# Effect of fluticasone propionate/salmeterol plus tiotropium *versus* tiotropium on walking endurance in COPD

*To the Editor:*

Exercise intolerance is a hallmark feature of chronic obstructive pulmonary disease (COPD) and is associated with premature mortality [1]. Tiotropium (TIO) is effective in improving cycling exercise tolerance [2, 3] and walking endurance time in COPD [4]; these properties are thought to be associated with reductions in operating lung volume and the perception of dyspnoea during exercise [2, 3, 5]. What is less certain, however, is the extent to which these benefits of TIO on exercise duration can be further improved with the use of additional inhalational therapy.

We examined whether the addition of fluticasone propionate/salmeterol combination (FSC) to TIO improved endurance time during the endurance shuttle walking test (ESWT) more than TIO alone in patients with COPD. Our specific objectives were to compare endurance time during the ESWT and evaluate the impact on lung function of TIO alone or in combination with FSC. We hypothesised that the addition of FSC to TIO would improve endurance time during the ESWT compared to TIO alone. This was an 8-week, multicentre, placebo-controlled, double-blind, randomised, parallel group study. Patients received either FSC (Advair/Seretide; GlaxoSmithKline, Research Triangle Park, NC, USA) 250/50 μg administered *via* DISKUS twice daily plus TIO (Spiriva; Boehringer Ingelheim GmbH and Co.KG, Ingelheim, Germany) 18 μg administered *via* Handihaler once daily or placebo DISKUS twice daily plus TIO 18 μg once daily. The study was conducted at 24 sites in the USA and Canada between July 19, 2010 and May 2, 2011. Eligible patients were aged $\geqslant$40 years and had a documented clinical history of COPD. All patients gave written informed consent. The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (clinicaltrials.gov registration: NCT01124422). Patients completing the 4-week open-label TIO run-in were randomised to TIO+placebo or TIO+FSC for 4 weeks of treatment and then returned to the clinic for the final study visit. FSC was double-blind and TIO was open-label. Albuterol/salbutamol was provided on an as-needed basis throughout the study. The primary outcome variable was the between-group difference in the change in exercise endurance time from ESWT performed 2.5 h post study drug administration from baseline to week four (end of the treatment period). Pre- and post-study drug medication pulmonary function was evaluated at baseline and week four. Safety assessments included incidence of adverse events (defined by the Medical Dictionary for Regulatory Activities). It was estimated that 111 patients per treatment group would provide 90% power to detect a 70-s difference (the proposed minimally important difference for bronchodilatory interventions) [6] in exercise endurance time change from baseline to week four between the two treatment groups. This was based on a two-sample two-sided t-test with a significance level of 0.05 and a standard deviation estimate of 160 s. Primary and secondary efficacy measures were compared between treatment groups using ANCOVA; the covariates included treatment group, investigator, randomisation stratum and baseline value. Statistical tests were conducted at the two-sided 0.05 significance level and statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) in a UNIX reporting environment.

255 patients with COPD (aged 62.7$\pm$9.4 years, post-albuterol predicted forced expiratory volume in 1 s ($FEV_1$) 54.7$\pm$13.2% predicted) were randomised into the study with a similar completion rate of 92% between the two groups. The difference in the change in exercise endurance time from ESWT at baseline to week four, was not significantly different between the TIO+FSC *versus* TIO alone groups ($p=0.181$; table 1). Pre-dose (trough) and post-dose responses in $FEV_1$, forced vital capacity (FVC), and inspiratory capacity were all significantly greater in the TIO+FSC group *versus* the TIO group at week four (fig. 1) (all nominal $p<0.04$). The post-dose response at week four in residual volume was also significantly improved in the TIO+FSC group *versus* the TIO group (fig. 1b) (nominal $p<0.04$). Adverse events were reported for 20 (15%) patients in the TIO group and 22 (18%) patients in the TIO+FSC group. No pneumonia adverse events occurred.

This study is the first multicentre clinical trial using the ESWT to evaluate the effects of pharmacotherapy on exercise endurance in patients with COPD. The major findings of the study are that 1) no difference was

TABLE 1 Exercise endurance time

| Group | Exercise endurance time s | | | | |
|---|---|---|---|---|---|
| | Baseline | Week 4 (end of study treatment) | Change | Change (least squares mean) | Difference (least squares mean)[#] |
| **TIO** | 380.2±19.2 (n=131) | 406.9±22.5 (n=122) | 23.3±15.5 (n=122) | 24.4±20.8 (n=122) | -27.6±20.6; p=0.181 |
| **TIO+FSC** | 383.5±20.6 (n=124) | 384.8±23.0 (n=115) | 6.0±16.2 (n=115) | -3.2±21.6 (n=115) | |

Data are presented as mean±SEM. TIO: tiotropium; FSC: fluticasone-salmeterol combination. [#]: difference calculated as TIO+FSC-TIO.

observed between TIO and TIO+FSC for exercise endurance time assessed by the ESWT following 4 weeks of therapy; and 2) trough and post-dose lung function were significantly improved in those patients receiving TIO+FSC *versus* TIO alone. The effect of pharmacotherapy on the ESWT has thus far only been assessed in a few single-centre trials [4, 7, 8, 9], which have tested an intervention against placebo. Here we tested the additive effect of two established interventions in a multicentre trial. The rationale for selecting the ESWT was that walking is a typical activity of daily living and the test has been shown to be responsive to bronchodilation [4, 8]. A minimally important difference for the ESWT of 70 s has also been proposed [6], and our study was powered on this difference.

