Acute effects of indacaterol on lung hyperinflation in moderate COPD: A comparison with tiotropium

Andrea Rossi a,*, Stefano Centanni b, Isa Cerveri c, Carlo Gulotta d, Antonio Foresi e, Mario Cazzola f,g, Vito Brusasco h

a Unità Operativa Complessa di Pneumologia, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
b Clinica di Malattie dell'Apparato Respiratorio, Ospedale San Paolo, Università degli Studi di Milano, Italy
c Clinica Malattie dell’Apparato Respiratorio, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
d Pneumologia-Fisiopatologia Respiratoria, Azienda Ospedaliera Universitaria S. Luigi, Orbassano, Torino, Italy
e Divisione di Medicina Respiratoria, A.O. Istituti Clinici di Perfezionamento, Ospedale di Sesto San Giovanni, Italy
d Pneumologia-Fisiopatologia Respiratoria, Azienda Ospedaliera Universitaria S. Luigi, Orbassano, Torino, Italy
e Divisione di Medicina Respiratoria, A.O. Istituti Clinici di Perfezionamento, Ospedale di Sesto San Giovanni, Italy
f Dipartimento di Medicina Interna, Università di Roma, Tor Vergata, Italy
g Dipartimento di Riabilitazione Polmonare, IRCCS, Ospedale San Raffaele Pisana, Roma, Italy
h Dipartimento di Medicina Interna, Università di Genova, Italy

Received 3 May 2011; accepted 16 September 2011
Available online 27 October 2011

KEYWORDS
Indacaterol;
Tiotropium;
COPD;
Lung hyperinflation

Summary
Background: Evidence has been provided that high-dose indacaterol (300 μg) can reduce lung hyperinflation in moderate-to-severe chronic obstructive pulmonary disease (COPD).
Aim: To study whether low-dose indacaterol (150 μg) also reduces lung hyperinflation in comparison with the recommended dose of tiotropium (18 μg) in moderate COPD.
Methods: This was a multicenter, randomized, blinded, 3-period cross-over, placebo-controlled study. Spirometry and lung volumes were measured before and 30, 60, 120, 180 and 240 min after the administration of single-doses of indacaterol, tiotropium, or placebo. The primary end-point was the change in peak inspiratory capacity (IC). The area under the 4-h curve (AUC0–4) for IC, 1-s forced expiratory volume (FEV1) and forced vital capacity (FVC) were secondary variables.
Results: 49 patients completed the study. On average, peak IC and AUC0–4 for IC were significantly greater after indacaterol than placebo by 177 mL (p = 0.007) and 142 mL (p = 0.001), respectively. Differences in peak IC and AUC0–4 for IC between tiotropium and placebo were 120 mL (p = 0.07) and 85 mL (p = 0.052), respectively. Differences between indacaterol and tiotropium were statistically insignificant. Peak IC increased by >20% in 12 patients with indacaterol and 9 with tiotropium (p = 0.001), and by >30% in 8 patients with indacaterol.

Abbreviations: COPD, chronic obstructive pulmonary disease; LABA, long-acting beta-agonist.
* Corresponding author.

E-mail addresses: andrea.rossi2@ospedaleuniverona.it (A. Rossi), stefano.centanni@unimi.it (S. Centanni), icerveri@smatteo.pv.it (I. Cerveri), c.gulotta@sanluigi.piemonte.it (C. Gulotta), antonio.foresi@icp.mi.it (A. Foresi), mario.cazzola@uniroma2.it (M. Cazzola), vito.brusasco@unige.it (V. Brusasco).

0954-6111/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
Introduction

Long-acting bronchodilators are central to the management of chronic obstructive pulmonary disease (COPD). Several clinical trials have shown that sustained bronchodilation is associated with improvements in the so-called patient-centered outcomes, namely, symptoms, exacerbations, exercise tolerance and health status. These effects were obtained with either long-acting β₂-agonists (LABA) or the muscarinic antagonist, tiotropium. However, when directly compared with LABA, tiotropium showed some superiority, which was attributed to its longer duration of action, i.e., 24 vs 12 h.

