Pro: Clinical remission in asthma – implications for asthma management

Stefania Principe[1] and Nizar N. Jarjour[2]

[1]Amsterdam UMC, Location Vrije University Medical Center, Department of Respiratory Medicine, Amsterdam, The Netherlands. [2]Department of Medicine, University of Wisconsin, Madison, WI, USA.

Corresponding author: Nizar N. Jarjour (nnj@medicine.wisc.edu)

Shareable abstract (@ERSpublications)
With improvements in therapy achieving asthma remission (high asthma control, no exacerbations and stable or normal lung function) became a feasible goal. Here we review the evidence that remission should be a reasonable target in asthma management. https://bit.ly/42BlsCt

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Abstract

Asthma treatment has seen significant advancements over the recent years. However, despite improvements in disease control, some patients continue to experience persistent symptoms and exacerbations, necessitating a deeper understanding of disease mechanisms and optimisation of treatment strategies. The introduction of biologics has marked a new era in severe asthma management, targeting underlying molecular mechanisms and raising the possibility of achieving asthma remission. Key indicators of remission include high asthma control, absence of exacerbations and stabilised, or normalised, lung function. However, there is currently no common definition for remission, with various studies using different criteria. Real-world studies and *post hoc* analyses of clinical trials emphasise the potential of biologics in achieving clinical remission in a significant proportion of patients. Here, we provide a comprehensive review of studies in support of incorporating asthma remission as potential goal in asthma management. Despite the lack of a universally accepted definition and large prospective studies focused on remission, we believe that incorporating long-term outcomes and the currently accepted elements of remission in the approach to asthma care will shift the emphasis from reactive symptom control to proactive disease management, ultimately aiming for better asthma outcomes.

Introduction

Asthma is a heterogeneous complex disease that affects millions of people worldwide [1]. It is characterised by symptoms that vary over time such as cough, wheezing, chest tightness and dyspnoea. Over the past 15 years, there has been a significant advance in asthma treatment leading to lower morbidity and mortality rates, with many patients achieving effective asthma control. Nonetheless, some patients continue to have ongoing asthma symptoms and exacerbations, underlying the need for deeper consideration of the disease mechanisms and an optimisation of its treatment [2]. The management of asthma is a continuous process of monitoring asthma control and risk factors, adjusting medications appropriately with a step-by-step approach, starting from low to medium and high dose of inhaled corticosteroids (ICS) and/or long-acting β-agonists (LABAs) [1]. Despite the optimisation of treatment strategies, a proportion of patients remain uncontrolled and need add-on therapies to keep the disease stable such as long-acting muscarinic antagonists (LAMAs), oral corticosteroids (OCS) and, in the more severe forms, monoclonal antibodies such as anti-IgE, anti-interleukin (IL)5/anti-IL5R, anti-IL-4Rα and anti-thymic stromal lymphopoietin (TLSP) [2, 3].

The advent of the biologics as targeted therapies has ushered in the new era of precision medicine in severe asthma management, by providing treatments that are specifically designed to target the underlying molecular and cellular mechanisms of the disease.

The success of these treatments has allowed for setting a higher bar in determining our goals in severe asthma. We are now considering asthma remission as a feasible outcome in patients on biologics, because

achieving remission represents a higher therapeutic goal beyond mere symptom control, aiming for sustained disease-free periods and minimal use of medications. Biologics offer the potential to not just manage but significantly alter the course of asthma, reducing exacerbations, improving lung function and enhancing the overall quality of life. This shift reflects a move towards a more ambitious and holistic approach to asthma care, focusing on long-term outcomes. Figure 1 illustrates the concept of achieving remission as the primary treatment goal in managing severe asthma.

What is asthma remission?

Asthma remission in severe asthma, particularly with the use of biologic therapies, is a complex and evolving concept. Between 2 and 52% of adult asthma patients have been reported to achieve spontaneous remission [4]. The concept of asthma remission is having a lasting and consistent improvement in asthma-related outcomes that leads to prolonged patient benefits. Several statements have tried to define asthma remission [5]. Current remission definitions generally include high level of asthma control, the absence of asthma exacerbations and normalisation and/or stabilisation of lung function over a period of ⩾12 months [6]. There has also been an emphasis on the importance of healthcare professional and patient agreement in achieving remission, in addition to reduction of inflammation markers (*e.g.* exhaled nitric oxide fraction (F_{ENO}), sputum eosinophils, *etc.*). Nevertheless, a uniform consensus has not yet been reached. Distinctions between clinical and complete remission, as well as remission on and off treatment has been explored; however, several areas of uncertainties still exist. Real-life studies show promising outcomes, but the heterogeneous nature of patients and varying study methodologies pose challenges in drawing definitive conclusions.

The importance of identifying remission in asthma management

Given these insights, identifying remission can become a promising future main goal in asthma trials, to reconsider disease control and to define new treatment strategies. Understanding what remission is and identifying to whom it applies might improve personalised disease management by identifying new, specific remission markers. Furthermore, the question of whether asthma remission could evolve into a cure requires further comprehension, presenting a potential paradigm shift in our approach to the condition. However, challenges persist, given the current limited information on what constitutes remission and the differences between response to treatment and optimal disease control. Studies such as COMET and

