Con: clinical remission in asthma – not yet there

Lauren Eggert [1], Sarah Rhoads[2], Michael E. Wechsler[3] and Praveen Akuthota[4]

[1]Division of Pulmonary, Allergy and Critical Care Medicine, Stanford University, Stanford, CA, USA. [2]Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado, Denver, CO, USA. [3]Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO, USA. [4]Division of Pulmonary, Critical Care, Sleep Medicine and Physiology, University of California San Diego, La Jolla, CA, USA.

Corresponding author: Praveen Akuthota (pakuthota@ucsd.edu)

Shareable abstract (@ERSpublications)
Achieving remission in asthma remains an aspirational goal, yet current definitions lack practical applicability in clinical settings. https://bit.ly/4iMDPdj

Cite this article as: Eggert L, Rhoads S, Wechsler ME, *et al*. Con: clinical remission in asthma – not yet there. *Eur Respir Rev* 2025; 34: 240182 [DOI: 10.1183/16000617.0182-2024].

Received: 20 Aug 2024
Accepted: 16 Dec 2024

Abstract

The ideal definition of asthma remission should be practical, measurable and meaningful for both patients and physicians, while also representing true disease modification. Unfortunately, current proposals to define asthma remission fall short of this standard, not for lack of careful consideration, but due to the challenges presented by asthma, including but not limited to variability in symptom perception, intrinsic variability in lung function, seasonality and the impact of comorbidities. This article discusses obstacles and challenges to developing a widely adopted, consensus definition of asthma remission. We searched the literature for keywords including “asthma”, “remission” and “super-responder” and identified interventional trials in asthma that highlight the challenges inherent in defining asthma remission.

Remission in the context of chronic disease refers to a sustained period during which the signs and symptoms of the disease are reduced or absent. For asthma in particular, the idea that remission is an achievable clinical outcome has gained traction over recent years with the emergence of biologic agents and their demonstrated real-world effectiveness. Great strides have been made in understanding asthma pathophysiology and mechanisms, allowing for the development of these targeted, *potentially* disease modifying agents. It is now understood that persistent inflammation underlies much of the disease manifestations in asthma, leading to bronchoconstriction, restricted airflow, symptomatic episodes and, in some cases, eventual fixed obstruction. Unchecked inflammation can lead to recurrent exacerbations, airway remodelling and, eventually, fixed airflow obstruction. Progressive organ damage due to uncontrolled inflammatory activity in asthma mirrors the trajectory of other chronic diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), in which achieving remission has long been the therapeutic objective.

Based on these parallels, efforts have been made in recent years towards constructing an asthma-specific definition of remission. Traditionally, asthma guidelines have emphasised attaining disease control, a combination of minimised symptoms and mitigated exacerbation risk. Remission in asthma takes this a step (or steps) forward, towards a total elimination of symptoms and exacerbations and normalisation or stabilisation of lung function. While complete remission off therapy is the ideal, it is unrealistic with current therapeutic options for most patients, so clinical remission on treatment has been identified as a more realistic goal for current asthma management purposes. However, is it truly a useful benchmark in the clinical and/or research setting? The ideal definition of remission should be practical, measurable and meaningful for both patients and physicians, while also representing true disease modification. Unfortunately, current proposals to define asthma remission fall short of this standard, not for lack of careful consideration, but due to the challenges presented by asthma, including but not limited to variability in symptom perception, intrinsic variability in lung function, seasonality and the impact of comorbidities.

