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Editorial

# Personalized Medicine in Severe Asthma: Bridging the Gaps

## Medicina personalizada en el asma grave: Salvando las distancias

Asthma, a heterogeneous disease affecting 262 million people globally, presents significant challenges due to its high morbidity and mortality.[1] Among these, severe asthma affects 6–10% of patients, who often experience uncontrolled symptoms despite intensive treatment with inhaled corticosteroids, long-acting beta-agonists, and other medications.[2] The classification of asthma has evolved from Rackemann's classical differentiation between extrinsic and intrinsic asthma to include various phenotypes based on clinical and histological characteristics, as well as endotypes related to specific molecular mechanisms.[3]

Severe asthma is now understood through the lens of T2 inflammation, mediated by IgE, IL-4, IL-5 and IL-13, with Th2 cells, eosinophils and innate lymphoid cell type II (ILC2) as the main effector cells. Identifying these phenotypes is crucial for implementing personalized medicine, particularly with the advent of biological drugs targeting specific pheno-endotypes. However, these phenotypes often overlap, complicating treatment.[4]

This editorial explores the role of personalized medicine in treating severe allergic and eosinophilic asthma, focusing on the need for better biomarkers and the inclusion of additional variables such as comorbidities, age of onset, and prior biologic response. Knowledge of the underlying immunology has led to the development of six biological treatments for severe asthma: omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5), benralizumab (anti-IL5R), dupilumab (anti-IL4R), and tezepelumab (anti-TSLP).[5] Despite these options, many patients remain uncontrolled.[6]

Allergic asthma represents 40–50% of severe asthma and has an atopic basis, orchestrated by the activation of T-helper type 2 (Th2) cells, the production of interleukin (IL) 4, IL-5 and IL-13 and the isotype shift in B-lymphocytes towards the production of IgE.[7] It is often accompanied by rhinoconjunctivitis and atopic dermatitis. Early-onset allergic asthma, occurring before age 12, is more likely to persist into adulthood, especially with sensitization to perennial aeroallergens. Key biomarkers include positive skin prick or specific IgE tests, elevated Th2 cytokines, sputum eosinophils, and FeNO levels.[8]

Nonallergic eosinophilic asthma, often presenting in adulthood, involves eosinophilic inflammation driven by IL-5, IL-13, and TSLP without classical TH2-mediated allergy.[9] This phenotype is characterized by chronic airway inflammation, severe airflow obstruction, frequent exacerbations, and poor corticosteroid response.[10] Biomarkers include peripheral blood eosinophils, sputum eosinophils, IL-5 levels, eosinophil cationic protein, and FeNO.[9]

A significant portion of severe asthma patients exhibit both allergic and eosinophilic characteristics, complicating treatment. Studies show that 22–56% of severe asthma patients meet criteria for both phenotypes, and nearly 40% of perennial allergen-sensitized patients also have eosinophilia.[11] Properly defining this overlap requires considering clinical symptoms, specific IgE levels, and eosinophil counts. Given the limitations of current biomarkers, including comorbidities, age of onset, and prior biologic response can improve phenotype classification and treatment personalization. Notably, in clinical trials, the distinction between atopy and allergy is often blurred. Atopy refers to a predisposition to develop allergic reactions, measured by positive skin tests or specific IgE, but not necessarily accompanied by clinical symptoms of allergy.

Precision medicine aims to tailor treatment to individual variability in genes, environment, and lifestyle, increasing the likelihood of effective, personalized therapy.[12] Current biomarkers, such as blood eosinophil count, serum IgE, FeNO, and sputum eosinophils, are essential for managing asthma but may not fully capture the complexity of overlapping phenotypes. The inclusion of additional variables like comorbidities, age of onset, and previous biologic response can enhance patient stratification and treatment outcomes.

Six biological drugs have been evaluated in patients with severe uncontrolled asthma featuring T2 inflammation. Notably, many trials reporting overlapping phenotypes include patients with features of atopy, with only some accurately reporting allergic status.[11]

Omalizumab, an anti-IgE monoclonal antibody, is approved for poorly controlled severe allergic asthma with specific IgE levels. While initial trials did not account for eosinophil counts, patients with high baseline biomarker levels (fractional exhaled nitric oxide, peripheral blood eosinophil count, and serum periostin) were found to benefit more from omalizumab therapy in reducing asthma exacerbations.[13]

Mepolizumab, reslizumab, and benralizumab target IL-5 or its receptor, addressing severe eosinophilic asthma. The OSMO trial demonstrated mepolizumab's efficacy in patients uncontrolled on omalizumab, with significant reductions in exacerbations.[14] Similar results were seen with reslizumab in a Spanish study.[15] Benralizumab, through apoptosis of eosinophils and basophils, showed efficacy in atopic and non-atopic patients, although no significant differences were noted.[16]

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Dupilumab, inhibiting IL-4 and IL-13 signaling, is effective in various T2 pathologies. The LIBERTY ASMA QUEST study showed reduced exacerbations in all subgroups except those with low FeNO and eosinophils. A subsequent subanalysis indicated better outcomes in patients with perennial allergic rhinitis, highlighting the potential for overlap.[17] Additionally, a recent study by Brusselle et al.[18] highlights that dupilumab is effective across different patient subgroups, regardless of allergic status, suggesting that its use should not be limited to patients with a specific IgE profile. Importantly, the article emphasizes that allergic status, as traditionally defined by IgE levels and specific allergen sensitivities, may not be the most relevant factor when determining the suitability of dupilumab, and instead, biomarkers like blood eosinophil counts and FeNO should be considered more critical.

Tezepelumab, an anti-TSLP monoclonal antibody, plays a vital role in airway inflammation. Tezepelumab studies uniquely accounted for allergic clinical symptoms, rather than just atopy, highlighting its significance in accurate phenotyping. Notably, in patients with overlapping allergic and eosinophilic asthma, tezepelumab reduced exacerbations by 71%.[19] This makes it a promising treatment regardless of phenotype or endotype, potentially offering better outcomes for patients with mixed characteristics.[20]

The management of severe asthma requires a nuanced approach that considers the complexity of overlapping phenotypes. The distinction between atopy and allergy in clinical trials is critical. Atopy refers to a genetic predisposition to develop allergic reactions, measured by skin tests or specific IgE, while allergy involves clinical symptoms following exposure to an allergen. A patient can be atopic without being allergic, which can interfere with the response to biologicals. Clinical trials often report atopy rather than allergy, potentially leading to incorrect phenotypic classification and affecting treatment outcomes. Incorporating additional variables like comorbidities, age of onset, and previous biologic response, alongside current biomarkers, can enhance personalized treatment strategies. Future research should focus on refining phenotype definitions and expanding the use of comprehensive biomarkers to achieve optimal control in severe asthma.

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## Conflicts of interest

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