SUPPLEMENTARY MATERIAL

Results of EPI-SURVEY

	N	%
Topic 1: Pathogenesis of severe asthma		
Of the total number of patients you see in outpatient clinics, indicate the approximate proportion of patients with severe asthma		
• < 20% • 20-40% • 41-60% • 61-80% • > 81%	110 45 22 21 1	54.1 22.4 10.9 11.4 0.5
In relation to the non-T2 asthma phenotype, which of the following circumstances is the biggest challenge (or problem) for you?		
• Difficult and expensive diagnosis. Special techniques are required, e.g., induced sputum.	19	9.5
• Affected patients are more severely affected.	31	15.4
• It does not exist. It is a catch-all of patients in whom no T2 biomarkers are found.	27	13.4
• No specific biological treatment is available (orphan disease).	71	35.3
• Its pathogenesis is too complex and heterogeneous.	53	26.4
Bronchial remodeling plays a major role in the chronicity of severe asthma.		
• Considerably agree • Moderately agree • Neither agree nor disagree • Slightly agree	100 85 12 4	49.8 42.3 6.0 2.0
Which of the following cytokines is capable of mediating bronchial hyperresponsiveness in all endotypes of asthma?		
• IL-13 • IL-17 • IL-4 • TSLP	28 3 13 157	13.9 1.5 6.5 78.1

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Topic 2: Epithelium and alarmins		
Epithelial cells play a pivotal role in the pathogenesis of asthma		
• Considerably agree • Moderately agree • Neither agree nor disagree	109 87 5	54.2 43.3 2.5
The structural integrity of the bronchial epithelium is established by...		
• Type 2 inflammatory cytokines	13	6.5
• Surfactant action	1	0.5
• Mucus production	1	0.5
• Tight intercellular junctions involving strong junction proteins, adherens junction, desmosomes, and hemidesmosomes	186	92.5
What are "alarmins"?		
• Eosinophilic-released cytokines involved in the pathogenesis of asthma	3	1.5
• Epithelial-released cytokines involved in asthma pathogenesis	112	55.7
• Bronchial eosinophilic inflammation alarm signaling molecules	35	17.5
• Epithelial rupture alarm signal transmission molecules	51	25.4
"Alarmins" play a major role in the pathogenesis of asthma		
• Considerably agree • Moderately agree • Neither agree nor disagree	94 94 13	46.8 46.8 6.5
Can TSLP act on ILC2s in asthma?		
• No, ILC2s do not express the receptor for TSLP and, therefore, do not respond to this cytokine.	2	1.0
• No, ILC2s are only activated by IL-33.	1	0.5
• Yes, inducing their apoptosis and cell death.	4	2.0
• Yes, 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

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What pathophysiological mechanisms explain the contribution of TSLP in neutrophilic non-T2 asthma?		
• Its direct action on the bronchial epithelium.	38	18.9
• Its direct action on smooth muscle.	8	4.0
• Its direct action on fibroblasts.	8	4.0
• Its ability to act on dendritic cells and to promote the polarization, under certain circumstances, of Th17 responses.	147	73.1
Topic 3: Treatment		
In your opinion, what is the most frequent cause of incomplete response to biologics in the current treatment of severe uncontrolled asthma?		
• Occurrence of autoimmune phenomena, e.g., antibodies to the biologic.	4	2.0
• Change of the patient's asthma phenotype after initial biologic treatment.	21	10.4
• Combination of different phenotypes in the same patient.	77	38.3
• Recurrent bronchial infections.	10	5.0
• Current biologics have such a selective mechanism of action that they do not inhibit the heterogeneous inflammatory cascade of asthma.	89	44.0
Regarding the current treatment of severe uncontrolled asthma with biologics, which of the following statements do you most agree? (check only one option)		
• The majority of patients (> 80 %) respond well.	48	23.9
• Clinical improvement declines over time.	15	7.5
• Patients improve but do not achieve complete remission.	53	26.4
• Biologic treatment is available for each asthma phenotype.	1	0.5
• A significant fraction (> 50 %) do not respond fully.	84	41.8
Current biologics used in the treatment of severe uncontrolled asthma provide complete remission (control of symptoms and exacerbations, lung function, inflammation, and airway remodeling) in...		
• < 20 % of cases	37	18.4
• 20-40 % of cases	53	26.4
• 41-60 % of cases	62	30.8

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• 61-80 % of cases • > 80% of cases	39 10	19.4 5.0
In your opinion, alarmin inhibitor drugs would be effective in patients with asthma... (several options could be selected) (only options selected by ≥ 5 respondents are shown)		
• Allergic	2	1.0
• Adult-onset	11	5.5
• Eosinophilic	1	0.5
• Eosinophilic + Allergic	5	2.5
• Eosinophilic + Allergic + Adult-onset	4	2.0
• Eosinophilic + Allergic + Neutrophilic	11	5.5
• Eosinophilic + Allergic + Allergic + Neutrophilic + Adult-onset	15	7.5
• Eosinophilic + Allergic + Neutrophilic + Paucigranulocytic	19	9.5
• Eosinophilic + Allergic + Neutrophilic + Paucigranulocytic + Adult-onset	68	33.8
• Eosinophilic + Allergic + Paucigranulocytic + Eosinophilic + Allergic + Paucigranulocytic	4	2.0
• Eosinophilic + Allergic + Paucigranulocytic + Adult-onset	2	1.0
• Eosinophilic + Neutrophilic	4	2.0
• Eosinophilic + Neutrophilic + Adult-onset	2	1.0
• Eosinophilic + Neutrophilic + Paucigranulocytic	5	2.5
• Eosinophilic + Neutrophilic + Paucigranulocytic + Adult-onset	6	3.0
• Eosinophilic + Paucigranulocytic + Paucigranulocytic	1	0.5
• Eosinophilic + Paucigranulocytic + Adult-onset	1	0.5
• Neutrophilic	10	5.0
• Neutrophilic + Adult-onset Neutrophilic + Adult-onset	3	1.5
• Neutrophilic + Paucigranulocytic	8	4.0
• Neutrophilic + Paucigranulocytic + Adult-onset	7	3.5

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• Paucigranulocytic	12	6.0
In clinical trials in which TSLP was inhibited, ...		
• No inhibition of eosinophils was observed	21	10.4
• No reduction in biomarkers of inflammatory pathways other than TSLP itself was observed	44	21.9
• An increase in total IgE levels was observed	4	2.0
• Decreased levels of FeNO	132	65.7
Would you be interested in receiving specific information on the role of the epithelium, alarmins, and their blockade in asthma?		
• Very interested • Fairly interested • Not very interested • Not interested at all • No preference	109 76 6 2 8	54.2 37.8 3.0 1.0 4.0

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

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