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A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD

Mario Cazzola[a,*], Filippo Andò[b], Pierachille Santus[c], Paolo Ruggeri[b], Fabiano Di Marco[c], Alessandro Sanduzzi[d], Maria D'Amato[e]

[a]*University of Rome Tor Vergata, Department of Internal Medicine, Unit of Respiratory Diseases, Rome, Italy*
[b]*University of Messina, Institute of Respiratory Medicine, Messina, Italy*
[c]*University of Milan, San Paolo Hospital, Unit of Respiratory Medicine, Milan, Italy*
[d]*University Federico II, Department of Cardiovascular and Respiratory Sciences, Unit of Pneumology, Naples, Italy*
[e]*A. Cardarelli Hospital, Department of Respiratory Medicine, Unit of Pneumology and Allergology, Naples, Italy*

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Abstract

The aim of this pilot study was to explore the relative efficacy in terms of improvement in symptoms and lung function of combining fluticasone propionate/salmeterol combination (FSC) and tiotropium in patients with severe-to-very severe stable COPD. Ninety patients were randomized to receive 3 months of treatment in one of three treatment groups: (1) FSC 500/50 μg Diskus, 1 inhalation twice daily + placebo Handihaler 1 inhalation once-daily daily; (2) tiotropium 18 μg Handihaler, 1 inhalation once daily + placebo Diskus, 1 inhalation twice daily; (3) FSC 500/50 μg Diskus, 1 inhalation twice daily + tiotropium 18 μg Handihaler, 1 inhalation once-daily daily. Patients attended the clinic before and after 1 month, 2 months, and 3 months of treatment for evaluations of pulmonary function, and dyspnea, which was assessed using a visual analog scale (VAS). Also the supplemental salbutamol use was measured. Eighty-one patients completed the 3-month treatment period: 26 patients receiving FSC, 26 patients receiving tiotropium, and 29 patients receiving FSC + tiotropium. Patients were withdrawn for COPD exacerbation. Improvements in trough FEV_1 with all treatments medications were observed by the first month when trough FEV_1 had improved significantly above baseline by 74 mL ($p<0.05$) in the tiotropium group, by 117 mL ($p<0.05$) in the FSC group and by 115 mL ($p<0.05$) in FSC + tiotropium group. At the end of the study, trough FEV_1 had improved significantly above baseline by141 mL ($p<0.05$) in the tiotropium group, by 140 mL ($p<0.05$) in the FSC group and by 186 mL ($p<0.05$) in FSC + tiotropium group. The difference between FSC and tiotropium appeared to decrease, that between FSC and FSC + tiotropium appeared to increase and that between tiotropium and FSC + tiotropium remained almost similar with study duration. Our results suggest that adding FSC and tiotropium may provide benefits in symptomatic patients with severe-to-very severe stable COPD.

Keywords: Salmeterol; Fluticasone propionate; Combination therapy; Tiotropium; COPD; Dyspnea; Lung function

1. Introduction

The Global Initiative for Obstructive Lung Disease (GOLD) guidelines, which were updated in July 2003, highlighted the role of long-acting bronchodilators in symptomatic management of all stages of chronic obstructive pulmonary disease (COPD) [1]. They also warranted that regular treatment with inhaled corticosteroids is only appropriate for symptomatic COPD patients with an $FEV_1<50\%$ predicted (Stage III: severe COPD; and Stage IV: very severe COPD) and repeated exacerbations requiring treatment with antibiotics or oral corticosteroids.

Afterwards, Tashkin and Cooper [2] emphasized the advantage of tiotropium on long-acting β_2-agonists, and suggested a single long-acting bronchodilator plus an

*Corresponding author. Tel.: +39 081 7473334; fax: +39 081 404188.
E-mail address: mcazzola@qubisoft.it (M. Cazzola).

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as-needed, short-acting agent in moderate disease (stage II of the GOLD classification [1]), the combination of long-acting anticholinergic and long-acting β_2-adrenergic therapy with progression of disease severity, with or without the addition of inhaled corticosteroids for patients with frequent exacerbations or inadequate symptom control despite optimal treatment with bronchodilators alone (stage III/IV). In effect, some papers have documented the advantage for COPD patients in combining long-acting anticholinergic and long-acting β_2-adrenergic agents [3–6]. Other papers [4–15] have clearly shown that both long-acting β_2-agonists and inhaled corticosteroids have an important role in COPD, which increases when the two drugs are combined in the same therapeutic regimen.

