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ORIGINAL ARTICLE

Effects of indacaterol versus tiotropium on exercise tolerance in patients with moderate COPD: a pilot randomized crossover study

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Study carried out at Pavilhão Pereira Filho, Santa Casa de Porto Alegre, Porto Alegre (RS) Brasil.

Abstract

Objective: To compare a once-daily long-acting β_2 agonist (indacaterol 150 µg) with a once-daily long-acting anticholinergic (tiotropium 5 µg) in terms of their effects on exercise endurance (limit of tolerance, Tlim) in patients with moderate COPD. Secondary endpoints were their effects on lung hyperinflation, exercise-related dyspnea, and daily-life dyspnea. **Methods:** This was a randomized, single-blind, crossover pilot study involving 20 patients (mean age, 60.9 ± 10.0 years; mean FEV_1, 69 ± 7% of predicted). Spirometric parameters, Transition Dyspnea Index scores, Tlim, and exertional dyspnea were compared after three weeks of each treatment (with a one-week washout period between treatments). **Results:** Nineteen patients completed the study (one having been excluded because of COPD exacerbation). Improvement in Tlim from baseline tended to be greater after treatment with tiotropium than after treatment with indacaterol (96 ± 163 s vs. 8 ± 82 s; p = 0.06). Tlim significantly improved from baseline after treatment with tiotropium (having increased from 396 ± 319 s to 493 ± 347 s; p = 0.010) but not after treatment with indacaterol (having increased from 393 ± 246 to 401 ± 254 s; p = 0.678). There were no differences between the two treatments regarding improvements in Borg dyspnea scores and lung hyperinflation at "isotime" and peak exercise. There were also no significant differences between treatments regarding Transition Dyspnea Index scores (1.5 ± 2.1 vs. 0.9 ± 2.3; p = 0.39). **Conclusions:** In patients with moderate COPD, tiotropium tends to improve Tlim in comparison with indacaterol. No significant differences were observed between the two treatments regarding their effects on lung hyperinflation, exercise-related dyspnea, and daily-life dyspnea. Future studies, including a larger number of patients, are required in order to confirm our findings and explore mechanistic explanations.

(ClinicalTrials.gov identifier: NCT01693003 [http://www.clinicaltrials.gov/])

Keywords: Pulmonary disease, chronic obstructive; Exercise; Bronchodilator agents.

INTRODUCTION

Bronchodilators have consistently been shown to result in long-term improvements in clinical outcomes (symptoms, exercise capacity, and airflow limitation) and are currently considered the therapeutic mainstay for patients with COPD.[1] According to current guidelines, all symptomatic patients with COPD should be prescribed a short-acting bronchodilator to be used on an as-needed basis. A long-acting bronchodilator should be added and used regularly if symptoms are inadequately controlled with short-acting bronchodilator therapy or if patients are at an increased risk for poor outcomes, such as frequent exacerbations and disease that is more severe.[1,2]

Until recently, a long-acting anticholinergic (LAMA) was preferred over a long-acting β_2 agonist (LABA) because most of the effects of once-daily LAMAs appeared to be superior to those of twice-daily LABAs.[3-8] The advent of once-daily LABAs (ultra-LABAs) changed that, studies comparing once-daily LAMAs with once-daily LABAs having demonstrated the clinical benefits of the latter.[9,10] However, no studies have compared once-daily LABAs with once-daily LAMAs regarding clinical outcomes during exercise, including exercise tolerance, dyspnea, and dynamic hyperinflation. Therefore, we conducted a pilot study aimed at comparing a once-daily LABA (indacaterol) with a once-daily LAMA (tiotropium) in terms of their effects on exercise tolerance in patients with moderate COPD. Indacaterol and tiotropium were also compared in terms of their effects on lung hyperinflation, exercise-related dyspnea, and daily-life dyspnea.

METHODS

This was a phase IV, randomized, single-blind (i.e., with single-blind masking of outcome assessors), placebo-controlled, two-period, crossover pilot study conducted at a single center specializing in respiratory care (ClinicalTrials.gov identifier: NCT01693003).[11] The study protocol was approved by the local research ethics committee.

