



Early View

Series

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Please cite this article as: Thomas D, McDonald VM, Pavord ID, *et al.* Asthma remission- what is it and how can it be achieved?. *Eur Respir J* 2022; in press (<https://doi.org/10.1183/13993003.02583-2021>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

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Title: Asthma remission- what is it and how can it be achieved?

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Conflict of interest

Dr. Thomas has nothing to disclose. Dr. McDonald reports grants and personal fees from GSK and AstraZeneca, and personal fees from Menarini, outside the submitted work. Dr. Pavord reports speaker's honoraria for sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi, Regeneron, and GSK; and payments for organizing educational events from AstraZeneca, GSK, Sanofi, Regeneron, and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi, Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi, Knopp, Almirall, Dey Pharma, Napp Pharmaceuticals, RespiVert, and Schering-Plough. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca, Teva, Sanofi, Regeneron, and Chiesi. He has received a grant from Chiesi to support a Phase II clinical trial in Oxford. He is co-patent holder of the rights to the Leicester Cough Questionnaire; and has received payments for its use in clinical trials from Merck, Bayer, and Insmmed. Dr. Gibson reports grants and personal fees from GSK and AstraZeneca, personal fees from Novartis, Chiesi, and Sanofi, outside the submitted work.

Abstract

Asthma treatment goals currently focus on symptom and exacerbation control rather than remission. Remission is not identical to cure but is a step closer. This review considers the current definitions of remission in asthma, the prevalence and predictors, the pathophysiology of remission, the possibility of achieving it using the available treatment options and the future research directions. Asthma remission is characterised by a high level of disease control, including the absence of symptoms and exacerbations, and normalisation or optimisation of lung function with or without ongoing treatment. Even in those who develop a symptomatic remission of asthma, persistent pathological abnormalities are common, leading to a risk of subsequent relapse at any time. Complete remission requires normalisation or stabilisation of any underlying pathology in addition to symptomatic remission. Remission is possible as part of the natural history of asthma, and the prevalence of remission in the adult asthma population varies between 2% and 52%. The factors associated with remission include mild asthma, better lung function, better asthma control, younger age, early-onset asthma, shorter duration of asthma, milder bronchial hyper-responsiveness, fewer comorbidities and smoking cessation or never smoking. Although previous studies have not targeted treatment-induced remission, there is some evidence to show that the current long-term add on therapies such as biologics and azithromycin can achieve some criteria for asthma remission on treatment, at least in a subgroup of patients. However, more research is required. Long-term remission could be included as a therapeutic goal in studies of asthma treatments.

Introduction

Asthma is a common chronic respiratory disease affecting over 300 million people around the world with significant morbidity and mortality.¹ It is a heterogeneous disease characterised by variable airflow limitation, bronchial hyper-responsiveness (BHR), mucus hypersecretion and airway inflammation, leading to airway narrowing which causes symptoms of wheeze, breathlessness and chest tightness for people with the disease.² Persistent or repeated inflammation of the airways may lead to airway structural changes such as epithelial hyperplasia and metaplasia, changes in mucus secreting cells, subepithelial fibrosis, muscle cell hyperplasia and angiogenesis. These pathological alterations in the airways may result in a change in composition, distribution, thickness, mass or volume and/or the number of structural components observed in the airway wall. This is believed to contribute to a progressive irreversible loss of lung function referred to as airway remodelling.³⁻⁵ Based on the underlying pathological changes and the corresponding physiological consequences in the airways, people may experience mild, moderate, severe or refractory asthma. Some of these individuals also might be at risk of irreversible airway remodelling and/or fixed airflow limitation.

A fundamental feature of asthma is variability, characterised by inconsistency in the expression of the disease. While it is well recognised that variability in asthma may cause asthma attacks, it is less well understood that some people may spontaneously become asymptomatic with or without resolving their underlying pathological airway impairment and enter into a symptom-free state.^{6,7} This is referred to as 'asthma remission'. These individuals who remit or resolve the manifestations of asthma constitute a very interesting cohort who have recently gained much attention among the research community.^{8,9} Understanding the mechanisms of remission may shed light on novel therapeutic approaches to asthma. In addition, a proportion of people who have achieved asthma remission or have 'grown out of asthma' may relapse later in life. The reason for relapse is unclear, but it might be due to the ongoing dysfunction of underlying pathology. Consequently, these symptom-free patients have a certain risk of relapse, which may occur at any time, and this capricious phenomenon of diminution of disease is called remission.⁹

Although the term remission is rarely used in the current management of asthma, it is well defined in other chronic inflammatory conditions such as rheumatoid arthritis, Crohn's disease, ulcerative colitis and systemic lupus erythematosus.^{8,12} In asthma, the treatment goals are still minimisation of acute attacks and achievement of symptom control, with less attention paid to achieving remission. Furthermore, although remission in childhood asthma is a common phenomenon,^{13,14} remission in adults with asthma is a relatively new concept and a less researched area, however has recently gained attention. Since remission is possible as part of the natural history of the disease (for example, childhood asthma remission), it might also be possible to induce remission with treatments. Developing or identifying a treatment that can induce remission in asthma will be a paradigm shift in the asthma management goals, a step closer to the cure. Such success has already been achieved in rheumatoid arthritis, largely with the widespread use of effective targeted therapy using monoclonal antibodies.^{12,15} Effective monoclonal antibody therapies are now increasingly used in asthma,^{16,17} raising the hope of asthma remission as a realistic therapeutic goal. In this review, we critically evaluate the current concept of asthma remission, what it constitutes, the prevalence and predictors of remission, the pathophysiology of remission, the possibility of achieving remission in the current clinical environment and future research directions (Figure 1).

