An expert consensus framework for asthma remission as a treatment goal

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With novel therapies in development, there is an opportunity to consider asthma remission as a treatment goal. In this Rostrum, we present a generalized framework for clinical and complete remission in asthma, on and off treatment, developed on the basis of medical literature and expert consensus. A modified Delphi survey approach was used to ascertain expert consensus on core components of asthma remission as a treatment target. Phase 1 identified other chronic inflammatory diseases with remission definitions. Phase 2 evaluated components of those definitions as well as published definitions of spontaneous asthma remission. Phase 3 evaluated a remission framework created using consensus findings. Clinical remission comprised 12 or more months with (1) absence of significant symptoms by validated instrument, (2) lung function optimization/stabilization, (3) patient/provider agreement regarding remission, and (4) no use of systemic corticosteroids. Complete remission was defined as clinical remission plus objective resolution of asthma-related inflammation and, if appropriate, negative bronchial hyperresponsiveness. Remission off treatment required no asthma treatment for 12 or more months. The proposed framework is a first step toward developing asthma remission as a treatment target and should be refined through future research, patient input, and clinical study. (J Allergy Clin Immunol 2020;145:757-65.)

Key words: *Asthma, remission, treatment, consensus, lung, biomarkers, inflammation, surveys and questionnaires, exacerbation, hyperresponsiveness, airway remodeling*

Asthma is the most common long-term respiratory disease, affecting more than 300 million people worldwide with significant morbidity and mortality.[1] The estimated annual cost of asthma in the United States, taking into account direct medical costs, mortality, and loss of attendance at school and work, was estimated to be in excess of $80 billion.[2] The mainstay of asthma therapy, inhaled and oral glucocorticoids, has not changed for

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This research was funded by AstraZeneca.

Disclosure of potential conflict of interest: A. Menzies-Gow has attended advisory boards for GlaxoSmithKline, Novartis, AstraZeneca, Boehringer Ingelheim, Teva, and Sanofi; has received speaker fees from Novartis, AstraZeneca, Vectura, Boehringer Ingelheim, and Teva; has participated in research for which his host institution has been remunerated by AstraZeneca; has attended international conferences sponsored by Teva and Boehringer Ingelheim; and has consultancy agreements with AstraZeneca, Vectura, and Sanofi, outside the submitted work. M. Bafadhel has received honoraria and travel expenses for attendance at educational meetings from AstraZeneca, Chiesi, GlaxoSmithKline, Boehringer Ingelheim, Novartis, and Pfizer, outside the submitted work. W. W. Busse reports personal fees from Boston Scientific, AstraZeneca, GlaxoSmithKline, Novartis, Sanofi/Genzyme-Regeneron, Teva, Genentech, Elsevier, and Medscape, outside the submitted work. T. B. Casale is a consultant for Novartis, Genentech, Teva, AstraZeneca, and Sanofi/Regeneron and receives research support from Genentech, MedImmune/AstraZeneca, Novartis, Teva, and Sanofi/Regeneron, outside the submitted work. J. W. H. Kocks has received grants and personal fees from AstraZeneca and Boehringer Ingelheim, personal fees and nonfinancial support from GlaxoSmithKline, and grants from Chiesi and Mundi Pharma, outside the submitted work. I. D. Pavord has received honoraria in the past 5 years for speaking at sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, and GlaxoSmithKline and a payment for organizing an educational event from AstraZeneca; has received honoraria for attending advisory panels with Almirall, Genentech, Regeneron, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme, Schering-Plough, Novartis, Dey Pharma, Napp Pharmaceuticals, and RespiVert; and has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, and Napp Pharmaceuticals, outside the submitted work. S. J. Szefler has served as a consultant to Aerocrine, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Genentech, GlaxoSmithKline, Novartis, Propeller Health, Regeneron, Roche, Sanofi, and Teva, outside the submitted work. P. G. Woodruff has received personal fees from AstraZeneca, Regeneron, Sanofi, Genentech, Novartis, GlaxoSmithKline, 23andMe, and Janssen, outside the submitted work. A. de Giorgio-Miller, M. Fageras, and C. S. Ambrose are employees of AstraZeneca. F. Trudo is an employee and shareholder of AstraZeneca.

Received for publication June 25, 2019; revised September 23, 2019; accepted for publication December 10, 2019.

Available online December 19, 2019.

