Advances and Controversies in the Treatment of Adult Asthma 2015

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Airway Pathology in Asthma

Normal

Asthma
Role of Inflammation and Bronchoconstriction in Asthma

- Reduced airway opening
- Excess mucus
- Muscle layer

- Bronchiole
- Tightened muscle
- Alveolus filled with trapped air

**Inflammation**

**Bronchoconstriction**
Entities that may Complicate Asthma

- GERD
- Sinus Disease
- Infections
- Allergies/ Allergic rhinitis
Aberrant Injury-Repair Responses Promote Airflow Obstruction in Asthma

>100 Years of Asthma Treatment


- Epinephrine
- Oral corticosteroids
- Theophylline
- Inhaled $\beta_2$-agonists
- Sodium cromoglycate
- Inhaled anticholinergic
- Inhaled corticosteroids
- Long-acting $\beta_2$-agonists
- Leukotriene inhibitors
- Anti-IgE
Current Asthma Therapies
PROBLEMS WITH CURRENT DRUG THERAPIES

• ONE SIZE DOES NOT FIT ALL
  – NOT EVERYONE RESPONDS BENEFICIALLY TO ALL THERAPIES

• THERE IS NO SUCH THING AS A FREE LUNCH
  – ADVERSE DRUG REACTIONS:
    • > 2 MILLION ADR/YEAR; >100,000 DEATHS/YEAR

• THERE IS A HUGE PLACEBO EFFECT
What is the solution?

How can we maximize response to therapy and minimize adverse effects?
Individualizing therapy

- Pharmacogenetics
- Biomarkers
- Race
- Novel Targeted therapies
Cellular elements and their products involved in asthma

- Mast cell
- Basophil
- Eosinophil
- Neutrophil
- Macrophage
- Dendritic cell
- Lymphocyte
- Fibroblast

Images from:
http://www.bloodline.net/
http://csi.washington.edu/education/inMotion/
http://biodidac.bio.uottawa.ca/Thumbnails/searchresults.htm?auteur=Harris
Potential Asthma Targets

- IL-4
- IL-13
- IL-2Rα
- IL-5
- GM-CSF
- T cell
- CD40
- CD40L
- B cell
- IL-4Rα
- FcεRI
- Plasma Cell
- IgE
- Mediators
- Cytokines
- Bone Marrow
- Eosinophil
- IL-9
- TNF-α
- VLA-4
- ICAM
- Blood Vessel
- Vessel Inflammation
Eosinophilic cytokines contribute to the chronic inflammatory process

**allergen/irritant**
- epithelial cell
- basophil
- smooth muscle cell

**IL-3, IL-6**
- IL-8, ECP
- RANTES
- MBP

**neutrophil**
- IL-8
- GM-CSF

**endothelial cell**
- IL-3
- IL-4
- GM-CSF
- TNF-α

**eosinophil**
- IL-4
- IL-5

**macrophage**
- RANTES
- IL-3, IL-5
- GM-CSF

**T_h0**
- IL-1
- IL-2
- IL-4
- IL-10
- IL-16

**T_h1**
- IL-4

**T_h2**
- IL-4

**RANTES**
- IL-3, IL-5
- GM-CSF

**neuron**

**myofibroblast**

**Eosinophilic cytokines contribute to the chronic inflammatory process**
Effector functions of eosinophil-derived cytokines

Spencer, Eosinophils in Health and Disease, 2010
Potential Eosinophil Selective Targets
IL-5
The targets: IL-5 or eosinophils (IL-5Rα)

**Eosinophil**
- Raised levels present in 40–60% of asthmatics
- Release toxins that promote airway inflammation in asthmatic patients

**IL-5**
- Principal eosinophilic regulatory cytokine
- Involved in the maturation, differentiation, survival and activation of eosinophils

IL, interleukin
Scientific rationale

• IL-5 is responsible for stimulating precursor cells to differentiate into eosinophils instead of other granulocytes

• Anti-IL-5 acts by binding circulating IL-5 and preventing binding to the IL-5 receptor

• Human diseases with selective eosinophilia are often accompanied by overproduction of IL-5

