Special Article

Severe Asthma Network Italy Definition of Clinical Remission in Severe Asthma: A Delphi Consensus

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Severe asthma affects about 10% of the population with asthma and is characterized by low lung function and a high count of blood leukocytes, mainly eosinophils. Various definitions are used in clinical practice and in the literature to identify asthma remission: clinical remission, inflammatory remission, and complete remission. This work highlights a consensus for asthma remission using a Delphi method. In the context of the Severe Asthma Network Italy, which accounts for 57 severe asthma centers and more than 2,200 patients, a board of six experts drafted a list of candidate statements in a questionnaire, which has been revised to minimize redundancies and ensure clear and consistent wording for the first round (R1) of the

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analysis. Thirty-two statements were included in the R1 questionnaire and then submitted to a panel of 80 experts, which used a 5-point Likert scale to measure agreement regarding each statement. Then, an interim analysis of R1 data was performed, and items were discussed and considered to produce a consistent questionnaire for round 2 (R2) of the analysis. Then, the board set the R2 questionnaire, which included only important topics. Panelists were asked to vote on the statements in the R2 questionnaire afterward. During R2, the criteria of complete clinical remission (the absence of the need for oral corticosteroids, symptoms, exacerbations or attacks, and pulmonary function stability) and those of partial clinical remission (the absence of the need for oral corticosteroids, and two of three criteria: the absence of symptoms, exacerbations or attacks, and pulmonary stability) were confirmed. This Severe Asthma Network Italy Delphi analysis defined a valuable and independent tool that is easy to use, to test the efficacy of different treatments in patients with severe asthma enrolled into the SANI registry. **(J Allergy Clin Immunol Pract 2023;11:3629-37)**

Key words: *Asthma; Asthma remission; Allergy; Inflammation; Delphi analysis*

INTRODUCTION

Asthma is a long-term respiratory inflammatory disease characterized by chronic lung inflammation, which affects up to 18% of people worldwide.[1,2]

According to the European Respiratory Society/American Thoracic Society, in severe asthma a high-dosage inhaled corticosteroid (ICS) plus a second controller (such as long-acting β_2-agonists) is required to maintain the disease controlled. Most of the time, disease remains uncontrolled, leading to different asthma exacerbations, hospitalizations, and a low quality of life.[3,4] Severe asthma can be characterized by various and unspecific symptoms (such as cough, wheeze, and breathlessness), numerous comorbidities, and increased bronchial hyperresponsiveness with frequent exacerbations.[5,6]

To date, epidemiologic data describing severe asthma are limited. According to the European Network for Understanding Mechanisms of Severe Asthma,[7] about 10% of the population with asthma develops severe asthma.[7] Patients with severe asthma are usually older and receive a late diagnosis of asthma. Also, severe asthma is characterized by low lung function and a high count of blood leukocytes, mainly eosinophils and neutrophils. Moreover, patients with severe asthma experience a high impact on the quality of life.[8]

A chronic inflammatory response, characterized by leukocyte recruitment and cytokine production, can be related to the development of severe asthma. This immune dysregulation in severe asthma is highly heterogeneous.[9]

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The differential diagnosis should be mandatory when severe asthma needs to be assessed, and a multidisciplinary approach (which includes patient communication, education, and follow-up) should be applied. Diagnosis begins with assessing medication adherence and inhaler technique. Other comorbidities such as rhinosinusitis, nasal polyps, gastrointestinal reflux, obstructive sleep dyspnea, obesity, and some psychiatric conditions, also need to be evaluated.[10] Moreover, asthma management should be continuously personalized and adjusted to prevent exacerbations.[11] In this context, high doses of ICS and long-acting β-agonists, and often a maintenance dose of oral corticosteroids, are currently used to treat severe asthma.[12] Asthma is a variable disease that may deteriorate or improve over time, depending on the patient's growth, avoidance of the inducer or trigger, comorbidities, and pharmacologic treatment, potentially leading in some cases to spontaneous remission (on treatment) of the disease.

Various definitions are used in clinical practice: clinical remission, inflammatory remission, and complete remission. Whereas in previous years remission was used to describe the lack of symptoms with no regular treatment, for severe asthma this outcome was considered too optimistic; the concept of on-treatment remission is used in the current study.

