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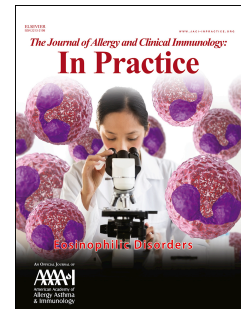
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How Do Asthma Biologics Relate to Remission for Asthma?

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Abstract

Asthma treatments have evolved from bronchodilators to interventions directed towards the regulation of airway inflammation. From these advances has come greater disease control and reduced morbidity. The addition of biologics directed toward specific pathways of inflammation have advanced the efficacy of asthma control. With these treatment advances, a renewed interest in achieving a remission in asthma has arisen. Although asthma remission has been considered to reflect a “cure,” new evaluations of this concept have proposed criteria for remission while on treatment. These criteria reflect a high level of disease control including absence of symptoms, optimization and stabilization of lung function, and absence of the use of systemic corticosteroids and have been proposed to indicate a remission of disease activity. Given the added efficacy found with biologics in asthma treatment for patients with moderate-to-severe disease, the question has arisen as to whether the use of biologics meets criteria for remission and may this change a component of underlying disease and risks. Biologics are highly effective in reducing exacerbations, diminishing symptoms and improving lung function in well-defined asthma populations. At present, however, biologics achieve some, but in most cases not all criteria for a remission on treatment. However, the concept of promoting treatment efforts to achieve disease remission in asthma is important, potentially achievable, and merits consideration for future guideline-directed care approaches.

Keywords

Asthma; Remission; Treatment; Consensus; Lung; Biomarkers; Inflammation; Surveys and
Questionnaires; Respiratory Hyperresponsiveness; Airway Remodeling; Asthma Biologics

List of Abbreviations – obtained from remission paper – to be revised

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
COPD	Chronic Obstructive Pulmonary Disease
FeNO	Fractional exhaled nitric oxide
FEV ₁	Forced expiratory volume in 1 second
FVC	Forced vital capacity
IL	Interleukin
PROSPERO	Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab

Introduction

Over the last 80 years, there have been significant advances in asthma therapy resulting from interactions between clinical care, broad-spectrum science efforts and the pharmaceutical industry (**Figure 1**).¹ Attention in the mid-1970s was directed toward relieving symptoms and airflow obstruction with a therapeutic focus placed on β -adrenergic agonists.¹ In the 1980s, airway inflammation was recognized as a critical and causative feature of asthma and that certain medications could block allergic reactions leading to development of inhaled corticosteroid (ICS) therapy.¹ In the 1990s, ICS therapy emerged as the cornerstone of asthma management with bronchodilators serving as reliever therapy or supplementary therapy.¹ A major limitation of ICS therapy has been its failure to alter the natural history of asthma, including asthma progression.² The early 2000's witnessed the introduction of asthma biologic therapies, initially with anti-IgE (omalizumab), followed 10 years later by the approval of anti-eosinophilic therapies (mepolizumab, benralizumab, reslizumab) and more recently anti-interleukin (IL)-4/-13 directed treatment (dupilumab).¹ The latter agents have noteworthy properties of decreasing asthma exacerbations and oral corticosteroid exposure. Biologics in development against epithelial derived cytokines hold great promise to fundamentally alter the airways inflammation that is driving asthma. It remains to be seen whether biologics can alter the course of asthma by inducing remission, preventing disease progression or perhaps even blocking the onset of asthma. In managing populations of asthma patients, for example, in a medical system, principles of individualized therapy based on biomarkers, genetics and patient characteristics will be incorporated in selecting asthma medications.¹

This review will consider current concepts of asthma remission, evaluate experience suggesting that biologic therapies may have the potential to induce remission, review the steps necessary to determine how we could evaluate a medication's capability of inducing remission and how we might apply this methodology to current clinical management.

What does remission mean in asthma?

