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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

inhaled corticosteroids were continued by the patients; systemic administration of corticosteroids, antibiotics, mucolytic or antitussive were permitted just for the treatment of exacerbations.

2.3. Outcomes

The primary endpoint was exacerbation rate over 1 year of carbocisteine treatment compared with the previous year without carbocysteine therapy. Exacerbation was defined according to Anthonisen criteria: persistence for a minimum of 2 days of at least two major symptoms (increased dyspnea and increased sputum volume or purulence) or one major plus one more minor symptom (infection of the upper airways, increased wheezing or unexplained fever) [13].

Secondary endpoints included the evaluation of other parameters analyzed during the study: 6MWT, Bode index, EGA, PFR. The evaluation of quality of life was made comparing each SGRQ at the end of treatment with the one at baseline, thus each patient acted as the control of himself [14].

The correlation between the reduction of exacerbations and exposure to secondhand smoking in pediatric age, the severity of COPD according to the GOLD stage, the use of inhaled corticosteroids, the level of education and occupational exposure to harmful substances were investigated as well.

Because the aim of the present study was to value the role of carbocisteine as antioxidant rather than mucolytic agent, we didn't register sputum amount or its purulence.

2.4. Statistical analysis

A sample size of 77 subjects was required to detect a reduction in the mean number of exacerbation per year equal to 0.5 assuming a standard deviation of the differences equal to 1.5 (effect size equal to 0.33) with a power of 80% and a two sided significance level of 0.05. The number of patients was then increased by 15% in order to account for the non normal distribution of the primary outcome variable.

Numerical variables were described by median [25th – 75th percentile], while categorical variables were summarized through absolute frequencies and percentages. Treatment effect on longitudinal variations of the primary outcome in the whole study sample was assessed using the nonparametric Wilcoxon test and then compared between the COPD phenotypes using the Mann Whitney test. The time trend of the variables number of exacerbations" and "BODE index" was later dichotomized separating the subjects with improvement in the follow-up (fewer exacerbations and reduction of BODE index from baseline) by those without improvement. The subgroups so obtained were compared (Mann Whitney test for numerical variables and Fisher's exact test for categorical variables) in order to identify potential factors associated with improvement. All statistical tests were two-tailed, and p values less than 0.05 were considered statistically significant. It was not undertaken to adjust the analysis for multiple comparisons.

The analyzes were performed using SPSS statistical software vers.20.

3. Results

The study population was analyzed at the end of the study period (T12) of daily administration of carbocisteine. 4 patients were lost in follow-up: 2 because of gastrointestinal disorders related to the drug, 1 suffered hemoptysis due to a recently discovered lung cancer and 1 because of poor adherence to therapy. Other patients reported mild side effects that have not compromised the study because they didn't required the discontinuation of treatment.

The analysis of the study, reveals that there is a statistically significant reduction in the exacerbation frequency compared to previous year (median exacerbations at T0: 2 [1,3] vs at T12: 1 [1,2]; $p < 0.001$) (Table 2).

This reduction is more significant in the "chronic bronchitis phenotype" (40 patients, 85,1%) than "emphysematous" phenotype, (7 patients, 14.9%) ($p < 0.001$).

A statistically significant increase of the distance in meters walked (6MWT) (distance in meters T0: 396 [352; 440] vs T12: 418 [356; 484]; $p < 0.001$) was observed in T12 as well. The distance in meters to 6 MWT is one of the items of the BODE Index, an important prognostic index for COPD patients, also improved in T12 (BODE INDEX T0: 1 [0.5; 3] vs T12 [0; 2]; $p < 0.001$) (Table 2).

The comparison of results of tests of the quality of life at baseline and at the end of the study showed a statistically significant improvement in quality of life in the study population, both with the items of SGRQ (activity, symptoms and impact) and the sum of all these ($p < 0.001$), both with CAT ($p < 0.001$) (Fig. 1).

The association between exacerbation frequency reduction and disease severity, after treatment, according to GOLD stage, was not statistically significant (Table 3).

The reduction of exacerbation frequency did non correlate with active or passive exposure to cigarette smoking, use of inhaled steroids, exposure to occupational pollutants and level of education of the patients.

4. Discussion

The results of our study demonstrate that the daily use of carbocisteine, administered for twelve consecutive months, significantly reduces the number of exacerbations ($p < 0.001$). The primary end point was reached after 12 months of therapy whereas the PEACE study achieved the same result in six months [11]. Poole

Table 2
Number of Exacerbations and Quality of Life improvement described by median [25 th–75th percentile].

