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REVIEW

Clinical remission and control in severe asthma: agreements and disagreements

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Abstract

Over the last two decades, we have witnessed great advancements in our understanding of the immunological pathways of asthma, leading to the development of targeted therapies, such as biologic drugs, that have radically and definitively changed the clinical outcomes of severe asthma. Despite the numerous therapeutic options available, ~4–10% of all people with asthma have severe or uncontrolled asthma, associated with an increased risk of developing chronic oral corticosteroid use, fixed airflow limitation, exacerbations, hospitalization and, finally, increased healthcare costs. The new concept of disease modification in asthma comes from the evolution of asthma management, which encompasses phenotyping patients with different inflammatory endotypes characterizing the disease, followed by the advent of more effective therapies capable of targeting the proximal factors of airway inflammation. This treat-to-target approach aims to achieve remission of the disease. Because the novel treatment paradigm for severe asthma with the advent of biologic therapies is no longer clinical control but rather clinical remission – a step closer to the concept of cure – a deeper and more accurate understanding of the critical causal mechanisms and endotypes of asthma is necessary to achieve the goal of clinical remission, which has the potential to generate real life-changing benefits for patients. This review aims to frame the evolution of the debated concept of clinical remission and provide clinicians with insights that may be helpful in achieving remission in the greatest number of patients.

Keywords: biologics, control, exacerbations, inflammation, oral corticosteroids, remission, response, severe asthma.

Citation

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Introduction

Over the last two decades, we have witnessed a great advancement in our understanding of the immunological pathways of asthma, which has led to the development of targeted therapies, such as biologic drugs, that have radically and definitively changed the clinical outcomes of severe asthma.

The backbone of asthma management remains inhaled corticosteroids (ICS) alone or, more often, in combination with long-acting β2 agonist bronchodilators, which very often provide good symptom control.[1] However, based on case reports, between 4% and 10% of all people with asthma have severe or uncontrolled asthma, which frequently carries a much higher risk of developing fixed airflow limitation, chronic use of oral corticosteroids (OCS), exacerbations, hospitalizations and even increased healthcare costs.[2,3]

In 2014, the European Respiratory Society/American Thoracic Society Task Force on severe asthma included an updated definition, emphasizing in detail how it should be distinguished from difficult-to-treat asthma. Indeed, the definition of severe asthma includes the following items: exclusion of poor control related to inadequate adherence to ICS, incorrect inhalation technique, and coexisting

comorbidities or even inappropriate behaviours.[4] Severe asthma is defined as asthma when control remains poor despite the implementation of all measures that adequately address these factors. In particular, it is described as asthma that requires treatment with high-dose ICS plus a second controller (and/or OCS) to prevent it from becoming 'uncontrolled' or as asthma that remains 'uncontrolled' despite optimized maximal therapy.[5]

When assessing the severity of asthma, criteria for uncontrolled disease are required. The European Respiratory Society Task Force identified four criteria to qualify a patient as having uncontrolled asthma: (1) poor symptom control, (2) frequent severe exacerbations, (3) serious exacerbations (defined as at least one hospitalization, intensive care unit stay and/or mechanical ventilation in the previous year) and (4) airflow limitation. The definition of severe asthma also extends to individuals who do not meet all the criteria for uncontrolled asthma but whose asthma worsens after undertaking OCS tapering.[5]

Long-term OCS therapy has many well-known side-effects, which is why patients with severe refractory asthma despite optimized inhaled therapy require a tailored treatment with add-on treatment like biologic therapies following the identification of an underlying inflammatory endotype.[6]

The five approved and effective monoclonal agents for the treatment of severe asthma are omalizumab, which targets immunoglobulin E (IgE); mepolizumab, benralizumab and dupilumab, which target IL-5/IL-5Rα and IL-4/IL-13Rα, respectively; and tezepelumab, which targets the thymic stromal lymphopoietin receptor.[7] Each of these has been demonstrated, through a large body of literature, to be effective in randomized clinical trials and real-world evidence in terms of clinical control, improvement of respiratory function and reduction in the use of OCS in severe refractory asthma.[8]

This narrative review aims to frame the evolution of the debated concept of clinical remission as an ambitious and now concretely achievable outcome in modern asthma management, to highlight correct management of inhaled therapies, OCS and biological drugs in this context, and, finally, to provide clinicians with insights that could be useful to achieve remission in the greatest possible number of patients.