Unfortunately, although tiotropium has entered the market with a wide and solid documentation of its efficacy in stable COPD, the interesting comparison of the combination inhaler with a long acting β_2-agonist and an inhaled corticosteroid versus tiotropium has not yet been undertaken [16]. Moreover, we do not know if there is a real advantage in administering a long-acting β_2-agonist/inhaled corticosteroid combination together with tiotropium for treating severe-to-very severe COPD.

For this reason, the current study was designed to compare the efficacy and safety of 12 weeks' therapy with fluticasone propionate/salmeterol combination (FSC) and tiotropium with that of individual treatments alone in patients with severe-to-very severe stable COPD.

2. Patients and methods

Ninety patients with well-controlled COPD were enrolled. All were 50 years of age or older, and were current or former smokers with a 20 pack-year or more history. Inclusion criteria required a baseline FEV_1 of less than 50% of predicted, and a post-bronchodilator FEV_1/FVC < 70% following salbutamol 400 μg according with the GOLD criteria of severity [1]. Exclusion criteria were as follows: current evidence of asthma as primary diagnosis; unstable respiratory disease requiring oral/parenteral corticosteroids within 4 weeks prior to beginning the study; upper or lower respiratory tract infection within 4 weeks of the screening visit; unstable angina or unstable arrhythmias; concurrent use of medications that affected COPD; and evidence of alcohol abuse. Table 1 outlines some characteristics and the smoking history of the population studied.

The study was conducted according to the rules of the declaration of Helsinki and was approved by an independent Ethics committee. All patients gave written informed consent before any study procedure was undertaken. The trial was performed using double-blind, double-dummy, randomized, parallel group design. It compared the efficacy and safety of three treatments for 12 weeks: (1) FSC 500/50 μg Diskus, 1 inhalation twice daily + placebo Handihaler 1 inhalation once-daily; (2) tiotropium 18 μg Handihaler, 1 inhalation once-daily + placebo Diskus, 1 inhalation twice daily; (3) FSC 500/50 μg Diskus, 1 inhalation twice daily + tiotropium 18 μg Handihaler, 1 inhalation once-daily. Patients were randomized to receive FSC, tiotropium or their combination by a computer-generated list. Randomization was performed in blocks of 9.

Patients entered a 2-week run-in period during which their regular treatment for COPD (all were under regular treatment with a long-acting β_2-agonist and an inhaled corticosteroid, many [81 out of 90] with also theophylline) was stopped with the exception of stable regimens of theophylline (no change in dose for 1 month prior to screening) and they received salbutamol for relief of breakthrough symptoms. Use of all other inhaled or oral bronchodilators, systemic corticosteroids, ipratropium bromide, oxitropium bromide, or leukotriene modifiers was prohibited. Patients returned to the clinic at the end of the 2-week run-in period for visit 2, at which time they were randomized to their treatment regimen. Afterwards, they attended the clinic after 4, 8, and 12 weeks of treatment for evaluations of pulmonary function. At each visit, three FEV_1 and FVC measurements were taken, and the highest of each was recorded. Spirometric testing was performed according to the procedures described in the American Thoracic Society 1987 update [17]. These measurements were performed on the morning of each visit, before any

Table 1
Clinical characteristics of the population studied

Variables	Group 1	Group 2	Group 3
Age, yr	64.4 (58.8–70.0)	66.1 (59.9–72.2)	66.9 (59.0–74.8)
Sex, No.	26 M–4F	28 M–2 F	26 M–4 F
Smoking, pack-yr	55.1 (45.1–65.1)	50.7 (42.6–58.8)	46.9 (39.7–54.1)
Current smokers, No. (%)	28 (93.3)	25 (83.3)	24 (80.0)
FEV_1, predicted (%)	36.9 (31.4–42.4)	38.5 (32.2–44.8)	39.0 (34.4–43.6)
Reversibility, baseline (%)	11.5 (8.7–14.3)	13.1 (9.0–17.2)	12.8 (8.1–17.5)
FEV_1/FVC ratio (before bronchodilator)	51.6 (43.4–59.8)	50.7 (45.6–55.8)	52.9 (44.7–61.1)
FEV_1/FVC ratio (after bronchodilator)	52.8 (43.4–62.2)	51.5 (41.3–61.7)	52.1 (41.8–62.4)
VAS	6.0 (5.3–6.6)	6.3 (5.6–6.9)	6.1 (5.5–6.7)
Inhaled corticosteroid use, No.	21	23	20
Oral corticosteroid use, No.	5	3	2

Data are presented as mean (95% CI) unless otherwise indicated. M, male; F, female.

drug had been taken. Changes in the perception of dyspnea assessed through use of a bipolar visual anagogic scale (VAS), and supplemental salbutamol use were also monitored at each visit. The VAS consisted of a 20-cm horizontal line scoring between 0 (very much better) at the left end, and 10 (very much worse) at the right, with 'no change' in the middle. All patients were familiarized with the VAS before the study. The supplemental salbutamol use was recorded by the patient daily throughout the 3-month treatment period.

