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Disease Modification in Asthma: Are We on the Right Way? A Multidisciplinary Expert Delphi Consensus (MODIASTHMA Consensus)

Juan Carlos Miralles-López[1,2], Francisco J Alvarez-Gutiérrez[3], Julio Delgado-Romero[4], Santiago Quirce[5,6], Jose Gregorio Soto-Campos[7], Ruben Andújar-Espinosa[2,8], Sheila Cabrejos-Perotti[2,9], Manuel Castilla-Martínez[2,10], Isabel Flores-Martín[2,11], Manuel José Pajarón-Fernández[2,12], José Valverde-Molina[2,13,14]

[1]Allergy Department, University General Hospital Reina Sofia, Murcia, Spain; [2]Severe Asthma Association of the Region of Murcia. ASGRAMUR, Murcia, Spain; [3]Medical and Surgical Unit of Respiratory Diseases, Hospital Universitario Virgen Del Rocío, Seville, Spain; [4]Allergology Clinical Management Unit, Hospital Virgen Macarena, Seville, Spain; [5]Department of Allergy, La Paz University Hospital, IdiPAZ, Madrid, Spain; [6]CIBER of Respiratory Diseases (CIBERES), Madrid, Spain; [7]Pneumology and Allergy Clinical Management Unit, University Hospital of Jerez, Jerez, Spain; [8]Pulmonology Department. H. U. Virgen de la Arrixaca, Murcia, Spain; [9]Allergy Department, University General Hospital Santa Lucia, Cartagena, Spain; [10]Pulmonology Department, University General Hospital Los Arcos, San Javier, Spain; [11]Allergy Department, Hospital Comarcal del Noroeste, Caravaca, Murcia, Spain; [12]Allergy Department, Hospital de la Vega Lorenzo Guirao, Cieza, Spain; [13]Paediatrics Department, University General Hospital Santa Lucia (Cartagena University Hospital Complex), Cartagena, Spain; [14]IMIB Biomedical Research Institute, Murcia, Spain

Correspondence: Juan Carlos Miralles-López, Allergy Department, University General Hospital Reina Sofia, Murcia, Spain, Email juancmiralleslopez@gmail.com

Purpose: With the advent of biological therapies, emerging concepts regarding establishing new targets in asthma management, such as disease modification, have entered the debate among the scientific community. The definitions that form the conceptual basis of this goal need to be agreed upon.

Methods: A multidisciplinary expert group was assembled as the steering committee. A systematic literature review was conducted to identify the scientific background for constructing appropriate definitions. Based on the literature review and the clinical experience of the experts, the committee built a list of statements that could be applied to establish the definition of disease modification in asthma. After that, a Delphi validation was performed to assess the appropriateness of the list of statements. The questionnaire included a total of 22 statements, divided into "Essential criteria for disease modification in asthma" (5 statements) and "Disease modification indicators and other considerations" (17 statements). Panelists used a 9-point Likert scale to measure agreement on each statement. The cut-off point for high consensus was defined as a minimum score of 7 and had to be reached by at least two-thirds of the experts.

Results: A total of 192 asthma experts voted on statements anonymously. Of those, 104 (54%) were Pneumologists, 65 (34%) were allergologists, and 23 (12%) were Pediatricians. An interim analysis of round 1 data was performed. All statements reached consensus on the first round, with a median score above 7 in all cases.

Conclusion: In conclusion, in this Delphi study, a large number of experts in the management of severe asthma from different specialties agreed on the clinical-functional and pathophysiological aspects to be considered in order to try to achieve disease modification.

Keywords: severe asthma, disease modification, delphi process, remission

Introduction

In the era of biologics, asthma management has evolved substantially as the underlying mechanisms of the disease have been identified with acceptable accuracy. Therefore, treatment can be targeted in a personalized way for most patients.[1] This personalization and higher thresholds of efficacy and effectiveness have led us to introduce concepts such as remission.[2] However, in analyzing the response to biologics in asthma, we note a lack of unity in establishing which components should be included and the magnitude of improvement that can be considered sufficient to achieve that goal.[3–7]

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Now that future perspectives on asthma management are under debate, we would like to raise a question that goes even deeper into the foundations of the goal to be pursued: are current (and future) treatments capable of modifying the disease? This assumption arises naturally if we consider that biological treatments have, under certain circumstances, the capacity to induce remission in asthma patients, but what are the implications of achieving this state for the long-term evolution of the disease?

