



Editorial

Bronchiectasis and Eosinophils

Bronquiectasias y eosinófilos

Bronchiectasis not due to cystic fibrosis (hereafter bronchiectasis) is a heterogeneous and complex disease, not only from a clinical perspective but also from an etiological, pathophysiological, prognostic and therapeutic viewpoint.^{1–3} This complexity is derived, at least in part, from the fact that what we now call bronchiectasis is a form of pulmonary involvement caused by more than 150 pulmonary and extra-pulmonary diseases with very different characteristics.⁴

It is commonly accepted that bronchiectasis is characterized by a chronic airway inflammation, usually caused by a bronchial infection (most often bacterial), and that both these two processes feed on each other over time, creating a pathogenic vicious circle that determines the evolution of the disease. The bronchial inflammation is usually markedly neutrophilic, except in cases where the predominant cell type is monocytic or eosinophilic, as a result of the underlying disease or associated comorbidities (e.g., asthma, various systemic diseases, allergic bronchopulmonary aspergillosis, certain types of infection and pulmonary eosinophilia).⁵

It has been observed, however, that, even beyond this spectrum of diseases, up to a third of bronchiectasis patients may present an increase in the number or percentage of eosinophils in both respiratory mucosae and peripheral blood samples, and this may even be the predominant inflammatory pattern in some cases.⁵ Several authors have observed that these eosinophils are biologically activated by the increase in the concentration of some of their proteolytic products, such as ECP (eosinophil cationic protein), which has been shown to have a bactericidal capacity.⁶

It is not yet known what value eosinophils (in the form of either eosinophilia or eosinopenia) may have as a clinical, diagnostic, prognostic or therapeutic (response to treatment) biomarker in bronchiectasis as has been postulated in chronic obstructive pulmonary disease (COPD).⁷ Nevertheless, the scientific literature offers some clues that surely deserve to be investigated in greater depth in the future.

Wang et al.⁸ recently showed in an observational study including 906 patients from the Spanish bronchiectasis registry (RIBRON)⁹ that those subjects with more than 100 peripheral eosinophils/ μL (70%) had milder severity of bronchiectasis, significantly better clinical outcomes, nutritional status and lung function and lower systemic inflammation suggesting that peripheral eosinophil count could be a good biomarker of severity of bronchiectasis.

On the other hand, according to some authors and international guidelines, inhaled corticosteroids (ICs) are not indicated in the treatment of bronchiectasis, due to their marked immunosuppressive nature, except in very specific cases (especially when associated with asthma).^{10–15} ICs could increase the risk of exacerbations or bronchial infections, even though more than 60% of patients with bronchiectasis use them.¹⁶ Some authors have observed, however, that (as in the case of COPD patients^{17–20} the use of this treatment in bronchiectasis could reduce the number of exacerbations (a key prognostic factor in both COPD^{21–23}) and bronchiectasis^{24–26}), or improve some clinical aspects in the subgroup of individuals with peripheral eosinophilia.^{27–29}

In a pooled post hoc analysis of two randomized clinical trials, Martínez-García et al. observed in 93 bronchiectasis patients (after excluding those with COPD and asthma) that 42% and 23.6% presented a stable percentage of peripheral eosinophils ($\geq 3\%$ and $\geq 4\%$, respectively) for at least 6 months.²⁷ These patients did not present distinct baseline characteristics but both the number and severity of their exacerbations were significantly reduced after treatment with ICs (although ICs did not modify the percentage of peripheral eosinophils).²⁸ This finding is of enormous interest, given that both the number and severity of exacerbations have been shown to affect the prognosis of the disease and have constituted a main outcome in randomized clinical trials on bronchiectasis.

Similarly, Aliberti et al. observed that treatment for 6 months with fluticasone propionate improved the quality of life in 86 patients with bronchiectasis without asthma or concomitant COPD, but only in those with at least 3% (≥ 150 cells/ μL) of peripheral eosinophils.²⁹ This effect could vary, however, from one corticosteroid to another.³⁰

Although the evidence accumulated both *in vivo* and *in vitro* on the role of bronchial and peripheral eosinophils in bronchiectasis is still very scarce and is based on observations of COPD patients, it raises many questions that need to be studied in the future.

Is the presence of eosinophilia in bronchiectasis a good clinical, diagnostic or prognostic biomarker? Is “eosinophilic” bronchiectasis a different endo-phenotype? Is eosinophilia in bronchiectasis a marker of a good response to treatment with ICs, even in the absence of asthma? Is peripheral eosinophilia a good indicator of bronchial eosinophilia in bronchiectasis? Is the number of peripheral eosinophils stable over time in bronchiectasis? Do bronchiectasis patients with eosinophilia or eosinopenia present a

greater or lesser risk of infection or exacerbations compared to the rest? What is the number or percentage of eosinophils that marks a pathological situation in bronchiectasis? Could some biological treatments be effective in patients with asthma and eosinophilia or, in other words, is eosinophilia a treatable trait in bronchiectasis?