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0091-6749

https://doi.org/10.1016/j.jaci.2019.12.006

Abbreviations used
ACQ: Asthma Control Questionnaire
ACT: Asthma Control Test
CD: Crohn disease
HCP: Health care provider
PMR: Polymyalgia rheumatica
RA: Rheumatoid arthritis
SLE: Systemic lupus erythematosus
UC: Ulcerative colitis

decades, and although they remain very effective medications, their nonspecific anti-inflammatory mechanism of action has not been shown to have a significant long-term impact on the course of the disease. Other chronic inflammatory diseases, such as rheumatoid arthritis, have seen a transformation in the available treatment options, moving from glucocorticoids to disease-modifying antirheumatic drugs and on to targeted biologic therapies, which can slow down or even halt the progression of disease. Alongside these advances, the treatment paradigm in these diseases has advanced to "treat to target" key pathophysiologic pathways with the goal of inducing sustained disease remission or, when remission is not achievable, sustained reduction in disease activity.[3]

With several novel therapies currently being used and developed for asthma, it is a logical time to consider whether remission in asthma is now an achievable treatment target.[4] Disease remission is broadly defined as a state or period with low to no disease activity and can be spontaneous or a result of therapy.[5,6] Assessments of disease activity can include clinical signs and patient symptoms of the disease as well as markers of disease processes derived from laboratory testing and/or imaging. To date, remission of asthma has only been described as the spontaneous cessation of asthma disease activity (eg, due to the transition from childhood to adulthood) and not as a therapeutic target.[7-10] A consensus definition of asthma remission could become a new asthma treatment goal and allow further exploration and comparison of the efficacy of novel treatment regimens.[8] A comprehensive and pragmatic definition of remission as a treatment target must add value beyond the existing treatment goal of asthma control, which is based on current symptom control and future risk of adverse outcomes.[11,12] Although there are clear criteria for optimal control of a patient's symptoms in the past 4 weeks, we lack explicit goals for symptom control over longer time intervals and for minimization of future risk, which is complicated by the high number of risk factors for poor outcomes and the fact that some risk factors are not modifiable.

Assessment of asthma disease should be based on both objective and subjective measures and should incorporate all important aspects of the disease, including symptom control, exacerbation frequency, pulmonary function, and laboratory markers of inflammation.[11] The ideal definition of asthma remission should address current asthma symptom burden, recent exacerbation incidence, and future exacerbation risk and include the absence of ongoing airway inflammation and prevention of accelerated lung function decline and airway remodeling. The definition should require a sufficient duration of assessment to address the inherent variability in asthma, including seasonality of disease activity, and should be suitable for assessment in clinical studies as well as implementation in routine clinical practice. The definition of remission should be relevant across the entire spectrum of asthma severity and take into account the presence or absence of background medication.

The current project therefore aims to develop a framework for asthma remission that satisfies the above criteria, based on expert consensus collected via a multistage Delphi survey and relevant medical literature in other chronic inflammatory conditions and asthma. This framework is envisioned as an initial step of an iterative, multistep journey toward a commonly accepted definition of asthma remission. Rather than create a single specific definition of remission, the goal of the current project was to propose a generalized framework that can be further refined and evaluated by future studies, interventional trials, clinical practice, patient input, and expert opinion.

DELPHI SURVEY TO DERIVE EXPERT CONSENSUS

A modified Delphi survey was conducted among a small group of US and European experts in the primary and specialty care of asthma (authors A.M.G., M.B., W.W.B., T.B.C., J.W.H.K., I.D.P., S.J.S., and P.G.W.). The goal of the survey was to derive a consensus framework for asthma remission as a treatment goal, using an approach similar to that used to derive remission frameworks for other chronic inflammatory diseases.[13-15] Phase 1 identified other chronic inflammatory diseases with established definitions of remission as a treatment target. Phase 2 identified the key components of these definitions on the basis of published definitions of remission in these reference diseases as well as recent studies of spontaneous remission in asthma. Phase 3 tested a framework for asthma remission and clarifying statements based on phase 2 findings. Consensus was defined a priori as no more than 1 respondent dissenting from majority agreement. A more detailed description of the survey process in each phase can be found in this article's Methods section in the Online Repository at www.jacionline.org.

Phase 1: Identification of chronic inflammatory diseases with established definitions of remission as a treatment target

The structured literature search identified 6 diseases with established definitions of remission as a treatment target: rheumatoid arthritis (RA), Crohn disease (CD), ulcerative colitis (UC), systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR), and psoriasis. These 6 diseases were categorized into 2 groups on the basis of rigor of the definition: group 1 (RA, CD, UC, and SLE) had clear definitions endorsed by regulatory authorities and/or internationally recognized professional societies, whereas group 2 (PMR and psoriasis) had less well-developed definitions and/or less consensus. Details regarding these definitions are outlined in this article's Results section in the Online Repository at www.jacionline.org. Although definitions beyond the 6 diseases above exist in the medical literature, none were identified in our structured search for more established definitions. In the first Delphi survey, most respondents (88%; see Table E1 in this article's Online Repository at www.jacionline.org) agreed to include RA, UC, CD, and SLE, but not PMR or psoriasis, because they were deemed less developed and not as relevant to asthma.