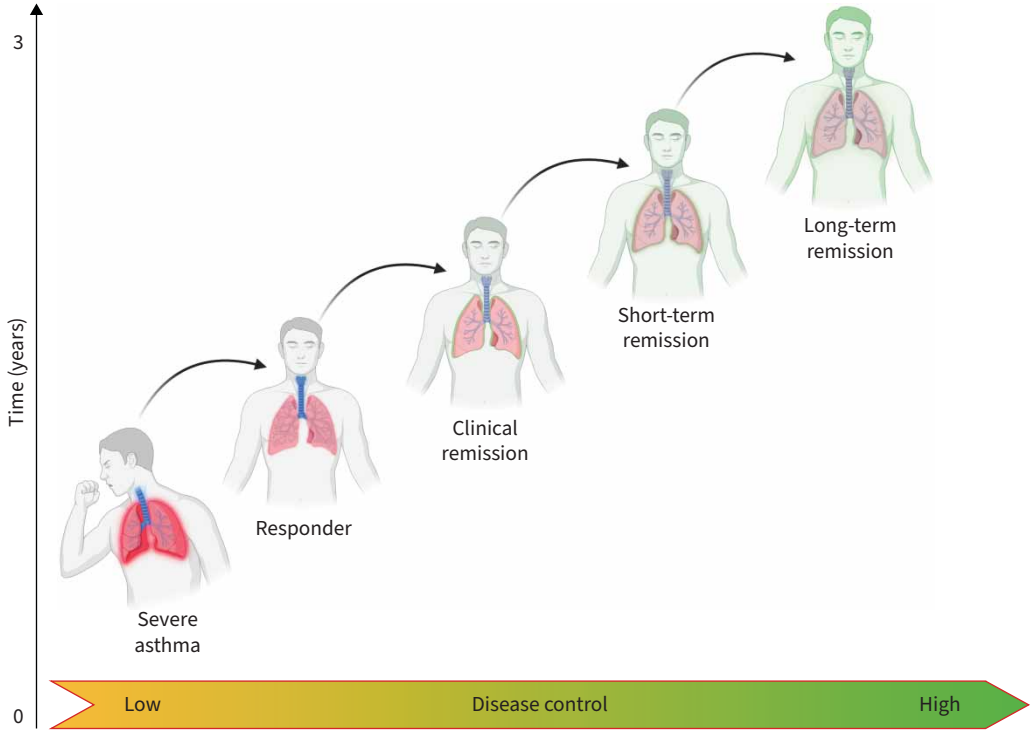

FIGURE 1 Remission on treatment as a treatment goal. The concept of achieving remission as the primary treatment goal in managing severe asthma. Created in BioRender.

COLUMBA provide new perspectives on whether biologics can be safely discontinued after achieving remission, emphasising the importance of sustaining remission in severe asthma through a practical approach [7, 8]. Defining remission could also clarify some aspects of the disease that are still unclear, especially regarding the permanence of airway remodelling and the irreversible loss of lung function.

In this review, we aim to provide a better understanding of asthma remission in patients with severe asthma as well as the positive implications of achieving remission as a future goal in asthma management.

Literature search

A targeted literature search was conducted across major medical databases, such as PubMed, Scopus and Google Scholar. The search focused on articles published within the last decade, using key terms such as "asthma remission", "biologic therapies" and "severe asthma". Inclusion criteria were studies that provided definitions of asthma remission, explored predictors of success and evaluated clinical outcomes with biologic treatments. The review included randomised controlled trial (RCTs), cohort studies and expert consensus statements to offer a well-rounded perspective. We have summarised the main criteria used to define remission and presented the differences between the consensus statements and clinical studies.

Understanding asthma remission

Understanding remission in severe asthma is a crucial step in asthma management for several reasons. It represents a shift in treatment goals, moving from a short-term symptom control to long-term symptom prevention [9]. Moreover, it can provide new insights in the context of selecting the most effective biologic therapy. It is important to define specific criteria for achieving remission as a main outcome in the context of biologic therapies for future treatments [10].

Discrepancies between definitions and criteria of asthma remission

Defining asthma remission as treatment goal is one of the biggest challenges. Overall, we should not consider achieving asthma remission as a cure. However, it is crucial to recognise that achieving remission is an important step in asthma management and it should be the desired goal.

Menzies-Gow *et al*. [5] provided a definition of asthma remission, even though the authors acknowledged that the framework should be tested in prospective studies (table 1). As a matter of fact, many studies have used different definitions of disease remission with several domains of interest. Therefore, understanding how to prioritise remission criteria remains to be clarified. Based on a three-phase consensus, Menzies-Gow *et al*. [5] performed a literature search of the definition of remission used in studies of six chronic, nonrespiratory, inflammatory diseases that report remission as treatment target (rheumatoid arthritis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, polymyalgia rheumatica and psoriasis).

TABLE 1 Summary of the current statements (English language available)

First author [ref.]	Outcomes	Main results	Limitations
Menzies-Gow [5]	ACT score ⩾20, ACQ score ⩽0.75, lung function optimisation/stabilisation, patient/provider agreement, no systemic corticosteroids	Provided a definition of asthma remission Identified potential components of remission as a target in asthma	Framework should be tested in prospective studies Small group of experts
Blaiss [11]	No exacerbations, no absenteeism from work/school, stable pulmonary function, continued low-to-medium dose ICS, symptom control (ACT score >20, AirQ score <2, ACQ score <0.75), minimal reliever use	Identified key criteria of asthma clinical remission on treatment	Lack of consensus on some criteria Limited data
Canonica [12]	Absence of symptoms, absence of exacerbations, stable lung function, no OCS, partial clinical remission (no need for OCS, two of three primary criteria)	Defined clinical and partial remission in severe asthma	No consensus on reduction of ICS Specific value for lung function improvement
Álvarez-Gutiérrez [14]	ACT score ⩾20, no rescue medication, normal lung function for ⩾12 months, F_{ENO} <40 ppb, sputum eosinophils <2%, no nasal symptoms (SNOT-22 score <30), normal nasal endoscopy for CRSwNP	Established consensus on clinical, complete remission and remission in asthma with CRSwNP	Potential bias due to respiratory specialists Geographical constraint as Spain-specific

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; CRSwNP: chronic rhinosinusitis with nasal polyps; F_{ENO}: fraction exhaled nitric oxide; ICS: inhaled corticosteroids; OCS: oral corticosteroids; SNOT: Sinonasal Outcome Test.

