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Combining triple therapy and pulmonary rehabilitation in patients with advanced COPD: A pilot study

Franco Pasqua^a, Gianluca Biscione^a, Girolmina Crigna^a, Laura Auciello^a, Mario Cazzola^{b,*}

^a Division of Pulmonary Rehabilitation, San Raffaele Hospital, Velletri (Rome), Italy

^b Division of Respiratory Medicine and Unit of Respiratory Clinical Pharmacology, Department of Internal Medicine, University of Rome Tor Vergata, Rome, Italy

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Summary

Background: The synergistic interactions between pharmacotherapy and pulmonary rehabilitation has been provided, but it remains to be established whether this may also apply to more severe patients.

Objectives: We have examined whether tiotropium enhances the effects of exercise training in patients with advanced COPD ($FEV_1 \leq 60\%$ predicted, hypoxemia at rest corrected with oxygen supplementation, and limitations of physical activity).

Methods: We enrolled 22 patients that were randomised to tiotropium 18 μ g or placebo inhalation capsules taken once daily. Both groups (11 patients in each group) underwent an inpatient pulmonary rehabilitation program and were under regular treatment with salmeterol/fluticasone twice daily. Each rehabilitation session was held 5 days per week (3 h/day) for a total of 4 weeks.

Results: Compared to placebo, tiotropium had larger impact on pulmonary function ($FEV_1 + 0.164L$, $FVC + 0.112L$, $RV - 0.544L$ after tiotropium, $FEV_1 + 0.084L$, $FVC - 0.039L$, $RV - 0.036L$ after placebo). The addition of tiotropium allowed a longer distance walked in 6 min (82.3 m vs. 67.7 m after placebo) and reduced dyspnoea (Borg score) (-0.4 vs. $+0.18$ after placebo) when compared with baseline (pre pulmonary rehabilitation program). The changes in SGRQ from baseline to the end of treatment were: total score $-28.3U$, activity $-27.8U$, impact $-14.5U$, and symptoms $-33.4U$ in the placebo group; and total score $-19.1U$, activity $-18.9U$, impact $-16.4U$, and symptoms $-33.8U$ in the tiotropium group.

* Corresponding author at: Dipartimento di Medicina Interna, Università di Roma Tor Vergata, Via Montpellier 1, 00133 Roma, Italy.
E-mail address: mario.cazzola@uniroma2.it (M. Cazzola).

Conclusions: Our study clearly indicates that there is an advantage in combining pulmonary rehabilitation with an aggressive drug therapy in more severe patients.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) often complain of exercise intolerance. Despite the traditional belief that exercise is primarily limited by the inability to adequately increase ventilation to meet increased metabolic demands in these patients, significant deficiencies in muscle function, oxygen delivery and cardiac function are observed that contribute to exercise limitation. This means that exercise intolerance in COPD is complex and multifactorial and implies that, in order to reach optimal status, an array of interventions will be necessary.¹

Pulmonary rehabilitation is designed to reverse these exercise-limiting factors through supervised exercise training, respiratory care, and education.² It is defined as "a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy".³ In fact, a rather recent meta-analysis found statistically significant improvements in all the examined outcomes.⁴

There is now evidence that pulmonary rehabilitation of patients with COPD is more effective when the optimal bronchodilation has been reached.¹ Bronchodilators play a central role in patients with COPD.⁵ They have been shown to improve airflow limitation but, unfortunately, have an inconsistent effect on various measures of exercise capacity.⁵ In fact, leg fatigue will prevent patients with COPD from obtaining full advantage of bronchodilation, but muscle fatigue can be improved with exercise training.¹ It was not surprising, therefore, that the benefits of rehabilitative exercise were amplified when participants received the long-acting anticholinergic agent tiotropium⁶ and it was suggested that the relatively modest improvements in health-related quality of life and exercise tolerance seen when bronchodilators are administered will be amplified when combined with pulmonary rehabilitation.⁷

Since Casaburi et al.⁶ enrolled patients with moderate COPD, it remains to be established whether their findings may also apply to more severe patients. Therefore, we aimed to examine whether tiotropium enhanced the effects of exercise training also in patients with advanced COPD ($FEV_1 \leq 60$ predicted, hypoxemia at rest corrected with oxygen supplementation, and limitations of physical activity), who were under regular treatment with salmeterol/fluticasone.

