Survey of Opinion of Spanish Physicians on the Role of Eosinophils in Asthma and Other Diseases

Plaza V[1], Blanco M[2], Delgado J[3], Martínez I[4], Zubeldía JM[5], Molina J[6]

[1]*Director del Comité Ejecutivo de la Guía Española para el Manejo del Asma (GEMA), Servei de Pneumologia i Allèrgia, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Universitat Autònoma de Barcelona, Barcelona, Spain*

[2]*Servicio de Neumología, Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain*

[3]*Hospital Universitario Virgen Macarena, Sevilla, Spain*

[4]*Hospital Universitario Son Espases, Palma, Spain*

[5]*Hospital Universitario Gregorio Marañón, Madrid, Spain*

[6]*Centro de Salud Francia, Fuenlabrada, Spain*

J Investig Allergol Clin Immunol 2019; Vol. 29(6): 456-458
doi: 10.18176/jiaci.0423

Key words: Eosinophils. Biomarker. Severity. Biologic drug. Quality of life.

Palabras clave: Eosinófilos. Biomarcador. Gravedad. Fármaco biológico. Calidad de vida.

Eosinophilic asthma is the most common inflammatory phenotype, accounting for over 25% of all patients with severe asthma. It is characterized by abnormal production of cytokines from type 2 helper T lymphocytes and type 2 innate lymphoid cells (ILC-2s), such as IL-4, IL-5, and IL-13, as well as a persistent increase and activation of eosinophils in blood and airways despite treatment with high-dose corticosteroids [1,2]. Blood and sputum eosinophilia are associated with more severe disease, poorer control, and worse prognosis [3]. The most direct way to diagnose severe eosinophilic asthma is through diagnosis of severe asthma, which is characterized by ≥2 exacerbations per year, dependence on oral corticosteroids to achieve asthma control, and a persistent increase in the eosinophil count in blood and the airways [2]. Eosinophils represent approximately 1% of peripheral blood leukocytes, and their differentiation, survival, and activation are regulated mainly by IL-5 [4]. Irrespective of the presence of allergy, severe, uncontrolled eosinophilic asthma is treated with biological drugs that target either eosinophils or the IL-5 pathway. On the one hand, biologic therapies targeting eosinophils include drugs blocking eosinophil recruitment, such as bertilimumab, which prevents accumulation of these cells in tissues [5]. On the other hand, drugs targeting the IL-5 pathway may be used, either directly against IL-5 (mepolizumab and reslizumab) or the IL-5 receptor (IL-5Rα) (benralizumab) [6-9]. By blocking the interaction between IL-5 and its receptor, the eosinophil count in blood and the airway decreases, as does survival of these cells, thus decreasing the symptoms of the disease. Another treatment approach includes inhibition of IL-4Rα by blocking the action of IL-4 and IL-13. This strategy prevents the stimulation of type 2 inflammation,

Table. Majority Answer for the Most Important Questions

Item Proposed	Preferred Option According to Each Specialty
Is the blood eosinophil count requested at the first visit?	• All: Always
Other factors associated with eosinophilia in asthma patients	• All: Increased risk of exacerbations
Significance of an increase in blood eosinophils in patients with nonsevere asthma	• Ph, P, A: Increased risk of exacerbations • HP: Patients with allergic asthma
Significance of an increase in blood eosinophils in patients with severe asthma	• Ph, HP: I assume it is allergic asthma • P, A: I rule out other possibilities, such as parasitic infection
Cut-off of blood eosinophils to define eosinophilia	• Ph, P: 300/μL • A, HP: 500/μL
Blood eosinophil count to define primary hypereosinophilic syndrome	• P, A: > 1500/μL • Ph, HP: I don't know
Parameter considered for treatment in patients with severe asthma: total IgE or blood eosinophilia	• All: Both
Consequences of long-term complete suppression of eosinophils by any biologic drug	• Ph, P, A: I don't know • HP: NA
Do you need more training on eosinophils and asthma?	• All: Yes

Abbreviations: A, allergists; HP, hospital pharmacists; NA, no answer; P, pulmonologists; Ph, primary care physicians.

which contributes to asthma. Dupilumab is a monoclonal antibody targeting IL-R4α [10]. It was recently approved by the United States Food and Drug Administration for the treatment of moderate and severe asthma in patients with the eosinophilic phenotype.

