December 9, 2012
Particle Deposition and Small Airways in Asthma

Lanny J. Rosenwasser, M.D.
Dee Lyons/Missouri Endowed Chair in Immunology Research
Professor of Pediatrics
Allergy-Immunology Division
Children's Mercy Hospital
Kansas City, Missouri

Professor of Pediatrics, Medicine and Basic Science
University of Missouri Kansas City School of Medicine

World Allergy Organization (WAO)
is an international coalition of
89 regional and national allergy and clinical immunology societies.

WAO Mission
WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

Individual Membership
All active members of dues-paying Member Societies are Individual Members of the World Allergy Organization (WAO)

Small Airways Working Group
The WAO's Small Airways Diseases aims to provide a credible, evidence-based, global platform for physicians and other health care professionals around the world to have ease of access to the most relevant scientific, clinical and educational resources on small airway disease.

Small Airways Steering Committee
Meet the Web Editor of the Small Airways Working Group

Ves Dimov, MD
Allergist/Immunologist
Assistant Professor of Pediatrics and Medicine
University of Chicago, Illinois
Editor-at-Large, WAO Web Editorial Board

Dr. Ves Dimov, the working group's Web Content Editor, oversees the site's scientific literature database, ensuring it is current and relevant. Each month he writes a column, "What Is New in Small Airways Research," in which he highlights new research articles of particular value to physicians who treat patients with small airways diseases.

Disclosure Statement
Lanny J. Rosenwasser, MD

- **RESEARCH STUDIES**
  Genentech, Novartis, National Institutes of Health
- **CONSULTANT**
  A-Z, Genentech, Novartis, Regeneron, Sanofi-Aventis
- **SPEAKERS' BUREAU**
  Alcon, A-Z, Genentech, Novartis

Learning Objectives

- Understand the Concept of Particle Deposition
- Understand How Particle Size Impacts Deposition of Inhaled Asthma Medications
- Understand the Relationship of Particle Size and Deposition to Physiologic Responses of Small Airways

Characterization of aerosol output from various nebulizer/compressor combinations

![Graph showing aerosol output comparison](Image)

The Disease Process in Asthma is Located in All Parts of the Bronchial Tree, Small Airways and Alveoli.
**Small Airway Inflammation in Asthma: Background**

- Inflammation and airway remodeling in asthma extends into the small airways (< 2 mm diameter).
- This small airway inflammation may contribute to difficult-to-control asthma.

**Inflammation of Small Airways in Asthma**

Q Hamid et al. J Allergy Clin Immunol 1997;100:44-51

Surgical lung specimens from 6 patients with asthma and 10 controls were examined. There was a similar inflammatory process present in the peripheral (<2mm diameter) compared with the central airways.

**Immunohistochemical Markers in the Large & Small Airways**

![Immunohistochemical Markers](image)

**Difficult-to-Control Vs. Stable Asthmatics**

- There were no significant differences in lung function except increased closing volume and closing capacity in the difficult to treat asthmatics.
- “This is indicative of small airway pathology in these patients”
- “Delivery of anti-inflammatory medication to the small airways in this subgroup is of specific clinical relevance”.

**Andersen Sampler Simulates Human Respiratory System**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>Particle Size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11+</td>
</tr>
<tr>
<td>1</td>
<td>7.0-11.0</td>
</tr>
<tr>
<td>2</td>
<td>4.7-7.0</td>
</tr>
<tr>
<td>3</td>
<td>3.3-4.7</td>
</tr>
<tr>
<td>4</td>
<td>2.1-3.3</td>
</tr>
<tr>
<td>5</td>
<td>1.5-2.1</td>
</tr>
<tr>
<td>6</td>
<td>0.65-1.1</td>
</tr>
<tr>
<td>7</td>
<td>0.43-0.65</td>
</tr>
</tbody>
</table>

**Steroid Particle Size**

![Steroid Particle Size](image)

Adapted from Bensch and Newman. AJRCCM 2001:163(5) A440 at ERS 200
Study Design

- Crossover design
- 9 healthy subjects aged 18-52 years
- Randomized to receive inhaled technetium-99m labeled
  - HFA-beclometasone
  - CFC-fluticasone
  - CFC-beclometasone
Conclusions

- HFA-BDP is evenly distributed throughout the lungs and therefore reaches all sites of inflammation
- CFC-fluticasone is deposited primarily in the large and intermediate airways
- CFC-BDP is deposited almost exclusively in the large airways

Hydrofluoroalkane-134a Beclomethasone or Chlorofluorocarbon Fluticasone: Effect on Small Airways in Poorly Controlled Asthma


Study Design

Randomized, Open Label, Parallel Group

Randomization

Visit 1 Day 1
Visit 2 Week 4
Visit 3 Week 12

Asthma not controlled on med-high dose ICS

Endpoints

Screening Period
Visit 1 Visit 2 Visit 3
Pre-Bronchodilator
Spicrometry X X X
Closing volume X

Post-Bronchodilator (albuterol x 2 Puffs)
Spicrometry X
Plethysmography X

Results: Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>HFA-BDP (20)</th>
<th>CFC-FP (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>59%</td>
<td>55%</td>
</tr>
<tr>
<td>FEV25-75</td>
<td>33%</td>
<td>28%</td>
</tr>
<tr>
<td>RV</td>
<td>196%</td>
<td>205%</td>
</tr>
<tr>
<td>CV (L)</td>
<td>0.51</td>
<td>0.57</td>
</tr>
<tr>
<td>CV/VC</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>ICS (med/high)</td>
<td>5/15</td>
<td>3/6</td>
</tr>
<tr>
<td>Albuterol P/D</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Asthma score</td>
<td>4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Exacerbations