These definitions were explored to identify potential components of remission as a target in asthma. A Delphi survey to achieve consensus was performed within a small group of experts in the US and Europe. Consensus was obtained for all the questions and statements regarding specific criteria of the definition of remission in asthma and this resulted in a generalised framework for asthma remission; specifically, clinical and complete remission can be achieved if for ⩾12 months with the following criteria:

- Absence of significant symptoms using a validated instrument (Asthma Control Questionnaire (ACQ) score ⩽0.75 or Asthma Control Test (ACT) score ⩾20)
- Lung function optimisation/stabilisation
- Patient/provider agreement on remission status
- No use of systemic corticosteroids for exacerbations or long-term control

Complete remission can be achieved if all the clinical remission criteria are met, plus a documented resolution of asthma inflammation (*e.g.* normalisation of blood eosinophils and F_{ENO}) and no bronchial hyperresponsiveness (BHR)). The expert consensus also distinguishes remission on and off treatment. Even though those results represent an important first step towards asthma remission as a treatment target, the consensus is limited to a small number of clinical experts and cannot be viewed as a broad consensus, but rather as a first hint to encourage further discussions.

In line with this approach, consensus from an American College of Allergy, Asthma, and Immunology, American Academy of Allergy, Asthma, and Immunology (ACAAI) and American Thoracic Society [11] workgroup was established specifically to identify the key criteria of asthma clinical remission on treatment. With an expert panel composed of 11 members from major allergy and pulmonary societies, they performed a pragmatic review of existing literature and utilised a modified Delphi approach to reach consensus on remission criteria. Six main criteria were identified:

- No exacerbations for at least 12 months that require physician visits, emergency care, hospitalisation or systemic corticosteroids
- No absenteeism from work/school due to asthma
- Stable pulmonary function, measured at least twice over 1 year
- Continued use of controller therapies only at a low-to-medium dose of ICS
- Symptom control: ACT score >20, AirQ score <2, ACQ score <0.75 (at least two measurements in a year)
- Minimal reliever use (no more than once a month).

The proposed criteria set a high bar for defining clinical remission in asthma, even though a lack of consensus on some criteria has been presented due to limited data (no defined minimal acceptance reliever use, unclear cut-offs in symptoms control and no exact definitions of continued controller therapy use). Nonetheless, the lack of comprehensive data and the need for further research were acknowledged as contributing factors to these disagreements.

In the Delphi consensus from the Severe Asthma Network in Italy (SANI) [12], the authors defined clinical and partial remission in severe asthma, pre-selecting the main domain of interest based on a previous independent definition linked to the concept of disease-modifying asthma medications [13]. The process involved 80 experts, including pulmonologists and allergists, from the SANI network. Over two rounds of surveys, the panellists evaluated 32 statements using a five-point Likert-scale. A cut-off to reach consensus was based on agreement from a minimum of two-thirds of the experts. Clinical remission in severe asthma was defined by the following composite measures:

- Absence of asthma symptoms
- Absence of exacerbations
- Stable lung function
- No requirement for OCS.

To achieve complete clinical remission, all the criteria should be met, whereas partial clinical remission was defined by the absence of the need for OCS with two of the three primary criteria (no symptoms, no exacerbations and stable lung function).

Furthermore, the panel agreed that remission should be defined by at least 1 year without exacerbations, with persistent remission requiring a duration of 3 years, although this longer period did not achieve full consensus. No consensus was reached regarding the reduction of ICS in patients on biologics, nor were specific thresholds or values established for lung function improvement, highlighting that the criteria prioritise maintaining lung function over achieving an improvement. Similarly, consensus was not reached

on pre-defined cut-off values for markers of inflammatory remission, such as an eosinophil count of less than 300 cells·μL^{-1} or an F_{ENO} level below 25 ppb.

Recently, a statement from the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) [14] aimed to establish a consensus on the definition of clinical, complete remission and remission in asthma with chronic rhinosinusitis with nasal polyps (CRSwNP). Using the Delphi methodology, the study recruited over 120 asthma specialists to develop criteria for remission, defining clinical remission as controlled asthma (ACT score ⩾20) without the need for rescue medication or exacerbations, with normal lung function maintained for at least 12 months. Complete remission required additional criteria, including no evidence of bronchial inflammation (F_{ENO} <40 ppb, sputum eosinophils <2%) or remodelling, maintained for at least 3 years. While the agreement of inclusion of remodelling as additional criteria reflects its importance in asthma pathophysiology, the SEPAR definition did not provide specific guidance on how to evaluate the absence of remodelling. However, the statement acknowledged the future potential of incorporating imaging tests to assess remodelling more effectively. Furthermore, complete remission in patients with asthma with CRSwNP is reached if, in addition to the criteria of complete remission for 3 years, no nasal symptoms (Sinonasal Outcome Test-22 score <30) are reported and normal nasal endoscopy is observed. The study identified limitations such as potential bias due to the predominance of respiratory medicine specialists and the geographical constraint of being Spain-specific. It highlighted the need for validation of these definitions through prospective clinical studies to confirm their relevance to long-term outcomes.

The ACAAI consensus adds criteria such as minimal reliever use and no absenteeism from work or school, which are not explicitly mentioned in the other statements. On the other hand, the SANI consensus also highlights the importance of stable lung function and the absence of OCS, with a distinction between clinical and partial remission based on the number of criteria met. A common thread across these definitions is the absence of symptoms and exacerbations, stable lung function, and minimal medication use. However, discrepancies remain in specific cut-off values for lung function and inflammatory markers, such as blood eosinophils and F_{ENO} levels, as well as the exact duration required to confirm remission. Moreover, the role of CRSwNP, as highlighted by SEPAR, adds another layer of complexity. To reach a final consensus, further research is needed to validate these criteria prospectively and to harmonise the definitions across different clinical contexts and populations. This will require broad international collaboration and standardised guidelines to ensure a consistent approach to defining and achieving asthma remission. Achieving a definition of remission may be possible with current treatments; however, more research is needed to understand the pathophysiology of remission and to develop a precise, internationally accepted definition.