The established paradigm of asthma management aims to improve asthma control with any definition of asthma remission being of theoretical interest at best.³ Improved understanding of the pathophysiology of asthma, in combination with the development of targeted biologic therapies with improved control of disease, however, mandates the development of an asthma remission definition, as it may now, or soon, be an achievable treatment target and become a component of guideline-directed care.

When formulating a definition of asthma remission, it is logical to review the literature to understand how remission is defined in other chronic inflammatory conditions. A structured literature search identified six diseases with established definitions of remission,⁴ including rheumatoid arthritis and inflammatory bowel disease. When reviewing these definitions, it becomes clear that remission can be subdivided into clinical and inflammatory components and that all definitions allow for the continuation of at least some background therapy. For instance, the ACR/EULAR 2011 provisional definition of rheumatoid arthritis remission⁵ contains a core set of clinical and biomarker parameters that are easily measurable in trials and routine clinical practice, which predict a good outcome, but are severity, duration and medication independent.

We have to be careful when designing, and applying, a definition of asthma remission. If, for example, we set the bar too high, e.g. no symptoms, no inflammation on no therapy for a prolonged period of time, we are approaching cure, which, at the moment, is not achievable. Moving from asthma control to asthma remission should be viewed as an important step on the journey towards asthma cure rather than as the final destination.

To see whether remission is an achievable goal, it is also of benefit to ascertain whether asthma remission can occur spontaneously. A review of the published literature⁴ has demonstrated that spontaneous remission can occur in both early⁶ and late onset⁷ asthma. The incidence of spontaneous remission varies between 1.5 and 33.3% across studies based on the definition applied.⁴ Clinical remission definitions focus on patient reported symptoms and medication burden, whereas complete remission definitions include additional requirements including normalization of lung function, airways inflammation and absence of bronchial hyperreactivity.

Given the evidence confirming that an asthma remission is possible as part of the natural history of the condition and the development of disease remission definitions for other chronic inflammatory conditions in which biologic agents are available, it is timely to develop and iterate a remission definition for asthma. One key issue for an asthma remission definition to take into account is the variability of the disease over time. Any remission definition needs to be durable and there remains significant debate regarding how long patients need to meet the definition before they are 'in remission.' Asthma remission has to be more than prolonged phase of control

and, at the same time, needs to be testable in clinical trials, clinically relevant and measurable in routine clinical practice.

In an attempt to produce an initial remission definition to promote wider discussion and iteration, a modified Delphi survey approach was used to gain expert consensus on the core components of an asthma remission definition.⁴ After reviewing remission definitions for other chronic inflammatory conditions and the evidence based on a spontaneous asthma remission, the consensus view was that symptoms, exacerbations, asthma control, airways physiology and inflammation were all important components of the proposed definition. A generalized framework for definitions of clinical and complete remission, on and off treatment, was developed, producing four subtypes of asthma remission ranging from clinical remission on treatment to complete remission off treatment (**Figure 2**). Complete remission is the goal for all patients, but may not always be achievable or measurable, in which case the focus should switch to clinical remission. Similarly, whilst remission off all treatment is the ultimate goal, this may well not be achievable with currently and soon to be available therapies, in which case remission on treatment remains a valuable treatment target and will be the focus of our discussion.

Does the use of biologics lead to a remission in asthma?

The use of biologics for severe asthma has provided therapeutic efficacy to achieve disease control when standard guideline-directed treatments are not effective. Five monoclonal antibodies (**Table 1**) are currently approved for use in severe asthma and target components of Type (T)2 pathways of inflammation, including IL-4, -5 and -13, which are present in

approximately 70% of asthma patients.^{8,9} Given the added efficacy achieved when biologics are added to previous treatment that did not produce disease control, do the associated improvements in disease control reflect an asthma remission? The following discussion will consider whether biologic treatment in severe asthma meets noted criteria for an asthma remission (**Figure 2**).

Our discussion will focus on outcome features that align with “Clinical Remission on Treatment:” (1) sustained absence of significant asthma symptoms based upon a validated instrument, (2) optimization and stabilization of lung function, and (3) no use of systemic corticosteroid therapy for exacerbation treatment or long-term disease control.

