EPI-SURVEY: Grade of Awareness Among Spanish Allergists, Hospital Pharmacists, and Pulmonologists of the Relevance of Bronchial Epithelium and Alarmins in the Pathogenesis and Management of Severe Asthma

Plaza V[1], Eguíluz I[2], Garin N[3], Martínez Moragón E[4], Palomares Ó[5], Dávila I[6]

[1]*Director of the Executive Committee of the Spanish Guide for the Management of Asthma (GEMA), Pneumology and Allergy Service, Hospital de la Santa Creu i Sant Pau, Sant Pau Institute of Biomedical Research (IIB Sant Pau); Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain*

[2]*Allergy Unit and Research Laboratory, Málaga Regional University Hospital and IBIMA-Plataforma BIONAND; RICORS Inflammatory Diseases Network, Málaga, Spain*

[3]*Department of Pharmacy, Hospital de la Santa Creu i Sant Pau; Universitat Autònoma de Barcelona, Barcelona, Spain*

[4]*Pneumology Service, Dr Peset University Hospital, Valencia, Spain*

[5]*Department of Biochemistry and Molecular Biology, School of Chemistry, Complutense University, Madrid, Spain*

[6]*Allergy Service, University Hospital of Salamanca. Biomedical and Diagnostics Sciences, Faculty of Medicine, University of Salamanca; RICORS Inflammatory Diseases Network RD21/0002/000, Salamanca, Spain*

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The bronchial epithelium plays a relevant role in airway inflammation and remodeling in asthma [1]. Upon insult, the epithelium releases alarmins, such as thymic stromal lymphopoietin (TSLP). TSLP is a key upstream regulator of many inflammatory pathways in asthma. It can induce bronchial remodeling and mediates bronchial hyperresponsiveness in all phenotypes of asthma (T2 [allergic or eosinophilic] and 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 that blocks TSLP. It is effective and safe in the treatment of severe uncontrolled T2 and non-T2 asthma, reducing exacerbation rates and improving lung function, asthma control, and health-related quality of life, while enabling the dose of oral corticosteroids to be decreased in certain subgroups of patients [3-5]. Drugs targeting TSLP act upstream in the asthma inflammatory cascade and are 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, in contrast with targeting the cytokines classically associated with asthma. The degree of knowledge of and relevance given to the epithelium and alarmins by the health care specialist is unknown. EPI-SURVEY was designed to fill this gap, namely, to determine the degree of awareness of Spanish allergists, hospital pharmacists, and pulmonologists of 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 2 pulmonologists, 2 allergists, 1 hospital pharmacist, and 1 biochemist. It 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 in the survey.

A total of 201 experts participated in the survey. Most were between 41 and 60 years of age (61.6%) and women (55.7%) and came from the central and western regions of Spain (34.8% and 30.8%, respectively). The main specialties were pulmonology (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 shown in the Table.

Most respondents (92.1%) "considerably" and "moderately" agreed on the importance of bronchial remodeling in the chronicity of severe asthma and that TSLP is capable of mediating bronchial hyperresponsiveness in all asthma phenotypes (78.1%). However, 26.4% felt that the main challenge concerning the non-T2 asthma phenotype is that its pathogenesis is very complex and heterogeneous, and 35.3% stated that no specific biological treatment is available. This is noteworthy, 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 the fact that it is a catch-all term for 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 in asthma, promoting their activation and production of IL-5 and IL-13, thus contributing to activation and recruitment of eosinophils to the airways, local eosinophilopoiesis, and mucus production.

Finally, concerning the treatment of severe uncontrolled asthma, 44% of respondents 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 to be due to the combination of different phenotypes in the same patient. However, it is noteworthy that only 33.8% considered alarmin inhibitors effective in patients with eosinophilic, allergic, neutrophilic, paucigranulocytic, or late-onset asthma. There was significant heterogeneity

Table. Response Choices With Higher Consensus (>45%) Ordered by Frequency.

The most frequently chosen response options	No.	%
TSLP can act on ILC2s in asthma, promoting their activation and production of IL-5 and IL-13, which contribute to 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 junctions, 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 T_H17 responses	147	73.1
In clinical trials in which TSLP was inhibited, FeNO levels were decreased	132	65.7
Alarmins are cytokines released by epithelial cells that are involved in the pathogenesis of asthma	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 the epithelium, alarmins, and 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

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

regarding complete or incomplete responses to biologics, possibly owing to the criteria respondents could have considered when defining a complete response and total nonresponse.

EPI-SURVEY showed that experts understand the role of the bronchial endothelium and alarmins in the pathogenesis of asthma, although there is a knowledge gap with respect to 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, despite the 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 for those issues on which experts show divergence of opinion. A statement on the positioning of tezepelumab in severe asthma was recently published [9].

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Conflicts of Interest

In the last 3 years, Vicente Plaza has received honoraria for speaking at meetings sponsored by AstraZeneca, Boehringer-Ingelheim, Chiesi, Gebro, GSK, Luminova-Medwell, and Sanofi. He has received assistance with travel to meetings from AstraZeneca and Chiesi and acted as a consultant for AstraZeneca, Chiesi, GSK, and Menarini.

In the last 3 years, Ibon Eguíluz has received lecture fees from AstraZeneca, GSK, Novartis, Sanofi, Chiesi, ALK, Diater, LetiPharma, Inmunotek, and AbbVie and consultancy fees from AstraZeneca, GSK, Novartis, Sanofi, ALK, LetiPharma, Allergy Therapeutics, and Viatris.

In the last 3 years, Noé Garin has received honoraria for speaking at meetings or lectures sponsored by Novartis, Sanofi, AstraZeneca, Boehringer-Ingelheim, and GSK.

In the last 3 years, Eva Martínez Moragón has received speaking or consultancy fees from ALK, AstraZeneca, BIAL, Boehringer-Ingelheim, Chiesi, GSK, Novartis, Teva, and Sanofi.

In the last 3 years, Óscar Palomares has received research grants from Ministerio de Economía, Industria y Competitividad, Ministerio de Ciencia e Innovación, Inmunotek, Novartis, and AstraZeneca and fees for scientific lectures or participation on advisory boards from AstraZeneca, Pfizer, GSK, Inmunotek, Novartis, Sanofi-Genzyme, and Regeneron.

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Vicente Plaza
Servei de Pneumologia
Hospital de la Santa Creu i Sant Pau
C/ Sant Antoni M. Claret 167
08025 Barcelona, Spain
E-mail: vplaza@santpau.cat