Asthma remission: what is it?

Remission is not cure. Cure requires reversing to the normal pathological state of the airways in addition to prolonged absence of symptoms, typically in the absence of ongoing treatment requirements. An objective demonstration of normal airway function, normal airway responsiveness, and the absence of any airway pathology suggestive of asthma are required to establish that asthma has been cured. Once cured, no treatment is required. Suboptimal treatment outcomes in asthma are mainly attributed to the fact that a large number of factors contribute to the clinical features of asthma, and some are not modifiable. Moreover, it is far from clear whether currently available treatments normalise the underlying pathology such as airway remodelling. Hence, a cure for asthma may not be achievable in the current environment.

We may need a more realistic and achievable goal. The absence of signs and symptoms of a disease for a prolonged time with or without normalising underlying pathology may be referred to as remission. It can be a complete remission or partial remission based on the rigidity of the definition (e.g., no symptoms, absence of pathology etc.) with or without background treatment.¹⁸ In rheumatology, there was a shift in disease management after the introduction of disease-modifying antirheumatic drugs (DMARDs) and targeted anti-tumour necrosis factor (TNF) therapies from a treatment model aiming at disease control to disease remission.¹⁹⁻²¹ It is now a logical time to consider a similar paradigm shift in the asthma management goals with the increased understanding of the pathobiology of asthma (e.g., the role of epithelial-derived cytokines in asthma) and the introduction of targeted biological therapies (e.g., mepolizumab, omalizumab, benralizumab, dupilumab, reslizumab).^{9,22-24}

Current definition: Menzies-Gow et al.⁸ proposed a generalised framework for asthma remission based on the evidence from other chronic inflammatory diseases with remission definitions (Rheumatoid arthritis, Crohn disease, ulcerative colitis and systemic lupus erythematosus) and considering the components of published definitions of spontaneous asthma remission. The framework derived from the literature was subject to a modified Delphi survey to gain expert consensus on the core elements of an asthma remission definition.⁸

The authors produced four subtypes of asthma remission definitions with varying degrees of rigour in criteria. Clinical remission requires stabilisation of lung function and patient/clinician agreement on remission in addition to absence of significant asthma symptoms and acute attacks for a minimum duration of 12 months. Whereas complete remission also requires normalisation of underlying pathology (e.g., resolution of airway inflammation) in addition to clinical remission. Both are further subdivided into remission on treatment and off treatment.

Strength and limitation of current definition: The definition of asthma remission derived by Menzies-Gow et al. is comprehensive and covers the complex nature and impacts of the disease, including symptoms, acute attacks and airways pathology, and is applicable across the range of asthma severity. The definition also includes remission on treatment which is a

pragmatic and valuable goal in more severe asthma cases, albeit none of the previous studies which evaluated spontaneous asthma remission included remission on treatment. There are also four independent definitions of remission provided (Figure 2), and researchers and clinicians have the flexibility to adapt a definition that is achievable and measurable based on their clinical setting and study population.

The Menzies-Gow definition for asthma remission is lenient on reliever (rapid onset beta-2-agonist) use, which might be a questionable element. Rapid onset beta-2-agonists are mainly used on an ad hoc basis to relieve symptoms when people experience symptoms. Since the absence of symptoms is one of the main criteria for remission in all four definitions, we propose the absence of reliever use also should be included. The authors acknowledge that the framework needs to be further tested in prospective studies and streamlined based on input from experts, professional bodies and patients, so the opportunity exists to further develop this definition.

Assessment of remission: Recognition of remission requires an assessment of asthma status. Key variables may include evaluation of asthma symptoms and exacerbations, and assessment of lung function and underlying pathology. Figure 2 summarises the key variables of asthma remission and measures to assess them.

Several validated tools exist for the assessment of symptoms in asthma, however these have seldom been applied to the definition of remission. The Asthma Control Questionnaire (ACQ) is a useful tool for reliably assessing symptoms in asthma, and has established criteria for symptom control. Mean scores range from 0=no impairment to 6=maximum.²⁵ Harvey et al. assessed super response to mepolizumab therapy in severe asthma patients using a cut off of less than one using the 5-item Asthma Control Questionnaire (ACQ-5)²⁶ indicating the value of an asthma control measure to address possible remission of symptoms in asthma. The Asthma Control Test (ACT) is another widely used tool to assess symptom control.²⁷ The total scores range from 5=poor asthma control to 25=complete asthma control. An ACT score >19 indicates well-controlled asthma. The PROSPERO (Prospective Observational Study to Evaluate Predictors of

Clinical Effectiveness in Response to Omalizumab) study classified responders as an ACT score greater than or equal to 20²⁸ while Tuomisto et al. used a cut of 25 in Seinäjoki Adult-onset Asthma Study (SAAS).²⁹ These studies indicate the potential to use asthma control measurements when assessing remission in future work.

Exacerbations, or attacks, are a key outcome in asthma. There are many criteria available to assess exacerbations such as attacks causing hospitalisation, emergency department visit or unscheduled doctor visit. The most widely used is the Oral Corticosteroid (OCS) burst, which records OCS treatment to manage acute attacks of asthma.^{26,30} Use of OCS for acute attack or long-term disease control is not permitted during the remission period.

