Clinical Recommendations for the Management of Biological Treatments in Severe Asthma Patients: A Consensus Statement

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Abstract

Background: The definition of severe uncontrolled asthma and the best phenotype-driven management are not fully established.
Objective: We aimed to reach a consensus on the definition of severe uncontrolled asthma and give recommendations on optimal management with phenotype-targeted biological therapies.
Methods: A modified Delphi technique was used. A scientific committee provided statements addressing the definition of severe uncontrolled asthma and controversial issues about its treatment with biologics. The questionnaire was evaluated in 2 rounds by expert allergists. With the results, the scientific committee developed recommendations and a practical algorithm.
Results: A panel of 27 allergists reached agreement on 27 out of the 29 items provided (93.1%). A consensus definition of severe uncontrolled asthma was agreed. Prior to initiation of therapy, it is mandatory to establish the asthma phenotype and assess the presence of clinically important allergic sensitizations. Anti-IgE, anti–IL-5, anti–IL-5 receptor, and anti–IL-13/IL-4 receptor inhibitors are suitable options for patients with allergic asthma and a blood eosinophil level >300/μL (>150/μL in patients receiving oral corticosteroids). IL-5 and anti–IL-5 receptor inhibitors are recommended for patients with an eosinophilic phenotype and can also be used for patients with severe eosinophilic allergic asthma with no or a suboptimal response to omalizumab. Dupilumab is recommended for patients with moderate-severe asthma and a T_H2-high phenotype. Only physicians with experience in the treatment of severe uncontrolled asthma should initiate biological treatment.
Conclusion: We provide consensus clinical recommendations that may be useful in the management of patients with severe uncontrolled asthma.

Key words: Asthma. Delphi technique. Consensus. Biological therapy. Monoclonal antibodies. Algorithms.

Resumen

Antecedentes: La definición de asma grave no controlada y el mejor tratamiento según el fenotipo no está bien establecido.
Objetivo: Alcanzar a un consenso sobre la definición de asma grave no controlada y dar recomendaciones sobre el manejo óptimo con terapias biológicas según el fenotipo.
Métodos: Se utilizó una técnica Delphi modificada. Un comité científico proporcionó aseveraciones sobre la definición de asma grave no controlada y cuestiones controvertidas sobre su tratamiento con biológicos. El cuestionario fue evaluado en 2 rondas por alergólogos expertos. Con los resultados, el comité científico desarrolló recomendaciones y un algoritmo práctico.
Resultados: Un panel de 27 alergólogos alcanzó un consenso en 27 de 29 ítems propuestos (93,1%). Se acordó una definición consensuada de asma grave no controlada. Antes del inicio del tratamiento, es obligatorio establecer el fenotipo del asma y evaluar la presencia de alguna sensibilización alérgicas clínicamente importante. Los tratamientos anti-IgE, anti-IL-5, anti-receptor de IL-5 o anti-receptor de IL-13/IL-4 son opciones adecuadas para pacientes con asma alérgica y un nivel de eosinófilos en sangre >300 células/μL (>150 células/μL en pacientes que reciben glucocorticoides orales). Los anti-IL-5 y anti-receptor de IL-5 se recomiendan para pacientes con un fenotipo eosinofílico, y también se pueden utilizar para pacientes con asma alérgica eosinofílica grave con respuesta nula o subóptima a omalizumab. Se recomienda dupilumab para pacientes con asma moderada/grave y un fenotipo T2 alto. Solo los médicos con experiencia en el tratamiento del asma grave no controlada deben iniciar un tratamiento biológico.
Conclusión: En este trabajo se ofrecen recomendaciones clínicas consensuadas que pueden ser útiles en el manejo de pacientes con asma grave no controlada.

Palabras clave: Asma. Técnica Delfos. Consenso. Terapia biológica. Anticuerpos monoclonales. Algoritmos.

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Introduction

Around 334 million people have asthma worldwide [1], thus making it the most common chronic lung disease [2]. Approximately 5% to 10% of asthma patients are affected by severe asthma [3,4]. In a notable proportion of patients with severe asthma, symptoms continue to be suboptimally controlled, even with optimal therapy, probably because they have truly refractory severe asthma, or, in many cases, owing to comorbidities, persistent environmental exposures, or inadequate adherence to treatment or medical recommendations [4].

