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A prospective study of the effects of carbocysteine lysine salt on frequency of exacerbations in COPD patients treated with or without inhaled steroids

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Abstract. – OBJECTIVE: COPD is one of the major causes of morbidity and mortality worldwide and represents one of the most important issues for public health. Frequent exacerbations induce a faster decline in lung function and poorer quality of life, increase mortality, and have a socio-economic impact with a high burden in terms of resources and healthcare costs. The clinical trials evaluated the effect of mucolytics in COPD and showed that the long-term carbocysteine, associated with bronchodilators, anticholinergics, and steroids, reduces the frequency of exacerbations and improves the quality of life.

PATIENTS AND METHODS: The aim of this prospective real-life study was to evaluate the long-term impact on exacerbations (at 1 year) in COPD patients treated with carbocysteine lysine salt (single dose of 2.7 g once a day) in addition to background therapy with or without inhaled steroids.

RESULTS: In a total of 155 evaluable patients, our study showed that the addition of a single dose of carbocysteine lysine salt to background therapy determines a statistically significant reduction of the average number of exacerbations vs. the number observed in the previous year (from 1.97±0.10 to 1.03±0.11; $p<0.01$), irrespective of treatment with or without inhaled steroids. In particular, in patients with ≥2 exacerbations in the previous year, the addition of carbocysteine lysine salt resulted in a statistically significant reduction in the exacerbations rate from 69% to 33% and from 58% to 25%, respectively ($p<0.01$) in patients with or without inhaled steroids.

CONCLUSIONS: In summary, our data highlighted the efficacy of long-term administration of a single daily dose of carbocysteine lysine salt (2.7 g/day) in reducing the number and rate of exacerbations in COPD patients, independently from the use of inhaled steroids.

Key Words:
COPD, Exacerbations, Mucolytics, Carbocysteine, Steroids.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities. COPD pathogenesis seems based on the innate and adaptive inflammatory response to continued exposures to risk factors, especially cigarette smoking. The inflammatory response causes damage with consequent lung remodeling and irreversible airflow wall thickening[1,2]. Moreover, oxidative stress may play an important role in COPD pathogenesis. In fact, oxidative stress biomarkers are increased in exhaled breath condensate, sputum, and blood samples of COPD patients[1]. The most common respiratory symptoms include dyspnea, cough, and/or sputum production[1]. COPD is currently the fourth leading cause of death and morbidity in the world and is predicted to become the third cause of death by 2020 due to continuous exposure to risk factors[3,4]. The estimated number of