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Patients were randomly assigned to receive three weeks of treatment with 150 µg of inhaled indacaterol (Onbrize® Breezhaler®; Novartis, Basel, Switzerland) delivered via a capsule-based dry powder inhaler (DPI), followed by another three weeks of treatment with 5 µg of inhaled tiotropium (Spiriva® Respimat®; Boehringer Ingelheim, Ingelheim, Germany) delivered via a soft mist inhaler (SMI), with a one-week washout period between the two treatment periods; or three weeks of treatment with 5 µg of inhaled tiotropium (Spiriva® Respimat®; Boehringer Ingelheim) delivered via an SMI, followed by another three weeks of treatment with 150 µg of inhaled indacaterol (Onbrize® Breezhaler®; Novartis) delivered via a capsule-based DPI, with a one-week washout period between the two treatment periods (Figure 1). After a screening visit (on day 7), all long-acting bronchodilators were discontinued. Patients were allowed to use short-acting bronchodilators, being instructed to use two puffs every 4 h as rescue medication. They were also allowed to use inhaled corticosteroids, provided that the dose, schedule, and formulation remained unchanged.

At the baseline visit, patients underwent clinical evaluation, pulmonary function testing, and incremental symptom-limited cardiopulmonary exercise testing (CPET). At visits 1 through 4, patients underwent constant-rate CPET to the limit of tolerance (Tlim), at ~80% of the maximum load reached during incremental CPET. Activity-related breathlessness was assessed at baseline with the Baseline Dyspnea Index (BDI), and changes in daily breathlessness were assessed with the Transition Dyspnea Index (TDI),[12] being recorded at the end of each treatment period (Figure 1).

Patients

Patients presenting with stable COPD (FEV_1/FVC < 0.7 and 50% < post-bronchodilator FEV_1 < 80% of predicted) and a long smoking history (> 20 pack-years) were enrolled. The exclusion criteria were as follows: cardiovascular or neuromuscular disease potentially affecting exercise tolerance; recent exacerbation (in the last month); long-term oxygen therapy or resting SaO_2 < 90%; and treatment with oral corticosteroids.

Procedures

All spirometric tests were performed with a calibrated pneumotachograph (Vmax29®; SensorMedics, Yorba Linda, CA, USA). Spirometric variables were measured at the baseline visit (before and 20 min after inhalation of 400 µg of albuterol via a metered dose inhaler); at visits 1 and 3 (after a one-week long-acting bronchodilator washout period and before CPET); and at visits 2 and 4 (2 h after administration of the study medications and before CPET). A constant-volume body plethysmograph (Vmax Autobox®; SensorMedics) was used in order to measure RV, functional residual capacity, and TLC. Single-breath DLCO was measured using a Vmax System (SensorMedics). All pulmonary function tests were performed in accordance with international standards.[13-15] The variables obtained were expressed as absolute and percent predicted values.[16-18]

All exercise tests were performed on an electromagnetically braked cycle ergometer (Corival; Lode, Groningen, the Netherlands), with the use of a computer-based breath-by-breath CPET system (Vmax29®; SensorMedics). HR was determined from the R-R interval of a 12-lead electrocardiogram, and SaO_2 was measured by pulse oximetry. All CPET variables were presented as 20-s averages. Participants rated their shortness of breath and leg effort using the 0-10 Borg scale[19] every 2 min. During incremental CPET, the workload was increased every 1 min from a baseline of 2 min of loadless pedaling at a rate of 5-10 W/min to Tlim. Incremental load increases were highest in patients with FEV_1 > 1 L. Constant-rate CPET was performed with loadless pedaling for 2 min at a pedaling frequency of 60 ± 5 rpm, immediately followed by loaded pedaling at ~80% of the maximum workload achieved during incremental CPET. Assuming that resting TLC remains constant during exercise, we considered that changes in inspiratory capacity (IC) reflected changes in end-expiratory lung volume, i.e., end-expiratory lung volume = TLC − IC.[20] IC maneuvers were performed every 2 min. Exercise responses were compared at peak exercise and at "isotime", i.e., the longest exercise duration common to all constant-rate cardiopulmonary exercise tests performed by a given individual.