Normal or stabilised lung function (e.g., normal spirometry assessments) and absence of airway inflammation (e.g., reduced blood or sputum eosinophils, FeNO etc) and BHR (e.g., histamine or methacholine provocation tests) are the other important factors that researchers and clinicians could consider including in the remission definition.

A broad range of symptom-free periods has been used in previous studies ranging from 6 months to three years with an average of one year.¹⁰ The minimum 12 months duration seems to be reasonable, which will cover the seasonality of the disease activity. The majority of the clinical trials have 12 months follow-up, and hence it is feasible to use in research. However, wherever possible, a longer duration should be considered as the disease stabilisation, and relapse may depend on the length of remission.³¹

The risk of relapse depends on how strict remission is defined. For example, the risk of relapse might be minimal for those who achieved “complete remission off treatment” with an ACT score of 25 for a long period of time.¹¹ However, it might not be feasible to achieve complete remission in all severities of asthma¹⁰ and adapting a feasible and achievable remission definition based on the study population is important.

The super responder model: Upham et al. recently developed an international consensus-based definition for severe asthma super responders using a modified Delphi process.³² The

definition encompassed two domains, major and minor criteria. The major criteria include an absence of exacerbation, a large improvement in asthma control and cessation of maintenance OCS or weaning to adrenal insufficiency. The minor criteria were composed of a 75% exacerbation reduction, having well-controlled asthma and 500 mL or greater improvement in FEV1. Improvement in three or more criteria (including at least two major criteria) assessed over 12 months is required to meet the super responder definition. The proposed super responder definition is more relaxed and looking for improvement rather than normalisation, and hence not meeting the requirements for remission. Two recent studies have identified severe asthma super responders to biological agents, but they didn't use the composite outcome remission.^{26,32,33} Eger et al. identified super responders after 2 years of treatment with anti-IL-5 agents. The authors used a composite outcome (no chronic OCS use, no OCS bursts in the past 3 months, ACQ score <1.5, FEV1 ≥80% predicted, FENO <50ppb, and complete control of comorbidities such as chronic rhinosinusitis, nasal polyps, chronic otitis, allergic rhinoconjunctivitis, and atopic dermatitis). Although this definition resembles remission, it was more lenient on OCS use, i.e., assessing OCS bursts only in the past 3 months and considering only the current use of maintenance OCS.³⁴ Remission represents an important step beyond super response, eliminating exacerbations and asthma symptoms for a sustained period rather than reducing the number of attacks.

Prevalence and predictors of asthma remission

Many studies have evaluated the incidence of spontaneous remission in asthma. The rate varied considerably across studies mainly because of the clinical heterogeneity between study populations, designs, definitions and assessments. For example age, these studies evaluated a range of age groups including children, adolescents and adults, used several design types such as birth cohort, cross-sectional surveys, extended follow-up of clinical trials and national databases, and applied variable rigour to the definition of remission, for example clinical and complete, length of remission (6 months to 3 years) and assessment methods (e.g., questionnaire-based and objective assessment).^{8,11} The majority of these studies included a mix of childhood and adult asthma, which most likely caused an overestimation of the remission rate since the rate of remission in childhood asthma is much higher than that in adult asthma.³⁵⁻³⁷ The overall incidence rate reported in these studies ranged from 2% – 74%, and there was a higher incidence of clinical remission compared to complete remission.¹¹

Remission in the adult asthma population

A handful of studies (N=14) have evaluated the remission rate and factors associated with remission in the adult asthma population. Of these, five studies exclusively included new adult-onset asthma.^{29,38-41} Although the remaining nine studies included both adult- and childhood-onset asthma,⁴²⁻⁵⁰ the participants were adults at the time of enrolment. Tupper et al. included 62% adult-onset asthma and 38% childhood-onset asthma, and this report includes only data from the former group. The studies were predominantly conducted in Europe. A majority of the studies (N=11) were longitudinal studies with a baseline assessment and a follow-up assessment. Two studies identified the asthma population from the medical records and conducted a follow-up interview^{43,50} and one study was a cross-sectional survey.⁴⁴ The characteristics of the studies are presented in Table 1.

The follow-up duration ranged from 5 years to 33 years. All the adult-onset asthma studies used objective assessments to confirm asthma diagnosis, whereas only one study in the mixed adult/childhood onset group used objective assessments.⁴⁶ The remission period evaluated ranged from 6 months to 3 years. The majority of studies assessed clinical remission (no symptoms and no asthma medications) for a duration of 12 months or more.

The incidence of remission in the adult-onset asthma population ranged from 2% to 17%, whereas it ranged from 6% to 52% in the other group. Three studies reported a remission rate <10%, eight reported a remission rate between 10% and 20% and four reported >20%. Four studies included some objective measures of remission and the rate ranged from 2% to 17%. All of these studies assessed spontaneous remission. It is important to note that none of the studies assessed treatment-induced remission, which identifies a significant knowledge gap that needs to be addressed.

The predictors of asthma remission are summarised in Table 1. Baseline factors such as mild asthma,^{41,46-49} better lung function,^{29,38,41} better asthma control,^{40,45} younger age,^{40,43} early onset asthma,^{43,44} shorter duration asthma,^{39,44} milder BHR^{38,40} and no/few comorbidities,^{40,41,43,44,49} smoking cessation or never smoking^{41,46,48} were consistently associated with remission. The

majority of the listed factors are well established due to the fact that these are also inversely related to uncontrolled asthma.² An important factor which may influence remission might be the severity of the disease. The disease activity stays much the same over a longer period of time in moderate to severe asthma, while mild asthma cases are likely to experience remission.¹¹ This will have a major impact on the ability to achieve remission based on the population or asthma severity that are studied.

