Small Airways: How To Confident Diagnosis and Management?

Assistant Prof. Siwasak Juthong, M.D.
Division of Respiratory and Respiratory Critical Care Medicine
Faculty of Medicine
Prince of Songkla University
Outlines

• Definition of small airways
• Small airways inflammation in asthma, COPD
• Techniques for assess small airways
• Treatment small airways
Airway generations

<table>
<thead>
<tr>
<th>Large airways (&gt; 2 mm)</th>
<th>Bronchi</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trachea</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Bronchioles</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Small airways (&lt; 2 mm)</td>
<td>Terminal Bronchioles</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Respiratory bronchioles</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Alveolar ducts</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Alveolar sacs</td>
<td>22</td>
<td>23</td>
</tr>
</tbody>
</table>
Small Airways Dysfunction in Asthma
Asthma control is still not optimal

- Asia Pacific region
  - 51% daytime asthma symptoms
  - % of severe persistent asthma well or completely controlled
- ICS/LABA: GOAL study
  - 71% asthma well controlled
  - 41% ‘totally’ controlled

Small airways phenotype

- asthma complex clinical syndrome
- ‘umbrella’ term heterogeneous group of phenotypes and endotypes
- different treatment responses
- one treatment not fit to all
- personalising asthma therapy based on specific phenotypes
Small airways phenotype

- Poor asthma control and frequent exacerbations exhibit persistent airways inflammation that is not controlled by existing anti-inflammatory treatments.
- Small airways phenotype.

- Small airways inflammation and dysfunction, not being targeted or controlled by current therapies;
- Inability of inhaler to deliver and deposit aerosolised medicine to treat small airway region of the lung.
Clinical pattern recognition of the small airway asthma phenotype

Suboptimum asthma control

- Asthma control questionnaire score > 1.5
- Daytime and night-time symptoms
- Regular use of relievers in response to allergen
- Oral corticosteroid use with viral exacerbations
- Failure to respond to conventional coarse-particle ICS /LABA
Clinical pattern recognition of the small airway asthma phenotype

Small airways dysfunction

- Normal FEV1 in conjunction with any of:
  - Reduced FEF25–75
  - Abnormal airway resistance (R5–R20, Raw) or reactance area (AX)
- Evidence of air trapping (closing volume, residual volume)
- Abnormal ventilation heterogeneity (Sacín and Scond)
Asthma and small airways

- Asthma inflammation involves large airways
- Histopathological inflammation also involves small airways
- Inflammation complete airway tree
- Small airways major site of airflow limitation in asthma and COPD
- Known as the ‘quiet zone’ as conventional physiological measurements unable to sensitively evaluate small airway
Evidence for small airways inflammation

- nocturnal asthma inflammatory involvement of small airways
- nocturnal asthma increased eosinophil and macrophage counts in biopsies distal airways during night\(^1\)
- significantly eosinophils in distal airways compared to proximal airway tree in biopsies undertaken during the night.
- increased peripheral airways resistance, both during night and mid-afternoon\(^2\)

Evidence for small airways inflammation

- Small airways dysfunction exercise-induced asthma and severity of exercise-induced bronchoconstriction
  - Increase peripheral resistance

Small airways dysfunction

- more severe, difficult-to-treat, unstable asthma.
- single-breath nitrogen washout: closing volume (CV), air-trapping due to early small airways closure
- CV sensitivity to small airways inflammation than (FEF<sub>25-75%</sub>)
- difficult-to-treat asthmatics with frequent exacerbations enhanced airway closure (CV) vs severe asthmatics without recurrent exacerbations
- multiple-breath nitrogen washout test

Small airways dysfunction

- Different exhaled nitric oxide : alveolar nitric oxide
- Small airway dysfunction in GINA 2-4
- Alveolar nitric oxide concentrations predict response to treatment with small particle aerosols ICS

Impulse oscillometry (IOS)

- IOS utilises indices of reactance (X), resistance (R) and impedance (Z)
- Based on oscillating pressure/flow signals of moving air within the lungs
- Different frequencies determine airway mechanics from different lung region
- Changes in resistance between 5 and 20 Hz (R5-R20 Hz) and capacitive reactance at 5 Hz (X5 Hz) arising from more distal airways
- Higher frequencies are considered to reflect changes from more central larger airways
Impulse oscillometry (IOS)

- Impair R5-R20 Hz in 2/3 of GINA step 2-4
- small particle corticosteroid treatment significantly lowered total airway resistance (R5 Hz) compared to standard corticosteroid

Small airways dysfunction

- small airways impairment (body Box lung hyperinflation FRC, RV,RV/TLC)
  - in 40% stable moderate-to-severe asthma treated with ICS/LABA, normal FEV1
- conventional physiological measurements unable to sensitively evaluate small airways