In asthma, approaches such as allergen immunotherapy have opened the door to disease modification in specific patient subgroups. However, clinical evidence is still modest.[8] Yet, disease modification is a mature concept in other pathologies, such as immune-mediated inflammatory diseases (IMIDs). In this case, two domains are established that allow us to characterize the disease: activity and damage. In inflammatory diseases mediated by immune dysregulation, activity strongly marks the signs and symptoms of the disease. In addition, it has been observed that sustained uncontrolled activity triggers damage to the affected tissue.[9] In the case of asthma, we might assume that, at least in a proportion of patients, this activity-damage binomial might reflect what is happening at the bronchial level (Figure 1). Thus, by activity, we might include exacerbations (and the associated need for corticosteroid use), significant asthma symptoms, and bronchial hyperresponsiveness, and this activity could be identified, among others, by ACT, elevation of biomarkers such as the fraction of exalted nitric oxide (FeNO) and eosinophilia (Eos) in blood or sputum or other markers.[10–12] On the other hand, steadily insufficient control of this activity may be linked to damage to bronchial tissue, known as airway remodeling.[13] In this case, such damage could be reflected in the loss of forced expiratory volume in 1-second post-bronchodilator (post-BD FEV_1), structural alterations detected by imaging techniques,[14] biopsies,[15] or other methods such as oscillometry,[16] and emerging biomarkers as galectins.[17] Although this cause-effect approach between activity/inflammation and damage may be acceptable in a large proportion of patients, given the enormous heterogeneity of asthma, in some cases, there may be alternative processes where damage is not linked to high detectable activity, or high activity does not a priori generate great damage.[18]

Airway obstruction deserves a separate mention, given its multifactorial etiology. In some cases, it will indefeasibly be the product of airway narrowing because of the remodeling process, which includes smooth muscle hyperplasia, basement membrane thickening, and sub-epithelial fibrosis, principally.[19,20] Alternatively, it may be predominantly due to mucus accumulations or plugs linked to interleukin IL-13 activity, mucin expression, and

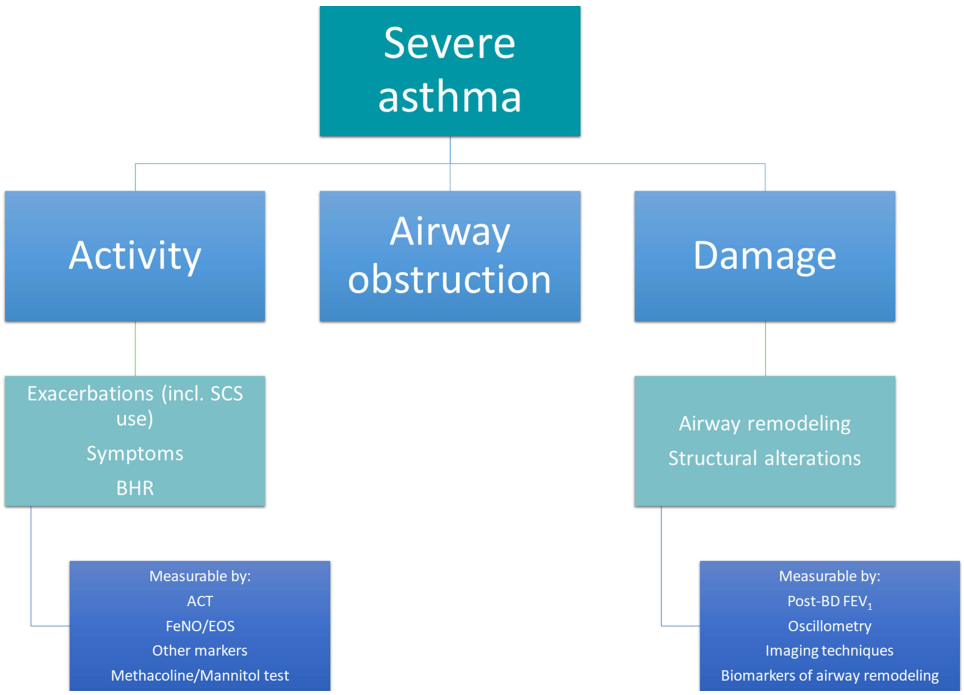

Figure 1 Proposed scheme to reflect activity and Damage in severe asthma. Model created by the authors.

extracellular traps produced by eosinophils.[21–23] Obstruction can be caused by both activity and cumulative damage to bronchial tissue.

The role of biologics in activity control seems clear, provided that each patient's phenotype is correctly identified.[24] What role they might play in modulating, halting, or, more interestingly, reversing or preventing damage remains to be elucidated. Some studies have generated results that give us a glimpse of the possible effects of airway remodeling and progressive loss of lung function.[25] Furthermore, some results indicate that, among the predictors of good response, time from diagnosis and baseline lung function are important for achieving a complete response, suggesting that an earlier start is better.[26] Therefore, there are two lines of work: the first is to establish which definitions apply to the concept of disease modification so that, unlike in remission, all specialties involved in the management of asthma have the same conceptual starting point. The other line of work should encourage studies to be conducted to assess the reduction in lung function decline, analyzing associated baseline characteristics and risk factors. Some studies are aimed at this end, some of which integrate clinical parameters with structural analysis through imaging techniques.[27–34]

Focusing on establishing unified theoretical definitions of disease modification, we have coordinated a working group to validate a list of statements that we consider key to determining the basis for this concept. We then subjected its rigor and validity to a Delphi consensus process.