TABLE I. Characteristics of established remission definitions in reference chronic inflammatory diseases

Condition/reference	Descriptor*	HCP-rated disease activity	Patient symptoms	Can a patient be receiving treatment and qualify?	Laboratory measures	Imaging, diagnostic procedures, histology	Relevant time frame for symptoms	Relevant time frame for laboratory measures or imaging/histology
RA (Felson et al,[25] 2011, Anderson et al,[27] 2012, Singh et al,[17] 2016, European Medicines Agency,[28] 2018)	Clinical	Yes (tender/swollen joint count†)	Yes (patient global assessment†)	Yes	Yes (CRP†); not required for clinical practice definition	Not included	Current	Current
UC (Travis et al,[24] 2011, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER),[29] 2016)	Clinical	No	Yes (stool frequency, rectal bleeding‡)	Yes	Not included	Yes (endoscopy)	Current	Current
	Corticosteroid-free	No	Yes (stool frequency, rectal bleeding‡)	Yes, but chronic corticosteroid use not allowed	Not included	Yes (endoscopy)	Current	Current
CD (Lichtenstein et al,[30] 2018)	Clinical/ symptomatic	Yes (weight, abdominal mass, 6 extraintestinal findings§)	Yes (soft/liquid stools, abdominal pain, general well-being, antidiarrheal drug use§)	Yes, but chronic corticosteroid use not allowed	Yes (hematocrit)	Not included	Past 7 d	Current
SLE (van Vollenhoven et al,[13] 2017)	On therapy	Yes (with SLEDAI: 16 clinical signs and 8 laboratory values, plus physician global assessment‖)	No	Yes, but corticosteroids must be ≤5 mg/d (prednisone equivalent)	Yes (routine laboratory assessments)	Not included	"Durable" requirement but duration not specified because of uncertainty	Current
	Off therapy	Yes (with SLEDAI: 16 clinical signs and 8 laboratory values, plus physician global assessment‖)	No	Yes, but allows only maintenance antimalarials	Yes (routine laboratory assessments)	Not included	"Durable" requirement but duration not specified because of uncertainty	Current

CRP, C-reactive protein; *SLEDAI*, Systemic Lupus Erythematosus Disease Activity Index.
*This column captures the wording used to describe the type of remission (eg, clinical and complete).
†RA disease activity measures can be found at https://www.rheumatology.org/Practice-Quality/Clinical-Support/Quality-Measurement/Disease-Activity-Functional-Status-Assessments.
‡UC disease activity measures are numerous and not reviewed together at any one Web site. Please refer to the original references for more information.
§CD Activity Index can be found at https://www.merckmanuals.com/medical-calculators/CDAI.htm.
‖SLE Disease Activity Index can be found at https://www.mdcalc.com/systemic-lupus-erythematosus-disease-activity-index-2000-sledai-2k.

Phase 2: Identification of key components of asthma remission as a treatment target

Phase 2a: Remission definitions in other chronic inflammatory diseases. The results of the literature summary on definitions of remission in RA, UC, CD, and SLE are presented in Table I. Efforts to define remission focused as a first stage on "clinical remission" based on systematic evaluations of disease signs and symptoms and routine laboratory (or in UC, endoscopic) assessments. All definitions allowed patients to receive ongoing treatment and still qualify for remission; however, definitions for UC, CD, and SLE required the patient to not be receiving long-term corticosteroid therapy due to associated toxicity (for SLE, this was specific to >5 mg/d prednisone or equivalent). Relevant laboratory measures routinely available in clinical practice are included in clinical remission in RA, CD, and SLE. Clinical remission in RA, CD, and SLE did not require imaging, histology, or other nonroutine diagnostic procedures, whereas UC remission required endoscopy assessment.

A current assessment of these factors was deemed sufficient to determine remission in RA, UC, and CD; there were no time/duration requirements. SLE included a nonspecific requirement that remission be "durable" due to the relapsing/remitting nature of the disease, although experts did not agree on the specific duration. More complex levels of remission such as endoscopic, histologic, complete, and deep were proposed in RA, CD, and SLE, based on imaging, histology, and other nonroutine diagnostic procedures; however, consensus definitions were generally not available for these levels of remission.

The clinical experts were provided the summary of remission definition components in Table I and a survey to identify the general concepts most relevant for remission in asthma. All 8 experts provided responses, and the level of agreement for each statement is summarized in Table II (see individual responses in Table E2 in this article's Online Repository at www.jacionline.org). All respondents agreed with the conclusions from the literature review of remission definitions in RA, UC, CD, and SLE, and consensus was achieved for several general statements regarding asthma remission. For other statements, a 75% majority and free-text responses provided insights for the general framework tested in phase 3. Although RA, UC, and CD had no duration requirement for remission, most experts felt that asthma remission should have a required duration, with 50% suggesting a 12-month duration.

