Clinical Pharmacology of Allergen-Induced Asthma

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Potential for Conflict of Interest

- **Advisory Boards**: AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, Merck, Verona.
- **Speakers Fees**: AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Takeda.
- **Grants-in-Aid**: AIM, Amgen, AstraZeneca, Axican, Genentech, GlaxoSmithKline, Novartis, Ono Pharma.
- **Employed by McMaster University.**
New Drug Development in Asthma

**Activity**
- Can it work?

**Efficacy**
- Does it work?

**Effectiveness**
- How well does it work? How safe is it? (in real life)

**Efficiency**
- Is it worth it?

**APPROVAL FOR USE**
- Phase IIa/b: Placebo controlled, n = 30-500
- Phase III: Placebo controlled, n = >5000

**FDA Approved Drugs**
- 2001: 30
- 2006: 25
- 2011: 20

<table>
<thead>
<tr>
<th>Year</th>
<th>Drugs Approved</th>
<th>Cost per New Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>2006</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>2011</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

- Pragmatic trials
- Phase IV studies

2001-2011:
- Approval for use
- FDA approved drugs
- Activity, Efficacy, Effectiveness, Efficiency
<table>
<thead>
<tr>
<th>STEP</th>
<th>REDUCE</th>
<th>INCREASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>asthma education</td>
<td>oral glucocorticosteroid (lowest dose)</td>
</tr>
<tr>
<td>2</td>
<td>environmental control</td>
<td>anti-IgE treatment</td>
</tr>
<tr>
<td>3</td>
<td>as needed rapid-acting $\beta_2$-agonist</td>
<td>medium- or high-dose ICS plus long-acting $\beta_2$-agonist</td>
</tr>
<tr>
<td>4</td>
<td>low-dose ICS*</td>
<td>leukotriene modifier</td>
</tr>
<tr>
<td>5</td>
<td>low-dose ICS plus long-acting $\beta_2$-agonist</td>
<td>sustained-release theophylline</td>
</tr>
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*inhaled glucocorticosteroids
** receptor antagonist or synthesis inhibitors
Challenges of New Drug Development for Difficult to Control Asthma

• Heterogenous population
  – Severe eosinophilic asthma
  – Non-eosinophilic asthma

• Co-morbidities
  – Rhinosinusitus
  – ABPA
  – Obesity
  – GERD
  – CHF
  – COPD

• Psychosocial issues

• Smoking

• Poor adherence
What Outcomes to Use to Determine Activity in Phase II?

- Asthma exacerbations
  - Impractical in Phase II
- Measure of asthma control (ACT, ACQ)
  - Difficult to achieve a clinically important difference when adding a new treatment
- AQLQ
  - As above
- Pulmonary function
  - Only when the new treatment is a bronchodilator
# GINA 2013

## Treatment Steps

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<th>Increase</th>
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### Controller Options

- **Low-dose ICS**
- **Leukotriene modifier**
- **Medium- or high-dose ICS**
- **Sustained-release theophylline**
- **Anti-IgE treatment**

*Inhaled glucocorticosteroids

**Receptor antagonist or synthesis inhibitors**
Allergen-Induced Bronchoconstriction

**FEV₁ (L)**
- Grass Pollen
- D. Pteronyssinus

**Time Post-Inhalation (h)**
- 0, 1, 2, 3, 4, 5, 6, 7, 8
Allergen-Induced Airway Hyperresponsiveness

MCh PC (mg/ml)

Sputum Eosinophils (x10 /ml)

Sputum MCC (x10 /ml)

% Fall in FEV

Baseline 7h 24h 2d 4d 7d

Diluent Allergen

Pharmacology of Allergen-Induced Responses

**TRUE POSITIVES**
- All conventional ICS
- LABAs
- Combination ICS/LABA
- SABAs
- Cromones
- Anti-LTs
- Anti-IgE
- Theophylline
- Anti-IL-5

**TRUE NEGATIVES**
- Esterase-sensitive steroids
- PAF antagonists
- Inhaled anti-LTs
- Thromboxane antagonists

**POSSIBLY TRUE NEGS**
- ? selectin inhibitors
- ? VLA4 antagonists
- ? CPG oligio
- ? Heparin derivitives
Pharmacology of Allergen-Induced Responses

**FALSE POSITIVES**
- Anti-histamines
- Anti-CD11a
- Inhaled PGE\(_2\)
- PDE4 antagonists
- PGE\(_1\) analogue

**FALSE NEGATIVES**
Effect of salmeterol compared with beclomethasone on allergen-induced asthmatic and inflammatory responses

