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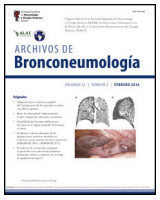

SEPAR's Voice

Spanish Consensus on Remission in Asthma (REMAS)

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ABSTRACT

The concept of "remission" in asthma has been around for a long time and it has been a controversial topic. Despite the attempts of some studies to characterize this entity, the discussion continues.

In the case of asthma there is still no clear definition, either in terms of its meaning or the parameters that should be included or whether it should be divided into clinical or complete remission.

To help defining these controversial concepts, SEPAR has advocated the multidisciplinary working group REMAS (REMission in ASthma). Following the Delphi methodology and with the involvement of more than 120 specialists in asthma management, this group has arrived at a consensus on the definitions of remission in asthma and establishing the criteria and characteristics that will be of use in future studies evaluating the efficacy or effectiveness of treatments.

Introduction

The advent of biological therapies for severe asthma and the results obtained in both clinical trials and routine clinical practice settings have reopened the debate on the definition of disease remission and other associated aspects.[1,2] Despite the attempts of some studies to characterize this entity,[1] the discussion continues.

The concept of "remission" in asthma is nothing new: it has been a controversial topic since the first attempts to define it were made in the 1980s, when Bronnimann and Burrows[3] used the term to describe the absence of asthma attacks or symptoms in a patient with no asthma medication use for ≥1 year. Another concept is that of complete remission, which requires not only the prolonged absence of symptoms, but also the objective demonstration of normal airway function and negative bronchial hyperresponsiveness (BHR), no evidence of bronchial inflammation, and even the absence of any airway pathology suggestive of asthma.[4,5]

The following predictive markers for remission have been proposed: mild asthma; better lung function; better asthma control; younger age; early onset of the disease; shorter duration of asthma; milder BHR; no or few comorbidities; and no history of smoking.[6]

The current concept of remission is based on experience from other inflammatory diseases, such as rheumatoid arthritis, and the effect of treatment. However, in the case of asthma, while guidelines have begun to implement the term,[7] there is still no clear definition, either in terms of its meaning or the parameters that should be included (clinical, functional, inflammatory, BHR, etc.) or whether it should be divided into different concepts (clinical or complete remission). It is also unclear how long it takes to be able to speak of remission, or whether the expression should be used in patients on or off treatment.

It is equally uncertain how a definition might contribute to the long-established concept of disease control, the assessment of treatment response using the scores and indices that are currently accepted or under validation (FEOS [FEV1, Exacerbations, Oral corticosteroids, Symptoms][8] and EXACTO scores [Exacerbations, ACT, Corticosteroids and Obstruction-FEV1][9]), or the concept of super-responders to biological therapies.[10]

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A number of validated tools are used to assess asthma symptoms, although they have not been specifically designed to determine disease remission. This is the case with the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT), which have been used in some studies to assess the response to monoclonal drugs and define the concept of clinical remission, using different cut-off points. For these purposes, the ACQ applies a cut-off point of <1, lower than that generally used,[11] while the ACT habitually uses scores of >20 (PROSPERO), and even 25, as cut-off points.[12,13]

Other parameters to consider as remission criteria are the absence of exacerbations and no need for systemic steroids for a set period of time.[1]

In type 2 inflammation, different diseases often coexist that share a common underlying inflammatory pathophysiological mechanism, such as atopic dermatitis or chronic rhinosinusitis with nasal polyposis, leading to the concept of asthma as a type 2 systemic disease.[14] Consequently, it may be important to include evaluation of the upper airway in the concept of united airway remission.[15]

To analyze these proposals, taking into account their relevance in current asthma management options, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) has advocated the multidisciplinary working group REMAS (REMission in ASthma) through the Autonomic Asthma Forum (FORASMA) and the working group of the Spanish Asthma Management Guidelines (GEMA). This group has set itself the objective of reaching consensus on the definitions of remission in asthma and establishing criteria and characteristics that will be of use in future studies evaluating the efficacy or effectiveness of treatments.

Methods

This study was carried out following the consensus methodology developed by the RAND/UCLA.[16] The Recommendation Development Group (RDG) was composed of 26 experts (respiratory medicine specialists, allergy specialists, family physicians, pediatricians, and pharmacists) with experience in the management of asthma patients. The first meeting held in January 2023 defined the concepts on which consensus was to be developed.

Based on the concepts, a non-systematic review of the literature related to complete and/or clinical remission in asthma was carried out in the PubMed databases (data closure: June 2023). The RDG was able to add studies they considered pertinent and subsequently performed a critical reading of the publications. The group then formulated the statements relating to the concepts previously defined to submit them to a vote by the panelists, proposing a total of 42 statements.