A recent independent definition of clinical disease remission in asthma, linked to the concept of disease-modifying anti-asthmatic drugs, was proposed according to four main criteria: the sustained absence of asthma symptoms, the sustained absence of asthma exacerbations, stable lung function, and no need for systemic corticosteroids for the treatment of asthma for at least 12 months.[13] This has been our basis for developing the Delphi consensus presented here.

Inflammatory remission is characterized by a low concentration or the absence of an inflammatory marker, such as eosinophils, allergen-specific IgE, periostin, FeNO, and eventually airway obstruction.

Complete remission is defined as the complete absence of symptoms with no medication. In this case, lung function is completely restored and no bronchial hyperresponsiveness can be detected.[14]

This work highlights a consensus for asthma remission using a Delphi method with the contribution of a panel of experts belonging to the Severe Asthma Network Italy (SANI), a network of 57 Centers of Excellence[15] in treating more than 2,200 patients with severe asthma patients in Italy.

METHODS

This study was conducted using a Delphi method to reach expert consensus on the definition of asthma remission, as previously described.[15,16]

The Delphi method is defined as a structured technique that guides a group of experts dealing with complex problems.[17] It is applied to a wide range of application and topics. Specifically in health care, this method is used to gain consensus on topics for which accurate tested data are not available, guidelines are insufficient, or knowledge is uncertain or incomplete,[18,19] providing qualitative and quantitative elaboration data.[20] To do this, the Delphi method must include three crucial stages: selection of a panel, development of surveys, and iterative processes to gain consensus.[19]

The goal of multiple iterations in the Delphi method is to reduce responses gradually and gain consensus[19] through three pivotal points: anonymity, controlled feedback, and statistical group response.[21]

Briefly, a board of six expert (four pneumologists and two allergists) was appointed as a scientific committee. During the first meeting, experts discussed and clearly defined the scope of the survey. Afterward, according to the state of the art of the literature and the experts' clinical expertise, they drafted a list of candidate statements in a questionnaire, which was revised to minimize redundancies and ensure clear and consistent wording for the first round (R1) of the analysis.

A total of 32 statements divided in four main categories (general questions about remission; clinical remission criteria; complete or partial clinical remission and its duration; and cutoff values of different scores regarding disease control, lung function, and inflammation) were included in the R1 questionnaire. Then, they were submitted to a panel of 80 experts (both pneumologists and allergists) selected from the SANI network.

Panelists used a 5-point Likert scale to measure agreement about each statement, in which 1 indicated strongly disagree; 2, disagree; 3, neither agree nor disagree; 4, agree; and 5, strongly agree). The cutoff for high consensus was defined as grade 4 and needed to be reached for at least two-thirds of the experts (66.6%). Then, the board of experts proceeded with an interim analysis of R1 data and selected bibliographic references. During this phase, panelists had the opportunity to write comments for each item, which were also discussed and considered to produce a consistent questionnaire for round 2 (R2) of the analysis. After this, the board set the R2 questionnaire, which included only the important topics. Panelists were then asked to vote on statements in the R2 questionnaire. Ultimately, the final data analysis and generation of the final Delphi report was performed with the support of a methodology expert.

RESULTS

The board developed a total of 32 statements. A group of 80 experts was included in the expert panel and invited to vote on statements anonymously. During R1, 53 experts voted on statements (66.25%) (Table I). A consensus was reached for 13 of 23 statements. Of 32 items included in R1, nine were exploratory items in which panelists were not asked to express a consensus but instead a choice regarding multiple options (the mode was always a single-choice question except in the case of item 4, in which multiple options could be selected). These were called exploratory items because they were useful for drafting R2 items. Exploratory items of R1 were 2, 3, 4, 18, 22, 24, 28, 29, and 30.