Two widely disseminated definitions for clinical remission in asthma have been published by Menzies-Gow *et al.* [1] and Blaiss *et al*. [2]. Menzies-Gow *et al.* [1] convened a 2020 expert consensus panel that

used a modified Delphi approach to define clinical remission as 12 or more months with 1) the absence of significant symptoms by validated instrument, 2) lung function optimisation/stabilisation, 3) patient/provider agreement regarding remission and 4) no use of systemic corticosteroids [1]. The publication from Blaiss *et al*. [2] similarly used an expert panel, commissioned by three major US allergy and pulmonary societies comprising adult and paediatric pulmonologists and allergists, to develop a consensus definition for remission in asthma, again using a modified Delphi approach. This consensus statement defined remission on treatment and proposed that a patient on biologic therapy in remission must experience no exacerbations, no missed work or school due to asthma symptoms, stable or optimised pulmonary function on at least two measurements, only low-or medium-dose inhaled corticosteroid (ICS) therapy, Asthma Control Test (ACT) score >20, AirQ score <2 or Asthma Control Questionnaire (ACQ) score <0.75 measured on at least two occasions, and rescue inhaler use no more than once per month, all over the course of 1 year [2].

Although remission may in the future be a goal for asthma management, the available evidence suggests it is premature for such a paradigm shift. Clinical remission on treatment, the most pragmatic form of remission, has already been extensively shown to be possible for only a minority of patients with these current definitions. Multiple *post hoc* analyses of clinical trials have been conducted to determine the prevalence of remission in patients receiving biologics using varying definitions of remission of varying stringency. A recent review by Lugogo *et al.* [3] effectively summarised the outcomes from some of these trials, demonstrating that remission rates ranged from 14 to 43%, with most cases falling between 20 and 30%. Interestingly, in many of these studies, a significant proportion of patients receiving placebo were also able to achieve remission according to study criteria [4]. This placebo effect phenomenon is pervasive in asthma trials [5]. Objective and patient-reported outcomes may be improved compared to baseline either because participation in a clinical trial leads to better adherence to prescribed medications or as a result of the placebo effect itself. Furthermore, the potential for spontaneous remission, a rarity in most chronic diseases, occurs in 22–27% of paediatric patients with asthma [6, 7] and 2–17% of adult patients [8]. Thus, a major issue with targeting clinical remission with biologics in asthma is that it is currently only possible for a small percentage of patients and may be even smaller when considering the significant placebo effect seen in these trials, as well as the potential that some proportion of cases may constitute spontaneous remission.

Determining the optimal target for duration of remission is also an issue. The two most used definitions for clinical remission both use a lack of exacerbations, stable symptoms and lung function over 12 months as the time criteria, in order to best take into account the variability and seasonality of the disease. However, there are no data to support this time frame as ideal for considering a patient to have achieved remission. Even after prolonged periods of meeting remission criteria, a significant number of adult patients relapse, often without warning and often after years of remission [9]. Similarly, Sears *et al.* [6] showed that in children with asthma, even after achieving remission, a proportion relapse by age 26. Whether this is due to some underlying low-level disease activity, genetic predisposition and/or environmental factors, or a combination of all three, is unknown.

What does this mean practically for physicians treating to the goal of achieving clinical remission in asthma? In our experience, one of the most common questions physicians are asked at the time of initial biologic prescription is how long patients will need to be on the medication for. The answer is, *we really don't know*. There is a lack of data on how long patients need to be on these drugs, but multiple studies have shown an increase in exacerbations after discontinuing biologics. In the COMET study, for instance, patients who stopped mepolizumab had more exacerbations than those who continued (61% *versus* 47%) [10]. In RA, another chronic inflammatory illness on which much of the clinical remission work in asthma is based upon, a study by Lillegraven *et al.* [11] demonstrated that patients with RA in remission ⩾12 months on stable tumour necrosis factor inhibitor therapy who were then tapered off of therapy had a significantly increased risk of flares over the subsequent 12 months compared to those who remained on stable therapy (63% *versus* 5%). These results, across multiple disease states, illustrate the challenges in weaning or discontinuing biologic therapy, regardless of the degree of control attained.

Upham *et al*. [12] have previously defined biologic "super-responders", those patients who meet at least two out of the three major criteria over 12 months (elimination of exacerbations, large improvement in asthma control, cessation of maintenance oral steroids). About one-third of patients receiving biologics for severe asthma are considered super-responders [13]. Algorithms have been proposed wherein these super-responders, who have many overlapping features with patients in clinical remission, may be able to successfully discontinue biologics [14], but further research is needed to see if this is truly feasible and it will be necessary to follow these patients longitudinally for an adequate period of time to assess for relapse.