	T0	T12	p
Nr. of Exacerbations	2 [1; 3]	1 [1; 2]	<0.001
St. George Symptoms	56 [42.5; 70]	42 [20.5; 55]	<0.001
St. George Activity	72 [59; 89.5]	60 [45; 80]	<0.001
St. George Impacts	47 [29; 60.5]	36 [15; 56.5]	<0.001
St. George Total	58 [42.5; 70]	45 [25.5; 62.5]	<0.001
CAT	19 [12; 25]	17 [10; 23]	<0.001
6MWT (mt)	396 [352; 440]	418 [352; 484]	<0.001

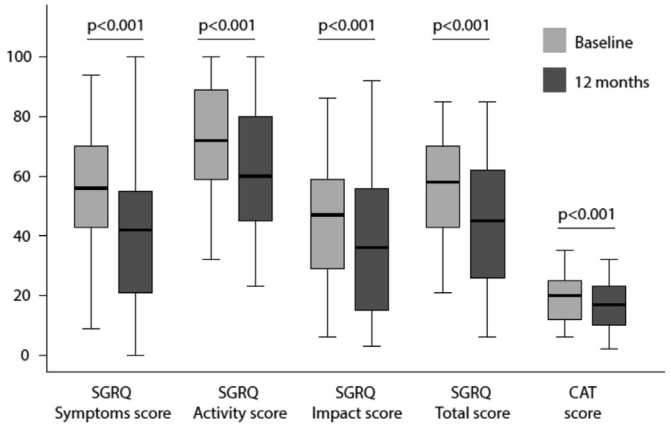

Fig. 1. Graphic representation of improvement of quality of life.

Table 3
Association between exacerbation frequency reduction and disease severity, after treatment, according to GOLD stage.

Gold stage at baseline	More or equal exacerbations (n = 34)	Less exacerbations (n = 47)	p
II	21 (61.8)	35 (74.5)	0.082
III	11 (32.4)	6 (12.8)	
IV	2 (5.9)	6 (12.8)	

Table 4
Side effects of carbocisteine in our population.

	N = 85
Gastrointestinal disorders	4
Headache	2
Hemoptysis	1

and Black (2006), analyzing 26 randomized controlled studies with a total of 7335 participants in treatment with mucolytic drugs for at least two months documented a significant reduction in exacerbation frequency. But, subsequently, further contributions in the literature suggested different results and the recommendations for the use of mucolytic drugs in addition to the basic therapy in COPD to reduce the number of exacerbations and improve quality of life, lost power [10,15–17].

Our results, instead, seem to support this recommendation, and considering the very low number of adverse events recorded and the good tolerability (Table 4) suggest to extend the administration of the drug for at least 12 months.

An important point of our study is that the cut in exacerbation frequency in our patients was completely independent from the use of inhaled corticosteroids. This finding differs from the BRONCUS study, in which N-acetylcysteine was used as mucolytic agent [18]. Among the secondary end points, there is an improvement in the quality of life assessed by a statistically significant decrease in SGRQ score, according to the PEACE study [11]. A significant improvement in lung function (FEV1, FVC, FEV1/FVC), as expected and in agreement with other similar studies was not achieved. However, a significant increase of the distance walked (6MWT) and, consequently, a significant reduction in the BODE index were observed. The improvement of BODE index is very important, being the BODE a more predictive parameter than FEV1 about the risk of mortality from general cause and from respiratory causes in patients with COPD [19].

5. Conclusions

Oxidative stress is a key point in the pathogenesis of COPD. For this reason, to act on oxidative stress both with pharmacological antioxidants and by increasing endogenous levels of oxidants, is today an important target in the treatment and management of COPD. Carbocisteine is a mucolytic drug with anti-inflammatory and antioxidant action and this latter effect may be what led to the achievement of the results reported. Another interesting aspect of carbocisteine is its supposed ability to modulate the function of epithelial cells of the lining of the airways, including the expression of ICAM1a, which is a receptor for the rhinovirus pathogens most commonly implicated in the genesis of the cold. Therefore, this molecule could play a very important role for the long-term treatment of patients with COPD and it is for this reason that in recent years has attracted considerable interest. In spite of that, mucolytic agents, although widely used in clinical practice for short periods, are not currently recommended by the GOLD recommendations (Evidence D) [1]. Our results, although have to be supported by other similar studies, seem to be in favor of the long term use of these drugs as powerful antioxidant agents capable to contribute to improve the management of COPD patients.

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