Study Design

Day 1

Screening Allergen challenge

Day 8

Wash-out

Diluent challenge

Placebo

Day 9

Wash-out

Allergen challenge

Bronchial biopsy

Allergen challenge

Bronchial biopsy

Budesonide

Day 10

Wash-out

Allergen challenge

Bronchial biopsy

Bud/Form

Day 11

Wash-out

Allergen challenge

Bronchial biopsy

Pre-treatment

Blood

Mch PC$_{20}$

Sputum

Mch PC$_{20}$

Sputum

Allergen Challenge

FEV$_1$ 0 - 7 hrs

Sputum 7 hrs

Bronchial biopsy

Post-treatment

Mch PC$_{20}$

Sputum
Airway Myofibroblasts after Allergen Inhalation

Figure E3

Airway Myofibroblasts / mm²

- Placebo: P = 0.024
- Budesonide: P = 0.036
- Budesonide/Formoterol: NS

Comparisons with Placebo:
- Budesonide: P = 0.024
- Budesonide/Formoterol: NS
Airway Smooth Muscle

*Figure E5*

A

B

C

D

SM

BV

SM

SM

SM

SM

SM
Airway Smooth Muscle and Myofibroblast Transition

Area smooth muscle (%)

Myofibroblasts (per mm²)

- **Placebo**
- **Budesonide**
- **Budesonide/Formoterol**

Significant differences are indicated by *p* values:
- **p = 0.001**
- **p = 0.03**
- **p = 0.024**
- **p = 0.036**
- **p = 0.004**
Clinical Investigator Collaborative
• Modifications of existing drugs:
  – Ultra long-acting inhaled $\beta_2$-agonist
  – Non-steroid GR agonist

• New approaches
  – Anti-sense against IL-3, IL-5, GM-CSF and CCR3
  – Anti-sense IL-4R
  – Anti-IL-9
  – Anti-IL-13
  – Anti-C5a
  – Anti-Ox 40L
  – CXCR2 antagonist
  – $\alpha_7$ nicotinic agonist
  – Cys LT1 and LT2 antagonist
  – Anti-M1prime
  – Anti-TSLP
M1 Prime

M1 Prime

**Cellular Mechanisms**

- **Allergen**
  - Dendritic cell
  - T_{h}2 cell
  - IL-13
  - IL-4

**Cellular Response**

- Naïve B cell
- IgE-switched B cell
- IgE plasmablast
- IgE plasma cell
- Mast cell
- Basophil
- Allergen

**Activation**

- Histamine, leukotrienes, etc.

**Eosinophil influx**
Study Design

Gauvreau GM, et al. Submitted for publication
Effects on IgE

A Challenge specific allergens

B Total IgE

C Irrelevant allergens

Gauvreau GM, et al. Submitted for publication
Characterization of thymic stromal-derived lymphopoietin (TSLP) in murine B cell development in vitro

B cell development is dependent on both direct interactions with stromal cells and their secreted cytokines. The precise mechanisms by which these interactions regulate B cell differentiation are currently unknown. We report here that a novel growth factor thymic stromal-derived lymphopoietin (TSLP) can replace the activity of interleukin-7 (IL-7) in supporting B cell development in vitro. TSLP was found to promote the proliferation and differentiation of committed B220+ B cell progenitors from day 15 fetal liver. Phenotypic analysis of these...
Thymic stromal lymphopoietin and allergic disease

Steven F. Ziegler, PhD
Immunology Program, Benaroya Research Institute, and the Department of Immunology, University of Washington, Seattle, Wash

[Diagram showing the interactions of TSLP, TSLPR, IL-17Ra, Jak2, and Jak1 with Stat5 (Stat1,3,4,6) and DC activation, B cell development, and T cell homeostasis.]

[Another diagram illustrating the effects of TSLP on various cell types and factors such as viruses, inflammatory cytokines, protease allergens, bacteria, and bacterial products.]
Conclusions

• Allergen challenge is a valuable clinical model:
  – to study mechanisms of asthma.
    • Mast Cells
    • Basophils
    • Eosinophils
    • T-cells
    • Dendritic cells
    • Myofibroblasts
  – to evaluate potential new therapies for asthma
• AllerGen CIC is a unique consortium for new drug development for allergic asthma.
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