Studies performed in the last few years are beginning to define phenotypic biomarkers of severe asthma, and, in line with the findings, phenotype-targeted biological therapies have been rapidly approved for the management of severe asthma [5,6]. Monoclonal antibodies that target IgE (omalizumab), interleukin-5 (IL-5) (mepolizumab, reslizumab) or its receptor, IL-5Rα (benralizumab), and the α subunit of the interleukin-4 receptor (anti–IL-4Rα), which blocks the signaling of both IL-4 and IL-13 (dupilumab), are currently approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [3,5].

Several guidelines focusing on the management of patients with severe asthma [3,5,7] or with at least specific references addressing this issue [4,8] are available to help physicians. However, guideline recommendations on key topics, such as the definition of severe asthma or uncontrolled asthma, the measurement of a specific biomarker to guide treatment, or the best phenotype-driven management, are inconsistent [3-5,7,8]. In addition, large-scale, real-world clinical studies are scarce. In this regard, the clinical experience of professionals who routinely use this type of treatment and deal with clinical questions that arise in their daily practice may be valuable.

The objective of the present study was to reach a consensus on the definition of severe uncontrolled asthma and provide consensus recommendations on the management of the disease, mainly on the most appropriate treatment for the individual patient. To this end, a modified Delphi methodology was used by a panel of allergists with experience in the management of this condition.

Materials and Methods

We used a modified Delphi approach [9,10] (see Supplementary Material).

Results

The questionnaire consisted of 29 items divided into 3 blocks addressing fundamental aspects of severe asthma, phenotyping, and treatment options with biologics (Supplementary Tables 1-3).

The questionnaire was submitted to a panel of 27 allergists. All panelists responded to both rounds of evaluation. Consensus was reached on 26 out of the 29 statements evaluated during the first round. An additional statement was agreed after the second round of evaluation. Subsequently, after 2 rounds of evaluation, a consensus was reached on 27 of the 29 proposed items (93.1%). The results of the consensus are shown in Supplementary Tables 1-3.

The Table summarizes the main statements agreed by the panelists and shows recommendations on monitoring the disease.

Discussion

Adults and children with severe asthma represent a relatively small proportion of the asthma population. However, the impact of severe disease on health-related quality of life, consumption of health care resources, and costs is significant [12]. Despite recent advances in our understanding of pathogenesis and treatment, much remains unclear regarding the best approaches to the management of severe asthma or concerning the underlying mechanisms of the disease. The recent incorporation of specific treatments for severe asthma has defined a new scenario in patient management. It could prove useful to describe clinical experience with these drugs beyond the evidence generated in the premarketing clinical trials. The present study compiles the experience of clinicians specifically dedicated to the treatment of severe asthma. Together, the participants have managed and assessed the response of more than 1000 patients treated with biological drugs. In this article, the expert panel reached a consensus on aspects related to the definition of severity and control of asthma and provided recommendations on how to manage this condition with biological therapies.

Block I. Fundamentals

Regarding the definition of severity of asthma, the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines on definition, evaluation, and treatment of severe asthma [3], the Canadian Thoracic Society (CTS) guidelines on recognition and management of severe asthma [7], the Spanish Guideline on the Management of Asthma (GEMA) [8], and the Global Initiative for Asthma (GINA) guidelines [4] agree that severity has to be assessed irrespective of the level of treatment required to control symptoms and exacerbations. The ATS/ETS, CTS, and GEMA guidelines are more precise than the GINA guidelines with respect to the time of evaluation, eg, high-dose inhaled corticosteroids during the preceding year or systemic corticosteroids for ≥50% of the time during the preceding year. As for the definition of uncontrolled asthma, all guidelines include the criteria of poor symptom control and frequent severe or serious exacerbations [3,4,7,8]. However, the ATS/ETS, CTS, and GEMA guidelines [3,7,8] add spirometry criteria indicating flow limitation, which are not present in the GINA guidelines [4].

Consistent with the abovementioned guidelines, the panelists agreed that severe asthma is defined by the level of treatment with multiple drugs at high therapeutic doses (steps 5-6 of the GEMA and 5 of the GINA guidelines) and highlighted the need to rule out common problems such as incorrect inhaler techniques, comorbidities, ongoing environmental exposures, and poor adherence. Concerning, the definition of control, the panelists partially assumed

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Table. Conclusions and Recommendations