The BDI and TDI were used in order to measure daily-life dyspnea, and both have three domains: 1) functional impairment, which determines the impact of breathlessness on the ability to carry out activities; 2) magnitude of task, which determines the type of task that causes breathlessness; and 3) magnitude of effort, which establishes the level of effort that results in breathlessness. The BDI domain scores range from 0 (very severe impairment) to 4 (no impairment) and are summed to determine the total score, which can range from 0 to 12. The TDI domain scores range from −3 (major deterioration) to +3 (major improvement). The sum of all domains yields the total score, which can range from −9 to +9.[12] The minimal clinically important difference for the TDI score is 1.[21]

Safety

Safety assessments included adverse events and serious adverse events at the end of each treatment period. HR correction of the QT interval was performed using Bazett's correction.

Statistical analysis

Data are reported as mean ± SD or median (range), except where otherwise indicated. Generalized estimating equations were used in order to test for significant differences between treatments at different visits and time points. Paired t-tests were used in order to compare TDI scores after each treatment and calculate the sample size required to detect a significant difference ($p < 0.05$) between treatments

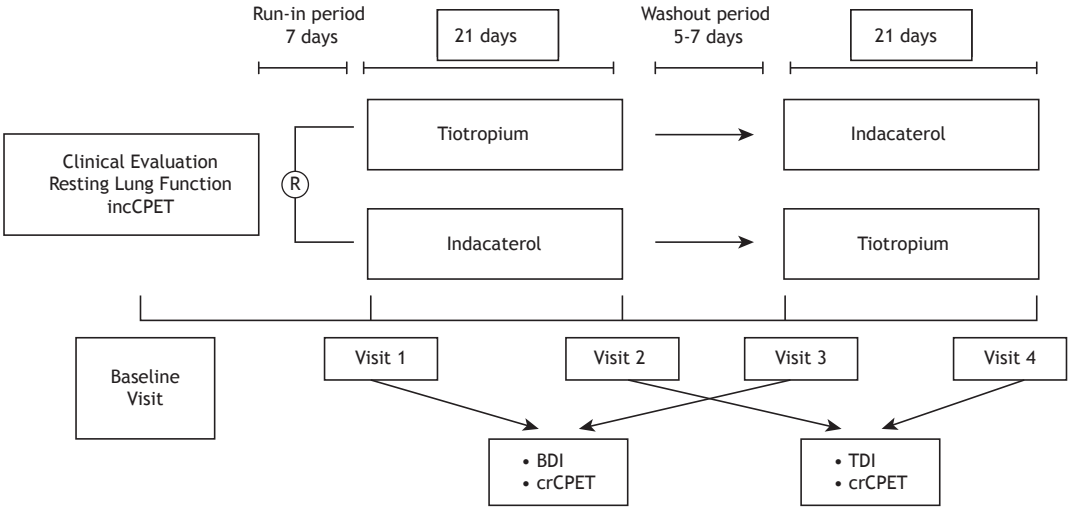

Figure 1. Flowchart of the study design. incCPET: incremental cardiopulmonary exercise testing; crCPET: constant-rate cardiopulmonary exercise testing; BDI: Baseline Dyspnea Index; and TDI: Transition Dyspnea Index.

regarding improvement in exercise tolerance (with a type II error of 20%). The chi-square test was used in order to compare categorical data. Differences were considered significant if $p < 0.05$.

RESULTS

Of the 69 patients who were screened, 20 were randomized. Of those, 19 (95%) completed the study. One patient (in the group of patients assigned to receive indacaterol first) was excluded because of COPD exacerbation (during treatment with indacaterol).

The baseline demographic, anthropometric, and clinical characteristics of the patients studied are described in Table 1. A Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is shown in Figure 2.

Effects on spirometric variables and daily-life dyspnea

After three weeks of treatment, FEV_1 was significantly improved from baseline in both groups (Table 2). However, in addition to having resulted in greater improvement in FEV_1, indacaterol significantly improved FVC when compared with tiotropium. There were no significant differences between indacaterol and tiotropium regarding TDI scores (1.5 ± 2.1 vs. 0.9 ± 2.3; $p = 0.39$) or the proportion of patients in whom TDI scores were ≥ 1 (58% vs. 37%; $p = 0.19$).

