Role of dual bronchodilation in COPD

Canadian Respiratory Conference,
Calgary, May 25th, 2014

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Disclosure

- Speaker bureau: Boehringer Ingelheim, Pfizer, Novartis and Grifols.
- Advisory board: Boehringer Ingelheim, Novartis.
- Multicenter trials sponsored by GlaxoSmithKline, Boehringer Ingelheim, Altana Pharma, Merck, Astra Zeneca, Nycomed and Novartis.
- Unrestricted research grant from Boehringer Ingelheim.
- CIHR/GSK research chair on COPD.
Objectives

- Review the place of dual bronchodilation in the GOLD and CTS guidelines.
- Discuss the rationale for combining bronchodilators in COPD.
- Review the evidence for dual bronchodilation in COPD.
- Discuss the role of dual bronchodilation (vs LABA/ICS) in the management of COPD.
Case study

- 65 years old woman, ex-smoker.
- Reports shortness of breath during walking on flat course and one «bad cold» per year.
- Spirometry: $\text{FEV}_1 = 58\%$ predicted and $\text{FEV}_1/\text{FVC} = 0.6$. 
Q&A. What would be your first pharmacological recommendation?

- Short acting $\beta_2$-agonist only.
- Initiation of a LAMA.
- Initiation of a LABA.
- Initiation of a LABA/ICS combination.
- Initiation of a LABA + LAMA simultaneously.
COPD treatment

- Early Dx (spirometry) + prevention
- Prevent/ Tx Exacerbation
- End of life care
- Pulmonary function impairment
  - Mild
  - Very severe
- Dyspnea, MRC
  - II
  - V

- Inhaled Corticostéroids
- Pulmonary rehabilitation
- Long-acting BD
- PRN short-acting BD(s)
- Smoking cessation/ exercise / self-management/education
- Oxygen
- Surgery

Pulmonary function impairment

Dyspnea, MRC

Early Dx (spirometry) + prevention
Prevent/ Tx Exacerbation
Follow-up
End of life care

The new GOLD classification

Severity (GOLD stage)

4 | C
3 | D
2 | A
1 | B

mMRC <2 | CAT <10
mMRC ≥2 | CAT ≥10

Exacerbation risk (Exacerbation history)

0 | >2
1 | ≥2

www.goldCOPD.com; update 2014
The new GOLD classification

Severity (GOLD stage)

4
3
2
1

mMRC <2
CAT <10

mMRC >2
CAT ≥10

Exacerbation risk

0
1
>2

LABA/ICS combination or a LABA/LAMA combination or a long-acting bronchodilator + Anti-PDE4

LABA/ICS combination ± a LAMA or LABA/ICS combination + anti-PDE4 or a LABA/LAMA combination or a LAMA + anti-PDE4

Short-acting bronchodilator as needed or a combination of short-acting bronchodilators or a long-acting bronchodilator

Long-acting bronchodilator or a LABA/LAMA combination

www.goldCOPD.com; update 2014
A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*
**Objective:** Determine if Tiotropium 18 \( \mu \text{g} \) OD reduces the rate of FEV\(_1\) decline in patients with COPD.

**Design:** randomized. double-blinded. placebo-controlled*

**Duration:** 4 years

**# Patients randomized:** 5,992

**Main outcomes:**
- pre and post-BD FEV\(_1\) and FVC decline
- SGRQ. exacerbations. mortality

* All respiratory medications were allowed except anticholinergics
## Inclusion/exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Clinical dx of COPD</td>
<td>• Asthma. CF. bronchiectasis. Interstitial lung disease. thromboembolic disease. Other significan pathology</td>
</tr>
<tr>
<td>• Post-BD FEV&lt;sub&gt;1&lt;/sub&gt; ≤ 70% predicted</td>
<td>• Oxygen therapy &gt;12 hours/day</td>
</tr>
<tr>
<td>• Post-BD FEV&lt;sub&gt;1&lt;/sub&gt;/FVC ≤ 70%</td>
<td>• COPD exacerbation within 4 weeks of study participation or during run-in</td>
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<tr>
<td>• Men or women ≥ 40 years</td>
<td>• Recent myocardial infarction. arythmias. heart failure</td>
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<tr>
<td>• Smoking history ≥ 10 pack-years</td>
<td>• Lung resection</td>
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</table>
Pre and post-bronchodilator $\text{FEV}_1$

![Graph showing FEV1 levels over time for Tiotropium and Controls with significant difference indicated by * symbols.](image-url)

**Tashkin et al. NEJM 2008;359:1543-1554.**
Pre and post-bronchodilator FEV₁

Post-BD FEV₁
Δ = 47 – 65 mL

Pre-BD FEV₁
Δ = 87 – 103 mL

COPD exacerbation

- Probability of an exacerbation (%)
- Months

- Tiotropium
- Controls

Odds ratio = 0.86
(CI 95 %. 0.81. 0.91)

p<0.0001 (test Mantel-Haenzel)

All causes mortality
On-Treatment + Vital Status – Day 1470

Hazard ratio = 0.89
95% CI: (0.79, 1.02)
P = 0.086 (log-rank test)

Proven benefits of bronchodilation

- ↓ dyspnea
- ↑ respiratory function
- ↑ quality of life
- ↓ exacerbations
- ↓ hyperinflation
- ↑ exercise tolerance
- ↓ mortality (possible)
Case study

- Your patient followed your advices!
- She has been on a OD LAMA since her last visit, six months ago.
- Despite this, she is still short of breath and has experienced a new exacerbation that was treated with antibiotics and systemic corticosteroids.
Q&A. What would your next step be?

