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Changes of clinical outcomes and health care resources in moderate and in severe COPD treated uniquely with tiotropium 18 mcg od for twenty-four months

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a complex and progressive respiratory disease characterized by incompletely reversible bronchial obstruction. The effects of current therapeutic options in early stages of COPD have been poorly investigated in the past, being this specific topic revamped by the results of recent secondary analyses from large international trials.

Aim: To measure and monitor in real life the changes in main clinical *outcomes* and health care resources in patients suffering from mild-to-moderate and severe COPD treated with only tiotropium br. for twenty-four months.

Methods: The population sample of the present observational retrospective study consists of 319 COPD subjects (214 males; average age 71.7 years ± 06 se) automatically extracted from the DataBase of the Health Care Institution. Inclusion criteria were: age ≥ 40 y; basal FEV1 < 80% predicted and FEV1/FVC < 70%; regular treatment with only 18 mcg tiotropium br. for the following two years. All subjects were divided into two subsets according to their FEV1 basal value: (Group A ≤ 50%, and Group B >50% predicted). Lung function; n. exacerbations; n. hospitalizations; absenteeism; n. GP's visits, and use of systemic steroids or antibiotics were checked during the observational period and mean values compared in both subsets with those of the twelve months preceding tiotropium br. (such as during other therapeutic strategies). *T* test was used for checking the comparability of groups, while ANOVA – Duncan test was used to compare the trends of all variables over time; $p < 0.05$ was accepted.

Results: Group A, 154 individuals (104 males; mean age 72.1 years ± 0.51 se) had a mean FEV1 value of 45.4% pred. ±0.61 se, while the remaining 165, Group B (111 males; mean age 71.4 years ± 0.60 se) had a mean FEV1 value of 65.5% pred. ± 5.7 se ($p < 0,01$). The two subsets were well matched for gender, age, and previous use of systemic steroids, but significantly different in terms of basal lung function, COPD morbidity, and antibiotic use. Basically, the impact of COPD confirmed higher in severe patients even if it was unexpectedly remarkable in mild-to-moderate individuals in terms of consumption of health care resources. The overall reduction in COPD morbidity was significant in both groups, but the improvement in FEV1 and in other main long-term outcomes observed in subjects with mild-to-moderate COPD was particularly significant and substantial ($p < 0.001$), these subjects confirming to be worth of earlier therapeutic attention.

Conclusions: 18 mcg tiotropium br. monotherapy for twenty-four months on a regular daily basis enables a significant minimization of COPD impact, and consents the progressive lung function recovery also in mild-to-moderate individuals, thus suggesting a possible role of tiotropium br. in affecting the natural history of COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an airway disorder characterized by incompletely reversible bronchial obstruction [1]; it is one of the most common causes of morbidity and mortality worldwide, and its prevalence in Italy is about 5% within the general population [2].

The management of the disease is complex and includes stopping smoking (which plays a leading role in more than 60% of cases); symptom control; improvement in respiratory function; reduction in exacerbation rate; improvement in quality of life; health care cost control. Regarding the duration and the natural

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history of COPD (several decades), most of *outcomes* were (and very often still are) assessed over a short timeframe that does not allow their absolute value as indicators of effective disease management to be established.

According to the most reputable Guidelines and on the basis of well established scientific evidence [1], a gradual escalation in medications is regarded as the most effective therapeutic strategy as the disease gets worse.

However, despite the wide consensus concerning COPD as a progressive disease, up to a recent past clinicians have mainly focused the assessment of the effects and the convenience of therapy in the most severe stages of COPD (GOLD stages 3 and 4), almost completely neglecting the hypothesis that current therapeutic options might also be effective in earlier stages of COPD and might be able to influence the disease progression.

Only since when the analyses of data from the two most important international clinical trials carried out in the last years have become available [3,4], researchers have begun to accept and support the hypothesis that also the earlier treatment of COPD might be useful and convenient [5–9]. To note that this interesting suggestion comes only from *post-hoc* and secondary analyses of these large studies, which were originally designed for other *primary end-points*, still being such evidence not confirmed in *real life* on the basis of studies specifically designed.

The aim of the present study was to measure the changes in lung function; main clinical *outcomes*, and health care resources achievable in patients suffering from severe and from mild-to-moderate COPD [1] both treated with only tiotropium 18 mcg daily for two years.

2. Materials and methods

The population sample was extracted automatically from the Data Base of our Institution which contains files related to more than 52,000 subjects suffering from respiratory diseases. Procedures for data extraction are based on the most complete selection criteria of Boolean algebra [10]. The Data Base is ISO 9001-2000 certified since 1999. In order to avoid any confounding factor or basic bias in the study, those selection/extraction procedures, and the subsequent creation and management of the data bank were outsourced to IT professionals employed by a third party, such as not working in the Lung dept.