The 42 proposed statements were evaluated using a 2-round iterative Delphi process according to a 9-point Likert scale (1: strongly disagree; 9: strongly agree) using an online questionnaire. The RAND/UCLA methodology was used for analysis of consensus in Delphi panels.[16] Each item in the questionnaire was classified according to the level of agreement and the median score of the panel as "appropriate" (median in the 7–9 range), "uncertain" (median in the 4–6 range or any median with disagreement) or "inappropriate" (median in the 1–3 range). Agreement was reached if at least one third of the sample responded within the same score range as the median. Disagreement was considered to occur if the median score was at either of the 2 extremes and more than one third of the sample responded in the opposite extreme range, or if the median was in the central range, and at least one third of the sample responded in one of the other 2 ranges. If the assessment of the statement did not meet any of the previous criteria, it was considered neutral. Of the 139 panelists invited, 123 completed the first round (88% response rate) and 120 completed the second round (97% response rate) (a detailed description of professional activity can be found in the Supplementary Figs. 1–4).

After the 2 rounds of voting, the expert panel reached consensus on the agreement or disagreement of 71.5% of the statements (a total of 30 of the 42 proposed). The distribution of the voting ranges can be found in Supplementary Fig. 5. Below is the rationale for each point raised and the results obtained, which are summarized in the respective tables.

Results

Concept of remission

The panel approved a definition for the term "complete remission" (Table 1, statement 1) and a series of definitions that included the possibility of using this concept in patients on and off treatment, at any level of disease severity, the possibility of treatment de-escalation, and the inclusion of the upper airway. Agreement was reached on the likelihood of future relapses and how remission is not comparable to that of cure. Finally, it was agreed that the definition should include a period of ≥3 years free of clinical and inflammatory expression of the disease, while stating the absence of scientific evidence (Table 1, statements 2–9). Previous definitions for which no consensus was reached are presented in Table 2 (statements 31–34). It is interesting to note that uncertainty was expressed surrounding the statement that the concept of clinical remission does not contribute anything relevant to the concepts of disease control or treatment response using the current response assessment indices or scores.

The statements proposed to the panelists on the specific parameters for establishing the diagnosis of remission were based on those included in various studies, such as the evaluation of symptoms with commonly used tests such as the ACQ and ACT, questioning the specific cut-off points; the presence or absence of exacerbations; lung function, with specific cut-off points for FEV_1 (forced expiratory volume in the first second) and FEV_1/FVC (forced vital capacity); the need to perform a challenge test; and the study of inflammation using FeNO cut-off points or the induced sputum cell count, if available. The parameters that the panelists found appropriate for establishing the diagnosis of remission can be found in Table 1 (statements 10–22). Cut-off points for ACT > 20 and ACQ < 0.75 are highlighted (although the possibility of more stringent values, with cut-off points of ACT = 25 and ACQ = 0, was also agreed). Agreement was reached in terms of lung function, both an FEV_1 > 80% and an FEV_1 equal to or close to patient's personal best historical FEV_1 (>90% of their historical best), a negative bronchodilator test, and a negative non-specific provocation test. The FeNO cut-off point was set at <40 ppb. The possibility of considering the absence of lesions associated with remodeling in imaging tests was also mentioned. Parameters that did not reach the appropriate level of consensus are listed in Table 2 (statements 35–36). Notably, no agreement was reached with regard to eosinophil count < 300/μL or FeNO value < 25 ppb.

In the concept of united airway remission, the question arose regarding specific data on the clinical course of nasal polyposis. Consensus was reached on the recovery of smell, a sinonasal outcome test 22 (SNOT-22) score < 30, normal nasal polyp endoscopy score, and no need for systemic glucocorticoids (Table 1, statements 23–26).

Effects of medication in relation to remission

Taking into account the specific evidence on the effect of discontinuing biologics, a series of statements were proposed. Those

Table 1
Statements agreed by the panel.