- Continue on the same treatment.
- Prescribe azithromycin.
- Add a LABA.
- Add roflumilast.
- Add a LABA/ICS combination.
The new GOLD classification

**Severity (GOLD stage)**

4  
3  
2  
1

**mMRC** 

<2  
>2

**CAT** 

<10  
>10

**Exacerbation risk**

0  
1  
>2

- Short-acting bronchodilator as needed or a combination of short-acting bronchodilators or a long-acting bronchodilator
- Long-acting bronchodilator or a LABA/LAMA combination
- LABA/ICS combination ± a LAMA or LABA/ICS combination + anti-PDE4 or a LABA/LAMA combination or a long-acting bronchodilator + Anti-PDE4
- LABA/ICS combination or a LABA/LAMA combination or a LABA/LAMA combination or a LABA/ICS combination ± a LABA/LAMA combination + Anti-PDE4 or a LABA/LAMA combination + Anti-PDE4

www.goldCOPD.com; update 2014
Annals of Internal Medicine

Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease: A Randomized Trial

Shawn D. Aaron, MD; Katherine L. Vandemheen, BScN; Dean Fergusson, PhD; François Maltais, MD; Jean Bourbeau, MD; Roger Goldstein, MD; Meyer Balter, MD; Denis O’Donnell, MD; Andrew McIvor, MD; Sat Sharma, MD; Graham Bishop, MD; John Anthony, MD; Robert Cowie, MD; Stephen Field, MD; Andrew Hirsch, MD; Paul Hernandez, MD; Robert Rivington, MD; Jeremy Road, MD; Victor Hoffstein, MD; Richard Hodder, MD; Darcy Marciniuk, MD; David McCormack, MD; George Fox, MD; Gerard Cox, MB; Henry B. Prins, MD; Gordon Ford, MD; Dominique Bleskie, BHScN; Steve Doucette, MSc; Irvin Mayers, MD; Kenneth Chapman, MD; Noe Zamel, MD; and Mark FitzGerald, MD, for the Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium
Hospitalizations for AECOPD

<table>
<thead>
<tr>
<th></th>
<th>Tio + Placebo</th>
<th>Tio + Salmeterol</th>
<th>Tio + Flutic./Salm.</th>
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</thead>
<tbody>
<tr>
<td>Hospitalizations for</td>
<td>49</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td>AECOPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate ratio vs</td>
<td>0.83</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>(0.54-1.27)</td>
<td>(0.33-0.86)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.38</td>
<td>0.01</td>
<td></td>
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</table>

Quality of Life- One-year changes in SGRQ Total Score

Decline in health status

Mean change in SGRQ total score from baseline

Improvement in health status

Tio + Flut/Sal 50/500 mcg bid

Tio + Sal 50 mcg bid

Tio + Placebo

-10

-8.6

-6.3

-4.5

\( a \) \( p=0.01 \) vs placebo

\( b \) \( p=0.02 \) vs placebo

Dual bronchodilation in COPD: is two better than one?
Combining different classes of bronchodilation is a new concept.
Combining LAMA/LABA offers undeniable clinically important benefits over monotherapy.
Combining LAMA/LABA provides superior bronchodilation over monotherapy.
Combining LAMA/LABA increases the risk of adverse effects.
SAMA and SABA combination

Percent Change in FEV<sub>1</sub>

Hours After Test Dose

Day 57

Combivent®
Ipratropium
Salbutamol

Rationale for combining long-acting BD

- Inhaled bronchodilation is the foundation of COPD treatment.
- Most patients with COPD are improved with bronchodilation.
- Maximal bronchodilation is not achieved with only one class of bronchodilator.
- There could be synergistic interactions between β2-agonists and anticholinergics.

Formoterol and tiotropium

OD dual bronchodilation

- Umeclidinium vilanterol
- Glycopyrronium indacaterol
- Tiotropium olodaterol
Dual versus single BD

26-week, multicentre, randomised, double-blind, parallel-group, placebo- and active-controlled

Pre-randomisation period

Pre-screening
Day -21 to day -15
Visit 1

Run-in period
Day -14 to day -1
Visit 2

Randomisation visit 3
Day 1 to day 184

Placebo
QVA149 110 µg indacaterol/50 µg glycopyrronium once daily
Indacaterol 150 µg once daily
Glycopyrronium 50 µg once daily
Tiotropium 18 µg once daily

Two versus one: effects on FEV$_1$
Two versus one: effects on FEV$_1$

Data from Anoro® Ellipta® monography.
Two versus one: effects on $\text{FEV}_1$

* Mean values adjusted for baseline, treatment and centre

Maltais et al. ERJ 2010; P5558:1014s.
Two versus one: effects on clinical outcomes

