Searching for Targets to Control Asthma

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Inflammation and Remodeling in Asthma
The most important cell in asthma is?

• A. Smooth muscle cell
• B. T-helper-2 cell
• C. Eosinophil
• D. Mast cell
• E. Epithelial cell

• Answer
Pathogenesis of Allergy

Dendritic Cell

MHC II
T-cell Receptor

activation

IL-4
IL-13

B-Cells

GATA3
STAT6

Th2 T-cell

IL-13R

Mast Cell
Basophil

allergen

IgE

Mucins

Airway epithelium

MMPs

Airway Remodeling

TGF-β

Airway Inflammation

Environment
Genetics

allergen

Environment
Genetics

allergen

IgE

receptor
Airway Remodeling in a 6-Year-Old

Asthma Is a Chronic Inflammatory Disease of Both the Large and Small Airways

**Adult**

<table>
<thead>
<tr>
<th>Location</th>
<th>Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea</td>
<td>0</td>
</tr>
<tr>
<td>Bronchi</td>
<td>1</td>
</tr>
<tr>
<td>Bronchioles</td>
<td>2</td>
</tr>
<tr>
<td>Terminal bronchioles</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory bronchioles</td>
<td>4</td>
</tr>
<tr>
<td>Alveolar ducts</td>
<td>T3, T20</td>
</tr>
<tr>
<td>Alveolar sacs</td>
<td>T2, T21, T22</td>
</tr>
<tr>
<td>T 23</td>
<td></td>
</tr>
</tbody>
</table>

- **Normal**
- **Asthma**
- **Fatal asthma**

**Small airway in adult control subject**

**Small airway in adult subject with fatal asthma**

*Images reproduced with permission from Dr. Francis Green, Department of Pathology and Lab Medicine, University of Calgary.*
IgE Production

**T-Cell**
- MHC-Class II
- TCR
- CD4
- CD-40L
- IFN-γ

**B-Cell**
- Adhesion molecules
- CD40L
- CD40
- IL-4
- IL-13

**Signals**
- + (positive)
- - (negative)

**Immunoglobulin** (specific to Ag)

**IgE**
First exposure to allergen

Antigen activation of T_{H2} cells and stimulation of IgE class switching in B cells

Production of IgE

Binding of IgE to FceRI on mast cells

Repeat exposure to allergen

Activation of mast cell: release of mediators

Mast cell

Immediate hypersensitivity reaction (minutes after repeat exposure to allergen)

Vasoactive amines, lipid mediators

Late phase reaction (6-24 hours after repeat exposure to allergen)

Cytokines

Abbas & Lichtman: Basic Immunology 3e, Updated Edition. Copyright © 2010 by Saunders, an imprint of Elsevier, Inc. All rights reserved.
What Happens After Mast Cell Activation?

Leucocyte adhesion
Leucocyte activation
IL-5 TNF-α
IL-5 IL-6
IL-5 IL-6
Leucocyte activation
Mast Cell
IL-4
Histamine PGD₂ LTC₄ Kinins Chymase Bronchoconstriction
Mast Cell
Histamine PGD₂ LTC₄ Kinins
Histamine PGD₂ LTC₄ Kinins
Oedema Vasodilatation
Nerve stimulation
IgE production
Mucus secretion
Smooth muscle cell is active in inflammation
Increased airway smooth muscle mass in severe asthma with chronic persistent obstruction

Epithelial-Mesenchymal Trophic Unit

IL-13 stimulates epithelial cells to release periostin that stimulates fibrosis

Inflammation and Remodeling in Asthma

(a) Normal

(b) Moderate asthma

(c) Severe asthma

Shifren et al. J Allergy, 2012
Exacerbation in uncontrolled asthma

1. Eosinophil mediator release 
   => tissue damages

2. Inflammation cytokine production: TNF-α, IL-6, IL-8

3. Activation Th1
   => IFN-γ secretion
   => Increased leucocyte recruitment

4. Induction of FcεRI expression on polymucleated cells and APC
   => increased fixation of IgE
   => increased cellular activation

5. Tissue damage

6. Smooth muscle contraction

Histamine, neutral protease,
PGD2, LTC4/D4/E4

Mucus secretion
TGF-β => lung re-modeling

Increase during uncontrolled asthma compared to chronic symptoms
Increased loss of FEV$_1$ in asthma

Male non-smokers

P <0.001

Of the endotypes which one is obese and responds best to weight loss?

