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Severe asthma phenotyping: does the definition of different phenotypes matter?

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Phenotyping severe asthma is a key component of asthma management, not only because of its pathobiological complexity and clinical heterogeneity, but also because of high costs of biologic treatment. Although severe asthma is uncommon, with an estimated prevalence between < 1%[1] and 3.7%[2] among all asthma patients, it is responsible for a major part of the disease burden. In Brazil, it has been shown that severe asthma is accountable for very high costs to families and to the Brazilian Unified Health Care System. [3]

The recently published Brazilian Thoracic Association "Recommendations for the Management of Severe Asthma"[4] adopted the 2014 International European Respiratory Society/American Thoracic Society definition of severe asthma.[5] Accordingly, severe asthma is defined as that confirmed by an objective method, with good patient adherence to treatment, and which, despite the elimination or minimization of factors associated with lack of disease control, requires high doses of inhaled corticosteroids (fluticasone propionate ≥ 1,000 µg or equivalent) associated with a second controller drug (a long-acting β_2 agonist and/or a long-acting muscarinic antagonists and/or an antileukotriene) or oral corticosteroids ≥ 50% of the days in the previous year in order to try to maintain disease control. The Global Initiative for Asthma (GINA)[6] defines severe asthma in a similar way, except for the dose of inhaled corticosteroids (fluticasone propionate > 500 µg or equivalent). The adoption of one of the definitions is relevant because the GINA's definition includes patients regarded by others as having moderate asthma.

In this issue of the *Jornal Brasileiro de Pneumologia*, Athanazio et al.[7] report the results of large (n = 385) cross-sectional multicenter study (designated the BRAEOS study) on phenotyping severe asthma. The authors used both prospective (blood sample and questionnaires of asthma control and quality of life) and retrospective data. The primary outcome was the prevalence of eosinophilic and allergic phenotypes. Inclusion criteria were having severe asthma as defined by the GINA for at least one year. Patients were excluded if they were current/former smokers (≥ 10 pack-years), had had a moderate/severe asthma exacerbation or any changes in their treatment within the past four weeks. Other exclusion criteria were treatment with biologics within the last three months (except omalizumab) and the presence of other lung diseases. Eosinophilic phenotype was defined by the presence of blood eosinophils ≥ 300 cells/mm^3. Allergic phenotype was defined as a combination of serum IgE > 100 UI/mL and history of allergy (clinically documented by history of respiratory allergy or atopy (positive specific IgE or skin prick test for aeroallergens). Late-onset asthma was defined as the onset of asthma symptoms by the age of ≥12 years. Point prevalence of eosinophilic asthma (primary outcome) was 40.0%. Additionally, 73.2% of the subjects had atopy (history of allergy confirmed by specific IgE or skin prick test).

We congratulate the authors of the BRAEOS study [7] for producing relevant data and providing insights on severe asthma across Brazil. But, has this large study provided us with definitive answers on the prevalence of severe eosinophilic asthma? One question that arises at first is the definition of severe asthma used in the study. It could be argued that a cutoff point > 500 µg/day of fluticasone propionate might have allowed the inclusion of less severe asthma patients in the study population and, therefore, had an influence on the data. However, the results of the study by Athanazio et al.[7] showed that most subjects were on higher doses of inhaled corticosteroids, and this is reassuring.

How about the definition of eosinophilic phenotype? It is undisputable that induced sputum cell count is the gold standard method to phenotype eosinophilic asthma. Yet, because it is perceived as a difficult method to perform, induced sputum is available only in a few asthma research centers. Currently, severe asthma phenotypes are based on the ease of accessible biomarkers aiming at introducing biologic treatment. In this regard, peripheral blood eosinophil count is an asset. The cutoff point for the eosinophilic phenotype, nonetheless, varies according to the biologic drug under study. In the BRAEOS study,[7] the authors chose the cutoff point of > 300 eosinophils/mm^3 to define eosinophilic asthma, which occurred in 40% of subjects. However, the eosinophilic phenotype raised to 70% when the cutoff point > 150 eosinophils/mm^3 was tested. These results illustrate the lack of agreement on what the eosinophilic phenotype is when measured by peripheral blood cell counts.

Having said that, could the BRAEOS study [7] underestimate the prevalence of eosinophilic asthma in our country for other reasons? Possibly. It is well known that peripheral blood eosinophil count suffers the influence of various factors, including the dose of inhaled and oral corticosteroids, diurnal variation, recent respiratory or systemic infections, etc. Therefore, a single blood cell count does not exclude blood eosinophilia. Hence, the Brazilian Thoracic Society[4] and the GINA[6] recommendations suggest that the exclusion of eosinophilic phenotype requires up to three blood eosinophil counts on different occasions. If necessary, corticosteroid treatment should be carefully tapered down to allow blood eosinophils to

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resurface. Although the BRAEOS study [7] excluded patients with a recent history of respiratory infection, the study used a single measurement of blood eosinophils. This might also explain the low prevalence of the eosinophilic phenotype reported.

Another key finding from the BRAEOS study,[7] in keeping with current knowledge was that most of the subjects had atopy. Surprisingly, only 31.9% of those with a history of allergy had blood eosinophilia. This paradox is rather unsettling and it is not supported by the current knowledge of allergic asthma pathophysiology, a T2-high disease driven by IgE, IL-4, IL-5, eosinophils, basophils and mast cells.[8] Thus, biological plausibility suggests that allergic asthma is an eosinophilic disease, which makes us question again the low prevalence of the eosinophilic phenotype reported in the BRAEOS study.[7]

Finally, in the BRAEOS study,[7] nearly half of the subjects had late-onset asthma, defined as the onset of asthma symptoms in subjects ≥ 12 years of age. Although the cutoff point to define late-onset asthma is far from settled, varying from 12 to 65 years of age in different studies,[9] we argue that individuals who are 12 years old are children. Perhaps a better way to tackle this issue is to adopt a more rational classification of late-onset asthma by the cutoff points proposed in a recent multi-database cohort study.[10] In that study, Baan et al.[10] based the characterization of asthma on the age of the first diagnosis of the disease as documented by the treating physician on a database, classifying the participants as having either childhood-onset asthma (asthma diagnosis before 18 years of age), adult-onset asthma (asthma diagnosis between 18 and 40 years of age) or late-onset asthma (asthma diagnosis ≥ 40 years of age).

In conclusion, regardless of the points raised herein, the BRAEOS study[7] is the first to evaluate the phenotype of a large group of subjects with severe asthma in Brazil. The study shows the challenges of phenotyping severe asthma with the current definitions of a complex, uncommon, and heterogeneous subgroup of the asthma. Similar large-scale studies, with detailed longitudinal information on asthma phenotypes and repeated blood eosinophil measurements, would be ideal to build further evidence in Brazil. As the authors have pointed out, understanding the inflammatory profile of our patients with severe asthma is essential for specific target treatment and development of local public health policy strategies.

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