Severe asthma is understood as asthma requiring multiple drugs at high doses for treatment (steps 5-6 of the GEMA and 5 of the GINA guidelines), in which a correct inhalation technique has been proven, adherence to the treatment is good, and comorbidities and aggravating factors have been controlled.
Lack of control of severe asthma is defined as the presence of at least 1 of the following characteristics: (*a*) Symptoms of uncontrolled asthma according to clinical questionnaires (Asthma Control Questionnaire [ACQ] ≥1.5 points or Asthma Control Test [ACT] <20); (*b*) Two or more exacerbations in the preceding year that required administration of systemic corticosteroids for ≥3 days or an increase in the systemic corticosteroid dose for patients already taking these agents; (*c*) Hospitalization, intensive care unit stay, or mechanical ventilation for exacerbation during the preceding year.
Candidates for biological therapy are patients aged 6 years or older, with an objective diagnosis of severe uncontrolled asthma. Only a specialist physician with experience in the treatment of severe and poorly controlled asthma can initiate biological treatment.
Patients with severe asthma should always undergo an adequate evaluation to assess the presence of clinically relevant allergic sensitization. This includes a compatible medical history, demonstration of the presence of specific IgE by skin prick tests, and/or measurement of serum levels or specific exposure tests when the clinician deems it necessary.
When the administration of biological therapy is being considered for severe asthma, it is important to define the phenotype in order to select the appropriate drug and identify the best candidate. At least 1 peripheral eosinophil count is required to help characterize the presence of the eosinophilic inflammatory phenotype of asthma. Performing an eosinophil count in sputum may provide additional information. Available evidence is insufficient to recommend routine measurement of periostin levels for severe asthma phenotyping.
In patients with severe uncontrolled allergic asthma aged ≥6 years, treatment with omalizumab should be considered. The response to omalizumab should be evaluated after 4 to 6 months, taking into account the level of asthma control, its effect on exacerbations, and unscheduled medical visits, as well as the improvement in quality of life. If there is no positive response after that period of time, discontinuation should be considered. Some patients may present a late response.
Omalizumab should not be prescribed, at least as a first option, to patients with nonallergic severe asthma.
Omalizumab, anti–IL-5, anti–IL-5 receptor, and anti–IL-13/IL-4 receptor inhibitors are suitable options for patients with severe uncontrolled allergic asthma and in the case of blood eosinophil counts >300/μL or >150 /μL in patients receiving treatment with oral corticosteroids.
The use of an IL-5 and/or an IL-5 receptor inhibitor is recommended for the following:
a. Patients with uncontrolled asthma and a blood eosinophil level >300/μL (mepolizumab and benralizumab) or >400/μL (reslizumab).
b. Patients with an eosinophilic phenotype and severe allergic asthma with no or suboptimal response to omalizumab.
The IL-4/IL-13 inhibitor, dupilumab, is indicated for patients aged ≥12 years with moderate-to-severe asthma who have a T_H2-high phenotype (characterized by levels of FeNO >25 ppb and/or peripheral blood eosinophils >150/ μL), with or without dependence on oral corticosteroids.
Mepolizumab, benralizumab, and dupilumab could be considered as biological therapy options for adolescents aged ≥12 and <18 years with severe eosinophilic asthma. Mepolizumab can be used in patients aged ≥6 years.
According to current evidence, none of the IL-5 or IL-5 receptor inhibitors has proven to be more effective than the others in reducing exacerbations and improving asthma control in adult patients with severe eosinophilic asthma. No IL-5 or IL-5 receptor inhibitor has been proven to be safer or better tolerated than the others.
Mepolizumab and benralizumab have demonstrated efficacy in reducing treatment with oral corticosteroids.
Currently, there is no recommended biological therapy for patients with non–type 2 asthma. It is too early to determine which biologics targeting IL-4/IL-13 would be the most appropriate treatment.

the definition from the ERS/ATS, ATS/ETS, and CTS guidelines on symptom control and exacerbations; however, as in the GINA guidelines, they did not reach a consensus on spirometry criteria. The statement proposed to panelists regarding spirometry criteria comes from the ERS/ATS guidelines [5]. The current discrepancy between the different guidelines regarding the spirometry criteria to be included in the definition of control may be the reason for the lack of agreement between the panelists. In any case, these consensus statements regarding severity and control may help clinicians to distinguish between severe asthma and uncontrolled asthma, eg, due to poor adherence or incorrect inhaler technique.

In addition, panelists agreed with the current guidelines, which stipulate that when patients aged 6 years or older with an objective diagnosis of severe uncontrolled asthma are considered candidates for biological therapy, then biologic therapy should be initiated by specialist physicians with experience in managing poorly controlled asthma.