• Blockade of the interaction between IL-5 and its receptor decreases eosinophilia and associated tissue remodeling and fibrosis
# Anti-IL-5 drugs in development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Target</th>
<th>Mode of action</th>
<th>Effects</th>
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</thead>
<tbody>
<tr>
<td>Mepolizumab¹</td>
<td>GlaxoSmithKline</td>
<td>IL-5</td>
<td>Neutralising</td>
<td>Eosinophil counts decreased, eosinophil activation decreased, steroid-sparing effect in eosinophilic asthma (phase 3)</td>
</tr>
<tr>
<td>Reslizumab¹</td>
<td>TEVA pharmaceuticals</td>
<td>IL-5</td>
<td>Neutralising</td>
<td>Eosinophil counts decreased, airway function improved, asthma control possibly improved in patients with eosinophilic asthma (phase 3)</td>
</tr>
<tr>
<td>Benralizumab²</td>
<td>MedImmune</td>
<td>IL-5Rα</td>
<td>Cytotoxic and neutralising</td>
<td>Eosinophil counts decreased in a dose-dependent fashion (phase 1)</td>
</tr>
</tbody>
</table>

Effect of anti-IL-5 on blood eosinophil count

Anti-IL-5 did not improve lung function

Randomized Trial of Mepo (n=9) vs. Placebo (n=11) x 5 Months in Patients with Sputum Eosinophils and Asthma Symptoms Despite Prednisone

Mepolizumab in severe eosinophilic asthma

- Significant reduction in exacerbations (p=0.002)
- Significant reduction in steroid dose (84 vs. 48% reduction)
- Sustained benefit x 8 wks
- Reduced EOS
- No serious adverse events

Randomized Trial of Mepo (n=29) vs. Placebo (n=32) x 12 Months in Patients with Sputum Eosinophils and Refractory Asthma with Exacerbations

Mepolizumab and asthma exacerbations

Significant reduction in exacerbations

No effect on lung function, symptom scores or NO

Total exacerbations over time are reduced with mepolizumab vs. placebo

Inclusion criteria
- sputum eos >3%
- FeNO>50
- blood eos >300
- deterioration of asthma after <25% reduction in ICS or OCS
- >2 asthma exacerbations in previous year

Mepolizumab for severe eosinophilic asthma

- ~50% reduction in exacerbations/patient/year
- No effects on $\text{FEV}_1$, ACQ or AQLQ

MEPOLIZUMAB NEJM 2014

ORTEGA NEJM 2014

BEL NEJM 2014
Reslizumab for Poorly Controlled, Eosinophilic Asthma
A Randomized, Placebo-controlled Study

Mario Castro1, Sameer Mathur2, Frederick Hargrave3, Louis-Philippe Boulet4, Fang Xie5, James Young6, H. Jeffrey Wilkins6, Timothy Henkel6, and Parameswaran Nair7; for the Res-L-0010 Study Group

1Washington University School of Medicine, St. Louis, Missouri; 2University of Wisconsin, Madison, Madison, Wisconsin; 3McMaster University, Hamilton, Ontario, Canada; 4Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Quebec, Canada; 5Cephalon, Inc., Frazer, Pennsylvania; and 6United BioSource Corporation, Ann Arbor, Michigan

Rationale: Eosinophilic asthma is a phenotype of asthma characterized by the persistence of eosinophils in the airways. IL-5 is involved in the activation and survival of eosinophils.

Objectives: To evaluate the effect of the antibody to IL-5, reslizumab, in patients with eosinophilic asthma that is poorly controlled with high-dose inhaled corticosteroid.

Methods: Patients were randomly assigned to receive infusions of reslizumab at 3.0 mg/kg (n = 53) or placebo (n = 53) at baseline and at Weeks 4, 8, and 12, with stratification by baseline Asthma Control Questionnaire (ACQ) score less than or equal to 2 or greater than 2. The primary efficacy measure was the difference between the reslizumab and placebo groups in the change in ACQ score from baseline to end of therapy (Week 15 or early withdrawal).

Measurements and Main Results: Mean changes from baseline to end of therapy in ACQ score were −0.7 in the reslizumab group and −0.3 in the placebo group (P = 0.054) and in FEV1, were 0.18 and −0.08 L, respectively (P = 0.022). In those patients with nasal polyps, the changes in ACQ score were −1.0 and −0.1, respectively (P = 0.012). Median percentage reductions from baseline in sputum eosinophils were 95.4 and 38.7%, respectively (P = 0.007). Eight percent of patients in the reslizumab group and 19% of patients in the placebo group had an asthma exacerbation (P = 0.08). The most common adverse events with reslizumab were nasopharyngitis, fatigue, and pharyngolaryngeal pain.

