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EDITORIAL

Bronchodilators in bronchiectasis: we urgently need more trials

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Bronchiectasis is an irreversible dilatation of the bronchial lumen as a consequence of a pathophysiological vicious circle in which infection, inflammation and remodeling of the bronchial wall play a fundamental role. This situation causes the usual symptoms of bronchiectasis patients: an excess of bronchial secretions, sometimes purulent, and exacerbations of an infectious profile [1]. Even in the absence of concomitant COPD or asthma (diseases with which bronchiectasis is often associated), the most common lung function pattern is airflow obstruction (35–50% of patients), which is sometimes (at least partially) reversible and associated with air trapping and hyperinflation [2]. Therefore, it is not surprising that physicians use a variety of inhaled bronchodilators in patients with bronchiectasis and airflow obstruction and/or dyspnea. In fact, according to the data offered by the most important bronchiectasis registries in the world, between 50 and 70% of patients with bronchiectasis use long-acting β2-adrenoceptors (LABA) and between 15 and 45% use long-acting muscarinic antagonist (LAMA) [3]. Accordingly, some international guidelines on bronchiectasis empirically recommend the use of bronchodilators under certain therapeutic circumstances (i.e., associated COPD or asthma, presence of airflow obstruction and/or significant dyspnea or associated to respiratory physiotherapy programs) [4–8]. However, although clinical experience suggests that the use of bronchodilators would be beneficial in bronchiectasis with airflow obstruction, this supposition often leads to the conclusion that this benefit is beyond doubt, especially after taking into account the proven benefits in other chronic inflammatory airway diseases with airflow obstruction. Nevertheless, such equivalencies are not always well-founded: one clear example is the gap between the great efficacy of inhaled corticosteroids (IC) in asthma, and in some patients with COPD, and their negligible effect in the vast majority of bronchiectasis patients (although ICs are used in more than 30–50% of bronchiectasis patients without COPD or asthma) [9], as well as between the proven effectiveness of DNase or inhaled antibiotics in cystic fibrosis and the poor response (at least for the moment) in bronchiectasis of other etiologies [10, 11].

This widespread use of bronchodilators and their recommendation in the guidelines contrast, however, with the limited scientific evidence available on the effects of LABA, LAMA or a combination of the two in patients with clinically stable bronchiectasis. Thus, whereas in COPD and asthma there are dozens of studies with thousands of patients to corroborate their efficacy, a recent systematic review with respect to bronchiectasis included a mere five studies, of which only one was a randomized controlled trial (RCT) in which the efficacy of a combination of formoterol-budesonide was analyzed in 40 patients [3]. Very recently, Jayaram et al. published the first RCT using placebo on the effect of tiotropium in 85 patients with bronchiectasis and airflow obstruction for 6 months, concluding that tiotropium improved the patients' lung function but not the frequency of exacerbations, quality of life, symptoms or cellular counts in blood and sputum [12].

In the present issue of *LUNG*, Shi et al. [13] conducted an observational study in a prospective cohort including 169 patients with bronchiectasis and airflow obstruction who were not taking LABA or ICs and were followed for 12 months. They found, as in the Jayaram study, a significant improvement in lung function, but in this case they

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also observed a reduction in the adjusted risk of moderate exacerbations and a longer time before the first-time severe exacerbation in those patients who took tiotropium.

Looking beyond the different designs of the studies, numbers of patients included and duration of the follow-up, the discrepancies observed between Shi and Jayaram´s results regarding the effect of tiotropium on exacerbation rates could be explained by various factors related to the different baseline characteristics of the individuals and, above all, by the fact that in the study of Jayaram almost 50% of the subjects were also on regular therapy with LABA/ICs, probably leaving little room for improvement in the tiotropium group.

Therefore, although the latest studies discussed shed more light on the effect of bronchodilators, and more specifically antimuscarinic drugs, the scientific evidence is still very scarce with regard to patients with bronchiectasis. Large-scale clinical trials are needed to determine which bronchiectasis patient phenotypes can benefit most from bronchodilators. This is especially important given that ICs are not indicated, except in some circumstances such as bronchiectasis associated with asthma or COPD with an eosinophilic component [14, 15], and in these cases therapy with bronchodilators (alone or in combination) probably could be crucial for improving symptoms (mainly dyspnea) in bronchiectasis patients with airway obstruction or air trapping, or for improving expectoration. Moreover, any RCTs in this field must clearly exclude patients with COPD and asthma to assess the true role of bronchodilators in bronchiectasis endotypes and phenotypes and determine whether airway obstruction is a real treatable trait in bronchiectasis. This will not be easy, however, especially when it comes to excluding asthma, since up to 20% of bronchiectasis patients may have peripheral eosinophilia [16–18], a positive bronchodilator test or airway hyperresponsiveness [19].

For all these reasons, it is striking that there have not been any large-scale clinical trials on the effect of bronchodilators in patients with bronchiectasis, a disease that is associated with more than 25% of COPD and severe asthma cases [20, 21] and is, moreover, the third most frequent chronic inflammatory disease of the airway, after COPD and asthma [1]. May this editorial serve as a wake-up call for the scientific community to carry out these necessary clinical trials to confirm what physicians seem to have already decided: that long-acting bronchodilators, whether alone or in combination, are effective, at least in the improvement of some fundamental outcomes in patients with bronchiectasis and airflow obstruction such as exacerbations [22–24], and the impact of this treatment in some specific traits in bronchiectasis such as neutrophilic inflammation [25] or the microbiome [26–28]. Until this scientific evidence arrives, studies such as those by Shi et al. are important for assessing which individuals with bronchiectasis are most suited for inclusion in an RCT. At the moment, the best alternative continues to be to follow the recommendations established by the international bronchiectasis guidelines.

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Declarations

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