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Editorial

MUCOLYTICS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: THE RETURN OF A LONG-FORGOTTEN THERAPY?

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Chronic obstructive pulmonary disease (COPD) is a major and growing global health issue, ranking as the third leading cause of death worldwide and a major cause of morbidity. This disease is characterized by chronic inflammation, progressive airflow limitation, and recurrent exacerbations, which accelerate lung function decline, impaire health-related quality of life (HRQoL), and increase mortality (1,2). Given these

consequences, reducing the frequency of exacerbations remains a primary treatment goal.

Airway mucus hypersecretion is a key pathogenic factor associated with COPD exacerbations (3–5). Excessive mucus production combined with impaired clearance leads to accumulation in the airways as plugs (6). Recent findings have shown that mucus plugs are commonly observed on chest computed tomography (CT) in individuals with COPD and are independently associated with increased mortality, accelerated functional decline, and heightened exacerbation risk (7,8). Notably, up to 30% of patients with COPD report neither cough nor sputum production, despite radiological the presence of mucus plugs (7–9). These findings have renewed interest in the potential therapeutic value of mucoactive agents in COPD.

Carbocysteine is a mucolytic agent that can help relieve mucus by reducing the production of high-viscosity mucins and enhancing sputum clearance (10–12) . It may also decrease bacterial colonization by downregulating the expression of adhesion molecule-1 (13), decreasing risk of COPD exacerbation. In addition, recent studies have shown that carbocysteine also acts as a potent scavenger of hypochlorous acid and free radicals, and exhibits notable anti-inflammatory effects (11). Evidence indicates that carbocysteine reduces the production of key pro-inflammatory cytokines, including IL-8 and IL-6 (14), which are implicated in neutrophilic airway inflammation and mucus hypersecretion. Furthermore, it has been shown to inhibit activation of NF-κB, a central transcription factor in the inflammatory cascade, thereby attenuating the inflammatory response and potentially mitigating disease progression, and improving clinical outcomes in COPD (15).

Over the years, numerous studies have investigated the role of mucolytics in COPD treatment, yielding heterogeneous results. Several studies have demonstrated their efficacy, such as the PEACE study (16), conducted in China, which found that long-term carbocysteine use significantly reduced the frequency of exacerbations and improved HRQoL in patients with severe to very severe COPD. Similarly, the CAPRI study (17), carried out in a Caucasian population, showed that the daily administration of carbocysteine lysine salt for 12 months led to a significant reduction in exacerbations, independent of inhaled corticosteroid use. A 2019 Cochrane systematic review, which included 38 studies with over 10,000 participants, provided a more nuanced assessment of mucolytics, confirming a moderate reduction in exacerbation risk and disability days, along with a potential decrease in hospitalizations (18). However, its findings also indicated a limited impact on lung function and overall HRQoL, with study populations

primarily composed of patients with moderate to severe COPD. The review highlighted substantial heterogeneity among studies, with more recent trials reporting smaller benefits compared to earlier ones (18).

Conversely, other studies and meta-analyses have failed to demonstrate significant efficacy of mucolytics in reducing COPD exacerbations, particularly in recent trials where improvements in inhaled therapies may have influenced outcomes (19,20). These discrepancies may be partly explained by differences in studies design, populations, as well as the evolving standard of care, which has improved COPD management overall. While previous studies have demonstrated the efficacy of carbocysteine in moderate to severe COPD, its impact on mild-to-moderate cases remains unclear. To address this gap, a phase 4, multicenter, double-blind, randomized, placebo-controlled trial, publish in this issue of *Archivos de Bronconeumología,* was conducted to evaluate the effect of carbocysteine on annual rate of exacerbations and lung function in patients with mild-to-moderate COPD (21). The study enrolled 539 patients who were randomized in a 2:1 ratio to receive either carbocysteine (1500 mg/day) or a placebo for 48 weeks. Contrary to prior findings in more severe cases, the study found no statistically significant difference in the annualized exacerbation rate between the carbocysteine and placebo groups. The exacerbation rate was 0.39 per patient-year in the carbocysteine group and 0.46 per patient-year in the placebo group (relative risk, 0.85; 95% CI, 0.64 to 1.13; P=0.273). Similarly, no significant difference was observed in the change in pre-bronchodilator forced expiratory volume in the first second (FEV_1) between the two groups.

Although these results may suggest that carbocysteine is less effective in reducing exacerbations in mild-to-moderate COPD, several factors should be considered. First, the study failed to achieve the target sample size due to recruitment difficulties during the COVID pandemic. This limitation particularly affects the conclusions regarding the impact on FEV_1 decline, which was underpowered, but does not invalidate the overall findings related to the annualized exacerbation rate, as the sample size for this coprimary outcome was achieved. Second, previous meta-analyses, such as that by Cazzola et al (22), have indicated that mucolytics may be more effective in patients with frequent exacerbations. In this study, most participants had a low baseline exacerbation frequency, potentially reducing the observed benefit of carbocysteine. Third, differences in disease severity may influence the response to mucolytics. Patients with moderate to severe COPD typically experience greater mucus hypersecretion, and airway inflammation, which carbocysteine is designed to alleviate. In contrast, those with milder

disease may have less mucus production, reducing the potential impact of mucolytic therapy. Finally, the presence of mucus plug was not studied, however, they are likely to be less prevalent in patients with mild or moderate disease (7).

This recent trial highlights the potential limitations of carbocysteine in mild-to-moderate COPD, contrasting with prior evidence supporting its efficacy in more severe cases. The lack of a significant effect on exacerbation rates and lung function suggests that carbocysteine may not be a universally effective intervention in all COPD patients. Mucoactive therapies, should be now being reappraised in light of new imaging data showing mucus plugs.

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Conflict of interest:

JJSC has received speaker fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, FAES, GlaxoSmithKline, Grifols, Menarini, Sanofi and Zambon, and consulting fees from AstraZeneca, Bial, Chiesi, GSK, Grifols and Sanofi, and grants from GSK. MS declare non conflict of interest.

Ethics in publishing

1. Does your research involve experimentation on animals?:

No

2. Does your study include human subjects?:

No

3. Does your study include a clinical trial?:

No

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:

Yes

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