Methods

This study used a Delphi method to reach an expert consensus on the definition of disease modification in asthma. The Delphi consisted of four phases: selection of an expert panel, systematic literature review, development of surveys, and iterative processes to obtain consensus.

A board of eleven experts (six allergists, four pulmonologists, and one pediatrician) was appointed to the scientific committee. During the first meeting, the experts discussed and clearly defined the scope and methodology to follow.

A systematic literature review was conducted using PRISMA guidelines.[35] The board systematically searched PubMed, Medline, and Embase to identify articles published between January 1st, 2000, and May 31st, 2024 (inclusive) that contained keywords relating to disease modification, remission, asthma, biologic therapies, and airway remodeling. Two reviewers independently screened the results based on the titles and abstracts and then assessed the eligibility of the publications.

During the second meeting, based on the literature review and the clinical experience of the experts, the committee convened to draw up a list of statements that could be applied to establish the definition of disease modification in asthma, which was revised to minimize redundancies and ensure clear and consistent wording. These included a total of 22 statements, divided into ESSENTIAL CRITERIA FOR DISEASE MODIFICATION IN ASTHMA (5 statements) and DISEASE MODIFICATION INDICATORS AND OTHER CONSIDERATIONS (17 statements). Panelists used a 9-point Likert scale to measure agreement on each statement, with 1–3 indicating strongly disagree/not appropriate, 4–6 neither agree nor disagree/neutral, and 7–9 totally agree. The cut-off point for high consensus was defined as a minimum score of 7 and had to be reached by at least two-thirds of the experts (66.6%). Thus, any statement reaching a score of 1, 2, or 3 would achieve consensus on disagree/not appropriate, those scoring 4,5 or 6 should be restated and go through a second round of validation, and those scoring 7,8 or 9 would achieve consensus on agree/appropriate. Finally, the analysis of the data and the preparation of the final Delphi report were conducted with the support of a methodology expert.

The questionnaire was submitted to the asthma network groups of the main Allergology (SEAIC), Pneumology (SEPAR), and Pediatrics Pneumology (SENP) Scientific Societies in Spain.

The study was reviewed and approved by the Clinical Research Ethics Committee of the Santa María del Rosell University Hospital (Cartagena University Hospital Complex, Cartagena, Spain), Health Areas II and VIII of the Murcian Health Service (CEI. 24–78. DELPHI. 27/03/2024). Informed consent was obtained from the participants, and it was carried out following the guidelines established in the Declaration of Helsinki.

Results

A total of 192 experts voted on statements anonymously. All (100%) completed the full set of questions. Of those, 104 (54%) were Pneumologists, 65 (34%) were allergists, and 23 (12%) were Pediatricians. The average number of years of experience of the participants was 18.7. All participants belonged to the asthma groups of the above-mentioned scientific societies.

All statements reached consensus on the first round, with an average score above 7 in all cases. The results are shown in Table 1. Seven out of 22 statements reached a median score of 9 (maximum score), and 14 scored a median of 8, showing a wide degree of consensus. This is a remarkable result, considering the number of participants and the multidisciplinary nature of the sample.

Table 1 Statements with Respective Levels of Consensus Reached During First Round