TABLE II. Survey responses regarding general concepts for a definition of remission in asthma*,†

Question/statement	Agreement for question/statement (% of respondents, N = 8)
Statements achieving consensus	
Remission is a desirable outcome for the patient with asthma.	Yes (100)
Remission in asthma is not the same as a cure.	Yes (100)
A definition of remission in asthma should be stringent but achievable.	Yes (100)
A definition of remission in asthma should be able to be applied in clinical studies and clinical practice.	Yes (100)
To maximize the applicability of any definition, the criteria for remission in asthma should be limited to core, essential elements, preferably those that are easily assessed in routine clinical practice.	Yes (100)
Any definition of asthma remission should be tested to determine its ability to predict long-term positive outcomes.	Yes (100)
Defining clinical remission, based primarily on patient symptoms, HCP assessment of disease activity, and routine clinical assessments (exact criteria to be defined), is an important first step in defining remission in asthma.	Yes (100)
Because of associated toxicity, chronic use of systemic corticosteroids for asthma treatment should preclude a patient from being considered in remission.	Yes (100)
As with remission in RA, UC, CD, and SLE, remission in asthma should apply to all levels of disease severity.	Yes (100)
Being in remission in asthma does not eliminate the risk of severe and even fatal asthma events.	Yes (88)‡
It is important to have objective measures of disease activity in a definition of asthma remission.	Yes (88)§
Statements not achieving consensus but with 75% agreement	
As with remission in RA, UC, CD, and SLE, remission in asthma is a clinical state and should be defined regardless of the type of asthma treatment(s) the patient is receiving (with the possible exception of chronic systemic corticosteroid therapy).	Yes (75)
As with SLE remission, remission in asthma should have the option of being described as "on treatment" or "off treatment" to acknowledge the presence or absence of ongoing asthma medication use.	Yes (75)
There is currently no appropriate, routine laboratory measure that is applicable for all patients with asthma and can be included in a standard definition of clinical remission in asthma.	Yes (75)
Just as radiographic joint changes are excluded from the definition of RA remission but are an important long-term outcome, a patient's long-term lung function trajectory should be excluded from the core definition of remission in asthma but should be one of the outcomes against which remission definitions are evaluated.	Yes (75)
Free-text response only: RA, UC, and CD remission definitions do not have a duration requirement (focusing only on the patient's current clinical state), whereas SLE remission has an undefined requirement for a "durable" state. For remission in asthma, how should duration be addressed? Please explain your answer.	Duration necessary (75% [1 y: 50%; unspecified: 25%])

*Consensus was defined as ≤1 respondent dissenting from majority agreement.
†Full survey responses, including all free-text questions and dissenting opinions, are included in Table E2.
‡Dissenting opinion: "This is a tough one. If patients are in proper remission, the risk of a (fatal) exacerbation occurring with 1 week of 'prodromes' would be unacceptable. If this would occur, this should be VERY low in frequency."
§Dissenting opinion: "We do need it for complete remission, but will be hard to do with our current understanding of T2-low asthma (ie, we don't have any markers of disease activity for this)."

Phase 2b: Remission definitions in asthma. The published definitions of asthma remission that we evaluated described spontaneous cessation of asthma disease activity unrelated to asthma treatment (Table III). None represented a pragmatic treatment goal. However, the definitions were evaluated to identify potential components of remission as a treatment target. No definitions used health care provider (HCP)-rated disease severity, and all definitions required no asthma symptoms reported by patients within 6 months to 3 years. Definitions of clinical remission relied solely on patient-reported symptoms and medication use, whereas definitions of complete remission included requirements of current normal lung function and/or negative airway hyperresponsiveness (with 1 definition requiring normal fractional exhaled nitric oxide). The incidence of spontaneous remission varied considerably across studies based on the patient population, methods, and definition criteria.

The results described above were presented to the clinical experts for the phase 2b Delphi survey. Based on components of the definitions (Table III), the survey tested specific criteria for potential inclusion in our framework of asthma remission as a treatment goal. Because of a technical issue, responses from 1 of the 8 experts were not recorded. Table IV summarizes the level of agreement for each statement surveyed that attained consensus (individual responses are presented in Table E3 in this article's Online Repository at www.jacionline.org). All respondents agreed with the conclusions drawn from the literature review, and consensus was achieved for several statements. These conclusions, as well as feedback on other statements, were incorporated into the general framework and additional clarifying statements tested in phase 3. Individual responses to open-ended questions and statements that did not achieve consensus can be found in Table E3.