Adverse events were collected through non-specific questioning or direct observation by investigators at each clinic visit and through spontaneous reports by patients. Patients who experienced exacerbation resulting in hospitalization or, at least, treatment with an oral corticosteroid and/or antibiotic during the study period were withdrawn. The definition of exacerbation used in the present study was "a worsening of respiratory symptoms, which requires treatment with oral corticosteroids or antibiotics, or both [18]".

The primary efficacy measure was the mean change from baseline in predose FEV_1 after 3-month treatment. Secondary efficacy measures included change from baseline in VAS score assessing dyspnea and in supplemental salbutamol. 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.

3. Results

Eighty-one patients completed the 3-month treatment period: 26 patients receiving FSC, 26 patients receiving tiotropium, and 29 patients receiving FSC + tiotropium. Patients were withdrawn for COPD exacerbation resulting in hospitalization or even treatment with an oral corticosteroid. There was no significant difference among the baseline spirometric values of the three treatment groups (FEV_1, $p>0.05$)).

Significant ($p<0.05$) improvements in trough FEV_1 above baseline with all treatments medications were observed by the first month when trough FEV_1 had improved above baseline by 117 mL (95% CI: 102–131) in the FSC group, by 74 mL (95% CI: 52–96) in the tiotropium group, and by 115 mL (95% CI: 96–134) in FSC + tiotropium group (Fig. 1). The difference between the improvements in FSC and tiotropium and that in tiotropium and FSC + tiotropium were statistically significant ($p<0.05$), whereas the difference between the improvements in FSC and FSC + tiotropium was not statistically significant ($p>0.05$). At the end of the study, trough FEV_1 had improved significantly ($p<0.05$) above baseline by 140 mL (95% CI: 119–161) in the FSC group, by 141 mL (95% CI: 115–165) in the tiotropium group and by 186 mL (95% CI: 162–210) in FSC + tiotropium group. The difference between the improvements in FSC and tiotropium was not statistically significant ($p>0.05$), whereas the difference between the improvements in FSC and FSC + tiotropium and that in tiotropium and FSC + tiotropium were statistically significant ($p<0.05$). It is noteworthy that the difference between FSC and tiotropium appeared to decrease, that between FSC and FSC + tiotropium appeared to increase and that between tiotropium and FSC + tiotropium remained almost similar with study duration.

At the end of treatment, tiotropium and FSC + tiotropium experienced greater improvements in dyspnea (the VAS scores decreased by −2.31 [95% CI:−2.70 to −1.92], and −2.34 [95% CI: −2.60 to −2.09], respectively), than FSC (−2.00, 95% CI: −2.41 to −1.58). All improvements

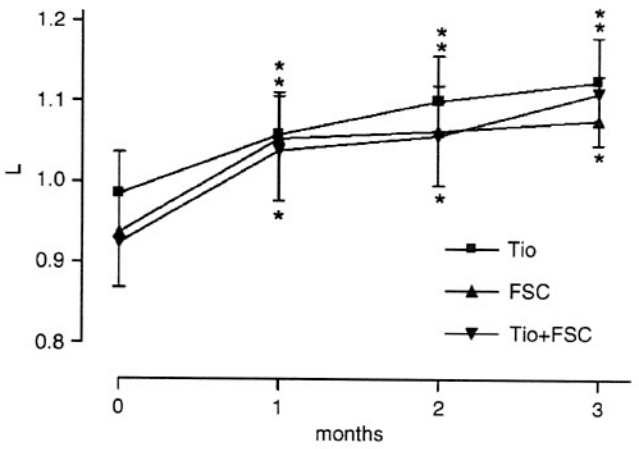

Fig. 1. Mean FEV_1 values during 3 months of therapy with fluticasone propionate 500 μg/salmeterol 50 μg twice daily, tiotropium 18 μg once daily, and their combination in patients suffering from severe to very severe COPD. Tio, tiotropium; FSC, fluticasone/salmeterol combination. Values are mean ± SE. $^*p<0.05$ vs. baseline. Differences between treatments were non-significant.

