Shaping a Dynamic Future in Respiratory Practice

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Inhaled Therapy in COPD: Past, Present and Future

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Disclosures:

Who
• Boehringer Ingelheim
• GlaxoSmithKline
• Teva UK Limited
• AstraZeneca
• Pfizer
• Napp
• British Lung Foundation
• Editor at Int J COPD

What
• Paid speaker
• Advisory boards
• Clinical trial investigator
• Travel support
• Support our patients!
• Increase our impact factor!

I have no shares in pharmaceutical companies and do everything I can to hinder tobacco companies.
Breathe
What you need to know about COPD, the lung disease that claims 30,000 lives in the UK each year
ICS therapies in COPD, the past...

- Numerous studies have looked at ICS therapies to improve outcomes in COPD
  - ISOLDE\(^1\)
  - TORCH\(^2\)
  - INSPIRE\(^3\)
  - FORWARD\(^4\)
  - BUD/FORM\(^5\)

5. Calverley PM, et al. ERJ 2003 (BUD/FORM vs BUD vs FORM vs Pla)
ICS monotherapy is more effective than placebo in stable COPD  
(ICS monotherapy is NOT licenced in COPD)

**Lung function**
- Significant improvement of lung function vs placebo
- Use of ICS for > 6 months did not have a major effect on the rate of decline in FEV₁ (mean benefit of 5.80 mL/year with ICS over placebo, 95% CI: -0.28 to 11.88, n=2333)

**Exacerbations**
- Reduced exacerbation rates (mean difference of -0.26 exacerbations/patient/year, 95% CI: -0.37 to -0.14, n=2586)
- Increased risk of reported pneumonia

**Mortality**
- No significant effects on mortality (OR: 0.98, 95% CI: 0.83 to 1.16, n=8390)

**Health status**
- Slowing of the rate of decline in QoL (improvement in SGRQ of 1.22 units/year, 95% CI: -1.83 to -0.60, n=2507)

Conclusions from a Cochrane systematic review of 55 primary studies published up to and including 2011 (n=16,154)
ICS significantly reduces the rate of exacerbations needing medical intervention.

**Szafranski**

- Budesonide: -15%*
- Formoterol: -2%

* p<0.05 vs placebo

**Calverley**

- Budesonide: -12% *
- Formoterol: +3%

* p<0.05 vs placebo

Fewer future attacks

The risk of acute exacerbations in the TRISTAN study.

There were no differences between the three active treatment groups.

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Mahler and Hanania studies – no significant differences between groups.
The TORCH study: All-cause mortality at 3 years

The TORCH study: Rate of moderate and severe exacerbations over 3 years

Mean number of exacerbations/year

- Placebo: 1.13
- SALM: 0.97*
- FP: 0.93*

*<p<0.001 vs placebo

Long-term inhaled steroids in COPD

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Duration</th>
<th>Severity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen City</td>
<td>290</td>
<td>3 years</td>
<td>Mild</td>
<td>No effect</td>
</tr>
<tr>
<td>EUROSCOP</td>
<td>1277</td>
<td>3 years</td>
<td>Mild</td>
<td>No effect</td>
</tr>
<tr>
<td>ISOLDE</td>
<td>751</td>
<td>3 years</td>
<td>Moderate</td>
<td>No effect</td>
</tr>
<tr>
<td>Lung Health 2</td>
<td>1116</td>
<td>3.5 years</td>
<td>Moderate</td>
<td>No effect</td>
</tr>
</tbody>
</table>

- $1^o$ outcome = decline in FEV$_1$ over 3 years
- Cochrane Review: >16,000 COPD patients
  - No ↓ FEV$_1$ decline
  - No ↓ mortality
What are we doing now? The present...
COPD: What is on our wish list?

Unmet needs of patients with COPD
- More effective diagnosis and primary prevention
  - Better symptom control
  - Fewer exacerbations
  - Slowing of disease progression
- Better life expectancy
- Less systemic disease secondary to COPD and fewer comorbidities

Unmet needs of the medical community
- Optimising disease prevention
  - Improving symptom control
  - Preventing exacerbations and decreasing their clinical impact
  - Preventing disease progression
- Reducing disease-related mortality
- Identifying systemic effects and comorbidities

COPD, chronic obstructive pulmonary disease

FEV₁ decline: The traditional view

Modified version of the Fletcher and Peto graph showing the decline in FEV₁.

FEV₁, forced expiratory volume in 1 second.

More recent analyses concluded that, in contrast with earlier findings, \( \text{FEV}_1 \) decline was fastest in the early stages of COPD, particularly in GOLD 2 disease.

\( \text{FEV}_1 \), forced expiratory volume in 1 second.

Affecting disease progression

- UPLIFT (subgroup)
- TORCH (subgroup)

- Real GOLD II FEV1 loss 61ml/year
- UPLIFT GOLD II loss 49ml/year
- UPLIFT GOLD III 38ml/year
TORCH study: FEV$_1$ loss

Jenkins et al, Respiratory Research 2009; 10:59
UPLIFT: GOLD II analysis

Decamer et al. Lancet 2009 374,9696;1171-1178
How do patients feel?

Decamer et al. Lancet 2009 374,9696;1171-1178
### Median time to first exacerbation (months [95% CI])

<table>
<thead>
<tr>
<th>GOLD stage</th>
<th>Median (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD stage II</td>
<td>23.1 (21.0–26.3)</td>
<td>0.82 (0.75–0.90)</td>
</tr>
<tr>
<td>GOLD stage III</td>
<td>13.2 (11.5–14.6)</td>
<td>0.87 (0.79–0.95)</td>
</tr>
<tr>
<td>GOLD stage IV</td>
<td>9.7 (8.2–12.0)</td>
<td>0.99 (0.81–1.21)</td>
</tr>
</tbody>
</table>

Decramer et al. Lancet 2009 374,9696;1171-1178
Paradigm of COPD management is shifting

High levels of off-guidelines ICS use worldwide*

Patients at GOLD Stage II with no history of exacerbations in the past year who were receiving ICS at baseline on enrolment

*Data from 11 studies in 44 countries with a total of 9482 patients

So what are we doing now?

It seems almost random:

• Population database study n=24,957
  - 17% no treatment
  - 24% ICS
  - 26% ICS/LABA
  - 23% ICS, LABA, LAMA
  - 2% LAMA alone

• Irrespective of GOLD stage or GOLD group (A-D)

NICE Clinical Guidance (2010)

When the 2010 guideline was being written, the available evidence for LABA plus LAMA combination therapy was relatively limited.

As the NICE guidelines are purely evidence-based, the recommendation for LABA plus LAMA therapy is restricted in the 2010 guideline.
Expiratory flow limitation has systemic effects in COPD

- Exacerbations
- Air trapping/hyperinflation
- Breathlessness
- Deconditioning
- HRQoL
- Inactivity
- Reduced exercise capacity
- Progression: decline in lung function
- Disability
- Mortality

COPD, chronic obstructive pulmonary disease; HRQoL, health-related quality of life

Bronchodilation and its consequences

- Relaxation of ASM
- Not the same as increased radius from reduction in oedema/cells
- Change in the degree/location of EFL
- Reduced static hyperinflation (EELV)
- Delays onset of dyspnoea when exercising
Beta-agonists and muscarinic antagonists