TABLE III. Published definitions of spontaneous remission in asthma

Study	Descriptor*	HCP-rated disease activity	Patient symptoms	Can a patient be receiving treatment and qualify?	Laboratory measures	Lung function measures	AHR	Relevant time frame for symptoms, medications, attacks	Relevant time frame for laboratory measures or lung function	Proportion achieving (study duration)
Westerhof et al,[9] 2018	Clinical	Not included	No symptoms reported on 6-item ACQ, no medications	No	Not included	Not included	Not included	1 y (symptoms and medications)	NA	15.9% (5 y)
Tuomisto et al,[31] 2016	Clinical	Not included	No symptoms based on ACT score = 25, no medications	No	Not included	Not included	Not included	6 mo (symptoms, medications) to 2 y (oral prednisone courses)	NA	3% (12 y)
Tuomisto et al,[31] 2016	Complete	Not included	No symptoms based on ACT score = 25, no medications	No	FENO ≤20 ppb	Pre-BD FEV_1 >80% predicted; FEV_1/FVC >0.7; post-BD ΔFEV_1 ≤12% and <200 mL	Not included	6 mo (symptoms, medications) to 2 y (oral prednisone courses)	Current	1.5% (12 y)
Sozener et al,[32] 2015	Clinical	Not included	No symptoms based on ACT score = 25, no medications	No	Not included	Not included	Not included	2 y (symptoms and medications)	NA	11.3% (7 y)
Sozener et al,[32] 2015	Complete	Not included	No symptoms based on ACT score = 25, no medications	No	Not included	Not included	Negative methacholine challenge	2 y (symptoms and medications)	Current	33.3% of those with clinical remission who took the AHR test
Cazzoletti et al,[33] 2014	Clinical	Not included	No symptoms, attacks, or medication	No	Not included	Not included	Not included	1 y (symptoms and attacks); current for medications	NA	29.7% (8 y)
Wu et al,[10] 2014	Complete	Not included	No symptoms, no relapse, no medication	No	Not included	Not included	Not included	3 y (symptoms), 1 y (medications)	NA	23%-49% by age of onset (lifetime)
Boulet et al,[34] 2012	Symptomatic	Not included	No symptoms or medication	No	Not included	Not included	Not included	2 y (symptoms and medications)	NA	ND
Boulet et al,[34] 2012	Complete	Not included	No symptoms or medication	No	Not included	Not included	Negative methacholine challenge	2 y (symptoms and medications)	Current	ND
Volbeda et al,[35] 2010	Complete	Not included	No symptoms, attacks, or medication	No	Not included	FEV_1 >90% predicted	Negative AMP and histamine challenges	3 y (symptoms and attacks); current for medications	Current	23% (duration not specified)
Ronmark et al,[36] 2007	Clinical	Not included	No symptoms, attacks, or medication	No	Not included	Not included	Not included	1 y (symptoms, attacks, medications)	NA	4.8% (4-8 y)
Ronmark et al,[36] 2007	Clinical with normal lung function	Not included	No symptoms, attacks, or medication	No	Not included	FEV_1 >80% predicted	Not included	1 y (symptoms, attacks, medications)	Current	4.8% (4-8 y)
Ronmark et al,[36] 2007	Complete (AHR definition #1)	Not included	No symptoms, attacks, or medication	No	Not included	FEV_1 >80% predicted	Negative methacholine challenge (PC_{20} ≥4 mg/mL)	1 y (symptoms, attacks, medications)	Current	4% (4-8 y)
Ronmark et al,[36] 2007	Complete (AHR definition #2)	Not included	No symptoms, attacks, or medication	No	Not included	FEV_1 >80% predicted	Negative methacholine challenge (PC_{20} ≥8 mg/mL)	1 y (symptoms, attacks, medications)	Current	3% (4-8 y)
Holm et al,[7] 2007	Clinical	Not included	No symptoms or medication	No	Not included	Not included	Not included	2 y (symptoms); current for medications	NA	19% (5-12 y)

AHR, Airway hyperresponsiveness; *AMP*, adenosine 5'monophosphate; *BD*, bronchodilator; *FVC*, forced vital capacity; *NA*, not applicable; *ND*, not determined; PC_{20}, provocative concentration causing a 20% decrease in FEV_1; *ppb*, parts per billion.
*The wording used to describe the type of remission within the reference was captured in this column. If only "remission" was given, this was considered clinical remission. If there was more than 1 definition given, the more stringent definition was considered complete remission unless described otherwise.

Phase 3: Proposed generalized framework for asthma remission as a treatment target

On the basis of expert feedback in phase 2, survey administrators assembled a generalized framework for definitions of clinical and complete remission in asthma, on and off treatment (Fig 1). Complete remission requires that the criteria for clinical remission be met, along with additional criteria related to markers of inflammation and bronchial hyperresponsiveness. This framework was designed to be general in several areas to facilitate achievement of consensus. A final Delphi survey was conducted

TABLE IV. Survey responses regarding specific criteria for a definition of remission in asthma*,†