The objective of this study was to know the opinion of a large number of Spanish asthma experts on the role of eosinophils in the comprehensive management of patients with severe asthma. A multidisciplinary scientific committee of 5 asthma experts designed and validated a 20-question on-line survey according to the different profiles of health professionals involved in the management of asthma. The expert panel consisted of a multidisciplinary team that included 348 primary care physicians, 200 pulmonologists, 136 allergists, and 42 hospital pharmacists. The Table shows the majority answer for the most important questions. The results are shown in detail in the Supplementary Material.

Most of the experts were over 50 years old (51.8%) and men (58.8%). Spanish geographical representativeness was acceptable, except for those from the south of Spain (<3%). All of the experts have broad experience in the care of asthmatic patients and are mainly pulmonologists and allergists. The only exception was hospital pharmacists; most of their representatives were aged 30-50 years old (76.2%) and were women (71.4%).

More than 65% of respondents always request a blood eosinophil count during the first visit (75.52% of pulmonologists, 55.1% of allergists). This difference between specialties is probably due to the importance that each specialist gives to peripheral eosinophilia. For example, allergists are likely to attribute a more etiological role to it. It is therefore necessary to define the role of peripheral eosinophilia in asthma, even in nonsevere asthma.

The respondents agreed that eosinophilia in asthma is associated with an increased risk of exacerbation (47.7%), even in nonsevere asthma (50.9%), followed by greater severity of asthma (20.5%) and worse current control (15.1%), possibly because of recent publications about the application of eosinophilia as a biomarker for driving treatment choices in asthma [11]. However, their attitude towards eosinophilia in severe asthma varies according to the specialty: while pulmonologists and allergists rule out parasitic infection in the first place, in primary care, the diagnosis of severe asthma is assumed.

Although there is no consensus on eosinophil cut-off, it seems reasonable to accept an absolute count of ≥400/μL in blood or ≥3% in sputum on more than 1 occasion, particularly during an exacerbation [1]. In our survey, most primary care physicians (35.6%) and pulmonologists (61.0%) agreed that 300/μL was a good cut-off, but allergists (41.9%) and hospital pharmacists (42.9%) agreed on a cut-off of 500/μL. Nevertheless, favorable agreement was only recorded for pulmonologists, as the other specialists' opinions were very disparate. In addition, only pulmonologists and allergists (66.0% and 64.7%, respectively) appear to have a clear cut-off for eosinophils (>1500/μL) in the diagnosis of primary hypereosinophilic syndrome.

Blood eosinophilia and elevated levels of total IgE were considered the most important parameters when deciding on treatment of severe asthma (>38%). However, more than 10% of the experts either did not know the answer or did not answer the question. In addition, almost half of the experts did not know (or did not answer) about the long-term consequences of complete suppression of eosinophils by any of the biologic drugs. In this way, benralizumab has been shown to achieve eosinophil depletion of >95%, which is higher than that described for mepolizumab (84%) and reslizumab (82%) [6-9].

Primary care physicians and pulmonologists (42.2% and 40.0%, respectively) give preference to pulmonologists in the treatment of patients with asthma and hypereosinophilic

syndrome, whereas allergists (39.0%) give preference to allergists. Regardless of the specialty, most experts (>77%) felt it was necessary to provide further training on the role of eosinophils in asthma.

