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Effect of CArbocisteine in Prevention of exaceRbation of chronic obstructive pulmonary disease (CAPRI study): An observational study

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a chronic and progressive lung disease characterized by irreversible airflow obstruction, airway inflammation, oxidative stress and, often, mucus hypersecretion. The aim of this study is to determine if carbocisteine, a mucolytic and antioxidant agent, administered daily for 12 months, can reduce exacerbation frequency in COPD patients.
Methods: This observational study was conducted in Naples (population approximately 1000,000), Italy. It included 85 out-patients (mean age of 67.8 ± 8.6 years) followed by Clinic of Respiratory Diseases of the University Federico II. Every patient underwent spirometry demonstrating airflow obstruction not fully reversible according to ERS/ATS criteria for COPD diagnosis (Tiffenau index less than 70% after administration of salbutamol, a beta2 agonist drug). Patients enrolled had diagnosed COPD since 2 years and suffered at least one exacerbation in the previous year. None of the patients had been treated with carbocisteine or other mucolytic agent for a longer period of time than 7 days and no more than 4 times in the previous year to the enrollment. All of them assumed daily 2.7 g of carbocisteine lysine salt for a year in addition to their basic therapy.
Results: The comparison of exacerbation frequency between the previous year (T0) and the end of study treatment (T12), documents a statistically significant reduction of exacerbations(number of exacerbations at T0: 2 [1,3] vs number of exacerbations at T12: 1 [1,2]; $p < 0.001$).Quality of life was also reported and showed a statistically significant improvement at the end of the study ($p < 0.001$).We did not find correlation between reducing exacerbation frequency and exposure to cigarette smoking, passive smoking exposure in childhood, the use of inhaled steroids, the level of education of our patients and the GOLD stadium.
Interpretation: Daily administration of a mucolytic drug such as carbocisteine for prolonged periods in addition to the bronchodilator therapy can be considered a good strategy for reducing exacerbation frequency in COPD.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD), a term used to describe progressive lung disease including bronchitis, emphysema and the newly phenotypes “overlap COPD-asthma”, is a preventable and treatable chronic respiratory disease associated with significant comorbidities and extrapulmonary effects that may contribute to its severity. COPD is characterized by irreversible, persistent and progressive airflow obstruction related to airways remodeling, mucus hypersecretion and breakage of alveolar septa [1]. In addition to lung function decline, COPD patients have chronic sputum, cough, and dyspnea [2]. These symptoms are particularly evident after an exacerbation of COPD that is defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and may warrant additional treatment. Currently the disease is the fourth leading cause of death and morbidity worldwide imparting a substantial economic burden on individuals and society. Recent studies have also predicted that if current smoking trend continues, by 2020 COPD will become the third cause of death worldwide

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[3,4]. COPD develops as a significant chronic inflammatory response to inhaled irritants, above all cigarettes smoking. The cells responsible for the inflammatory response are mainly neutrophils and macrophages [5]. In the smokers are involved cytotoxic T lymphocytes and eosinophils too; the main role of this response is carried out by inflammatory mediators such as chemotactic factors. Oxidative stress due to high concentrations of free radicals released by tobacco smoke and inflammatory cells is involved in pulmonary damage too. Pulmonary epithelium, constantly exposed to toxic exogenous pollutants inhaled and endogenous oxidants, undergoes profound changes.

Lung, because of its big blood supply and the wide surface area, is highly susceptible to oxidative stress [6]. In smokers and in COPD patients, there is a small antioxidant capacity in plasma because of the increased release of ROS (reactive oxygen species) by neutrophils and monocytes of peripheral blood and the reduction of protein's sulfidrilic groups [7]. It was also recently reported that antioxidants, such as glutathione, vitamin E and ascorbate, are reduced in smokers and associated with the severity of exacerbations of COPD [8]. From 2006, several Cochrane reviews that evaluated the effectiveness of drugs in the prevention of exacerbations have been published. Mucolytic agents show a statistically significant reduction in exacerbation frequency and a decrease in the number of disability days [9]; although this correlation was less incisive in successive publications [10]. In any case, none of this work had verified the effect of mucolytics for a long period of time. Zheng et al. (2008) published a multicenter, randomized, placebo-controlled study performed in China, which showed that a long-term treatment (for 12 months) with carbocisteine associated with long-acting and short-acting bronchodilator, anticholinergics and inhaled steroids therapy was able to reduce exacerbation frequency. This study also demonstrated that the effect on exacerbations occurred regardless of the degree of disease severity, smoking and use of inhaled steroids [11].

