CHEST

Eosinophils in Bronchiectasis

A U-Turn for Bronchiectasis Management

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Neutrophils have historically been branded "the bad guys of bronchiectasis" as much research has shown them to dominate bronchiectatic airways as key players in the chronic inflammation driving the development, progression, and severity of disease. However, in recent years, it has become clear that bronchiectasis is not a "neutrophils only" game.

Eosinophils, innate granulocytic cells from the same precursor cells as neutrophils, have arisen as the inflammatory underdogs of bronchiectasis. This comes following evidence that approximately 20% of patients with bronchiectasis have a blood eosinophil count (BEC) $\geq$ 300 cells/μL, despite the absence of classical eosinophil-driven conditions including asthma and allergic bronchopulmonary aspergillosis.[1] This finding marked a new endotype of disease that has since been termed "eosinophilic bronchiectasis" (Fig 1).

BECs have been validated as a surrogate marker for eosinophilic airway inflammation in bronchiectasis, and an elevated BEC has been identified as a risk factor for exacerbation after adjustment for infection status.[1] Eosinophilic disease has also been associated with bronchiectasis severity, impaired lung function, and reduced quality of life.[2] Furthermore, previous work investigating the relationship between eosinophilic airway inflammation and bronchiectasis disease severity shows an association between eosinophil granule proteins (specifically, eosinophil peroxidase) and increased severity,[3] further highlighting a pathogenic role for eosinophils in bronchiectasis.

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In this issue of *CHEST*, Martínez-García et al[4] corroborate these previous findings through their own investigation into the relationship between eosinophilic inflammation and bronchiectasis severity, using data collected via the Spanish Bronchiectasis Registry. Here, the authors use different BEC cutoff values to determine the impact of eosinophils in bronchiectasis and further report an association between eosinophilia (defined as $>$ 300 cells/μL) and bronchiectasis severity, with the highest percentage of exacerbating patients also being eosinophilic. Given the mounting evidence, blood eosinophils likely represent a treatable trait in bronchiectasis; as such, the potential for anti-eosinophil therapies, including inhaled corticosteroids (ICS) and anti-IL-5/anti-IL-5 receptor biologics, as a treatment for eosinophilic bronchiectasis is in question.

BECs are reported to represent a predictive biomarker of response to ICS in bronchiectasis.[5] As such, off-label use of ICS and other anti-eosinophil therapies in bronchiectasis has been observed. Nonetheless, studies assessing the clinical efficacy of ICS in bronchiectasis are limited and largely report increased morbidity and mortality among participants who used ICS.[6] ICS use is also frequently associated with negative side effects, which include an increased risk of non-TB mycobacterial infections.[7] As such, current treatment guidelines recommend against the use of ICS in those patients with bronchiectasis.[8] However, these findings originate from heterogeneous bronchiectasis cohorts without stratification based on BEC. A post hoc analysis of two randomized clinical trials investigating the efficacy of ICS in bronchiectasis reports a significant reduction in exacerbations and hospitalizations among those with documented eosinophilia who used ICS, while participants without eosinophilia who used ICS show negative outcomes at 6-month follow-up.[9] Significant improvements in quality of life were also observed among participants with eosinophilia who used ICS.[5] Martínez-García et al[4] further advocate for the use