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patients in 2010 was 384 million[1,5]. Viegi et al[6] evaluated that the prevalence of COPD in Italy is approximately 11%, using the spirometric criteria of the European Respiratory Society (ERS). COPD has a huge economic impact since new and more expensive drugs have begun to be used[7]. COPD is characterized by periods of acute worsening of airway function and respiratory symptoms, also known as exacerbations, that result in additional therapy[1,8]. This condition is usually associated with inflammation commonly triggered by viral or bacterial infections[9,10] and a key aspect of the treatment of COPD should be exacerbation prevention. Frequent exacerbations induce a faster decline in lung function, poorer quality of life and increased mortality; in addition, these episodes have a socio-economic impact with very high healthcare costs[11]. Therefore, treatments that reduce the frequency and duration of acute exacerbations will provide benefits for both individual patients and healthcare systems[12]. From 2006, several Cochrane reviews that evaluated the efficacy of drugs in the prevention of exacerbations have been published. The use of mucolytic agents has led to a statistically significant reduction in exacerbation frequency and a decrease in the number of disability days[12]. Clinical studies have been carried out to evaluate the effect of mucolytic agents on the prevention and the reduction of exacerbation episodes. Zheng et al[13] in the PEACE Study, a randomized placebo-controlled study carried out in China on 709 patients, showed that long-term use (12 months) of carbocysteine, associated with a bronchodilator, anticholinergics, and steroids therapy, reduced the frequency of exacerbations and improved the quality of life. More recently, in an observational study on a Caucasian population (CAPRI study), Esposito et al[14] demonstrated that the daily administration of carbocysteine lysine salt for 12 months significantly reduces the number of exacerbations (p<0.001), in a manner completely independent from the use of inhaled corticosteroids. Carbocysteine (S-carboxymethyl L-cysteine also available in the lysinate form, SCMC-Lys) is a thiol derivative of the amino acid L-cysteine. It is conventionally used as a mucolytic agent because of its effectiveness in normalizing mucus; however, it should be more properly defined as a mucoactive agent or mucoregulator because of its effect in normalizing mucus properties. Carbocysteine has antioxidant and anti-inflammatory properties and has shown to restore the balance between sialomucins and fucomucins contributing to the viscoelastic properties of mucus, along with a capability to reduce neutrophil infiltration into the airway lumen and IL8. Furthermore, carbocysteine lysine salt reduces exhaled IL6- and 8-isoprostane in COPD[15-18]. Carbocysteine action on inflammation levels and oxidative stress may play an important role in reducing COPD exacerbations[19]. Carbocysteine was effective in suppressing inflammation in human alveolar epithelial cells upon stimulation with TNF-α *in vitro*. These effects are intimately associated with the inhibition of the NF-κB and ERK1/2 MAPK signaling pathways, suggesting that carbocysteine may have a considerable therapeutic potential for the prevention and management of airway inflammation in COPD[20]. Carbocysteine may also modulate airways inflammation by decreasing virus-induced cytokine production and inhibiting bacterial adherence to epithelial cells[21,22]. The aim of our study was to evaluate the long-term effect (1 year) of carbocysteine lysine salt on COPD exacerbations in addition to background therapy with or without inhaled steroids in the Caucasian population.

Patients and Methods

This is an observational prospective real-life study in COPD patients treated with a single daily dose of carbocysteine lysine salt (2.7 g/day) in addition to background therapy with or without associated inhaled steroids. COPD exacerbations were defined according to Anthonisen criteria [23]: at least 2 days' persistence of 2 major symptoms (worsening of dyspnea, increase in sputum purulence, or volume, or both), and any major symptom plus more than one minor symptom (upper airway infection, unexplained fever, increase of wheezing). Patients on systemic steroids or with respiratory diseases other than COPD or systemic diseases involving lungs or diffuse bilateral bronchiectasis were excluded from the study. At baseline, our study population was stratified by the number of COPD exacerbations during the previous years (<2 or ≥2 exacerbations). Patients received carbocysteine lysine salt 2.7 g/day (Fluifort®) for 12 months together with baseline therapy with or without inhaled steroids. The patients were evaluated at baseline and after 12 months when pulmonary function tests and physical examinations were performed. The study was

Table I. Gender.

Treatment	Female		Male		Total		*p*-value
	No.	%	No.	%	No.	%	
Carbocysteine lysine salt (no inhaled steroids)	32	40.5	47	59.5	79	100.0	0.9999 (N.S.)
Carbocysteine lysine salt + inhaled steroids	15	41.7	21	58.3	36	100.0	
Total	**47**	**40.9**	**68**	**59.1**	**115**	**100.0**	–

approved by the local Ethics Committee (#144 August 2011) and all patients gave their written informed consent.

Statistical Analysis

Age was analyzed using ANOVA performing multiple comparisons between groups and, where applicable, within groups. Gender was analyzed by the Chi square test with Yates correction. The changes in the mean number of exacerbations between time assessments (at baseline and after 12 months) were analyzed using the *t*-test for paired data. McNemar test was used to compare changes in the frequency of subjects with exacerbations, expressed as a dichotomous parameter (<2/≥2 exacerbations), between baseline, and after treatment. The number of exacerbations after 12 months, expressed as binary data (<2/≥2 exacerbations), was also analyzed using a multivariate logistic regression model, testing the prognostic effect of treatment, age, gender, and a number of exacerbations (<2/≥2 exacerbations) in the previous year (baseline). The primary endpoint was the exacerbation rate over 12 months of carbocysteine lysine salt treatment, in addition to standard therapy, compared with the previous years. The Statistical Analysis was performed using SAS v.9.4.