The purpose of our study is to verify how can change the exacerbation frequency in a Caucasian population suffering from COPD, during daily administration for 12 months of carbocisteine lysine salt.

2. Methods

2.1. Patients

Participants were eligible for inclusion if they were diagnosed as having COPD with a post bronchodilator forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio (FEV1/FVC) of less than 0.70 and an FEV1 between 25% and 79% of predicted value. The severity of COPD was defined according to GOLD recommendations [1]. At the end of run in period, we enrolled 89 COPD patients followed at our clinic: Monaldi Hospital, Naples, southern Italy (Table 1).

Besides, we divided our study population into two phenotypes, predominant emphysema (n. 36, 44, 4%) and predominant chronic bronchitis (n.45, 55,6%) according to both HRCT pattern and clinical features.

Patients aged between 40 and 80 years, have a history of at least 1 COPD exacerbation within the previous year, both smokers and non-smokers, women and men, with good oral and writing skills; smoking status was recorded and verified by history. Our patients were stratified into three groups, according to GOLD recommendations (GOLD II 67.4%; GOLD III 21%; GOLD IV 11.6%) [1].

Patients were excluded if they had limited mobility, neoplastic diseases, diffuse bilateral bronchiectasis, psychiatric disorders, transplant, systemic diseases with pulmonary involvement, known or suspected hypersensitivity to the study medication or part of its ingredients, treatment with carbocisteine for a longer period of 7 days and more than 4 cycles and involvement in an investigational drug trial in the previous 12 months. We monitored previous year exacerbation frequency by administering a clinical diary where the patient pinned any exacerbations. None of patients used oral corticosteroids, alcohol or drugs. Participants have all signed free informed consent. The study was approved by local ethics committees.

Table 1
Patient demographics and baseline characteristics.

Age, yr; mean ± std. dev	67.8 ± 8.6
Gender; n (%)	
Female	19 (22.4)
Male	66 (77.6)
BMI; mean ± std. dev.	27.6 ± 4.8
Professional exposure/yes; n (%)	19 (47.5)
Smoking habit; n (%)	
No smokers	10 (11.8)
Former smokers	39 (45.9)
Current smokers	36 (42.4)
Pack/Yr; median [25th − 75th percentile]	50 [40; 86.25]
Stage; n (%)	
GOLD II	58 (69.3)
GOLD III	18 (20.9)
GOLD IV	9 (9.8)
Secondhand smoke; n (%)	
No	27 (31.8)
Yes	58 (68.2)
Years from diagnosis; median [25th–75th percentile]	4 [2,10]
COPD phenotype; n (%)	
Emphysematous	38 (44.4)
Chronic bronchitis	47 (55.6)
BMI; median [25th − 75th percentile]	28 [24.8; 31]

Data are number (%) unless otherwise specified. COPD = Chronic obstructive pulmonary disease. GOLD = Global Initiative for Chronic Obstructive Lung Disease.

2.2. Study design

CAPRI (Carbocysteine in Prevention of exaceRbation of COPD) is an observational and prospective study. Enrolled patients were treated with daily administration of 2.7 g/day carbocysteine lysine salt equivalent to 1.5 g/day carbocysteine (1 packet of granules for oral solution/day). The patients were examined every three months until the end of the study to assess the vital signs, record any exacerbations, adverse events, and to verify their adherence to the study regimen. At baseline, demographic and anthropometric parameters, age, sex, weight, height, hypertension, pulse, medical history, diseases/concomitant medications, history of smoking status and exposure passive smoking in childhood, were collected. We also recorded the date of COPD diagnosis, COPD features, spirometry (TLC, FEV 1, FVC), arterial blood gas analysis (EGA), 6-min walking test (6MWT) and administered to each participant two questionnaires to investigate the quality of life: the COPD Assessment Test (CAT) and the St. George's Respiratory

Questionnaire (SGRQ), designed and validated by PW Jones, of St George's Hospital Medical School, in its Italian version [12].

At each checkup, 3, 6, 9 months, current therapy, exacerbation frequency and the eventual treatment was recorded. New spirometry (FEV 1, FVC, TLC) and EGA were performed. The adherence to current treatment with confirmation/amendment if needed and assessment of adverse events were verified. We made the final visit after 12 months or previously in case of early termination of the study. In this particular case, exacerbation frequency and any treatment related and adverse events were assessed. A last spirometry (FEV1, FVC, TLC) and EGA examination, as well as a 6MWT, SGRQ and CAT were performed. Conventional treatment for COPD, short- and long-acting bronchodilator and