During R1, a wide consensus was obtained among statements related to the composite nature of clinical remission, the absence of symptoms, the absence of exacerbations or acute attacks, the stability of lung function, and the lack of a need for OCS. Similarly, a consensus was obtained in the statement regarding whether complete remission was achieved when there was no need for OCS and all of the following criteria were present: the absence of asthmatic symptoms, the absence of exacerbations or attacks, and the stability of lung function. Moreover, a consensus was also obtained in the statement addressing partial clinical remission, which was defined as when there was no need for OCS and two of three criteria were met: the absence of symptoms, the absence of exacerbations or attacks, and the stability of

TABLE I. Statements with respective levels of consensus reached during first round (R1) and second round (R2)

		Round 1		Round 2	
Statements R1	**Statements R2**	**n (%) agreement R1**	**Median R1**	**n (%) agreement R2**	**Median R2**
1. Clinical remission of severe asthma should be defined by a composite measure of multiple criteria.	1. Clinical remission of severe asthma should be defined by a composite measure of multiple criteria.	49 (92.5%)	5.00	42 (97.7%)	5.00
2. A definition of clinical remission of severe asthma can first be made after a period of treatment of at least (please choose one of the following): a) 6 mo b) 12 mo c) 24 mo d) 60 mo	2. A definition of clinical remission of severe asthma can first be made after a period of treatment of at least 12 mo			36 (83.7%)	4.00
3. When measuring the outcomes of a treatment of severe asthma, which of these would provide the clearest evidence? (only one response allowed) a) Clinical remission b) Inflammatory remission c) Histologic remission d) Evidence based on something other than remission (please use comments to provide more detail)	3. When measuring the outcomes of a treatment of severe asthma, clinical remission would provide the clearest evidence.			34 (79.1%)	4.00
4. When measuring the outcomes of a treatment of severe asthma, which of these would provide an acceptable evidence? (multiple responses allowed) a) Clinical remission b) Inflammatory remission c) Histologic remission d) Evidence based on something other than remission (please use comments to provide more detail)	4. When measuring the outcomes of a treatment of severe asthma, clinical remission would provide acceptable evidence.			29 (67.4%)	4.00
Please indicate the extent to which you agree on the importance of each item on the following list as a criterion for the definition of clinical remission of severe asthma:	Please indicate the extent to which you agree on the importance of each item on the following list as a criterion for the definition of clinical remission of severe asthma:				
5. No further need for OCS use		52 (98.1%)	5.00		
6. Absence of asthma symptoms	5. Absence of asthma symptoms	40 (94.3%)	5.00	40 (93.0%)	5.00
7. Absence of asthma exacerbations or attacks	6. Absence of asthma exacerbations or attacks	53 (100.0%)	5.00	43 (100.0%)	5.00
8. Stable lung function	7. Stable lung function	44 (83.0%)	4.00	39 (90.7%)	4.00
9. Clinically relevant improvement in lung function	8. Clinically relevant improvement in lung function	36 (67.9%)	4.00	23 (53.5%)	4.00
10. Stepping down of baseline treatment (ICS and other controllers)		35 (66.0%)	4.00		
11. Normalization of airway hyperreactivity		23 (43.4%)	3.00		
12. Normalization of asthma-related quality of life	9. Normalization of asthma-related quality of life	48 (90.6%)	4.00	40 (93.0%)	4.00
13. Clinically relevant reduction in lung inflammation	10. Clinically relevant reduction in lung inflammation	46 (86.8%)	4.00	37 (86.0%)	4.00
14. Agreement of both patient and HCP regarding disease remission	11. Agreement of both patient and HCP regarding disease remission	40 (75.5%)	4.00	39 (90.7%)	4.00

(continued)