• A. type 1 which is almost always allergic
• B. type 2 which is the most common endotype
• C. type 3 which often do not respond to conventional therapies
• D. type 4 which is late onset
• E. type 5 which is often associated with severely decrease FEV1

• Answer-
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

FIG 1. Asthma is made up of different endotypes, each characterized by its pathophysiology.

Allergy, Asthma & Immunology. (J Allergy Clin Immunol 2011;127:355-60.)
Distribution of Variables

Composite variables | Objective Data

- PFTs: Baseline, Max
- Demos: Race, Gender, Ages
- Alopys: Skin tests
- Meds
- Triggers: Infxn, ASA, Allergy
- Sxs: Activity level
- HCU: Past 12 months
- Family Hx: Parents, Sibs
- Smoke Exposure
- Hormones
- PMH: GERD, HTN

34 Total Variables, equally weighted

Moore et al. AJRCCM 2010; 181:315-323
### Asthma Cluster Analysis: 5 Clusters

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Mild Allergic Asthma</strong></td>
<td>Early onset asthma (EOA); 80% female; Normal lung function ≤ 2 Controllers; Minimal Health Care Utilization (HCU) (decreased EOS)</td>
</tr>
<tr>
<td><strong>2 Mild-Moderate Allergic Exacerbating Asthma</strong></td>
<td>Most common cluster; EOA; 87% female; Borderline normal FEV1 but reverses to normal; ≤ 2 Controllers; Very low HCU, but some steroid bursts (decreased EOS)</td>
</tr>
<tr>
<td><strong>3 Moderate-to-Severe Older Onset Asthma</strong></td>
<td>Older; LOA; higher BMI; 71% female; Less atopic; Moderate decrease in FEV1, some reversibility; On higher IC8; &gt; 3 Controllers, but despite this more OCS bursts (increased EOS)</td>
</tr>
<tr>
<td><strong>4 Severe Variable Allergic Asthma</strong></td>
<td>Young; EOA; 53% female; Severely decreased FEV1, but very reversible to near normal; OCS; &quot;Variable&quot; with need for frequent steroid bursts; High BAG &amp; GSS (increased EOS)</td>
</tr>
<tr>
<td><strong>5 Severe Fixed Airflow Asthma (&quot;COPD similarities&quot;)</strong></td>
<td>Older; LOA (longest duration); 83% female; Less atopic; Severely decreased FEV1, more fixed, less reversibility; On OCS; higher BMI; more GERD-HTN; high HCU, BAG &amp; GSS (increased PMN, EOS)</td>
</tr>
</tbody>
</table>

Moore et al. AJRCCM 2010; 181:315-323
Which is the correct statement for response to therapy?

• A. all patients respond to inhaled corticosteroids.
• B. All patients respond to montelukast, an anti-leukotriene receptor antagonist
• C. Salmeterol (LABA) is more effective than tiotropium (LAMA)
• D. Both tiotropium and salmeterol are about equal in efficacy in asthma

Answer:
Variability in Response to ICS Treatment:
Distribution of Responses Recorded in 3 Studies

Change in FEV₁ From Baseline, %

Adult Study (flunisolide)
CAMP (budesonide)
ACRN (triamcinolone)

Patients, %
Variability in Treatment Response:
Distribution of Individual Responses for FEV$_1$*

- Montelukast sodium 10 mg qd$^b$ (n=387)
- Beclomethasone$^c$
  200 mcg (4 puffs) bid$^d$ (n=251)

---

*$^a$FEV$_1$=forced expiratory volume in 1 second. $^b$qd=once daily. $^c$At the time of the study, the approved daily dose of beclomethasone was 6 to 20 puffs or 252 to 840 mcg/d.

$^d$bid=twice daily.

Genetic Variation in Leukotriene Pathway Genes and LTRA Responsiveness

Effect of SNPs in ALOX5 and MRP1 genes on FEV₁ following montelukast sodium therapy

% Change in % Predicted FEV₁

- ALOX5 rs2115819
  - P = 0.017

- MRP1 rs119774
  - P = 0.004

Genotypes: GG, GA, AA, CC, CT

*Analyses reported here were performed in 61 white participants who received 6 months of montelukast sodium therapy.