Review

OCS sparing

For patients with severe uncontrolled asthma despite maximal inhaled therapy, asthma guidelines generally recommend adding low-dose OCS (≤7.5 mg/day prednisone equivalent) always as a last resort after exclusion of other contributing factors and additional treatments, including biologics.[1] Short-term or maintenance OCS add-on therapy is still widely used. In fact, it is estimated that approximately 30% of adults with severe asthma add OCS to ICS to maintain asthma control.[5] Furthermore, reports suggest that 20–60% of patients with severe or uncontrolled asthma use long-term OCS therapy, with use more likely in those with the greatest number of exacerbations.[9]

Regular, daily exposure to OCS causes a wide range of well-known adverse events that are more frequent than those caused by intermittent OCS intake following asthma exacerbations. Furthermore, treatment with OCS for more than 30 days/year poses a greater overall risk of possible corticosteroid-related adverse events than no OCS treatment.[10] The most frequent morbidities described are diabetes, hypertension, osteoporosis, dyspeptic disorders, weight gain, cataracts and adrenal suppression as well as psychological adverse events like depression and anxiety.[11,12] The risk of developing acute or chronic OCS adverse events is dose-dependent, even though the risk is also present with OCS exposures as low as ≤1 mg/day.[13]

The benefit of reducing long-term OCS use must be balanced with the risk of asthma exacerbations and an increased need for short-term OCS.[14] Because guidelines recommend the intermittent use of OCS for the management of acute asthma exacerbations, asthma control and reduction of exacerbations are the primary goals of treatment with all biologics, with the crucial aim of reducing the intermittent use of systemic corticosteroids.[15]

Treatable traits concept

Currently, the new treatment paradigm for chronic airway diseases is based on precision medicine with tailored programmes based on the genetic, phenotypic and psychosocial characteristics of individual patients, including tailored pharmacological and non-pharmacological interventions just to reach a better outcome with fewer side-effects.[16]

Asthma guidelines recommend focusing on the search for factors and comorbidities that can coexist and worsen an airway disease at the diagnosis stage.[5] Agusti et al. proposed a preliminary diagnostic protocol for suggestive airway disease. The protocol involves assessing the clinical history and presence of risk factors of airway diseases (occupation, smoking, allergies, family history, respiratory disease in early life) before phenotyping patients through measurement of biomarkers

(fractional exhaled nitric oxide (FeNO) and blood eosinophils) and lung function assessment.[17]

It is widely known that asthma is a complex and heterogeneous disease, driven by complex, varied and distinct molecular mechanisms, identified as endotypes. Wenzel proposed two different pathological endotypes underlying the phenotype of severe asthma based on the presence or absence of eosinophils in the airways.[18] Following this concept, the main endotypes of severe asthma were classified as type 2 (T2)-high (eosinophilic) and T2-low (non-eosinophilic). An early approach to this complexity was based on the concept of clinical phenotypes, defined as a single or combination of disease attributes that describe differences between individuals with the same disease as they relate to clinically meaningful outcomes. The concept of clinical phenotypes has evolved towards that of treatable traits, therapeutic targets identified through validated biomarkers objectively measured and evaluated as an indicator of pathogenic processes, or biological responses to a therapeutic intervention.

The concept of 'treatable traits' was proposed by Agusti et al. in 2016 and elaborated by McDonald et al. in 2019, and involved dividing the 24 identified traits into 3 main domains (pulmonary, extra-pulmonary and behaviour/lifestyle risk factors), emphasizing the characteristics that these traits should have, namely being clinically relevant, identifiable, measurable and treatable.[17,19] McDonald et al. also identified 10 traits from the original 24 associated with an increased risk of future asthma attacks. In particular, they described past-year exacerbation, depression, vocal cord dysfunction, inhaler device polypharmacy and obstructive sleep apnoea as best predictors of uncontrolled disease, emphasizing how the treatable traits approach can lead to early and better outcomes.[20]

Notwithstanding, asthma inflammatory endotypes have long been simplified through a dichotomous approach (T2-high and T2-low asthma) and treatable traits are present in different phenotypes and endotypes, providing further opportunities for targeted therapy. This knowledge allows us to identify new treatment targets for patients that do not neatly fit into T2-high or T2-low phenotypes. Therefore, Carr and Peters proposed novel treatable traits in asthma, focusing on inflammatory traits (T helper 17 (T_H17) cells and neutrophilic inflammation, T cells and natural killer cells, IL-6 trans-signalling and T2-high asthma), physiological traits (chronic airway remodelling, mucus hypersecretion, nasal polyposis and comorbid asthma, epithelial barrier loss, and endoplasmic reticulum stress) and traits mediated by viral and/or bacterial infections.[21]

Due to this complexity and because literature reviews on treatable traits showed a range of variation in traits and trait definition, a consensus through a Delphi process will be necessary on trait identification markers.[22,23]

Because the novel treatment paradigm for severe asthma with the advent of biologic therapies is no longer clinical control but clinical remission – a step closer to the concept of cure – to achieve this goal, a deeper understanding of the critical causal pathways and sub-phenotypes of asthma is required.[24]

The treatable traits approach focused more on the two treatable lung traits of T_H2 inflammation and airflow obstruction, which together with other features can discriminate between people with severe and mild asthma, with a focus also on behavioural and lifestyle traits related to smoking, obesity, anxiety and depression.[25]

A real problem in the in-depth analysis of asthma phenotypes is that asthma phenotype clusters change over time. Kupczyk et al.[26] conducted a study that enrolled 169 patients, describing clusters defined by physiological variables (lung function, reversibility and age of disease onset) or biomarkers (mainly eosinophils and neutrophils in induced sputum). The results showed that, in the severe asthma cohort, 30% and 48.6% of patients changed assignments based on physiological and biomarker clustering, respectively.[26,27]

In light of the available evidence, a trait-based approach is desirable as a possible replacement for guidelines for the management of severe asthma, until the mechanisms driving the broader and more comprehensive concept of asthma are conclusively established through further studies.