A potentially important difference between this and previous trials [2, 3, 10] is that patients were not selected on the basis of resting hyperinflation. Although the absence of resting hyperinflation does not preclude use of long-acting bronchodilators to improve exercise capacity [4, 8] the inclusion of patients without hyperinflation may have contributed to the observation that triple combined therapy did not further reduce the level of dynamic hyperinflation and of dyspnoea during walking exercise. Though no further gain in walking capacity was observed with triple therapy, improved expiratory flow and inspiratory capacity as well as reduced residual volume were observed. It is possible that the amount of additional bronchodilation provided by the triple combination therapy was insufficient to translate into better exercise tolerance. Long-acting bronchodilators usually provide a 150–200 mL gain in $FEV_1$ over placebo, an effect typically associated with better exercise capacity [2–4, 10, 11] and one which is larger than that observed in the present trial. In the present study, patients in both arms received a potent long-acting muscarinic antagonist which reduced the likelihood of a large positive effect. Indeed, FSC improves cycling exercise endurance compared to placebo, but not compared to salmeterol [12].

In conclusion, the results did not support our hypothesis that triple combination therapy is superior to monotherapy in improving walking exercise capacity in patients with COPD. The extent to which exercise

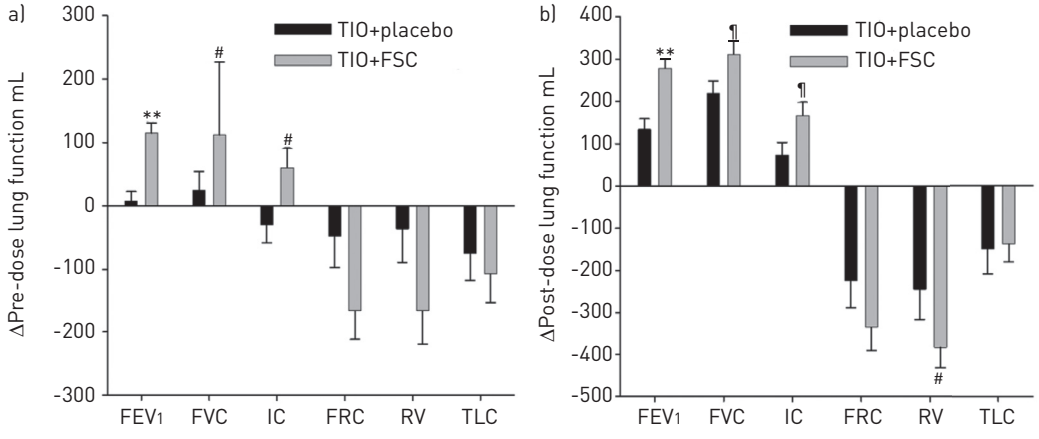


FIGURE 1 Changes in resting pulmonary function with therapy. a) The pre-dose values represent the differences in trough response at week four (end of study treatment) in comparison with baseline (first day of study treatment). b) The post-dose values represent the difference between post-dose values at week four in comparison with baseline. Data are presented as mean±SEM. $FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; FSC: fluticasone-salmeterol combination; TIO: tiotropium. **: $p<0.001$; [#]: $p<0.04$; [¶]: $p<0.02$.

capacity can be improved with combination pharmacological treatments over TIO monotherapy remains to be demonstrated.

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**Whether exercise capacity can be further improved by combination therapies over TIO alone remains to be demonstrated** http://ow.ly/lsXBx

**François Maltais[1], Donald A. Mahler[2], Véronique Pepin[3], Eric Nadreau[1], Glenn D. Crater[4], Andrea N. Morris[5], Amanda H. Emmett[5] and Thomas J. Ferro[5]**
[1]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, QC, [3]Centre de Recherche, Hôpital du Sacré-Coeur de Montréal, Montréal, QC, and [4]GlaxoSmithKline, Mississauga, ON, Canada. [2]Geisel School of Medicine at Dartmouth, Hanover, NH, and [5]GlaxoSmithKline, Research Triangle Park, NC, USA.

Correspondence: F. Maltais, Centre de Pneumologie, IUCPQ, 2725 Chemin Ste-Foy, Québec, QC, G1V 4G5, Canada. E-mail: francois.maltais@fmed.ulaval.ca

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