*P values are for ANOVA tests for differences in mean percentage changes.

LTRA = leukotriene receptor antagonist.

CLIC Primary Outcome: FEV$\textsubscript{1}$ Response

- Concordance Correlation: 0.55 (0.43, 0.65)
- Montelukast sodium alone: n=6 (5%)
- Both medications: n=22 (17%)
- Fluticasone propionate alone: n=29 (23%)
- ≥7.5% MT response
- Neither medication: n=69 (55%)
253 participants enrolled in 4-week run-in treatment with fluticasone propionate

92 underwent bronchoscopy and randomization

80 were PCR-negative for *M. pneumoniae* or *C. pneumoniae*
- 39 received placebo added to fluticasone
- 41 received clarithromycin added to fluticasone

12 were PCR-positive for *M. pneumoniae* or *C. pneumoniae*
- 6 received placebo added to fluticasone
- 6 received clarithromycin added to fluticasone

161 were excluded
- ACO score too low: 70
- Respiratory infection: 35
- Withdrew: 25
- Nonadherence: 13
- Lost to follow-up: 9
- Other: 6
- Nonasthma adverse event: 2
- Exacerbation: 1

FIG 1. Enrollment, randomization, and follow-up of participants.
FIG 2. Change in ACQ score over 16 weeks, within PCR strata by treatment allocation. There was a between-group difference of $0.2 \pm 0.2$ units ($P = .3$) in those who were PCR-negative and $0.3 \pm 0.5$ in those who were PCR-positive ($P = .6$).
Figure 2. Outline of Study Protocol.

Shown are the durations of the common run-in, treatment, and washout periods, along with periods in which baseline data for variables that were collected daily were obtained before each treatment period. During the 4-week run-in period and the 2-week washout periods, all patients received beclomethasone at a dose of 80 μg (2 puffs of 40 μg) twice daily. Only three of the six possible treatment sequences are presented graphically.
Increased exacerbations in the beclo group
Decrease response to albuterol in the salmeterol group
Figure 2E. Individual Responses to Tiotropium and Salmeterol: Asthma Control Days

Concordance Correlation Coefficient = 0.043
95% CI = (-0.110, 0.195)

- Neither medication: n=71 (43%)
- Tiotropium alone: n=21 (13%)
- Salmeterol alone: n=26 (16%)
- Both medications: n=48 (29%)
## Important cytokines as targets

<table>
<thead>
<tr>
<th>Function</th>
<th>Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulates eosinophils</td>
<td>IL-3</td>
</tr>
<tr>
<td></td>
<td>IL-5</td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
</tr>
<tr>
<td>Stimulates Mast Cells</td>
<td>IL-3 (SCF)</td>
</tr>
<tr>
<td></td>
<td>IL-4, IL-9</td>
</tr>
<tr>
<td>Stimulates IgE production</td>
<td>IL-4</td>
</tr>
<tr>
<td></td>
<td>IL-13</td>
</tr>
<tr>
<td>Suppresses T-helper-2 reactions</td>
<td>IL-2, IL-10 and IL-12</td>
</tr>
<tr>
<td></td>
<td>IF-gamma</td>
</tr>
</tbody>
</table>
## Allergic Cytokines