Statement	Median	Level of appropriateness	Level of agreement
1. "COMPLETE REMISSION" in asthma (hereinafter "REMISSION") must include the absence of symptoms, non-use of systemic glucocorticoids, absence of exacerbations and sustained normal lung function in accordance with its predicted value or best historical value, together with evidence of control of inflammation and bronchial hyperresponsiveness.	8.0	Appropriate	Agreement
2. REMISSION can occur in patients on and off treatment.	8.0	Appropriate	Agreement
3. The concept of REMISSION should be applicable at all levels of disease severity.	8.0	Appropriate	Agreement
4. The definition of the concept of REMISSION must include a period of ≥3 years free of clinical and inflammatory expression of the disease.	8.0	Appropriate	Agreement
5. A patient in REMISSION may have relapses in the future.	8.0	Appropriate	Agreement
6. The concept of long-term REMISSION with treatment is equivalent to cure.	2.0	Inappropriate	Agreement
7. In patients in REMISSION, treatment should be de-escalated prior to discontinuation.	8.0	Appropriate	Agreement
8. The definition of REMISSION should also include the control of inflammatory diseases of the upper airway.	8.0	Appropriate	Agreement
9. There is currently no scientific evidence to support the concept of REMISSION.	8.0	Appropriate	Agreement
10. Absence of exacerbations in the last year.	9.0	Appropriate	Agreement
11. Complete withdrawal of maintenance systemic glucocorticoids (except for the use of systemic glucocorticoids due to adrenal insufficiency).	9.0	Appropriate	Agreement
12. No need to use relief or rescue medication.	9.0	Appropriate	Agreement
13. ACT scores ≥ 20 and ACQ < 0.75 at visits during the last year.	9.0	Appropriate	Agreement
14. ACT = 25 and ACQ = 0 scores at visits during the last year.	9.0	Appropriate	Agreement
15. FEV_1 value ≥ 80% and FEV_1/FVC ≥ 70 in adults, and FEV_1/FVC ≥ 85 in children.	8.0	Appropriate	Agreement
16. Equal or close to best personal historical FEV_1 (>90% of best historical value).	8.0	Appropriate	Agreement
17. Negative bronchodilator test.	8.0	Appropriate	Agreement
18. Patient's perception that they have achieved a normal quality of life.	9.0	Appropriate	Agreement
19. Negative non-specific bronchoprovocation test.	8.0	Appropriate	Agreement
20. If the induced sputum technique is available, sputum eosinophil count < 2% and neutrophils < 65%.	8.0	Appropriate	Agreement
21. FeNO value < 40 ppb.	7.0	Appropriate	Agreement
22. Absence of lesions associated with bronchial remodeling in imaging tests.	7.0	Appropriate	Agreement
23. Recovery of smell.	8.0	Appropriate	Agreement
24. SNOT-22 score < 30.	8.0	Appropriate	Agreement
25. Normal nasal endoscopic score.	8.0	Appropriate	Agreement
26. No need for systemic glucocorticoids for polyposis.	9.0	Appropriate	Agreement
27. The term "drugs capable of modifying the natural history of the disease" should be used instead of "drugs to achieve REMISSION."	8.0	Appropriate	Agreement
28. Treatments capable of modifying the natural history of asthma help achieve disease REMISSION.	7.0	Appropriate	Agreement
29. REMISSION in severe asthma treated with a biologic should be considered when remission is sustained without control treatment and without a biologic.	8.0	Appropriate	Agreement
30. Treatment of severe asthma with azithromycin helps achieve REMISSION.	2.0	Inappropriate	Agreement

ACT, asthma control test; ACQ, 5-item asthma control questionnaire; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; EXACTO, exacerbations, ACT, systemic corticosteroids and obstruction-FEV_1; SNOT-22, 22-item sinonasal outcome test.

Table 2
Statements not agreed by the panel.

Statement	Median	Level of appropriateness	Level of agreement
31. The concept of CLINICAL REMISSION does not contribute anything relevant to previous definitions of current control and control of future risk.	3.0	Uncertain	Disagree
32. In patients with severe asthma treated with biological drugs, the concept of CLINICAL REMISSION does not contribute anything relevant to the concept of complete response with treatment, using scores such as EXACTO or FEOS for its assessment.	5.5	Uncertain	Disagree
33. The concept of REMISSION must include a period of 1 year free of clinical and inflammatory expression of the disease in its definition.	7.0	Appropriate	Neutral
34. The concept of long-term REMISSION off treatment is equivalent to cure.	7.0	Uncertain	Disagree
35. Blood eosinophil count < 300/μL.	7.0	Appropriate	Neutral
36. FeNO value < 25 ppb.	7.0	Appropriate	Neutral
37. Biologics modify the natural history of severe asthma only while administered.	7.0	Appropriate	Neutral
38. REMISSION in severe asthma treated with a biologic should be considered when sustained with control treatment and with a biologic.	5.0	Uncertain	Disagree
39. REMISSION in severe asthma treated with a biologic should be considered when sustained with control treatment and without a biologic.	5.0	Uncertain	Disagree
40. REMISSION in severe asthma treated with a biologic should be considered when sustained without control treatment and with a biologic.	4.0	Uncertain	Disagree
41. Treatment of severe asthma with bronchial thermoplasty helps achieve REMISSION.	2.0	Inappropriate	Neutral
42. Allergen immunotherapy can provide REMISSION.	7.0	Appropriate	Neutral

FEOS, FEV_1, exacerbations, oral corticosteroids, symptoms score; FeNO, fractional exhaled NO.

approved by the panel can be found in Table 1 (statements 27–29). It is interesting to note that the panelists found it preferable to use the term "drugs capable of modifying the natural history of the disease" instead of "drugs to achieve remission" and how precisely treatments capable of modifying the natural history of the disease would allow remission to be achieved. The report also highlights that asthma treated with biologics should be considered in remission when remission is maintained without control treatment and without a biologic. No consensus was reached on the other options, as can be seen in Table 2 (statements 37–40).