Pathophysiology of remission

Asthma is a heterogeneous disease. The aetiology and pathophysiology of asthma are complex and poorly understood. Moreover, there is a paucity of research that has sought to understand the pathophysiology of asthma remission. However, some previous research suggests that people with remitted asthma might still have some degree of ongoing inflammation, BHR and airway remodelling^{10,11,51,52} which may determine the future risk of relapse.^{53,54}

Previous reviews have reported that the level of airway inflammation is related to the development of asthma remission over time.^{10,55} Caprpaij et al. reviewed the studies comparing inflammatory markers in people with asthma remission and current asthmatic and/or healthy individuals. The authors noted that inflammatory markers were generally lower in remission compared to current asthma but higher compared to healthy individuals, albeit some studies report no difference between groups.^{11,56,57} Likewise, some previous studies have shown that BHR persists in a considerable proportion of people with symptomatic asthma remission.^{54,56 58} Chronic or frequent inflammation in asthma may damage the surface epithelium of the airways leading to airway remodelling. A specific characteristic of airway remodelling is thickening of the subepithelial reticular basement membrane resulting from subepithelial fibrosis. It can even occur in the early stages of life and is more prominent in severe disease.⁵⁹ The consequences of airway remodelling may include increased BHR, fixed airflow limitation, and irreversible loss of lung function. The exact sequence of events that take place during the remodelling process is hard to disentangle and the mechanisms regulating these changes are poorly understood, and as well, studies assessing airway remodelling in asthma remission are scarce. Available

evidence suggests that basement membrane thickening is still present in asthma remission.^{11,53,60} These findings indicate that some aspects of asthma pathophysiology remain during remission. However, the results should be interpreted with some caution, carefully considering the clinical heterogeneity between studies. For example, factors such as asthma severity of the included population, duration of asthma, duration of remission and rigour of remission definition may modify the underlying pathology and affect the study results.⁵⁷

The question remains, how this ongoing airway inflammation and remodelling will affect asthma remission and how it can be effectively treated to prevent relapse in those who are in clinical remission. Currently, there are no effective treatments that halt or reverse the changes of airway remodelling and its effects on lung function. Existing asthma treatments are aimed at controlling airway inflammation and may subsequently reduce the progress of airway remodelling. However, this approach is only partially successful in treating airway remodelling. The search for novel therapies that can directly target individual components of the remodelling process should be made a priority, which may provide a more effective strategy to prevent or reverse structural changes and restore lung function. The interrelationship between airway remodelling, inflammation and BHR should be clearly evaluated and demonstrated. A clear understanding of the molecular events leading to airway remodelling and factors influencing each of the components of remodelling may facilitate the development of new treatment approaches.⁵

Another important element contributing to asthma pathobiology is genetic. Although, previous genome-wide association studies have identified multiple genes associated with asthma origin and remission, more research is required in this area.⁶¹

Enablers and challenges of achieving asthma remission

The multifaceted aetiology and the complex pathology make asthma a difficult disease to cure. Although advances in asthma treatments have improved the symptoms of asthma and reduced the frequency of attacks and the overall burden experienced by people with asthma, the treatments and advances in care still fail to cure the disease, and to date, asthma treatment has mainly focused on disease control over cure. A few studies have identified super-responders to

biological agents,^{26,33} a step closer to remission,³² but these failed to evaluate their effectiveness in inducing remission. Previous work which demonstrated that a certain percentage of individuals spontaneously outgrow the disease for a certain period of time, or the rest of their lives is promising. The question is whether the proportion of individuals attaining remission can be increased or is it possible to prolong the remission period with treatment?

The lack of disease-modifying agents in asthma is a weakness. Reversing the remodelling that has already occurred might be a challenge which requires the development of new therapies. Although the person with asthma may be asymptomatic in remission, the underlying disease might be active and continuing to progress, and treatment with ongoing anti-inflammatory agents might be useful.¹⁸ This is an important lesson in asthma, since history reveals that minimising symptoms with beta-agonists without addressing the underlying airway inflammation is associated with severe acute attacks and asthma deaths. This lesson would argue that a proposed clinical definition of remission, and seeking treatments to induce that may be risky without an accompanying measure of airway pathophysiology in asthma.

Treatments to induce remission

The introduction of inhaled corticosteroids (ICS) in the 1980s has revolutionised asthma treatment, and currently, they are the cornerstone of asthma therapy. Although ICSs are generally very effective in reducing asthma symptoms, preventing exacerbations and improving lung function in mild to moderate asthma, their ability to alter the natural history of asthma and effectiveness on disease progression are questionable.^{62,63} Likewise, the introduction of a combination of inhaled ICS and long-acting beta2-agonist (LABA) further improved asthma management, but their effectiveness on disease progression needs to be evaluated.⁶⁴

