Clinical Recommendations for the Management of Biological Treatments in Severe Asthma Patients: A consensus statement

Short title: Biological treatments for severe asthma

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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 the 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 therapy initiation, 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 or anti-IL-13/IL4 receptor therapies are suitable options for patients with allergic asthma and a blood eosinophil level> 300 cells/µL (>150 cells/µL in patients receiving oral glucocorticoids). IL-5 andanti-IL-5 receptors are recommended for patients with an eosinophilic phenotype, and can also be used for patients with severe eosinophilic allergic asthma with no or suboptimal response to omalizumab. Dupilumab is recommended for patients with moderate/severe asthma and a T2-high phenotype. Only physicians with experience in the treatment of severe uncontrolled asthma should initiate a biological treatment.

Conclusion: This work offers consensus clinical recommendations that may be useful in the management of patients with severe uncontrolled asthma.

Key words: Asthma. Delphi Technique. Consensus. Biological Therapy. Antibodies. Monoclonal. 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 suffer from asthma worldwide[1], which makes it the most common chronic lung disease[2].Approximately 5% to 10% of asthma suffers are affected by severe asthma[3,4].A notable proportion of patients with severe asthma continue to have their symptoms suboptimally controlled even with maximal therapy, which may be due to truly refractory severe asthma, or, in many cases, due to comorbidities, persistent environmental exposures, or inadequate adherence to treatment or medical recommendations[4].

In the last few years, studies are beginning to define phenotypic biomarkers of severe asthma, and in line with these studies, there has been a rapid introduction of phenotype-targeted biological therapies 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), or the alpha subunit of interleukin-4 receptor (anti-IL4Rα), that blocks the signaling of both IL-4 and IL-13 (dupilumab),are currently approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA)[3,5].

To guide clinicians, there are guidelines focusing on the management of patients with severe asthma[3,5,7] or with at least specific references addressing this issue[4,8]. However, guideline recommendations about 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 real world clinical studies are currently 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 usual practice may be valuable.

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

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Materials and methods

In this project a consensus method (modified Delphi) was used[9,10].This section is detailed in the Supplementary Material.

Results

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

The questionnaire was submitted to the panel of the 27 allergists. All panelists responded to both rounds of evaluation. Consensus was reached on 26 out of the 29 statements evaluated in 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 out of the 29 proposed items (93.1%). All of them reached consensus on agreement. The results of the consensus are shown in Supplementary Tables 1-3.

Table 1 summarizes the main statements agreed by the panelists and shows recommendations on the monitoring of 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, and healthcare resource consumption and costs is significant[12]. Despite recent advances in understanding its 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 patients with severe asthma has defined a new scenario in the management of these patients. It may be necessary to describe the clinical experience with the use of these drugs, beyond the evidence generated in the pre-marketing clinical trials. The present work gathers the experience of clinicians specifically dedicated to the treatment of severe asthma. Together, the participants in this work have managed and assessed the response of more than 1,000 patients treated with biological drugs. In this article, the qualified group of allergists with experience in the management of

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severe asthma 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[8], and the Global Initiative for Asthma(GINA) guidelines[4]agree that asthma severity has to be assessed irrespectively 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 about the time of evaluation, e.g. high dose inhaled corticosteroids (*ICS*) during the preceding year or systemic corticosteroid (SC) for ≥50% of time during the preceding year. Regarding the definition of uncontrolled asthma, all guidelines include 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 that are not present in the GINA guidelines[4].

In line with these guidelines, the panelists agreed that severe asthma is defined by the level of treatment with multiple drugs and 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, on-going environmental exposures, or poor adherence. Concerning, the definition of control, the panelist partially assumed the definition from the ERS/ATS ATS/ETS, CTS guidelines about symptom control and exacerbations, but, as in the GINA guidelines, they did not reach a consensus on spirometry criteria. The asseveration proposed to panelists regarding these 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. Anyway, these consensus declarations regarding severity and

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control may help clinicians to distinguish between severe asthma and uncontrolled asthma, e.g. due to poor treatment adherence or incorrect inhaler technique.