Omalizumab was approved for severe allergic asthma in 2003 and has a longstanding record of safety and efficacy with a primary efficacy outcome of a prevention of exacerbations.¹⁰ What has been learned about omalizumab’s effects on features of remission? PROSPERO (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab)¹¹ was designed to evaluate the efficacy of omalizumab in a real-world, open-label design. A number of findings from PROSPERO provide insight into omalizumab’s effect on criteria for an asthma remission. 622 patients who were enrolled in PROSPERO by their physicians based upon an appropriate need for “next-step” treatment. Measures of disease control monitored during omalizumab treatment included exacerbations, health care utilization, and asthma control by the Asthma Control Test (ACT). The investigators pre-specified responder criteria, which included changes from uncontrolled to controlled as measured by an ACT score ≥ 20 at study completion. They also measured the effects of omalizumab on exacerbations, but at a pre-specified 50% reduction from baseline, not an absence as defined for a remission. At

baseline in PROSPERO, 83.8% of the enrolled subjects had uncontrolled asthma (ACT <19). About 50% of the uncontrolled subjects achieved asthma control while on omalizumab, e.g. ACT ≥ 20 . Symptom control (i.e. ACT) responders had higher baseline blood eosinophil levels, ≥ 300 cells/ μ L. Exacerbation rates were also reduced by omalizumab treatment, falling from a mean baseline value of 3.00 ± 3.34 events in the previous 12 months to 0.78 ± 1.37 exacerbations ($p < 0.001$) on omalizumab. Moreover, 62.7% of subjects experienced no exacerbations with omalizumab during PROSPERO. The investigators also conducted responder analyses, which they defined as meeting one or more pre-defined responder criteria. 77.8% were considered responders by a 50% or more reduction in exacerbation, and 64.7% were responders by improved ACT, which was a minimally important difference in ACT of 3 or greater. When considering a responder by two criteria, ACT and exacerbation, 54.1% were responders. Thus, a portion of the PROSPERO subjects met two criteria of remission: absence of exacerbations and improved symptoms. Lung functions did not improve. Whether the degree to which omalizumab achieved features of an asthma remission relates to its treatment target, e.g. IgE vs cytokines, is not established.

Anti-cytokine biologics

IL-4, -5, and -13 are the central mediators for T2 inflammation.¹² Monoclonal antibodies directed against IL-5 and IL-4/IL-13 are approved for treatment of severe asthma (**Table 1**). Collectively, but to varying degrees, T2 antagonists prevent asthma exacerbations, improve airflow obstruction, and reduce symptoms, all target features incorporated into the definition for remission. Furthermore, as will be reviewed, long-term observation periods with some

monoclonals provide enriched insight into achievement of remission over an extended timeframe.

Anti-IL-5 treatment

Mepolizumab was the first monoclonal antibody directed against IL-5 to demonstrate efficacy in large-scale, placebo-controlled, randomized trials¹³ and was approved for clinical treatment of severe, eosinophilic asthma in 2015. MENSA¹⁴ compared two doses and routes of administration of mepolizumab (75 mg every 4 weeks intravenous and 100 mg every 4 weeks subcutaneous vs placebo) in a 32-week trial with a primary outcome of the annualized frequency of exacerbations. Secondary outcomes included changes in FEV₁ and patient-related outcomes: Asthma Control Questionnaire (ACQ)-5 and St. George Respiratory Questionnaire (SGRQ). Both mepolizumab doses significantly reduced the frequency of asthma exacerbations, 75 mg intravenous by 47% (p <0.001) and 100 mg subcutaneous by 53% (p <0.001). In addition, both mepolizumab doses improved baseline and post-bronchodilator FEV₁ values (100 ml over placebo with intravenous mepolizumab (p=0.02) and 98 ml over placebo with subcutaneous mepolizumab (n=0.03). These improvements did not restore normal lung function. Although ACQ-5 values improved, the degree of change did not exceed the mean clinical significant improvement of 0.5 as a group. What was not established in this study is the frequency of patients who met criteria for an asthma remission. The impact of biologic interactions on remission cannot be made with group mean data, but rather responder analyses.

