Safety of β2-agonists in asthma

Sanjeeva Dissanayake

IPAC-RS/UF Orlando Inhalation Conference March 20, 2014
Overview

• Origin of concerns
• Mechanistic hypotheses
• Large scale clinical datasets
  – Interpretation
  – Issues for consideration
• Dose selection
• Conclusion
Genesis of a saga

National mortality rates in 5 to 34 year olds (Sears 1994)

- Fenoterol launch in NZ
- Fenoterol warning
- Fenoterol withdrawn in NZ

Mechanistic hypotheses

1. Loss of bronchoprotective effect / ↑ AHR
2. Increased inflammation
3. Increased early/late asthmatic response
4. Altered cytokine milieu

5. ICS under-use + over-reliance β2-agonists + delayed ER presentation
Increased AHR

Mean $PD_{15}$ hypertonic saline following 6 weeks treatment
(from Aldridge 2000)

- Placebo: $5.34$ µmol
- Terbutaline 1000 qid: $3.18$ µmol
- Budesonide 400 bid: $11.44$ µmol
- Budesonide 400 bid / Terbutaline 1000 qid: $8.00$ µmol

$p = 0.019$ for Placebo vs. Terbutaline 1000 qid
$p = 0.039$ for Budesonide 400 bid vs. Budesonide 400 bid / Terbutaline 1000 qid

**Sputum eosinophilia**

Median % sputum eosinophils following 6 weeks treatment (from Aldridge 2000)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median % Eosinophils</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Terbutaline 1000 qid</td>
<td>8.3</td>
<td>0.049</td>
</tr>
<tr>
<td>Budesonide 400 bid</td>
<td>1.7</td>
<td>0.409</td>
</tr>
<tr>
<td>Budesonide 400 bid / Terbutaline 1000 qid</td>
<td>2.1</td>
<td></td>
</tr>
</tbody>
</table>

Late asthmatic response

Mean change (SEM) in FEV1 post-allergen challenge
(Cockcroft JACI 1995)

Altered cytokine milieu

Effect of terbutaline on Th1 cytokine production (interferon-γ)

Effect of terbutaline on Th2 cytokine production (IL-10, IL-4, IL-5)

Agarwal, J Allergy Clin Immunol 1999;104:91-8
Consistency & clinical relevance?

Adenosine monophosphate PC$_{20}$ following 4 weeks treatment (adapted from Aziz Chest 2000)

![Graph showing the comparison of various treatments on Adenosine monophosphate PC$_{20}$ levels. The graph includes Placebo, Formoterol 24 OD, Budesonide 800 OD, and Formoterol 24 OD + Budesonide 800 OD. The *p<0.05 vs placebo indicates statistical significance.](image-url)
Bronchoprotection sustained with combination treatment

**AMP PD$_{20}$ following 4 weeks treatment**

- Fluticasone/formoterol 500/20 bid: 4.9 mg
- Placebo: 1.1 mg

$p<0.001$

Unpublished data
Summary

- Evidence somewhat conflicting

- Overall evidence suggests loss bronchoprotection with repeat SABA / LABA dosing

- Possibly related to a “permissive effect” of β2-agonists on inflammation
  - May plausibly contribute to mortality with LABA monotherapy

- BUT for maintenance combination ICS/LABA clinically relevant bronchoprotection appears sustained
  - No consistent evidence of clinically relevant antagonism by LABA of ICS effect
A shift in focus

Safety of long-acting $\beta$ agonists for the treatment of asthma: clearing the air

Gustavo J Rodrigo,¹ José A Castro-Rodríguez²

Combination therapy (LABAs plus ICS) is associated with a decreased risk of serious asthma-related events.

Safety of formoterol in asthma clinical trials: an update

Malcolm R. Sears¹ and Finn Radner²

Formoterol in asthma patients is not associated with an increased risk of asthma-related deaths.
The FDA meta-analysis

Risk difference estimates for deaths, intubations, asthma-related hospitalisation composite

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Risk difference (95% CI)</th>
<th>[Sample sizes]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABA w/o randomised ICS vs. no LABA</td>
<td>3.63 (1.51, 5.75)</td>
<td>[350/22286 279/24474]</td>
</tr>
<tr>
<td>LABA with randomised ICS vs. randomised ICS</td>
<td>0.25 (-1.69, 2.18)</td>
<td>[31/7862 26/7330]</td>
</tr>
<tr>
<td>LABA vs. no LABA</td>
<td>2.80 (1.11, 4.49)</td>
<td>[381/30148 304/30806]</td>
</tr>
</tbody>
</table>

Large volume of AZ data not included – impact on results?

No deaths or intubations on fixed combination therapy

Long-Acting Beta-Agonists and Adverse Asthma Events Meta-Analysis
The FDA mandated trials

≥ 1 exacerbation past 12 months
Asthma warranting ICS-LABA

ICS + LABA
- Trial 1 Symbicort pMDI
- Trial 2 Seretide Diskus
- Trial 3 Dulera pMDI
- Trial 4 Foradil DPI + Flixotide Diskus

Primary endpoint: Relative risk of asthma-related:
- Deaths
- Intubations
- Hospitalisations

Composite

Non-inferiority if UL 95% CI for relative risk ≤ 2

Potential limitations

- Death vs. hospitalisation rate\(^1\)
- Multiplicity\(^1\)
- Foradil + Flixotide study

Death

- Pooled analysis for death
  - Assume 7 ICS-LABA vs. 1 ICS
  - → RR 7.0 (95% CI 0.9 – 56.9)