Patients and methods

Considering that physical activity is reduced in patients with COPD from GOLD II/BODE 1 and clinical characteristics of patients with COPD only incompletely reflect their physical activity,⁸ we enrolled 22 in-patients suffering from advanced COPD ($FEV_1 \leq 60$ predicted, hypoxemia at

rest corrected with oxygen supplementation, and limitations of physical activity). All were ex-smokers. They were capable of performing a walking test. Patients with overt comorbidity preventing them from safely performing an exercise test could not participate in this trial. In particular, patients did not suffer from cardiovascular, neurological disorders or advanced osteoarthritis. Table 1 illustrates basic anthropometric data of the studied population. All trial procedures were conducted according to the Declaration of Helsinki and the protocol was approved by an independent ethics committee.

All patients were randomised to tiotropium 18 µg or placebo inhalation capsules taken once daily to be inhaled at 8 AM. Both groups (11 patients in each group) underwent an in-patient pulmonary rehabilitation program. All were under regular treatment with salmeterol/fluticasone 50/500 µg twice daily from at least one month. The in-patients pulmonary rehabilitation program included the following: exercise and muscle training (upper and lower extremity endurance training, respiratory muscle training and stretch); mucus evacuation techniques; disease education; psychosocial intervention; instruction in the use of medication; and relaxation techniques. Each session was held 5 days per week (3 h/day) for a total of 4 weeks.

Functional tests were conducted at the initial screening (visit 1); randomization (visit 2), which served as the baseline measurement, and after 4 weeks of treatment (visit 3) 24 h after the last inhalation of tiotropium and 12 h after the last inhalation of salmeterol/fluticasone. Lung function tests were performed using a body plethysmograph (Masterlab, Jaeger, Wurzburg, Germany) according to the current recommendations of the ATS/ERS Task Force on standardisation of pulmonary function tests.^{9–11}

Also the 6 min walking tests (6MWT) were performed at the initial screening (visit 1), randomization (visit 2), which served as the baseline measurement, and after 4 weeks of treatment (visit 3). They were conducted in an enclosed corridor on a flat course 30 m in length according to the procedures recommended by the American Thoracic

Table 1 Basic anthropometric data of the studied population.

	Without tiotropium	With tiotropium
Sex (M/F)	10/1	9/2
Age (yrs)	69.82 ± 3.12	70.00 ± 2.11
Height (cm)	168.9 ± 1.8	169.6 ± 1.9
Duration of COPD (yrs)	21.36 ± 4.00	14.36 ± 3.82
BMI	24.82 ± 1.33	25.91 ± 0.91
BODE	4.46 ± 0.47	3.36 ± 0.53
FEV ₁ (% predicted)	41.55 ± 3.09	51.73 ± 2.81
PaO ₂ (mmHg)	55.33 ± 0.95	57.03 ± 1.02
Values are mean ± SE.		

Table 2 Changes in pulmonary function from baseline. All values are mean \pm SE. NS, *p* not significant vs. pre pulmonary rehabilitation (PR) program.

	FEV ₁	FVC	IC	TLC	VR
Without tiotropium					
Before PR	1.145 \pm 0.089	2.500 \pm 0.128	2.310 \pm 0.262	6.553 \pm 0.747	3.779 \pm 0.507
After PR	1.229 \pm 0.132	2.461 \pm 0.149	2.056 \pm 0.131	6.672 \pm 0.316	3.743 \pm 0.373
	<i>p</i> = 0.354	<i>p</i> = 0.701	<i>p</i> = 0.355	<i>p</i> = 0.816	<i>p</i> = 0.899
	NS	NS	NS	NS	NS
With tiotropium					
Before PR	1.419 \pm 0.093	2.811 \pm 0.144	2.282 \pm 0.170	6.515 \pm 0.426	3.704 \pm 0.444
After PR	1.580 \pm 0.183	2.923 \pm 0.201	2.399 \pm 0.155	6.961 \pm 0.450	3.160 \pm 0.338
	<i>p</i> = 0.290	<i>p</i> = 0.603	<i>p</i> = 0.468	<i>p</i> = 0.464	<i>p</i> = 0.240
	NS	NS	NS	NS	NS

Society (ATS).³ To avoid interference with the patients' exercise performance, patients walked unaccompanied and no encouragement was given. Oxygen saturation (SpO₂) and heart rate (HR) were recorded continuously by pulse oximetry (Pulsox 5 portable pulse oximeter; Minolta, Tokyo, Japan). At the end of the walking tests, the participant was told to stop, and total distance covered was calculated to the nearest metre. Assessment for the level of dyspnoea was carried out via the Borg CR10 scale¹² that was proposed by the same staff member who ensured full comprehension on the part of the patient.