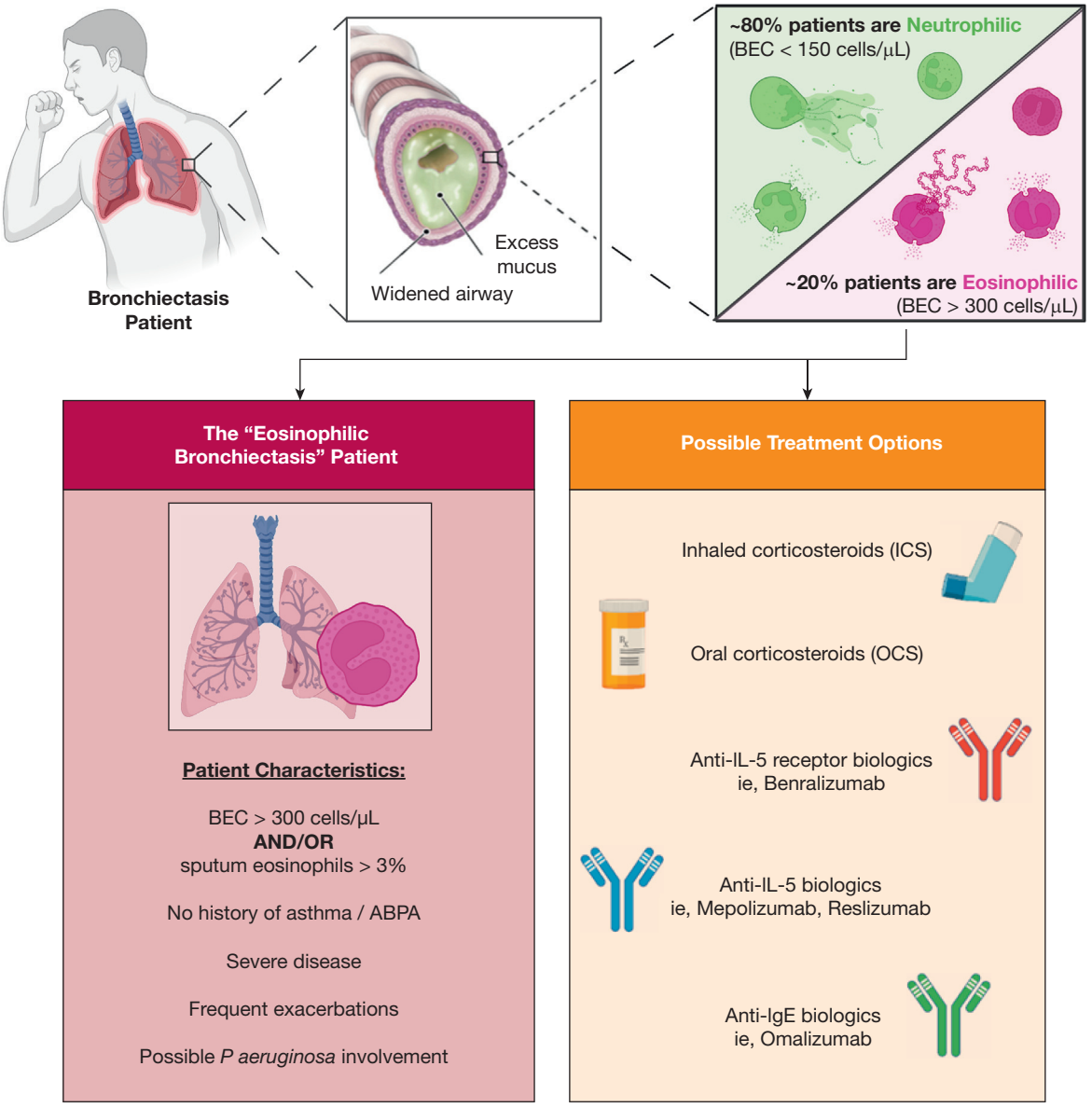

Figure 1 – *Our current understanding of the patient with eosinophilic bronchiectasis and possible treatment options for this disease subset. ABPA = allergic bronchopulmonary aspergillosis; BEC = blood eosinophil count.*

of ICS in eosinophilic bronchiectasis, reporting reduced exacerbations and hospitalizations among eosinophilic participants who used ICS while those with low/normal BECs who used ICS saw no clinical benefit. Together, these data stress the need for new randomized clinical trials investigating ICS use in eosinophilic bronchiectasis specifically, and the importance of the use of BECs as a biomarker of ICS response to avoid ICS use in patients for whom ICS may be deleterious.

In addition, no randomized trials investigating the efficacy of anti-IL-5 (eg, mepolizumab and reslizumab) or anti-IL-5 receptor therapies (eg, benralizumab) in bronchiectasis have been conducted. However, case series and smaller trials in severe asthma with concomitant bronchiectasis show a positive effect of anti-IL-5 and anti-IL-5 receptor therapy.[2,10] In addition, a recent case series investigating the effect of both mepolizumab and benralizumab in patients with a primary diagnosis of bronchiectasis with eosinophilia also reports significant improvements in lung function, symptoms, exacerbation frequency, and quality of life after 6 months of biologic therapy.[11]

Interestingly, in line with previous findings,[1] Martínez-García et al[4] also report that those patients with eosinopenia (defined as < 50 cells/μL) experienced the

greatest levels of disease severity across all study groups, somewhat hinting a partially protective role of eosinophils in bronchiectasis. This is an important observation, given the current efforts to secure eosinophil-depleting therapies for the treatment of bronchiectasis. However, although a protective role for eosinophils is not implausible given their antimicrobial and antiinflammatory capabilities,[12] it is unlikely that the increased severity observed among eosinopenic patients is the direct result of a loss of eosinophil-mediated lung protection. Similar concerns have been raised in severe asthma, however, many studies report no adverse events or increased risk of infection following complete eosinophil depletion by benralizumab.[13]

In general, an increase in severity with eosinopenia can be explained by marked neutrophilia. Strikingly, Martínez-García et al[4] report no difference in neutrophil levels between those patients with eosinophilia and those with eosinopenia. The lung microbiome, particularly when dominated by *Pseudomonas* and/or *Haemophilus*, is linked to bronchiectasis severity[14]; therefore, differences in the microbiome may account for these findings. There is currently a lack of research aiming to determine the link between the lung microbiome and airway inflammatory profiles in bronchiectasis, particularly in the context of eosinophilic inflammation. Chronic *P aeruginosa* infection is common in bronchiectasis and is known to drive an extensive neutrophilic response; however, elevated Th2/eosinophilic inflammatory responses have also been observed.[1,15] Along with reports that *P aeruginosa* directly drives Th2 inflammation,[16] *P aeruginosa* infection may explain the source of eosinophilia in those with bronchiectasis. Here, Martínez-García et al[4] further hint at a role for *Pseudomonas* in eosinophilic bronchiectasis; as such, these findings require further investigation.

The work by Martínez-García et al,[4] in which a U-shaped relationship between eosinophil count and bronchiectasis severity was seen, has added to our clinical understanding of eosinophilic bronchiectasis. Bronchiectasis is no longer considered a solely neutrophil-driven disease, and a U-turn in the way we manage bronchiectasis is necessary. However, much is yet to be understood about the phenomenon that is eosinophilic bronchiectasis and whether therapies that are currently frowned upon are a perfect fit for this clinically meaningful subset of patients.

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