Asthma super-response and remission

Asthma is a heterogeneous disease characterized by variability in symptoms over time. Some people may enter a free-of-symptoms state with or without the resolution of the underlying disease.

Westerhof et al. conducted a longitudinal study that showed that approximately 16% of adults newly diagnosed with asthma can reach a remission phase (defined by the absence of symptoms and not requiring asthma medication for at least 1 year) within 5 years.[28] This remission state can be achieved spontaneously as an evolution of the natural history of the disease or also through optimized background therapy.

It is well known that, over the last years, asthma treatment goals radically changed from symptom control with reliever drugs to symptom prevention through anti-inflammatory drugs like ICS, long-acting β2 agonist bronchodilators, long-acting muscarinic receptor

antagonists and allergen immunotherapies, called 'disease-modifying anti-asthmatic drugs' aimed to modify the disease process.[29] In a study published in 2023, Couillard et al. proposed measuring inflammation and treating enrolled patients with anti-inflammatory therapy at an early stage, with a view to a predict-and-prevent model instead of the classic downstream firefighting approach.[30]

The new concept of disease modification in asthma comes from the evolution of asthma management, which contemplates phenotyping patients with different inflammatory endotypes characterizing the disease, and then the advent of effective therapies targeting proximal drivers of airway inflammation. This treat-to-target approach aims to achieve remission of the disease.[31] On-treatment disease remission is a concept historically first developed based on other diseases like polymyalgia rheumatica, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel diseases and antineutrophil cytoplasmic antibody-associated vasculitis, and was then applied to asthma, after overcoming the previous idea of remission as a spontaneous symptom-free condition or symptom-free state after completing a treatment.[32–36] This paradigm shift has been possible through the increased understanding of the pathobiology of asthma and the evident effectiveness of biological therapies in severe asthma. Currently, the definition of clinical remission 'on treatment' differs from that of a patient who is a super-responder to treatment and is limited to a good response to treatment.[37,38] In this regard, Menzies-Gow emphasized that asthma symptom control is still primarily oriented towards the patient's current clinical status and cannot be considered a treatment goal.[39] A consensus definition of the super-response to therapy in severe asthma came from a Delphi process published by Upham et al.,[40] who defined super-response to therapy as improvements in at least two of the main criteria (no exacerbations, >2 improvements in the minimum clinically important difference in asthma control, or no habitual use of OCS) and improvement in one of the minor criteria (>75% exacerbation reduction, >500 mL improvement in forced expiratory volume in 1 second (FEV_1) or well-controlled asthma). The current definition of super-response is mainly based on a number of clinical features, whilst many aspects of severe asthma inflammation and lung function are still poorly considered. Furthermore, many of the criteria of super-response to severe asthma tend to overlap with those of clinical remission, leaving room for possible misclassification.[41]

The evolution of knowledge in the pathobiology of asthma identified management needs and treatment goals. In 2020, Menzies-Gow et al. conducted a modified Delphi survey amongst asthma experts, aimed at deriving a consensus framework for asthma remission as a treatment goal. They divided the concept of remission into clinical and complete remission, on and off treatment, noting that complete remission (no evidence of inflammatory T2 biomarkers) was unlikely to be achievable in severe asthma but on treatment clinical remission was a pragmatical valuable goal.[39]

Clinical remission is defined as a period of at least 12 months without symptoms (assessed with validated tests like the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ)), stabilization or optimization of lung function, patient involvement and agreement about remission, and no use of systemic corticosteroids. Complete remission is defined as clinical remission with resolution of inflammation and bronchial hyperresponsiveness.[39] As the definition of clinical remission gained increased support in the scientific world in recent years, in 2023, national societies proposed different definitions of asthma remission, largely defining it as the treatment goal of the disease in their guidelines (Table 1).