Indacaterol is a new LABA with a 24-h bronchodilator effect (Ultra-LABA), which proved to be superior to both formoterol and salmeterol based on measurements of 1-s forced expiratory volume (FEV₁)10–13 However, FEV₁ is poorly correlated with symptoms and exercise intolerance, which is more likely determined by dynamic pulmonary hyperinflation in COPD. Indeed, a reduction in pulmonary hyperinflation, as reflected by an increase in inspiratory capacity (IC), has been shown to occur in moderate-to-severe COPD patients treated with either salmeterol19 or tiotropium, and this was consistently associated with a reduction in dyspnea and an increase in exercise tolerance. In a recent study, Beier and colleagues found that high-dose indacaterol (300 μg) caused a significantly larger increase in IC than the recommended dose of formoterol.

The present study was designed to investigate whether the lower available dose of indacaterol (150 μg) can also reduce pulmonary hyperinflation in comparison with either placebo or the recommended dose of tiotropium (18 μg), the other available once-daily bronchodilator, in patients with moderate COPD.

Methods

The study protocol was approved by the Ethics Authority of each participating center. Written informed consent was obtained from each patient before entering the study.

Patient characteristics

All patients were at least 40 years old with a smoking history. They were required to have a clinical diagnosis of COPD confirmed by post-bronchodilator (salbutamol 4 × 100 μg) FEV₁/FVC < 0.71 and FEV₁/VC below the lower limit of normality. Based on FEV₁, they had to be classified as moderate, i.e., GOLD stage II. Patients were not included if they had a history of asthma or other allergic diseases, an elevated blood eosinophil count, or a recent respiratory tract infection.

Study design

This was a multicenter, randomized, single blinded, single dose, 3-period cross-over (Latin-square design), placebo-controlled study. Seven Pulmonary Units from University/General Hospitals participated in the study by recruiting patients from their outpatient clinics. At the first visit, patients were screened for eligibility to take part in the study. Those who met the inclusion criteria were asked to suspend any regular treatment with long-acting bronchodilators (tiotropium or LABA) and inhaled corticosteroids for the duration of the study. Inhaled salbutamol was allowed as rescue medication on demand (up to a maximum of 8 puffs/day). After seven days, patients had a second screening visit to assess whether they still met the inclusion criteria and were still willing to participate in the study. Those who were still eligible to take part in the study were randomized to receive single-doses of indacaterol (150 μg), tiotropium (18 μg) or placebo on three occasions, separated by 5-day washout periods. All doses were inhaled between 08:00 and 10:00 h, a.m.

On each study day, lung volumes and spirometry were measured before and again 30, 60, 120, 180 and 240 min after the administration of trial treatments. Investigator staff and persons performing assessments and data analysis remained blind to the treatment sequence from the time of randomization until database lock. Study drugs were received by a designated person at each study site and kept in a secured location to which only the designated unblinded site personnel had access.

Lung function measurements

Lung volumes were measured by a constant-volume variable-pressure body plethysmograph according to ATS/ERS recommendations. After a few regular tidal breaths, functional residual capacity (FRC) was measured by having the patient panting against a closed shutter at a frequency slightly <1 Hz. After the opening of the shutter and a few quiet tidal breaths without disconnecting from the mouthpiece, the patient fully inspired to total lung capacity (TLC) and IC was measured as the difference between TLC and FRC. Measurements were taken in triplicate and the average values of FRC and IC retained for analysis. Residual volume was calculated as the difference between TLC and the largest slow vital capacity (VC) from three acceptable maneuvers. Forced expiratory maneuvers were then
obtained and analyzed according to the ATS/ERS recommendations. The largest FEV\textsubscript{1} and FVC from three acceptable and repeatable maneuvers were taken, even if they were not from the same curve.

**Statistical analysis**

The primary efficacy variable was the peak increase in IC from pre-dose among the readings at 30, 60, 120, 180, 240 min post dose, and was summarized by sequence and treatment for the per-protocol population. We calculate an IC peak clinical difference of 65 ml with 80% power, assuming a standard deviation of 170 ml, with a one-tailed 0.025 level of significance. Secondary variables were the normalized area under the 4-h curve ($\text{AUC}_{0\rightarrow4}$) for IC, FEV\textsubscript{1} and FVC, and the number of patients with peak IC increments exceeding predetermined thresholds, i.e., 10%, 20% and 30%. Statistical significance was tested by analysis of variance (ANOVA) with the following factors: treatment, period, sequence and patient-within-sequence. Least square means and associated standard errors were calculated for each treatment group as well as treatment differences with 95% confidence intervals. McNemar test was used for categorical data. $P < 0.05$ was considered statistically significant.