Health-related quality of life was determined using the St. George's respiratory questionnaire (SGRQ) and was explored at each visit.

This was a pilot study and the first known evaluation of the additive effect of tiotropium on a combination of salmeterol/fluticasone and pulmonary rehabilitation in patients with advanced COPD. In view of the lack of previous experiences, no statistical hypotheses were drawn and consequently no formal sample size calculation was made. The use of a pilot study such as the current study in clinical research is a well-established scientific procedure and only through the use of a pilot study can statisticians clarify data distributions and determine appropriate sample sizes for full-scale clinical trials.¹³

Student's *t*-test for paired data and repeated ANOVA measurements were used for statistical analysis. Values of *p* < 0.05 were considered as significant.

Results

Compared to placebo, tiotropium had larger impact on pulmonary function at the visit 3 (FEV₁ +0.164L, FVC +0.112L, RV -0.544L after tiotropium, FEV₁ +0.084L, FVC -0.039L, RV -0.036L after placebo), although all differences were statistically non significant when compared with basal values (Table 2).

The addition of tiotropium allowed a longer distance walked in 6 min (82.3 m vs. 67.7 m after placebo) and reduced dyspnoea (Borg score) (-0.4 vs. +0.18 after placebo); all differences, but not the change in Borg score after tiotropium, were statistically significant when compared with basal values (pre pulmonary rehabilitation program) (Fig. 1; Table 3).

The changes in SGRQ from baseline to the end of treatment were: total score -28.3U, activity -27.8U, impact -14.5U, and symptoms -33.4U in the placebo group; and total score -19.1U, activity -18.9U, impact -16.4U, and symptoms -33.8U in the tiotropium group. Almost all changes were statistically significant when compared with the baseline values (Table 4).

Discussion

In the present study, we have observed that pulmonary rehabilitation led to an improvement in lung function in

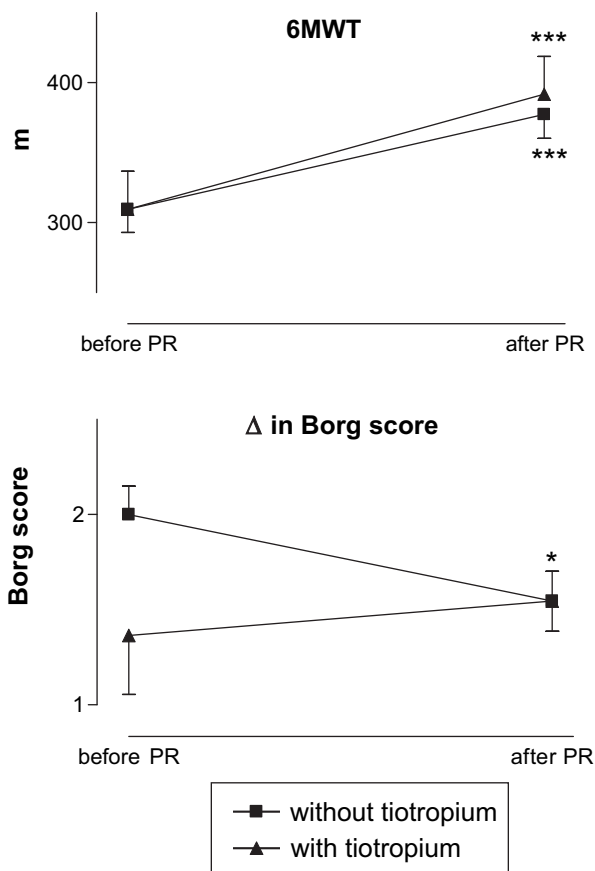


Figure 1 Changes in distance walked in 6 min (6MWT) and in the exercise-induced dyspnoea (Borg score) from baseline. Values are mean \pm SE. **p* < 0.05, ****p* < 0.001 vs. pre pulmonary rehabilitation (PR) program.