Evaluating small airways dysfunction and asthmatic patient phenotypes
Schematic overview most widely used tests to identify small airway dysfunction

Verbanck S. Respiration 2012;84:177–188
<table>
<thead>
<tr>
<th>Assessment Method</th>
<th>Small Airway Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td>FVC/SVC, FEV3, FEV6, FEF25-75</td>
</tr>
<tr>
<td>Body Plethysmography</td>
<td>RV/TLC, DLCO, Raw</td>
</tr>
<tr>
<td>Single Breath Nitrogen Washout</td>
<td>CV, CC</td>
</tr>
<tr>
<td>Multiple Breath Nitrogen Washout</td>
<td>Sacin, Scond</td>
</tr>
<tr>
<td>Forced Oscillation Technique</td>
<td>R5-R20, X5, AX, Fres</td>
</tr>
<tr>
<td>Exhaled Nitric Oxide</td>
<td>FVC/SVC</td>
</tr>
<tr>
<td>Bronchoconstrictor airway challenge</td>
<td>AMP</td>
</tr>
<tr>
<td>Prolonged Sputum Induction</td>
<td>Late-phase sputum</td>
</tr>
<tr>
<td>High Resolution Computed Tomography</td>
<td></td>
</tr>
</tbody>
</table>

Usmani OS. Allergy Asthma Immunol Res. 2014 September;6(5):376-388
Rationale to treat the lung periphery

- 2X ICS dose not decrease alveolar nitric oxide,
- conventional inhaler devices large particles ICS unable to target persistent distal airways inflammation
- anti-inflammatory treatment reach small airways - oral corticosteroid 2 weeks of treatment, alveolar nitric oxide dramatically reduced

Inhalation drug

- 20% reach lung
- 80% oropharynx
size-dependent deposition of particles in lungs

small drug particles (1.5 microns) better total lung deposition and peripheral airways distribution compared with larger particles (3.0 and 6.0 microns)

van Rijt SH et al Eur Respir J 2014; 44: 765–774
ICS particle size depends upon the formulation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation/device</th>
<th>MMAD μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP [27]</td>
<td>dry powder/DPI</td>
<td>5.4</td>
</tr>
<tr>
<td>BUD [27]</td>
<td>dry powder/DPI</td>
<td>4.0</td>
</tr>
<tr>
<td>Mometasone furoate [28]</td>
<td>dry powder/DPI</td>
<td>3.7</td>
</tr>
<tr>
<td>FP [29]</td>
<td>HFA suspension/pMDI</td>
<td>2.4</td>
</tr>
<tr>
<td>BDP/formoterol [30]</td>
<td>HFA solution/pMDI</td>
<td>1.5</td>
</tr>
<tr>
<td>BDP [31]</td>
<td>HFA solution/pMDI</td>
<td>1.1</td>
</tr>
<tr>
<td>CIC [32]</td>
<td>HFA solution/pMDI</td>
<td>1.1</td>
</tr>
</tbody>
</table>

M MAD = Mass median aerodynamic diameter

Usmani OS. Respiration 2012;84:441–453
Drug delivery to the peripheral airways

- DPI larger particles < HFA-pMDI inhalers
- HFA-solution pMDI inhalers smallest aerosol particle sizes compared to HFA-suspension aerosols
- small particle aerosols of ICS/LABA improve total lung dose levels 30 to 50%
- small aerosol particles are able to effectively deliver inhaled drug to the periphery of the lungs

Usmani OS. Allergy Asthma Immunol Res. 2014 September;6(5):376-388
Small Particle Aerosols

- small particle (~1.5 microns) BDP/Form HFA-solution pMDI
  - 2/3rd central airways deposition
  - 1/3rd peripheral airways deposition
- BDP/Form novel DPI particle (~1.5 microns) sized aerosols
  - 2/3rd central
  - 1/3rd peripheral
- small particle aerosols now allows us to achieve deposition to treat the whole airway tree; that is, simultaneously targeting drug to the large and also the small airways

Drug delivery to the peripheral airways

- Deposition drug differing severities of airflow obstruction.
- Small particle (~1.5 microns) HFA-solution pMDI BDP/Form
  - 34% total lung deposition in healthy FEV1 112% pred
  - 31% asthmatic patients FEV1 75% of pred
  - 33% COPD FEV1 44% of pred