TABLE I. *(Continued)*

		Round 1		Round 2	
Statements R1	**Statements R2**	**n (%) agreement R1**	**Median R1**	**n (%) agreement R2**	**Median R2**
15. The degree of clinical remission of severe asthma can be defined by means of a composite measure from a combination of: the absence of asthma symptoms, the absence of asthma exacerbations or attacks, the stability of lung function, and no further need for OCS use.	12. The degree of clinical remission of severe asthma can be defined by means of a composite measure from a combination of: absence of asthma symptoms, the absence of asthma exacerbations or attacks, stability of lung function, and no further need for OCS use.	50 (94.3%)	5.00	42 (97.7%)	5.00
16. Complete clinical remission of severe asthma is obtained when there is no further need to use OCS and all three criteria are met: the absence of asthma symptoms, the absence of asthma exacerbations or attacks, and stable lung function.	13. Complete clinical remission of severe asthma is obtained when there is no further need to use OCS, and all three following criteria are met: the absence of asthma symptoms, the absence of asthma exacerbations or attacks, and stable lung function.	48 (90.6%)	5.00	37 (86.0%)	5.00
17. Partial clinical remission of severe asthma is obtained when there is no further need to use OCS and two of three criteria are met: the absence of asthma symptoms, the absence of asthma exacerbations or attacks, and stable lung function.	14. Partial clinical remission of severe asthma is obtained when there is no further need to use OCS and two of three criteria are met: the absence of asthma symptoms, the absence of asthma exacerbations or attacks, and stable lung function.	39 (73.6%)	4.00	29 (67.4%)	4.00
18. Persistence of remission in severe asthma can be defined as a period of at least (please choose one of the following): a) 1 y b) 3 y c) 5 y	15. Persistence of remission in severe asthma can be defined as a period of at least 1 y.			34 (79.1%)	4.00
	16. Persistence of remission in severe asthma can be defined as a period of at least 3 y.			28 (65.1%)	4.00
19. Remission means asthma is fully controlled with biologic therapy and treatment is stepped down to two-thirds of Global Initiative for Asthma levels.		24 (45.28%)	3.00		
20. Remission means asthma is fully controlled with biologic therapy and treatment is maintained at four-fifths of Global Initiative for Asthma levels.		27 (45.3%)	4.00		
21. Remission means asthma is fully controlled after suspension of biologic treatment.		21 (50.9%)	3.00		
22. Remission means the complete absence of exacerbations in the past: a) 1 y b) 3 y c) 5 y					
	17. Remission means asthma is fully controlled with biologic therapy and the deescalation of inhaled treatment.			25 (58.1%)	4.00
23. Remission means no use of regular or burst OCS.	18. Remission means no use of regular or burst OCS.	46 (86.8%)	4.00	33 (76.7%)	5.00

(continued)

TABLE I. *(Continued)*

Statements R1	Statements R2	Round 1		Round 2	
		n (%) agreement R1	Median R1	n (%) agreement R2	Median R2
24. Remission means an Asthma Control Test score of: a) 25/25 b) 20 to 25/25	19. Clinical remission means an Asthma Control Test score of 20 to 25/25.			33 (76.7%)	4.00
25. Remission means a lung function improvement of at least 100 mL of FEV_1 compared with the uncontrolled period.		11 (20.8%)	3.00		
26. Remission means obtaining a normalized pulmonary function (FEV_1 ≥80%).		23 (43.4%)	3.00		
27. Remission means obtaining an improvement of at least 200 mL and a 12% improvement in FEV_1 compared with the uncontrolled period.	20. Remission means obtaining an improvement of at least 200 mL and a 12% improvement in FEV_1 compared with the uncontrolled period.	13 (24.5%)	3.00	16 (37.2%)	3.00
28. Remission means reaching an eosinophil count of: a) <300 cells/μL b) <150 cells/μL	21. Inflammatory remission means reaching an eosinophil count of <300 cells/μL			14 (32.6%)	3.00
29. Remission means reaching an FeNO level of: a) <50 ppb b) <25 ppb	22. Inflammatory remission means reaching an FeNO <25 ppb			21 (48.8%)	3.00
30. Remission means reaching a severe Asthma Control Questionnaire score of: a) <1,5 b) <0,5	23. Clinical remission means reaching a severe Asthma Control Questionnaire score of <1,5.			34 (79.1%)	4.00
31. Remission means reaching a severe asthma questionnaire score of >96 and a severe asthma questionnaire−global scale score of >85.		31 (58.5%)	4.00		
32. Because there are no validated HCP-reported disease activity instruments in asthma, HCP and patient concurrence regarding asthma remission should be required for a patient to be considered in remission.	24. Because there are no validated HCP-reported disease activity instruments in asthma, HCP and patient concurrence regarding asthma remission should be required for a patient to be considered in remission.	34 (64.2%)	4.00	32 (74.4%)	4.00

HCP, health care professional; *OCS*, oral corticosteroids.
A cutoff value for a high and low consensus is defined according to grade 4 and at least two-thirds of agreement among experts (66.6%) and less of two-thirds of agreement among experts (66.6%), respectively.