COLUMBA¹⁵ was an open-label extension of subjects who had received mepolizumab in the DREAM study.¹³ The mepolizumab dose for COLUMBA was 100 mg subcutaneous every 4

237 weeks. The COLUMBA trial design had inherent complexities. Prior to subject enrollment in
238 COLUMBA, the COLUMBA enrolled subjects had a 17.8 month interval (median value) off
239 treatment with mepolizumab following DREAM. Once enrolled, the mean duration of
240 mepolizumab treatment in COLUMBA was 3.5 years.

241
242 COLUMBA enrolled 347 patients, mean age of 52.2 years, with 65% being females. The
243 annualized rate of exacerbations during treatment in COLUMBA was 0.68 events/year; this
244 represents a 61% reduction in exacerbations from that experienced during the off-treatment
245 period following completion of DREAM¹³ and eventual enrollment in COLUMBA (**Figure 3**).
246 The effect of mepolizumab on exacerbations was seen equally in patients with early onset
247 asthma, <33 years and late onset asthma ≥ 33 years. Furthermore, 33% did not experience an
248 exacerbation while on mepolizumab over the 3.5 year average duration of COLUMBA. In
249 COLUMBA, interestingly, sustained beneficial effects on lung functions did not parallel the
250 long-term reductions in exacerbation risks. By week 200, the initial improvements in FEV₁ were
251 lost. Symptom control was also improved and sustained in COLUMAB with a mean reduction in
252 ACQ-5 by 0.47 points. Approximately 50% of the subjects had a mean improvement (decrease in
253 score) of 0.5 or more. There are no data on the percentage of subjects who had both a sustained
254 prevention of exacerbations and improved symptom control. However, from the data available,
255 mepolizumab's sustained effects, in relation to achieving a remission, were gained primarily by a
256 prevention of exacerbation in 33% of subjects.

257
258 Benralizumab is directed against the IL-5R, reduced exacerbation rates, and improved
259 FEV₁ values in the pivotal clinical trials.^{16, 17} The targeted peripheral blood eosinophil values for

associated efficacy is ≥ 300 cells/ μ L. A subsequent analysis by Fitzgerald and colleagues of these two major trials^{16, 17} to identify the clinical characteristics to predict improved outcomes found, in an unbiased analysis, that previous rates of exacerbations, baseline eosinophil counts and baseline lung functions, were criteria which most consistently predicted reductions in exacerbations by benralizumab.¹⁸ In addition, baseline lung functions, particularly if accompanied by reversibility and elevated eosinophil counts, predicted an eventual improvement in FEV₁. These analyses provide historical and biomarker values to predict beneficial outcomes and, possibly, identify asthma patients most likely to reach criteria of a remission, or partial remission.

To more fully assess sustained effects of benralizumab and effects on criteria of a remission, BORA,¹⁹ which was a double-blind, randomized, parallel-group phase 3 extension trial with subjects who had completed either the SIROCCO¹⁶ or CALIMA¹⁷ trial. Patients on active benralizumab in SIROCCO (48 weeks) and CALIMA (56 weeks) continued benralizumab for an additional 56 weeks in BORA to provide a two-year assessment of treatment. Subjects who received placebo in the initial trials were given benralizumab, either 30 mg q 4 weeks or q 8 weeks, for 56 weeks. The final analysis included 1576 patients. Of the 1046 subjects with blood eosinophil counts ≥ 300 cell/ μ L, 753 (72%) did not experience an exacerbation in BORA. In contrast, for subjects with eosinophils < 300 cells/ μ L, benralizumab had no effect on exacerbation rates. Subjects who had received benralizumab during SIROCCO or CALIMA continued to maintain improved FEV₁ values, but not consistently when baseline eosinophils were < 300 cells/ μ L (**Figure 4**). Thus, data on “long-term” effects with benralizumab suggest that significant populations of patients with eosinophil counts ≥ 300 cells/ μ L meet features of

remission: prevention of exacerbation, stabilized improved lung function and symptom control, ACQ-6 <1.5.

