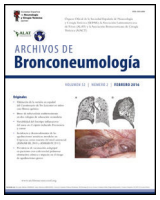
Archivos de Bronconeumología 59 (2023) 787–788

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Dual Broncodilator and Triple Therapy in Bronchiectasis. Clinical Trials are Urgently Needed

A recent study using data from 16 963 individuals in the European Bronchiectasis registry (EMBARC) reported that 51.3% of patients had used an inhaled corticosteroid (ICS), 50.9% a long-acting beta-agonist (LABA), and 27.7% a long-acting muscarinic antagonist (LAMA). However, only 34.9% of the cohort had documented bronchial airflow obstruction.[1] Data analysis has also revealed marked differences between countries in prescribing these drugs, which are commonly used without verifying the presence of chronic obstructive pulmonary disease (COPD) or asthma.[1,2]

This frequent use of ICS, LABA, and LAMA contrasts with the limited existing evidence on the efficacy and safety of these molecules in treating bronchiectasis. International guidelines agree that ICS are not indicated as a routine treatment in patients with bronchiectasis, except for conditions such as allergic bronchopulmonary aspergillosis, asthma, COPD, or significant bronchorrhea that cannot be controlled with other therapies.[3] The guidelines also do not recommend the routine use of bronchodilators, limiting it to bronchiectasis with symptomatic airflow obstruction (mainly cough or dyspnea), when other treatments have not produced the desired effect or if it is associated with respiratory physiotherapy programs.[4]

There are several reasons for the overuse of ICS and long-acting bronchodilators in subjects with bronchiectasis.[3,4] Diagnostic confusion between COPD and bronchiectasis is common, as is a tendency to extrapolate the established signs and symptoms of COPD and asthma, the best known chronic inflammatory airway diseases, to bronchiectasis. Given the critical role of bronchial inflammation in bronchiectasis, physicians may believe that ICS are indicated in this disease due to their potent anti-inflammatory activity. Moreover, they may be prompted to undertake an aggressive treatment approach even in the absence of bronchial obstruction, probably because they consider dyspnea a critical indicator of bronchiectasis that can be corrected with appropriate therapy. Furthermore, a combination of long-acting bronchodilators and ICS is often prescribed to patients with symptomatic bronchiectasis or airflow obstruction, given the significant percentage of inhaler devices on the market in which bronchodilators are combined with ICS, potentially leading to misuse of ICS.[4]

However, regardless of these causes, there is a solid pharmacological rationale that supports a broader and possibly combined use of ICS and long-acting bronchodilators in bronchiectasis in some patients.[5]

Reducing inflammation may have favorable effects because of an underlying inflammatory bronchial response that is present even when the patient is not experiencing acute bronchiectasis.[3] Numerous inflammatory cells are inhibited by corticosteroids, preventing their recruitment in the airways. Furthermore, these molecules suppress resident structural cells, decreasing mediator release and expression on epithelial and endothelial cells, blood vessel microvascular leak, angiogenesis, mucus glands, and mucus production.[4]

The presence of airflow obstruction, air trapping, hyperinflation, and restriction in many patients with bronchiectasis should never be overlooked. Air trapping is an essential mechanism of dyspnea.[6] Solid evidence indicates that bronchodilators facilitate lung emptying, decrease air trapping, and reduce dyspnea.[5] Although bronchomotor tone control associated with bronchiectasis has not been directly investigated in basic research, it is likely that in bronchiectasis, in which increased airway hyperreactivity and airway smooth muscle (ASM) mass have been documented, vagal activity is also increased. Since the weak sympathetic tone does not counteract the enhanced parasympathetic activity, pharmacological interventions with LABA/LAMA combinations, which optimize bronchodilation, can shift the relaxant/contractile imbalance toward a relaxant profile of ASM.[7]

Preclinical studies have shown that co-administration of a LABA with a LAMA causes a synergistic increase in ASM relaxation, an effect confirmed in patients with COPD by assessing changes in FEV_1.[8] Furthermore, several meta-analyses have documented that LABA/LAMA combinations are consistently more effective than either LABA or LAMA alone in treating COPD.[8] Although a retrospective, observational study from South Korea did not confirm a better efficacy for LABA/LAMA combinations than LABAs or LAMAs alone in bronchiectasis patients,[9] data from a specifically designed randomized clinical trial (RCT) are still lacking.

Adding an ICS to LABA/LAMA would exploit not only the synergistic increase in ASM relaxation but also the bidirectional molecular interactions between corticosteroids and β_2-agonists for the reciprocal enhancement of the pharmacological effects of ICS and LABA, and the bronchodilator, anti-inflammatory, and anti-remodeling activities induced by the interaction between a LAMA and an ICS,[4] effects that are undoubtedly important in bronchiectasis. Experimental research on isolated human bronchi has shown that ICS/LABA/LAMA combinations induce synergistic bronchorelaxant effects and a significant reduction in the release of T2 and T1 cytokines, such as interleukin (IL)-4, IL-5, IL-6, IL-9, IL-13, tumor necrosis factor-α, thymic stromal lymphopoietin, and also neurokinin A, substance P and non-neuronal acetylcholine, and a

https://doi.org/10.1016/j.arbres.2023.07.013

massive increase in the intracellular concentration of cyclic adenosine monophosphate.[10]