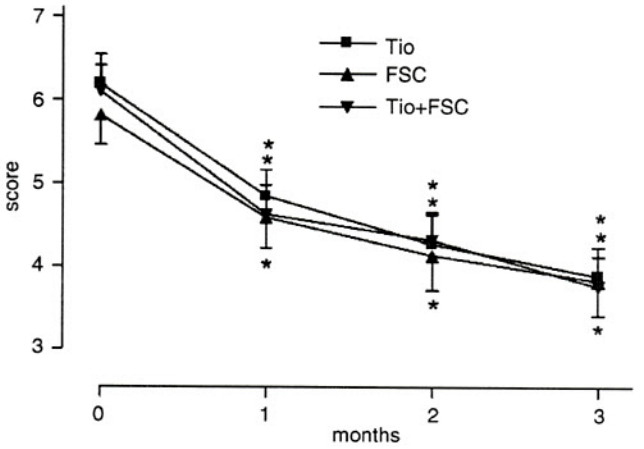

Fig. 2. Mean VAS score during 3 months of therapy with fluticasone propionate 500 μg/salmeterol 50 μg twice daily, tiotropium 18 μg once daily, and their combination in patients suffering from severe to very severe COPD. Tio, tiotropium; FSC, fluticasone/salmeterol combination. Values are mean ± SE. $^*p<0.05$ vs. baseline. Differences between treatments were non-significant.

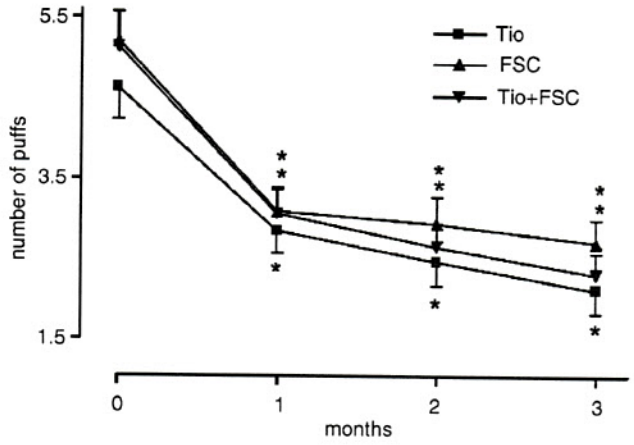

Fig. 3. Mean daily numbers of puffs of rescue medication (salbutamol) averaged over the last 7 days of the run-in period (time point 0) and over the week preceding each visit at 1–3 months of therapy with fluticasone propionate 500 μg/salmeterol 50 μg twice daily, tiotropium 18 μg once daily, and their combination in patients suffering from severe to very severe COPD. Tio, tiotropium; FSC, fluticasone/salmeterol combination. Values are mean ± SE. $^{*}p<0.05$ vs. baseline. Differences between treatments were non-significant.

were significant ($p<0.05$) when compared with baseline values (Fig. 2). However, the differences between the three treatments were always statistically not significant ($p>0.05$).

Mean use of salbutamol during the baseline run in period was 4.61 puffs per day (95% CI: 3.90–5.43) in the tiotropium group, 5.20 puffs per day (95% CI: 4.44–5.96) in the FSC group, and 5.13 puffs per day (95% CI: 4.23–6.03) in the tiotropium + FSC group. In all groups, the daily use of relief medication was significantly ($p<0.05$) lower during treatment than during run in. FSC + tiotropium group required fewer supplemental puffs of rescue salbutamol (−2.82 puffs/day; 95% CI:−3.30 to −2.34) than tiotropium (−2.50 puffs/day; 95 CI: −2.97 to −2.03) or FSC (−2.49 puffs/days; 95% CI: −2.93 to −2.05) (Fig. 3), but, again, the differences between the three treatments were always statistically not significant ($p>0.05$).

The number of patients experiencing an adverse event was: 13 patients (43.3%) in tiotropium group, 8 patients (26.7%) in FSC group, and 15 patients (50.0%) in tiotropium + FSC group. The most common adverse events seen in patients receiving tiotropium were dry mouth, headache, and cough, whereas patients receiving FSC experienced irritation, hoarseness/dysphonia, headaches, and candidiasis of the mouth and throat. No patient experienced a serious adverse event according to International Conference on Harmonization criteria [19].