The discrepancies presented in defining asthma remission highlight the complexity of establishing uniform criteria. Defining asthma remission as a treatment goal remains challenging due to variations in criteria across studies and expert consensus statements. The presented frameworks agree on the importance of symptom control, stable lung function and absence of exacerbations, but differ in terms of specific criteria such as the use of inflammatory markers or minimal medication use. To address these challenges, real-world studies as well as *post hoc* analysis of clinical trials have been performed to implement and validate these diverse definitions of asthma remission in clinical practice, where potential predictors of remission can also be more extensively explored.

Asthma remission: one outcome and multiple definitions in clinical trials and clinical cohorts

While the different definitions of asthma remission underline the need of uniform criteria, they also underscore the need for practical validation of these definitions in clinical settings. Real-world studies as well as *post hoc* analysis of clinical trials and cohorts have aimed to identify the prevalence and the minimal criteria to achieve remission in patients on biologics. Asthma remission has been evaluated in various ways across studies, mainly exploring clinical, functional and immunological parameters. Some common criteria include absence of asthma symptoms, no requirement for OCS, controlled or normalised lung function, and no exacerbations. These studies provide valuable insights into the predictors and outcomes of clinical remission in severe asthma patients treated with biologic therapies (table 2).

Clinical cohort and real-world studies

Perez-De-Llano *et al*. [15] aimed to identify predictors of clinical remission in a longitudinal cohort study involving 23 countries within the International Severe Asthma Registry (ISAR). The study included severe asthma patients on anti-IgE (n=1390), anti-IL-5/IL-5R (n=2021) and anti-IL-4Rα (n=306). Clinical remission was defined across four domains, namely absence of exacerbations and long-term OCS use (one domain), partly or well-controlled asthma (three domains), and forced expiratory volume in 1 s (FEV_1) ⩾80% pred (four domains). Within 1 year, 20.3% of patients achieved remission across all four domains,

TABLE 2 Summary of the main real-world and registry-based studies

First author [ref.]	Outcomes	Main results	Limitations
Perez-De-Llano [15]	Clinical remission achieved by 20% within 1 year	Significant predictors included shorter asthma duration, lower pre-treatment impairment and higher blood eosinophil counts for anti-IL5s	Specific patient population Retrospective assessment
Milger [20]	Remission rate for patients treated with biologics: 37% Remission rate for patients treated without biologics: 17%	Significant reduction in exacerbations, OCS use and improvement in ACT scores	Retrospective design and real-life nature of the cohort Potential loss-to-follow-up Did not differentiate between biologics
McDowell [16]	18% achieved remission	Remission more common in males, shorter asthma duration, nonsmokers, associated with nasal polyps, white ethnicity, lower BMI, higher blood eosinophils and F_{ENO}	Retrospective analysis, need for further studies to clarify early intervention benefits
Pavord [17]	30% and 37% achieved clinical remission based on first and second definition, respectively	Remission more common in patients with higher baseline eosinophil count, lower OCS usage, higher ACT score and better lung function	Retrospective observational study
Maglio [18]	30% with mepolizumab and 40% with benralizumab	Both biologics effective in inducing clinical remission	Observational, real-life setting
Pini [19]	69% achieved complete remission at 12 months, 84% maintained remission up to 3 years	Long-term effectiveness in reducing exacerbations, improving lung function, enhancing control and minimising OCS use	Retrospective data Specific patient population and settings
Thomas [21]	29% achieved remission in AMR cohort, 23% in AXR cohort	Remission more common in patients with higher post-bronchodilator FEV_1, lower BMI, lower baseline ACQ scores; lower odds with maintenance OCS use, hospitalisation and comorbidities	Observational study Importance of addressing comorbidities
Hansen [22]	79% achieved clinical response, 19% achieved clinical remission	Remission more likely with shorter disease duration, lower BMI, higher blood eosinophils, higher IgE levels, male, lower ACQ-6 and higher FEV_1	Observational cohort Wide variation in remission rates by biologic class
Oishi [23]	68% achieved clinical remission, 31% achieved deep remission	Predictors of remission were shorter asthma duration, higher baseline FEV_1 % predicted Varying remission rates by biologic	Small sample size Unspecified switching medication
Portacci [24]	39% achieved remission	Remittent patients had higher blood eosinophil counts and lower BMI Step down from LAMA treatment	Small sample size Short duration
Quarato [25]	55% achieved remission at 12 months, 60% at 24 months	Obesity associated with a reduced likelihood of achieving remission at 24 months	Small sample size Retrospective design

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; AMR: Australian Mepolizumab Registry; AXR: Australian Xolair Registry; BMI: body mass index; F_{ENO}: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in 1 s; IL: interleukin; OCS: oral corticosteroids; LAMA: long-acting antimuscarinic agent.

with higher remission rates observed when fewer domains were included. Significant predictors included shorter asthma duration, lower pre-treatment impairment and higher blood eosinophil counts, the latter specifically for anti-IL-5/IL-5R. It is important to mention that patients on all classes of biologics achieved remission, but adding lung function as a criterion had a notable impact on the overall remission rates, reducing the rate from 33.5% to 20.3%.

In a retrospective analysis of the UK Severe Asthma Registry [16] that included data from 1111 severe asthma patients pre-biologic therapy, clinical remission was defined as an ACQ-5 score <1.5, no OSC for disease control and FEV_1 above the lower limit of normal or no more than 100 mL less than baseline after 1 year treatment. 18.3% of patients achieved remission in this cohort. Remission was more common in patients who were male, had a shorter duration of asthma, were nonsmokers and was associated with nasal polyps, white ethnicity and a lower body mass index (BMI). A higher rate of remission was registered for patients who had elevated baseline blood eosinophils and F_{ENO}. Further studies are needed to clarify whether earlier intervention with biologics can improve long-term clinical outcomes.

A *post hoc* analysis of the severe asthma patients included in the real-world, retrospective observational REDES study [17] aimed to analyse clinical remission in patients on mepolizumab for at least 1 year. In this study, two different definitions of remission were included. The first was a four-component clinical

remission definition that required patients to meet all of the following criteria at 1 year: no OCS use, no exacerbations, ACT score ⩾20 and an FEV_1 post-bronchodilator ⩾80%. The second was a three-component definition that included all the previous criteria, except for the FEV_1 post-bronchodilator. After 1 year of mepolizumab, 30 (37%) patients achieved clinical remission based on the first and second definitions, respectively. Patients who achieved remission had a higher baseline eosinophil count, lower OCS usage and better ACT score and lung function.