- Death subverted in composite analysis

<table>
<thead>
<tr>
<th></th>
<th>ICS-LABA N=23.400</th>
<th>ICS N=23.400</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4</td>
<td>1</td>
<td>4.00 (0.45-35.79)</td>
</tr>
<tr>
<td>Intubations / hospitalisations</td>
<td>176</td>
<td>176</td>
<td>1.00 (0.81-1.23)</td>
</tr>
<tr>
<td>Composite endpoint</td>
<td>180</td>
<td>177</td>
<td>1.02 (0.83-1.25)</td>
</tr>
</tbody>
</table>

Multiplicty

- Each study 90% powered
  - 10% risk of failure to exclude ↑ risk where none exists

- 4 individually powered studies
  - 34% risk of failure to exclude ↑ risk in one study (where none exists)
  - 41% risk if paediatric study included

Foradil + Flixotide

Risk difference for asthma hospitalization for Salmeterol

<table>
<thead>
<tr>
<th>Salmeterol product</th>
<th>Comparator</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALM + ICS background vs ICS background</td>
<td>198 10264 vs 151 10135</td>
<td>46.02 (8.10, 83.93)</td>
</tr>
<tr>
<td>SALM + ICS separate inhalers vs ICS study drug</td>
<td>16 2841 vs 14 3040</td>
<td>14.48 (-30.83, 59.79)</td>
</tr>
<tr>
<td>ADVAIR vs ICS study drug</td>
<td>31 11437 vs 29 11163</td>
<td>0.28 (-18.51, 19.06)</td>
</tr>
</tbody>
</table>
Indacaterol experience

- FDA dose selection for COPD based partly on 26 wk asthma trial

- R, DB, background ICS therapy only

### Asthma-related SAEs

<table>
<thead>
<tr>
<th></th>
<th>Indacaterol 300 µcg OD N=268</th>
<th>Indacaterol 600 µcg OD N=268</th>
<th>Salmeterol 50 µcg BID N=269</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma-related SAEs</td>
<td>2 (0.75%)</td>
<td>3 (1.12%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Uniform class effect?

Asthma-related hospitalisation:
Advair (fixed combination) vs. Fluticasone

<table>
<thead>
<tr>
<th></th>
<th>Advair n/N</th>
<th>Fluticasone n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31 / 6259</td>
<td>29 / 6399</td>
</tr>
<tr>
<td>Odds Ratio (95% CIs)</td>
<td>1.01 (0.60, 1.69)</td>
<td></td>
</tr>
</tbody>
</table>

Asthma-related hospitalisation:
Budesonide + formoterol (fixed & free combination) vs. Budesonide

<table>
<thead>
<tr>
<th></th>
<th>Symbicort or Budesonide + Formoterol n/N</th>
<th>Budesonide n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61 / 10852</td>
<td>60 / 7309</td>
</tr>
<tr>
<td>Odds Ratio (95% CIs)</td>
<td>0.68 (0.47, 0.99)</td>
<td></td>
</tr>
</tbody>
</table>
Doses of generic / novel LABAs?

- *De facto* FDA approach benchmarking of FEV1
  - vs. Foradil (12 µcg) or Salmeterol
  - Greater emphasis on FEV1 matching than for ICSs?

- Residual concerns re Foradil dose-related safety?
  - Dose-related asthma SAE signal in Foradil NDA\(^1\,^2\)

**Asthma-related SAEs (Foradil NDA pivotal trials)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.4%</td>
</tr>
<tr>
<td>Foradil 12 mcg bid</td>
<td>2.0%</td>
</tr>
<tr>
<td>Foradil 24 mcg bid</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

2. Mann, CHEST 2003; 124:70–74
Foradil post-market safety study

16-week safety study, N=2085 (Wolfe 2006)

Any asthma-related AE  Systemic steroids  Respiratory-related SAEs

Formoterol 24 bid: 13.7% 6.3% 0.4%
Formoterol 12 bid + prn: 10.3% 4.4% 0.2%
Formoterol 12 bid: 14.0% 5.9% 0.6%
Placebo: 15.8% 8.8% 0.2%

Wolfe, Chest 2006;129;27-38
Incidence of asthma related hospitalisation by formoterol dose (AstraZeneca 2008)
FEV1 as safety benchmark?

• Epidemiological evidence that ↑ SABA dose / use associated with ↑ risk
  – Marker of asthma severity or cause?
  – No evidence that desire for greater lung function associated with ↑ mortality

• No pathophysiological data to support use of FEV1 as safety marker
  – i.e., no evidence ↑ inflammation associated with ↑ FEV1

• Further potential confounders
  – Deposition pattern
  – Pharmacological differences between LABAs
FEV1 differences may reflect differential deposition

Bronchodilation with 30 μg monodisperse salbutamol:
6 μm vs. 1.5 μm (Usmani 2005)

6 μm (total lung deposition 46.0%)

1.5 μm (total lung deposition 56.3%)

Pharmacological differences complicate comparison

**Intrinsic β2-receptor efficacy**

cAMP production following ligand binding (as % of isoprenaline Emax)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Emax (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoprenaline</td>
<td>98</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>73</td>
</tr>
<tr>
<td>Formoterol</td>
<td>90</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>38</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>47</td>
</tr>
</tbody>
</table>

Is it more logical to rely on putative causes of ↑ risk - e.g., inflammatory surrogates?

Battram, J Pharmacol Exp Ther. 2006 May;317(2):762-70
Summary and Conclusions

• Delayed presentation & permissive inflammatory effect plausible hypotheses for ↑ risk of LABA monotherapy

• Less consistent mechanistic data to support risk with combination therapy

• Large scale clinical data does not support fixed combination risk

• FDA trials
  – May further elucidate within-class differences (formoterol vs. salmeterol)
  – Risk incurred by multiplicity and free combination hopefully addressed pre-results

• FEV1 as a benchmark / surrogate of risk for new products
  – ? Utility / evidence-based / confounded
  – Models assessing inflammatory response arguably more compelling