The Importance of Small Airway Dysfunction in Asthma: The GEMA-FORUM III Task Force

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The small airways have an internal diameter of 2 mm or less. Their role in asthma and other obstructive lung diseases is important, as inflammation or smooth muscle contraction induced by inhalation of allergic and nonallergic irritants reduces their diameter, thus increasing resistance in the airways [1-3]. Peripheral airway obstruction, also known as small airway dysfunction (SAD), can occur in patients with asthma irrespective of severity, and prevalence increases with severity [1,2,4]. SAD also considerably worsens the clinical expression and control of asthma, is associated with more frequent exacerbations and more severe bronchial hyperresponsiveness and requires higher doses of inhaled corticosteroids (ICS) [1,2,5]. The main predictors of SAD are exercise-induced asthma, overweight, asthma-related night awakenings, smoking, and older age [5]. Although conventional spirometry measurements lack sensitivity for evaluation of SAD, their combination with physiological tests, oscillometry, body plethysmography, chest computed tomography (CT), multiple breath nitrogen washout, and nitric oxide would facilitate assessment of the complexity of this dysfunction and the response to drug therapy [4,6].

While involvement of the small airways in asthma highlights their role as a target for treatment with small drug particles [7], the difficulties in exploring and studying these structures make them less well known than other aspects of respiratory diseases, especially asthma. In addition, the COVID-19 pandemic has limited many lung function examination procedures and highlighted the need for new techniques to assess SAD [8].

However, the evidence that justifies the assessment and specific treatment of SAD is not completely sound, and the recent GEMA 5.0 guidelines [9] do not include the possible role of SAD in asthma. Therefore, the GEMA-FORUM task force proposed a consensus debate on this topic among a group of experts in asthma. The objective of the present study was to know the opinion of a multidisciplinary expert panel on the assessment and treatment of SAD in patients with asthma. After reviewing the most recent literature, a scientific committee of 3 coordinators and 12 experts in pulmonology, allergology, and primary care proposed a questionnaire comprising 50 items that addressed the most controversial areas in the diagnosis and treatment of SAD in patients with asthma (Supplementary material). Following the Delphi methodology used in the GEMA-FORUM II report [10], the items were sent to a panel of 87 pulmonologists and allergists involved in the care of asthma patients throughout Spain to ascertain their degree of agreement. Consensus was defined as a score of 7-9 on a Likert-type scale from more than two-thirds of the respondents (median, >7). Disagreement was defined as a score of 1-3 by 100% of respondents (median, <3). Consensus was defined as undetermined if the score was in the 4-6 range (median, 4-6).

Table. Items With The Highest Degree of Consensus Achieved After the 2 Rounds

	Median (IQR)	Agreement, %
Topic 1. Diagnosis		
SAD is present in asthmatics at all levels of severity.	8 (1)	77.9
The presence of symptoms requiring controller medication accompanied by normal lung function implies involvement of small airways.	7 (0)	75.6
The development of specific tools is necessary to confirm SAD.	9 (1)	87.2
Impulse oscillometry should be incorporated into pulmonary function units and laboratories.	7 (2)	69.8
Topic 2. Treatment		
If SAD is suspected, a therapeutic trial with drugs capable of better reaching the distal airway should be performed.	8 (2)	84.9
Extrafine particle ICS are more effective for treating SAD than non–extrafine particle ICS.	7 (2)	66.3
Extrafine particles ensure more homogeneous pulmonary deposition than that obtained with non–extrafine particles.	7 (1)	76.8
Since only indirect methods are available, several should be used to evaluate response to treatment of SAD.	8 (1)	80.2

Abbreviations: ICS, inhaled corticosteroids; SAD, small airway dysfunction.

After 2 rounds, a consensus was reached on 25 of the 50 items (50.0%; all in agreement). Assessment of the remaining 25 items (50.0%) yielded neither agreement nor disagreement. The Table shows the items with the highest degree of consensus reached by the experts after 2 rounds. The results for the 50 items are shown in the Supplementary material.

