Control of Asthma, the role of Small Airway Dysfunction and the Utility of ICS/LABAs (Fluticasone/Formoterol) in the Treatment of Bronchial Asthma

Speaker: Dr Sri Wahyu Taher  
Department: Family Medicine, KK Simpang Kuala, Alor Setar  
Country: Malaysia  
Date: 3 August 2017
Asthma therapy has come a long way!

Adapted from David Price Illustration on Evolution of Treatment for Asthma
Prevalence of asthma symptoms among 13-14 year olds (ISAAC).

Prevalence of symptoms of asthma in the past 12 months among persons aged 18 to 45 years in 70 countries

The burden of asthma, is greatest in children approaching adolescence (ages 10-14) and the elderly (ages 75-79).

- 334 million people have asthma.
- 14% of the world’s children experience asthma symptoms.
- 8.6% of young adults (aged 18-45) experience asthma symptoms.
- 4.5% of young adults have been diagnosed with asthma and/or are taking treatment for asthma.
- The burden of asthma is greatest for children aged 10-14 and the elderly aged 75-79.
- Asthma is the 14th most important disorder in the world in terms of the extent and duration of disability.

Institute for Health Metrics and Evaluation (IHME)
Physicians perceive that asthma control for patients means absence of symptoms

- Physicians perceive that patients relate ‘well-controlled asthma’ with absence of symptoms, especially shortness of breath (34%), cough (19%) and wheezing (12%)

<table>
<thead>
<tr>
<th>(Perceived) Patients’ understanding of well-controlled asthma</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Asthma symptoms are non-existent/minimal</td>
<td>58%</td>
</tr>
<tr>
<td>No /reduced attacks</td>
<td>40%</td>
</tr>
<tr>
<td>Minimal impact on patients daily life</td>
<td>35%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minimal/ no symptoms of respiratory symptoms</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No shortness of breath/no dyspnea/</td>
<td>34</td>
</tr>
<tr>
<td>no difficulty in breathing</td>
<td></td>
</tr>
<tr>
<td>No coughing</td>
<td>19</td>
</tr>
<tr>
<td>Minimal/no symptoms from asthma (general)</td>
<td>17</td>
</tr>
<tr>
<td>No wheezing</td>
<td>12</td>
</tr>
<tr>
<td>No chest tightness</td>
<td>7</td>
</tr>
</tbody>
</table>

“(Well-controlled asthma means) patient does not feel symptoms and have no inconveniences in daily life.”
- Respiratory specialist, South Korea

“No asthma attack for the whole month. They can do normal activities. No shortness of breath/ no difficulty of breathing.”
- Primary care physician, Philippines

REALISE Asia
There is Discrepancy in Perceived vs. GINA-defined Asthma Control Status

- Patients overestimate their own asthma to be well-controlled vs clinical symptoms
- Physicians perceive a higher proportion of their patients to have well-controlled status (53%)
- This is especially so among PCPs compared with respirologists/allergologists

**Perception of Control**
- Patients: 89% perceived control, 11% did not
- Physicians: 50% perceived control, 31% did not

**GINA-defined control status among patients**
- GINA-defined: 32% well-controlled, 18% not well-controlled

**(Perceived) asthma control status among current patients**
- Physicians: 53% perceived control, 16% did not
- Patients: 50% perceived control, 32% did not

Data are shown as percentage of patient respondents n=2467 [SK (500), MY (151), SG (200), HK (200), CH (800), TW (300), ID (166), PH (150)].

REALISE Asia
What are the reasons for poor Asthma control?

Asthma Control Assessed

Uncontrolled

Incorrect Diagnosis
Poor Adherence
Inhaler Technique
Inadequate Treatment

Asthma Pathology involves Large & Small Airways

The majority of bronchial tree generations are made up of small airways (<2mm diameter)

Figure adapted from: Weibel ER. Morphometry of the Human Lung. 1963
The Small Airways (<2 mm diameter) account for ~98.9% of Total Lung Volume

2. Figure adapted from: Weibel ER. Morphometry of the Human Lung. 1963.
Pathophysiology of Small Airway Dysfunction
Impact on Structure, Function and Asthma Outcomes

- Small airway inflammation
  - Deposition of inflammatory infiltrate
  - Sub-epithelial fibrosis
  - Increased smooth muscle mass
  - Low collagen

- Mucus plugging
- Air trapping

- Peripheral Airway Resistance
  - Increased Residual Volume
  - Increased Forced Vital Capacity
  - Normal FEV1/FVC ratio
  - Low or normal FEV1
  - Low FEF 25-75%

- Increased Risk of Future Exacerbations

3. van den Berge et al, Chest 2011;139;412-423
4. Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)
Abnormalities of the peripheral airways (Alveolar NO) are implicated in Asthma Control in Mild Untreated Asthma (n=78)