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-4</td>
<td>T cells</td>
<td>Increases production of IgE, increases number of Th2 cells</td>
</tr>
<tr>
<td>IL-5</td>
<td>T cells</td>
<td>Increases number of eosinophils</td>
</tr>
<tr>
<td>IL-9</td>
<td>T cells</td>
<td>Increases number of mast cells</td>
</tr>
<tr>
<td>IL-13</td>
<td>T cells, mast cells, basophils, eosinophils</td>
<td>Increases production of IgE, induces airway remodeling</td>
</tr>
<tr>
<td>IL-17</td>
<td>T cells</td>
<td>Increases neutrophil number, induces production of cytokines by airway epithelium</td>
</tr>
<tr>
<td><strong>Proinflammatory Cytokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>Epithelial cells, macrophages, mast cells</td>
<td>Proinflammatory</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Epithelial cells, macrophages</td>
<td>Proinflammatory</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Epithelial cells, macrophages, mast cells</td>
<td>Proinflammatory</td>
</tr>
<tr>
<td>TSLP</td>
<td>Epithelial cells</td>
<td>Activates dendritic cells, increases number of Th2 cells</td>
</tr>
<tr>
<td><strong>Chemokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCL2</td>
<td>Epithelial cells, macrophages, T cells</td>
<td>Recruits monocytes, T cells, dendritic cells</td>
</tr>
<tr>
<td>CCL5</td>
<td>Epithelial cells, macrophages, T cells</td>
<td>Recruits T cells, eosinophils, basophils</td>
</tr>
<tr>
<td>CCL11</td>
<td>Epithelial cells, macrophages</td>
<td>Recruits eosinophils</td>
</tr>
<tr>
<td>CXCL8</td>
<td>Epithelial cells, macrophages, mast cells</td>
<td>Recruits neutrophils</td>
</tr>
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</table>
Targets of monoclonal antibodies for asthma include?

• A. IL-2
• B. IL-13
• C. IL-4
• D. IL-5
• E. IL-9

• Answer-
Exacerbation

Reduces asthma exacerbations and symptoms

Plasma cell

B lymphocyte

\( \varepsilon \)-switch

Release of IgE

Omalizumab

Binds to free IgE, reducing cell-bound IgE

Reduces high-affinity receptors

Reduces mediator release

Allergic inflammation: eosinophils and lymphocytes

Omalizumab Mechanism of Action

Release of allergens

Allergic mediators

Mast cells

Basophils

Reduces asthma exacerbations and symptoms
Inflammation & Remodeling: Interleukin-13

• T-helper 2 cytokine

• Directs many of the processes involved in the allergic asthmatic response

• IL-13 alone is sufficient to induce responses in murine models of allergen challenge that resemble human asthma

• A relevant target for asthma therapy
Airway Remodeling in Asthma

- IL-13
- airway epithelium
- myofibroblast
- smc
- Th2 cell
- eosinophil
Murine models

IL-13 expression alone stimulates:
• Airway eosinophilia
• Goblet cell metaplasia and mucus hypersecretion
• Subepithelial airway fibrosis
• Methacholine airways hyperresponsiveness
• Airways obstruction
• Compliance alterations
• Airway epithelial cell hypertrophy

• Increased pulmonary expression of
  • TGFβ1
  • MMPs
  • VEGF
  • Hyaluronic acid
  • PDGF-AA and –CC
  • Eotaxin
IL-13 Overexpression = Remodeling

Homer RJ. Physiology 20:28-35, 2005
Increasing Doses of IL-13 Stimulated Airway Fibroblast Invasion in Asthma

8 asthma (FEV1: 85 ± 5%)
5 normal (FEV1: 105 ± 3%)

Lebrikizumab Treatment in Adults with Asthma

Jonathan Corren, M.D., Robert F. Lemanske, Jr., M.D., Nicola A. Hanania, M.D., Phillip E. Korenblat, M.D., Merdad V. Parsey, M.D., Ph.D., Joseph R. Arron, M.D., Ph.D., Jeffrey M. Harris, M.D., Ph.D., Heleen Scheerens, Ph.D., Lawren C. Wu, Ph.D., Zheng Su, Ph.D., Sofia Mosesova, Ph.D., Mark D. Eisner, M.D., M.P.H., Sean P. Bohan, M.D., Ph.D., and John G. Matthews, M.B., B.S., Ph.D.
Comparing anti-IL-13 receptor with placebo using periostin as a biomarker for IL-13

**Figure 1. Schematic Representation of the Study Design.**
Eligibility of the patients was established during a 2-week run-in period. This period was followed by a double-blind, randomized, placebo-controlled treatment period (day 1 to week 24) during which patients recorded their peak expiratory
All patients

Patients with high periostin levels

Patients with low periostin levels

Change in FEV1
CONCLUSIONS

Lebrikizumab treatment was associated with improved lung function. Patients with high pretreatment levels of serum periostin had greater improvement in lung function with lebrikizumab than did patients with low periostin levels. (Funded by Genentech; ClinicalTrials.gov number, NCT00930163.)
Mepolizumab: a humanized monoclonal antibody that binds to and inactivates interleukin-5.
Methods

• Randomized, double-blind, placebo-controlled study consisting of 61 subjects with refractory eosinophilic asthma and a history of recurrent severe exacerbations despite high doses of inhaled corticosteroids.