The panelists reach consensus on the disagreement that azithromycin does help achieve remission (Table 1, statement 30). Conversely, no consensus was reached on the disagreement regarding whether thermoplasty helps achieve remission (Table 2, statement 41), nor was consensus reached on the item referring to allergen immunotherapy (AIT) and remission (Table 2, statement 42).

Based on the above results, the RDG agreed on a concept of clinical remission that involves fulfilling all of the following conditions: disease control (ACT = 20–25), absence of exacerbations, no need for systemic steroids, lung function with $FEV_1 \geq 80\%$ predicted or, if previous spirometries are available, a value equal to or close to $FEV_1 > 90\%$ of the patient's best historical value, and a negative bronchodilator test. This situation must be maintained for at least 12 months, and it should be specified whether it is with treatment or once treatment has been discontinued.

Discussion

As the repeated attempts described in the literature and the results of this consensus reveal, the definition of remission in asthma is controversial. Nevertheless, it can and should be the ultimate goal in the asthmatic patient.

One of the milestones of this study was to reach consensus on a definition for complete remission and on the period it must span to be considered as such, in addition to other important factors. Thus, in order to consider a patient in remission, in addition to the complete absence of symptoms and exacerbations and no need for oral steroids, they must have sustained normal lung function and show evidence of control of inflammation and negative BHR. The panelists agreed that this situation must be maintained for at least 3 years. This is clearly a stricter definition than those established so far in the majority of recent articles.[17] On the other hand, although a consensus could not be reached on the concept of clinical remission, there was disagreement on the proposal that this concept does not contribute anything to the existing concepts of disease control or response to treatment determined with indices such as the FEOS[8] and EXACTO scores.[9] Therefore, in the absence of further evidence, the need to use a concept derived from the cut-off points with which there is agreement was suggested, for which the RDG established a concept of clinical remission that included these clinical and functional parameters.

In one of the earliest references on clinical remission in asthma, the criterion used for its definition was no asthma attacks or symptoms in the absence of treatment for 1 year.[3] Several articles were subsequently published in which this concept was used, usually defining it as the absence of symptoms for a long period of time. In addition, the common denominator of most definitions includes not using medication and a period of at least 1 year, which in some articles can be as long as 2 or even 3 years.[3,18–23]The prevalence of clinical remission according to this concept is estimated to be between 2% and 52% of patients, depending on the study and the definition, in most cases these were not very stringent and population samples were small.[12,18–20,24–33] Follow-up in these studies ranges between 5 and 70 years.[12,18–20,24–33] However, the natural history of asthma must be taken into account: the disease changes throughout life, so childhood asthma cannot be compared with that of adults. This factor would explain the different remission rates observed in studies conducted in children (6–52%), compared with adults (2–17%).[34]

Menzies-Gow et al.[35] recently proposed different types of definitions for remission:

- Clinical remission, defined as the absence of symptoms and exacerbations for at least 12 months; optimization and stabilization of lung function; absence of use of corticosteroids for exacerbation or asthma control; and agreement between the patient and physician regarding disease remission.
- Complete remission, when patients also present no BHR or bronchial inflammation.[35]

Furthermore, both these concepts are considered on and off treatment.

Using criteria similar to those described for clinical remission, the same authors subsequently published a post hoc study of patients enrolled in the SIROCCO/CALIMA and ZONDA benralizumab clinical trials.[36] The parameters were evaluated for 6 months in ZONDA and for 6–12 months in SIROCCO and CALIMA. Based on these criteria, the results from the ZONDA study showed 22.5% remission in the treatment group versus 7.5% in the placebo group, while for SIROCCO and CALIMA, the authors reported 14.5% remission in the benralizumab group versus 7.7% in the placebo group.[36]