Effects on exercise responses

Improvement in Tlim from baseline (the primary study outcome) tended to be greater after treatment with tiotropium than after treatment with indacaterol (96 ± 163 s vs. 8 ± 82 s; $p = 0.06$; Figure 3). Additionally, Tlim significantly improved from baseline after treatment with tiotropium (having increased from 396 ± 319 s to 493 ± 347 s; $p = 0.010$) but not after treatment with indacaterol (having increased from 393 ± 246 s to 401 ± 254 s; $p = 0.678$). A sample size of 28 was estimated to be required in order to detect a significant difference in exercise tolerance between the two treatments.

There were no differences between the two treatments regarding the magnitude of improvement in Borg dyspnea scores (at isotime and peak exercise) or lung hyperinflation, as estimated from serial measurements of IC (at rest, isotime, and peak exercise). Lung hyperinflation was found to have improved significantly after treatment with bronchodilators (2.00 ± 0.33 L vs. 2.09 ± 0.31 L; $p = 0.03$) at all time points analyzed (i.e., at rest, isotime, and peak exercise). The same was true for exercise-related dyspnea ($p = 0.067$).

Safety

The overall incidence of adverse events was exactly the same in both treatment groups (i.e., 58%), the majority of the events being mild in severity. No serious adverse events (hospitalization or death) were reported during the study period. There was no difference between indacaterol and tiotropium in terms of their effects on the resting corrected QT interval (445 ± 48 ms vs. 439 ± 47 ms; $p > 0.05$), post-bronchodilator values being no different from baseline values (456 ± 34 ms).

DISCUSSION

This was a pilot study designed to collect preliminary data regarding the comparative effects of indacaterol 150 µg (the lowest available dose in most countries) and tiotropium 5 µg on exercise tolerance in patients with moderate COPD. Previous studies[22,23] have demonstrated that indacaterol 300 µg results in significant improvement in exercise tolerance and lung hyperinflation at rest and during exercise when compared with placebo in patients with moderate to severe COPD. Surprisingly, the present study showed that a lower dose of indacaterol (150 µg) in a subset of patients with less severe disease did not increase

exercise tolerance from baseline. In contrast, tiotropium 5 µg significantly improved exercise tolerance from baseline, a finding that is consistent with those of previous studies in which a different drug dose and delivery system were used (i.e., 18 µg of tiotropium delivered via a DPI).[24-27]

In the present study, both drugs resulted in significant improvement in lung hyperinflation and exercise-related dyspnea, as previously described for tiotropium (18 µg delivered via a DPI)[12,19-21] and indacaterol (300 µg),[17,18] with no significant difference between the two treatments. However, it is possible that our small sample size did not allow us to detect individual drug effects on the aforementioned variables or differences between the two treatments.

Table 1. Baseline characteristics of the patients studied (N = 19).[a]

Variable	Result
Demography and anthropometry	
Age, years	60.9 ± 10.0
Male/female, n/n	9/10
BMI, kg/m^2	24.8 ± 3.5
Smoking history, pack-years[b]	45 (6-108)
Pulmonary function	
Pre-BD spirometry	
FEV_1, L	1.86 ± 0.62
FEV_1, % of predicted	67.4 ± 8.6
FVC, L	3.26 ± 0.83
FVC, % of predicted	94.1 ± 10
FEV_1/FVC	57 ± 8
Post-BD spirometry	
FEV_1, L	1.89 ± 0.58
FEV_1, % of predicted	68.7 ± 7.4
FVC, L	3.27 ± 0.8
FVC, % of predicted	94.6 ± 11.2
FEV_1/FVC	58 ± 8
Plethysmography	
IC, L	2.15 ± 0.9
IC, % of predicted	66.3 ± 20.5
TLC, L	5.67 ± 1.4
TLC, % of predicted	109.1 ± 12.7
IC/TLC	0.37 ± 0.1
RV, L	2.36 ± 0.73
RV, % of predicted	122.5 ± 33.6
DLCO, mmol/min/kPa	4.4 ± 1.4
DLCO, % of predicted	67.4 ± 18.3
Symptoms	
mMRC score	2.3 ± 1.1
BDI score	8.4 ± 2.4
Peak incremental CPET	
VO_2, mL/min	1,083 ± 349
VO_2, % of predicted	74.7 ± 16.6
V_E, L	42.4 ± 14.9
V_E/MVV	0.69 ± 0.17
SaO_2, %	96 ± 2
HR, % of predicted	79 ± 12
VO_2/HR, mL/min/bpm	8.45 ± 2.12
Borg scale, dyspnea score[b]	4 (0.5-10)
Borg scale, leg effort score[b]	7 (1-10)

