

Survey of opinion of Spanish physicians on the role of eosinophils in asthma and other pathologies

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Eosinophilic asthma is the most common inflammatory phenotype accounting for over 25% of the total severe asthma population and is characterized by an abnormal production of cytokines from T helper type 2 (Th2) lymphocytes and type 2 innate lymphoid cells (ILC-2s), such as IL4, IL-5, or IL-13, and a persistent increase and activation of eosinophils in blood and airways despite receiving treatment with high-doses of corticosteroids [1, 2]. Blood and sputum eosinophilia are associated with more severe disease, worse control, and worse prognosis [3]. The most direct way to diagnose severe eosinophilic asthma is the diagnosis of severe asthma, to have ≥ 2 exacerbations per year, dependence on oral corticosteroids to achieve asthma control, and to demonstrate the persistent increase of eosinophils in blood and airways [2]. Eosinophils represent approximately 1% of peripheral blood leukocytes and their differentiation, survival, and activation are mainly regulated by IL-5 [4]. For the treatment of severe, uncontrolled eosinophilic asthma, irrespective of the presence of allergy, biological drugs have been developed targeting either eosinophils or IL-5 pathway. On the one hand, biologic therapies targeting eosinophils include drugs blocking eosinophils recruitment, such as bertiimumab, avoiding the accumulation of these cells in tissues [5]. On the other hand, drugs directed against the IL-5 pathway may be used, either directly to IL-5 (mepolizumab and reslizumab) or to IL-5 receptor (IL-5R α) (benralizumab) [6-9]. By blocking the interaction between IL-5 and its receptor, the count of eosinophils in blood and airway decreases, as well as the survival of these cells, decreasing the symptomatology of the disease. Another treatment approach include the inhibition of IL-4R α , blocking the action of IL-4 and IL-13. This strategy avoids the stimulation of type 2 inflammation that contributes to asthma. Dupilumab is a monoclonal antibody directed against IL-R4 α [10]. It has been recently approved by the FDA for the treatment of both moderate and severe asthma patients with eosinophilic phenotype.

The objective of this study was to know the opinion of a large number of Spanish experts in asthma about the role of eosinophils in the comprehensive management of patients with severe asthma. A multidisciplinary scientific committee of 5 experts in asthma designed and validated an on-line survey of 20 questions 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. Table 1 shows the majority answer for the most important questions. The results are shown in detail in the supplementary material.

Most of the experts are over 50 years old (51.8%), male (58.8%), and with acceptable Spanish geographical representativeness, except those coming from the south of Spain (<3%). All of them have a notable implication in the assistance to the asthmatic patient, mainly pulmonologists and allergists. The only exception was hospital pharmacists; most of their representatives were between 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, ranging from 75.52% of pulmonologists to 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 non-severe asthma.

Respondents agreed that eosinophilia in asthma is associated with an increased risk of exacerbations (47.7%), even in non-severe asthma (50.9%), followed by greater severity of asthma (20.5%) and worse current control (15.1%). This could be related to the recent publications about eosinophilia as a biomarker to drive 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 the eosinophils cut-off levels, it seems reasonable an absolute count of ≥ 400 eosinophils/ μl in blood or $\geq 3\%$ in sputum on more than one occasion particularly at the time of an exacerbation [1]. In our survey, most primary care physicians (35.6%) and pulmonologists (61.0%) agreed that 300 eosinophils/ μl could be a good cut-off level, but allergists (41.9%) and hospital pharmacists (42.9%) agreed a cut-off of 500 eosinophils/ μl . Nevertheless, only pulmonologists showed the most level of agreement as the other specialists showed high degree of dispersion. In addition, only pulmonologists and allergists (66.0% and 64.7% respectively) appear to have a clear cut-off value of eosinophils ($>1,500$ eosinophils/ μl) for the diagnosis of primary hypereosinophilic syndrome.

Blood eosinophilia and elevated levels of total IgE were considered together the most important parameters for choosing 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 a complete suppression of eosinophils by any of the biologic

drugs. In this way, benralizumab has shown to achieve an eosinophil depletion of >95%, 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 to control patients with asthma and hypereosinophilic syndrome, but allergists (39.0%) give preference to allergists. Regardless of the specialty, the majority of 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 is explored in all specialties involved in the management of asthma. The results of this study have shown a notable disparity of opinions in the management of patients with eosinophilic asthma and uncertainty about the arrival of new biological treatments. In addition, blood eosinophils count to define their implication in the pathogenesis of asthma is still not fully known, and there is uncertainty both in relation to the severity of the disease and its exacerbations. Therefore, professionals point out the need to establish complementary teaching actions to increase their knowledge about eosinophilic asthma. It would be advisable to implement them as a matter of urgency, since the rational use of new antieosinophilic drugs, recently licensed for the treatment of severe, uncontrolled eosinophilic asthma, require specific training.

Treatment and diagnosis of patients with severe asthma are complex. Therefore, it is necessary to unify patterns of action in the management of these patients among the different groups involved. The results of this study are a first step for this.

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Conflicts of interests

VP in the last three years received honoraria for speaking at sponsored meetings from AstraZeneca, Chiesi, GSK, and Novartis; received help assistance to meeting travel from Chiesi and Novartis; act as a consultant for ALK, AstraZeneca, Boehringer, MundiPharma, and Sanofi; and received funding/grant support for research projects from a variety of Government agencies and not-for-profit foundations, as well as AstraZeneca, Chiesi, and Menarini.

MB in the last three years received speaker's honoraria from AstraZeneca, GSK, Teva, and Novartis; and received help assistance to meeting travel from Chiesi and Novartis.

JD in the last three years has been on advisory boards for Sanofi and Mundipharma; received speaker's honoraria from AstraZeneca, Chiesi, GlaxoSmithKline, and Pfizer; and received help assistance to meeting travel from Menarini and Novartis.

IM in the last three years 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.

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

JM in the last three years 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 not-for-profit foundations, as well as Boehringer-Ingelheim.

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Table 1. Majority answer for the most important questions

Item proposed	Preferred option according each specialty
Blood eosinophil count is requested on first visit?	<ul style="list-style-type: none"> All: Always
Other factors associated with eosinophilia in asthma patients	<ul style="list-style-type: none"> All: Increased risk of exacerbations
Meaning of an increase in blood eosinophils in patients with NON-SEVERE ASTHMA	<ul style="list-style-type: none"> Ph, P, A: Increased risk of exacerbations HP: Patients with allergic asthma
Meaning of an increase in blood eosinophils in patients with SEVERE ASTHMA	<ul style="list-style-type: none"> Ph, HP: I assume it's allergic asthma P, A: I rule out other possibilities, such as parasitic infection
Cut-off value of blood eosinophils to define eosinophilia	<ul style="list-style-type: none"> Ph, P: 300 cells/μl A, HP: 500 cells/μl
Blood eosinophils count to define primary hypereosinophilic syndrome	<ul style="list-style-type: none"> P, A: > 1500 cells/μl Ph, HP: I don't know
Parameter considered for treatment in patients with SEVERE ASTHMA: total IgE or blood eosinophilia	<ul style="list-style-type: none"> All: Both
Consequences of long-term complete suppression of eosinophils by any biologic drug	<ul style="list-style-type: none"> Ph, P, A: I don't know HP: NA
Do you need more training on eosinophils and asthma?	<ul style="list-style-type: none"> All: Yes

A: Allergists; HP: Hospital Pharmacists; NA: No answer; Ph: Primary Care Physicians; P: Pulmonologists.