Conclusions: Patients receiving reslizumab showed significantly greater reductions in sputum eosinophils, improvements in airway function, and a trend toward greater asthma control than those receiving placebo. Reslizumab was generally well tolerated.

Keywords: eosinophils; asthma; interleukin-5; reslizumab

Asthma is a chronic disease of the airways of the lungs characterized by airflow obstruction and airway hyperresponsiveness and inflammation. Although most patients with asthma are able on high doses, which can result in time off from work or hospitalization (1, 2).

Eosinophilic asthma is a phenotype of asthma that is characterized by the persistence of eosinophils in the lung and sputum.

The numbers of eosinophils in the blood and bronchial fluid can correlate with asthma severity (3). Eosinophils are involved in lung tissue remodeling, including airway thickening and fibrosis, and angiogenesis, which promotes further tissue growth and remodeling (4). Treatment strategies that aim to reduce the level of eosinophils in the sputum have resulted in improved control of asthma symptoms and fewer exacerbations (5, 6).

The proinflammatory cytokine IL-5 is a key mediator in the maturation, recruitment, and activation of eosinophils (7). Inhi-
Efficacy of reslizumab on ACQ score

- 106 patients randomized to Reslizumab 3 mg/kg vs placebo (IV dosing at weeks 0, 4, 8 and 12)

- Mean change in ACQ score was –0.7 in the reslizumab group and –0.3 in the placebo group (p=0.0541)
  - improvement of ≥0.5 in 59% of patients receiving reslizumab versus 40% with placebo (odds ratio 2.06; p=0.0973)

- Greater change from baseline in patients with nasal polyps –1.0 vs –0.1 with placebo (p=0.012)

Other efficacy results

- Mean change in FEV₁ was –0.08 in the placebo group versus +0.18 in reslizumab group (p=0.0023)
- Sputum eosinophil count reduced by 95.4% in reslizumab group vs. 38.7% in placebo group (p=0.0068)
  - reduction from baseline in blood eosinophil count also significantly greater with reslizumab (p<0.0001)
- Asthma exacerbations reported among 8% of patients receiving reslizumab and 19% of those receiving placebo (p=0.0833)

RESLIZUMAB AND EXACERBATIONS 2014

Placebo: N=244, median (95% CI) = 34.9 (23.3, NA)
Reslizumab 3.0 mg/kg: N=245, median (95% CI) = NA

Description of Planned Arm

- PLACEBO
- RESLIZUMAB 3.0 MG/KG

Censored observations: ↓↓↓
RESLIZUMAB AND FEV1

![Graph showing the LS Mean Change from Baseline in FEV1 for Placebo and Reslizumab 3.0 mg/kg. The graph includes data points at various visits (Baseline, Weeks 4, 8, 12, and Endpoint). There are annotations indicating statistical significance (* and **).]

Castro ERS 2014
**Benralizumab & Exacerbations**

By eosinophil status

- **Eosinophilic**
  - Placebo: RR=9% p=0.781
  - Benralizumab 2 mg: RR=36% p=0.173
  - Benralizumab 20 mg: RR=41% p=0.096*

- **Non-eosinophilic**
  - Placebo: RR=22% p=0.284

By baseline eosinophil level

- **≥200 cells/µL**
  - Benralizumab 2 mg: RR=-6% p=0.327
  - Benralizumab 20 mg: RR=43% p=0.049*
  - Benralizumab 100 mg: RR=57% p=0.002*

- **≥300 cells/µL**
  - Benralizumab 2 mg: RR=24% p=0.362
  - Benralizumab 20 mg: RR=57% p=0.015*
  - Benralizumab 100 mg: RR=70% p=0.024*

- **≥400 cells/µL**
  - Benralizumab 2 mg: RR=30% p=0.131*
  - Benralizumab 20 mg: RR=41% p=0.049*
  - Benralizumab 100 mg: RR=57% p=0.002*

*p < 0.169 versus placebo is statistically significant.