These and many more questions have emerged from the relationship between bronchiectasis and eosinophilia, which is encouraging as the clinical-therapeutic implications could be substantial. So far, some pilot studies have observed a positive effect from biological treatments such as mepolizumab³¹ or benralizumab³² in patients with clinically relevant severe bronchiectasis (especially when associated with multiple exacerbations) and eosinophilia with both concomitant and non-concomitant asthma, with a reduction in peripheral eosinophils accompanied by a clinical and functional improvement in the quality of life.

Once again, reality insists on showing us that the picture is much more complex than it seems at first sight. There are very few absolute paradigms or pathognomonic concepts in medicine. Although it was once thought that neutrophilic inflammation was universal in bronchiectasis (when not associated with asthma), this does not seem to be the case, and it is highly probable that eosinophils may play a role – a role that may be very important in some patients with bronchiectasis, as has proven to be the case also in individuals with COPD. Identifying this special endo-phenotype of “eosinophilic bronchiectasis” seems crucial, as there are various treatments on the market with a great capacity to inhibit eosinophilic inflammation (eosinophils as a treatable trait), so discovering their risk-benefit in patients with bronchiectasis should certainly be investigated.

Conflict of interest

No conflict of interest or other disclosure to declare.

References

- Martínez-García MA, Agustí A. Heterogeneity and complexity in bronchiectasis: a pending challenge. *Arch Bronconeumol*. 2019;55:187–8.
- Martínez-García MA, Oliveira C, Máiz L, Girón RM, Prados C, de la Rosa D, et al. Bronchiectasis: a complex, heterogeneous disease. *Arch Bronconeumol*. 2019;55:427–33.
- Martínez-García MA, Perpiña M, Soler JJ, Roman P, Lloris A, Gonzalez A. Dissociation of lung function, dyspnea ratings and pulmonary extension in bronchiectasis. *Respir Med*. 2007;101:2248–53.
- Oliveira C, Padilla A, Martínez-García MA, de la Rosa D, Giron R, Vendrell M, et al. Etiology of bronchiectasis in a cohort of 2047 patients. An analysis of the Spanish Historical Bronchiectasis Registry. *Arch Bronconeumol*. 2017;53:366–74.
- Fuschillo S, de Felice A, Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. *Eur Respir J*. 2008;31:396–406.
- Lehrer RI, Szklarek D, Barton A, Ganz T, Hamann KJ, Gleich GJ. Antibacterial properties of eosinophil major basic protein and eosinophil cationic protein. *J Immunol*. 1989;142:4428–34.
- Golpe R, Dacal D, Sanjuán-López P, Martín-Robles I, Pérez-de-Llano L. Plasma eosinophil count and patient-centered events in chronic obstructive pulmonary disease in real-life clinical practice. *Arch Bronconeumol*. 2020;56:129–30.
- Wang X, Villa C, Dogarbanes Y, Oliveira C, Giron R, Garcia-Clemente M, et al. Phenotypic clustering in non-cystic fibrosis bronchiectasis patients: the role of eosinophils in disease severity. *Int J Environ Res Public Health*. 2021;18:8431. <http://dx.doi.org/10.3390/ijerph18168431>.
- Martínez-García MA, Villa C, Dogarbanes Y, Giron R, Maiz L, Garcia-Clemente M, et al. RIBRON: The Spanish Online Bronchiectasis Registry. Characterization of the first 1912 patients. *Arch Bronconeumol*. 2021;57:28–35.
- Martínez-García MA, de la Rosa D, Cantón R, Oliveira C, Máiz-Carro L, Girón R, et al. Bronchiectasis: when the published scientific evidence proves insufficient. *Arch Bronconeumol*. 2019;55:283–5.
- Redondo M, Chalmers JD. Bronchiectasis guidelines – recommendations into practice. *Arch Bronconeumol*. 2019;55:286–8.
- Martínez-García MA, Maiz L, Oliveira C, Giron RM, de la Rosa D, Blanco M, et al. Spanish guidelines on treatment of bronchiectasis in adults. *Arch Bronconeumol*. 2018;54:88–98.
- Martínez-García MÁ, Máiz L, Oliveira C, Girón RM, de la Rosa D, Blanco M, et al. Spanish guidelines on the evaluation and diagnosis of bronchiectasis in adults. *Arch Bronconeumol*. 2018;54:79–87.
- Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebing M, et al. European Respiratory Society Guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50:1700629. <http://dx.doi.org/10.1183/13993003.00629-2017>.