Block II. Phenotyping

Asthma is a heterogeneous disease, with different underlying processes. Phenotypes are recognizable clusters of demographic, clinical, and pathophysiological characteristics [4]. Allergic asthma, eosinophilic type 2 asthma,

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and non–type 2 asthma [8] are the 3 severe asthma phenotypes primarily targeted in randomized controlled trials investigating newer biologic therapies [13].

The panelists concurred that the use of biologic therapy in patients with severe asthma should be guided by phenotypes and that the relevant phenotypes are severe allergic asthma or severe eosinophilic asthma, which are also consistently recommended by current guidelines [3-5,7,8]. The phenotype-based indication for the biologic agents varied, with some (such as omalizumab) requiring evidence of allergy [14], others (benralizumab, mepolizumab, and reslizumab) requiring evidence of eosinophilia [15-17], and emerging agents (dupilumab) [18] requiring evidence of either eosinophilia or corticosteroid dependence. To this end, the panel highlighted that patients should undergo (or have undergone) tests to identify allergy (skin prick aeroallergen testing and specific serum IgE levels) or eosinophilia (sputum or peripheral eosinophil count) prior to initiating biologic therapy.

Guidelines are not fully consistent in their recommendations on the measurement of eosinophils in sputum or peripheral blood [3-5,7,8]. A key advantage of blood eosinophil measurement is that it is readily accessed through a complete blood count [19]. Eosinophil levels can also be measured in induced sputum, which is noninvasive, although tests for this parameter are expensive and less readily available than blood counts [19]. While a parameter that combines measurements of eosinophil levels and eosinophil activation markers could help, there is currently insufficient evidence to support such a parameter, and further information is needed. Probably for practical purposes, our panelists recommended measurement of eosinophils in peripheral blood rather than in induced sputum, although they considered that performing an eosinophil count in sputum might provide additional information. This is also consistent with the PRACtical ALLergy (PRACTALL) consensus report on asthma endotyping [20].

There is no consensus on guidelines for the use of fraction of exhaled nitric oxide (FeNO) to guide treatment, although an elevated FeNO generally reflects an underlying T_H2-mediated pathophysiology [3-5,7,8]. Some authors recommend FeNO as an optional biomarker when deciding on the use of add-on therapy in patients with severe asthma. It is also recognized that, while FeNO has been associated with an increased risk of exacerbation, poor symptom control, and consumption of health care resources, the accuracy of this marker in predicting eosinophilic airway inflammation is low [13]. According to the 2019 ERS/ATS guidelines update, FeNO levels may prove useful when choosing the patients most likely to achieve a more positive response during exacerbations and an improvement in lung function when treated with omalizumab as opposed to placebo [5]. One advantage of FeNO is that it can be measured noninvasively [7]. The panelists did not reach an agreement when asked whether FeNO can help identify potential candidates for certain biological drugs. This is somewhat contradictory to the consensus on item 18, which states that dupilumab is indicated for patients who have a T_H2-high phenotype (characterized by FeNO >25 ppb and peripheral blood eosinophils >150/ μL). This recommendation is supported by current evidence [21-23]. At the time the study was conducted, dupilumab was not licensed in Spain, and, therefore, the experience of some panelists in its use might be limited. This may explain the lack of consensus on the use of FeNO to identify potential candidates for specific biological drugs.

Periostin levels in sputum have been associated with persistent airflow limitations and resistance to inhaled corticosteroids in patients with eosinophilic asthma [24]. The Spanish guidelines (GEMA) consider that periostin in blood or sputum is a good biomarker for the T_H2-high phenotype [8], and a comparison of various biomarkers revealed serum periostin level to be the single best predictor of airway eosinophilia compared with blood eosinophil levels, FeNO, and serum IgE in a group of patients with severe asthma [25]. Nevertheless, the threshold for sputum periostin remains undefined [26]. In addition, the test is not readily available in clinical practice and is rarely used outside research settings [19]. Moreover, levels of periostin are influenced by age, skeletal growth, and puberty (periostin is produced from growing bone) [27]. The panelists considered that the available evidence is insufficient to recommend routine measurement of periostin levels for severe asthma phenotyping.

Block III. Therapeutic Options

The panelists' agreement on the use of omalizumab is similarly supported by current guidelines and the prescribing information for omalizumab [3,4,7,8,14]. In addition, there was agreement on the statement that patients who do not have allergic asthma are unlikely to benefit from omalizumab and, therefore, are not candidates for omalizumab therapy.