The German Respiratory Society published new asthma guidelines for chest physicians in March 2023, in which asthma remission is defined by four criteria (for at least 12 months): sustained absence of asthma symptoms, sustained absence of exacerbations, stable lung function and no need for systemic glucocorticoids.[42] The Spanish Society of Pneumology and Thoracic Surgery updated their guidelines in March 2023, defining clinical remission as a condition that fulfils four criteria for at least 12 months, that is: absence of symptoms and exacerbations without the use of systemic steroids and optimization and stabilization of lung function. Furthermore, complete remission was defined as clinical remission plus the absence of bronchial hyperreactivity and bronchial inflammation for at least 12 consecutive months.[43] Similarly, the Japan Asthma Society introduced the concept of clinical remission in the Practical Guidelines for Asthma Management using criteria on symptom control (ACT >23 points), exacerbations (absence) and the use of systemic corticosteroids (zero use), omitting lung function as a necessary criterion to define remission.[44] The Severe Asthma Network Italy developed and published a Delphi consensus for asthma remission, dividing clinical remission into partial and complete. Partial clinical remission requires, for at least 12 months, the absence of OCS and two of three additional criteria (ACT ≥20, absence of exacerbations and/or stable lung function). Complete clinical remission is defined as no OCS use, ACT score ≥20, no exacerbations and stable lung function for at least 12 months.[45] Finally, an American College of Allergy, Asthma and Immunology, American Academy of Allergy, Asthma and Immunology, and American Thoracic Society workgroup has proposed a clinical remission definition, adding to the usual four

Table 1. Criteria for clinical remission from leading international scientific societies.

	Criteria for clinical remission					
	No asthma symptoms	**No exacerbations**	**No systemic steroids**	**Stable lung function**	**No missed work or school**	**Controller therapies ONLY at low-medium dose of ICS or less**
German Respiratory Society	✓	✓	✓	✓	–	–
Spanish Society of Pneumology and Thoracic Surgery	✓	✓	✓	✓	–	–
Severe Asthma Network Italy	✓	✓	✓	✓	–	–
ACAAI, AAAAI	✓	✓	✓	✓	✓	✓
Japan Asthma Society	✓	✓	✓	–	–	–

AAAAI, American Academy of Allergy, Asthma and Immunology; ACAAI, American College of Allergy, Asthma and Immunology; ICS, inhaled corticosteroids.

criteria of symptoms, exacerbations, lung function and OCS use, a criterion concerning the socio-economic burden of the disease (no missed work or school over 12 months) and a maintenance therapy criterion (continued use of controller therapies only at low–medium dose of ICS or less).[46]

Assessment of remission

To achieve clinical remission in a pragmatic and concrete dimension, clinicians should address multidimensional aspects concerning asthma. Reduction of asthma symptom burden, exacerbation risk prediction, prevention of lung function worsening associated with airway remodelling and absence of ongoing airway inflammation are actions that should be implemented to achieve a state of clinical remission. In this context, considering the duration of assessment and background medication is crucial to better understand the real course of the disease.[39]

The four-item composite definition derived by criteria from two expert consensus statements has been widely used by most studies in the literature including domains such as OCS use, exacerbations, lung function and symptom control.[39,40] Each domain can be evaluated with different criteria and different combinations of these criteria can be used to define remission. Because of the absence of exacerbations and no use of systemic corticosteroids are part of the definitions of clinical remission in all prior publications, the greatest variability of criteria concern lung function and patient-reported outcome (PRO) domains.

The role of lung function in the definition of clinical remission is still debated. Some patients with severe asthma may present poor lung function due to persistent underlying inflammation, not proportionally correlating with symptom burden.[47] Therefore, achieving spirometry values within the normal range could be challenging, if not unachievable.[48]

Given the heterogeneous nature of the disease, some people with asthma may present a normal lung function or develop incomplete reversibility, and given this variability, including lung function amongst criteria to define clinical remission could be an opportunity to avoid permanent, irreversible loss of lung function with early treatment.[49]

Some authors do not include lung function in their work on treatment clinical remission,[50,51] others analyse the data difference on the primary outcome (clinical remission) considering different criteria of the lung function domain. Breslavsky et al. conducted a cross-sectional study on adult patients receiving biological agents for severe asthma (omalizumab, reslizumab, mepolizumab, benralizumab, dupilumab) for at least 6 months, comparing different remission criteria in the four domains; they showed that more patients achieved a FEV_1 improvement >100 mL (76%) compared to lung function normalization, defined as FEV_1/forced vital capacity >0.75 (48%).[52]

Oppenheimer et al. confirmed that strict criteria on lung function could significantly reduce the number of patients achieving remission according to the definition. They demonstrated that by including a criterion of predicted post-bronchodilator FEV_1 >80% in the remission definition, ~30% fewer patients achieved remission *versus* the number of patients with the three-component definition (without lung function). Furthermore, using the change from baseline in post-bronchodilator FEV_1

categories, patients who achieve remission progressively increase with decreasing post-bronchodilator FEV_1 improvement.[53]