In line with these results, Maglio *et al*. [18] conducted a small observational multicentre retrospective study of 113 severe asthma patients on mepolizumab (n=83) or benralizumab (n=30). Both biologics were effective in inducing clinical remission after 1 year in a real-life setting. Clinical remission was achieved in 30% of mepolizumab and 40% of benralizumab patients. The definition followed that described by Menzies-Gow *et al*. [5]. The study confirms the efficacy of mepolizumab and benralizumab in treating severe eosinophilic asthma, with a significant proportion of patients achieving clinical remission after 1 year of treatment.

Another real-life study [19] aimed to assess the long-term remission of severe asthma patients on benralizumab. 108 patients from nine Italian centres, as part of the SANI, were followed-up for 3 years and assessed either for complete or partial clinical remission. Partial clinical remission was defined using three criteria, specifically no OCS use, accompanied by two of the following: either good asthma control (ACT score ⩾20) and/or elimination of exacerbations and/or pulmonary stability. Complete clinical remission was achieved by patients who met all four of the following criteria. Interestingly, at 12 months, 69.57% achieved complete clinical remission and 84.31% maintained complete clinical remission up to 3 years. This study demonstrates not only the long-term effectiveness of benralizumab in reducing exacerbations, improving lung function, enhancing asthma control and minimising the use of OCS, but also the potential of benralizumab as a disease-modifying therapy, capable of inducing long-term clinical remission in a substantial proportion of patients. However, although the results seem encouraging, data has been assessed retrospectively and should be not generalised due to the specific patient population and settings.

The study by Milger *et al*. [20] aimed to analyse remission rates in adults with severe asthma following biologic treatments. The study included 443 adults not using biologics at baseline, divided into two groups, as follows: group A (233 patients treated without biologics) and group B (210 patients started on biologics after baseline and continued for 1 year). Clinical remission was defined as achieving an ACT score of 20 or more, absence of exacerbations and no daily OCS use for 1 year, while remission with lung function improvement additionally required an FEV_1 increase of at least 100 mL. The results showed that, after 1 year, group B had significantly higher remission rates compared to group A, with 37.6% achieving clinical remission *versus* 17.2% in group A and 32.1% achieving remission with lung function improvement *versus* 9.5% in group A. Despite having more severe asthma at baseline, patients treated with biologics demonstrated markedly better outcomes, highlighting the effectiveness of biologic treatments in achieving clinical remission in severe asthma.

Thomas *et al*. [21] explored remission with an observational multicentre study of 453 severe asthma patients receiving either mepolizumab or omalizumab. Data were retrieved from the Australian Mepolizumab Registry (AMR) and the Australian Xolair Registry (AXR). Clinical remission was defined as no exacerbations or need of OCS and an Asthma Control Questionnaire (ACQ-5) score of ⩽1 at 12 months. Additional criteria were considered as optimisation or stabilisation of lung function (post-bronchodilator FEV_1 ⩾80% or not more than a 5% decline from baseline). In the AMR cohort, 29.3% achieved clinical remission and 25.2% achieved clinical remission plus lung function criteria. In the AXR cohort, 22.8% achieved clinical remission with 19.1% of patients achieving remission plus meeting lung function criteria. Potential predictors of clinical remission were higher post-bronchodilator FEV_1, lower BMI and lower baseline ACQ scores. On the contrary, maintenance OCS use and hospitalisation for asthma exacerbation in the previous year reduced the odds of remission. Comorbidities such as depression, obesity and osteoporosis were associated with lower remission rates. The findings highlight the importance of addressing comorbidities to increase the likelihood of achieving asthma remission.

In an observational cohort study using data from the Danish Severe Asthma Register, 501 biologic-naïve patients who commenced biologic therapy were analysed to identify predictors of both response and remission [22]. Clinical response and clinical remission were defined as a reduction of at least 50% in the annualised exacerbation rate and/or a 50% reduction in maintenance OCS (mOCS) dose (response), absence of exacerbations, no mOCS use, well-controlled symptoms (ACQ score ⩽1.5) and normalisation of lung function (FEV_1 >80%) after 12 months of treatment (remission). 79% of patients achieved a clinical response and 19% of the total population achieved clinical remission after 12 months. In line with

some of the above-mentioned studies, remission was more likely in patients with shorter disease duration, lower BMI, higher blood eosinophil counts and higher total IgE levels. Patients achieving remission were more likely to be male, have lower ACQ-6 scores and have higher FEV_1 at baseline. Interestingly, clinical remission rates varied widely by biologic class, 6% with anti-IgE, 19% with anti-IL-5/IL-5R and 30% with anti-IL-4Rα. The study demonstrates that early initiation of biologic therapy, particularly in patients with a shorter disease duration and less severe disease, is associated with better chances of achieving remission.

A Japanese smaller cohort study of 54 severe asthma patients on biologics aimed to explore the achievement rate and predictors of clinical remission and deep remission in severe asthma patients treated with biologics [23]. Clinical remission was defined as no asthma symptoms, exacerbations and use of OCS, while deep remission included all the criteria of clinical remission plus normalised pulmonary function and suppressed type 2 inflammation (blood eosinophils and F_{ENO}) in 1 year. Clinical remission was obtained in 68% of the cases and deep remission in 31.5%. Predictors of remission were a shorter asthma duration and higher baseline FEV_1 % pred. In this study, clinical remission was achieved in 10.8% of the patients receiving omalizumab, 2.7% receiving mepolizumab, 37.8% receiving benralizumab and 29.7% receiving dupilumab. Deep remission was achieved in patients on benralizumab (35.3%) and dupilumab (41.2%). 24% of the total sample were also switchers, but the specific medication they switched to was not specified.