More recently, in Italy, 80 panelists reached a consensus on the concepts of complete clinical remission and partial clinical remission. For complete clinical remission it was agreed, after the second round, that the following 4 criteria should be met: absence of asthma symptoms (ACT ≥ 20 or ACQ < 1.5); absence of asthma exacerbations or attacks; stable lung function; and no need for treatment with oral corticosteroids. On the point of functional stability, no consensus was reached on the value required to consider lung function stable (improvement of 100–200 mL or $FEV_1 \geq 80\%$). Another parameter evaluated was the normalization of asthma-related quality of life, although no consensus was reached on this item regarding the questionnaire cut-off point. With respect to the clinically relevant reduction in inflammatory parameters in asthma, the cut-off points of <300 eosinophils and FeNO < 25 ppb were considered good markers of a reduction in inflammation, but consensus was not reached for this statement as a criterion for inflammatory remission. In the case of partial clinical remission, the need to meet the criterion of no need for oral corticosteroid treatment and 2 of the following 3 criteria was indicated: absence of symptoms, absence of exacerbations, and stable lung function. The time frame for considering clinical remission was set at ≥12 months.[17]

The concept of remission agreed in our study can thus be considered more stringent than previous proposals, in terms of the inclusion of normality in symptoms, lung function, BHR and inflammation, as well as a minimum period of 3 years. Furthermore, independently of the treatment, it considers the future possibility of including imaging tests to assess the absence of remodeling.

On the other hand, the term clinical remission agreed by the RDG is similar to that suggested by Menzies-Gow et al.,[36] with the exception that clearer cut-off points are provided for lung function (current FEV_1% and as it relates to the best historical value; negative bronchodilator test).

However, in our study, the required level of agreement was not reached to include a blood eosinophil count < 300/μL as a parameter to be taken into account for the diagnosis of remission. The reasons given in the participants' comments were that the eosinophil count could also be related to the presence of

other conditions with a type 2 profile such as atopic dermatitis, allergic rhinitis and nasal polyposis.[37] In this sense, a recent meta-analysis showed that the cut-off point for eosinophil levels could range between 157 and 280 eosinophils/μL in asthma in general (22 studies) or 200–400 eosinophils/μL in the case of severe asthma (8 studies); however, these values are affected by various factors, such as smoking, positive skin-prick test, elevated total IgE, comorbid allergic rhinitis, age ≤ 18 years, male sex, spirometric asthma/chronic obstructive pulmonary disease, metabolic syndrome, and obesity.[38]

The appropriate level of agreement was not reached for the statement that biological treatments are capable of altering the natural history of the disease when administered. Although biological treatments have shown a reduction in exacerbations and improvements in disease control, quality of life and lung function, their impact in modifying the pathophysiology of asthma in a sustained way and, therefore, changing the natural history of the disease, remains to be demonstrated. Some promising results with new biological treatments in terms of controlling BHR,[39] inflammation, and even remodeling parameters, such as mucous plugs[40] have recently been published, but long-term studies are needed to evaluate these outcomes and whether they are maintained once treatment is withdrawn.

In relation to AIT, the subanalysis of allergy specialists did reach the level of agreement. The treatment of asthma with AIT in children and adolescents shows the possibility of modifying the natural history of the disease.[41,42] However, this is yet to be demonstrated in populations treated at older ages, and the specific endophenotype in which it occurs must be identified.

The strengths of this study include the number of asthma experts who participated, its multidisciplinary nature, and the participation of international experts.

Regarding the limitations of this study, the type of professionals involved could be questioned, since there could be a bias toward 1 group. The fact that the consensus process was conducted under the auspices of SEPAR could lead, on the one hand, to a predominance of respiratory medicine specialists and, on the other, to a geographical constraint, since the exclusively Spanish setting may be a limitation for its international use. Furthermore, the definitions of remission, both complete and clinical, should be validated by clinical studies to demonstrate that achieving these goals is associated with better long-term outcomes.

Conclusions

In this study, consensus was reached on the definition of complete remission in asthma (referred to as remission). The concept of remission should include the absence of symptoms, no need for systemic glucocorticoids, absence of exacerbations and sustained normal lung function, in accordance with its predicted value or best historical value, together with compliance with the parameters for control of inflammation and BHR. It can occur in patients on or off treatment, and it should be applicable at all levels of disease severity and include a period of ≥3 years free of clinical and inflammatory expression of the disease and control of upper airway inflammatory diseases (Table 1). Although the statements regarding the concept of clinical remission did not reach the necessary level of agreement (Table 2, statements 31 and 32), there was disagreement on the statement that this concept contributes nothing relevant to previous definitions of current control and control of future risk, or to the concept of complete response to treatment, using scores such as EXACTO or FEOS. Accordingly, the RDG states that the concept of clinical remission could be applied if all of the following conditions are met: disease control (ACT ≥ 20), absence of exacerbations; no need for systemic steroids; lung function with FEV_1 ≥ 80% predicted, or, if previous spirometries are available, a value equal to or close to FEV_1 > 90% of the patient's best historical value; and a negative bronchodilator test. This situation should be maintained for at least 12 months, and it should be specified whether remission is associated with treatment or occurs once treatment has been discontinued (Table 3).