Anti-IL-4/IL-13

Dupilumab binds to IL-4R to block the IL-4/IL-13 pathway, which contributes to many aspects of airway inflammation and altered lung function.⁹ Clinical trials with dupilumab have found a nearly 50% reduction in exacerbations, improved lung function, and lessening of symptoms.²⁰ In the Liberty Asthma Quest clinical trial, Castro et al reported on 1,902 evaluated subjects who were 12 years of age or older and received 52 weeks of treatment.²⁰ The active treatment arms included dupilumab, 200 mg or 300 mg every two weeks, versus respective placebo.²⁰ Both treatment dosing regimens significantly reduced severe asthma exacerbations: 47.7% with 200 mg dupilumab and 46.0% with 300 mg dupilumab, overall and irrespective of peripheral blood eosinophil counts. The greatest prevention of exacerbations to both doses of dupilumab was seen with peripheral eosinophils of ≥ 300 cells/ μ L. Subjects with eosinophils <150 cells/ μ L had a similar frequency of exacerbations to placebo. The clinical trial data do not indicate the frequency of subjects who experienced no exacerbations with dupilumab and would, therefore, be considered a remission responder. The target group for greatest efficacy was in subjects with FeNO ≥ 25 ppb and eosinophils ≥ 150 cells/ μ L (**Figure 5**).

Lung function improvement was a secondary outcome in QUEST. FEV₁ improvements were apparent following 2 weeks of treatment and maximal at the 12-week treatment interval and then sustained. Statistical improvements in FEV₁ were noted when blood eosinophils were ≥ 150

cells/ μ L but maximal with eosinophils ≥ 300 cells/ μ L. Post-bronchodilator FEV₁ values at study's completion showed a 40 ml loss of volume in the placebo-treated groups over the year-long study, but there was no loss of FEV₁ with dupilumab. Whether this protective effect on lung function indicates that dupilumab prevents the progressive loss of lung function seen in asthma and represents a "remission" in disease progression, is not established. It will be helpful to do sub-analyses on dupilumab-treated subjects to determine the frequency of patients who reach criteria for remission and what are their phenotypic characteristics.

Effect of reductions of systemic corticosteroids with biologic treatment on asthma control

The need for systemic corticosteroid treatment to maintain disease control identifies asthma patients with the most severe disease and greatest recalcitrance to current treatment approaches. In considering whether biologics may contribute to asthma remissions, an argument can be made that a reduction, or elimination, of systemic corticosteroids leads to a remission of a component of severe asthma. Evaluations of the effects of biologics in these patients are, we believe, important to consider in our discussion on remissions.

Rabe et al²¹ reported on glucocorticoid sparing effects with dupilumab with 210 patients enrolled and randomized to either dupilumab, 300 mg q 2 weeks or placebo. Following a systemic corticosteroid adjustment to establish baseline prednisone requirements, a downward corticosteroid adjustment was made from week 4 to week 20, with the primary endpoint being the percentage reduction in the systemic glucocorticoid dose. Key outcomes with dupilumab vs placebo were: glucocorticoid reduction, $70.1 \pm 4.9\%$ vs $41.9 \pm 4.6\%$ ($p < 0.001$); no longer

requiring systemic corticosteroids, 48% vs 25% ($p = 0.002$). With dupilumab, the exacerbation rate was 59% less than in the placebo arm. FEV₁ values improved by 0.22L greater than placebo. Although corticosteroid reductions are not part of the definition for remission, these corticosteroid-sparing traits suggest that biologics may create a “remission” of a component of disease associated with the need for systemic corticosteroids. Reducing or eliminating systemic corticosteroids is a disease re-adjustment and may represent a form of remission, at least reflecting disease severity.

What are the next steps in designing and assessing therapies to induce remission?