Results

Overall, 115 subjects completed the 1-year follow-up, of whom 79 (68.7%) were treated with carbocysteine lysine salt without inhaled steroids and 36 (31.3%) with carbocysteine lysine salt plus inhaled steroids; 68 were males (59.1%) and 47 females (40.9%) with an average age of 70.4 years (SD 9.6). Demographic characteristics tabulated by treatment group are reported in Table I and Table II.

Over one year of treatment with carbocysteine lysine salt, the number of patients with <2 exacerbations increased to 72.2% from 38.3% in the previous year, whereas the number of more severely affected patients with ≥2 exacerbations dropped from 61.7% to 27.8% ($p<0.01$) (Figure 1). The average number of exacerbations fell from 1.97±0.10 in the previous year to 1.03±0.11 after 12 months of carbocysteine lysine salt treatment (mean±SE; $p<0.01$) (Figure 2) .

This latter parameter is even more interesting, if we look at the effect of the single treatments: for carbocysteine lysine salt without inhaled steroids, the reduction was from 1.82±0.10 to 0.96±0.12 (mean±SE; $p<0.01$) while for carbocysteine lysine salt plus inhaled steroids the effect seems even more evident dropping from 2.31±0.19 to 1.19±0.21 (mean±SE; $p<0.01$) (Figure 2).

The effect of treatment with carbocysteine lysine salt without inhaled steroids is statistically significant ($p<0.01$); in particular, the number of patients with ≥2 exacerbations decreases from 58.2% to 25.3% (Figure 3). Similarly, the effect of treatment with carbocysteine lysine salt + inhaled steroids shows statistically significant results ($p<0.01$); here, the number of patients with ≥2 exacerbations decreases from 69.4% to 33.3% (Figure 3).

Table II. Age.

Treatment	No.	Mean ± SD	Min	Max	*p*-value
Carbocysteine lysine salt (no inhaled steroids)	79	70.6 ± 9.2	40.0	84.0	–
Carbocysteine lysine salt + inhaled steroids	36	69.9 ± 10.4	43.0	84.0	–
Total	**115**	**70.4 ± 9.6**	**40.0**	**84.0**	–

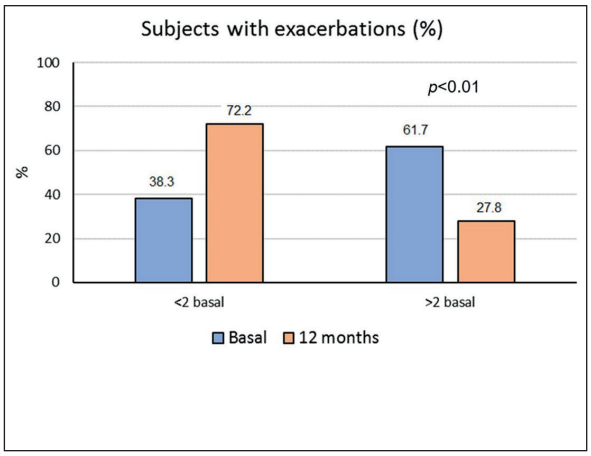

Figure 1. Percentage of subjects with exacerbations before and after treatment with carbocysteine lysine salt.

The results of the multivariate analysis show that the sole variable with a statistically significant prognostic effect ($p<0.01$) on exacerbations at 12 months is the number of exacerbations (<2 or ≥ 2) observed in the previous year. Older age seems to increase the risk of exacerbations ≥2, but this observation does not reach the statistical significance. Similarly, the risk of exacerbations ≥2 in females is lower than in males, but again without statistical significance. As far as treatment is concerned, the probability of observing a number of exacerbations ≥2 is slightly lower in the group receiving only carbocysteine lysine salt than in the group treated with carbocysteine lysine salt + inhaled steroids, irrespective of the basal state of the subjects. No significant side effects were reported during the study period.

