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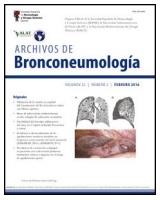

Editorial

Antialarmins in Severe Asthma

Research into the mechanisms involved in the development and progress of severe asthma has led to the appearance of a broad arsenal of drugs with specific action against cytokines and inflammatory cells. The importance of the Th2 cell-mediated adaptive immune response in eosinophilic asthma has been widely demonstrated, and monoclonal antibodies targeting mediators such as IgE (omalizumab), IL5 (mepolizumab, reslizumab, and benralizumab) and IL4/IL13 (dupilumab) are now the basis of the "add-on" treatment used in the most severe cases.[1] Despite this approach, a high percentage of patients (30%–45%) continue to present suboptimal responses to these therapies.[2] The discovery of new mediators and the role of innate immunity have been revolutionized by the discovery of group 2 innate lymphoid cells (ILC2) in the airway mucosa. These cells produce a mixed cytokine pattern: on the one hand they show similarity to the Th2 pattern (IL4, IL5, IL9, IL13), while on the other, they interact with Th17-mediated immune responses that may play a more important role in non-eosinophilic asthma.[3]

The ILC2 group expresses receptors for a set of mediators, globally known as alarmins, such as thymic stromal lymphopoietin (TSLP), IL33 and IL25. These molecules are produced by the epithelial cells of the mucous barriers in response to stimuli such as proteases, pollution, tobacco smoke, viruses and allergens; their alarm and defense functions against these aggressions regulates the inflammatory response and repair. Alarmins also multiply in response to endogenous stimuli such as proinflammatory cytokines or IgE itself, which explains their interaction with the various immunological mechanisms of asthma ("upstream" regulation).

Alarmins act by transmitting their message not only to ILC2 and ILC3 cells, but also to myofibroblasts, basophilic mast cells and eosinophils. Specifically, TSLP promotes the action of antigen-presenting dendritic cells by increasing T cell differentiation in Th2, and by inducing the polarization of naive T cells toward a Th17 phenotype and the production of IL17, a potent neutrophil chemotactic. This dual downstream effect suggests that antialarmin drugs may be more effective than other biologics in asthma.[3,4] The role of alarmins has been corroborated both in animal asthma models and in biopsies of patients with severe asthma in which increased expression in bronchial biopsies has been detected.

TSLP belongs to the IL2 family and has two isoforms, a short form that is expressed under stable conditions and increases its expression in an inflammatory state, and a long, inducible isoform that increases in asthma, rheumatoid arthritis, eosinophilic esophagitis or systemic sclerosis.[5] It is the first alarmin for which an anti-TSLP drug is already available – a human IgG2 monoclonal antibody marketed as *tezepelumab* that binds to the TSLP receptor preventing binding.[6]

The efficacy and safety of tezepelumab have been demonstrated primarily in 2 phase 2 and 3 clinical trials. The PATHWAY[7] study was a phase 2b pivotal trial in 550 patients with severe asthma who received tezepelumab at different doses (70, 210, and 280 mg) every 4 weeks for 52 weeks. A significant reduction in exacerbations (71%) was observed with no differences in eosinophilia or FeNO levels. A *post hoc* analysis comparing patients with Th2-high asthma (IgE > 100 IU/mL or eosinophils > 140 cells/μL) or Th2-low asthma showed no differences in efficacy. The conclusion was that tezepelumab reduces exacerbations in poorly controlled asthma regardless of eosinophil, FeNO, or Th2 status. The effect on exacerbations was accompanied by a significant decrease in FeNO, IgE and eosinophils. In a subsequent phase 3 trial, (NAVIGATOR[8]) conducted in 1062 patients, a 56% reduction in exacerbations was observed with an improvement in FEV_1, quality of life, and asthma control. These effects were more significant in patients with higher eosinophil and FeNO levels (77% reduction in exacerbations if eosinophils were >300 cells/μL and FeNO >25 ppb), but tezepelumab was also effective in patients with non-eosinophilic asthma (29% reduction), making this the first biological that has shown activity in Th2-low patients. Efficacy in patients with cortico-dependent asthma and low eosinophil levels could not be confirmed (SOURCE study[9]). Subsequent studies describing the mechanism of action of tezepelumab (CASCADE[10]) in asthma patients undergoing bronchial biopsy found an 89% reduction in eosinophils but no differences in the number of neutrophils, mast cells, CD3 and CD4 cells, or basement membrane thickness. The currently approved indication for tezepelumab is poorly controlled asthma with more than 2 exacerbations per year treated with medium-to-high doses of inhaled corticosteroids and another maintenance medicinal product.

Ecleralimab is the first inhaled anti-TSLP drug[11]; phase 2A studies conducted to date have analyzed its efficacy and safety against allergen bronchoprovocation in 28 patients with mild atopic asthma. Results showed both early and late attenuated response and a reduction in FeNO. Phase 2B studies in severe uncontrolled asthma are currently underway.

Etokimab is an IgG1 antibody with high affinity for IL33 that was discontinued after showing no effect at 8 weeks. *Itepekimab*, another anti-IL33, has been compared in a phase 2 study with dupilumab alone or in combination in patients receiving LABA/ICS in whom LABA was discontinued and ICS was tapered. Patients receiving itepekimab had a 58% lower chance of loss of asthma con-

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trol compared to dupilumab or placebo. In contrast to dupilumab alone, combination therapy was not associated with increases in eosinophilia. No significant improvement was observed in patients with a Th2-low profile.[12]

Other anti-IL33 drugs, such as tozorakimab, astegolimab[13] and melrilimab (ZENYATTA study), are in phase 2 and have been shown to reduce exacerbations by 43% in patients with both elevated and low blood eosinophils.

In the absence of comparative studies, the positioning of antialarmin drugs in the treatment of asthma is still to be determined.[14] A recent meta-analysis showed that tezepelumab produces a greater reduction in exacerbations than other biologics, regardless of eosinophil or FeNO levels. However, the clinical and biological heterogeneity between the studies is too wide for them to be considered first line.[15] In patients with a high Th2 profile, tezepelumab has shown similar efficacy and safety to other biologics and therefore could be used, especially in patients with higher eosinophil and FeNO values in whom other drugs may be associated with adverse effects, with the proviso that the reduction in eosinophils is lower than that of other biologics. Tezepelumab is the only drug that has shown benefit in patients with a Th2-low profile or neutrophilic asthma, although efficacy is lower.

Conflict of Interest

Alfredo de Diego Damia has received grants from GSK, AstraZeneca and SANOFI.

Ana María Martinez Valle declares no conflict of interest.

Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2023.09.008.

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