- During the blinded period 5/20 subjects receiving HFA-BDP and 0/10 receiving CFC-FP experienced exacerbations treated with prednisone.
- Subjects were tested at least one month following their last prednisone.
- Post-treatment parameters in these 5 subjects fell within +/- one SD of those of the other 15 HFA-BDP subjects.
Results: Pulmonary Function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HFA-BDP</th>
<th>CFC-FP</th>
<th>p (B)</th>
<th>p (BvF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV (L)</td>
<td>Pre</td>
<td>Post</td>
<td>p</td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>.51</td>
<td>.44</td>
<td>.57</td>
<td>.76</td>
</tr>
<tr>
<td>CV/VC</td>
<td>Pre</td>
<td>Post</td>
<td>p</td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>14.2</td>
<td>.02</td>
<td>15.8</td>
</tr>
<tr>
<td>RV%</td>
<td>Pre</td>
<td>Post</td>
<td>p (BvF)</td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>196</td>
<td>184</td>
<td>.005</td>
<td>205</td>
</tr>
<tr>
<td>FEV1 Post Br Dil</td>
<td>67.6</td>
<td>71.9</td>
<td>.02</td>
<td>66.4</td>
</tr>
<tr>
<td>FEF25-75 (post)</td>
<td>42.5</td>
<td>51</td>
<td>.002</td>
<td>36.8</td>
</tr>
</tbody>
</table>

Clinical Results

PEF 25%-75% Post Bronchodilator

Small Airway Patency

Closing Volume/Vital Capacity (CV/VC)

Pre-bronchodilator

Results: Diary & Peak Flows

Parameter | HFA-BDP | CFC-FP | p (B)  | p (BvF) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AM-PEF</td>
<td>Pre</td>
<td>Post</td>
<td>p</td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>363</td>
<td>333</td>
<td>.04</td>
<td>300</td>
</tr>
<tr>
<td>Phlegm</td>
<td>Pre</td>
<td>Post</td>
<td>p</td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>.14</td>
<td>.05</td>
<td>0</td>
</tr>
<tr>
<td>Albuterol use</td>
<td>Pre</td>
<td>Post</td>
<td>p</td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>.28</td>
<td>.02</td>
<td>.4</td>
</tr>
</tbody>
</table>

Conclusions

In patients with moderate to severe persistent asthma who were not adequately controlled on medium to high doses of inhaled corticosteroids.

The addition of HFA-BDP provided greater effects than the addition of a similar dose of CFC-FP on small airway parameters.
Comparison of ciclesonide and fluticasone propionate on small airway function

Baseline period 8 weeks

Ciclesonide 100 µg BID
Fluticasone 100 µg BID

Randomized, open-label, parallel group study with a treatment period of 8 weeks to compare effectiveness of small particle ICS (ciclesonide) and large particle ICS (fluticasone DPI) on small airway function.

Fluticasone DPI: particle size 5.4 µm diameter
Ciclesonide HFA: particle size of 1.1 µm diameter

Impulse oscillometry (IOS), a measure of small and large airway function

- RS: large and small airway resistance (5 Hz)
- R20: large airway resistance (20 Hz)
- R5-R20: small airway resistance
- X5: capacitive reactance in small airways (5 Hz)
- AX: area of low-frequency reactance

Changes in large and small airway resistance with ciclesonide and fluticasone propionate

Data are presented as mean values

Changes in capacitive reactance in small airways and in area of low-frequency reactance

Data are presented as mean values

Changes in eosinophil percentage of late-phase sputum with ciclesonide and fluticasone propionate

- Significant reduction of eosinophils in late-phase sputum in the ciclesonide group
- The percentage of early-phase sputum eosinophils remained unchanged in both groups

Changes in asthma control test (ACT) scores in the ciclesonide and fluticasone propionate groups

- Ciclesonide improved asthma control significantly
- Lung function was maintained in both groups
Summary and conclusions

- Ciclesonide improves small airway function and inflammation
- In mild patients pre-treated with fluticasone DPI, asthma control improved significantly if switched to the small particle ICS ciclesonide
- This study provides evidence that IOS and late-phase induced sputum allows detection of changes in the small airways that can not be detected by spirometry

The Utility of Forced Expiratory Flow between 25% and 75% of Vital Capacity in Predicting Childhood Asthma Morbidity and Severity


<table>
<thead>
<tr>
<th>Severity of asthma</th>
<th>Low FEV₁/FVC (n = 33)</th>
<th>Low FEF₂₅₋₇₅ (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>19.7% (5)</td>
<td>19.7% (5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>44.7% (15)</td>
<td>44.7% (15)</td>
</tr>
<tr>
<td>Severe</td>
<td>34.8% (13)</td>
<td>34.8% (13)</td>
</tr>
<tr>
<td>Non-asthma controls</td>
<td>34.8% (13)</td>
<td>34.8% (13)</td>
</tr>
</tbody>
</table>

Note: Comparison of age, gender, and severity differences. FEV₁/FVC and FEF₂₅₋₇₅ were measured using standardized spirometry. FEV₁/FVC was determined using the FEF₂₀⁻₁₂₀ technique. FEF₂₅₋₇₅ was determined using the FEF₂₀⁻₁₂₀ technique. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.5.1.