64-week. multicentre. randomised. double-blind. parallel-group and active controlled study

- Pre-randomisation period
- Double-blind treatment period*
- Variable double-blind treatment period*

Pre-screening
Screening/Run-in period

Day -21 to Day -15
Day -14 to Day -1
Day 1 to Week 64
Week 64 to Week 76

Visit 1
Visit 2
Randomisation Visit 3
Visit 16
Visit 18

QVA149 110/50μg qd via Breezhaler®
Glycopyrronium 50μg qd via Breezhaler®
Open-label tiotropium 18μg qd via Handihaler®

Two versus one: effects on clinical outcomes

3865 screened
2224 randomised
1641 excluded

741 assigned to QVA149
736 received drug
5 did not receive drug

741 assigned to glycopyrronium
739 received drug
1 did not receive drug
1 randomised twice

742 assigned to OL tiotropium
739 received drug
3 did not receive drug

171 discontinued treatment
59 adverse event
33 withdrew consent
21 death
18 unsatisfactory therapeutic effect
15 administrative problems
13 protocol deviation
5 lost to follow-up
3 abnormal laboratory test
3 inability to use inhaler
1 abnormal laboratory value

203 discontinued treatment
67 adverse event
50 withdrew consent
22 death
32 unsatisfactory therapeutic effect
8 administrative problems
12 protocol deviation
6 lost to follow-up
2 abnormal test result
1 inability to use inhaler
3 abnormal laboratory value

183 discontinued treatment
47 adverse event
44 withdrew consent
24 death
38 unsatisfactory therapeutic effect
9 administrative problems
12 protocol deviation
4 lost to follow-up
1 abnormal test result
4 abnormal laboratory value

570 completed study
7 excluded from analysis
729 analysed for safety
729 analysed for efficacy

538 completed study
740 analysed for safety
739 analysed for efficacy

559 completed study
2 excluded from analysis
737 analysed for safety
737 analysed for efficacy

Two versus one: effects on clinical outcomes

Two versus one: effects on dyspnea

Mahler DA et al. ERJ 2013. [Epub ahead of print]
Two versus one: effects on QOL

Two versus one: effects on exercise

Two versus one: effects on exercise

Exercise endurance time (s)

Δ=12
Δ=24
Δ=66*
Δ=60*

Day 1
n=77  n=77  n=82

Day 21
n=74  n=77  n=80

Is two better than one?

- Clearly, when looking at pulmonary function.
- More difficult to demonstrate when looking at clinical outcomes. Why?
- There could be a limit to the translation of better lung function on clinical outcomes.
- It may not be realistic to expect the same benefit when one medication is added to none than when a second medication is added to an already existing one.
- We may not be examining this question in the right way (consider for example using responder analysis).
LABA/LAMA versus LABA/ICS
Figure 2. Pre-dose trough FEV$_1$ (L) at Weeks 12 and 26 for overall and sub-group population

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th>Sub-group</th>
<th>Overall population</th>
<th>Sub-group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 12</strong></td>
<td>1.61</td>
<td>1.52</td>
<td>1.63</td>
<td>1.49</td>
</tr>
<tr>
<td><strong>Week 26 (LOCF)</strong></td>
<td>1.60</td>
<td>1.50</td>
<td>1.62</td>
<td>1.47</td>
</tr>
</tbody>
</table>

Δ = 0.09*  Δ = 0.14*  Δ = 0.10*  Δ = 0.15*

*p<0.001, values are LSM±SE
FEV$_1$ = forced expiratory volume in 1 sec; LOCF = last observation carried forward; LSM = least squares mean; SE = standard error; SFC = salmeterol/fluticasone

Mezzi et al. ERJ 2013.P3636.
Figure 1. Forest plot of HRs for QVA149 110/50 µg (n=1,547) versus placebo (n=2,141) deaths, serious CCV events, MACE, serious pneumonia, serious COPD exacerbation and atrial fibrillation/flutter.

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Death</td>
<td>0.922 (0.338, 2.511)</td>
</tr>
<tr>
<td>Serious CCV</td>
<td>0.597 (0.287, 1.241)</td>
</tr>
<tr>
<td>MACE</td>
<td>0.984 (0.417, 2.319)</td>
</tr>
<tr>
<td><strong>Serious pneumonia</strong></td>
<td><strong>1.076 (0.526, 2.203)</strong></td>
</tr>
<tr>
<td>Serious COPD exacerbation</td>
<td>0.598 (0.395, 0.906)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>1.017 (0.479, 2.157)</td>
</tr>
</tbody>
</table>

MACE events included non-adjudicated events from the indacaterol and glycopyrronium studies, and adjudicated events from the QVA149 program; all atrial fibrillation/flutter events were adjudicated.

CCV = cardio- and cerebro-vascular; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; MACE = major adverse cardiovascular events.
Conclusions

- Dual bronchodilation provides unequalled bronchodilation in COPD.
- LAMA/LABA provides superior bronchodilation compare to monotherapy that may translate into important clinical benefits.
- The positioning of the upcoming dual bronchodilation FDC in the COPD armamentarium will be further clarified with upcoming studies.