**Results**

Fifty-four out of 62 patients screened were randomized and 49 of them completed the study. The five withdrawals were due to protocol violations (Fig. 1).

Their demographic and functional characteristics are shown in Table 1.

34 patients had TLC $>100\%$ predicted; 43 patients had FRC $>110\%$ predicted and 37 patients had RV $>120\%$ predicted. No significant difference was observed among baseline values for any of the variables considered in the study and treatment sequences. Before the study, 18\% of patients were not assuming any regular pharmacotherapy; 38\% of them were on fixed dose LABA + ICS combinations; 33\% were on tiotropium, and 11\% were on LABA monotherapy.

Compared with placebo, the mean increments of peak IC (Fig. 2) and $\text{AUC}_{0\rightarrow4}$ for IC (Fig. 3) were significantly larger.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69 ± 9</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>45/4</td>
</tr>
<tr>
<td>Smoking habit (current/former)</td>
<td>13/36</td>
</tr>
<tr>
<td>BMI (Kg/m\textsuperscript{2})</td>
<td>27.4 ± 4.6</td>
</tr>
<tr>
<td>VC (L)</td>
<td>3.18 ± 0.71</td>
</tr>
<tr>
<td>IC (L)</td>
<td>2.33 ± 0.54</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.11 ± 0.69</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (L)</td>
<td>1.81 ± 0.40</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (% of predicted)</td>
<td>68.7 ± 9.7</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC (%)</td>
<td>58.2 ± 7.7</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>4.97 ± 1.16</td>
</tr>
<tr>
<td>FRC (% of predicted)</td>
<td>147.5 ± 33.6</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>7.32 ± 1.52</td>
</tr>
<tr>
<td>TLC (% of predicted)</td>
<td>114.4 ± 19.2</td>
</tr>
<tr>
<td>RV (L)</td>
<td>3.67 ± 1.10</td>
</tr>
<tr>
<td>RV (% of predicted)</td>
<td>158.4 ± 40.5</td>
</tr>
</tbody>
</table>

Data are ± SD unless otherwise stated. All lung function data are post-bronchodilator.
with indacaterol (by 177 mL, \( p = 0.007 \) and 142 mL, \( p = 0.001 \), respectively). With tiotropium the mean increments of peak IC and AUC\(_{0-4}\) for IC tended to be larger than after placebo without reaching the predetermined level of statistical significance (by 120 mL, \( p = 0.07 \) and 85 mL, \( p = 0.052 \), respectively). Differences between indacaterol and tiotropium in peak IC and AUC\(_{0-4}\) for IC were not statistically significant (\( p = 0.18 \) and \( p = 0.38 \), respectively).

The distribution of percent changes in peak IC from baseline with indacaterol or tiotropium is shown in Fig. 4. Peak IC increased by >10% in 27 patients with indacaterol and 29 with tiotropium (\( p = 0.06 \)), by >20% in 12 patients with indacaterol and 9 with tiotropium (\( p = 0.001 \)) and by >30% in 8 patients with indacaterol and 3 with tiotropium (\( p = 0.001 \)).

Both indacaterol and tiotropium increased the AUC\(_{0-4}\) of FEV\(_1\) and FVC (Fig. 5) significantly compared with placebo (\( p < 0.01 \)), without significant differences between them.

**Discussion**

The main findings of this study are that: 1) 150 \( \mu \)g of indacaterol significantly increased IC in patients with...
and baseline values, because there were no differences in baseline lung function between treatment sequences. Furthermore, our results cannot be due to differences in the doses of the drugs, because the effects on FEV₁ and FVC were not significantly different.

There is a solid evidence showing potent bronchodilator efficacy of indacaterol in COPD. Beier and colleagues have also shown that 300 μg indacaterol had a significantly greater effect than formoterol on both FEV₁ and IC. The present study is the first one directly comparing the effects of low-dose indacaterol with the marketed dose of tiotropium on lung hyperinflation. The decrease in RV, and FRC appeared to be greater with indacaterol than with tiotropium.