- de la Rosa Carrillo D, López-Campos JL, Alcázar B, Calle M, Cantón R, García-Rivero JL, et al. Consensus document on the diagnosis and treatment of chronic bronchial infection in chronic obstructive pulmonary disease. *Arch Bronconeumol*. 2020;56:651–64.
- Henkle E, Curtis JR, Chen L, Chan B, Aksamit TR, Daley CL, et al. Comparative risks of chronic inhaled corticosteroids and macrolides for bronchiectasis. *Eur Respir J*. 2019;54.
- López-Campos JL, Soler-Cataluña JJ, Miravittles M. Global strategy for the diagnosis management, and prevention of chronic obstructive lung disease 2019 report: future challenges. *Arch Bronconeumol*. 2020;56:65–7.
- Díaz López JM, Giron B, Alcázar B. Personalized medicine in chronic obstructive pulmonary disease: how close are we? *Arch Bronconeumol*. 2020;56:420–1.
- Iribarren M, Alonso T, Soriano JB, Ancochea J. Adjusting the level of intervention in patients with chronic obstructive pulmonary disease according to the risk stratification proposed by the Spanish COPD Guidelines (GesEPOC) Version 2017. *Arch Bronconeumol*. 2020;56:183–5.
- Gea J, Pascual S, Castro-Acosta A, Hernández-Carcereny C, Castelo R, Márquez-Martín E, et al. The BIOMEPOC Project: personalized biomarkers and clinical profiles in chronic obstructive pulmonary disease. *Arch Bronconeumol*. 2019;55:93–9.
- Kim J, Lee CH, Lee MG, Shin KC, Yoo KH, Lim S, et al. Acute exacerbation according to GOLD 2017 categories in patients with chronic obstructive pulmonary disease. *Arch Bronconeumol*. 2019;55:414–20.
- Navarrete B, Ancochea J, García-Río F, Izquierdo JL, Miravittles M, Rodríguez González-Moro JM. Patients with chronic obstructive pulmonary disease exacerbations: recommendations for diagnosis treatment and care. *Arch Bronconeumol*. 2019;55:478–87.
- Padilla A, Oliveira C. Bronchiectasis in COPD and asthma more than just a coincidence. *Arch Bronconeumol*. 2019;55:181–2.
- Martínez-García MA, Athanazio R, Gramblicka G, Corso M, Cavalcanti-Lundgren F, Fernandes de Figueiredo M, et al. Prognostic value of frequent exacerbations in bronchiectasis: the relationship with disease severity. *Arch Bronconeumol*. 2019;55:81–7.
- Posadas T, Oscullo G, Zaldivar E, Villa C, Dogarbanes Y, Giron R, et al. C-reactive protein concentration in steady-state bronchiectasis: prognostic value of future severe exacerbations. data from the Spanish Registry of Bronchiectasis (RIBRON). *Arch Bronconeumol*. 2021;57:21–7.
- Chen CL, Huang Y, Yuan JJ, Li HM, Han XR, Martínez-García MA, et al. The roles of bacteria and viruses in bronchiectasis exacerbation: a prospective study. *Arch Bronconeumol*. 2020;56:621–9.
- Martínez-García MA, Posadas T, Sotgiu G, Blasi F, Saderi L, Aliberti S. Repetability of circulating eosinophil measures and inhaled corticosteroids effect in bronchiectasis. A post hoc analysis of a randomized clinical trial. *Arch Bronconeumol*. 2020;56:681–3.
- Martínez-García MA, Posadas T, Sotgiu G, Blasi F, Saderi L, Aliberti S. Role of inhaled corticosteroids in reducing exacerbations in bronchiectasis patients with blood eosinophilia: pooled post-hoc analysis of 2 randomized clinical trials. *Respir Med*. 2020;172:106127.
- Aliberti S, Sotgiu G, Blasi F, Saderi L, Posadas T, Martínez-García MA. Blood eosinophils predict inhaled fluticasone response in bronchiectasis. *Eur Respir J*. 2020;56:2000453.
- Aliberti S, Sotgiu G, Martínez-García MA. Blood eosinophils do not predict inhaled budesonide response in bronchiectasis. *Eur Respir J*. 2020;56:2002210. <http://dx.doi.org/10.1183/13993003.02210-2020>.
- Carpagnano GE, Scioscia G, Lacedonia D, Curradi G, Foschino Barbaro MP. Severe uncontrolled asthma with bronchiectasis: a pilot study of an emerging phenotype that responds to mepolizumab. *J Asthma Allergy*. 2019;12:83–90.
- Rademacher J, Konwert S, Fuge J, Dettmer S, Welte T, Ringshausen FC. Anti-IL5 and anti-IL5R α therapy for clinically significant bronchiectasis with eosinophilic endotype: a case series. *Eur Respir J*. 2020;55.

Miguel Ángel Martínez-García
 Servicio de Neumología, Hospital Universitario y Politécnico la Fe de
 Valencia, Spain
 E-mail address: mianmartinezgarcia@gmail.com