Given that there is no good plan for tapering or discontinuing these medications and the associated significant costs to patients and the healthcare system with their ongoing use, advocating for their initiation with the goal of achieving remission, which still will only be achieved by a small proportion of patients, seems premature.

It is also likely that patients and providers, in accordance with Global Initiative for Asthma (GINA) guidelines, will step down inhaled therapies when patients are well controlled [15]. In the recently published SHAMAL trial, 61% of patients treated with benralizumab were able to taper their ICS to as needed anti-inflammatory reliever (AIR) therapy and maintain asthma control with stable symptom scores and lack of exacerbations [16]. However, in the *post hoc* analysis of groups stratified by ICS-formoterol dose at week 32, patients who decreased their ICS to AIR only therapy had a significant reduction in forced expiratory volume in 1 s and significant increase in fraction of exhaled nitric oxide (F_{ENO}). Elevated F_{ENO} levels have previously been shown to predict lung function decline in dupilumab-treated patients [17] and given that stabilisation and or optimisation of lung function is a central tenet of most definitions of clinical remission in asthma, the significance of this finding remains to be seen.

Although the SHAMAL trial showed no significant change in symptoms when stepping down to AIR therapy, the two SYGMA trials on which the use of budesonide–formoterol AIR therapy are based clearly demonstrated that AIR therapy was less effective at controlling symptoms than daily maintenance ICS therapy [18]. If clinical remission is the target, the data from SHAMAL, demonstrating increased F_{ENO} and reduced lung function with tapering ICS, and the data from SYGMA, which showed increased symptoms with AIR therapy, together suggest achieving clinical remission dictates that patients treated with biologics should stay on at least a low daily dose of ICS to maintain stable lung function and adequately controlled symptoms. The problem with this contention is that the idea for AIR therapy over daily maintenance therapy originated from the long-running observation that in general patient adherence to daily maintenance therapy is poor and patients tend to discontinue their inhalers when they are doing well. Thus, it is likely that when patients are feeling improved after starting biologics, the tendency will be for patients to step down their inhaled therapy. These downstream consequences of focusing treatment on achieving asthma remission are concerning because they could result in physicians encouraging patients to use additional inhaled steroids beyond what would otherwise be recommended, without data to suggest a clear benefit and when there are known dose-dependent steroid-related morbidities associated with the use of ICS. Data from numerous studies demonstrate an increased risk of adrenal suppression, cataracts, fractures and diabetes from the long-term use of inhaled steroids [19–21]. There also increased costs to the healthcare system associated with keeping patients on maintenance inhaled therapies.

The implication that earlier and more aggressive treatment of asthma is needed if clinical remission is the ultimate goal raises additional issues. There are accumulating data that patients with less severe asthma, less cumulative systemic corticosteroid exposure and better lung function are more likely to achieve asthma remission. In a *post hoc* analysis of the REDES study, a real-world retrospective observational study of adults with severe eosinophilic asthma across Spain who were newly prescribed mepolizumab, clinical remission was more likely in patients with higher blood eosinophil counts, better lung function and lower maintenance oral corticosteroid (OCS) requirements [22]. In a retrospective study of patients in the UK Severe Asthma Registry published by McDowell *et al.* [23], remission was associated with shorter duration of symptoms, while nonremission was associated with a higher number of exacerbations, emergency department visits and hospital admissions in the previous year, higher baseline symptom burden, and more impaired baseline quality of life. In a recently published longitudinal cohort study using data from the International Severe Asthma Registry, 20% of patients achieved four-domain remission within 1 year of biologic treatment initiation and those patients who achieved remission had less severe impairment and shorter asthma duration at initiation [24]. As a result of these findings, the authors concluded that if the goal for asthma treatment is remission, biologic treatment should not be delayed. In theory, this makes sense. However, as previously discussed, the concern with starting these drugs early is the lack of evidence that they truly modify the disease course and the indefinite length of time patients are required to be on these drugs, with the associated expense. In addition, it is likely to magnify inequities driven by differential access to biologic drugs and their cost. While GINA guidelines recommend initiating biologics for patients with uncontrolled asthma despite high-dose ICS–long-acting β-agonist therapy, in many countries patients are required to be on maintenance OCS or suffer from at least 2–3 exacerbations prior to qualifying for these drugs and still in other countries patients may need to pay high out of pocket costs to access these drugs. Within the US as well, variations in insurance coverage affect the ability of individuals to consistently and affordably access these medications. Remission as a goal is premature without additional data to show that these drugs improve long-term outcomes, as well as maximise benefits and reduce risk when started at an earlier stage.