4. Discussion

In this study, the improvement in pulmonary function, expressed as a change in FEV_1, did not differ between tiotropium and FSC, but the simultaneous administration of the two treatments provided greater improvements in through FEV_1 compared to therapy with the other two therapeutic regimens. This is an intriguing finding, but our data do not allow to establish if the improvements in lung function caused by combining fluticasone propionate/salmeterol and tiotropium in severe-to-very severe COPD was linked to the effect of the combination of two long acting bronchodilators, as suggested by Tashkin and Cooper [2], or due to a synergistic interaction between the inhaled corticosteroid and the long acting bronchodilators, with the resulting synergetic effect being greater than the sum of responses achieved from each drug alone. It must be stressed that this type of synergetic effect has only been documented with inhaled corticosteroids and long acting β_2-agonists [20]. However, in addition to the up-regulation of β_2-adrenergic receptors and anti-inflammatory effects by corticosteroids, part of the beneficial effect of corticosteroids in COPD therapy may include a reduction in muscarinic receptor expression in airway smooth muscle, allowing for easier muscle relaxation by β-adrenergic agonists. In fact, it has been shown that, at least in dogs, a chronic treatment with methylprednisolone led to a decreased expression of both M2 and M3 muscarinic receptors in airway smooth muscle [21]. More recently, it has also been documented that dexamethasone decreases airway responsiveness to vagal stimulation via two mechanisms: increased M2 receptor function that results in decreased acetylcholine release, and increased degradation of acetylcholine by cholinesterases [22].

In assessing the therapeutic benefit of tiotropium + FSC, it is important to understand how the sustained bronchodilation translates into other health-outcome measures that relate to a given patient's quality of life. Although the combination of FCS and tiotropium was significantly more active in inducing improvements in FEV_1 than the single treatments alone, we did not observe a similar trend in use of rescue medication and changes in VAS scores. We have measured changes in dyspnea from baseline with VAS because it is simpler and easier to determine than other dyspnea measurements, it permits a subjective rating of this symptom [23] and, moreover, its reproducibility is maintained over intervals when memory for the score given is unlikely to be an important factor [24]. We must highlight, in any case, that we do not know how the observed changes in VAS scores of dyspnea were clinically significant. In effect, to our best knowledge, minimal clinically important change in the VAS score of dyspnea after a chronic pharmacological intervention in COPD patients has not been established yet. In acute setting, improvement in VAS assessing changing in the perceived effect on shortness of breath after inhalation of a bronchodilator was 15% in high COPD perceivers and 1% in low COPD perceivers [25]. In the present study, improvements in VAS were 37% after tiotropium, 34% after FSC and 38% after tiotropium + FSC.

In our study, patients who experienced an exacerbation resulting in hospitalization or treated with an inhaled or oral corticosteroid during the study period were withdrawn to ensure that the concomitant use of these agents did not confound our ability to assess treatment effects on the primary efficacy measures of FEV_1 [9]. This action precluded examination of the effect of the treatments on rate of exacerbations. Nonetheless, it must be highlighted that no difference in number of withdraws has been observed between tiotropium and FSC alone, whereas in the group of patients treated with FSC + tiotropium it was lower than that observed in those patients treated with individual treatments alone. However, due to the small number of patients and the short period of observation, we cannot make any conclusion on this point.

We must highlight that it is likely that the failure to show a statistically significant difference between treatments when we explored the impact of different treatments on dyspnea and salbutamol use was likely associated with an insufficient statistical power in the study. We believe that there was a possibility of a type II error, which supported the lack of significance that we have repeatedly observed [26] and, possibly, a study with a larger sample would likely have reached statistical significance. We must also highlight that we have not evaluated other clinical outcomes and, in any case, our conclusions can be applicable only to the FSC 500/50 μg dosage because we did not explore the impact of adding tiotropium to FSC 250/50 μg and FSC 100/50 μg, and this is another limitation of our study. In any case, we have undertaken this pilot trial only to gather data and prove feasibility of adding an ICS to two long-acting bronchodilators in patients with severe-to very severe COPD as suggested by Tashkin and Cooper [2].

Obviously, our data require confirmation by larger studies before tiotropium + FSC therapy can be incorporated into clinical practice. Interestingly, tiotropium + FSC was demonstrated to provide superior efficacy relative to single treatments alone in spirometry but this observation was not accompanied by better symptom control and less reliance on rescue salbutamol. This intriguing finding highlights the need for the definition of outcomes that must be considered in clinical trials involving patients suffering from COPD.

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