In addition, panelists were in agreement with the current guidelines when considering as candidates for biological therapy patients aged 6 years or older, with an objective diagnosis of severe uncontrolled asthma, and recommending that 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 disease processes. Recognizable clusters of demographic, clinical or pathophysiological characteristics are often called asthma phenotypes[4]. Allergic or eosinophilic Type-2 asthma, and non-Type-2 asthma[8] are the three severe asthma phenotypes primarily targeted in randomized controlled trials investigating newer biologic therapies[13].

The panelists concurred that phenotyping should guide the use of biologic therapy in patients with severe asthma, and that the relevant phenotypes are severe allergic asthma or severe eosinophilic asthma, which are also consistently recommended by the current guidelines in general[3–5,7,8].The phenotypic 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 can be readily accessed through a full blood count[19].Eosinophil levels can also be measured in induced sputum, which is non-invasive, but tests for this parameter are expensive and less readily available compared with blood eosinophil levels[19].A parameter that combines measurements of eosinophil levels and eosinophil activation markers could help, but there is currently

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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 over the use of fraction of exhaled nitric oxide (FeNO) to guide treatment, although an elevated FeNO generally reflects an underlying T2-mediated pathophysiology[3–5,7,8].Some authors recommend FeNO as an optional biomarker when deciding the use of add-on therapy in patients with severe asthma. Itis also recognized that, although FeNO has been associated with increased exacerbation risk, poor symptom control, and healthcare resources consumption, the accuracy of this marker in predicting eosinophilic airway inflammation is low[13]. According to the 2019 ERS/ATS guidelines update, FeNO levels may be useful in choosing patients most likely to achieve a more positive response during exacerbations and an improvement in lung function when treated with omalizumab compared to placebo[5].One advantage of FeNO is that it can be measured non-invasively[7].The panelists did not reach an agreement when asked if 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 T2-high phenotype (characterized by levels of FeNO> 25 ppb and peripheral blood eosinophils >150/ µL), which is a recommendation 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 certain biological drugs.

Periostin levels in sputum have been associated with persistent airflow limitation and ICS resistance in patients with eosinophilic asthma[24]. The Spanish guidelines (GEMA) consider that periostin in blood or sputum is a good biomarker for Th2-high phenotype[8]. In addition, in a comparison of different biomarkers, serum periostin level was the single best predictor of airway eosinophilia compared to blood eosinophil levels, FeNO or serum IgE in a group of patients with severe asthma [25]. However, the

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threshold for sputum periostin has not yet been defined[26],this test is not readily available in clinical practice and is rarely used outside research settings[19].In addition, levels of periostin are influenced by age, skeletal growth and puberty because it is produced from growing bone[27].The panelists considered that the available evidence is insufficient to recommend that routine measurement of periostin levels should be performed for severe asthma phenotyping.

Block III. Therapeutic options

The panelists' agreement on the use of omalizumab is similarly supported by the current guidelines and the omalizumab prescribing information[3,4,7,8,14]. In addition, there was agreement on the statement that patients that 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 therefore may 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], but there are limited data to support this decision. Indirect meta-analyses comparing omalizumab with mepolizumab have shown no difference in efficacy between the two agents, although there was considerable heterogeneity among the studies[34,35].Not all patients with severe allergic asthma respond to omalizumab, so treatment with this agent should be suspended after 16 weeks (4 months) in non-responding patients, which is 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 recommendations are

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

The IL-4 receptor inhibitor dupilumab is currently available for the treatment of adults and adolescents older that 12 years as an 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 an 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 of dupilumab compare with those of the IL-5/IL-5 receptor inhibitors or omalizumab. The panelists agreed that dupilumab may be 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 ppb or peripheral blood eosinophils >150/µL), with or without dependence on systemic corticosteroids.