Scichilone et al, JACI 2013
Small Airways Dysfunction (SAD) Implicated in Asthmatic Patient Phenotypes

1. Kraft, AJRCCM 1996; Kraft, AJRCCM 2001
3. D’Amato, ERJ 2002; Zeidler, JACI 2006
4. Carroll, ERJ 1997
5. In’t Veen, AJRCCM 2000

- Nocturnal Asthma
- Exercise Induced Asthma
- Allergic Asthma
- Fatal Asthma
- Severe Asthma
- Mild Asthma
Nocturnal Asthma is associated with Small Airway Inflammation and increased Peripheral Resistance

Small airway dysfunction may explain the increased night symptoms in patients with nocturnal asthma

Kraft, AJRCCM 1996, 2001
Mild Asthmatics with Normal Lung Function demonstrate x7 increase in Peripheral Resistance

Increased small airway resistance may contribute to increased airway responsiveness in asthma

Addition of LABA to ICS improves Asthma Control

Asthma control was achieved in ~80% of the patients with addition of LABA to ICS

Bateman ED et al. Am J Respir Crit Care Med 2004; 170:836-44
Same inhaler is effective than Mixed Inhaler Devices

Retrospective observational study to compare outcomes for patients who were prescribed the same inhaler devices versus mixed device types for asthma controller and reliever therapy.

Patients who were prescribed the same device were significantly more likely to achieve asthma control and recorded significantly lower severe exacerbation rates than with mixed devices.

Combining Fluticasone & Formoterol in One Inhaler: UK Respiratory Specialists Perceptions

<table>
<thead>
<tr>
<th>Most effective combination (n = 82)</th>
<th>Why fluticasone/formoterol (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fluticasone/formoterol</em> 41%</td>
<td><em>Good/potent steroid</em> 79%</td>
</tr>
<tr>
<td><em>Budesonide/formoterol</em> 24%</td>
<td><em>Fast acting/rapid onset</em> 79%</td>
</tr>
<tr>
<td><em>Beclometasone/formoterol</em> 20%</td>
<td><em>Effective</em> 18%</td>
</tr>
<tr>
<td><em>Fluticasone/salmeterol</em> 7%</td>
<td><em>Long lasting</em> 18%</td>
</tr>
<tr>
<td><em>Beclometasone/salmeterol</em> 2%</td>
<td><em>Good/best LABA</em> 12%</td>
</tr>
<tr>
<td><em>Budesonide/salmeterol</em> 1%</td>
<td><em>Evidence</em> 9%</td>
</tr>
<tr>
<td>Other (please specify) 4%</td>
<td><em>Adjustable dosing</em> 6%</td>
</tr>
</tbody>
</table>

- UK practitioners surveyed selected FP/FORM as the most effective ICS/LABA combination for reasons that it were ‘good/potent steroid’ and ‘fast acting/rapid onset’

Particle Size and Inhalation Speed Influence Oropharyngeal Deposition after actuation

- **Temperature**
- **Particle Size**
  - Large
  - Fine
  - Extra-fine

Duration (ms)

Plume Velocity

High spray force may increase oropharyngeal deposition

Fast and cold plume may cause the ‘cold-Freon’ effect

Large particles impact with oropharynx
Smaller particles swept into lungs with laminar airflow

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CFC-pMDI\(^{1,2}\) approx. 50–80%

CFC-pMDI + spacer\(^{2,3}\) approx. 6–10%

DPIs\(^{4,5}\) approx. 40–80%

HFA solution-pMDI\(^1\) approx. 30%

Respimat SMJ\(^4\) approx. 20%

Particle Size and Inhalation Speed Influence Oropharyngeal Deposition after actuation

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Data shown are for healthy individuals and those with obstructive lung disease. CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; SMI, soft mist inhaler

Plume velocity of FP/FORM was 42.8% slower than the FP/SAL pMDI plume.

Mean maximum plume velocities (from 3 readings) observed across the three distances measured:

<table>
<thead>
<tr>
<th>Interval distance from actuator (cm)</th>
<th>Maximum velocity (m/s)</th>
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<tbody>
<tr>
<td>3.0</td>
<td>20.3</td>
</tr>
<tr>
<td>6.0</td>
<td>15.2</td>
</tr>
<tr>
<td>9.5</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Plume velocity of FP/FORM was 42.8% slower than the FP/SAL pMDI plume.

Statistical analyses were not performed for these data. Data from an *in vitro* study; pMDI, pressurized metered-dose inhaler.

Johal B, Murphy S *et al.* ERS Congress, September 2013; Barcelona, Spain.
FP/FORM plume is 50% less forceful than the FP/SAL pMDI plume

Mean spray force vs distance across all distances measured

- Mean value for FP/FORM plume was 104.0 mN
- Mean value for FP/SAL plume was 218.0 mN

Data from an *in vitro* study. Statistical analyses were not performed on these data. Graph shows average values for the two devices measured.