Biologics: Over the past decade, greater awareness of the underlying biology of asthma has led to the development of a new range of treatment targets. Researchers understood that the multifaceted aetiology of asthma includes many phenotypes caused by a variety of pathophysiological mechanisms referred to as endotypes. Two inflammatory subtypes are currently identified, the type 2 (T2) high and T2 low inflammatory pathways. The inflammatory cascade is often initiated by inhaled allergens, microbes or pollutants which interact with the airway epithelium. This interaction leads to the activation of mediators such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. Subsequent immune cell activation (ILC2 cells, Th2 cells etc.) releases IL-4, IL-5, and IL-13, leading to the attraction and activation of basophils, eosinophils, mast cells and immunoglobulin class-switching and secretion of IgE by B cells. This inflammatory process leads to bronchoconstriction, BHR, mucus production, and subsequent airway remodelling.⁶⁵ Current biological agents such as omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab mainly act on the effector molecules of the T2 inflammatory cascade (i.e., IL-4, IL-5, IL-13 and IgE).⁶⁶ Newer agents targeting the upstream targets of T2 inflammation (i.e., TSLP, IL-25, and IL-33) are under development.⁶⁷ Biologics are a promising tailored treatment approach for eosinophilic asthma with a high potential to achieve disease remission in at least a subset of patients.^{26,30} The improved efficacy achieved when biologics are added to previous treatment may meet the criteria for remission. However, it is challenging to evaluate biologics effectiveness in inducing remission using the current evidence since the majority of the previous studies aimed for disease control rather than remission.

Menzies-Gow et al.⁹ evaluated the efficacy of biologics in inducing remission using the current evidence. The authors critically reviewed the current studies and retrospectively extracted and constructed data related to remission. They used the remission definition “clinical remission on treatment”. The authors concluded that biologics are highly effective in reducing exacerbations and symptoms, and in improving lung function. These treatments achieve some but in most cases, not all criteria for remission.

A recent post-hoc analysis of dupilumab found that 20% of the dupilumab treated participants achieved clinical remission (no exacerbation, ACQ-5 total score <1.5 and post-bronchodilator FEV1 ≥80%) at 12 months.⁶⁸ Hence dupilumab has the potential to achieve asthma remission in a subset of people with severe asthma. However, it was a post-hoc analysis and it is important to include this outcome as an objective in future study designs.

Harvey et al.’s super responder study found that 31% of severe asthma patients treated with mepolizumab achieved well controlled asthma (ACQ-5 <1). Of that, 67% were free of OCS burst and 79% were free of maintenance OCS therapy. Although this study failed to identify the proportion of patients achieving the composite outcome remission, it provided an insight into the potential of mepolizumab in achieving remission in a subset of patients with severe asthma. Eger et al.’s super responder model was more or less similar to the proposed remission definition, and 14% (16/141) of patients treated with anti-IL-5 agents achieved the composite criteria. Shorter asthma duration, higher FEV1, and adult asthma onset predicted super response.

Biologics were initially used in rheumatology for end-stage severe disease conditions, but later they were integrated at an earlier stage of disease management to modify disease progression which resulted in a durable and treatment free remission in some patients.^{69,70} Asthma clinicians and researchers can learn from this experience and identify the future role of biologics in the management of asthma. Achieving remission in mild-moderate cases may help to hinder the further deterioration of airway remodelling and lung function decline, leading to more severe and uncontrolled asthma. Conceptually, timely introduction of biologics therapy may weaken the inflammatory process at the earlier stages of the disease activity, fading the exposure of

inflammatory mediators to the airway wall, lowering the potential for airway remodelling and halting the disease progression.

Since it is believed that underlying inflammation has a role in relapse, continuing the treatment with biologics might be an option to prolong remission and prevent relapse,⁷¹ but this needs to be evaluated in clinical trials. The dosing frequency of biologics is convenient, requiring administration only once a fortnight, month or every two months, depending on the treatment. It might also be logical to think about and explore the possibility of stopping all asthma treatments except biologics in a patient who has achieved remission with biological therapies. Continuing ongoing treatment with biologics may help to control underlying inflammation and subsequent relapse. In the COLUMBA (Open-label Long Term Extension Safety Study of Mepolizumab in Asthma Subjects) trial, 33% of participants did not experience exacerbation during the average 3.5 year study period.⁷² Moreover, the COMET study assessed the clinical impact of stopping mepolizumab after 3 years of use. The authors concluded that stopping mepolizumab was significantly associated with a shorter duration to first clinically significant exacerbation and reduced asthma control.⁷³

The effect of biologics on airway remodelling needs to be investigated. Previous research reported some beneficial effects.^{74 75,76} A recent study found anti-IL-13 monoclonal antibody lebrikizumab reduced the degree of subepithelial fibrosis and T2 high biomarkers in addition to improved lung function.⁷⁵ Anti-IgE monoclonal antibody omalizumab also improved airway structure and decreased inflammatory markers in many previous studies⁷⁶⁻⁸¹, although one recent small study reported no benefit on airway remodelling.⁸² Larger studies with longer follow-up are needed to show whether biologics can truly maintain improved airway structure.

Additionally, these agents are relatively newer therapies, and their long-term safety profiles are still emerging. Moreover, the long-term consequence of blocking a biological pathway for lifetime in an individual need to be explored.

Macrolide antibiotics: Low-dose long-term azithromycin (a macrolide antibiotic) significantly reduced asthma attacks in both eosinophilic asthma and non-eosinophilic asthma.^{83,84} Although azithromycin meets some criteria for remission (e.g., more than half of the patients in the azithromycin group did not experience attacks during the 12 months study period and azithromycin treatment improved asthma control, measured using ACQ-6), further research is required to evaluate its effectiveness in inducing sustained remission. Azithromycin has anti-inflammatory and immunomodulatory properties and is cost-effective, and currently, guidelines recommend its use in severe asthma.^{23,85,86} Azithromycin also could be considered for non-eosinophilic asthma in which no other promising treatment options are currently available. However, concerns such as the potential for antimicrobial resistance and side-effects including cardiac, sensory and gastrointestinal effects may limit its widespread use.^{86,87}

Although the exact mechanism of action of azithromycin in asthma is yet to be determined, it is believed that azithromycin operates by non-T2 pathways.⁸⁸ The alternate mechanism of action of azithromycin provides an opportunity to combine it with biologics, and that might provide additional benefits and may address residual disease burden (ongoing exacerbations despite treatment) of individual treatment.