A recent small prospective observational study explored remission on dupilumab in a real-life setting [24]. 18 patients underwent evaluations at baseline, 6 months and 12 months. Clinical remission was defined as no use of OCS, no exacerbations after 12 months of treatment, an ACT score ⩾20 and improvement and stabilization of lung function (increase in pre-bronchodilator FEV_1 ⩾100 mL from baseline). 38.9% patients achieved remission in this study and had significantly higher blood eosinophil counts and lower BMI compared to nonremitters. Patients achieving remission were able to step down from LAMA treatment. Although the study has a small sample size and relatively short duration, dupilumab seems to be effective in achieving clinical remission in severe asthma, improving asthma symptoms, lung function and reducing OCS use. A more extensive real-life study evaluated the effectiveness of dupilumab over 24 months in 20 patients with severe eosinophilic asthma [25]. Clinical remission, defined as no OCS use, no exacerbations, an ACT score ⩾20 and FEV_1 ⩾80% pred, was achieved by 55% of patients at 12 months and 60% at 24 months. Significant improvements were observed in asthma control and ACT scores, alongside reduced exacerbation rates and improved lung function. OCS dependence decreased from 50% at baseline to 25%, with a substantial reduction in the mean daily OCS dose. Obesity emerged as a negative predictor of remission (OR 0.03, p=0.004), while no other baseline factors were statistically significant. Despite its small sample size and real-world limitations, this study reinforces dupilumab's potential to achieve and sustain remission in severe asthma while reducing OCS dependency.

Post hoc analysis on RCTs of biologics

An overview of the current definition of remission in clinical trials has been described elsewhere [26]. A summary of the main *post hoc* analysis on RCTs on biologics are presented in table 3.

Dupilumab (anti-IL4Rα)

A *post hoc* analysis of the LIBERTY ASTHMA QUEST trial [27] showed that dupilumab helped some patients with moderate-to-severe asthma achieve clinical remission, defined as no exacerbations, an ACQ-5 score <1.5 and FEV_1 ⩾80%. At 24 weeks, 29.6% of dupilumab-treated patients achieved remission compared to 7.7% on placebo. At 52 weeks, the rates were 20.1% and 4.6%, respectively. Even patients who did not fully achieve remission experienced fewer exacerbations and improved asthma control with dupilumab. Similarly, the *post hoc* analysis of the QUEST and TRAVERSE trials [28] demonstrated that dupilumab could sustain remission over longer periods, with remission rates of 37.2% after 1 year and 42.8% after 2 years. Together, these studies confirm that dupilumab is effective in improving asthma outcomes and can help many patients achieve and maintain clinical remission, especially those with type 2 inflammation.

Benralizumab (anti-IL5R)

A *post hoc* analysis of the SIROCCO, CALIMA and ZONDA trials [29] evaluated the potential of benralizumab to achieve clinical remission in patients with severe eosinophilic asthma, using a composite end-point that included no exacerbations, no OCS use, improved lung function (FEV_1 ⩾100 mL) and an ACQ-6 score ⩽0.75 or <1.5. In the SIROCCO and CALIMA trials, 14.5% of patients treated with benralizumab achieved remission after 12 months compared to 7.7% of placebo patients. In the ZONDA trial, which focused on OCS-dependent patients, remission rates were higher, with 22.5% of benralizumab-treated patients achieving remission at 12 months compared to 7.5% of placebo patients. Additionally, a large proportion of benralizumab-treated patients achieved partial remission by fulfilling at least two or three remission components. Further insights came from the ANDHI and ANDHI In Practice (AIP) trials

TABLE 3 Summary of the main *post hoc* analyses of randomised controlled trials on biologics

First author [ref.]	Definition of remission	Remission rates	Limitations
Dupilumab			
Pavord [27]	No exacerbations ACQ-5 score <1.5 Post-bronchodilator FEV_1 >80%	LIBERTY ASTHMA QUEST: 30% (dupilumab) 8% (placebo) at week 24 20% (dupilumab) 5% (placebo) at week 52	Small group and short follow-up High placebo remission rates observed may reflect the natural history of asthma or other confounding factors
Pavord [28]	No exacerbations No OCS use Stabilised or improved lung function ACQ-5 score <1.5	QUEST: 37% (dupilumab) 22% (placebo) TRAVERSE: 43% (dupilumab/dupilumab) 33% (placebo/dupilumab) 30% (dupilumab/dupilumab) maintained remission up to 24 months	Criteria limited by original QUEST/TRAVERSE trial designs No assessment of long-term OCS reduction High placebo remission rates observed may reflect the natural history of asthma or other confounding factors
Benralizumab			
Menzies-Gow [29]	No exacerbations No OCS use ACQ-6 score <1.5 or ⩽0.75 Pre-bronchodilator FEV_1 ⩾100 mL	SIROCCO/CALIMA: 14% (benralizumab) and 8% (placebo) at 12 months ZONDA: 22% (benralizumab) and 7% (placebo) at 12 months	Excluded patients with high OCS use at baseline in SIROCCO and CALIMA Definitions of remission were based on trial-specific end-points
Harrison [30]	No exacerbations No OCS use ACQ-6 score <1.5	ANDHI and AIP: 40% at 6 months 35% at 18 months	Excluded OCS-dependent patients Preliminary findings
Lommatzsch [31]	No exacerbations No OCS use ⩽10% FEV_1 decrease from baseline ACQ-6 score <1.5	32% at 12 months (SIROCCO/CALIMA trial) Among them, 73% sustained remission in the BORA trial for another 12 months and among them 26% of patients maintained remission for another 12 months	Excluded OCS dependent patients Preliminary findings
Tezepelumab			
Wechsler [32]	No exacerbations No OCS use ACQ-6 score ⩽1.5 Stable lung function	NAVIGATOR: 28% (tezepelumab) and 22% (placebo) at 1 year DESTINATION: 33% (tezepelumab) 27% (placebo) at 2 years	High placebo remission rates observed may reflect the natural history of asthma or other confounding factors

ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 s; OCS: oral corticosteroids.