Table 3
Concepts related to remission.

Remission in asthma	
CLINICAL remission	- Controlled asthma (ACT ≥ 20). - No need for relief or rescue medication. - No exacerbations and no need for systemic steroid cycles. - Spirometry with FEV_1 ≥ 80%, or in previous tests, values >90% of your personal best. - Spirometry with negative bronchodilator test. - This situation must be maintained for ≥12 months, specifying whether it is with or without treatment.
COMPLETE remission	- All clinical remission criteria. - No evidence of systemic or bronchial inflammation (FENO < 40 ppb and eosinophils sputum < 2%, if performed). - No bronchial hyperresponsiveness. - No bronchial remodeling lesions on imaging tests. - This situation must be maintained for ≥3 years, specifying whether it is with or without treatment.
Remission in asthma and CRSwNP (single airway)	
COMPLETE remission	- All criteria for complete remission in asthma. - Recovery of smell. - SNOT-22 < 30. - Normal nasal endoscopy. - This situation must be maintained for ≥3 years, specifying whether it is ±treatment.

ACT, asthma control test; CRSwNP, chronic rhinosinusitis with nasal polyps; FENO, fractional-exhaled-nitric-oxide; FEV_1, forced expiratory volume in 1 s; SNOT-22, Sino-nasal Outcome Test.

In any case, prospective studies using remission as the study objective must be carried out to establish scientific evidence on remission (clinical or complete). In this way, the concept will obtain recognized scientific validity.

Conflict of interest

Francisco Javier Álvarez-Gutiérrez has received consulting fees from AstraZeneca, GSK, Sanofi, and

Bial has received speakers honoraria/manuscript support from AstraZeneca, Teva, GSK, Bial, Sanofi, and Orion Pharma and has received travel support from AstraZeneca, GSK, Bial, and Sanofi.

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Julio Delgado Romero has received fees for advisory boards from Bial, has received speaker's honoraria from AstraZeneca, Bial, Chiesi, GlaxoSmithKline Novartis, and Sanofi, and received Grant/Research Support from AstraZeneca and Orion. He also received help assistance with meeting travel from Sanofi and Menarini.

Alicia Padilla-Galo has received consulting fees from AstraZeneca, Sanofi, GSK, Chiesi, Menarini, Alk-Abelló, and Bial, and has received travel support from AstraZeneca and Sanofi.

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Appendix B. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.arbres.2024.04.002.

References

1. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. J Allergy Clin Immunol. 2020;145:757–65, http://dx.doi.org/10.1016/j.jaci.2019.12.006.
2. Lommatzsch M, Brusselle GG, Canonica GW, Jackson DJ, Nair P, Buhl R, et al. Disease-modifying anti-asthmatic drugs. Lancet. 2022;399:1664–8, http://dx.doi.org/10.1016/S0140-6736(22)00331-2.
3. Bronnimann S, Burrows B. A prospective study of the natural history of asthma. Remission and relapse rates. Chest. 1986;90:480–4, http://dx.doi.org/10.1378/chest.90.4.480.
4. Broekema M, Timens W, Vonk JM, Volbeda F, Lodewijk ME, Hylkema MN, et al. Persisting remodeling and less airway wall eosinophil activation in complete remission of asthma. Am J Respir Crit Care Med. 2011;183:310–6, http://dx.doi.org/10.1164/rccm.201003-0494OC.
5. Sekerel BE, Civelek E, Karabulut E, Yildirim S, Tuncer A, Adalioglu G. Are risk factors of childhood asthma predicting disease persistence in early adulthood different in the developing world? Allergy. 2006;61:869–77, http://dx.doi.org/10.1111/j.1398-9995.2006.01082.x.
6. Carpaij OA, Nieuwenhuis MAE, Koppelman GH, van den Berge M, Postma DS, Vonk JM. Childhood factors associated with complete and clinical asthma remission at 25 and 49 years. Eur Respir J. 2017;49:1601974, http://dx.doi.org/10.1183/13993003.01974-2016.
7. Lommatzsch M, Buhl R, Canonica GW, Ribas CD, Nagase H, Brusselle GG, et al. Pioneering a paradigm shift in asthma management: remission as a treatment goal. Lancet Respir Med. 2023, http://dx.doi.org/10.1016/S2213-2600(23)00415-0.
8. Perez de Llano L, Davila I, Martinez-Moragon E, Dominguez-Ortega J, Almonacid C, Colas C, et al. Development of a Tool to Measure the Clinical Response to Biologic Therapy in Uncontrolled Severe Asthma: The FEV(1), Exacerbations, Oral Corticosteroids, Symptoms Score. J Allergy Clin Immunol Pract. 2021;9:2725–31, http://dx.doi.org/10.1016/j.jaip.2021.01.033.
9. Casas-Maldonado F, Baynova K, Soto-Campos G, González-Barcala F, Blanco Aparicio M, González Ramírez A. EXACTO scale: Multidimensional tool for assessing the response to treatment with monoclonal antibodies in severe uncontrolled asthma. EACCI hybrid Congres, Prague 2022.
10. Upham JW, Le Lievre C, Jackson DJ, Masoli M, Wechsler ME, Price DB, et al. Defining a severe asthma super-responder: findings from a Delphi process. J Allergy Clin Immunol Pract. 2021;9:3997–4004, http://dx.doi.org/10.1016/j.jaip.2021.06.041.
11. Harvey ES, Langton D, Katelaris C, Stevens S, Farah CS, Gillman A, et al. Mepolizumab effectiveness and identification of super-

