EPI-SURVEY. Grade of awareness of Spanish allergist, hospital pharmacist, and pulmonologists on the relevance of bronchial epithelium and alarmins in the pathogenesis and management of severe asthma

Running Title: Bronchial epithelium in asthma

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The bronchial epithelium plays a relevant role in airway inflammation and remodeling in asthma [1]. Upon different aggressions, the epithelium releases alarmins, such as thymic stromal lymphopoietin (TSLP). TSLP is a key upstream regulator of many inflammatory pathways in asthma, which can induce bronchial remodeling, and also mediates bronchial hyperresponsiveness in all phenotypes of asthma (T2 [allergic or eosinophilic] or non-T2) [2]. This epithelial cytokine has an essential role in the promotion, activation, and production of the other mediators involved in the pathogenesis of asthma, such as IL-5 and IL-13 [2].

Tezepelumab is a monoclonal antibody blocking TSLP, effective and safe in the treatment of severe uncontrolled T2 and non-T2 asthma, providing reductions in exacerbation rates and improvements in lung function, asthma control, and health-related quality of life while reducing oral corticosteroids dose in certain subgroups of patients [3-5]. Targeting TSLP acts upstream in the asthma inflammatory cascade and is effective in T2 and non-T2 asthma and, more importantly, in patients with a combination of biomarkers [3, 6, 7].

Patients with severe asthma are heterogeneous and complex and require different therapeutic strategies [8]. Blocking an alarmin is an innovative way of treating severe asthma, different from acting on the cytokines classically associated with asthma. The

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degree of knowledge and relevance given to the epithelium and alarmins by the health care specialist is unknown. The present EPI-SURVEY survey was designed to fill this gap. This initiative aims to know the grade of awareness of Spanish allergists, hospital pharmacists, and pulmonologists on the relevance of the bronchial epithelium and its mediators in the pathogenesis and management of asthma.

The survey was developed by a multidisciplinary team of two pulmonologists, two allergists, one hospital pharmacist, and one biochemist. The survey consisted of 20 questions on the pathogenesis of severe asthma, the role of the bronchial epithelium and alarmins, and the treatment of severe uncontrolled asthma. All registered users of the Spanish Guide for the Management of Asthma (*Guía Española para el Manejo del Asma*, GEMA) web site (www.gemasma.com) were invited to participate anonymously to the survey.

A total of 201 experts participated in the survey. Most of them were between 41 and 60 years of age (61.6%), were mostly women (55.7%), and came from the central (34.8%) and western (30.8%) regions of Spain. The main specialties were pneumology (46.8%) and allergology (41.8%), followed by hospital pharmacy (7.0%). The complete survey results are shown in the supplementary material, and the most relevant results are in Table 1.

The vast majority of respondents (92.1%) “considerably” and “moderately” agreed with the importance of bronchial remodeling in the chronicity of severe asthma and that TSLP is the cytokine capable of mediating bronchial hyperresponsiveness in all asthma phenotypes (78.1%). However, 26.4% felt that the main challenge/problem concerning the non-T2 asthma phenotype is that its pathogenesis is very complex and heterogeneous,

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and 35.3% stated that no specific biological treatment is available. That calls attention since non-T2 asthma can be treated with tezepelumab [3-5]. Other problems described by respondents were the greater severity of patients with non-T2 asthma (15.4%) and that it is a catch-all of patients in whom no T2 biomarkers are found (13.4%).

Regarding the respondents' knowledge of the bronchial epithelium and alarmins, 97.5% "considerably" and "moderately" agreed on the role of epithelial cells in the pathogenesis of asthma, and 93.6% "considerably" and "moderately" agreed on the major role of alarmins in the pathogenesis of asthma. In this sense, 96.5% considered that TSLP can act on innate lymphocyte type 2 cells (ILC2) in asthma, promoting their activation and production of IL-5 and IL-13, which contributes to activation and recruitment of eosinophils to the airways, local eosinophilopoiesis, and mucus production.

Finally, concerning the treatment of severe uncontrolled asthma, 44% considered that the most frequent cause of an incomplete response to current biologics is their highly selective mechanism of action, which prevents them from acting on all the agents involved in the inflammatory cascade of asthma. Some participants (38.3%) considered this lack of response due to the combination of different phenotypes in the same patient. However, it is relevant to highlight that only 33.8% considered alarmin inhibitors effective in patients with eosinophilic, allergic, neutrophilic, paucigranulocytic, or late-onset asthma. There was significant heterogeneity in the responses regarding complete or incomplete responses to biologics. That may have been due to the criteria respondents could have considered when evaluating what is a complete response and total nonresponse.