A certain number of patients have allergic asthma in association with eosinophilia and may therefore be candidates for either omalizumab or anti–IL-5 treatment [28]. Studies with omalizumab demonstrated that this agent can reduce peripheral blood eosinophil levels in patients with allergic asthma [29] and that omalizumab is effective in allergic patients with or without elevated eosinophil levels [30-32]. Consequently, omalizumab or anti–IL-5 treatments have been recommended in patients with allergic eosinophilic asthma [33]. Some authors believe that omalizumab should be used before anti–IL-5 therapy in patients with allergic eosinophilic asthma, based on physician familiarity with this agent [33]; however, there are limited data to support this decision. Indirect meta-analyses comparing omalizumab with mepolizumab have shown no difference in efficacy between the 2 agents, although the studies were very heterogeneous [34,35]. Since not all patients with severe allergic asthma respond to omalizumab, treatment should be suspended after 16 weeks (4 months) in nonresponders, consistent with the product information and the ERS/ATS guidelines [3,14] and based on the fact that continued treatment is unlikely to provide a benefit [36].

The panelists agreed on the use of IL-5 and/or IL-5 receptor inhibitors for patients with severe allergic asthma and an eosinophilic phenotype. This recommendation is in line with data showing that mepolizumab is effective in patients previously treated with omalizumab [37] and with recommendations by other authors [33,38].

In clinical studies with IL-5 inhibitors, patients were identified as having eosinophilic asthma based on peripheral blood eosinophil levels >300/μL (mepolizumab or

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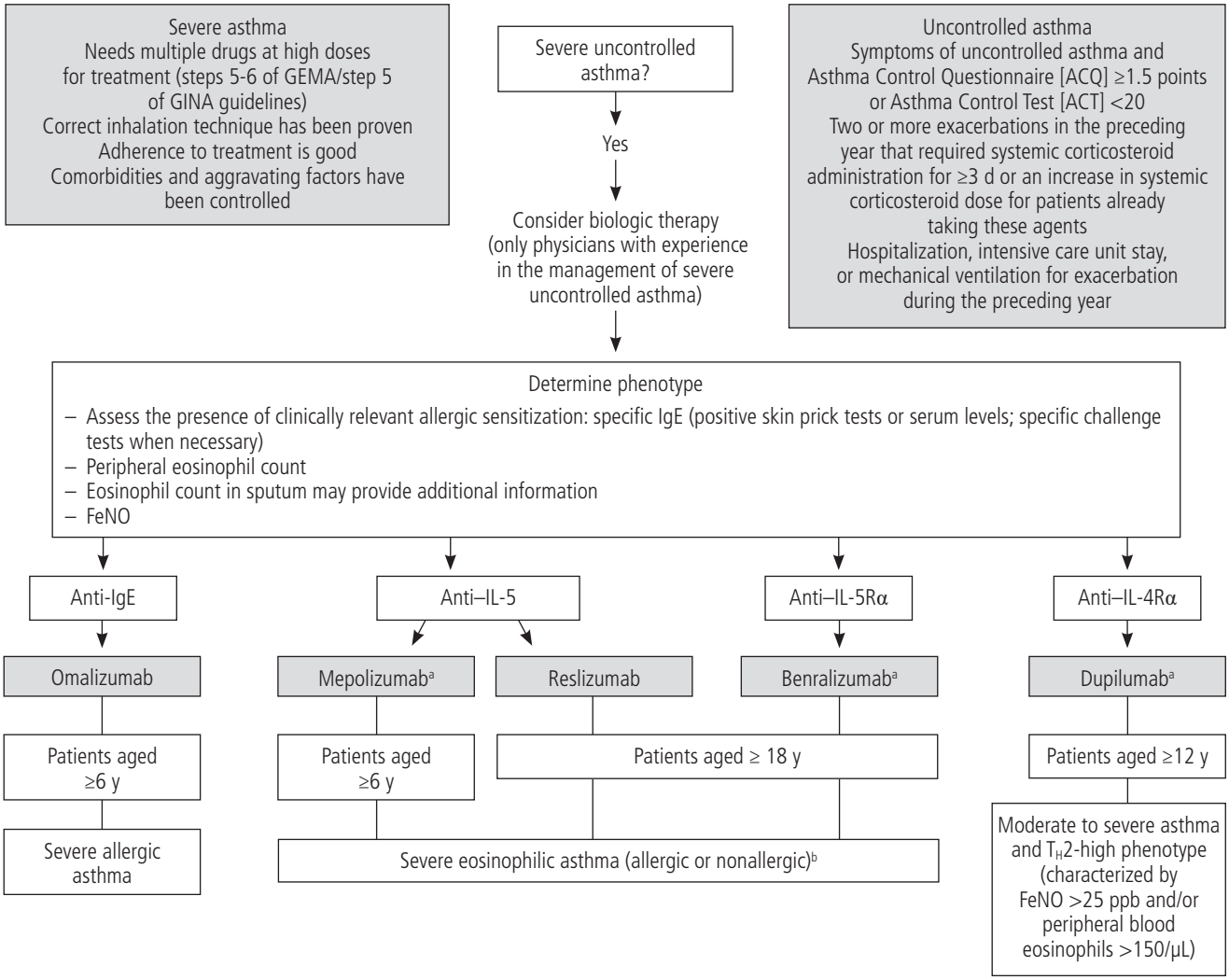