Solid evidence indicates that there is a role for triple therapy in COPD and asthma.[4] However, the efficacy of triple therapy in bronchiectasis has not been evaluated in any RCT to date. The apparent lack of interest in a treatment that includes an ICS may be due to two critical limitations to the use of these molecules in bronchiectasis: namely, that it is a disease with predominantly neutrophilic inflammation, notoriously resistant to corticosteroids, that confers a high likelihood of chronic bacterial bronchial infection; and because of their immunosuppressive properties, ICS can induce an increase in bacterial infections.[3]

However, there is significant discrepancy between the use of ICS, LABA, and LAMA in the treatment of subjects with bronchiectasis in daily practice[1,2] and the guideline recommendations.[3,4] This discrepancy can, in any case, be explained by the scarcity of scientific information on the efficacy and safety of these molecules in this disease and the type of patients in whom could be more effective, underlining the need for well-designed RCTs in patients with bronchiectasis to avoid an approach that is currently wholly empirical.[11] Specific endophenotypes of interest could be chronic bronchial infection by pathogenic microorganisms,[12] an eosinophilic profile,[13] the COPD or asthma overlap bronchiectasis syndromes, and the interaction of dual or triple therapy with other current or future anti-inflammatory and antibiotic treatments.[14] In the meantime, the best option remains to follow the bronchiectasis guidelines.

Authors' Contributions

All authors contributed equally to the conception, literature review and analysis, drafting and critical revision and editing of this editorial, and approval of the final version.

Funding

The authors received no support in the form of grants, gifts, equipment or drugs for the research, authorship, and publication of this article.

Conflict of Interests

The authors state that they have no conflict of interests.

References

1. Chalmers JD, Polverino E, Crichton ML, Ringshausen FC, De Soyza A, Vendrell M, et al. Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC). Lancet Respir Med. 2023;11:637–49.
2. Martínez-García MA, Villa C, Dobarganes Y, Girón R, Maíz L, García-Clemente M, et al. RIBRON: the Spanish online bronchiectasis registry. Characterization of the first 1912 patients. Arch Bronconeumol. 2021;57:28–35.
3. Martínez-García MÁ, Oscullo G, García-Ortega A, Matera MG, Rogliani P, Cazzola M. Inhaled corticosteroids in adults with non-cystic fibrosis bronchiectasis: from bench to bedside. A narrative review. Drugs. 2022;82:1453–68.
4. Martínez-García MÁ, Oscullo G, García-Ortega A, Matera MG, Rogliani P, Cazzola M. Rationale and clinical use of bronchodilators in adults with bronchiectasis. Drugs. 2022;82:1–13.
5. Matera MG, Page CP, Calzetta L, Rogliani P, Cazzola M. Pharmacology and therapeutics of bronchodilators revisited. Pharmacol Rev. 2020;72:218–52.
6. Cazzola M, Martínez-García MÁ, Matera MG. Bronchodilators in bronchiectasis: there is light but it is still too dim. Eur Respir J. 2022;59:2103127.
7. Calzetta L, Matera MG, Cazzola M, Rogliani P. Optimizing the development strategy of combination therapy in respiratory medicine: from isolated airways to patients. Adv Ther. 2019;36:3291–8.
8. Cazzola M, Page C, Rogliani P, Calzetta L, Matera MG. Dual bronchodilation for the treatment of COPD: from bench to bedside. Br J Clin Pharmacol. 2022;88:3657–73.
9. Lee SY, Lee JS, Lee SW, Oh YM. Effects of treatment with long-acting muscarinic antagonists (LAMA) and long-acting beta-agonists (LABA) on lung function improvement in patients with bronchiectasis: an observational study. J Thorac Dis. 2021;13:169–77.
10. Rogliani P, Ritondo BL, Facciolo F, Matera MG, Nikolaev I, Calzetta L. Indacaterol, glycopyrronium, and mometasone: pharmacological interaction and anti-inflammatory profile in hyperresponsive airways. Pharmacol Res. 2021;172:105801.
11. Martínez-García MÁ. Bronchodilators in bronchiectasis: we urgently need more trials. Lung. 2023;201:5–7.
12. Aogáin MM, Jaggi TK, Chotirmall SH. The airway microbiome: present and future applications. Arch Bronconeumol. 2022;58:8–10.
13. Martínez-García MÁ. Bronchiectasis and eosinophils. Arch Bronconeumol. 2021;57:671–2.
14. Navas-Bueno B, Casas-Maldonado F, Padilla-Galo A, González-Moya-Mondelo E, Arenas-Gordillo M, Bioque-Rivera JC, et al. High adherence, microbiological control and reduced exacerbations in patients with non-cystic fibrosis bronchiectasis treated with nebulised colistin. A prospective observational study. Arch Bronconeumol. 2022;58:834–6.

Mario Cazzola [a,*], Maria Gabriella Matera [b], Miguel Ángel Martínez-García [c,d]
[a] *Unit of Respiratory Medicine, Department of Experimental Medicine, University of Rome 'Tor Vergata', Rome, Italy*
[b] *Unit of Pharmacology, Department of Experimental Medicine, University of Campania 'Luigi Vanvitelli', Naples, Italy*
[c] *Respiratory Department, Polytechnic and University La Fe Hospital, Valencia, Spain*
[d] *CIBERES de Enfermedades Respiratorias, Madrid, Spain*

[*] Corresponding author.
E-mail address: mario.cazzola@uniroma2.it (M. Cazzola).