[a]Values expressed as mean ± SD, except where otherwise indicated. [b]Values expressed as median (range). BD: bronchodilator; IC: inspiratory capacity; mMRC: modified Medical Research Council; BDI: Baseline Dyspnea Index; CPET: cardiopulmonary exercise testing; VO_2: oxygen uptake; V_E: minute ventilation; and MVV: maximal voluntary ventilation.

Although both treatments improved FEV_1 from baseline, the magnitude of change was greater for indacaterol. Similar findings have previously been described.[10,28] With regard to clinical outcomes, a clinically relevant improvement in total TDI and Saint George's Respiratory Questionnaire scores is more likely to be achieved with indacaterol 150 µg than with tiotropium 18 µg in patients with moderate to severe COPD.[29] However, tiotropium has been reported to afford greater protection against exacerbations.[30] In the present study, indacaterol resulted in greater improvement in FEV_1 than did tiotropium (Table 2). However, it did not result in improved exercise tolerance, probably because constraints on tidal volume expansion as a result of lung hyperinflation constitute the main mechanism related to dyspnea and exercise capacity, independently of the magnitude of airflow obstruction.[20,26,31] Nevertheless, because of its small size, our sample was probably underpowered to detect differences between the two treatments regarding this physiological variable. Therefore, other mechanisms to explain improved exercise tolerance after treatment with tiotropium should be considered and further investigated.[32] For instance, it is impossible to rule out that our small sample size randomly included primarily patients who were more likely to benefit from one specific pharmacological class of bronchodilators. Polymorphisms of β_2-adrenergic receptors can result in differences in pharmacological responses to bronchodilators.[33,34] This underscores the need for further, larger studies. If our findings are confirmed, adequately powered studies will be required in order to investigate physiological and molecular mechanistic aspects.

The present study has methodological limitations that should be noted. First, because this was an exploratory study including only a small number of patients, the results should be interpreted with caution. Our sample was possibly underpowered to detect differences in important outcomes, such as dyspnea and lung hyperinflation, and our main findings should be confirmed in studies including a larger number of patients. Second, because the present study included only patients with moderate COPD, the results should not be generalized to patients with mild or severe COPD. Finally, we used a low dose of indacaterol and a full dose of tiotropium delivered via an SMI. The dose of indacaterol used in the present study (i.e., 150 µg) did not improve exercise tolerance as did the dose used in other studies (i.e., 300 µg).[22,23] In fact, it has been shown that indacaterol is more beneficial to resting pulmonary function at higher doses (> 200 µg) than at lower doses (of 50 µg and 100 µg); however, in comparison with placebo, even lower doses of the