[a]Mepolizumab, benralizumab, and dupilumab have been shown to be effective in reducing oral corticosteroid use.
[b]Blood eosinophil level >300/μL (mepolizumab and benralizumab) or >400/μL (reslizumab), or >150/μL in patients receiving oral corticosteroids.

Figure. Proposed management algorithm for severe uncontrolled asthma.

benralizumab) or >400/μL (reslizumab) [39,40]. In addition, it has been shown that mepolizumab is effective in patients with blood eosinophil counts of ≥150/μL if the patient is receiving oral corticosteroids daily [41]. In line with these findings, the panelists defined the blood eosinophil level thresholds that should be considered before initiation of the different biologic agents.

The IL-4 receptor inhibitor dupilumab is currently available for the treatment of adults and adolescents aged >12 years as add-on maintenance treatment for severe uncontrolled asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO [18]. Dupilumab has been investigated in phase 2 and 3 clinical trials in comparison with placebo as add-on therapy in patients with severe uncontrolled asthma, with or without evidence of eosinophilia or allergy [21-23]. No comparative information is available to determine how the efficacy and safety profile of dupilumab compares with that of IL-5/IL-5 receptor inhibitors or omalizumab. The panelists agreed that dupilumab may be indicated for patients aged ≥12 years with moderate-to-severe asthma who have a T_H2-high phenotype (characterized by levels of FeNO >25 ppb or peripheral blood eosinophils >150/μL), with or without dependence on oral corticosteroids.

Panelists noted that benralizumab and dupilumab are approved for use in pediatric patients (<18 years), but only for those aged ≥12 years [15,18]. Of note, benralizumab is approved by the FDA for the treatment of patients with severe asthma aged ≥12 years [42], although the EMA has only approved the drug for adult patients [15]. Similarly, reslizumab is approved for use only in adult patients [17]. Omalizumab and mepolizumab can be used in children aged ≥6 years [14,16].

There is good evidence that each of the available IL-5 inhibitors (mepolizumab, reslizumab) and IL-5 receptor

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inhibitors (benralizumab) significantly improves outcomes in patients with severe eosinophilic asthma in comparison with placebo [43]. The outcomes improved by these agents are reduced frequency of exacerbation rates, improved health-related quality of life, and improved lung function (FEV_1) [43]. To date, no studies have compared IL-5 or IL-5 receptor inhibitors in patients with severe eosinophilic asthma. However, 3 indirect network comparisons have yielded different conclusions [39,40,44]. The panelists considered that no single IL-5 or IL-5 receptor inhibitor is more effective than the others, possibly owing to the divergent results of these indirect meta-analyses [39,40,44]. The studies included in the indirect comparisons differed in terms of patient characteristics and inclusion criteria, including baseline eosinophil levels. Moreover, no direct comparisons between agents were performed. Similarly, while panelists considered that no single IL-5 or IL-5 receptor inhibitor is better tolerated than the others, 2 indirect meta-analyses suggest that tolerability is better for benralizumab and reslizumab [40,44].

Our consensus is subject to a series of limitations. The Delphi methodology prevents discussions of the statements in detail, with the result that some issues may have been overlooked. In addition, the study may have been affected by subjectivity associated with personal evaluations. Furthermore, there is a potential bias in the selection of the expert panel. However, panelists were selected taking into account their contrasted experience in the field of severe asthma, and no commercial funding was received for this work, thus strengthening the recommendations obtained.

In summary, this Delphi survey provided practical consensus-based recommendations on the definition of severe uncontrolled asthma and on optimal management with available biologic agents. Although new studies are reporting promising results and new therapies are expected to be approved, this consensus statement could help clinicians to establish general criteria that facilitate selection of the right drug for the right patient.