To date, no data exist about small airway disease in clinical remission. Evidence from histological and pathophysiological studies indicates that the distal airways of people with asthma undergo major structural changes that are often irreversible, associated with long-lasting inflammation that appears to influence measures of lung function. Structural changes in the distal airways were also evident in patients receiving ICS therapy, suggesting that this therapy did not adequately control inflammation at this level.[54] Cefaloni et al., in their cross-sectional study including 42 patients with uncontrolled severe asthma, distinguished into two cohorts depending on the presence of persistent airflow limitation (FEV_1/forced vital capacity post-bronchodilator <70%), showed that severe asthma with persistent airflow limitation presents a peculiar phenotype characterized by more impaired lung function and significant involvement of distal lungs.[55] Furthermore, the same working group demonstrated benefits on small airway disease with biological treatment with mepolizumab in 20 people with severe asthma, in parallel with improved lung function and asthma control.[55] In a retrospective observational study conducted on 150 patients with respiratory symptoms but no evidence of spirometry obstruction, Dhar et al. showed small airway disease in 79% of the patients (assuming cut-off >0.7138 kPa/Ls for derived resistance at 5 Hz minus 20 Hz (R5-R20)).[56]

However, to achieve the best results, patient perspectives on the benefits of treatment must be considered. Asthma guidelines recommend sharing the definition of disease control with the patient to achieve mutual agreement on a realistic treatment goal. Frequently, absolute asthma control is an unrealistic goal, especially for patients with severe asthma, so much so that focusing on day-to-day management rather than the long-term approach seems to be the best management of disease control.[57]

Asthma treatment goals include the reduction of disease burden and the improvement of quality of life of patients, measured with validated and pre-established questionnaires. One of the crucial topics on clinical remission is the differences between good control and total control, because real-life disease management leads to a balance between achievable control and total control.[58]

The ACQ is a validated and standardized instrument routinely used to assess the effectiveness of therapeutic interventions in asthma clinical trials, though the quality of the data may be influenced by the patient's recollection of symptoms in the previous period.[59] On the other hand, the Global Strategy for Asthma Management and Prevention recommended keeping track of asthma symptoms twice daily with a diary.[1] Using clinical trial data, Singh et al.[60] compared results with ACQ at baseline and at weeks 26 and 52 with results from eDiary, testing the hypothesis that ACQ and eDiary assessments of asthma control may differ. Data showed a higher proportion of patients meeting the ACQ-6 definition than the eDiary definition of uncontrolled asthma, with a similar improvement over time. The authors suggest including the use of both eDiary and ACQn clinical trials, as electronic clinical outcome assessment software, such as eDiary, more accurately reflects a patient's level of asthma control, whilst ACQ makes it easier to compare studies.[60]

Of note, ACQ-6 or the ACT are PROs, which evaluate asthma impairment but not risk, with an important limit on the assessment of asthma control.[61]

In addition, the low rates of ACQ score response at the threshold <0.75 compared to other objective domains of remission (exacerbation rate, lung functions) suggest other drivers of symptom perception beyond disease (i.e. deconditioning), especially in patients with a long history of asthma coexisting with chronic symptoms associated with therapy side-effects or comorbidities. Indeed, severe asthma ACQ cut points are not established, and thus this can be an inappropriate score for patients with a fixed airflow limitation. Therefore, a more comprehensive and objective grading of PROs in the assessment of asthma control is necessary for a definition of remission.[62,63]

Clinical remission and biological agents in the real world

Currently, there is a growing interest in asthma remission as a treatment goal, particularly in severe asthma treated with biologics. The efficacy of biologics may enable improvement in the four domains of the definition of clinical remission under treatment (zero exacerbations, zero OCS use, improved lung function and symptom control) in many patients. However, the prevalence of clinical remission in severe asthma treated with biologics in real life is not completely clear.

Recent data are available in the literature regarding the efficacy of anti-IL-5 and anti-IL-5R inhibitors leading to clinical remission in the real world.[64–70] Additionally, for biologics targeting IL-4/IL-13R, evidence on the ability to achieve on-treatment clinical remission is starting to become available, including retrospective comparisons with the other biologics.[71,72] Conversely, to date, no real-world evidence has been published on tezepelumab

due to the recent introduction of this biologic, but a *post hoc* exploratory analysis of the phase III DESTINATION study assessed the proportion of patients who received tezepelumab achieving on-treatment remission over 2 years.[73] In this study, about 27% of patients in the treatment group achieved on-treatment clinical remission at week 104.

In this regard, asthma registers can also provide useful and important evidence; results on the International Severe Asthma Registry confirm the effectiveness of all biologics in leading to clinical remission.[74] In this regard, a multi-country (n=23), registry-based study on 3348 adults with asthma remission in four endpoints was achieved in 18.7%.[74]

Table 2 summarises the main studies published so far on this topic.