The treatable traits concept: Many underlying treatable conditions contribute to the multifaceted aetiology of asthma, deterioration of health-related quality of life (HRQoL) in patients and suboptimal response to treatment.⁸⁹ The most prominent underlying risk factors in severe asthma include airflow limitation, eosinophilic and non-eosinophilic inflammation (also termed T2 high and T2 low disease), obstructive sleep apnoea, vocal cord dysfunction, inhaler device polypharmacy and non-adherence, upper airway disease, physical inactivity and obesity, systemic inflammation, anxiety and depression, and being exacerbation prone.⁹⁰⁻⁹² These treatable underlying conditions are referred to as treatable traits.^{93,94} Researchers identified an average of 10 treatable traits in severe asthma patients.^{89,91,92} The treatable traits concept has several useful implications for asthma remission. Since traits such as comorbidity and smoking are associated with remission, and some underlying comorbid conditions may trigger asthma-like symptoms and/or worsen asthma severity, it is possible that targeting treatable traits may

increase the chance of asthma remission, however this approach should be assessed in clinical studies. Remission includes the absence of asthma symptoms. It is hard to disentangle the symptoms caused by airflow limitation and other comorbid conditions, such as vocal cord dysfunction, and this may lead to inappropriate asthma assessment or symptom misattribution.⁹⁵ A treatable traits assessment will identify these other conditions, and identify and treat symptom misattribution, leading to a more accurate assessment of remission. Current treatments are mainly focused on airflow limitation, airway inflammation and exacerbation control, and the other traits are largely neglected. To achieve remission in severe asthma patients, we propose identifying and treating all underlying behavioural and biological treatable risk factors, so that their effect on asthma is minimised. It is crucial considering the absence of comorbidities was one of the key variables associated with remission in multiple spontaneous remission studies.

The trajectory of remission: Complete remission off treatment is the ultimate goal of asthma management, and it essentially constitutes a cure. It might not always be achievable and measurable in the current environment but nevertheless should remain as a goal. Aiming for complete remission in populations with early-onset and mild asthma and aiming for clinical remission on or off treatment in more severe and treatment-refractory asthma populations might be a practical and achievable approach.

The exact trajectory of remission still needs to be explored and defined. However, in most cases, achieving clinical remission on treatment might be the initial step and then aiming for complete remission. Hence, the initial aim of achieving remission is to eliminate the exacerbations and symptoms and halt the disease progression and further damage to the airway wall which will help the people to live a normal life. Subsequently, normalise the impairment already caused by the disease.

Future research should explore the possibility of withdrawing treatment after achieving remission and it may not be possible in more severe cases at least in the current scenario. Identifying the predictors and markers of successful treatment withdrawal will assist clinicians in trying deprescribing.

The way forward

The question arising is in what direction do scientists need to delve to discover a definitive cure for asthma. Is there a silver bullet to treat asthma? The current answer is no. But observations of spontaneous asthma remission (Table 1) offer hope that this may be possible. An analysis of patients treated with available treatment options such as biologics and macrolides might be useful to assess the proportion of people meeting the criteria for remission with these treatments. Better characterisation of patients responding to available therapies will help to streamline the treatment (e.g., some may respond to a particular biological agent, and some may respond to macrolides, or emerging therapies). Treatment also should target other modifiable underlying risk factors. A combination of therapies also could be considered to cover the multifaceted aetiology of asthma.

It is also important to identify the areas of remission that are met and not met with current treatments, which will help to identify the unmet areas for further research.⁹ Additionally, it is also crucial to identify the factors associated with lung function decline and develop treatments that could alter disease progression. Furthermore, evaluating the effect of early intervention to halt the onset of asthma or disease progression is also important as an early intervention might halt or delay the progression of the disease.⁹⁶ It is vital as people accumulate health and psychological issues over time including iatrogenic issues and timely intervention might radically modify this process. Table 2 presents a number of critical research questions associated with asthma remission. Of that, the priority might be making an international consensus on the remission definition.

Asthma guidelines in the future should also include a definition for remission as a treatment goal that could be implemented by researchers. Nevertheless, by acknowledging the aforementioned factors and evaluating the promising research skyline, we are much closer to reaching the treatment goal of remission in asthma management.

Table 1: Summary of studies that have evaluated adult asthma remission: Study characteristics, prevalence and predictors of remission

Study	Study characteristics	Remission definition	Proportion	Associated with remission	Comments
Adult-onset asthma					
Almqvist et al. 2020 ³⁸	N=205 Follow-up: 15.3 years Country: Sweden	No symptoms or asthma medications during the last 12 months.	11.2%	Better lung function and less-severe BHR	Objective assessment of asthma at baseline. Population: asthma onset after 20 years. Design: Prospective longitudinal study
Tuppe et al. 2020 ³⁹	N=78 Mean follow-up: 33.3 years Country: Denmark	No symptoms or asthma medications during the last 12 months. Fractional exhaled nitric oxide <50ppb, no bronchodilator reversibility, no airway hyperresponsiveness, and no airflow limitation.	17%	Shorter duration of asthma at baseline	Objective assessment of asthma both at baseline and follow-up. Design: Prospective longitudinal study
Westendorp et al.	N=170 Follow-up: 5	No symptoms or asthma medications during	15.9%	Independent predictors of remission include	Clinically assessed asthma at baseline.