This is the first time that this topic has been explored in all of the specialties involved in the management of asthma. Our results revealed a notable disparity of opinions in the management of patients with eosinophilic asthma and uncertainty about the development of new biological treatments. In addition, use of the blood eosinophil count to define the implication of these cells in the pathogenesis of asthma remains poor, and there is uncertainty in relation both to the severity of the disease and to its exacerbations. Therefore, professionals stress the need for complementary training to increase their knowledge of eosinophilic asthma. This training should be implemented urgently, since the rational use of new antieosinophilic drugs, which were recently licensed for the treatment of severe, uncontrolled eosinophilic asthma, requires specific knowledge.

Treatment and diagnosis of patients with severe asthma are complex. Therefore, it is necessary to harmonize the management of these patients among the various experts involved. The results of this study are a first step in this direction.

Acknowledgments

The authors wish to thank the Research Unit at Luzán 5 (Madrid) for coordination assistance and Dr. Fernando Sánchez Barbero for his support in the preparation of this manuscript.

Funding

AstraZeneca sponsored this project without participating in any way in the study design, data analysis, or drafting of the manuscript.

Conflicts of Interest

During the last 3 years, VP has received honoraria for speaking at sponsored meetings from AstraZeneca, Chiesi, GSK, and Novartis. He has also received travel assistance from Chiesi and Novartis and acted as a consultant for ALK, AstraZeneca, Boehringer, MundiPharma, and Sanofi. In addition, he has received funding/grant support for research projects from a variety of government agencies and nonprofit foundations, as well as from AstraZeneca, Chiesi, and Menarini.

During the last 3 years, MB has received speaker's honoraria from AstraZeneca, GSK, Teva, and Novartis and travel assistance from Chiesi and Novartis.

During the last 3 years, JD has been on advisory boards for Sanofi and Mundipharma and received speaker's honoraria from AstraZeneca, Chiesi, GlaxoSmithKline, and Pfizer. He has also received travel assistance from Menarini and Novartis.

During the last 3 years, IM has been on advisory boards for AstraZeneca, Boehringer Ingelheim, and Novartis and received speaker's honoraria from AstraZeneca, Biogen, Boehringer-Ingelheim, Novartis, Roche, and Sanofi.

During the last 3 years, JMZ has been on advisory boards for AstraZeneca and Novartis and received speaker's honoraria from AstraZeneca.

During the last 3 years JM has received speaker's honoraria from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Menarini, and Roche and received funding/grant support for research projects from a variety of government agencies and nonprofit foundations, as well as from Boehringer-Ingelheim.

References

1. Aleman F, Lim HF, Nair P. Eosinophilic endotype of asthma. Immunol Allergy Clin North Am. 2016;36:559-68.
2. Buhl R, Humbert M, Bjermer L, Chanez P, Heaney LG, Pavord I, et al. Severe eosinophilic asthma: a roadmap to consensus. Eur Respir J. 2017;49.
3. Schleich FN, Chevremont A, Paulus V, Henket M, Manise M, Seidel L, et al. Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. Eur Respir J. 2014;44:97-108.
4. Varricchi G, Bagnasco D, Borriello F, Heffler E, Canonica GW. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. Curr Opin Allergy Clin Immunol. 2016;16:186-200.
5. Ding C, Li J, Zhang X. Bertilimumab Cambridge Antibody Technology Group. Curr Opin Investig Drugs. 2004;5:1213-8.
6. Lugogo N, Domingo C, Chanez P, Leigh R, Gilson MJ, Price RG, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: A multi-center, open-label, phase iiib study. Clin Ther. 2016;38:2058-70 e1.
7. Murphy K, Jacobs J, Bjermer L, Fahrenholz JM, Shalit Y, Garin M, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. J Allergy Clin Immunol Pract. 2017;5:1572-81 e3.
8. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;388:2128-41.
9. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016;388:2115-27.
10. Sastre J, Dávila I. Dupilumab: A new paradigm for the treatment of allergic diseases. J Investig Allergol Clin Immunol. 2018;28:139-50.
11. Kostikas K, Brindicci C, Patalano F. Blood eosinophils as biomarkers to drive treatment choices in asthma and COPD. Curr Drug Targets. 2018.

Manuscript received November 8, 2018; accepted for publication June 4, 2019.

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