Standard-of-care background medication reduction

The current backbone of asthma treatment remains the use of ICS; however, as ICS therapy does not always modify the underlying pathophysiology of asthma, other treatment options had to be investigated. Considering the successful development of disease-modifying treatments in other settings, a practically achievable and pragmatic goal of asthma therapy is disease remission.[75] New therapeutic options, such as biologics, have been shown to have potentially disease-modifying characteristics despite data being observed in studies based on small sample sizes and short durations.[76] The European Academy of Allergy and Clinical Immunology guidelines on the management of biologic therapies in severe asthma state that none of the currently available biologics have demonstrated concrete disease-modifying effects and that all patients showed a decline in efficacy soon after discontinuation.[77] In clearer terms, discontinuation of treatment almost systematically results in a worsening of asthma control, with increased rates of exacerbations and the frequent need for courses of OCS.[78]

The efficacy of monoclonal antibodies in terms of dose reduction of the usual asthma drugs, such as ICS and OCS, has much more evidence.[79] A large body of literature confirms that biologics such as omalizumab, dupilumab and others allow simultaneous reduction of exacerbations and maintenance dose of ICS.[80,81] SHAMAL was a phase IV, randomized, open-label, actively controlled study of 168 patients[82] that was the first clinical trial to prospectively assess clinical remission amongst patients with severe asthma; nearly all patients (92%) had well-controlled disease with benralizumab add-on and were able to reduce their dose of ICS/formoterol by week 32: of these, 15% reduced to a medium dose, 17% to a low dose and 61% to a relief dose only. An even more interesting aspect was that more than 90% of patients in the treatment reduction arm did not experience any exacerbations during the reduction period despite the ICS/formoterol dose reduction, and more than 50% of patients who reduced background medication met the definition of clinical remission at week 48. In a recent 36-month real-life Italian multicentre study in patients with severe eosinophilic asthma, benralizumab not only reduced the exacerbation rate by 89% but also reduced OCS, ICS and other asthma drugs in 93% of patients. Overall, 84.3% of enrolled patients achieved partial or complete clinical remission.[83]

Over the years, the OCS-sparing effect of biologic drugs has been extensively studied, and there is now plenty of solid evidence. The current monoclonal antibodies have been shown to induce an OCS-sparing effect in randomized trials, effectively overcoming the main problem of OCS dependence in severe asthma.[84] In patients where resistance or dependence on OCS is demonstrated by high daily doses, current monoclonal-based therapeutic options often allow reversal of OCS dependence, leading in many patients to weaning from OCS therapy or at least a greater than 50% reduction in maintenance dose compared to baseline.[85–87] A systematic review highlighted how, in patients with OCS-dependent asthma, benralizumab, dupilumab and mepolizumab were effective in obtaining a significant reduction in the dose of OCS. This indirect comparison revealed no significant differences between the biologics examined.[88]

New evidence beyond clinical aspects

Beyond the important clinical aspects of remission, there is evidence concerning the effect of biologics on bronchial remodelling, bronchial hyperreactivity, ventilation and impact on small airways and mucus plugs. In an elegant and interesting study by Svenningsen et al.,[89] the anti-IL-4/IL-13 dupilumab biologic improved computed tomography (CT) biomarkers of mucus, airway remodelling and gas entrapment, improved ventilation assessed by magnetic resonance imaging (MRI) 129Xe, and parameters of small airway function assessed by oscillometry with improvement of respiratory system resistance 5–19 Hz and area of reactance. In this trial, patients with a higher mucus load at baseline were those who experienced greater improvements in lung function, ventilation and a higher reduction in mucus obstruction, which is confirmed as a relevant mechanism by which dupilumab improves lung function.

The VESTIGE trial (NCT04400318), a new imaging study, confirmed the effects of dupilumab on the reduction of airway inflammation and its functional structure.[90] Greater improvements compared to baseline

Table 2. Main real-world studies on clinical remission.

Study	Timing	CR criteria	Number of patients	Drug	% CR achieved
Pelaia et al.[50]	96 weeks	• Zero exacerbations ACT ≥16 or ACQ-6 <1.5 • No maintenance OCS use	1070	Benralizumab	37.5%
Maglio et al.[64]	12 months	• Zero exacerbations • Zero use of OCS • ACT score >20 • Pre-bronchodilator FEV_1 >80% predicted	83 30 Tot. 113	Mepolizumab Benralizumab	30% 40%
Núñez et al.[65]	12 months	• Zero exacerbations • Zero use of OCS • ACT score >20 • Improvement in FEV_1	22 24 Tot. 46	Mepolizumab Benralizumab	50% 45%
Kavanagh et al.[66]	12 months	• Super-responders • Exacerbation free • Zero use of OCS	99	Mepolizumab	28.3%
Kavanagh et al.[67]	48 weeks	• Super-responder • Zero exacerbations • Zero use of OCS	130	Benralizumab	39%
Xu et al.[68]	12 months	• 3-way clinical remission • Zero exacerbations, zero use of OCS, ACT >20 • 4-way clinical remission • Stabilization in lung function	170	Mepolizumab	28% 3-way clinical remission 23% 4-way clinical remission
Eger et al.[69]	2 years	• No chronic OCS use • No OCS bursts in the past 3 months • ACQ score less than 1.5 • FEV_1 at least equal to 80% of predicted • FeNO less than 50 ppb • Complete control of comorbidities	114	Mepolizumab Benralizumab Reslizumab	14%
Bagnasco et al.[70]	3 years	• Six different published sets of remission criteria	3348	Mepolizumab	51–73%
Portacci et al.[71]	12 months	• Zero exacerbations • Zero use of OCS • ACT ≥20 • FEV_1 improvement ≥100 mL from baseline	18	Dupilumab	38.9%
Sposato et al.[72]	12 months	• Zero exacerbations • ACT ≥20 • Zero use of OCS FEV_1% ≥80%	302 55 95 34 Tot. 486	Omalizumab Mepolizumab Benralizumab Dupilumab	21.8% 23.6% 35.8% 23.5%
Scelo et al.[74]	12 months	• Zero exacerbations • Zero LT-OCS use • Partly/well-controlled asthma • FEV_1 pred. >80%	3348	Omalizumab Mepolizumab Benralizumab Dupilumab	18.7%