2018 ⁴⁰	years Country: Netherlands	the last 12 months.		less BHR and no nasal polyps. Remission was associated with younger age, better asthma control, lower doses of ICS and lower levels of blood neutrophils.	Design: Prospective longitudinal study.
Tuomi et al. 2016 ²⁹	N=203 Follow-up: 12.2 years Country: Finland	No asthma symptoms, asthma Control Test (ACT) score of 25, no asthma medication during last 6 months, no use of oral prednisolone during the last 2 years. Objective assessment of normal lung function	Clinical remission :3% Normalisation of lung function: 2%	Better lung function and lower IgE-level both at baseline and at follow-up visit.	Objective assessment of asthma at baseline and follow-up. Asthma onset after adulthood (baseline age 46±14 years). Design: Prospective longitudinal study

Rönmark et al. 2007 ⁴¹	N=250 Follow-up: 5.8 Years Country: Sweden	Clinical: No asthma symptoms and no asthma medications in the last 12 months. Complete: No medications, no symptoms, FEV1>80% off predicted, and PC20 >8mg//ml.	Clinical: 4.8% Complete : ~3%*	Mild disease, normal lung function at onset, absence of allergic sensitisation, rhinitis, and being a non-smoker.	Objective assessment of asthma. Asthma onset after 20 years. Design: Prospective longitudinal study
Adult at the time of enrolment					
Traulsen et al. 2018 ⁴²	N=239 Follow-up: 9 years Country: Denmark	No current use of asthma medications and no asthma symptoms during the previous 12 months.	28%	Use of medication at baseline	Questionnaire based asthma diagnosis and remission. Age at enrolment: 20-44years. 19% had asthma and COPD. Design: Prospective longitudinal study.
Sözen et al. 2015 ⁴³	N=160 Follow-up: 7 years Country: Turkey	Clinical: No current use of asthma medications and no asthma symptoms during the previous 2	Clinical: 11.3% Complete : of the 9 undergone BHR	Younger age, younger onset, atopy, allergic rhinitis, and few comorbidities were associated with remission.	Asthma cohort identified from medical records and questionnaire survey at follow-up. Age at onset: 35.8 ±11.4.

		years. Complete remission: no BHR (assessed in 50% of clinical remission cases.	assessment, 3 achieved normalisation of BHR		Design: retrospective cohort followed up after 7 years.
Pesce et al. 2015 ⁴⁴	N=3,87 Follow-up: 7 years Country: Turkey	No asthma attacks in the last 2 years and no current use of medications.	52%	Presence of hay fever, the age at onset and the time since onset of asthma.	Questionnaire based asthma diagnosis. Age at enrolment: 20-84 years Design: cross-sectional cohort.
Cazzoletti et al 2014 ⁴⁵	N=214 Follow-up: 9 years Country: Italy	No current use of asthma medication, no asthma-like symptoms and no asthma attacks in the last 12 months	29.7%	Asthma control at baseline	Questionnaire based asthma diagnosis and remission. Age at enrolment: 21-47 years. Design: Prospective longitudinal study.
Lindstrom et al. 2012 ⁵⁰	N=119 Follow-up: 20 years Country: Finland	No asthma symptoms and using no asthma medication in the last 3 years	11.8%	Exercise test and spirometry results	Population: Military servicemen in 1987-1990. Age at enrolment: 18-27 years (20.1±1.4) Asthma diagnosis:

					<p>based on medical records (symptoms, medication use, lung function and allergy tests).</p> <p>Design: Retrospective cohort followed up after 20 years.</p>
Ekerljung et al. 2008 ⁴⁹	<p>N=295</p> <p>Follow-up: 10 years</p> <p>Country: Sweden</p>	<p>No symptoms or asthma medications during the last 12 months.</p>	14.6%	Mild disease and no rhinitis	<p>No objective assessments.</p> <p>Population based questionnaire survey 10 years apart.</p> <p>Age at enrolment: 20-69 years.</p> <p>Design: Prospective longitudinal study</p>
Holm et al. 2007 ⁴⁸	<p>N=1,153</p> <p>Follow-up: ~8.5 years</p> <p>(Iceland, Norway, Sweden, Sweden,</p>	<p>No asthmatic symptoms in two consecutive years and no current use of asthma medications.</p>	18.6%	Quitting smoking and the presence of mild disease at baseline	<p>No objective diagnosis of asthma (i.e., self-reported questionnaire-based asthma at baseline).</p> <p>Age at enrolment: 26-53 years.</p> <p>Design: Prospective</p>

	Estonia)				longitudinal study
de Marco et al. 2006 ⁴⁷	N=586 Follow-up: 9 years. Countries: Europe, North America and Oceania	No symptoms and no use of medications in the last 12 months	11.9%	Less severe asthma and lowest increase in BMI	No objective diagnosis of asthma (i.e., self-reported questionnaire-based). Age at enrolment: 20-44 years (34±7) Design: Prospective cohort study
Rönmark et al. 1999 ⁴⁶	N=267 Follow-up: 10 Years Country: Sweden	No asthma symptoms and no asthma medications in the last 12 months.	6%	Mild disease and smoking cessation	Objective assessment of asthma. Age at enrolment 35-66 years. Design: Prospective longitudinal study

BHR; Bronchial hyperresponsiveness; * visually presented in a figure.