TABLE II. Definitions of partial and complete remission according to main results obtained from Delphi analysis

Topics	Partial clinical remission	Complete clinical remission
Definition	Partial clinical remission is obtained when there is no further need to use oral corticosteroids and two of three criteria are met:	Complete clinical remission is obtained when there is no further need to use oral corticosteroids and all three criteria are met:
Criteria	Absence of asthma symptoms Absence of asthma exacerbations or attacks Stable lung function	Absence of asthma symptoms Absence of asthma exacerbations or attacks Stable lung function
Time	For at least 12 mo	For at least 12 mo
Scores	Asthma Control Test score of 20/25 to 25/25 Asthma Control Questionnaire score of <1,5	Asthma Control Test score of 20/25 to 25/25 Asthma Control Questionnaire score of <1,5

lung function (Table II). Regarding duration, most experts agreed that remission was defined as the absence of exacerbations for at least 1 year, and that persistent remission was defined as lasting 3 years (52.8% consensus) and 1 year (37% consensus). The absence of corticosteroids was reaffirmed. Regarding patients with severe asthma who were receiving biologic therapy, a

consensus was not reached about either discontinuation of biologic treatment or its maintenance. Similarly, there was no consensus about whether asthma could be completely controlled with biologic treatments.

During R2, the number of statements was reduced to 24. For this round, responses were provided by 43 panel members (53.75%). A consensus was reached for 18 of 24 statements (Table I). During R2, the composite definition of remission, criteria for complete clinical remission (the absence of the need for OCS, the absence of symptoms, the absence of exacerbations or attacks, and pulmonary stability), and those for partial clinical remission (the absence of the need for OCS; and two of three criteria: the absence of symptoms, the absence of exacerbations or attacks, and pulmonary stability) were confirmed.

Regarding the duration required to define a patient in remission, in this round, the item reporting a duration of 1 year obtained a greater consensus (in contrast to R1, in which the greatest consensus was obtained for a duration of 3 years).

Regarding the role of therapy, reducing inhaled therapy while the patient was receiving biologic therapy or maintaining it was excluded as an advisable criterion for remission since R1.

The last section of the questionnaire focused on quantitative parameters about the clinical and functional response and inflammatory parameters. During R1, experts reached a broad consensus saying that achieving an Asthma Control Test (ACT) score of 20 to 25 indicates clinical remission (73.8%), as does an Asthma Control Questionnaire (ACQ) score of less than 0.5 (56.6%). In this case, a value of 1.5 also achieved a fair amount of consensus (43.4%).

Regarding improvement in lung function as a criterion for remission, there was no consensus on the value to be used as a reference (not 100 or 200 mL, or a function greater than or equal to 80% over the uncontrolled phase).

Regarding markers of inflammation involved in inflammatory remission and their cutoffs, a consensus was achieved with an eosinophil value of less than 300 cells/L and an FeNO of less than 25 ppb.

Regarding the quality of life, a full consensus was not reached about a severe asthma questionnaire cutoff value greater than 96 (58.5%) or about the need for clinician–patient agreement in jointly defining remission, in the absence of validated tools (64.2%).

During R2, the consensus regarding having an ACT score of 20/25 to 25/25 was strengthened, and an ACQ less than 1.5 was reiterated as being enough to indicate clinical remission. Statements regarding improvement in lung function were removed because the experts had not reached a consensus on them.

Although a cutoff for eosinophils less than 300 cells/L was confirmed as a criterion to define inflammatory remission, a consensus was not reached for this statement. Similarly, although an FeNO lower than 25 ppm was defined as a good marker for a reduction in inflammation, there was no consensus when it was considered as a criterion for inflammatory remission. Moreover, the need for clinician–patient agreement about remission, in the absence of validated tools, achieved wide agreement.

Table III lists the definitions of clinical remission according to the main results obtained from the Delphi analysis. A consensus was reached for the first four criteria (the absence of asthma symptoms, the absence of asthma exacerbations or attacks, the stability of lung function, and no further need for OCS treatment), and these were used as criteria to define remission (partial or complete). The last three criteria included the time range and the ACT and ACQ scores that need to be considered for clinical remission. A consensus was not reached for these parameters for use in the priority definition of remission (partial or complete).