We can conclude, as a group, current biologics are efficacious in achieving improved disease control in patients with severe disease with characteristics of T2 inflammation but do not meet criteria for remission in all treated subjects, or all the criteria for remission. The criteria for remissions most frequently achieved were a reduction in exacerbations. What is needed next is an analysis on the frequency of patients treated by available biologic treatments meet and criteria for a remission and what are the patient characteristics. With the goal to identify treatments that could potentially induce remission and the properties of the asthma biologics identified in the previous discussion, the next step will be to better characterize available asthma biologics and define areas of remission that are met or not met with these therapies.

There is an element of disease progression in asthma as indicated by loss of pulmonary function over time, and a factor to consider in assessing features of remission. This may be more predominant in children than adults and was typified in the long-term follow-up on the National

Heart, Lung and Blood Institute Childhood Asthma Management Program.²² In this group of over 1,000 patients and followed for 15 years, there were four patterns in lung function that emerged; (1) those that followed a normal lung function trajectory, based on pre-bronchodilator FEV₁%, through childhood and early adult age; (2) those that had a normal trajectory during childhood but declined in early adulthood; (3) those that followed a low lung trajectory through the study period; and (4) those that had a low lung trajectory in childhood and declined even further in early adult age (**Figure 6**). Approximately 11% of this population met physiologic criteria for advanced COPD as young adults. A proportion of these patients were receiving either inhaled corticosteroid or cromolyn therapy for over 5 years at the start of follow-up. These patterns of lung function loss occurred despite the treatment arm. The question is whether these patterns in either adults or children could be prevented or resolved.

In order to evaluate whether a biologic for asthma might alter these patterns of lung function change in a clinical study, or individually, it is important to characterize the patient with lung function measures over time to define a “non-decliner,” “slow decliner” or “rapid decliner.” In regards to slow and rapid decliners in pulmonary function, it is not clear whether unresolved asthma exacerbations contribute to a decline in pulmonary function or whether the progressive loss in pulmonary function over time contributes to the risk for an asthma exacerbation. Therefore, long-term follow-up of pulmonary function and the frequency of exacerbations before and after intervention with an asthma biologic is important for clinical studies and for individualized care, to define the specific effect of an intervention and consider these effects in relation to remissions. Other measures of documenting the effect for potential disease remission

include following asthma composite scores, such as ACT for impairment or CASI/ASSESS for overall asthma burden.²³⁻²⁶

Besides the clinical trials of asthma biologics, there are other studies in progress to evaluate the potential of medications to alter the natural history of asthma including the PARK study and ORBEX. The PARK study will test whether anti-IgE administered in early child may alter the natural history of asthma (<https://parkstudy.org/>
<https://vector.childrenshospital.org/2016/08/asthma-prevention-xolair/>
And the clinical [trials.gov](https://clinicaltrials.gov) listing Clinical [trials.gov](https://clinicaltrials.gov) NCT02570984). Similarly, the ORBEX study will test whether inducing immunologic response with a killed bacterial lysate could play a role in preventing asthma exacerbations and reducing inflammation (clinicaltrials.gov registration: <https://clinicaltrials.gov/ct2/show/NCT02148796>)

Summary

Therefore, the future directions in asthma treatment to gain disease control, especially with asthma biologics, should determine whether they offer a unique feature beyond conventional therapy, including the establishment of a disease remission. It would be ideal if current or future medications could alter asthma progression and, perhaps, have the potential for early intervention to halt the onset of asthma and thus reflect disease remission. Asthma guidelines in the future should emphasize clinical assessment of the natural history of a patient's disease and include a definition of remission in treatment plans. It will be important to evaluate and characterize patients over time in regards to disease activity and potential for expression of

features of remission. Having criteria to assess remission will be a next important step forward towards a goal of greater asthma control and long-term safety as less effective medications, often with significant side effects, are replaced. This approach is reflective of treatment of hypertension where the goal is a reduction, or remission, in the sequela of the disease. A shift to include asthma remission in treatment planning will represent a new phase of achieving disease control and should become an aspect of treatment outcome evaluations that represent greater degrees of asthma control.