ESSENTIAL CRITERIA FOR DISEASE MODIFICATION IN ASTHMA N = 192		
	Scor 7–9	**N and % of agreement**
Mejoría completa de los signos y síntomas. Complete improvement of signs and symptoms.	9	180 (93)
Normalización en los biomarcadores/actividad biológica. Normalization in biomarkers/biological activity.	8	159 (83)
Reversión de la hiperreactividad bronquial. Reversal of bronchial hyperresponsiveness.	8	161 (83)
Mejoría o estabilización de las anomalías estructurales de las vías respiratorias. Improvement or stabilisation of structural airway abnormalities.	8	158 (82)
Mantenimiento a largo plazo de este estado, al menos tres años. Long-term maintenance of this status, at least three years.	8	170 (89)
DISEASE MODIFICATION INDICATORS AND OTHER CONSIDERATIONS		
Es necesaria una puntuación de la actividad de la enfermedad validada, objetiva y multidimensional. A validated, objective, and multidimensional disease activity score is needed.	9	187 (97)
En pacientes con alteraciones basales del TC potencialmente reversibles, se deben incluir criterios de imagen como marcador objetivo de modificación de la enfermedad a nivel estructural. In patients with potentially reversible baseline CT alterations, imaging criteria should be included as an objective marker of disease modification at the structural level.	8	143 (74)
A pesar de su etiología multifactorial, y de su variabilidad clínica, se pueden distinguir dos dominios en el asma, la actividad y el daño. Despite its multifactorial aetiology and clinical variability, two domains can be distinguished in asthma, activity, and damage.	8	154 (80)
El concepto de actividad incluye la inflamación subyacente. The concept of activity includes the underlying inflammation.	8	174 (91)
El concepto de actividad incluye la hiperreactividad bronquial. The concept of activity includes bronchial hyperresponsiveness.	8	170 (88)
El concepto de actividad incluye los signos y síntomas de la enfermedad. The activity concept includes the signs and symptoms of the disease.	9	181 (95)
El concepto de daño incluye las alteraciones estructurales y funcionales de las vías respiratorias. The concept of damage includes structural and functional alterations of the airways.	9	188 (98)
Deben buscarse y validarse indicadores de actividad, que nos ayuden a priorizar el abordaje precoz en pacientes con peor pronóstico. Indicators of activity should be sought and validated to help us prioritise early treatment in patients with a poorer prognosis.	9	189 (98)

(*Continued*)

Table 1 (Continued).

DISEASE MODIFICATION INDICATORS AND OTHER CONSIDERATIONS		
	Scor 7–9	**N and % of agreement**
Se deben utilizar indicadores que predigan la pérdida progresiva de la función pulmonar. Indicators that predict progressive loss of lung function should be used.	9	187 (97)
El asma debe abordarse longitudinalmente, valorando tanto la consecución como el mantenimiento de un estado de remisión clínica. Asthma should be approached longitudinally, assessing both the achievement and maintenance of a state of clinical remission.	9	185 (96)
En los pacientes incapaces de alcanzar una respuesta completa, también puede considerarse la modificación de la enfermedad definiendo el techo de respuesta individual. In patients unable to achieve a complete response, disease modification can also be considered by defining the individual response ceiling.	8	160 (84)
En pacientes con un rasgo tratable dominante, debe priorizarse el abordaje de dicho rasgo. In patients with a dominant treatable trait, priority should be given to addressing that trait.	8	167 (87)
La hipersecreción mucosa debe abordarse como un rasgo tratable Mucus hypersecretion should be addressed as a treatable trait.	8	167 (87)
La hipersecreción mucosa debe considerarse como una parte reversible de la obstrucción bronquial. Mucus hypersecretion should be considered as a reversible part of bronchial obstruction.	8	151 (78)
El remodelado puede ser reversible y ser considerado un rasgo tratable para la modificación de la enfermedad. Remodeling may be reversible and be considered a treatable trait for disease modification.	7	141 (74)
La modificación de la enfermedad supone un descenso del escalón terapéutico necesario para mantener el control de la enfermedad. Disease modification involves a lowering of the therapeutic step needed to maintain disease control.	8	149 (78)
El planteamiento de modificación de la enfermedad debe ser diferente en el asma de inicio en edades tempranas que en el asma de inicio tardío en el adulto. The approach to disease modification should be different in early-onset asthma than in late-onset asthma in adults.	8	151 (79)

The high level of concordance of these first-round results made it possible to avoid a second round, and we, therefore, consider the Delphi consensus phase closed.

Among the ESSENTIAL CRITERIA FOR DISEASE MODIFICATION IN ASTHMA, the five essential criteria were consensuated with a score of 9 (Complete improvement of signs and symptoms), or 8 (Normalization in biomarkers/ biological activity, Reversal of bronchial hyperresponsiveness, Improvement or stabilisation of structural airway abnormalities, and Long-term maintenance of this status, at least three years).

Of the DISEASE MODIFICATION INDICATORS AND OTHER CONSIDERATIONS, the statements that reached the highest score (9) were "A validated, objective, and multidimensional disease activity score is needed", "the activity concept includes the signs and symptoms of the disease", "the concept of damage includes structural and functional alterations of the airways", "indicators of activity should be sought and validated, which help us to prioritize the early approach in patients with worse prognosis", "Indicators that predict progressive loss of lung function should be used", and "asthma should be approached longitudinally, assessing both the achievement and maintenance of a state of clinical remission". The only statement reaching a median score of 7 but being equally successfully validated in the first round was "remodeling may be reversible and be considered a treatable trait for disease modification".