Table 2: Asthma Remission: Future Research Questions

Definition	
1	Does the definition of remission require measurement of inflammation?
2	How do asthma control and severity relate to asthma remission?
Treatment -induced remission	
3	Is treatment-induced remission possible?
4	How does treatment-induced remission compare to spontaneous asthma remission, based on prevalence, predictors, and risk of relapse?
5	Is it possible to increase the proportion of people achieving remission with treatment?
6	Is it possible to prolong the remission period with treatment?
7	What are the rates of remission with Maintenance and Reliever Therapy (MART) and step therapy?
8	Does prolonging asthma treatment after control is achieved increase the chance of asthma remission?
Trajectory of remission	
9	How long should the treatment be continued to achieve remission? When to move from one stage to another?
Pathophysiology	
10	What are the molecular events leading to airway remodelling?
11	Can airway remodelling be treated?
12	Does treating airway remodelling induce remission?
Relapse	
13	How does ongoing airway inflammation and remodelling affect relapse?
14	How can inflammation/remodelling be effectively treated to prevent relapse in those who are in clinical remission?
Biologics and asthma remission	
15	What is the prevalence of remission after biologics therapy for asthma?

16	Are biologics more effective than inhaled preventers at achieving asthma remission?
17	Does the early introduction of biologics modify the trajectory of asthma and halt the disease progression?
18	Does continuing the treatment with biologics prolong remission and prevent relapse?
19	Is it possible to stop all asthma treatments except biologics in a patient who has achieved remission with biological therapies?
Macrolide therapy	
20	What is the prevalence of remission after macrolide therapy for asthma?
Treatable traits	
21	Does targeting treatable traits increase the chance of asthma remission?

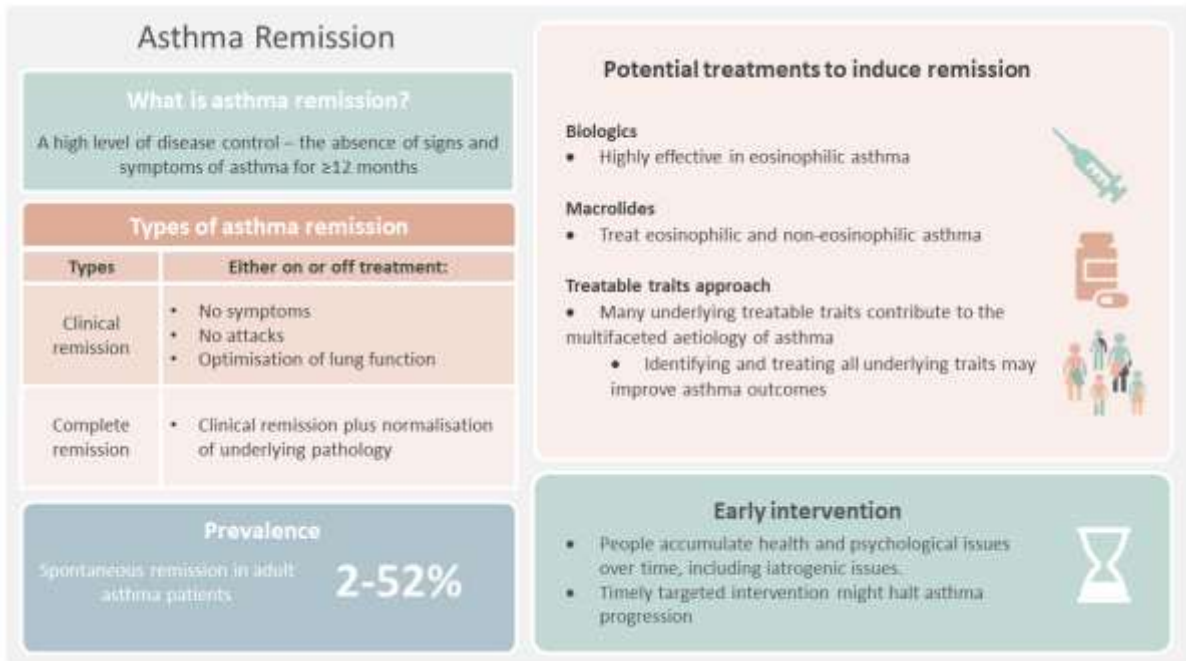


Figure 1: A visual summary of remission*

Types	Criteria	Assessments
Clinical remission	• No symptoms	Sustained absence of significant asthma symptoms established using a validated instrument (e.g., ACQ score ≤ 1 or an ACT score ≥ 20). The use of relievers is not permitted during the remission period.
	• No exacerbations	The use of systemic corticosteroids for exacerbation treatment is not permitted during the remission period. Hospitalisation or emergency department visit or unscheduled doctor visit for asthma exacerbation management are also not permitted during the remission period.
	• Optimisation of lung function	Example, post-bronchodilator FEV1 percentage predicted $\geq 80\%$.
Complete remission	• Clinical remission plus normalisation of underlying pathology	No evidence of current inflammation established using either blood eosinophil count (< 300 cells/microliter), sputum eosinophil count ($< 3\%$), or FeNO (< 40 ppb). ^{97, 98} Other measures of underlying pathology may include a negative bronchial hyperresponsiveness test (e.g., histamine or methacholine provocation tests) or degree of subepithelial fibrosis (subepithelial thickness).
Both clinical and complete remission can be achieved either on treatment or off treatment		

Figure 2: Types and measures of asthma remission

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