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Study Design</th>
<th>Efficacy Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFA-BDP/F (100/6 μg bd) N=228</td>
<td>moderate to severe asthma, as efficacious as FP/Salm for PEF and symptom-free days</td>
<td>BDP/F showed significantly faster bronchodilation than FP/S. BDP/F showed a significant increase in FVC compared to FP/Salm</td>
</tr>
<tr>
<td>HFA-FP/Salm (125/25 μg bd) 3 mon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFA-BDP/F (200/12 μg bd)</td>
<td></td>
<td>BDP/F as efficacious to BUD/F for DPI-morning PEF and symptom free days</td>
</tr>
<tr>
<td>BUD/F (400/12 μg bd)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFA-BDP/F (200/12 μg bd) N=422</td>
<td></td>
<td>BDP/F as efficacious as FP/Salm on DPI-morning PEF. Over 96% patients remain controlled on BDP/F (400/24 μg daily) after being stepped down from FP/Salm (1,000/100 μg daily)</td>
</tr>
<tr>
<td>asthma, 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP/Salm (250/50 μg bd)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFA-BDP/F (200/12 μg bd) N=10</td>
<td></td>
<td>BDP/F led to a significant decrease in closing volume whereas no significant changes from baseline were detected with FP/Salm</td>
</tr>
<tr>
<td>moderate asthma, 6 month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP/Salm (250/50 μg bd)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ICS monotherapy small particle vs large particle

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Population</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFA-CIC (200 μg od)</td>
<td>N=30 mild asthma</td>
<td>2 months CIC significantly improves small airway function (IOS R5-R20) and inflammation (late-phase sputum) and asthma control (ACT) compared with FPHFA-CIC (80 μg od)</td>
</tr>
<tr>
<td>DPI-FP (100 μg bd)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIC (80 μg od)</td>
<td>N=480 mild to moderate asthma, 6 months</td>
<td>Low-dose CIC as efficacious as high-dose FP in FEV1 improvement</td>
</tr>
<tr>
<td>HFA-FP (100 μg bd)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFA-CIC (80 μg od or 320 μg od)</td>
<td>N=554 mild to moderate asthma, 3 months</td>
<td>Both CIC doses as efficacious as BUD in DPI-asthma, 3 months improving pulmonary function FEV1, PEF and asthma symptom control. CIC was not associated with significant urinary cortisol suppression, unlike BUD</td>
</tr>
<tr>
<td>BUD (400 μg bd)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Usmani OS. Allergy Asthma Immunol Res. 2014 September;6(5):376-388
Effectiveness of small particle aerosol asthma treatments

(i) aerosol particle size
(ii) physicochemical properties of the corticosteroid,
(iii) airway drug deposition characteristics (greater lung deposition and lower oropharyngeal deposition)
(iv) need for less reliance on an optimal inhalation flow (particularly compared to conventional DPIs)

Conclusion

• small airways in patients with asthma, which till recently remained forgotten
• target small airways clinical efficacy superior to that of conventional larger particle size medications
• technology deliver drug to target the whole respiratory tree (large and small airways)
• developed more sensitive physiological techniques to assess distal airway tree

• The small airways are no longer silent!
Small Airways Obstruction in COPD
Small airway morphology in non-smoking subject and COPD patient

nonsmoker
peripheral airway (arrow) adjacent to pulmonary arteriole.
airway wall is thin,
lumen is wide open
intact alveoli are attached along its circumference

smoker with COPD
lumen of airway is narrowed
contains mucus and cellular debris
airway wall is thickened
airway smooth muscle and fibrosis
alveolar attachments broken
its circumference are broken

Baraldo S. Respiration 2012;84:89–97
<table>
<thead>
<tr>
<th>Structural changes in peripheral airways</th>
<th>Smokers with COPD</th>
<th>Smokers without COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal occlusion</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Goblet-cell metaplasia</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Squamous-cell metaplasia</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Muscle hypertrophy and hyperplasia</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Total wall thickening</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Loss of alveolar attachments</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>
The Nature of Small-Airway Obstruction in Chronic Obstructive Pulmonary Disease

Wall thickness

A

B

C

D

Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease

John E. McDonough, M.Sc., Ren Yuan, M.D., Ph.D., Masaru Suzuki, M.D., Ph.D., Nazgol Seyednejad, B.Sc., W. Mark Elliott, Ph.D., Pablo G. Sanchez, M.D., Alexander C. Wright, Ph.D., Warren B. Gefter, M.D., Leslie Litzky, M.D., Harvey O. Coxson, Ph.D., Peter D. Paré, M.D., Don D. Sin, M.D., Richard A. Pierce, Ph.D., Jason C. Woods, Ph.D., Annette M. McWilliams, M.D., John R. Mayo, M.D., Stephen C. Lam, M.D., Joel D. Cooper, M.D., and James C. Hogg, M.D., Ph.D.
terminal bronchiole

No. of Small Airways

No. of Airways per Generation

Terminal Bronchioles

levels of emphysematous destruction
narrowing and loss of terminal bronchioles preceded emphysematous destruction in COPD

narrowing and disappearance of small conducting airways before the onset of emphysematous destruction can explain the increased peripheral airway resistance reported in COPD

interaction between the peripheral airways and parenchyma

permanent enlargement of the distal airspaces may serve only as a structural biomarker, being a secondary result of small-airway inflammation and destruction
Two Models of Parenchymal Airspace Enlargement in COPD