TABLE III. Definition of clinical remission according to main results obtained from Delphi analysis

How clinical remission should be defined	
Definition	Clinical remission is defined by a composite measure of multiple criteria
Criteria	Absence of asthma symptoms
	Absence of asthma exacerbations or attacks
	Stable lung function
	No further need for oral corticosteroid treatment
	Normalization of asthma-related quality of life
	Stable lung function
	Clinically relevant reduction in lung inflammation
	Agreement of both patient and health care professional regarding disease remission
Time	For at least 12 mo
Scores	Asthma Control Test score of 20/25 to 25/25
	Asthma Control Questionnaire score of <1,5

Experts reached a consensus on the first four criteria (absence of asthma symptoms, absence of asthma exacerbations or attacks, stable lung function, and no further need for oral corticosteroid treatment). These were used as criteria to define remission (partial or complete). The last three criteria included the time range and the Asthma Control Test and Asthma Control Questionnaire scores that need to be considered for clinical remission. There was no consensus for these parameters for use in the priority definition of remission (partial or complete).

DISCUSSION

First mentioned in 1951,[22] Barach asthma remission is an important concept. Thus, it is crucial to define disease remission to identify the best strategies for modifying therapy. The aim of this work was to obtain a definition of severe asthma remission shared by all clinical stakeholders, especially considering the different biologic treatments available. We applied a Delphi methodology to achieve this aim.

In 2020, Menzies-Gow[23] classified the concepts of remission as clinical remission and complete remission. To date, remission is classified as complete clinical remission and partial clinical remission, as well as inflammatory remission or biological remission.

Clinical disease remission in asthma is defined according to three main criteria: the absence of exacerbations, no oral corticosteroid treatment and an improvement in lung function for at least 12 months. Lommatzsch et al[13] recently reported clinical disease remission in asthma to be defined according to four main criteria: the sustained absence of asthma symptoms, the sustained absence of asthma exacerbations, stable lung function, and the lack of a need for systemic corticosteroids to treat asthma. We took this to as the basis of our Delphi procedure.

During the first round of our analysis, clinical remission was chosen as the appropriate outcome to verify the effectiveness of

therapy. However, inflammatory remission, as indicated by 37% of experts, is also an important parameter to evaluate. During R2, the definition of remission as a composite set of several criteria was confirmed. Regarding the debate about whether clinical remission should be considered an outcome of severe asthma, the consensus obtained in R1 was confirmed.

According to Carpaij and colleagues,[24] asthma remission is defined by various criteria, such as the absence of symptoms, its period, the absence of treatment, the absence of lung function impairment, and bronchial hyperresponsiveness. On this matter, criteria suggested by Delphi should be applied to patients with severe asthma on treatment with biologic drugs. Regarding criteria defining a remission, during R1 the experts stated that the absence of the requirement for systemic corticosteroids, the absence of symptoms, and the absence of exacerbations should be criteria for defining clinical remission in severe asthma. As for lung function, a consensus was reached regarding both the stability of lung function and its improvement over time.

A consensus was not reached for the statements about the possibility of reducing ICS treatment and the normalization of airway hyperresponsiveness. Instead, there was a consensus on normalizing quality of life, achieving a clinically relevant reduction in bronchial inflammation, and the requirement that the physician and patient must agree that it is remission.

During R2, two items for which experts did not reach a consensus were removed: those concerning the possibility of reducing current inhaled treatments and the normalization of pulmonary hyperreactivity. In contrast, the statement on the improvement of lung function was removed owing to a lack of a consensus resulting from the lack of agreement about different criteria to be used to define a significant improvement in FEV_1. Items that had gained expert consensus during R1, including the absence of OCS use, the absence of symptoms, and the absence of exacerbations or attacks, were confirmed, as well as the one about the stability of lung function. Finally, the importance of normalizing the quality of life, of highlighting a clinically relevant reduction in lung function, and of reaching an agreement between the patient and clinician about remission were proposed. Nevertheless, these did not reach the priority level for inclusion in the criteria of remission.