Discussion

Many studies and the GOLD guidelines[1] underline the importance of exacerbation frequency in the progression of chronic obstructive pulmonary disease (COPD) together with the role of systemic inflammation in the disease process. According to GOLD 2019 Guidelines, regular treatment with mucolytics in COPD patients not receiving inhaled corticosteroids may reduce exacerbations and improve health status. Furthermore, several trials demonstrating the positive effects of mucoactive drugs on exacerbations rates and quality of life, underline that the drugs commonly used for their mucoactive properties have different mechanisms of action, including significant antioxidant activity. In a recent meta-analysis, Zeng et al[24] showed that the long-term use of carbocysteine may be associated with a reduced rate of exacerbations, a decrease in the number of patients with at least one exacerbation and an improvement of quality of life. A recent meta-analysis including 11 random-

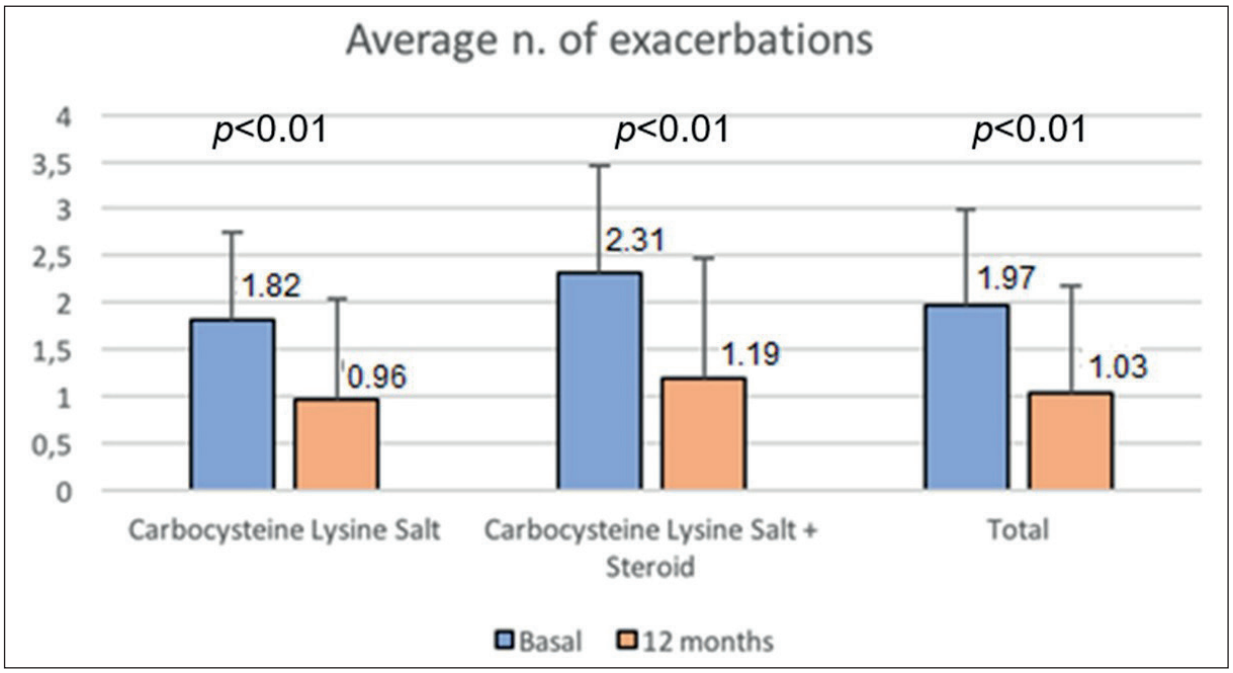

Figure 2. Average number of exacerbations.