First of all, the *cross sectional* sample of subjects to include in the study had to meet the following inclusion criteria: out-patients aged $\geq$40 years; of both sexes and from any part of the country; suffering from COPD with a baseline FEV1 value $\leq$ 80% predicted; not on treatment with anti-cholinergic compounds; who presented at the Unit for the first time between 01 April 2005 and 31 March 2006. As the aim of this first selection phase was to assess the subjects' basal management, only data contained in the file related to their first visit had to be used, thus avoiding any possible role due to our therapeutic intervention.

Variables to be extracted from the "1st visit" file of all subjects who met the preliminary entry criteria were the following:

- Gender;
- Age;
- Smoking status;
- Baseline pulmonary function (FEV1% pred. and FEV1/FVC %);
- Symptoms claimed;
- Annual number of hospital admissions; their duration; number of GP visits; number of exacerbations and number of days of inactivity;
- Daily home therapy (only pharmacological classes).

Table 1
Homogeneity of groups in baseline (mean ± SEM).

	Group A	Group B	*p*
Subjects n.	154	165	
Mean age (years)	72.1 ± 0.51	71.4 ± 0.60	ns
Gender (m)	104 (67.5%)	111 (67.3%)	ns
Smoker/ex-smoker	18.2%/46.1%	26.1%/42.4%	0.05
FEV1%	42.5 ± 0.61	65.5 ± 0.44	0.01
FVC%	63.6 ± 0.48	64.7 ± 0.85	0.01
n. hospital stays/year	0.5 ± 0.05	0.29 ± 0.05	0.002
Days in hospital	9.5 ± 0.69	1.7 ± 0.38	0.001
n. exacerbations	1.3 ± 0.07	0.50 ± 0.04	0.001
Days of inactivity	7.5 ± 1.21	1.8 ± 0.35	0.001
n. visits by GP	1.2 ± 0.20	0.7 ± 0.11	0.014
n. cycles of systemic steroids	0.25 ± 0.02	0.24 ± 0.05	ns
n. cycles of antibiotics	1.75 ± 0.04	0.41 ± 0.07	0.001

During the second selection phase, the additional criteria that had to be met were: the presence in the DataBase of data from visits and spirometric tests for the subsequent 24 months, and the regular monotherapy with 18 mcg tiotropium daily. Furthermore, eligible subjects had to have at least one spirometric test recorded in the DataBase for each year of observation. When more than one test had been performed in the same year, the mean value of all the tests (FEV1) performed throughout the year was taken into consideration. The same procedure was adopted for all other quantitative variables that could be gleaned from the medical examinations carried out in the period (no. hospitalizations; no. accesses to ER; no. exacerbations declared; no. medical examinations; no. courses of systemic steroids, no. courses of antibiotics).

According to the routine procedures of the lung function laboratory, spirometric data were related to measurements carried out after a 24 h pharmacological wash-out from any respiratory drugs (pre-bronchodilator FEV1).

All subjects extracted were subsequently divided into two groups according to their basal FEV1 value: $\leq$50% or >50% predicted (Group A and Group B, respectively).

Values of all individual variables taken into consideration were expressed in observational units (absolute values and/or percentages) and as mean ± SEM.

Statistical comparisons were carried out by using *t* tests to assess baseline homogeneity, and ANOVA – Duncan tests to assess the trends of every mean value over time vs the corresponding pre-Tiotropium values. A $p < 0.05$ was accepted as the minimum value for statistical significance.

3. Results

A total of 319 subjects ((215 males, 67.4%) mean age ± SEM 71.7 ± 0.6 years) were eligible; their most frequent comorbidities were cardiovascular (46.1%) and metabolic (26.6%) diseases.

At the first visit, 65.2% of subjects were already on treatment with respiratory drugs (Hospital Therapeutic Handbook "PTO" class R03): 38.9%, with short-acting bronchodilators only as needed; 25.4%, with daily long-acting bronchodilators; 23.6%, with long-acting bronchodilators + inhaled corticosteroids, and 12.1% with methylxanthines.

After the subjects had been divided according to their basal FEV1 value, the two subgroups were as follows:

1) Group A: 154 subjects (104 males, 67.5%), mean ± SEM age = 72.1 ± 0.51 years; FEV1 = pred. 45.4 ± 0.61; FVC % pred. = 63.6 ± 0.48;
2) Group B: 165 subjects (111 males, 67.3%), mean ± SEM age = 71.4 ± 0.60 years; FEV1 = 65.5% pred. ± 5.7; FVC = 64.7% pred. ± 0.85.