The majority of studies on indacaterol to date recruited patients with moderate-to-severe COPD, i.e., with FEV₁ <80% and >30% of the predicted value. The present study was designed to include only patients with moderate COPD, i.e., with FEV₁ <80% and >50% of the predicted value. A recent longitudinal study has shown that in this severity group tiotropium may improve lung function and slightly but significantly decrease the rate of decline of FEV₁ over a 4-year period. Therefore, patients with moderate COPD are likely to experience substantial benefit from regular therapy with long-acting bronchodilators.

A potential limitation may be that this study only examined acute effects. By not examining effects of the study drugs beyond a single day we might have underestimated the potential acute effect of both drugs because of the delay in the achievement of a pharmacodynamic steady state for these drugs. In addition we have only examined the acute effects of the study drugs over the first 4 h. Hence we do not know whether the comparison might have yielded the same results over the entire 24 h duration of action.

We must mention that a previous study which compared the acute effect of tiotropium versus a combination therapy with single inhaler budesonide/formoterol on the degree of resting pulmonary hyperinflation documented that tiotropium is able to modify IC even after an acute administration points out its capacity of influencing expiratory flow limitation in a very fast manner. In a 12-week study published recently, Buhl et al showed that...
indacaterol 150 mcg and tiotropium 18 mcg had similar effects on trough FEV\textsubscript{1} but indacaterol was superior in reducing dyspnea.

The results of the present study are encouraging for the design of longer and more complex studies. In this regard, it is worth noting that even patients with mild COPD (i.e., FEV\textsubscript{1} >80% of the predicted value) have a reduced exercise tolerance\textsuperscript{36} which can be improved by bronchodilatation.\textsuperscript{37} It has been suggested that patients with COPD might receive additional benefit from regular treatment with long-acting bronchodilators earlier in the course of their diseases than was traditionally thought, and that both airflow obstruction and lung hyperinflation should therefore be targeted.\textsuperscript{38} Data from our study and those by Beier and colleagues\textsuperscript{22} show that indacaterol is effective in improving spirometry and decreasing pulmonary hyperinflation on the first day of administration. Whether this rapid functional improvement may influence patient compliance to the treatment and patient-centered outcomes remains to be established in long-term studies.\textsuperscript{39,40}

The data of the present study also demonstrates that IC may be a more sensitive measure than FEV\textsubscript{1} in discriminating between the effects of indacaterol and tiotropium on lung function in patients with moderate COPD.

**Conclusion**

In summary, this study shows that the lower available dose of the new ultra-long-acting bronchodilator, indacaterol, acutely improved spirometry in a manner similar to the recommended dose of tiotropium, but it was slightly superior in reducing lung hyperinflation. Long-term studies are necessary to evaluate whether this difference translates into greater beneficial effects on clinical end-points such as exercise tolerance and dyspnea.

**Author contributions**

AR, SC, MC and VB conceived the study, participated in its design, in its implementation and in data interpretation. IC, CG and AF participated in study implementation and in data interpretation. All authors were involved in drafting the manuscript and have read and approved the final manuscript.

**Conflict of interest statement**

A. Rossi: received honoraria for speaking and consulting and/or financial support for attending meetings from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Novartis, Nycomed and Pfizer.

S. Centanni: received honoraria for speaking and consulting and/or financial support for attending meetings from Boehringer Ingelheim, Chiesi Farmaceutici, Novartis and Pfizer.

I. Cerveri: received honoraria for speaking and consulting and/or financial support for attending meetings from Boehringer Ingelheim, Glaxo-Smith-Kline, Novartis and Pfizer.

C. Gulotta: received honoraria for speaking and consulting and/or financial support for attending meetings from Boehringer Ingelheim, Novartis and Pfizer.

A. Foresi: received honoraria for speaking and consulting and/or financial support for attending meetings from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Menarini, Novartis and Pfizer.

M. Cazzola: received honoraria for speaking and consulting and/or financial support for attending meetings from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Day, GSK, Menarini Farmaceutici, Mundipharma, Novartis, Nycomed, Pfizer and Sigma-Tau.

V. Brusasco: received honoraria for speaking and consulting from Boehringer Ingelheim, Chiesi Farmaceutici, Dompe` , Novartis, GSK, Novartis and Nycomed.