Question/statement	Agreement for question/statement (% of respondents, N = 7)
Statements achieving consensus	
Remission in asthma should add value beyond the current definitions of asthma control based on ACT or ACQ.	Yes (100)
As has been done for spontaneous asthma remission, remission in asthma that allows for patients to be receiving treatment should be qualified as "clinical" for cessation of significant symptoms and "complete" for cessation of significant symptoms and inflammation (as evidenced by objective markers of inflammation).	Yes (100)
One criterion for clinical remission in asthma should be the absence of systemic corticosteroid–requiring attacks for a specified period of time (exact duration to be defined).	Yes (100)
One criterion for clinical remission in asthma should be the absence of significant asthma symptoms for a specified period of time (exact duration to be defined).	Yes (86)‡
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.	Yes (86)§
In research settings, absence of AHR could be required for complete remission. However, in routine clinical practice, it is not feasible to include AHR as a criterion for complete remission.	Yes (86)‖
Because complete remission requires the absence of inflammation by objective assessments (while clinical remission does not), the duration of time for which a patient meets certain criteria is less important for complete remission than for clinical remission.	Yes (86)¶

AHR, Airway hyperresponsiveness.
*Consensus was defined as ≤1 respondent dissenting from majority agreement.
†Full survey responses, including free-text questions, are included in Table E3.
‡Dissenting opinion: "See discussion on 'on-treatment remission' Absence of 'significant' symptoms? What happened to 'no symptoms'?"
§Dissenting opinion: "Confusing question."
‖Dissenting opinion: "This is intrinsic to asthma. I doubt that will change."
¶Dissenting opinion: "Objective assessments are also variable due to the variable nature of the disease."

to assess this framework and several clarifying statements regarding assessment of asthma symptoms, lung function, and biomarkers. As part of the phase 3 survey, clinical experts were provided with the phase 2 survey results.

All 8 experts provided responses in the phase 3 Delphi survey, and the level of agreement for each statement is summarized in Table E4 in this article's Online Repository at www.jacionline.org. All respondents agreed with the proposed generalized framework for asthma remission presented in Fig 1. When provided with additional questions, all experts agreed that "The Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT) are examples of appropriate, validated instruments to document the sustained absence of significant asthma symptoms," and that "An acceptable criterion for sustained absence of significant asthma symptoms is ACQ score less than 0.75 or ACT score greater than or equal to 20 (or equivalent measure in any future validated instruments)." Clinical experts rated the importance of asthma symptom components in the context of asthma remission, as summarized from major instruments for evaluating asthma control (Fig 2). Most respondents (≥50%) ranked nighttime symptoms/awakenings, patient self-assessment of asthma control, symptoms at waking, and wheezing as essential in a definition of remission.

THE PATH FORWARD

Using a modified, 3-phase Delphi approach, we have constructed a framework for asthma remission as a treatment target that is aligned with established definitions of remission in other chronic inflammatory diseases and the existing medical literature describing spontaneous asthma remission. On the basis of these results, we propose that definitions consistent with the framework in Fig 1 be tested and refined via direct patient research and prospective and retrospective analyses of clinical study data. An asthma remission treatment target must be measurable in routine clinical practice, meaningful for patients, and ideally will be associated with reduced disease progression. Our proposed remission framework encompasses the outcomes of clinical and complete remission, on and off treatment. Complete remission is the optimal outcome but may not be achievable or measurable in many settings, in which case clinical remission can be a pragmatic, valuable goal. Similarly, the ultimate goal of remission off all asthma treatment may not be achievable for many patients, in which case remission on treatment (not including systemic corticosteroid therapy) can have considerable value.

The development of novel targeted therapies for asthma provides an opportunity to reframe the treatment goal of asthma therapy from disease control to disease remission. The concept of "control" currently used in asthma is no longer used in other chronic inflammatory diseases. "Asthma control" certainly has clinical value, but asthma symptom control is oriented only to the patient's current state and is not as stringent a treatment goal as disease remission. Studies of spontaneous remission in individuals with asthma demonstrate that clinical and complete remission are achievable in subsets of patients. Developing asthma remission as a treatment goal will provide a more ambitious target for novel therapies and treatment regimens and may enable a paradigm shift in the management of the disease. There is much to be learned about the potential of novel therapies to induce asthma remission or even prevent asthma development in high-risk individuals. Clinical trials have shown that mAb therapies can prevent asthma exacerbations, reduce dependence on maintenance systemic corticosteroid therapy, and improve patient symptoms and quality of life,[16] but we know little about their potential to alter the natural course of asthma through preventing progression and reversing long-standing disease. RA has the most established remission definition and volume of published data regarding disease remission as a treatment goal. The "treat to target" strategy has transformed RA treatment, providing improved long-term clinical outcomes and enhanced