RR, rate ratio

Castro M et al. Lancet Resp Med 2014; S2213-26
Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.
Dupilumab in Asthma

Up to approximately 65 patients: dupilumab, 300 mg, subcutaneously, weekly
Up to approximately 65 patients: placebo, subcutaneously, weekly

Randomization
Day 29 Wk 4
Day 43 Wk 6
Day 50 Wk 7
Day 57 Wk 8
Day 64 Wk 9
Day 71 Wk 10
Day 78 Wk 11
Day 85 Wk 12

Background therapy, stable phase
Background therapy, withdrawal phase
Dupilumab monotherapy

Long-acting beta-agonist
Inhaled glucocorticoid

Fluticasone-
Dupilumab in Asthma

B. Time to Exacerbation

Cumulative Exacerbation Rate (%)

- Stable background therapy
- LABA withdrawal
- Tapering of inhaled glucocorticoid
- Dupilumab or placebo monotherapy

Placebo

- Hazard ratio: 0.10 (95% CI: 0.03-0.34)
- P<0.001

Dupilumab

No. at Risk

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<th>Week</th>
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</tr>
<tr>
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</tr>
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<tr>
<td>12</td>
<td>42</td>
<td>32</td>
</tr>
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</table>

Exacerbations — Primary End Point

- Placebo (N=52): 44%
- Dupilumab (N=52): 6%

87% reduction (P<0.001)
Periostin & Response to Lebrikizumab (Anti IL-13)

- Periostin is an IL-13 gene product
- Periostin may alter collagen fibrillogenesis or cross-linking and lead to stiffening of the matrix

Corren NEJM 2011
Sputum IL-13 and response to tralokinumab

- Placebo (sputum: all)
- Tralokinumab (sputum IL-13 <10 pg·mL⁻¹)
- Tralokinumab (sputum IL-13 ≥10 pg·mL⁻¹)

Change from baseline in ACQ-6 score

Piper ERJ 2013
Novel Asthma Therapies and Clinical Trials

- Anti IL5: mepolizumab, reslizumab
- Anti IL4-R alpha: dupilumab
- Anti IL13: lebrikizumab, tralokinumab
- Other Novel therapies:
  - New LABA/ICS
  - Anticholinergics: Tiotropium, Aclidinium
  - CRTH2 Antagonists
  - Anti TSLP
  - Anti M1’
  - TLR9 agonists
  - Antibiotics
  - Vitamin D
Bronchial Thermoplasty for Asthma
Reduction in Severe Exacerbations Maintained out to 5 years\(^1\)

- The reduction in severe exacerbations requiring systemic corticosteroids at 1 year (vs. sham-treated patients) was maintained out to at least 5 years.

Compared with 1 year prior to BT treatment (baseline):
- 44% average decrease in percentage of patients having severe exacerbations
- 48% average decrease in severe exacerbation event rates

Individualizing Asthma Therapy: Conclusions

- Response to asthma therapies is variable
- Need to understand who responds to what
- How will we decide which therapies work best in which patients?
- Can we use pharmacogenetics, biomarkers, or race to individualize therapeutic responses?
Asthma Biomarkers

- IGE
- FENO
- EOS
  - Sputum
  - Blood
- Periostin
- DPP4
Medicine currently

- Patient with medical condition seeks treatment
- Physician has 4 medication options
- Patient tries drug A: no response
- Patient tries drug B: Adverse reaction
- Patient tries drug C: Mild benefit
- Patient tries drug D: Good response
  - but 6 months have passed and underlying condition worsened!
Medicine: the future

• Patient with medical condition seeks treatment
• Physician has 4 medication options
• Patient gets blood test
• Patient gets started on Drug D and does well.
  – No waiting, no adverse effects

*Prescription based on science AND art of medicine*
Severe Asthma Pipeline

Novel drugs in Th2-mediated asthma space

- Dupilumab (Sanofi/Regeneron)
- Tralokinumab (AZ/MedImmune)
- Mepolizumab (GSK)
- Omalizumab (Genentech/Novartis)
- Benralizumab (AZ/MedImmune)
- Masitinib (AB Science)
- Tiotropium (Pfizer/BL)
- AZD-5069: CXCR2i (AZ)
- Brodalumab (IL17R) (AMG/AZ/MEDI)
- QGE-031 (Novartis)
- Lebrikizumab (Genentech)
- MEDI9929 (AMG/AZ/MEDI)
- Reslizumab (Teva)

Others:
- Masitinib
- Tiotropium
- AZD-5069: CXCR2i
- Brodalumab (IL17R)
- QGE-031
- Lebrikizumab
- MEDI9929
- Reslizumab

IL-5 Biologics
IL-13/4 Biologics
IgE Biologics
Other Biologics
Small Molecules
AZ/MEDI

Novel Non-Th2 Drugs