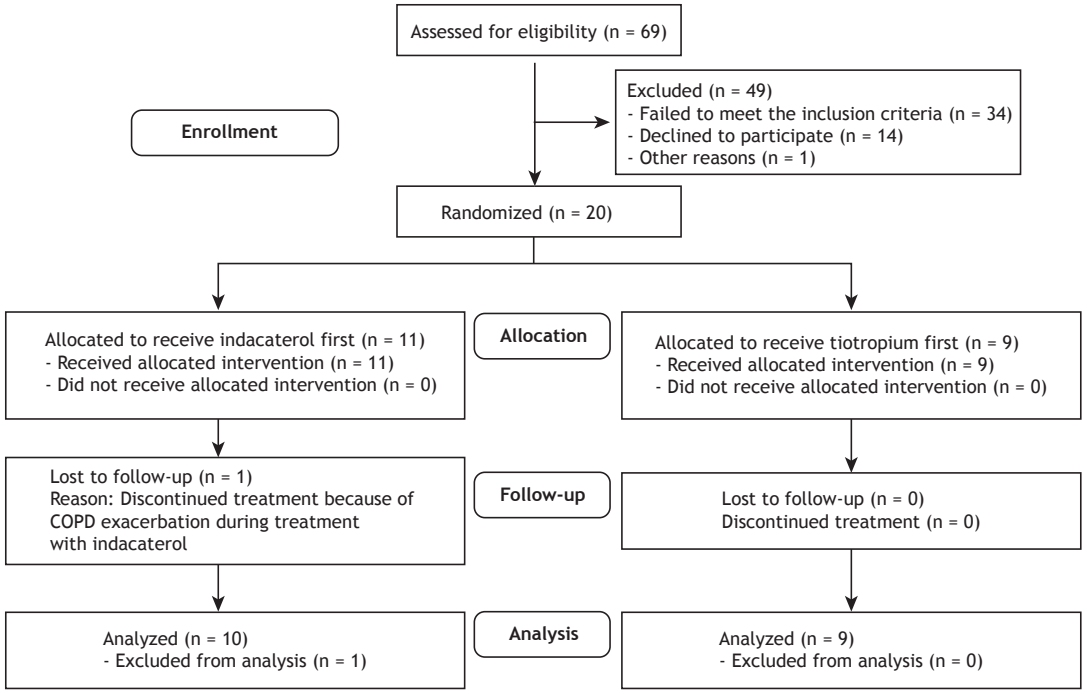

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study.

Table 2. Lung function parameters at baseline and after three weeks of treatment with indacaterol or tiotropium.[a]

Variable	Indacaterol		Diff	Tiotropium		Diff
	Baseline	Post-treatment		Baseline	Post-treatment	
FEV_1, L	1.62 ± 0.12	1.82 ± 0.12*	0.20	1.69 ± 0.13	1.79 ± 0.14*	0.10
FEV_1, % of predicted	56 ± 2	63 ± 2*	7†	58 ± 2	61 ± 2	3
FVC, L	2.94 ± 0.2	3.15 ± 0.17*	0.21†	3.06 ± 0.19	3.12 ± 0.2	0.06
FVC, % of predicted	80 ± 2	87 ± 2*	7†	84 ± 2	86 ± 2	2
FEV_1/FVC, %	55.5 ± 2.0	57.6 ± 1.6*	2.1	55.0 ± 1.9	56.9 ± 1.9*	1.9

[a]Data presented as mean ± SE. BD: bronchodilator; and Diff: difference between mean post-treatment values and mean baseline values. *p < 0.05 baseline vs. post-treatment. †p < 0.05 comparison between treatment changes.

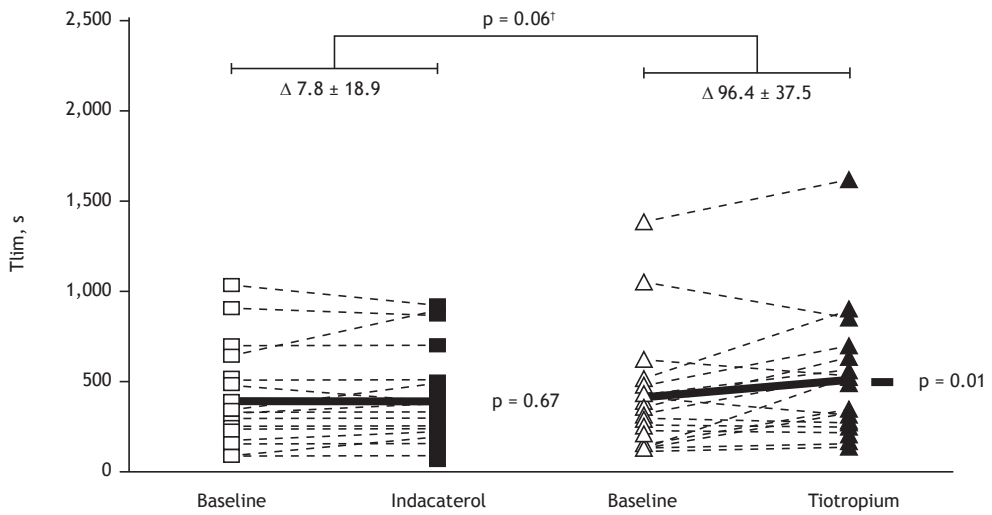

Figure 3. Individual values (dashed lines) and mean values (solid lines) of changes from baseline in the limit of tolerance (Tlim) during constant-rate cardiopulmonary exercise testing after three weeks of treatment with indacaterol (squares) or tiotropium (triangles). *p < 0.05 from baseline. †p = 0.06 for between-treatment difference.