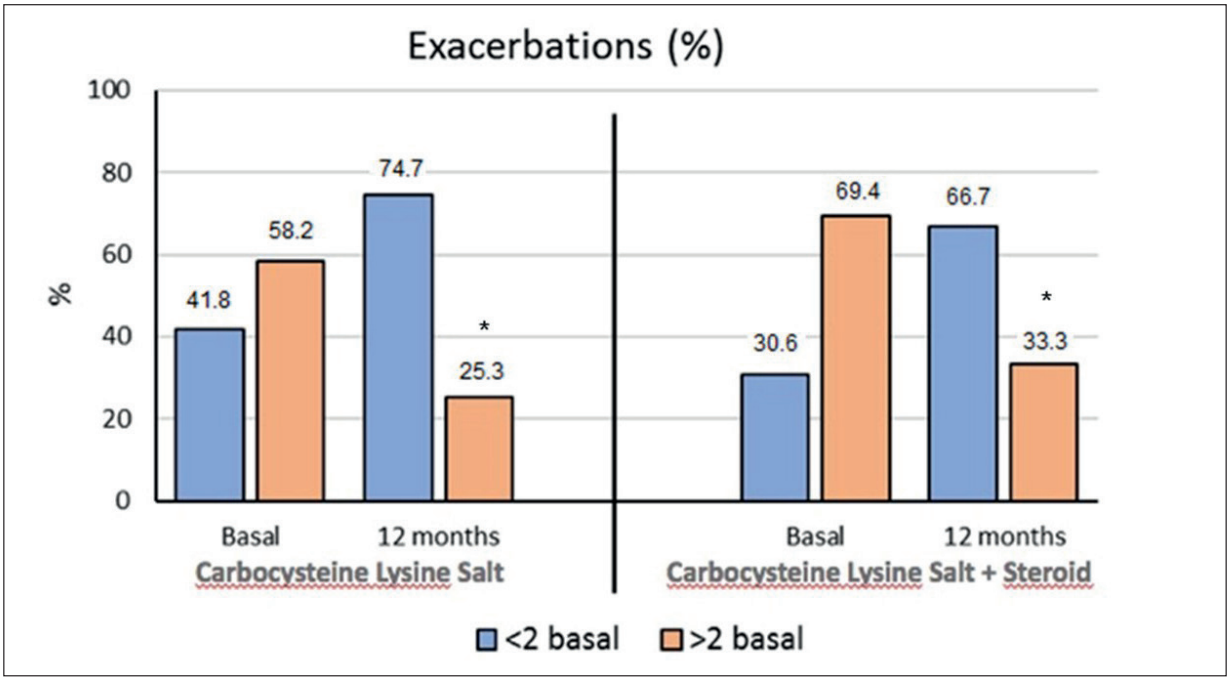

Figure 3. Effect of treatments on exacerbations.

ized clinical trials (RCTs) conducted by Cazzola et al[25] examined the impact of 4 mucolytics (N-acetylcysteine, carbocysteine, erdosteine, and ambroxol) on COPD exacerbations: the results showed that carbocysteine, erdosteine, and high dose of NAC are effective in reducing the rate of COPD exacerbations and that concomitant use of corticosteroids, both systemic and inhaled, does not modify the efficacy. In our study, we used carbocysteine lysine salt at a dosage of 2.7 g/day for 12 months; our results demonstrated that the regular use of carbocysteine lysine salt was effective into reducing the number of exacerbations both in patients treated and those not treated with inhaled steroids, confirming the results of other studies[13,14]. The effect of carbocysteine in reducing exacerbations and improving quality of life in COPD seems related to its anti-inflammatory, antioxidant, antimicrobial proprieties, in addition to its mucolytic activity, together with a possible action in reverting steroid resistance[18,26-37]]. Chronic obstructive pulmonary disease (COPD) is characterized not only by airways inflammation but also by the enhanced generation of reactive oxygen species[38,39]. In preclinical studies, Pace et al[28,29] demonstrated the effect on oxidative stress of carbocysteine in airway epithelial cells stimulated with Cigarette Smoke Extracts (CSE). In bronchial epithelial cells, carbocysteine was able to reduce the reactive oxygen species (ROS) production and to increase cytoprotective events including glutathione (GSH). Furthermore, oxidative stress increases the production of inflammatory mediators in the airway epithelial cells[40,41]. Carpagnano et al[18] demonstrated the presence of higher concentrations of 8-isoprostane and Interleukine-6 in the breath condensate of COPD subjects than in healthy controls, with an increase during acute exacerbations. Daily treatment with carbocysteine lysine salt monohydrate (SCMC-Lys) significantly decreased the levels of these markers after 6 months in patients, indicating that the drug has both antioxidant and anti-inflammatory properties. Our study shows a statistically significant reduction of the average number of exacerbations irrespective of the treatment groups (carbocysteine lysine salt without or with inhaled steroids) and that the long-term use of carbocysteine lysine salt was effective in reducing the number of exacerbations, particularly in more severe patients (with ≥2 exacerbations at baseline observation). At 12 months the effects of carbocysteine on exacerbations was similar in the 2 subsets of subjects, regardless of concomitant use of inhaled steroids. Our results in reducing exacerbations may be related to the