The panelists agreed with 16 of the 24 items related to the diagnosis of SAD (66.7%). There was neither agreement nor disagreement for the remaining 8 items (33.3%). The item with the highest degree of agreement (87.2%) was that stating that specific tools need to be developed to confirm SAD. Although the panelists are aware of the existence of various techniques for assessment of SAD (eg, oscillometry, body plethysmography, and CT scan), they do not fully trust them or consider them only partially reliable [4-6]. Interestingly, although panelists did not agree on specific testing for suspected SAD in patients with asthma, they did reach agreement for patients with uncontrolled asthma in whom modifiable factors have been ruled out. The panelists explained that owing to the complexity of the tests used to assess SAD, it is not necessary to perform them on patients with controlled asthma. Other items for which agreement was high included the observation that SAD is present at all degrees of asthma severity (77.9%) and that the presence of symptoms requiring controller treatment accompanied by normal lung function points to involvement of the small airways (75.6%). In addition, the panelists agreed that oscillometry should become part of the routine of pulmonary function laboratories (69.8%). Although neither agreement nor disagreement was achieved (indeterminate consensus), the diagnosis-related item with the lowest degree of agreement (16.3%) stated that magnetic resonance imaging may play a more relevant role in assessing SAD if its costs are reduced and its use becomes widespread.

Of the 26 items related to treatment of SAD, panelists agreed with 9 (34.6%); they expressed neither agreement nor disagreement for the remaining 17 (65.4%). The item with the highest degree of agreement (84.9%) states that therapy with drugs capable of better reaching the distal airway should be tried if SAD is suspected. In this way, panelists agreed that extrafine particle ICS are more effective for treating SAD than non–extrafine particle ICS (66.3%). However, although a group of panelists considered that the use of extrafine particle drugs (ICS+long-acting ß-agonists) could be considered from initiation of treatment, others argued that there is not enough evidence to support such a claim or that it would not be necessary in all patients, but only in specific cases. Consequently, full consensus was not reached on this item. In addition, panelists agreed that device type, inhalation technique, inspiratory flow for each device, and patient preference for a specific inhaler device should prevail over drug particle size. To assess response to treatment for SAD, most of the panelists agreed that several methods should be used, since only indirect methods are available (80.2%). This is in accordance with the ATLANTIS trial [4], in which no consensus was reached for measurement of FeNO, slow spirometry, plethysmography, chest CT, and dynamic hyperinflation after the 6-minute walk test (6MWT) as sensitive methods for evaluating response to treatment for SAD when used individually. Although no consensus was reached, the item "The improvement in cough is a good marker of good response to treatment for SAD" obtained 64.4% agreement, and the item with the lowest degree of agreement—5.8%—stated that "A decrease in the number of eosinophils in peripheral blood is a marker of good response to treatment for SAD".

Despite the large consensus on the use of extrafine particle drugs when SAD is suspected, the lack of consensus and

indeterminate responses for many of the items in the study highlight the lack of available information on SAD. However, the lack of consensus on the items was due to the dispersion of opinions, and not to polarization, thus indicating that the responses were indeterminate rather than controversial. Consequently, more studies are needed to resolve the experts' doubts. In addition, the lack of evidence means that SAD is a relatively unknown topic among panelists involved in the treatment of asthma, or at least less well known than other asthma-related topics such as comorbidities. Fortunately, more and more scientific evidence is becoming available. In fact, some of the studies were published during the development of the consensus [4,5]. The ATLANTIS study is the largest study of SAD in patients with asthma of all levels of severity [4].

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Conflicts of Interest

Vicente Plaza (last 3 years): Honoraria for speaking at sponsored meetings from AstraZeneca, Chiesi, GSK, and Novartis. Assistance with travel from Chiesi and Novartis. Consultancy services for ALK, AstraZeneca, Boehringer Ingelheim, Mundipharma, and Sanofi. Funding/grant support for research projects from a variety of government agencies and not-for-profit foundations, as well as from AstraZeneca, Chiesi, and Menarini.

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