Similar questions arise when considering treatment of children with asthma. Sears *et al.* [6] performed a longitudinal study of patients in a birth cohort in New Zealand. It was found that children who developed asthma before 6 years of age had impaired lung function at each assessment during childhood, adolescence and adulthood, which also predicted persistence and relapse of asthma, suggesting that these outcomes are determined at an early age. Asthma exacerbations lead to a decline in lung function [25], which increases the risk for future exacerbations and loss of lung function, as well as reduces the likelihood of achieving remission. If remission is the goal, this favours earlier and more aggressive treatment of disease in paediatric patients. However, before making this leap, more long-term data are needed to determine if starting drugs earlier in life in paediatric patients modifies the natural history of the disease or leads to improved outcomes. Alternatively, should we instead be focusing instead on preventing asthma before it even develops? The Preventing Asthma in high-Risk Kids (PARK) trial, a double-blind, placebo-controlled study, is currently underway to evaluate the effectiveness of omalizumab in preventing the development of asthma and reducing its severity in 2–3-year-old children at high risk for asthma (NCT02570984). The results of this trial are eagerly awaited.

In other inflammatory conditions such as RA, remission is an important outcome because if there is any ongoing low-level disease activity, progressive joint destruction may occur leading to progressive functional decline. In asthma, we suspect that there is ongoing inflammation when disease is poorly controlled with ongoing symptoms and/or bronchial hyperreactivity and/or low lung function, all of which may lead to progressive decline in lung function and thus more persistent symptoms. This is difficult to study because of the heterogeneity of the disease and lack of specific biomarkers. Complete remission as defined by Menzies-Gow *et al.* [1] is a combination of clinical remission plus objective resolution of asthma-related inflammation. Currently available biomarkers for asthma include blood and sputum eosinophil counts, IgE levels and F_{ENO}. However, asthma is a very heterogeneous condition with multiple endotypes, phenotypes and biomarker profiles that are only just beginning to be understood. Up to 85% of patients with severe asthma have evidence of type 2 inflammation [26], but how can we measure remission in patients with nontype 2 asthma and no discernibly elevated commercially available biomarkers at baseline?

Since it is not fully known what level of inflammation, if any, is associated with progression of disease and loss of lung function and/or progressive symptoms over time, or how currently available biomarkers in blood, sputum and exhaled breath correlate with disease activity at the tissue level, it is hard to pinpoint the exact biomarkers to use to define remission and the degree of suppression in inflammatory markers that should be required for remission. Complicating matters, available biomarkers may be altered by biologic therapies. For instance, dupilumab often causes at least a transient increase in peripheral blood eosinophils and omalizumab binds free IgE so that it cannot be accurately measured on conventional assays. Patients treated with benralizumab may also demonstrate a transient increase in F_{ENO} [27]. New and improved biomarkers, including “omics” approaches, will allow us to endotype patients with better precision and have the potential to serve as more reliable surrogates for ongoing disease activity at the tissue level. With the current state of asthma biomarkers, incorporating biomarker-based assessment in any definition of asthma remission is a major challenge.