Discussion

Asthma management is increasingly evolving towards more ambitious therapeutic goals as the arsenal and efficacy of treatments increases, led mainly by biologic therapy. Over the past few months, we have debated intensively the concept

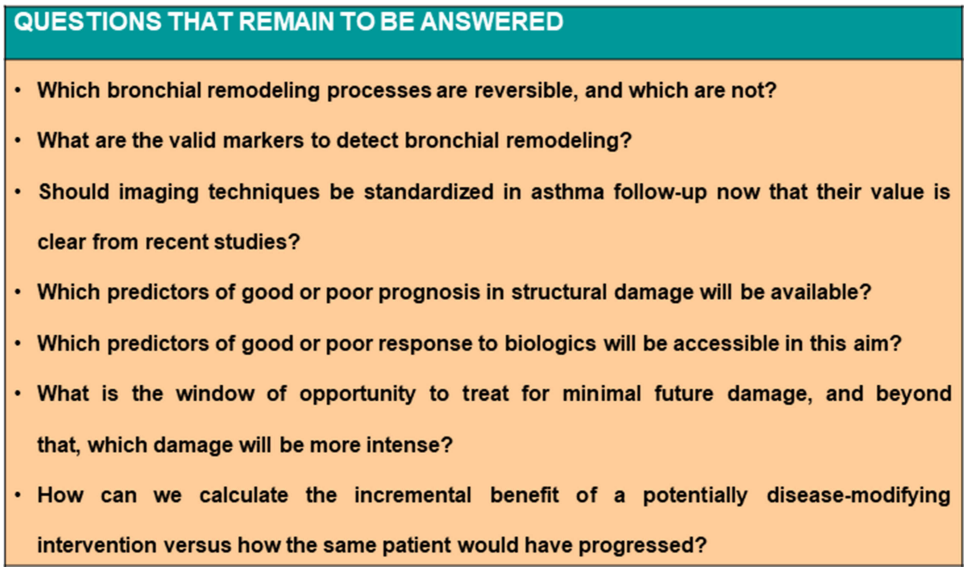

Figure 2 Questions that remain to be answered.

of remission and the ability of drugs to induce that state. Due to the latest definitions, considering different classifications based on varying degrees of rigor in criteria, clinical remission requires stabilization of lung function and patient/clinician agreement on remission in addition to the absence of significant asthma symptoms and acute attacks for a minimum duration of 12 months, while complete remission also requires, in addition to all the previous criteria, the normalization of underlying pathology. Other authors have included improvements in structural parameters in their definitions.[2–7,] there seems to be agreement that the immediate future is raising the bar to achieve these objectives.

Some recent studies have reported the maintenance of remission status in the medium and long term with biologics, such as a sustained remission with treatment of 42.1% after 24 months with benralizumab,[36] from 26.8% to 52.9% after 24 months based on the different definitions of remission,[37] and complete clinical remission in the 46.8% of patients after 6 years of treatment with mepolizumab.[38] Also, 42.8% of patients treated with dupilumab met clinical remission criteria with treatment after two years.[39]

However, we believe that the challenge of asthma management in the coming years must shift from achieving outcomes such as remission to an even more significant aspiration: detecting the potential of biologics to induce consistent and lasting disease modification. This implies directing our efforts to slow down, halt, or, if possible, reverse some components of airway remodeling, prevent lung function decline, and stabilize the progression of asthma to irreversible damage at a structural level.

Pulmonary function tests, including basic spirometry, especially the assessment of the post-BD FEV1 slope, as well as other techniques such as oscillometry or dynamic high-resolution CT functional imaging, can improve our understanding of the structural and functional abnormalities that trigger bronchial obstruction in asthma in a point-in-time manner. Small airway dysfunction is strongly evident across all severity grades of asthma, and in severe asthma, small airway disease has been related to disease control and risk of exacerbation. Oscillometry is the most suitable method for evaluating small airway disease and should complement spirometry as part of managing these patients in a routine clinical setting.[40,41] Assessing how biological drugs can improve hyperinflation in patients with severe asthma is also interesting.[42]

What we do not yet know sufficiently is the treatment's effect on this potential slowing or stopping of the accelerated loss of function, which requires measuring its evolution longitudinally.

It must also be noted that when predefining a trial's duration to investigate a treatment's disease-modifying effect, short-term studies will not provide sufficient data. Thus, long-term trials of at least one year are needed to elucidate any structural change or impact on disease progression.