[30], which analysed the potential of benralizumab to achieve clinical remission and reduce background medication use in patients with severe eosinophilic asthma. Clinical remission was defined as zero exacerbations, no OCS use and an ACQ-6 score <1.5. The study included 264 non-OCS dependent patients with blood eosinophil counts ⩾150 cells·μL^{-1} who had experienced at least two exacerbations in the prior year despite high-dose ICS use. In non-OCS dependent patients, 39.8% achieved remission after 6 months of treatment and 35.5% maintained remission at 18 months. Notably, 70.5% of patients in remission reduced their background medication use, compared to 41.7% of those not in remission. Other preliminary findings from Lommatzsch *et al*. [31] explored clinical remission in a *post hoc* analysis of the phase 3 SIROCCO, CALIMA and BORA extension trials. The long-term efficacy of benralizumab was considered for up to 24 months. This pooled *post hoc* analysis included 325 non-OCS-dependent patients. Among these, 104 patients (32%) achieved clinical remission at the end of the SIROCCO/CALIMA trials and 73% of them sustained remission with an additional 12 months of benralizumab treatment in the BORA trial. Furthermore, 26% of patients who did not achieve remission during the first 12 months achieved clinical remission during extended treatment in the BORA trial. Taken together, these studies demonstrate that benralizumab can effectively induce and sustain clinical remission in patients with severe eosinophilic asthma. The durability of remission over 24 months and its association with reduced medication burden highlight benralizumab as a promising option for long-term disease control. Moreover, the potential for delayed remission with extended treatment underscores the importance of continued therapy to maximise patient outcomes.

Tezepelumab (anti-TLSP)

Tezepelumab has shown promise in achieving clinical remission in patients with severe, uncontrolled asthma, as demonstrated in *post hoc* analyses of the NAVIGATOR and DESTINATION trials [32]. Clinical remission was defined as controlled asthma symptoms (ACQ-6 score ⩽1.5), stable lung function

(FEV_1 >95% of baseline), no exacerbations and no OCS use. After 1 year (NAVIGATOR), 28.5% of patients treated with tezepelumab achieved remission compared to 21.9% on placebo. Over 2 years (DESTINATION), these rates increased to 33.5% for tezepelumab *versus* 26.7% for placebo. Patients achieving remission typically had higher baseline lung function, fewer prior exacerbations and lower inflammatory biomarkers. While remission was associated with improvements in blood eosinophils and F_{ENO}, these biomarkers alone did not fully predict remission, suggesting the need for broader clinical markers used for predicting remission on treatment. However, these findings underscore the potential of tezepelumab to achieve and sustain clinical remission.

The definition of clinical remission varied across *post hoc* studies, reflecting differences in criteria such as symptom control or lung function definitions. This variability complicates direct comparisons between biologic therapies. Moreover, these studies show that a notable proportion of patients receiving placebo also met remission criteria while on medium-to-high doses of ICS or LABAs. This underscores the importance of effective asthma management and the significant impact of ICS on achieving remission as well as that results on achieving remission on biologics should be interpreted with caution. Future studies should focus on the long-term sustainability of remission and potentially investigate whether remission can be maintained while reducing ICS exposure, as explored in trials like the SHAMAL study [33].

In the context of asthma research, it is critical to establish standardised and harmonised criteria for defining remission outcomes. The concept of achieving remission is focused on ensuring sustained asthma control and prevents the disease from becoming uncontrolled. By shifting our focus from “reactive” target treatment, which involves late-stage intervention, to a proactive target treatment aimed at long-term disease management, we can potentially improve the overall outcomes in asthma.

Possible predictors of asthma remission

In parallel with the goal of defining the main remission criteria is the identification of predictive markers of asthma remission.

Eosinophilic inflammation plays a crucial role in asthma remission. In the study by Broekema *et al.* [34] lower levels of blood eosinophils were linked to complete remission, where patients become asymptomatic, exhibit no BHR and display normal lung function without the use of asthma medications. In contrast, clinical remission involves the absence of symptoms and medication use but with persistent BHR and inflammation, indicating ongoing disease activity.

In the study of Couillard and Côté [35] high baseline sputum IL-5 and eosinophil peroxidase (EPX) were associated with better responses to anti-IL-5 therapies. This was also in line with the study by Moermans *et al.* [36] where it was found that patients with elevated sputum IL-5 and EPX levels had significantly higher odds of achieving remission. However, no data are currently available for anti-IL-4Rα and anti-TSLP.

F_{ENO} levels, which indicate ongoing type 2 inflammation, can predict responsiveness to specific treatments such as anti-IL-4 receptor therapies. However, in the context of anti-IL-5 therapies, baseline blood eosinophil counts did not always predict remission, suggesting the need for multiple biomarkers to guide treatment decisions [35].

Despite these progress in understanding remission for type 2 high asthma, significant unmet needs remain for type 2 low asthma. This phenotype is characterised by neutrophilic or paucigranulocytic inflammation, for which, to date, no validated biomarkers or targeted therapies are currently available to predict or achieve remission. Addressing this gap will require the development of novel biomarkers and an improved understanding of the underlying mechanisms driving type 2 low inflammation, as well as tailored therapeutic strategies to achieve remission in this subset of patients.

The pros in asthma remission

Can we achieve short-term and long-term remission?