Table 3 Changes in Borg score and SpO₂ from baseline. All values are mean ± SE. **p* < 0.05, NS *p* not significant vs. pre pulmonary rehabilitation (PR) program.

	SpO ₂ before 6MWT (%)	SpO ₂ at the end of 6MWT (%)	Dyspnea (Borg score) before 6MWT	Dyspnea (Borg score) at the end of 6MWT
Without tiotropium				
Before PR	96.45 ± 0.28	94.00 ± 0.43	0.18 ± 0.12	2.09 ± 0.21
After PR	96.18 ± 0.35	93.27 ± 0.41	0.36 ± 0.15	1.91 ± 0.21
	<i>p</i> = 0.277	<i>p</i> = 0.038	<i>p</i> = 0.167	<i>p</i> = 0.167
	NS	*	NS	NS
With tiotropium				
Before PR	96.27 ± 0.33	94.18 ± 0.60	0.36 ± 0.15	1.73 ± 0.36
After PR	96.64 ± 0.34	93.36 ± 0.43	0.19 ± 0.14	1.73 ± 0.24
	<i>p</i> = 0.476	<i>p</i> = 0.260	<i>p</i> = 0.167	<i>p</i> = 1.000
	NS	NS	NS	NS

many patients and the addition of tiotropium amplified this effect, although its impact was not statistically significant. It is likely that the lack of statistical significance is related to the lack of statistical power of our sample. Obviously, there was a possibility of a type II error, which supported the lack of significance that we have repeatedly observed¹⁴ and, perhaps, a study with a larger sample would likely have reached statistical significance. We know that the relatively small sample of patients enrolled in this study could be regarded as a limitation, but again we must highlight that this study was conducted in a single centre as a pilot investigative trial designed only to examine if in patients suffering from more severe forms of COPD the combined treatment with pulmonary rehabilitation and a triple pharmacological therapy might have an advantage. In any case, it has been documented that, in general, pulmonary rehabilitation does not affect lung function.¹⁵

Recently, Ambrosino et al.,¹⁶ who explored whether tiotropium was able to enhance the effects of exercise training in patients with COPD and a FEV₁ ≤ 60% of predicted, reported that tiotropium significantly increased trough FEV₁ compared to placebo (adjusted mean differences between groups: 0.100 ± 0.05L on test week 4; *p* = 0.047) Tiotropium also increased trough FVC compared to placebo (adjusted mean differences between groups: 0.124 ± 0.061L, on test week 4; *p* = 0.044). There is no doubt that the trend that we have observed in our patients is similar to that reported by Ambrosino et al.¹⁶ It should be stressed, however, that the improvement that we have observed was obtained in patients under a regular

treatment with salmeterol/fluticasone, which can by itself lead to an improvement in respiratory function in patients with advanced COPD,¹⁷ and this might be another justification for the failure to reach statistical significance in our trial.

What is worthy of particular note is the fact that we observed a significant increase in the distance walked in the group treated with pulmonary rehabilitation plus the addition of salmeterol/fluticasone, and a further increase when patients were treated also with tiotropium. This finding contrasts with the observation of Ambrosino et al.¹⁶ that the addition of tiotropium to pulmonary rehabilitation did not improve the 6MWT.

Our data showed that a treatment with pulmonary rehabilitation plus salmeterol/fluticasone twice daily allowed not only to reach the minimal clinical significance limit (52 m) proposed by Troosters et al.,¹⁸ but also to obtain a significant change in Borg score for dyspnoea induced by the 6MWT when compared with the pre-treatment values. Intriguingly, the addition of tiotropium increased the distance walked without influencing the Borg score. This is not a real surprise because pulmonary rehabilitation relieves dyspnoea and fatigue, improves emotional function and enhances patients' control over their condition in a moderately large and clinically significant manner,¹⁹ and, consequently, it is likely that the addition of a bronchodilator is not perceived a further aid.