More evidence is needed in this respect, as although several studies have shown efficacy in bronchial remodeling-independent processes and bronchial obstruction, additional research should be undertaken to answer emerging questions such as potential reversibility of remodeling processes, validated biomarkers, techniques to be performed, and predictors of response to biologics, among several other (Figure 2). Special mention must be made of asthma comorbidities, such as gastroesophageal reflux disease, allergic rhinitis, obesity, depression, diabetes mellitus, and cardiovascular disease that can be particularly challenging in patients with severe asthma and may worsen asthma outcomes and should be assessed in clinical practice, ideally supported by multidisciplinary teams. Comorbidities should be considered in any definition of remission and disease modification, especially upper airway disorders, due to their anatomical, epidemiological, and immunoinflammatory linkage with asthma.[43,44] The Spanish Consensus on Remission in Asthma includes the concept of complete remission in asthma and chronic rhinosinusitis with nasal polyps.[7]

As a limitation of this consensus, we know that the Delphi methodology may bias independent opinions. However, the sample size and the results' robustness minimize this risk. This consensus focuses on the role of biologics, not considering other concurrent treatments or management strategies that patients might be receiving, which could confound the effects attributed solely to biologics. Addressing environmental and lifestyle factors such as smoking cessation, allergens or pollution exposure, or obesity can significantly impact the disease course. Additionally, while biologics show promising results in clinical trials, their real-world effectiveness and impact on long-term disease progression are less clear. This discrepancy may arise due to variations in patient adherence, different healthcare settings, and heterogeneous patient populations. Furthermore, this study does not discuss the economic implications and accessibility of biological treatments for asthma, which are significant factors influencing treatment choices and patient outcomes in real-world settings. In addition, other considerations, such as when to stop treatment in patients who have reached a prolonged "disease-free" state and how this state can be maintained, also need to be clarified in the future, as the field is currently uncertain.

What seems clear is that the paradigm of asthma management is shifting with the advent of biologics, and the scientific community increasingly accepts the approach of preventing damage by controlling activity. It remains to be seen whether, in a few years, and with a solid body of evidence, the approach to asthma management will become, in certain patients, preventive rather than palliative, preventing the disease from progressing to the point where patients have significant and irreversible limitations. Disease modification seeks to alter the disease's course at a fundamental level, potentially offering lasting changes. It requires targeted and sometimes earlier and more aggressive treatment strategies aimed at the biological foundations of asthma.

As future perspectives in disease modification, we consider it important to identify prognostic factors for poor disease progression. These factors would allow us to select patients in earlier stages of the disease for biological treatments and to prevent disease progression and damage. Identifying new biomarkers predicting good response/remission to biological treatment in patients with severe asthma is also important.

In conclusion, in this Delphi study, a large number of experts in the management of severe asthma from different specialties agreed on the clinical-functional and pathophysiological aspects to be considered in order to try to achieve disease modification. Five essential criteria for disease modification were agreed: complete improvement of signs and symptoms, normalization in biomarkers/biological activity, reversal of bronchial hyperresponsiveness, improvement or stabilisation of structural airway abnormalities, and long-term maintenance of this status at least three years. Indicators and other considerations of disease modification were also agreed.

Disclosure

Juan Carlos Miralles-Lopez has received Consulting fees from Chiesi, and Astra Zeneca, and Speaker fees from GSK, Novartis, Astra Zeneca, Sanofi, Chiesi, Bial, Gebro, Menarini, and Organon. Francisco Javier Alvarez-Gutiérrez has received Consulting fees from AstraZeneca, GSK, and Sanofi, and Speaker fees from Astra Zeneca, Bial, GSK, Orion Pharma, and Sanofi. Julio Delgado-Romero has received Speaker fees from GSK, Astra Zeneca, Sanofi, Bial, Gebro, and Menarini. Santiago Quirce has received Consulting fees from GSK and Speaker fees from AstraZeneca, GSK, Chiesi, Allergy Therapeutics, Sanofi, Novartis, and Gebro. José Gregorio Soto-Campos has received Speaker fees from Sanofi, Astra, and GSK. Rubén Andújar-Espinosa has received Speaker fees from GSK, Sanofi, Faes, AstraZeneca, Chiesi, and

Gebro. Sheila Cabrejos-Perotti has received Speaker fees from Sanofi, Novartis, GSK, and ASAC Pharma. Manuel Castilla-Martínez has received Speaker fees from AstraZeneca, GSK, Sanofi, and Chiesi. Isabel María Flores-Martín has received Speaker fees from AstraZeneca, Novartyis, GSK, Inmunotek, Sanofi, and Roxall. Manuel José Pajarón-Fernández has received Speaker fees from GSK, and Astra. José Valverde-Molina has received Speaker fees from GSK, AstraZeneca, Sanofi, and Gebro. The authors report no conflicts of interest in this work..