A. Initial alveolar destruction
- Axial tension
- Alveolar inflammation
- Rupture of alveolar walls
- Loss of alveolar walls with expanded airspaces

B. Initial terminal bronchiolde destruction
- Axial tension
- Neutrophils
- Small-airway inflammation
- Loss of acinar tethering; collapse and folding of alveolar walls

Mitzner W. NEJM 2011; 365: 1637-39
Small-Particle Aerosols and COPD

- small-particle HFA solution pMDI aerosol BDP/FOR (400/24 g daily) VS DPI-FP/SAL combination (500/100 g daily)
- 18 patients with severe stable COPD.
- compare baseline small particles of HFA-BDP/FOR achieved a significant reduction in the air-trapping physiological (RV),(TLC) and FRC not achieved with the DPI-FP/SAL
- Comparing HFA-BDP/FOR treatment to DPI-FP/SAL, significantly greater reduction in RV with small-particle HFA aerosols
- Improved dyspnea TDI > MCID point

Transition dyspnea index score

- HFA-pMDI BDP/formoterol (200/12 g, BID), DPI BUD/formoterol (400/12 g, BID) DPI formoterol alone (12 g, BID) for 48 wks
- Primary endpoint FEV1,AECOPD : similar
- 6 walk only small particle > MCID

Peripheral deposition of the small-particle aerosol and its physiological effects on dynamic hyperinflation and distal-airway air trapping

Conclusion

- Small airways dysfunction significant important in asthma and COPD
- New small particles aerosol drug improved clinical outcomes in airway inflammation
- Bright future for treatment airflow obstruction
Thank You for Your Attention
Effects of 24-week add-on treatment with ciclesonide and montelukast on small airways inflammation in asthma

Hitoshi Nakaji, MD *;†; Guergana Petrova, MD, PhD *; Hisako Matsumoto, MD, PhD *; Toshiyuki Iwata, MD *; Isao Ito, MD, PhD *; Tsuyoshi Oguma, MD *; Hideki Inoue, MD *; Tomoko Tajiri, MD *; Tadao Nagasaki, MD *; Yoshihiro Kanemitsu, MD *; Akio Niimi, MD, PhD *;†; and Michiaki Mishima, MD, PhD *

* Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan
† Department of Respiratory Medicine, Wakayama Red Cross Hospital, Wakayama, Japan
‡ Division of Respiratory Medicine, Department of Medical Oncology and Immunology, Nagoya City University School of Medical Sciences, Nagoya, Japan

ARTICLE INFO
Article history:
Received for publication October 5, 2012.
Received in revised form November 26, 2012.
Accepted for publication December 18, 2012.

ABSTRACT
Background: Eosinophilic inflammation of the small airways is a key process in asthma that often smolders in treated patients. The long-term effects of add-on therapy on the persistent inflammation in the small airways remain unknown.
Objective: To examine the effects of add-on therapy with either ciclesonide, an inhaled corticosteroid with extrathin particles, or montelukast on small airway inflammation.
Methods: Sixty patients with stable asthma receiving inhaled corticosteroid treatment were enrolled in a randomized, open-label, parallel comparison study of 24-week add-on treatment with ciclesonide or montelukast. Patients were randomly assigned to 3 groups: ciclesonide (n = 19), montelukast (n = 22), or no add-on as controls (n = 19). At baseline and at weeks 4, 12, and 24, extended nitric oxide analysis; pulmonary function tests, including impulse oscillometry; blood eosinophil counts; and asthma control tests (ACTs) were performed.
Results: A total of 18 patients in the ciclesonide group, 19 in the montelukast group, and 15 in the control group completed the study and were analyzed. With repeated-measures analysis of variance, ciclesonide produced a significant decrease in alveolar nitric oxide and a significant improvement in ACT scores over time. Montelukast produced significant decreases in alveolar nitric oxide concentrations and blood eosinophil counts over time and slightly improved ACT scores, whereas no such changes were observed in the control group. Alveolar nitric oxide concentrations with ciclesonide and reactance area at low frequencies with montelukast produced greater improvements over time compared with control.
Conclusion: Ciclesonide add-on therapy and montelukast add-on therapy may act differently, but both separately can improve small airway abnormalities and provide better asthma control.
Extrafine beclomethasone/formoterol combination via a dry powder inhaler (NEXThaler®) or pMDI and beclomethasone monotherapy for maintenance of asthma control in adult patients: A randomised, double-blind trial

Frank Kannies a,⁎, Mario Scuri b, Stefano Vezzoli b, Catherine Francisco c, Stefano Petruzzelli b