Anxiety, depression, obesity, vocal cord dysfunction, gastro-oesophageal reflux disease (GORD) and obstructive sleep apnoea are all common comorbidities associated with uncontrolled asthma, which may affect symptom scores and complicate the quest for asthma remission. By focusing on clinical remission in asthma treatment, there is concern that other important factors impacting asthma symptoms and disease control may be missed. In the UK Refractory Asthma Stratification Programme, the patients with higher symptom burden were predominantly female with higher body mass index and low T2 biomarkers, and were more likely to have GORD, depression and osteoporosis [28]. Targeting treatable traits and comorbidities is important and needs to be addressed to avoid overtreating or misassigning symptoms if trying to attain remission.

Achieving remission in asthma remains an aspirational goal, yet current definitions lack practical applicability in clinical settings. Further research is crucial to refine the concept of remission in asthma, aiming for a definition that is feasible for a significant proportion of patients to achieve, without an unacceptable increase in costs or risk of adverse effects. One key area requiring further investigation is the long-term impact of early intervention on the natural history of the disease and the effect on long-term outcomes. Other questions that remain to be answered are the criteria for withdrawing medications such as ICS and biologic therapies post-remission, and whether we should focus on withdrawal of ICS or biologic therapies as the priority; the answer to which will depend on the chosen definition of clinical remission. While the study of asthma biomarkers has improved spectacularly, better biomarkers are needed for more precise endotyping and phenotyping to better gauge tissue-level inflammation and disease activity to target

for remission. Addressing the impact of comorbidities on asthma symptoms remains an obstacle to attempts to achieve a consensus definition of remission. While proposals for defining asthma remission have sparked valuable discourse and started us down the path to defining and achieving remission, integrating remission into routine clinical asthma care akin to other inflammatory diseases remains a long way off.

Points for clinical practice

- Asthma remission at present is poorly characterised and, based on current definitions, unrealistic for the majority of patients on biologic therapy.
- There is no consensus recommendation for duration and tapering of biologic therapy, and many patients who are considered to be in remission will demonstrate relapse off of biologic treatments.
- Optimal asthma management requires assessment and control of comorbid conditions not addressed with biologic medications, such as anxiety/depression, vocal cord dysfunction and GORD.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: L. Eggert declares consulting fees from AstraZeneca, Sanofi and GSK, and honoraria from Sanofi. S. Rhoads has nothing to disclose. M.E. Wechsler declares consulting fees from Amgen, AstraZeneca, Avalo Therapeutics, Boehringer Ingelheim, Celldex, Cerecor, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Om Pharma, Rapt Therapeutics, Regeneron, Roche/Genentech, Sanofi/Genzyme and Upstream Bio, and honoraria from Sanofi/Genzyme, Avalo Therapeutics, Cytoreason, Incyte, Regeneron and Tetherex Pharmaceuticals. P. Akuthota declares consulting fees from AstraZeneca, GlaxoSmithKline, Connect Biopharma and Sanofi/Genzyme, and honoraria from AstraZeneca and Sanofi/Genzyme.