References

1. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med*. 2022;386(2):157–171. PMID: 35020986. doi:10.1056/NEJMra2032506
2. Thomas D, McDonald VM, Pavord ID, Gibson PG. Asthma remission: what is it and how can it be achieved? *Eur Respir J*. 2022;60(5):2102583. PMID: 35361633; PMCID: PMC9630609. doi:10.1183/13993003.02583-2021
3. Menzies-Gow A, Bafadhel M, Busse WW, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol*. 2020;145(3):757–765. doi:10.1016/j.jaci.2019.12.006
4. Lommatzsch M, Criée CP, de Jong CC, et al. S2k-Leitlinie zur fachärztlichen Diagnostik und Therapie von Asthma 2023 [S2k guideline for specialist diagnosis and treatment of asthma 2023]. *Pneumologie*. 2023;77:461–543 German.
5. Canonica GW, Blasi F, Carpagnano GE, et al. Severe asthma network Italy definition of clinical remission in severe asthma: a delphi consensus. *J Allergy Clin Immunol*. 2023;11:3629–3637.
6. Blaiss M, Oppenheimer J, Corbett M, et al. Consensus of an American college of allergy, asthma, and immunology, American academy of allergy, asthma, and immunology, and American thoracic society workgroup on definition of clinical remission in asthma on treatment. *Ann Allergy Asthma Immunol*. 2023;131(6):782–785. doi:10.1016/j.anai.2023.08.609
7. Álvarez Gutiérrez FJ, Casas-Maldonado F, Soto-Campos G, et al. Spanish consensus on remission in asthma (REMAS. *Archivos de Bronconeumología*. 2024;60(8):503–509. doi:10.1016/j.arbres.2024.04.002
8. Pfaar O, Creticos PS, Kleine-Tebbe J, et al. One hundred ten years of allergen immunotherapy: a broad look into the future. *J Allergy Clin Immunol*. 2021;9(5):1791–1803. doi:10.1016/j.jaip.2020.12.067
9. Lommatzsch M, Brusselle GG, Canonica GW, et al. Disease-modifying anti-asthmatic drugs. *Lancet*. 2022;399(10335):1664–1668.
10. Gelb AF, Taylor CF, Shinar CM, et al. Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics. *Chest*. 2006;129(6):1492–1499. doi:10.1378/chest.129.6.1492
11. Matsunaga K, Hirano T, Oka A, et al. Persistently high exhaled nitric oxide and loss of lung function in controlled asthma. *Allergol Int*. 2016;65(3):266–271. doi:10.1016/j.alit.2015.12.006
12. Wang K, Stonham C, Rutherford C, et al. Fractional exhaled nitric oxide (FeNO): the future of asthma care? British. *J. Gen. Pract*. 2023;73(737):565–568. doi:10.3399/bjgp23X735813
13. Varricchi G, Brightling CE, Grainge C, et al. Airway remodeling in asthma and the epithelium: on the edge of a new era. *Eur Respir J*. 2024;63(4):2301619. doi:10.1183/13993003.01619-2023
14. Hsieh A, Assadinia N, Hackett TL. Airway remodeling heterogeneity in asthma and its relationship to disease outcomes. *Front Physiol*. 2023;14(24). doi:10.3389/fphys.2023.1113100
15. Cosio BG, Shafiek H, Iglesias A, et al. Validation of a pathological score for the assessment of bronchial biopsies in severe uncontrolled asthma: beyond blood eosinophils. *Archivos de bronconeumologia*. 2023;59(8):502–509. doi:10.1016/j.arbres.2023.05.014
16. Cottini M, Bondi B, Bagnasco D, et al. Impulse oscillometry defined small airway dysfunction in asthmatic patients with normal spirometry: prevalence, clinical associations, and impact on asthma control. *Respir Med*. 2023;218:107391. doi:10.1016/j.rmed.2023.107391
17. Portacci A, Iorillo I, Maselli L, et al. The role of galectins in asthma pathophysiology: a comprehensive review. *Curr Iss Moleular Biology*. 2024;46(5):4271–4285. doi:10.3390/cimb46050260
18. Domvri K, Porpodis K. Targeting inflammation or remodeling in asthma? Is there a right way? *Front Med*. 2023;10:1241920. doi:10.3389/fmed.2023.1241920
19. James AL, Donovan GM, Green FH, et al. Heterogeneity of airway smooth muscle remodeling in asthma. *Am J Respir Crit Care Med*. 2023;207(4):452–460. doi:10.1164/rccm.202111-2634OC
20. Savin IA, Zenkova MA, Sen'kova AV. Bronchial asthma, airway remodeling and lung fibrosis as successive steps of one process. *Int J Mol Sci*. 2023;24(22):16042. doi:10.3390/ijms242216042
21. Nakagome K, Nagata M. The possible roles of IL-4/IL-13 in the development of eosinophil-predominant severe asthma. *Biomolecules*. 2024;14(5):546. doi:10.3390/biom14050546
22. Garrido CV, Mukherjee M, Svenningsen S, et al. Eosinophil-mucus interplay in severe asthma: implications for treatment with biologicals. *Allergol Int*. 2024;73(3):351–361. doi:10.1016/j.alit.2024.03.001
23. Arima M, Ito K, Abe T, et al. Eosinophilic mucus diseases. *Allergol Int*. 2024;73(3):362–374. doi:10.1016/j.alit.2024.03.002
24. Couillard S, Côté A. Predicting on-biologic remission in asthma: insight from the airways. *Chest*. 2023;163(6):1341–1343. doi:10.1016/j.chest.2023.04.030
25. Nolasco S, Campisi R, Crimi N, et al. Are we overlooking the lung function in the definition of severe asthma remission? *Pulmonology*. 2023;30(4):S2531–0437. doi:10.1016/j.pulmoe.2023.11.004
26. Oishi K, Hamada K, Murata Y, et al. A real-world study of achievement rate and predictive factors of clinical and deep remission to biologics in patients with severe asthma. *J Clin Med*. 2023;12(8):2900. doi:10.3390/jcm12082900
27. De Prado Gomez L, Pavord I, Busse W, et al. Long-term effect of dupilumab on prevention of lung function decline in patients with uncontrolled moderate-to-severe asthma: ATLAS trial design. *ERJ Open Res*. 2023;9(2):00417–2022. doi:10.1183/23120541.00417-2022
28. Preventing asthma in high risk kids (PARK). Available from: https://clinicaltrials.gov/study/NCT02570984. Accessed June 2024.
29. Efficacy of mepolizumab in severe asthmatics on a long term (MESILICO). Available from: https://clinicaltrials.gov/ct2/show/NCT04612556. Accessed June 2024.