antioxidant, anti-inflammatory, and antimicrobial effects of carbocysteine. Moreover, the reduction of exacerbations in patients treated with inhaled steroids may be also related to the effect of carbocysteine in reverting steroid sensitivity[18,26-37]. In the PEACE study, Zheng et al[13] demonstrated the positive effect on the frequency of exacerbations and quality of life using long-term carbocysteine (alone or in association with bronchodilatator, anticholinergics, and steroids therapy; of note, only 17% of enrolled individuals received inhaled corticosteroids). Esposito et al[14] have more recently showed similar results on Caucasian patients (median exacerbations at T0:2[1,3] *vs.* at T12:1[1,2]; $p<0.001$). Prevention of acute exacerbations of COPD could lead to substantial savings in terms of healthcare costs. Though steroids, long-acting beta-agonists and anticholinergics may be indicated ad more appropriate according to some treatment guidelines, while mucolytics could be more cost effective, particularly for long-term use[42] and are recommended by some national guidelines (Czech, Poland, Russia, Germany, and Spain at least in some patient subgroups)[43]. In the United States, COPD exacerbations are estimated to result in 110,000 deaths and more than 500,000 hospitalizations per year, with over $18 billion spent in direct costs annually[44,45]. In addition to the financial burden required to care for these patients, other "costs", such as days missed from work and severe limitations in the quality of life, are important features of this condition[9]. In Italy, the direct annual costs per COPD patient have been estimated to be $1172, while the indirect costs reach $1841[7]; other authors, using a different calculation approach, report that, on average, the Italian healthcare system spends €6725 a year per person[46] or €3291 (total cost to society)[47]. Hence, among the available effective treatments, mucolytics, and particularly carbocysteine lysine salt, could be more affordable and should be preferred, particularly for long-term use and in "low-income" countries. For instance, Zheng et al[13] reported that the annualized cost per patient for carbocysteine therapy (in China) is $90 which is equal to the US, while combined treatment with inhaled steroids and long-acting beta-agonists is six times higher ($580).

Conclusions

We showed that the addition of carbocysteine lysine salt to background therapy was effective in reducing the number of exacerbations even in patients with ≥2 exacerbations at baseline observation, and that at 12 months the effects of carbocysteine lysine salt on exacerbations was similar in the 2 subsets of subjects (with or without inhaled steroids). These results suggested that patients with COPD exacerbator phenotype may have better outcomes using carbocysteine lysine salt. Hence, our data indicate the effectiveness of a single daily dose of carbocysteine lysine salt (2.7 g/day) in reducing the number of exacerbations in COPD patients, independently from the use of inhaled steroids, and may support its recommendation in clinical practice. We are aware of the possible pitfalls of our study as it is a single site, observational, and non-RCT study and because of the limited number of enrolled subjects; however, as reported by Janson et al[48], it might be that, because of the observational design of the study, the applicability of our findings to general, real-life, clinical practice may be greater than controlled trials. Moreover, confirmation of effectiveness in prospective study design may be considered more exhaustive in patients with a chronic disease that leads to a sequential respiratory functional decline. We suggest that our data, together with those from other studies, should be taken into consideration for the future revision of guidelines, also with the aim of better managing the economic burden linked to exacerbations in the natural history of COPD.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

G. Puglisi designed the study, supervised and reviewed results and manuscript. G. Paone designed the study, wrote and reviewed the manuscript. S. Toti, P. Palermo, and C. Graziani enrolled, interviewed and evaluated the patients. M.C. Flore and M. Ramaccia helped write the manuscript and reviewed the statistical analysis. Funding/support: The study was supported by Dompé Farmaceutici S.p.A, Milan, Italy through an unrestricted grant.

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