Panelists noted that benralizumab and dupilumab are approved for use in pediatric patients (<18 years old), 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], but by the EMA it is indicated only for adult patients[15].Reslizumab is approved for use only in adult patients as well[17].Omalizumab and mepolizumab can be used in children aged 6 years or older[14,16].

There is good evidence that each one of the available IL-5 inhibitors (mepolizumab, reslizumab), and IL-5 receptor inhibitors (benralizumab) significantly improves outcomes in patients with severe eosinophilic asthma in comparison to placebo[43].Outcomes improved by these agents are a reduction in exacerbation

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rates, an improvement in health-related quality of life, and an improvement in lung function (FEV1)[43]. To date, there are no studies comparing different IL-5 or IL-5 receptor inhibitors in patients with severe eosinophilic asthma. However, three indirect network comparisons have been published with differing conclusions[39,40,44].The panelists considered that no single IL-5 or IL-5 receptor inhibitor is more effective than the others, which may be due to the divergent results of these indirect meta-analyses[39,40,44]. Studies included in the indirect comparisons had different patient characteristics and inclusion criteria, including baseline eosinophil levels. Moreover, no direct comparisons between agents were performed. Similarly, panelists considered that no single IL-5 or IL-5 receptor inhibitor is better tolerated than the others, although two indirect meta-analyses suggest that benralizumab and reslizumab have the best levels of tolerability[40,44].

There are several limitations of our consensus that must be noted. The Delphi methodology prevents discussions of the statements in detail and some issues may be overlooked. In addition, it may be subjectivity linked to personal evaluations, and there is a potential bias in the selection of the expert panel. However, panelists have been selected taking into account their contrasted experience in the field of severe asthma, and there is no commercial funding for this work, which can be considered as strengths of the recommendations obtained.

In summary, the results of this Delphi survey provided some practical consensus recommendations on the definition of severe uncontrolled asthma and on the best management with the different biologic agents available. Although, there are new studies with promising results and the approval of new therapies is to be expected, this consensus may be useful for clinicians to establish general criteria that allow the selection of the right drug for the right patient.

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Conflict of interest

Dr. Delgado in the last three years 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 meetings travel from Menarini and Novartis.

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Dr. Domínguez-Ortega has served as an advisor to LETI, Mundipharma, AstraZeneca, Chiesi, Novartis and GSK, and has received lecture fees by Chiesi, GSK, Novartis, Leti, AstraZeneca, Sanofi, Stallergenes and TEVA.

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References

1. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211–59.
2. Croisant S. Epidemiology of asthma: prevalence and burden of disease. Adv Exp Med Biol. 2014;795:17–29.
3. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Euro Respir J. 2014;43(2):343–73.
4. Global Initiative for Asthma. 2019 GINA Main Report.. [Internet]. [cited 2019 Dec 19];Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf
5. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline. Eur Respir J.2020;55(1):1900588.
6. Dávila I, Quirce S, Olaguibel J. Selection of Biologics in Severe Asthma: A Multifaceted Algorithm. J Investig Allergol Clin Immunol. 2019;29(4):325–8.
7. FitzGerald JM, Lemiere C, Lougheed MD, Ducharme FM, Dell SD, Ramsey C, et al. Recognition and management of severe asthma: A Canadian Thoracic Society position statement. Can J Respir Crit Care Sleep Med. 2017;1(4):199–221.
8. Guías Española para el Manejo del Asma. GEMA 4.4 [Internet]. Gemasma [cited 2019 Dec 19];Available from: https://www.gemasma.com/
9. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995;311(7001):376–80.
10. The RAND/UCLA Appropriateness Method User's Manual | RAND [Internet]. [cited 2013 Jan 16];Available from: http://www.rand.org/pubs/monograph_reports/MR1269.html
11. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014;67(4):401–9.
12. Fleming L, Heaney L. Severe Asthma—Perspectives From Adult and Pediatric Pulmonology. Front Pediatr. 2019;7:389.
13. Opina MTD, Moore WC. Phenotype-Driven Therapeutics in Severe Asthma. Curr Allergy Asthma Rep. 2017;17(2):10.
14. European Medicines Agency. Xolair (omalizumab). Summary of Product Characteristics. [Internet]. [cited 2019 Dec 19];Available from: https://www.ema.europa.eu/en/documents/product-information/xolair-epar-product-information_en.pdf
15. European Medicines Agency. Fasenra (benralizumab). Summary of Product Characteristics. [Internet]. [cited 2019 Dec 19];Available from: https://www.ema.europa.eu/en/documents/product-information/fasenra-epar-product-information_en.pdf
16. European Medicines Agency. Nucala (mepolizumab). Summary of Product Characteristics. [Internet]. [cited 2019 Dec 19];Available from: https://www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf

doi: 10.18176/jiaci.0638

17. European Medicines Agency. Cinqaero (reslizumab). Summary of Product Characteristics. [Internet]. [cited 2019 Dec 19];Available from: https://www.ema.europa.eu/en/documents/product-information/cinqaero-epar-product-information_en.pdf
18. European Medicines Agency. Dupixent (dupilumab). Summary of Product Characteristics. [Internet]. [cited 2019 Dec 19];Available from: https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf
19. Kim H, Ellis AK, Fischer D, Noseworthy M, Olivenstein R, Chapman KR, et al. Asthma biomarkers in the age of biologics. Allergy Asthma Clin Immunol. 2017;13(1):48.
20. Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol. 2011;127(2):355–60.
21. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med 2018;378(26):2486–96.
22. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet. 2016;388(10039):31–44.
23. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in Persistent Asthma with Elevated Eosinophil Levels. N Engl J Med. 2013;368(26):2455–66.
24. Bobolea I, Barranco P, Del Pozo V, Romero D, Sanz V, López-Carrasco V, et al. Sputum periostin in patients with different severe asthma phenotypes. Allergy. 2015;70(5):540–6.
25. Jia G, Erickson RW, Choy DF, Mosesova S, Wu LC, Solberg OD, et al. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. J Allergy Clin Immunol. 2012;130(3):647-654.e10.
26. Wan XC, Woodruff PG. Biomarkers in Severe Asthma. Immunol Allergy Clin North Am. 2016;36(3):547–57.
27. Izuhara K, Ohta S, Ono J. Using Periostin as a Biomarker in the Treatment of Asthma. Allergy Asthma Immunol Res 2016;8(6):491.
28. Albers FC, Müllerová H, Gunsoy NB, Shin J-Y, Nelsen LM, Bradford ES, et al. Biologic treatment eligibility for real-world patients with severe asthma: The IDEAL study. J Asthma. 2018;55(2):152–60.
29. Massanari M, Holgate ST, Busse WW, Jimenez P, Kianifard F, Zeldin R. Effect of omalizumab on peripheral blood eosinophilia in allergic asthma. Respir Med. 2010;104(2):188–96.
30. Hanania NA, Wenzel S, Rosén K, Hsieh H-J, Mosesova S, Choy DF, et al. Exploring the Effects of Omalizumab in Allergic Asthma: An Analysis of Biomarkers in the EXTRA Study. Am J Respir Crit Care Med. 2013;187(8):804–11.
31. Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Eur Respir J. 2018;51(5):1702523.