References

1 Menzies-Gow A, Bafadhel M, Busse WW, *et al.* An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol* 2020; 145: 757–765.
2 Blaiss M, Oppenheimer J, Corbett M, *et al.* Consensus of an American College of Allergy, Asthma, and Immunology, American Academy of Allergy, Asthma, and Immunology, and American Thoracic Society workgroup on definition of clinical remission in asthma on treatment. *Ann Allergy Asthma Immunol* 2023; 131: 782–785.
3 Lugogo NL, Mohan A, Akuthota P, *et al.* Are we ready for asthma remission as a clinical outcome? *Chest* 2023; 164: 831–834.
4 Menzies-Gow A, Hoyte FL, Price DB, *et al.* Clinical remission in severe asthma: a pooled post hoc analysis of the patient journey with benralizumab. *Adv Ther* 2022; 39: 2065–2084.
5 Wechsler ME, Kelley JM, Boyd IOE, *et al.* Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med* 2011; 365: 119–126.
6 Sears MR, Greene JM, Willan AR, *et al.* A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003; 349: 1414–1422.
7 Vonk JM, Postma DS, Boezen HM, *et al.* Childhood factors associated with asthma remission after 30 year follow up. *Thorax* 2004; 59: 925–929.
8 Thomas D, McDonald VM, Pavord ID, *et al.* Asthma remission: what is it and how can it be achieved? *Eur Respir J* 2022; 60: 2102583.
9 Almqvist L, Rönmark E, Stridsman C, *et al.* Remission of adult-onset asthma is rare: a 15-year follow-up study. *ERJ Open Res* 2020; 6: 00620-2020.
10 Moore WC, Kornmann O, Humbert M, *et al.* Stopping *versus* continuing long-term mepolizumab treatment in severe eosinophilic asthma (COMET study). *Eur Respir J* 2022; 59: 2100396.
11 Lillegraven S, Paulshus Sundlisæter N, Aga AB, *et al.* Effect of tapered *versus* stable treatment with tumour necrosis factor inhibitors on disease flares in patients with rheumatoid arthritis in remission: a randomised, open label, non-inferiority trial. *Ann Rheum Dis* 2023; 82: 1394–1403.
12 Upham JW, Le Lievre C, Jackson DJ, *et al.* Defining a severe asthma super-responder: findings from a Delphi process. *J Allergy Clin Immunol Pract* 2021; 9: 3997–4004.
13 Kavanagh JE, d'Ancona G, Elstad M, *et al.* Real-world effectiveness and the characteristics of a "super-responder" to mepolizumab in severe eosinophilic asthma. *Chest* 2020; 158: 491–500.
14 Hamada K, Oishi K, Murata Y, *et al.* Feasibility of discontinuing biologics in severe asthma: an algorithmic approach. *J Asthma Allergy* 2021; 14: 1463–1471.
15 Global Initiative for Asthma. 2024 GINA Main Report. Date last updated: 22 May 2024. Date last accessed: 13 August 2024. https://ginasthma.org/2024-report/

16 Jackson DJ, Heaney LG, Humbert M, *et al.* Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with Benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study. *Lancet* 2024; 403: 271–281.

17 Pavord ID, Brusselle G, Jackson D, *et al.* F_{ENO} as a potential prognostic and predictive marker of lung function decline in patients with uncontrolled, moderate-to-severe asthma: liberty asthma quest. *Am J Respir Crit Care Med* 2022; 205: A3418.

18 Bateman ED, Reddel HK, O'Byrne PM, *et al.* As-needed budesonide–formoterol *versus* maintenance budesonide in mild asthma. *N Engl J Med* 2018; 378: 1877–1887.

19 Israel E, Banerjee TR, Fitzmaurice GM, *et al.* Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med* 2001; 345: 941–947.

20 Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999; 159: 941–955.

21 Patel L, Wales JK, Kibirige MS, *et al.* Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. *Arch Dis Child* 2001; 85: 330–334.

22 Ribas CD, Pavord I, Conejero DB, *et al.* Impact of baseline characteristics on clinical remission achievement in severe asthma. *Eur Respir J* 2022; 60: Suppl. 66, 2436.

23 McDowell PJ, McDowell R, Busby J, *et al.* Clinical remission in severe asthma with biologic therapy: an analysis from the UK severe asthma registry. *Eur Respir J* 2023; 62: 2300819.

24 Perez-de-Llano L, Scelo G, Tran TN, *et al.* Exploring definitions and predictors of severe asthma clinical remission post-biologic in adults. *Am J Respir Crit Care Med* 2024; 210: 869–880.

25 Soremekun S, Heaney LG, Skinner D, *et al.* Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study. *Thorax* 2023; 78: 643–652.

26 Akenroye A, McCormack M, Keet C. Severe asthma in the US population and eligibility for mAb therapy. *J Allergy Clin Immunol* 2020; 145: 1295–1297.e6.

27 Pelletier G, Godbout K, Boulay MÈ, *et al.* Increase in F_{ENO} levels following IL5/IL5R-targeting therapies in severe asthma: a case series. *J Asthma Allergy* 2022; 15: 691–701.

28 Heaney LG, Djukanovic R, Woodcock A, *et al.* Research in progress: medical research council United Kingdom refractory asthma stratification programme (RASP-UK). *Thorax* 2016; 71: 187–189.