drug result in significant improvement.[28] In contrast, it has been shown that 5 µg of tiotropium delivered via an SMI and 18 µg of the same drug delivered via a DPI are comparable in terms of their effects on lung function[35,36] and clinical outcomes (rescue medication use, death, and exacerbation rate).[30] Given that the doses of indacaterol approved for use in different countries vary from 75 µg to 300 µg and that the only dose of SMI-delivered tiotropium approved for use in COPD patients is 5 µg, we sought to compare doses that are more commonly used in clinical practice.

In conclusion, although treatment with tiotropium at a daily dose of 5 µg resulted in a significant improvement in exercise tolerance in patients with moderate COPD, treatment with indacaterol at a daily dose of 150 µg did not. No significant differences were observed between the two treatments regarding their effects on lung hyperinflation, exercise-related dyspnea, and daily-life dyspnea. Further studies, including a larger number of patients, are required in order to confirm our findings and explore mechanistic explanations.

REFERENCES

1. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347-65. http://dx.doi.org/10.1164/rccm.201204-0596PP
2. Montes de Oca M, López Varela MV, Acuña A, Schiavi E, Rey MA, Jardim J, et al. ALAT-2014 Chronic Obstructive Pulmonary Disease (COPD) Clinical Practice Guidelines: questions and answers. Arch Bronconeumol. 2015;51(8):403-16. http://dx.doi.org/10.1016/j.arbres.2014.11.017
3. Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ Jr, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest. 2002;122(1):47-55. http://dx.doi.org/10.1378/chest.122.1.47
4. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax. 2003;58(5):399-404. Erratum in: Thorax. 2005;60(2):105. http://dx.doi.org/10.1136/thorax.58.5.399
5. Briggs DD Jr, Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther. 2005;18(6):397-404. http://dx.doi.org/10.1016/j.pupt.2005.02.013
6. Hodder R, Kesten S, Menjoge S, Viel K. Outcomes in COPD patients receiving tiotropium or salmeterol plus treatment with inhaled corticosteroids. Int J Chron Obstruct Pulmon Dis. 2007;2(2):157-67.
7. 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/formoterol on the degree of resting pulmonary hyperinflation. Respir Med. 2006;100(7):1277-81. http://dx.doi.org/10.1016/j.rmed.2005.10.008
8. van Noord JA, Aumann JL, Janssens E, Smeets JJ, Verhaert J, Disse B, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J. 2005;26(2):214-22. http://dx.doi.org/10.1183/09031936.05.00140404
9. Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting β-agonists for stable COPD: a systematic review. Chest. 2012;142(5):1104-10. http://dx.doi.org/10.1378/chest.11-2252
10. Vogelmeier C, Ramos-Barbon D, Jack D, Piggott S, Owen R, Higgins M, et al. Indacaterol provides 24-hour bronchodilation in COPD: a placebo-controlled blinded comparison with tiotropium. Respir Res. 2010;11:135. http://dx.doi.org/10.1186/1465-9921-11-135
11. ClinicalTrials.gov [homepage on the Internet]. Bethesda: National Institutes of Health [cited 2015 Jan 14]. Indacaterol Versus Tiotropium on Dynamic Hyperinflation in COPD. Available from: https://clinicaltrials.gov/ct2/show/NCT01693003
12. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984;85(6):751-8. http://dx.doi.org/10.1378/chest.85.6.751
13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. http://dx.doi.org/10.1183/09031936.05.00034805
14. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26(3):511-22. http://dx.doi.org/10.1183/09031936.05.00035005
15. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720-35. http://dx.doi.org/10.1183/09031936.05.00034905
16. Pereira CA; Sato T; Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. http://dx.doi.org/10.1590/S1806-37132007000400008
17. Crapo RO, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. Bull Eur Physiopathol Respir. 1982;18(3):419-25.
18. Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. Am Rev Respir Dis. 1981;123(2):185-9.
19. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-81 http://dx.doi.org/10.1249/00005768-198205000-00012
20. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006;3(2):180-4. http://dx.doi.org/10.1513/pats.200508-093DO
21. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med. 2014;189(3):250-5. http://dx.doi.org/10.1164/rccm.201310-1863PP
22. O'Donnell DE, Casaburi R, Vincken W, Puente-Maestu L, Swales J, Lawrence D, et al. Effect of indacaterol on exercise endurance and lung hyperinflation in COPD. Respir Med. 2011;105(7):1030-6. http://dx.doi.org/10.1016/j.rmed.2011.03.014
23. Beeh KM, Wagner F, Khindri S, Drollmann AF. Effect of indacaterol on dynamic lung hyperinflation and breathlessness in hyperinflated patients with COPD. COPD. 2011;8(5):340-5. http://dx.doi.org/10.3109/15412555.2011.594464
24. O'Donnell DE, Flüge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J. 2004;23(6):832-40. http://dx.doi.org/10.1183/09031936.04.00116004
25. Maltais F, Hamilton A, Marciniuk D, Hernandez P, Sciurba FC, Richter K, Kesten S, O'Donnell D. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest. 2005;128(3):1168-78. http://dx.doi.org/10.1378/chest.128.3.1168
26. O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. J Appl Physiol (1985). 2006;101(4):1025-35. http://dx.doi.org/10.1152/japplphysiol.01470.2005
27. Verkindre C, Bart F, Aguilaniu B, Fortin F, Guérin JC, Le Merre C, et al. The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. Respiration. 2006;73(4):420-7. http://dx.doi.org/10.1159/000089655
28. Rennard S, Bantje T, Centanni S, Chanez P, Chuchalin A, D'Urzo A, et al. A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison. Respir Med. 2008;102(7):1033-44. http://dx.doi.org/10.1016/j.rmed.2008.02.001
29. Buhl R, Dunn LJ, Disdier C, Lassen C, Amos C, Henley M, et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. Eur Respir J. 2011;38(4):797-803. http://dx.doi.org/10.1183/09031936.00191810