responders in severe asthma. Eur Respir J. 2020;55:1902420, http://dx.doi.org/10.1183/13993003.02420-2019.
12. Tuomisto LE, Ilmarinen P, Niemela O, Haanpaa J, Kankaanranta T, Kankaanranta H. A 12-year prognosis of adult-onset asthma: Seinajoki Adult Asthma Study. Respir Med. 2016;117:223–9, http://dx.doi.org/10.1016/j.rmed.2016.06.017.
13. Casale TB, Luskin AT, Busse W, Zeiger RS, Trzaskoma B, Yang M, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. J Allergy Clin Immunol Pract. 2019;7, http://dx.doi.org/10.1016/j.jaip.2018.04.043, 156–64.e1.
14. Bousquet J, Anto JM, Wickman M, Keil T, Valenta R, Haahtela T, et al. Are allergic multimorbidities and IgE polysensitization associated with the persistence or re-occurrence of foetal type 2 signalling? The MeDALL hypothesis. Allergy. 2015;70:1062–78, http://dx.doi.org/10.1111/all.12637.
15. Pavord I, Gardiner F, Heaney LG, Domingo C, Price RG, Pullan A, et al. Remission outcomes in severe eosinophilic asthma with mepolizumab therapy: analysis of the REDES study. Front Immunol. 2023;14:1150162, http://dx.doi.org/10.3389/fimmu.2023.1150162.
16. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, La Calle JR, Lazaro P, et al. The Rand/UCLA appropriateness method user's manual. Santa Monica: Rand; 2001.
17. Canonica GW, Blasi F, Carpagnano GE, Guida G, Heffler E, Paggiaro P, et al. Severe asthma network Italy definition of clinical remission in severe asthma: a Delphi consensus. J Allergy Clin Immunol Pract. 2023;11:3629–37, http://dx.doi.org/10.1016/j.jaip.2023.07.041.
18. de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M, et al. Prognostic factors of asthma severity: a 9-year international prospective cohort study. J Allergy Clin Immunol. 2006;117:1249–56, http://dx.doi.org/10.1016/j.jaci.2006.03.019.
19. Holm M, Omenaas E, Gislason T, Svanes C, Jogi R, Norrman E, et al. Remission of asthma: a prospective longitudinal study from northern Europe (RHINE study). Eur Respir J. 2007;30:62–5, http://dx.doi.org/10.1183/09031936.00121705.
20. Ronmark E, Jonsson E, Lundback B. Remission of asthma in the middle aged and elderly: report from the Obstructive Lung Disease in Northern Sweden study. Thorax. 1999;54:611–3, http://dx.doi.org/10.1136/thx.54.7.611.
21. Vonk JM, Postma DS, Boezen HM, Grol MH, Schouten JP, Koeter GH, et al. Childhood factors associated with asthma remission after 30 year follow up. Thorax. 2004;59:925–9, http://dx.doi.org/10.1136/thx.2003.016246.
22. Horak E, Lanigan A, Roberts M, Welsh L, Wilson J, Carlin JB, et al. Longitudinal study of childhood wheezy bronchitis and asthma: outcome at age 42. BMJ. 2003;326:422–3, http://dx.doi.org/10.1136/bmj.326.7386.422.
23. Boulet LP, Turcotte H, Brochu A. Persistence of airway obstruction and hyperresponsiveness in subjects with asthma remission. Chest. 1994;105:1024–31, http://dx.doi.org/10.1378/chest.105.4.1024.
24. Almqvist L, Ronmark E, Stridsman C, Backman H, Lindberg A, Lundback B, et al. Remission of adult-onset asthma is rare: a 15-year follow-up study. ERJ Open Res. 2020;6, http://dx.doi.org/10.1183/23120541.00620-2020.
25. Cazzoletti L, Corsico AG, Albicini F, Di Vincenzo EM, Gini E, Grosso A, et al. The course of asthma in young adults: a population-based nine-year follow-up on asthma remission and control. PLOS ONE. 2014;9:e86956, http://dx.doi.org/10.1371/journal.pone.0086956.
26. Ekerljung L, Ronmark E, Larsson K, Sundblad BM, Bjerg A, Ahlstedt S, et al. No further increase of incidence of asthma: incidence, remission and relapse of adult asthma in Sweden. Respir Med. 2008;102:1730–6, http://dx.doi.org/10.1016/j.rmed.2008.07.011.