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Conflicts of Interest

During the last 3 years, Dr Delgado has been on advisory boards for Sanofi and Bial and received speaker's honoraria from AstraZeneca, Chiesi, GlaxoSmithKline, TEVA, Leti, and Pfizer. He received assistance for travel to meetings from Menarini and Novartis.

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SUPPLEMENTARY MATERIAL

Materials and methods

In this project a consensus method (modified Delphi) was used.

Expert panel selection

A scientific committee, consisting of 27 experts with recognized experience in the management of asthma, was formed to lead the work. An expert panel with 27 members was selected by the scientific committee from the Spanish Scientific Society of Allergy and Clinical Immunology (SEAIC) considering their experience and knowledge in the field of severe asthma. These panelists were allergists from different hospitals in Spain. The selection process of the expert panelists was based on: 1) specific expertise in severe asthma and 2) currently working in severe asthma units as allergists with the possibility to prescribe biological treatments.

Study design

The goal of the Delphi method is to transform individual opinions into an expert group consensus [11]. After an exhaustive review of the literature and discussion, the scientific committee generated debatable statements addressing basic aspects of severe asthma, the measurement of specific biomarkers to guide treatment, and the best options to treat severe asthma with biologic treatments.

Afterwards, the statements were sent to panelists for an online evaluation and validation by voting in two rounds (from September to November 2019). Panelists assessed the statements with a nine-point ordinal scale (1 = full disagreement, 9 = full agreement). Responses were organized into three groups: points 1-3 were considered as disagreement, 4-6 were considered as neither agreement nor disagreement, and 7-9 were considered as agreement. Consensus on a statement was reached when the median of the responses was within the 7-9 category (consensus on agreement) or within the 1-3 category (consensus on disagreement), and less than one-third of the panelists voted outside these categories. In addition, the interquartile range (IQR) should have been less than 4. If a statement did not reach consensus in the first round of voting, it was re-evaluated in a second and last round, rephrasing the statement if needed to avoid

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ambiguity. Between the two rounds, the panelists were informed of the detailed responses from the first round.

Results are shown in tables as median and IQR of the panelists' responses, and degree of agreement, which was defined as the percentage of panelists who voted within the category that included the median of the answers (1-3, 4-6 or 7-9). Taking into account the consensus statements, the scientific committee developed a table of conclusions and recommendations (Table 1) and an algorithm for the management of the disease (Figure 1).

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Supplementary Table 1. Results of block I. Fundamentals

	Median (IQR)	Degree of agreement	Result
1. Candidates for biological therapy are patients aged 6 years or older, with an objective diagnosis of severe uncontrolled asthma.	9 (8-9)	92.6%	Agreement in 1st round
2. Severe asthma is understood as the asthma that needs multiple drugs and at high doses for treatment (steps 5-6 of the GEMA and 5 of the GINA guidelines), in which a correct inhalation technique has been proven, adherence to the treatment is good, and comorbidities and aggravating factors have been controlled.	9 (8-9)	100%	Agreement in 1st round
3. Severe uncontrolled asthma is understood as the asthma that has a lack of control, established by the presence of at least one of the following characteristics:			
a. Symptoms of uncontrolled asthma according to clinical questionnaires (Asthma Control Questionnaire [ACQ] ≥1.5 points or Asthma Control Test [ACT] < 20).	8 (7-9)	88.9%	Agreement in 1st round
b. Two or more exacerbations in the preceding year that required systemic corticosteroid administration for ≥3 days or an increase in systemic corticosteroid dose for patients already taking these agents.	9 (8-9)	92.6%	Agreement in 1st round
c. Hospitalization, intensive care unit (ICU) stay, or mechanical ventilation for exacerbation during the preceding year.	9 (8-9)	100%	Agreement in 1st round
d. Chronic airway obstruction (forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] <70% or FEV_1<80% after discontinuation of bronchodilator drugs.	3 (2-7)	51.9%	No consensus
4. Only a specialist physician with experience in the treatment of severe poorly controlled asthma can initiate a biological treatment.	9 (8-9)	96.3%	Agreement in 1st round

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Suplementary Table 2. Results of block II. Phenotyping