30. Decramer ML, Chapman KR, Dahl R, Frith P, Devouassoux G, Fritscher C, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respir Med. 2013;1(7):524-33. http://dx.doi.org/10.1016/S2213-2600(13)70158-9
31. O'Donnell DE, Laveneziana P, Webb K, Neder JA. Chronic obstructive pulmonary disease: clinical integrative physiology. Clin Chest Med. 2014;35(1): 51-69. http://dx.doi.org/10.1016/j.ccm.2013.09.008
32. Trevethick M, Clarke N, Strawbridge M, Yeadon M. Inhaled muscarinic antagonists for COPD–does an anti-inflammatory mechanism really play a role? Curr Opin Pharmacol. 2009;9(3):250-5. http://dx.doi.org/10.1016/j.coph.2009.02.003
33. Wechsler ME, Lehman E, Lazarus SC, Lemanske RF Jr, Boushey HA, Deykin A, et al. beta-Adrenergic receptor polymorphisms and response to salmeterol. Am J Respir Crit Care Med. 2006;173(5):519-26. http://dx.doi.org/10.1164/rccm.200509-1519OC
34. Umeda N, Yoshikawa T, Kanazawa H, Hirata K, Fujimoto S. Association of beta2-adrenoreceptor genotypes with bronchodilatory effect of tiotropium in COPD. Respirology. 2008;13(3):346-52. http://dx.doi.org/10.1111/j.1440-1843.2008.01259.x
35. Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med. 2013;369(16):1491-501. http://dx.doi.org/10.1056/NEJMoa1303342
36. van Noord JA, Cornelissen PJ, Aumann JL, Platz J, Mueller A, Fogarty C. The efficacy of tiotropium administered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. Respir Med. 2009;103(1):22-9. http://dx.doi.org/10.1016/j.rmed.2008.10.002