• Subjects randomly received infusions of either mepolizumab (29), or placebo (32) at monthly intervals for 1 year.

• The primary outcome measure was the number of severe exacerbations.
Results of asthma exacerbations
Results Blood and sputum eosinophils
Results Quality of Life Questionnaires

[Graphs showing comparison between placebo and Mepolizumab treatments over time with statistical significance marked.
P-values: 0.10 and 0.02]
Results - eNO and FEV1
Results

• Mepolizumab use reduced frequency of exacerbations and modestly increased asthma related quality of life AQLQ.

• There was no significant difference between the groups in peak flow, FEV₁, before/after bronchodilator or JACQ.

• In sputum samples collected during exacerbations, the mean eosinophil were lower on mepolizumab (1.5 vs 4.4%).
3-8 wks dose reduced weekly until there was an asthma exacerbation or an increase in ACQ-5 score by at least 0.5.
Wks 0-4 received the assigned study drug and continued to receive optimized dose of oral steroid.
Wks 4-20 the steroid dose was reduced according to a prespecified schedule by 1.25 to 10 mg per day every 4 weeks on the basis of asthma control and symptoms of adrenal insufficiency.
Effect of anti-IL5 on steroid sparing

Wks 20-24 no further adjustment made in oral steroid dose. Primary outcome measured at 24 weeks.

Wk 32 follow up safety visit.
Results

A Change from Baseline in Glucocorticoid Dose

- Placebo (N=66)
- Mepolizumab (N=69)

Median Change (%) vs. Week:

- Optimized dose
- Maintenance dose
**Results**

1.44 vs 2.12 exacerbations per year

CI 0.47-0.99

A clinically significant exacerbation was defined as a worsening leading to the doubling of the existing maintenance dose of steroids for 3 or more days or hospital admission or ER visit for asthma treatment.
Results

Between group difference - 0.52 points
CI -0.87 to -0.17

Improvement in the SGRQ score was also noted at week 24 (difference -5.8 points where change in 4 units considered clinically significant)
CI -10.6 to -1.0
Results

- Non-significant trend toward greater changes from baseline in the FEV1 before and after bronchodilation in the mepolizumab group (difference before 114 ml p=0.15, difference after 128 ml p=0.06).
- Mepolizumab significantly reduced blood eosinophil counts throughout the study (p<0.001).
A randomized, controlled trial to evaluate the effect of an anti-interleukin-9 monoclonal antibody in adults with uncontrolled asthma
Background

- Preclinical studies in animal models of asthma
  - support a contributing role for an IL-9 mast cell axis in the immunopathology of asthma
  - In one study, anti-IL-9 antibody treatment had a protective effect against airway remodeling in mouse models of airway inflammation, together with a concomitant reduction in the number and activation of mature mast cells
  - Furthermore, impaired lung function related to airway remodeling was reversed by IL-9 neutralization
- Evidence indicated that targeting IL-9 may offer a novel approach to the treatment of asthma
Methods

- Prospective double-blind, multicenter, parallel-group study
- 329 subjects were randomized (1:1:1:1) to subcutaneous placebo or MEDI-528 (30, 100, 300 mg) every 2 weeks for 24 weeks, in addition to their usual asthma medications.
- Randomization was stratified by asthma status (atopic or non-atopic) and ICS dose (medium or high).
  - High-dose ICS was defined as 1 puff twice a day of fluticasone/salmeterol (500 μg/50 μg)
  - Medium dose ICS was defined as 1 puff twice a day fluticasone/salmeterol (250 μg/50 μg) or 2 puffs twice a day budesonide/formoterol (160 μg/4.5 μg).
- Only subjects who were taking medium- to high-dose ICS at screening were enrolled
Study design

- **MEDI-528** 30 mg s.c. every 2 weeks (n = 80)
- **MEDI-528** 100 mg s.c. every 2 weeks (n = 80)
- **MEDI-528** 300 mg s.c. every 2 weeks (n = 80)
- Placebo s.c. every 2 weeks (n = 80)

