



Editorial

Present and Future of Biological Treatments in Bronchiectasis

Presente y futuro de los tratamientos biológicos en las bronquiectasias



Contrary to historical conceptions, bronchiectasis in adults is now defined as a permanent and irreversible dilation of the bronchi, in which chronic inflammation and infection play a central and interconnected role. It is increasingly evident that inflammation is a necessary condition for the development of bronchiectasis. This inflammatory response is typically mixed in nature and involves neutrophils, eosinophils, and lymphocytes in varying proportions. While neutrophils are usually predominant, both eosinophils and lymphocytes, despite being present in lower numbers, are known to participate actively in the pathophysiology of the disease, although the precise extent of their contribution remains to be fully elucidated.¹ A hallmark of bronchiectasis is the substantial impairment of local defense mechanisms, particularly the mucociliary clearance system. This dysfunction renders the host susceptible to recurrent and often chronic bronchial infections by pathogenic bacteria. Among these pathogens, *Pseudomonas aeruginosa* is particularly feared, as its presence is associated with worse clinical outcomes and a more rapid disease progression, especially in patients with diverse comorbidities.² The presence of such pathogens exacerbates local inflammation, further undermining bronchial integrity and perpetuating a self-reinforcing cycle of inflammation and infection. Without effective intervention, this cycle inevitably leads to disease progression.³

Current treatment strategies for bronchiectasis, encompassing both pharmacological and non-pharmacological approaches, rest upon 3 fundamental pillars: inflammation (addressed primarily through anti-inflammatory agents); infection (treated with antibiotics); and the management of excessive bronchial secretions (via respiratory physiotherapy and muco-active agents).^{4,5} Macrolides have demonstrated both anti-inflammatory and antibacterial properties.⁶ Furthermore, accumulating clinical experience suggests benefit particularly with the use of inhaled antibiotics and certain long-term mucolytic agents, which have been associated with a reduction in both the frequency and severity of exacerbations. However, there is a lack of formal indication and robust evidence supporting the widespread use of many other pharmacological agents,^{7,8} and the overuse of inhaled corticosteroids, in particular, remains a significant issue. This practice persists despite clear recommendations from international guidelines cautioning against their routine use in bronchiectasis due to the associated adverse effects and limited efficacy outside specific indications.^{4,5}

In recent years, biological therapies—monoclonal antibodies designed to target specific elements of the inflamma-

tory cascade—have revolutionized the management of severe eosinophilic asthma, especially in patients who require high-dose systemic corticosteroids to achieve disease control. These biologics act at various points along the type 2 (Th2) inflammatory pathway, targeting key mediators such as eosinophils, immunoglobulin E, interleukin-5 (IL-5), IL-5 receptor (IL-5R), IL-4, and IL-13.⁸ Six biologics are currently commercially available for asthma: benralizumab, dupilumab, mepolizumab, reslizumab, omalizumab, and tezepelumab.⁸ Notably, tezepelumab, a human monoclonal IgG2 λ antibody that blocks thymic stromal lymphopoietin (TSLP), stands out as the only product that does not require a Th2-skewed inflammatory profile for clinical efficacy.⁹ Other agents are also in development (www.clinicaltrials.gov).

Understanding the potential role of these agents in bronchiectasis requires careful consideration of both current and emerging clinical scenarios. Biologics are now used in patients with asthma who also present with bronchiectasis. It is worth noting that 20–25% of patients with severe asthma eligible for biological treatment are found to have concomitant bronchiectasis that is sometimes clinically active and associated with chronic bacterial infection.¹⁰ In such patients, the presence of bronchiectasis does not appear to diminish the therapeutic efficacy of biologics in managing asthma, nor does it seem to exacerbate chronic bacterial infections. This contrasts with corticosteroid therapy, which is known to compromise immune function and worsen infectious complications. The apparent safety of biologics in this setting may be attributed to several mechanisms: a marked reduction in bronchial inflammation (thereby facilitating the restoration of local immune defenses); the dissolution of mucus plugs that serve as bacterial reservoirs; and the immunomodulatory (rather than immunosuppressive) properties of these agents. Together, these effects may preserve critical components of the host immune response to infection.¹¹

Beyond their established indications in asthma, allergic bronchopulmonary aspergillosis, and chronic rhinosinusitis with nasal polyposis, conditions that frequently coexist with bronchiectasis, no other scenarios currently warrant the routine use of biologics in the management of bronchiectasis.¹² Nevertheless, several promising avenues merit further exploration.

One such emerging concept is that of “eosinophilic bronchiectasis”, a potential endotype marked by the ostensible absence of asthma, but the presence of peripheral blood eosinophilia (≥ 300 eosinophils/ μ L in peripheral blood), a potential surrogate

marker for eosinophilic inflammation in the airways.^{13,14} Preliminary studies have demonstrated that patients with this profile may benefit from inhaled corticosteroids,¹⁴ with reductions observed in both the frequency and severity of exacerbations. This phenotype provides a theoretical basis for the future use of biologics targeting eosinophilic inflammation, particularly in patients who either do not respond to corticosteroids or require doses that carry an unacceptable risk of adverse effects. Notably, the MAHALE trial (NCT05006573), a randomized clinical study currently in the recruitment phase, aims to evaluate the efficacy of benralizumab in non-asthmatic patients with bronchiectasis and a Th2 inflammatory profile. The outcomes of this study may significantly broaden the therapeutic landscape of bronchiectasis, particularly in identifying subpopulations who might benefit from biological therapy.

Another future consideration involves the potential extrapolation of biologic efficacy from evidence extracted from other chronic inflammatory diseases. For instance, biologics used to manage autoimmune conditions such as rheumatoid arthritis or inflammatory bowel disease—both of which may be associated with bronchiectasis—could influence the course of bronchiectasis, although systematic studies on this subject are currently lacking.^{15,16}

Additionally, indirect evidence suggests a potential role for biologics in neutrophilic airway diseases, such as chronic obstructive pulmonary disease (COPD). Recent clinical trials have shown that both mepolizumab and dupilumab can reduce exacerbation rates by 21–34% in patients with COPD, a condition that, like bronchiectasis, is associated with a predominance of neutrophilic inflammation. These findings raise the possibility of similar benefits in bronchiectasis.^{17,18}

Finally, among the currently available biologics, tezepelumab is particularly promising for future use in bronchiectasis. TSLP, its molecular target, is implicated not only in type 2 inflammation but also in mucus hypersecretion and airway remodeling. By reducing mucus plugs and infectious exacerbations, both hallmarks of bronchiectasis, tezepelumab offers a potentially unique advantage, especially since its efficacy does not depend on the presence of a Th2-high phenotype.⁹

In conclusion, controlling neutrophilic inflammation, which characterizes both COPD and bronchiectasis, remains significantly more challenging than managing the eosinophilic inflammation of asthma. Nevertheless, eosinophils clearly play a contributory role in the pathogenesis and progression of certain bronchiectasis phenotypes. Novel therapies targeting neutrophilic inflammation are now emerging. For example, brexobacatib,¹⁹ a potent non-steroidal anti-inflammatory agent currently in phase III trials, has shown promise by inhibiting neutrophil elastase and other proinflammatory mediators. Although it is not classified as a biologic, its mechanism of action reflects a broader trend toward the precision targeting of airway inflammation.

Looking ahead, the development of anti-neutrophilic biologics specifically designed for bronchiectasis cannot be ruled out. Precision medicine has made rapid strides in the management of asthma, and it is anticipated that similar progress will eventually be achieved in bronchiectasis, although this will require continued research, patience, and innovation.

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