*FP/SAL* 125/25 μg pMDI

*FP/FORM* 125/5 μg

- Mean value for *FP/FORM* plume was 104.0 mN
- Mean value for FP/SAL plume was 218.0 mN

Johal B, Tuohy J *et al.* Plume temperature and force of fluticasone propionate/formoterol pMDI compared with fluticasone propionate/salmeterol pMDI. Poster presented at the European Respiratory Society International Congress; September 2014; Munich, Germany.
Plume temperature of FP/FORM is warmer than most ICS/LABAs at any distance post actuation

Plume Temperature in Centigrade at Distance to target (mm)

**FP/FORM (125/5) plume impaction temperature** was +6°C versus −38°C for FP/SAL (125/5) at a distance of 25 mm

B.Johal et al, Adv Ther: 2015

**BP/FORM (100/6) plume impaction temperature** was -3°C versus −3°C for BUD/FORM (160/4.5) at 25 mm

D.A.Lewis et al, Drug Delivery to the Lungs 2012 Edinburgh
FP/FORM plume had a ~50% longer duration than the FP/SAL pMDI plume

Data from an *in vitro* study; duration of aerosol plume measured over a distance of 9.5 cm from the actuator (mean of three readings) Statistical analyses were not performed for these data pMDI, pressurized metered-dose inhaler

Oropharyngeal deposition and “Cold-Freon” Effect can reduce the delivered dose to the lung

Importance of particle size in lung deposition of inhaled drugs

Adapted from Pritchard JN. J Aerosol Med 2001;12(Suppl 1)
Based on data from a mathematical model
Particle size influences the total and regional site of airway drug deposition

<table>
<thead>
<tr>
<th>Particle size (microns)</th>
<th>Particle size of ICS medications, Mass Median Aerodynamic Diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6</td>
<td>DPI¹ 5.4 - DPIs and HFA suspension aerosol formulations generally have larger particles than HFA solution aerosols</td>
</tr>
<tr>
<td>2 – 6 ‘respirable range’</td>
<td>DPI¹ 4.0 - DPIs and HFA suspension aerosol formulations generally have larger particles than HFA solution aerosols</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>3.7 DPI²</td>
</tr>
<tr>
<td></td>
<td>2.4 HFA pMDI suspension³</td>
</tr>
<tr>
<td></td>
<td>1.1 HFA pMDI solution⁴</td>
</tr>
</tbody>
</table>

Gerrity (1979), Heyder (1986); James & Stahlhofen (1991), Chrystyn, Allergy 1999
FP/FORM had an in vitro FPF of ~40% at flow rates of 28.3 L/min and 60.0 L/min

Diffuse study: FPF of flutiform® compared with other ICS/LABAs

![Graph showing FPF comparison]

FP/FORM deposited throughout Central and Peripheral Airways with a Deposition Range of 36% to 44% Independent of Inhalation Profiles

van Holsbeke C, Marshall J et al. In vitro lung deposition of fluticasone propionate/formoterol (FP/FORM) pressurized metered dose inhaler (pMDI) with different inhalation profiles. Poster presentation at the European Respiratory Society International Congress; September 2014; Munich, Germany.
Factors Influencing Patient Decision about Use of Asthma Treatment

Bruce G Bender, AAIR, Vol 8, 2007

- If I could do things I can’t normally do now
- If I could feel it helping my asthma soon after taking it
- If it had long-lasting control of my symptoms
- If it controlled my symptoms better
- If it meant I would need rescue medications less often
- If I could be certain that it would be safe
- If it costs me less
- If it meant I would need fewer additional medications
- If I did not experience adverse effects of the medication
- If I could decide how much to take everyday according to how I feel
- If my doctor would take more time to explain my treatments
- If someone would remind me to take my medication

(n=75)
FP/FORM vs FP/SAL has a Significantly Faster Onset of Action (bronchodilatory effect in <3 minutes)

Uncontrolled Asthma increases Risk of future Exacerbation

Goal of Asthma Management is the Reduction of Exacerbation Risk

Predictors of future exacerbation include are:

- Prior Exacerbations
- Poor Asthma Control
- Rx Adherence
- Lower FEV1
- Allergic Rhinitis

“ICS/LABAs reduce the risk of exacerbations compared to ICS alone”
Long-Term FP/FORM Therapy Is Associated with a Low Incidence of Severe Asthma Exacerbations

Alberto Papi: Journal of Aerosol Medicine And Pulmonary Drug Delivery Volume 29, 2016
Desirable Characteristics of an Effective Asthma Inhaler Device

- Device is Robust
- Weather proof
- Cost Efficiency
- Stability of formulation
- Ease of Use
- Optimal Delivered Dose

Less than 20% patients use their inhaler daily!