27. Lindstrom I, Suojalehto H, Lindholm H, Pallasaho P, Luukkonen R, Karjalainen J, et al. Positive exercise test and obstructive spirometry in young male conscripts associated with persistent asthma 20 years later. J Asthma. 2012;49:1051–9, http://dx.doi.org/10.3109/02770903.2012.733992.
28. Pesce G, Locatelli F, Cerveri I, Bugiani M, Pirina P, Johannessen A, et al. Seventy years of asthma in Italy: age, period and cohort effects on incidence and remission of self-reported asthma from 1940 to 2010. PLOS ONE. 2015;10:e0138570, http://dx.doi.org/10.1371/journal.pone.0138570.
29. Ronmark E, Lindberg A, Watson L, Lundback B. Outcome and severity of adult onset asthma – report from the obstructive lung disease in northern Sweden studies (OLIN). Respir Med. 2007;101:2370–7, http://dx.doi.org/10.1016/j.rmed.2007.06.011.
30. Sozener ZC, Aydin O, Mungan D, Misirligil Z. Prognosis of adult asthma: a 7-year follow-up study. Ann Allergy Asthma Immunol. 2015;114:370–3, http://dx.doi.org/10.1016/j.anai.2015.02.010.
31. Traulsen LK, Halling A, Baelum J, Davidsen JR, Miller M, Omland O, et al. Determinants of persistent asthma in young adults. Eur Clin Respir J. 2018;5:1478593, http://dx.doi.org/10.1080/20018525.2018.1478593.
32. Tupper OD, Hakansson KEJ, Ulrik CS. Remission and changes in severity over 30 years in an adult asthma cohort. J Allergy Clin Immunol Pract. 2021;9, http://dx.doi.org/10.1016/j.jaip.2020.11.013, 1595–603.e5.
33. Westerhof GA, Coumou H, de Nijs SB, Weersink EJ, Bel EH. Clinical predictors of remission and persistence of adult-onset asthma. J Allergy Clin Immunol. 2018;141, http://dx.doi.org/10.1016/j.jaci.2017.03.034, 104–9.e3.
34. Thomas D, McDonald VM, Pavord ID, Gibson PG. Asthma remission: what is it and how can it be achieved? Eur Respir J. 2022:60, http://dx.doi.org/10.1183/13993003.02583-2021.
35. Menzies-Gow A, Hoyte FL, Price DB, Cohen D, Barker P, Kreindler J, et al. A response to: letter to the editor regarding "clinical remission in severe asthma: a pooled post hoc analysis of the patient journey with benralizumab". Adv Ther. 2022;39:3862–5, http://dx.doi.org/10.1007/s12325-022-02214-1.
36. Menzies-Gow A, Hoyte FL, Price DB, Cohen D, Barker P, Kreindler J, et al. Clinical remission in severe asthma: a pooled post hoc analysis of the patient journey with benralizumab. Adv Ther. 2022;39:2065–84, http://dx.doi.org/10.1007/s12325-022-02098-1.
37. Hassoun D, Malard O, Barbarot S, Magnan A, Colas L. Type 2 immunity-driven diseases: towards a multidisciplinary approach. Clin Exp Allergy. 2021;51:1538–52, http://dx.doi.org/10.1111/cea.14029.
38. Benson VS, Hartl S, Barnes N, Galwey N, Van Dyke MK, Kwon N. Blood eosinophil counts in the general population and airways disease: a comprehensive review and meta-analysis. Eur Respir J. 2022;59, http://dx.doi.org/10.1183/13993003.04590-2020.
39. Emson C, Diver S, Chachi L, Megally A, Small C, Downie J, et al. CASCADE: a phase 2, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the effect of tezepelumab on airway inflammation in patients with uncontrolled asthma. Respir Res. 2020;21:265, http://dx.doi.org/10.1186/s12931-020-01513-x.
40. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021;384:1800–9, http://dx.doi.org/10.1056/NEJMoa2034975.
41. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999;341:468–75, http://dx.doi.org/10.1056/NEJM199908123410702.
42. Eggleston PA. Allergen-specific immunotherapy in childhood asthma. Curr Opin Pediatr. 1997;9:582–4, http://dx.doi.org/10.1097/00008480-199712000-00006.