- **Run in**
- **Steroid stable treatment period**
  - Primary Endpoint: ACQ-6
- **Steroid reduction treatment period**
- **Follow-up**
  - Secondary Endpoints:
    - ACQ-6
    - Asthma exacerbations
    - FEV₁
Mean (SD) change from baseline to week 13 in ACQ-6 scores for placebo vs combined MEDI-528 groups was −1.2 (1.0) vs −1.2 (1.1) (p = 0.86).
Exacerbations of Asthma

- Asthma exacerbation rates (95% CI) at week 25 for placebo vs MEDI-528 were 0.58 (0.36–0.88) vs 0.49 (0.37–0.64) exacerbations/subject/year (p = 0.52)
Change in FEV-1

- Mean increase from baseline in pre-bronchodilator FEV1 was similar on all groups at 13 and 25 weeks
Conclusions

• The addition of MEDI-528 to existing asthma controller medications was not associated with:
  – any improvement in ACQ-6 scores
  – asthma exacerbation rates
  – FEV1 values
  – was it associated with any major safety concerns
Effects of an Anti-TSLP Antibody on Allergen-Induced Asthmatic Responses

Gail M. Gauvreau, Ph.D., Paul M. O’Byrne, M.B., Louis-Philippe Boulet, M.D.,
Ying Wang, Ph.D., Donald Cockcroft, M.D., Jeannette Bigler, Ph.D.,
J. Mark FitzGerald, M.D., Michael Boedigheimer, Ph.D., Beth E. Davis, Ph.D.,
Clapton Dias, Ph.D., Kevin S. Gorski, Ph.D., Lynn Smith, Ph.D.,
Edgar Bautista, B.S., Michael R. Comeau, B.S., Richard Leigh, M.B., Ch.B., Ph.D.,
and Jane R. Parnes, M.D.
Background

• Thymic stromal lymphopoietin (TSLP) is an epithelial cell derived cytokine that is produced in response to pro-inflammatory stimuli.
  – Drives allergic response through its activity on innate immune cells, including dendritic cells, mast cells, and CD34+ progenitor cells.
• Levels of human TSLP mRNA and protein are increased in the airways of patients with asthma.
  – Magnitude of this expression correlates with the severity of disease
• AMG 157 is a human anti-TSLP monoclonal IgG2λ that binds human TSLP and prevents receptor interaction.
Objectives

• Examine the effects of Anti-TSLP Ab on early and late asthmatic response as well as other markers of inflammation such as blood eosinophils and FeNo.

• Evaluate side effect profile of Anti-TSLP Ab.

• In this proof-of-concept study, they tested the hypothesis that AMG 157 would attenuate allergen-induced airway responses in patients with mild atopic asthma.
Patients were randomly assigned, in a 1:1 ratio, to receive 700 mg of AMG 157 or placebo in a 1-hour intravenous infusion on study days 1, 29, and 57.

Figure 1. Study Design, Including Timing of Allergen Challenge and Study-Drug Administration. Black arrows indicate days on which allergen challenge was performed, and red arrows indicate the days on which AMG 157 or placebo was administered. AHR denotes airway-hyperresponsiveness testing, FeNO fraction of exhaled nitric oxide, PB peripheral-blood testing, and SI sputum induction. Asterisks indicate that sputum was collected 7 hours after allergen challenge.
The max % decrease in the FEV1 during the late response was 34.0% smaller in the AMG-157 group than in the placebo group on day 42 (P = 0.09) and 45.9% smaller (a decrease of 11.7% vs. 21.6%) on day 84 (P = 0.02).
Figure 3. Changes in Eosinophils in Peripheral Blood and Sputum and in the Fraction of Exhaled Nitric Oxide.
Conclusion

• In conclusion, treatment for 12 weeks with Anti-TSLP reduced the FeNo and blood and sputum eosinophilis in patients with allergic asthma.

• This treatment also attenuated allergen-induced changes in these inflammatory measures, as well as the early and late asthmatic responses, and increased the methacholine PC20.
Summary

• Inflammation leads to remodeling and increase decline in lung function
• Asthma seems to be many different disease with similar manifestations
• Response to medications varies from person to person
• I patients that are refractory monoclonal antibodies targeting specific cytokines may be effective