ACQ-6, Asthma Control Questionnaire; ACT, Asthma Control Test; CR, clinical remission; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LT-OCS, long-term OCS; OCS, oral corticosteroids; ppb, parts per billion.

were observed in airway volumes (primary endpoint), in resistance to total lung capacity and in the change from baseline in the high-resolution CT mucus plug score. Finally, a significant reduction was observed in the mucus plug score for dupilumab compared to placebo (least squares mean difference: 24.92, standard error: 0.798, nominal $p<0.001$). Mucus plugs represent one of the many treatable features of asthma, and eosinophilic inflammation and the action of IL-13 play a crucial role in their formation. The impact of mucus plugs on asthma severity was also highlighted by McIntosh et al. in a study where a single dose of the anti-eosinophil benralizumab showed significant improvement in ventilation with Xenon-129 in patients with refractory asthma and significant mucus plugging.[91]

Clinical remission as an aspirational outcome

In a recent review by Busse et al.,[47] the authors discussed the concept of clinical remission as the main aspirational outcome in modern asthma management, similar to the past practice with other chronic diseases in which remission has long been considered a goal. The importance of shared decision-making between patients and healthcare providers to improve outcomes and achieve clinical remission is also emphasized. From our perspective, in order to provide concrete answers and truly achievable goals for clinicians, it is necessary to pragmatically address all the multidimensional aspects surrounding this issue.[92] A more widespread use of PROs would provide important and useful information regarding patient perspectives on the benefits and harms of treatment, measuring them beyond survival, exacerbations and biomarkers.[93] In addition, PROs in clinical practice can improve and strengthen patient involvement in their care taking this point of view into greater consideration. However, in order to achieve the best results, it would be essential to define an objective grading of PRO response that can be used easily and immediately, such as measuring the reduction of lost work or school days or improved exercise capacity. According to guidelines, ICS are the backbone of asthma management. However, even ICS treatment may be associated with some risk of local side-effects, and long-term high-dose therapy may lead to adverse effects that are also systemic. In addition, ICS treatment may be less effective in non-T2 asthma, so patients with low levels of T2 biomarkers are at risk of being exposed to excessive doses of ICS. Therefore, a proper treatment regimen with ICS guided by biomarkers (such as FeNO) reflecting the inflammatory phenotype is more appropriate. In this context, as highlighted by the recent SHAMAL study,[94] managing tapering of high-dose ICS when severe asthma is well controlled by add-on benralizumab by being guided by biomarkers may be justified to reduce corticosteroid burden in patients with T2-high and non-T2 asthma. Corticosteroid tapering based solely on biomarkers did not always result in a higher percentage of patients reducing their ICS dose compared to the control group. It is therefore crucial to understand what the most effective and practical strategy might be, in which certainly the measurement of respiratory function cannot be forgotten. In the case of a patient included in an ICS tapering process, the stability or reduction of FEV_1 cannot be ignored, especially from a long-term perspective and in relation to an increased risk of loss of asthma control.[95] Consequently, a pragmatic and multidimensional strategy could be the most concrete approach (Box 1). In conclusion, in a constantly changing management of asthma, the definition of common all-encompassing parameters is certainly a priority to allow clinical remission or complete remission to be achieved in as many patients as possible. This is certainly no longer a utopian goal but a concrete and achievable reality.

Box 1. **Asthma clinical remission on treatment criteria.**

All the following criteria must be met over a 12-months period and may be applied to those receiving monoclonal antibody therapy (biologic) for asthma:

1. NO exacerbations requiring a physician visit, emergency care, hospitalization, and/or systemic corticosteroid for asthma (i.e. oral, injectable)
2. NO missed work or school over a 12-months period due to asthma-related symptoms
3. Stable and optimized pulmonary function results on all occasions, when measured over a 12-month period, with ≥2 measurements during the year
4. Continued use of controller therapies ONLY at low-medium dose of ICS, or less, as defined by most recent GINA strategy
5. ACT >20, AirQ <2, ACQ-6 <0.75, evaluation of significant PROs modification after therapy
6. Agreement of both patient and healthcare professional regarding disease remission

ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; AirQ, Asthma Impairment and Risk Questionnaire; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting bronchodilator; PROs, patient-reported outcomes.

