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 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

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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

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

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 (mepolizumab and benralizumab) or >400 cells	8 (7-9)	92.6%	Agreement in 1st round

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