In 2022, Ribas et al[25] highlighted the multicomponent nature of clinical remission in severe asthma. In agreement with that in the current study, during R1 a wide consensus was obtained among statements related to the composite nature of clinical remission, the absence of symptoms, the absence of exacerbations and acute attacks, the stability of lung function, and the lack of a need for OCS. Similarly, a consensus was obtained in the statement regarding whether complete remission was achieved when there was no need for OCS and all of these criteria were present: the absence of asthmatic symptoms, the absence of exacerbations or attacks, and stable lung function. Moreover, a consensus was also obtained about the statement addressing partial clinical remission, which was defined as when there was no need for OCS and two of these three criteria were met: the absence of symptoms, the absence of exacerbations or attacks, and stable lung function (Table II). As for duration, most experts agreed that remission was defined as the absence of exacerbations for at least 1 year, and persistent remission was defined as lasting 3 years (52.8% consensus) and 1 year (37% consensus). The absence of corticosteroids was reaffirmed. Regarding patients with severe asthma who were receiving biologic therapy, a consensus was not reached on either the discontinuation of biologic treatment or its maintenance. Similarly, there was no consensus on whether asthma could be completely controlled with biologic treatments. These results found confirmation in the literature. In fact, all available data reported a success rate of 30% in patients using different biologics, even when different definitions for remission were used.[26] During R2, the composite definition of remission, the criteria of complete clinical remission (the absence of the need for OCS, the absence of symptoms, the absence of exacerbations of attacks, and pulmonary stability) and partial clinical remission (the absence of the need for OCS, and two of three criteria: the absence of symptoms, the absence of exacerbations or attacks, and pulmonary stability) were confirmed.

Regarding the duration required to define a patient in remission, in this round the item reporting a duration of 1 year obtained a greater consensus (in contrast to R1, in which the greatest consensus was obtained for a duration of 3 years).

Regarding the role of therapy, the reduction of inhaled therapy while receiving biologic therapy or maintaining it was excluded as advisable criteria for remission since R1.

The last section of the questionnaire focused on quantitative parameters about clinical and functional response and inflammatory parameters. During R1, experts reached a broad consensus to say that achieving an ACT score of 20 to 25 indicates clinical remission (73.8%), as does an ACQ score of less than 0.5 (56.6%). In this case, a value of 1.5 also achieved a fair amount of consensus (43.4%).

Regarding an improvement in lung function as a criterion for remission, there was no consensus on the value to be used as a reference (not 100 or 200 mL, or function greater than or equal to 80% over the uncontrolled phase).

Regarding the markers of inflammation involved in inflammatory remission and their cutoffs, a consensus was achieved with an eosinophil value of less than 300 cells/L and an FeNO of less than 25 ppb.

Regarding the quality of life, a full consensus was not reached about a severe asthma questionnaire[27] cutoff value greater than 96 (58.5%) or about the need for clinician−patient agreement in jointly defining remission, in the absence of validated tools (64.2%).

During R2, the consensus regarding having an ACT score of 20/25 to 25/25 was strengthened, an ACQ less than 1.5 was reiterated as being enough to indicate clinical remission, and statements regarding an improvement in lung function were removed because the experts had not reached a consensus about them.

Although a cutoff for eosinophils less than 300 cells/L was confirmed as a criterion to define inflammatory remission, a consensus was not reached for this statement. Similarly, although an FeNO value less than 25 ppm is defined as a good marker when defining a reduction in inflammation, there was no consensus when it was a criterion for inflammatory remission. Moreover, the need for a clinician−patient agreement about remission, in the absence of validated tools, achieved wide agreement.

CONCLUSIONS

Asthma is considered the most widespread respiratory disease. Ten percent of patients with asthma have severe disease, and it is crucial to define criteria clearly to address remission. Although

wide agreement among the scientific community has been reached about the general concept of remission and the criteria to define it, there is more variability regarding the concept of duration, the role of therapy during remission, and the concept of inflammatory remission. This prompted Corbett and Oppenheimer[28] to define remission as the ultimate goal of pediatric asthma management, and it highlights the need for a consensus definition of remission in pediatric asthma, as well.

The results obtained in this study appear to be congruent with the current popular concept of remission among the scientific community. Moreover, the definitions of partial and complete clinical remission obtained from the Delphi analysis will be those used to test the efficacy of different treatments in patients (greater than 2,200) enrolled into the SANI registry and observed. This work was designed to create an independent, valuable, easy to use, and effective tool, which might help clinicians to identify remission.

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