**Acknowledgments**

This study was sponsored by Novartis S.p.A. Medical writing support was provided by Dr Colin Gerard Egan (Primula Multimedia SRL, Pisa, Italy).

**References**


obstructive airways disease, with a tiotropium comparison. 
11. Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, 
et al. Efficacy of a new once-daily long-acting inhaled beta2-
agonist indacaterol versus twice-daily formoterol in COPD. 
et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: 
13. Donohue JF, Fogarty C, Ltvall J, Mahler DA, Worth H, 
Yorgancioglu A, et al. Once-daily bronchodilators for chronic 
obstructive pulmonary disease: indacaterol versus tiotropium. 
14. Cooper CB. The connection between chronic obstructive 
pulmonary disease symptoms and hyperinflation and its impact 
15. Milic-Emili J. Inspiratory capacity and exercise tolerance in chronic 
16. O’Donnell DE, Lam M, Webb KA. Spirometric correlates of 
 improvement in exercise performance after anticholinergic 
therapy in chronic obstructive pulmonary disease. Am J Respir 
17. Diaz O, Vilafranca C, Ghezzo H, Borzone G, Leiva A, Milic-
Emili J, et al. Role of inspiratory capacity on exercise tolerance in 
COPD patients with and without tidal expiratory flow limi-
18. O’Donnell DE. Hyperinflation, dyspnea, and exercise intoler-
ce in chronic obstructive pulmonary disease. Proc Am Thorac 
salmeterol on the ventilatory response to exercise in chronic 
inspiratory capacity and hyperinflation with tiotropium in 
COPD patients with increased static lung volumes. Chest 2003; 
Aguilaniu B, et al. Effects of tiotropium on lung hyperinflation, 
dyspnea and exercise tolerance in COPD. Eur Respir J 2004; 
Bronchodilator effects of indacaterol and formoterol in 
23. Pellegrino R, Vieggi G, Brusasco V, Crapo RO, Burgos F, 
24. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, 
25. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, 
Coates A, et al. ATS/ERS task force: standardization of 
26. Dal Vecchio L, Polege G, Poggi R, Rossi A. Intrinsic positive and 
—expiratory pressure in stable patients with chronic obstructive 
27. Tantucci C, Duguet A, Similowski T, Zelter M, Derenne JP, 
Milic-Emili J. Effect of salbutamol on dynamic hyperinflation in 
chronic obstructive pulmonary disease patients. Eur Respir J 
28. Calverley PM, Kolouri NG. Flow limitation and dynamic 
hyperinflation: key concepts in modern respiratory physiology. 
29. Marin JM, Carrizo SJ, Gascon M, Sanchez A, Gallego B, Celli BR. 
Inspiratory capacity, dynamic hyperinflation, breathlessness, 
and exercise performance during the 6-minute-walk test in 
chronic obstructive pulmonary disease. Am J Respir Crit Care 
30. O’Donnell DE, Lam M, Webb KA. Measurement of symptoms, 
lung hyperinflation, and endurance during exercise in chronic 
 obstructive pulmonary disease. Am J Respir Crit Care Med 
31. O’Donnell DE. Assessment of bronchodilator efficacy in symp-
32. Pellegrino R, Rodarte JR, Brusasco V. Assessing the reversibility 
33. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. 
Effect of tiotropium on outcomes in patients with moderate 
chronic obstructive pulmonary disease (UPLIFT): a prespecified 
subgroup analysis of a randomised controlled trial. Lancet 
34. Santus P, Centanni S, Verga M, Di Marco F, Matera MG, 
Cazzola M. Comparison of the acute effect of tiotropium versus 
a combination therapy with single inhaler budesonide/formo-
terol on the degree of resting pulmonary hyperinflation. Respir 
Blinded 12 week comparison of once daily indacaterol and 
tiotropium in COPD. Eur Respir J 2011. doi: 
10.1183/09031936.00191810.
Mechanisms of dyspnea during cycle exercise in symptomatic 
patients with GOLD stage I chronic obstructive pulmonary 
Evaluation of acute bronchodilator reversibility in patients with 
38. Decramer M, Cooper CB. Treatment of COPD: the sooner the 
of action of indacaterol in patients with COPD: comparison 
with salbutamol and salmeterol-fluticasone. Int J Chron 
40. Calverley PM. New options for bronchodilator treatment in 