30. Airway remodeling during mepolizumab treatment (REMOMEPO). Available from: https://clinicaltrials.gov/ct2/show/NCT03797404. Accessed June 2024.
31. Effect of benralizumab on airway remodeling in asthma (BENRAMOD). Available from: https://clinicaltrials.gov/ct2/show/NCT04365205. Accessed June 2024.
32. Benralizumab Airway Remodeling Study in Severe Eosinophilic Asthmatics (CHINOOK). Available from: https://clinicaltrials.gov/ct2/show/NCT03953300. Accessed June 2024.
33. REVErsing airway remodelling with tezepelumab (REVERT). Available from: https://clinicaltrials.gov/ct2/show/NCT05651841. Accessed June 2024.
34. Busse WW, Melén E, Menzies-Gow AN. Holy Grail: the journey towards disease modification in asthma. *Eur Respir Rev*. 2022;31(163):210183. doi:10.1183/16000617.0183-2021
35. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
36. Pelaia C, Crimi C, Benfante A, et al. Sustained remission induced by 2 years of treatment with benralizumab in patients with severe eosinophilic asthma and nasal polyposis. *Respirology*. 2024;29(10):869–879. PMID: 38847185. doi:10.1111/resp.14767
37. Crimi C, Nolasco S, Noto A, et al. Long-term clinical and sustained REMIssion in severe eosinophilic asthma treated with mepolizumab: the REMI-M study. *J Allergy Clin Immunol Pract*. 2024;(24):00852. PMID: 39197750. doi:10.1016/j.jaip.2024.08.033
38. Stanziola AA, Candia C, Nazzaro G, et al. Long-term effects of mepolizumab in patients with severe eosinophilic asthma: a 6-year real-life experience. *Front Pharmacol*. 2024;15. doi:10.3389/fphar.2024.1449220
39. Pavord ID, Rabe KF, Israel E, et al. Dupilumab induces long-term on-treatment clinical remission in patients with type 2 asthma. *J Allergy Clin Immunol*. 2024. doi:10.1016/j.jaip.2024.10.009
40. Menzella F, Antonicelli L, Cottini M, et al. Oscillometry in severe asthma: the state of the art and future perspectives. *Expert Rev Respir Med*. 2023;17(7):563–575. PMID: 37452692. doi:10.1080/17476348.2023.2237872
41. Washko GR, Lipworth BJ, Saralaya D, et al. Effect of dupilumab on airway oscillometry, ventilation/perfusion, and mucus plugging in moderate-to-severe asthma: the vestige trial (abstract). *Am J Respir Crit Care Med*. 2024;209:A2994.
42. Maniscalco M, Candia C, Calabrese C, et al. Impact of biologics on lung hyperinflation in patients with severe asthma. *Respir Med*. 2024;225:107578. PMID: 38431058. doi:10.1016/j.rmed.2024.107578
43. Cazzola M, Rogliani P, Ora J, et al. Asthma and comorbidities: recent advances. *Pol Arch Intern Med*. 2022;132(4):16250. doi:10.20452/pamw.16250
44. Portacci A, Dragonieri S, Carpagnano GE. Type-2 severe asthma comorbidities in the era of biologics: time to rethink clinical response? *Expert Rev Respir Med*. 2024;18(5):249–253. doi:10.1080/17476348.2024.2365841