doi: 10.18176/jiaci.0638

32. Vennera MDC, Pérez De Llano L, Bardagí S, Ausin P, Sanjuas C, González H, et al. Omalizumab Therapy in Severe Asthma: Experience from the Spanish Registry—Some New Approaches. J Asthma. 2012;49(4):416–22.
33. Zervas E, Samitas K, Papaioannou AI, Bakakos P, Loukides S, Gaga M. An algorithmic approach for the treatment of severe uncontrolled asthma. ERJ Open Res. 2018;4(1):00125–2017.
34. Cockle SM, Stynes G, Gunsoy NB, Parks D, Alfonso-Cristancho R, Wex J, et al. Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison. Respir Med. 2017;123:140–8.
35. Nachef Z, Krishnan A, Mashtare T, Zhuang T, Mador MJ. Omalizumab versus Mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: A network meta-analysis. J Asthma. 2018;55(1):89–100.
36. Trivedi A, Pavord ID, Castro M. Bronchial thermoplasty and biological therapy as targeted treatments for severe uncontrolled asthma. Lancet Respir Med. 2016;4(7):585–92.
37. Magnan A, Bourdin A, Prazma CM, Albers FC, Price RG, Yancey SW, et al. Treatment response with mepolizumab in severe eosinophilic asthma patients with previous omalizumab treatment. Allergy. 2016;71(9):1335–44.
38. Menzella F, Galeone C, Bertolini F, Castagnetti C, Facciolongo N. Innovative treatments for severe refractory asthma: how to choose the right option for the right patient? J Asthma Allergy. 2017;10:237-47.
39. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, et al. Anti–IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. J Allergy Clin Immunol. 2019;143(1):190-200.e20.
40. Cabon Y, Molinari N, Marin G, Vachier I, Gamez AS, Chanez P, et al. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials. Clin Exp Allergy. 2017;47(1):129–38.
41. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med. 2016;4(7):549–56.
42. U.S. Food and Drug Administration. FASENRA (benralizumab). Full prescibing information. [Internet]. [cited 2020 Jun 11];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf
43. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev. 2017;9(9):CD010834.
44. He L-L, Zhang L, Jiang L, Xu F, Fei D-S. Efficacy and safety of anti-interleukin-5 therapy in patients with asthma: A pairwise and Bayesian network meta-analysis. Int Immunopharmacol. 2018;64:223–31.

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Table 1. Conclusions and recommendations

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.
Lack of control of severe asthma is 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), 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, c) Hospitalization, intensive care unit (ICU) 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 a biological treatment.
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 intraepidermal tests and / or measurement of serum levels, or specific exposure tests when the clinician deems it necessary.
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 respondent. At least one 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. There is insufficient evidence available for the recommendation of routine measurement of periostin levels to perform severe asthma phenotyping.
In patients aged 6 years or older with severe uncontrolled allergic asthma, 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 the quality of life. 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. Omalizumab should not be prescribed, at least as a first option, to patients with non-allergic severe asthma.

Omalizumab, anti-IL-5, anti-IL-5 receptor or anti-IL-13/IL4 receptor biologic agents are suitable options for patients with severe uncontrolled allergic asthma and a blood eosinophil level >300 cells/µL, or >150 cells/µL in patients receiving treatment with oral glucocorticoids.

The use of an IL-5 and/or an IL-5 receptor inhibitor is recommended for:

a. Patients with uncontrolled asthma and a blood eosinophil level >300 cells µL (mepolizumab and benralizumab) or >400 cells µL (reslizumab).
b. Patients with an eosinophilic phenotype and a severe allergic asthma with no or suboptimal response to omalizumab.

The IL-4/IL-13 inhibitor, dupilumab, is indicated for patients aged 12 years or over with moderate to severe asthma who have a T2-high phenotype (characterized by levels of FeNO> 25 ppb and/or peripheral blood eosinophils >150/ µL), with or without dependence on systemic corticosteroids.

Mepolizumab, benralizumab or 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 and older.

According to current evidence, none of the IL-5 or IL5 receptor inhibitors has been 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 IL5 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 glucocorticoids.

Currently there is no recommended biotherapy for patients with non-Type-2 asthma. It is too early to determine in which patient biotherapy targeting IL-4/IL-13 would be the most appropriate treatment.

Figure 1. Proposed management algorithm for severe uncontrolled asthma