Our findings differ from that of Ambrosino et al.¹⁶ also with respect to their observation that tiotropium in combination with pulmonary rehabilitation significantly

Table 4 The changes in SGRQ from baseline. All values are mean ± SE. **p* < 0.05, ***p* < 0.01, ****p* < 0.001, NS *p* not significant vs. pre pulmonary rehabilitation (PR) program.

	Overall	Activity	Impacts	Symptoms
Without tiotropium				
Before PR	45.45 ± 5.86	56.36 ± 5.17	36.82 ± 6.92	53.64 ± 8.15
After PR	17.18 ± 3.28	28.55 ± 3.57	13.00 ± 3.12	20.18 ± 5.55
	<i>p</i> = 0.0024**	<i>p</i> = 0.0007***	<i>p</i> = 0.0127*	<i>p</i> = 0.0008***
With tiotropium				
Before PR	45.73 ± 5.79	61.09 ± 7.45	37.36 ± 5.68	44.64 ± 8.18
After PR	26.64 ± 6.98	42.18 ± 8.37	22.73 ± 8.37	10.82 ± 3.46
	<i>p</i> = 0.0068**	<i>p</i> = 0.0098**	<i>p</i> = 0.0811 NS	<i>p</i> = 0.0021**

improved dyspnoea but did not show any additional benefit induced by the pulmonary rehabilitation in exercise tolerance, as measured by the 6MWT. Ambrosino et al.¹⁶ suggested that the modest improvement in exercise capacity to either pulmonary rehabilitation or tiotropium observed in their study likely related to methodological issues, including the choice of the functional measurement of endurance. In effect, recent research has been suggested that the 6MWT test may not be as responsive to bronchodilation as the endurance shuttle walk.²⁰

We recognise that 6MWT is not physiologically pure because it is self-paced and, unless appropriately conducted, may be subject to learning and motivation effects.²¹ Furthermore, it is a physiological hybrid test that may produce erratic metabolic demand that may include peak or endurance performance.³ Nonetheless, the 6MWT is probably the most popular investigation because of its simplicity, relevance to daily life, widespread use and availability of reference values and, in any case, we documented that 6MWT seems to be an appropriate instrument for assessing the exercise response to a bronchodilator in COPD.²²

It is much more likely that the lack of efficacy of tiotropium in combination with pulmonary rehabilitation on exercise tolerance as measured by the 6MWT reported by Ambrosino et al.¹⁶ was due to the variability in the conduct of the test due to the enrolment of multiple sites with variable experience. Another explanation might be the fact that in the Ambrosino's study,¹⁶ at baseline patients had a relatively well preserved 6MWT (mean >400 metres), whereas in our study, focused on more severe patients with documented limitations of physical activity, the mean baseline value was 310 metres. Whatever the case may be, it must be mentioned that, apparently, there is a larger room for improvement in 6MWT in hypoxemic than in non-hypoxemic patients.²³

What our study confirms looking at the Ambrosino's paper¹⁶ is that pulmonary rehabilitation improves health related quality of life as it is expressed by the SGRQ and the addition of tiotropium does not bring further improvement. This was not an unexpected finding because it is well known that pulmonary rehabilitation results in greater improvements in important domains of health-related quality of life and functional exercise capacity when compared with other important modalities of care for patients with COPD such as inhaled bronchodilators or theophylline.^{24,25} In any case, we must mention that we observed surprising large changes in the different domains of the SGRQ that can only be justified considering the population included in the trial.

In conclusion, our study, despite its limitations, suggests that there is an advantage in combining pulmonary rehabilitation with an aggressive drug therapy in more severe patients. This is not a real surprise considering that the present prospective is to use a triple therapy in patients with more advanced COPD.^{26,27} As mentioned before, the failure to achieve the statistical significance in changes in some parameters is likely due to the lack of statistical power in the study, although it is possible that the inclusion of outcomes with different construct may lead to responses that are not always relevant because the construct of a specific outcome might not be really influenced by the treatment. In effect, although some outcomes have been

shown to change with therapy, their observed changes are not always reflected by changes in traditional measures of disease severity such as FEV₁. This is because other pathophysiological (e.g. dynamic hyperinflation of the lungs) and psychological (e.g. coexisting anxiety) influences also affect these outcomes.²⁸ Obviously, the results of this pilot study will aid planning for further large-scale confirmatory studies.

Conflict of interest

The authors declare that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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