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This survey shows that experts understand the role of bronchial endothelium and alarmins in the pathogenesis of asthma, but there is a knowledge gap about blocking alarmins as a therapeutic target. Even so, there was general agreement that treatments targeting TSLP would be effective in most severe asthma phenotypes, including non-T2 asthma, but there was a lack of unanimity in establishing response criteria for biologics. Given the need to update expert knowledge, especially regarding the complexity of non-T2 asthma, it would be desirable to propose training and consensus actions on those issues on which experts show divergence of opinion. A recent position document of tezepelumab in severe asthma has been published recently [9].

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Conflict of interest

Vicente Plaza, in the last three years, received honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer-Ingelheim, Chiesi, Gebro, GSK, Luminova-Medwell, and Sanofi; received help assistance with meeting travel from AstraZeneca and Chiesi: and acted as a consultant for AstraZeneca, Chiesi, GSK, and Menarini.

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Ibon Eguíluz, in the last three years, has received lecture fees from AstraZeneca, GSK, Novartis, Sanofi, Chiesi, ALK, Diater, LetiPharma, Inmunotek, and Abbvie; and advisory fees from AstraZeneca, GSK, Novartis, Sanofi, ALK, LetiPharma, Allergy Therapeutics, and Viatris.

Noé Garin, in the last three years, has received honoraria for speaking at meetings or lectures sponsored by Novartis, Sanofi, AstraZeneca, Boehringer-Ingelheim, and GSK.

Eva Martínez Moragón, in the last three years, has received speaker or consulting fees from ALK, AstraZeneca, BIAL, Boehringer-Ingelheim, Chiesi, GSK, Novartis, Teva, and Sanofi.

Óscar Palomares, in the last three years, has received research grants from *Ministerio de Economía, Industria y Competitividad, Ministerio de Ciencia e Innovación*, Inmunotek, Novartis, and AstraZeneca; and fees for giving scientific lectures or participation in Advisory Boards from AstraZeneca, Pfizer, GSK, Inmunotek, Novartis, Sanofi-Genzyme, and Regeneron.

Ignacio Dávila, in the last three years, has received payment for lectures, including service on speaker's bureaus from Allergy Therapeutics, AstraZeneca, Chiesi, Diater, GSK, Leti, Novartis, and Sanofi; for a consultancy from Allergy Therapeutics, ALK-Abello, AstraZeneca, GSK, Merck, MSD, Novartis, and Sanofi; and grants for Thermofisher Diagnostics, *Instituto de Salud Carlos III* and *Junta de Castilla y León*. He is also an associated editor of Journal of Investigational Allergology and Clinical Immunology.

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Table 1. Response choices with higher consensus (> 45%) ordered by frequency

The most frequently chosen response options	N	%
TSLP can act on ILC2s in asthma, promoting their activation and production of IL-5 and IL-13, which contributes to the activation and recruitment of eosinophils to the airways, local eosinophilopoiesis, and mucus production	194	96.5
The structural integrity of the bronchial epithelium is established by tight intercellular junctions involving strong junction proteins, adherens junction, desmosomes, and hemidesmosomes	186	92.5
TSLP is capable of mediating bronchial hyperresponsiveness in all endotypes of asthma	157	78.1
TSLP contributes to neutrophilic non-T2 asthma acting on dendritic cells and promoting the polarization, under certain circumstances, of Th17 responses	147	73.1
In clinical trials in which TSLP was inhibited, FeNO levels were decreased	132	65.7
Alarmins are epithelial-released cytokines involved in asthma pathogenesis	112	55.7
I considerably agree that epithelial cells play a pivotal role in the pathogenesis of asthma	109	54.2
I am very interested in receiving specific information on the role of epithelium, alarmins, and the blockade in asthma	109	54.2
Of the total number of patients who attended outpatient clinics, approximately < 20% have severe asthma	110	54.1
I considerably agree that bronchial remodeling plays a major role in the chronicity of severe asthma	100	49.8

FeNO: fractional exhaled nitric oxide; ILC2: innate lymphocyte type 2; TSLP: thymic stromal lymphopoietin.

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