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations.
  • Study 1: rate ratio [RR] 0.50 [95% CI 0.37-0.67]
  • Study 2: 0.41 [0.28-0.59]
  • Both p<0.0001) compared to placebo group.
• Common adverse events on reslizumab were similar to placebo.
• The most common adverse events were worsening asthma symptoms, URIs, and nasopharyngitis.
• Two patients in the reslizumab group had anaphylactic reactions. Both responded to standard treatment.
Reslizumab (Cinqair)

- Anaphylaxis has been observed in 0.3% of patients in placebo-controlled clinical studies.
- Anaphylaxis was reported as early as the second dose.
- In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg CINQAIR had at least 1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group.
- Eosinophils may be involved in the immunological response to some parasitic (helminth) infections. Treat patients with pre-existing helminth infections before initiating CINQAIR. If patients become infected while receiving treatment with CINQAIR and do not respond to anti-helminth treatment, discontinue treatment with CINQAIR until infection resolves.
CPK elevations and muscle-related adverse reactions

• Elevated baseline CPK was more frequent in patients randomized to CINQAIR (14%) versus placebo (9%).
• Transient CPK elevations in patients with normal baseline CPK values were observed more frequently with CINQAIR (20%) versus placebo (18%).
• CPK elevations >10 x ULN were 0.8% in the CINQAIR group compared to 0.4% in the placebo group.
• CPK elevations >10 x ULN were asymptomatic and did not lead to treatment discontinuation.
• Myalgia was reported in 1% (10/1028) of patients in the CINQAIR 3 mg/kg group compared to 0.5% (4/730) of patients in the placebo group.
• On the day of infusion, musculoskeletal adverse reactions were reported in 2.2% and 1.5% of patients treated with CINQAIR 3 mg/kg and placebo, respectively.
• These reactions included (but were not limited to) musculoskeletal chest pain, neck pain, muscle spasms, extremity pain, muscle fatigue, and musculoskeletal pain.