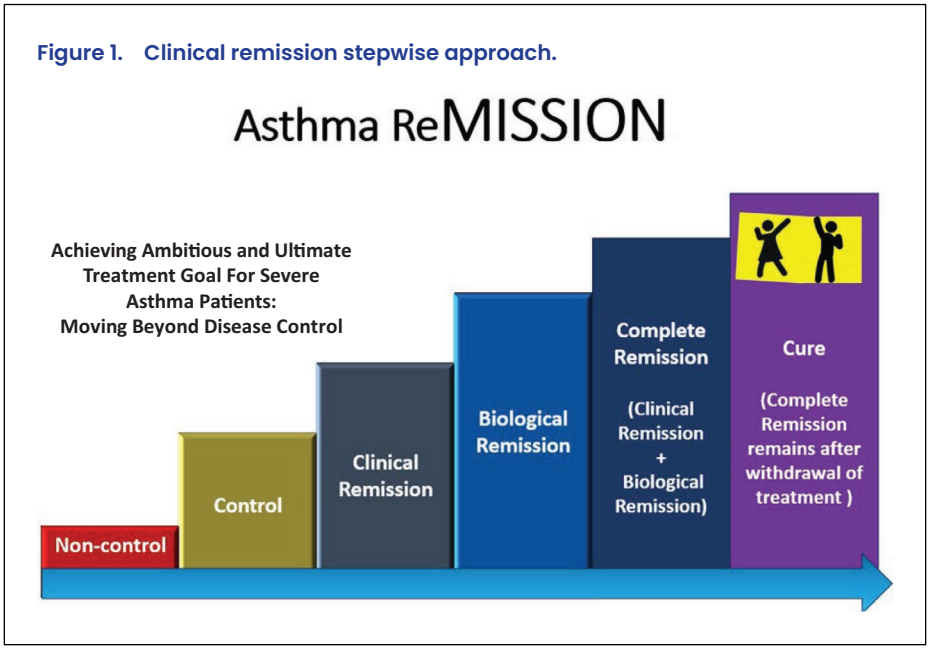
In other chronic conditions, such as rheumatic diseases, low disease activity is considered a crucial component of remission. In patients with established rheumatoid arthritis, the main therapeutic goal is to achieve low disease activity rather than simple remission. For these patients, remission of the disease, with or without treatment, and dropping the large burden of medication, are ambitious goals that can significantly improve quality of life and even prognosis. In asthma, expert consensus defines complete remission as clinical remission and current, objective evidence of resolution of previously confirmed inflammation and bronchial hyperresponsiveness.[96] Clinical remission should therefore be considered a clinically valid goal with the enormous potential to generate truly life-changing benefits, allowing patients to progressively transition from 'no control' to 'cure' (complete remission that remains after withdrawal of treatment; Figure 1).

Conclusion

The currently available data leave many questions open as to why clinical remission cannot always be achieved. An interesting study by Milger et al. analysed a cohort of 210 patients with severe asthma on biologic therapy.[97] To define clinical remission, an ACT result of 20 or more, no exacerbations in the previous 12 months, no OCS intake and an increase in FEV_1 of 100 mL or more were used as criteria.[97] Of the patients examined, only 32.1% achieved remission. Another interesting finding was that 9.5% of patients not receiving biologics also fulfilled the same criteria. If the stricter requirement of improved lung function is not considered, remission rates are only increased to 37.6%. The super-response rate to biologics is higher than the remission rate of 61.4% (eliminating the FEV_1 criterion). It must be understood in the context of a corresponding super-response rate of 34.8% in the group of patients not receiving biologics.

In the future, the most important aspect will be to identify the reasons why two-thirds of patients with severe asthma fail to achieve remission with biologics. Additionally, to what extent comorbidities contribute to sub-optimal outcomes either due to insufficient suppression of specific target pathways or as a consequence of concomitant activation of other inflammatory pathways that are not properly targeted by biologic agents needs to be addressed. Longitudinal comparison of biomarkers between patients reaching and not reaching remission could also be very important as well as better framing the role of airway remodelling. Clinical remission is an achievable goal with the potential to generate life-changing benefits for patients. It encompasses freedom from OCS use and exacerbations and complete symptom control; for these reasons, it differs substantially from the clinical response, which reflects reduction but not complete freedom from OCS use and exacerbations and improved control instead of complete symptom control. The trait-based approach is associated with superior outcomes, as in addition to gaining a better understanding of asthma phenotypes, which may help to better stratify clinical risk factors leading to sub-optimal control, the identification of patients with a higher risk of poor asthma control through accurate and continuous biomarker monitoring may allow for earlier, more targeted and more effective interventions.

Figure 1. Clinical remission stepwise approach.



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