Self Report of Controller Use: REALISE Asia

Data are shown as percentage of all respondents with a controller inhaler (n=1072).

Q: Which statement best describes how you take your regular asthma treatment (controller inhaler, which is usually brown, orange, red, purple, or pink)? Respondents could select from the identified choices.

Poster presentation at Asian Pacific Society of Respirology (APSR) Congress; 2014
Inhaler handling errors are related to poorer asthma stability

Frequency distribution of the number of errors in inhalation technique (left axis)
Relationship* between number of errors and AIS (right axis)

AIS: asthma impact survey;
*Linear regression analysis: $r=0.3$, $p<0.0001$

V Giraud, Misuse of corticosteroid MDI is associated with Asthma Instability; ERS Journal: 2002
More than 75% Patients make ≥1 potentially serious inhaler error


iHARP: Inhaler technique assessment initiative Helping Asthma in Real-life Patients
In which stages do inhaler handling errors occur?

Real-life factors interact with prescribed treatments leading to differential outcomes

Populations
- Broad
  - Managed as...
  - Clinical diagnosis
- Narrow
  - Confirmed diagnosis

Controlled studies:
- Highly controlled
- Pragmatically controlled
- Observational

Observational studies

Groups:
- Broader groups: more smokers, rhinitis, severe asthma, small airways inflammation
- Freer ecology of care: more realistic inhaler use and adherence

Nicolas Roche, Helen Reddel; Integrating Real Life Studies in the Global Therapeutic Research Framework; The Lancet, Respiratory Medicine
Real-life factors interact with prescribed treatments leading to differential outcomes

**Well adjusted and at least partially controlled**
- Confident at managing asthma
- Not concerned about their asthma

**In denial about symptoms**
- Socially conscious about their asthma
- Does not perceive their asthma as serious

**Adrift and poorly controlled**
- Socially conscious and concerned about their asthma
- Seeks out information about their asthma

**Tolerating poor control**
- Low confidence in managing asthma
- Does not seek out information about further control

**Worried with multiple symptoms**
- Very low confidence in managing their asthma
- Severe asthma with multiple symptoms
Fluticasone/Formoterol effect inside the airways

Fluticasone vs Budesonide and Beclometasone is:
• More lipophilic
• Slower dissolution through aqueous airway surface fluid layer
• Prolonged contact with airway epithelium
• Greater tissue binding
• Greater glucocorticoid receptor binding affinity

Formoterol vs Salmeterol
• Cytokines reduce the smooth muscle relaxation induced by salmeterol by (40%) than that induced by formoterol (16%)
• ICS administration completely reverses the cytokine-induced inhibition of formoterol
• cAMP production induced by formoterol is resistant to oxidative stress
• Formoterol reverses corticosteroid insensitivity under conditions of oxidative stress
Can patients in Real Life on FP/SAL be switched to without worsening Asthma? – ffLUX Study

To compare the real-life effectiveness of switching to FP/FORM 250/10 from FP/SAL 250/25 Evohaler in patients with asthma

Patient Eligibility:
FP/SAL 250 Evohaler >6 months
No asthma exacerbations <3 months

Enrolled N=259
Randomized N=225
FP/SAL N=74
FP/FORM N=151
Completed N=73
Completed N=134
Asthma Control (ACQ7)

Patients on FP/FORM were significantly better controlled per GINA criteria.

Non-inferiority at week 12

ACQ7 Score

Exacerbation %

Control Partial Worse Control Partial Worse

38% 45% 16.4% 53% 39% 7.5%
p=0.01

0.8 0.7
9.5 4.6

Anu Kemppinen, Pragmatic Trial Comparing FP/SAL MDI with Changing to FP/FORM in Asthma (ffLUX Study)
Favourable Characteristics of FP/FORM that may have contributed to Low Exacerbation Rates

Inhaler

Favorable plume characteristic:
- Slow velocity (less impaction)
- Warm (5-6C) plume (less Freon effect)
- Long duration of plume
- 40% dose delivered as HPF 
  Independent of inspiratory flow rate
- Less oropharyngeal impaction
- High lung deposition

Compound

- High B2 receptor specificity
- Bronchodilation: <3 min vs Seretide
- Bronchodilatory effects lasts >12 hrs
- Potent ICS anti-inflammatory effect
- FP/FORM synergy
- Long durability of effect

Outcomes

- Improvement in Lung Function (FEV1)
- Improvement in Symptom Control (ACS)
- <3% Exacerbations
  - vs ICS/LABAs (10%-15%)
- Low risk of oro-pharyngeal inf
- Low risk of ICS related systemic effects
- Flexibility to step up Rx
- Flexibility to step down Rx
- Can be used with spacer

Alberto Papi: 2016; JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY Volume 29, Number 0, 2016
Thank You for Your Attention