	Median (IQR)	Degree of agreement	Result
5. When the administration of biological drug therapy for severe asthma is being considered, it is important to define its phenotype in order to select the appropriate drug and identify the best responder.	9 (8-9)	100%	Agreement in 1st round
6. Patients with severe asthma should always undergo an adequate evaluation to assess the presence of a clinically relevant allergic sensitization, which includes a compatible medical history, demonstration of the presence of specific immunoglobulin E (IgE) by skin prick tests and / or measurement of serum specific levels, or specific challenge tests when necessary.	9 (9-9)	100%	Agreement in 1st round
7. At least one peripheral eosinophil count is required to help characterize the presence of the eosinophilic inflammatory phenotype of asthma.	9 (7-9)	85.2%	Agreement in 1st round
8. When the administration of biological therapy is being considered, performing an eosinophil count in sputum may provide additional information.	8 (7-9)	100%	Agreement in 2nd round
9. The eosinophilic pattern can be assessed from the levels of eosinophils in sputum or in peripheral blood, although both tests will not always be necessary.	8 (4-9)	74.1%	Agreement in 1st round
10. The fraction of exhaled nitric oxide (FeNO) can help identify potential candidates for certain biological drugs.	7 (5-8)	55.6%	No consensus
11. Currently, there is insufficient evidence available to recommend routine measurement of periostin levels to perform severe asthma phenotyping.	8 (7-9)	85.2%	Agreement in 1st round

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Supplementary Table 3. Results of block III. Therapeutic options

	Median (IQR)	Degree of agreement	Result
12. In patients aged 6 years or older with severe uncontrolled allergic asthma, treatment with omalizumab should be considered.	9 (8-9)	100%	Agreement in 1st round
13. Omalizumab should not be prescribed, at least as a first option, to patients with non-allergic severe asthma.	8 (7-9)	96.3%	Agreement in 1st round
14. Omalizumab, anti-IL-5, anti-IL-5 receptor or anti-IL4/IL-13 receptor biologic agents are suitable options for patients with allergic asthma and a blood eosinophil level> 300 cells/µL, or >150 cells/µL in patients receiving treatment with oral glucocorticoids.	8 (4-9)	74.1%	Agreement in 1st round
15. The response to omalizumab should be evaluated after 4 to 6 months, taking into account the level of asthma control, its effect on exacerbations and unscheduled medical visits, as well as the improvement in the quality of life.	9 (8-9)	96.3%	Agreement in 1st round
16. If there is no positive response after that period of time, discontinuation of the treatment should be considered. Some patients may present a late response.	8 (7-9)	81.5%	Agreement in 1st round
17. The use of IL-5 and / or IL-5 receptor inhibitors is recommended for patients with an eosinophilic phenotype and for those with severe allergic asthma with no or suboptimal response to omalizumab.	9 (8-9)	96.3%	Agreement in 1st round
18. The IL-4 / IL-13 inhibitor, dupilumab, is indicated for patients aged 12 years or older with moderate to severe asthma who have a T2-high phenotype (characterized by levels of FeNO> 25 ppband/or peripheral blood eosinophils >150/ µL), with or without dependence on systemic corticosteroids.	8 (7-9)	85.2%	Agreement in 1st round
19. Biotherapy with an IL-5 and / or an IL-5 receptor inhibitor is indicated in patients with uncontrolled asthma and a blood eosinophil level >300 cells µL	8 (7-9)	92.6%	Agreement in 1st round

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(mepolizumab and benralizumab) or >400 cells µL(reslizumab).			
20. Mepolizumab, benralizumab or dupilumab could be considered as biological therapy options for adolescents aged ≥ 12 and <18 years with severe eosinophilic asthma.	8 (7-9)	85.2%	Agreement in 1st round
21. Mepolizumab can be used in patients aged 6 years and older.	8 (7-9)	85.2%	Agreement in 1st round
22. None of the L-5 or IL5 receptor inhibitor has been proven to be more effective than the others in reducing exacerbations and improving asthma control in adult patients with severe eosinophilic asthma.	7 (6-9)	74.1%	Agreement in 1st round
23. Mepolizumab and benralizumab have demonstrated efficacy in reducing treatment with oral glucocorticoids.	8 (8-9)	100%	Agreement in 1st round
24. No IL-5 or IL5 receptor inhibitor has been proven to be safer or better tolerated than the others.	8 (7-9)	88.9%	Agreement in 1st round
25. It is too early to determine in what patients biotherapy targetingIL-4/IL-13 would be the most appropriate treatment.	8 (6-9)	74.1%	Agreement in 1st round
26. Currently there is no recommended biotherapy for patients with non-Type-2 asthma.	8 (8-9)	92.6%	Agreement in 1st round

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