The current literature highlights the necessity for further research to explore the feasibility of achieving both short-term and long-term asthma remission. Notably, only a limited number of studies have specifically targeted long-term remission as an outcome. Most research is still focused on determining the minimal duration required to achieve remission rather than identifying for how long remission can be maintained. The existing data suggests that a shorter timeframe to achieve remission may be obtained within 1 year with a prolonged remission of up to 3 years. However, other ongoing studies are essential to better understand and validate these timeframes [37]. This challenge is further complicated by the

uncertainties surrounding biologic therapy discontinuation. Evidence from the COMET study [8] demonstrated that stopping mepolizumab after long-term use led to a significant rise in exacerbations (hazard ratio 1.61, p=0.004) and a return of eosinophil counts to baseline levels within 12 weeks. Similarly, the XPORT study on omalizumab [38] showed that 33% of patients who stopped treatment experienced exacerbations within 1 year, compared to 19% of those who continued. In addition to these findings, the study by Jeffery *et al*. [39] showed that, for carefully selected patients, the risk of increased exacerbations after stopping biologics may not differ significantly from those who continue, with only 10.2% of stoppers experiencing exacerbation compared to 9.5% of continuers (OR 1.08, 95% CI 0.83–1.41). Meanwhile, tapering approaches such as those evaluated in the OPTIMAL study [40] show promise for extending treatment intervals without loss of control in selected patients. The study demonstrated that tapering anti-IL5 biologics through extended dosing intervals was feasible for 78% of patients, although some required re-escalation of therapy to maintain control. These findings highlight the need for personalised approaches to biologic therapy, guided by the evaluation of biomarkers and patient characteristics to achieve remission. By better understanding remission, clinicians may be able to identify patients who can safely taper or stop biologic treatments, helping to optimise asthma management.

Asthma trajectory in achieving remission and future perspectives

Based on the available literature, remission seems to be an achievable goal in severe asthma, especially among patients on biologics; however, defining remission is still a challenge. The timeline and best interventions to achieve remission need to be further explored. From a patient's perspective, priority should be given to symptom control and eliminating the need for OCS [41].

In this evolving landscape of severe asthma management, the concept of disease remission is emerging as a new goal for biologic therapies. However, achieving remission does not necessarily imply that patients can discontinue treatment, even though promising results are providing new insights on this topic [40]. With a well-defined framework for remission, there is the potential to identify the key points at which clinicians can decide when biological therapy can be safely discontinued. Moreover, a clear definition of remission could enable clinicians to initiate biological treatment earlier in the disease course. Early interventions with biologic therapies, might improve long-term outcomes and enhance the likelihood of achieving remission. Thus, the focus on disease remission not only redefines treatment goals but also opens new possibilities within research and in clinical practice, aiming for a future where asthma

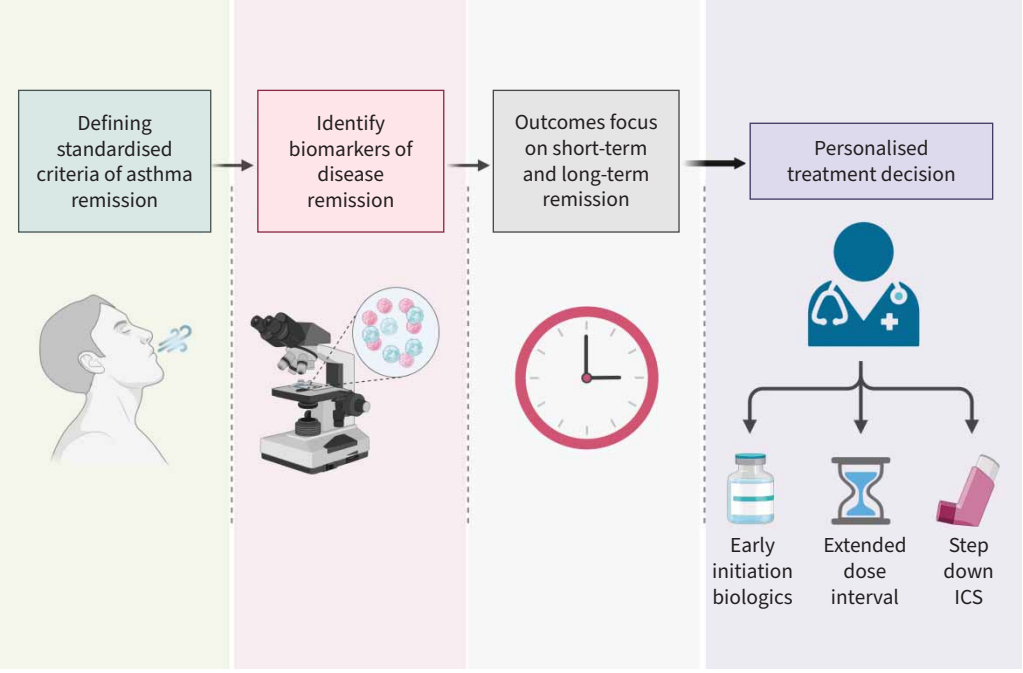

FIGURE 2 Next steps in severe asthma management. The progressive steps in the management of severe asthma, emphasising the importance of personalised treatment plans. ICS: inhaled corticosteroids. Created in BioRender.

management is not solely focused on disease control but potentially on long-term outcomes. Figure 2 shows the progressive steps in the management of severe asthma, emphasising the importance of personalised treatment plans.

Conclusion

Achieving asthma remission is an ambitious goal in the management of severe asthma, but it has become more attainable with the wider availability of biologic therapies. While the concept of remission is still evolving, we believe that the time has come to incorporate the elements of sustained disease control that lead to achieving remission as a desired management goal in asthma, even as we anticipate a more precise definition and validation through prospective clinical trials.

Points for clinical practice:

- Asthma remission as a new goal: clinicians should recognise asthma remission as a primary treatment goal, especially in patients with severe asthma who are candidates for biologic therapies.
- Personalised treatment strategies: treatment strategies should be personalised based on patient characteristics that are predictive of remission outcomes.

Questions for future research

- Consensus on remission definitions: how can we achieve a broad consensus on the definition of asthma remission that includes both clinical and biological markers?
- Understanding long-term remission: what are the long-term outcomes for patients who achieve remission and what strategies can sustain remission over time?
- Role of comorbidities: how do comorbidities such as CRSwNP influence the ability to achieve and maintain remission in severe asthma?
- Timing of biologic therapies: could earlier initiation of biologic therapy lead to higher remission rates and better long-term control in patients with severe asthma?
- Discontinuation of therapy: what are the risks and benefits of discontinuing biologic therapies after achieving remission and how can we identify patients who might be candidates for stopping treatment?

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