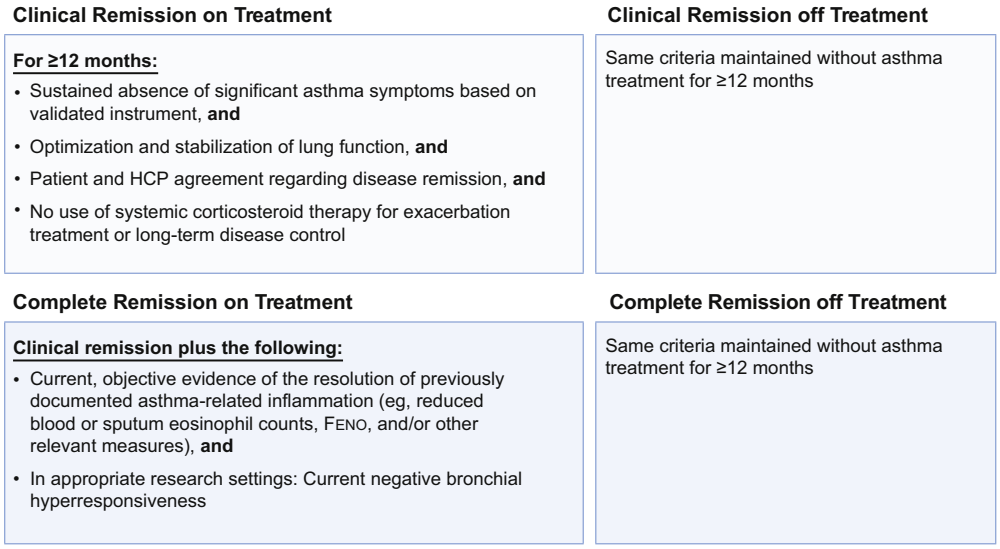

FIG 1. Generalized framework for remission in asthma. Criteria for clinical and complete remission, on and off treatment, were identified by consensus among clinical experts. *FENO,* Fractional exhaled nitric oxide. *Blood eosinophil counts and FENO are less relevant for T2-low asthma.

patient quality of life.[3,4] Remission is now the main therapeutic goal, requiring aggressive treatment of early disease.[17] The past 20 years have witnessed considerable improvements in treatment with combination disease-modifying antirheumatic drugs and anti-TNF therapies, and treatment-associated remission has been associated with improved long-term outcomes.[18]

The language agreed upon for our asthma remission framework was intended to be general and flexible for individual patient profiles and to be refined through future research with patients and in clinical studies. The language of "stabilization and optimization of lung function" arose from uncertainty regarding the degree of pulmonary function improvement that can be expected in patients with long-standing disease as well as concerns regarding individual patient variability. Similarly, although there was agreement about resolution of asthma inflammation as a core requirement for complete remission, we could not achieve agreement on specific target values for inflammatory biomarkers. An important difference between asthma and the other diseases reviewed as reference models for remission is that asthma has, in the context of inhaled corticosteroid treatment, well-described T2-high/low or eosinophilic/noneosinophilic phenotypes. Proper use of biomarkers such as blood eosinophil counts or fractional exhaled nitric oxide in defining complete remission requires reliable identification of the patient's phenotype. In the future, the precise role of biomarkers may become clearer with improved assays and increased knowledge of patient phenotypes and endotypes. As an example, promising research is underway in RA to identify baseline biomarkers that can predict sustained drug-free remission versus arthritis flare after disease-modifying antirheumatic drug cessation[19]; related research is ongoing in UC,[20] CD,[21] and SLE.[22]

Further research should be conducted to evaluate our existing tools for capturing patient-reported symptoms in the context of remission. The ACQ and ACT are in current clinical use and appear appropriate for near-term efforts to define remission, because they are validated and capture more than simple symptoms. All experts agreed that sustained absence of significant asthma symptoms was consistent with an ACQ score of less than 0.75 or an ACT score of greater than or equal to 20, because these scores are generally accepted standards of minimal symptoms and it was considered impractical to require the complete absence of any symptoms (eg, ACQ score = 0 or ACT score = 25). However, direct patient research is needed to understand the precise scores consistent with remission/non-remission and whether these instruments capture the full range of symptoms and disease manifestations that are relevant for remission from patients' perspectives. Different domains of asthma symptoms, as measured by the existing instruments, may be more important than others in the context of remission, as suggested by our Delphi survey results with clinical experts. Our remission framework highlights the need for patient and HCP agreement regarding disease remission, but additional work is required to determine how that agreement is best evaluated. Other disease states use an overall rating from the HCP and the patient with explicit questions.[13,23-25] Independent assessments by patients and HCPs would prompt discussion and avoid bias/influence between the 2 groups.

In addition to the limitations noted earlier, there are several additional aspects to consider with the proposed framework. To accomplish them in an efficient manner, the searches for definitions of remission in other inflammatory conditions and spontaneous remission in asthma were not comprehensive; instead, structured focused searches were used to identify major themes from other remission definitions. The current work was based on feedback from 8 clinical experts and cannot be viewed as a broad expert consensus. Instead, it is designed to be a first step toward developing asthma remission as a treatment goal, which will ultimately require further discussion and development with input from additional experts, professional societies, regulatory authorities, and patients. For the current effort, involvement of a small group of academic experts in asthma was considered essential given the multistage, iterative Delphi process that required in-depth review of multiple precedent studies and definitions of remission in our reference disease states and asthma. A similar approach was used to develop initial remission frameworks in PMR and UC.[14,15] With regard to the specifics of

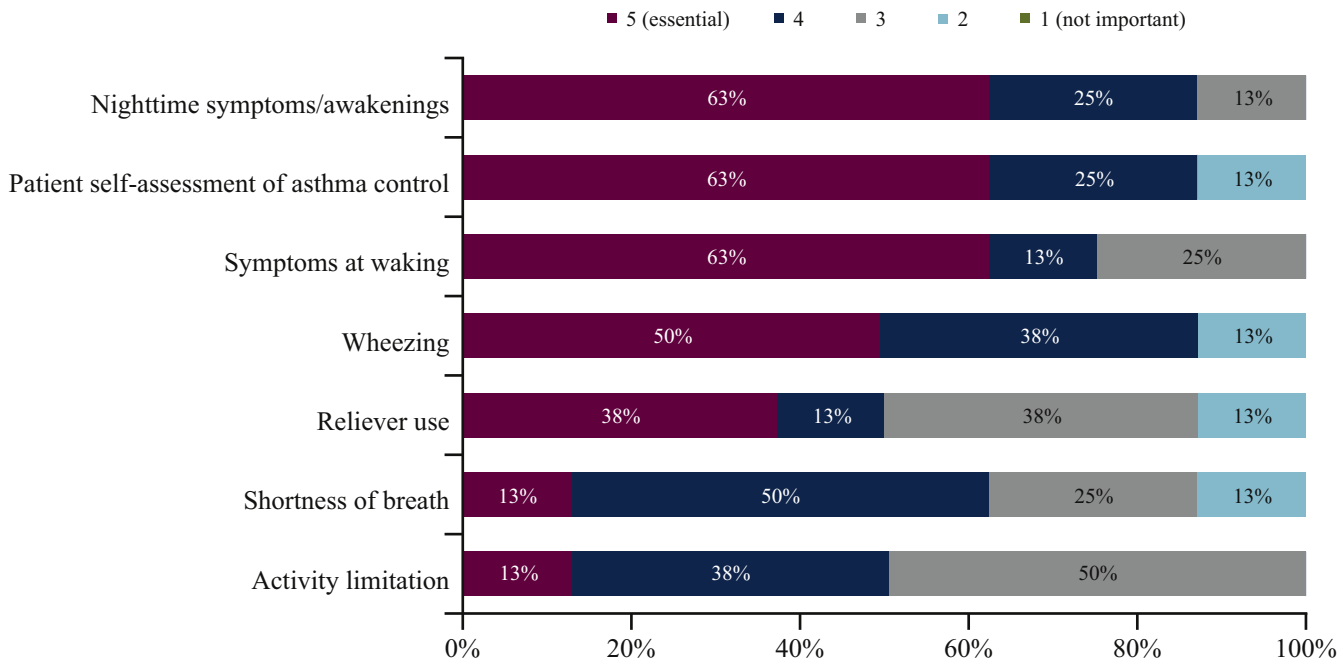

FIG 2. Importance of asthma symptoms in the context of asthma remission. Clinical experts rated the importance of suggested elements of asthma control from 1 (not important) to 5 (essential).

the proposed framework, use of the term "complete" remission with any specific definition could be problematic, because future assessments of inflammation or airway remodeling may allow for better assessment of undescribed aspects of the disease. In addition, our proposed time frame of 12 months does not eliminate the need for continued regular follow-up to reassess inflammation and clinical symptoms, and patients deemed in remission on treatment should be reminded of the necessity of continuing to treat and monitor their disease. The explicit designation of "on treatment" in our framework helps to underscore the necessity of continuing treatment. As agreed in our survey results, "remission in asthma does not eliminate the risk of severe and even fatal asthma events." The concept of remission remains distinct from a cure. Finally, our process was centered on adult asthma and did not include pediatric asthma. We recognize that children and adolescents likely require different considerations[26] because they are still undergoing lung development, and certain alterations of lung growth and irreversible changes in the airways may affect adult pulmonary function uniquely. Additional work is needed to define remission as a treatment goal in pediatric asthma.

CONCLUSIONS

By targeting asthma remission as a treatment goal, we hope to advance asthma treatment and improve outcomes for patients, similar to what has been accomplished in RA and other chronic inflammatory diseases. To bring significant value to patients and providers, our proposed asthma remission framework must be tested and refined through patient research and future studies, particularly studies evaluating longer-term clinical outcomes. This iterative process will require significant work across the asthma research community. Remission is an ambitious treatment goal, but it is one worth striving for.

Medical writing support was provided by Shane Walton, PhD, of MedErgy (Yardley, Pa), which was in accordance with Good Publication Practice (GPP3) guidelines and funded by AstraZeneca (Wilmington, Del).

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