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Table 1. What T2-Directed Biologics Are Available for Severe Asthma?

Agent	↓ Exacerbations	↑ Lung function	Symptoms	Special feature
Omalizumab (IgE)	25%	±	+/-	Aged >6 y; also approved for CIU
Mepolizumab (IL-5)	50%	+	+	Greatest experience of anti-IL-5s; also approved for EGPA
Reslizumab (IL-5)	50%	++	+	Weight-base dose (intravenously)
Benralizumab (IL-5R)	50%	++	++	Every 8 wk and IL-5R
Dupilumab (IL-4/IL-13)	50%	++	+++	Eosinophils, FeNO; also approved for AD and CRSwNP

Abbreviations: AD, atopic dermatitis; CIU, chronic idiopathic urticaria; CRSwNP, chronic rhinosinusitis with nasal polyps; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide, IL, interleukin; OCS, oral corticosteroid.

Legends for figures

Figure 1. Summary of changes in asthma management that integrate the focus of disease activity and the corresponding medications developed to address this therapeutic target. LABA, long-acting -agonist (reprinted with permission from Szefer SJ, *J Allergy Clin Immunol* 2018;142:773-80).¹

Figure 2. Generalized framework for remission in asthma. Criteria for clinical and complete remission, on and off treatment, were identified by consensus among clinical experts. FeNO, Fractional exhaled nitric oxide. *Blood eosinophil counts and FeNO are less relevant for T2-low asthma. From Menzies-Gow et al. *J Allergy Clin Immunol* 2020;145:757-65.⁴

Figure 3. Summary of efficacy end points. A, Exacerbation rate per year across DREAM and COLUMBA. A total of 286 patients with 156 weeks or more of open-label data in COLUMBA are summarized (DREAM: placebo, n = 62; mepolizumab, n = 224). B, ACQ-5 score change from baseline. C, Prebronchodilator FEV₁ change from baseline. D, Blood eosinophil geometric mean ratio to baseline. Pretreatment refers to the 12 months before enrollment in DREAM. ACQ-5 responders were defined as patients with a reduction in ACQ-5 score of 0.5 points or more from baseline. Vertical bars show 95% CIs. Minimum clinically important difference: ACQ-5, 0.5 points; FEV₁, 100 mL. From Khatri et al *J Allergy Clin Immunol* 2019;143:1742-51.¹⁵

Figure 4. Change from baseline in pre-bronchodilator FEV₁ by baseline blood eosinophil counts (full analysis set). Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Data at this time point are from adult patients only. From Busse et al Lancet Respir Med 2019;7:46-49.¹⁹

Figure 5. Forest plots of the risk of severe asthma exacerbations in the intention-to-treat population and in subgroups defined according to baseline blood eosinophil count and baseline FeNO. FeNO denotes fraction of exhaled nitric oxide, and ppb parts per billion. From Castro et al. N Engl J Med 2018;378:2486-96.²⁰

Figure 6. Possible lung-function trajectories during the first three decades of life are shown; the lung function plotted for each age is the percentage of the maximum forced expiratory volume in 1 second (FEV₁) in a person without lung disease; the maximum value is usually attained at the age of 18 to 30 years. A normal pattern of lung-function growth and decline is characterized by a steep increase during adolescence, a plateau in early adulthood, and a gradual decline into old age. Abnormal trajectories include reduced growth, normal growth and an early decline, and reduced growth and an early decline. The red brackets indicate FEV₁ criteria according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 (FEV₁ ≥50% and <80%) and stage 3 (FEV₁ ≥30% and <50%) of chronic obstructive pulmonary disease (COPD), when accompanied by a ratio of FEV₁ to forced vital capacity that is less than 0.70. The figure is adapted from Speizer and Tager. From McGeachie MJ et al. N Engl J Med 2016;374:1842-1852.²²

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Circulation	1000
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Title of new article	How Do Asthma Biologics Relate to Remission of Asthma
Lead author	Andrew Menzies-Gow
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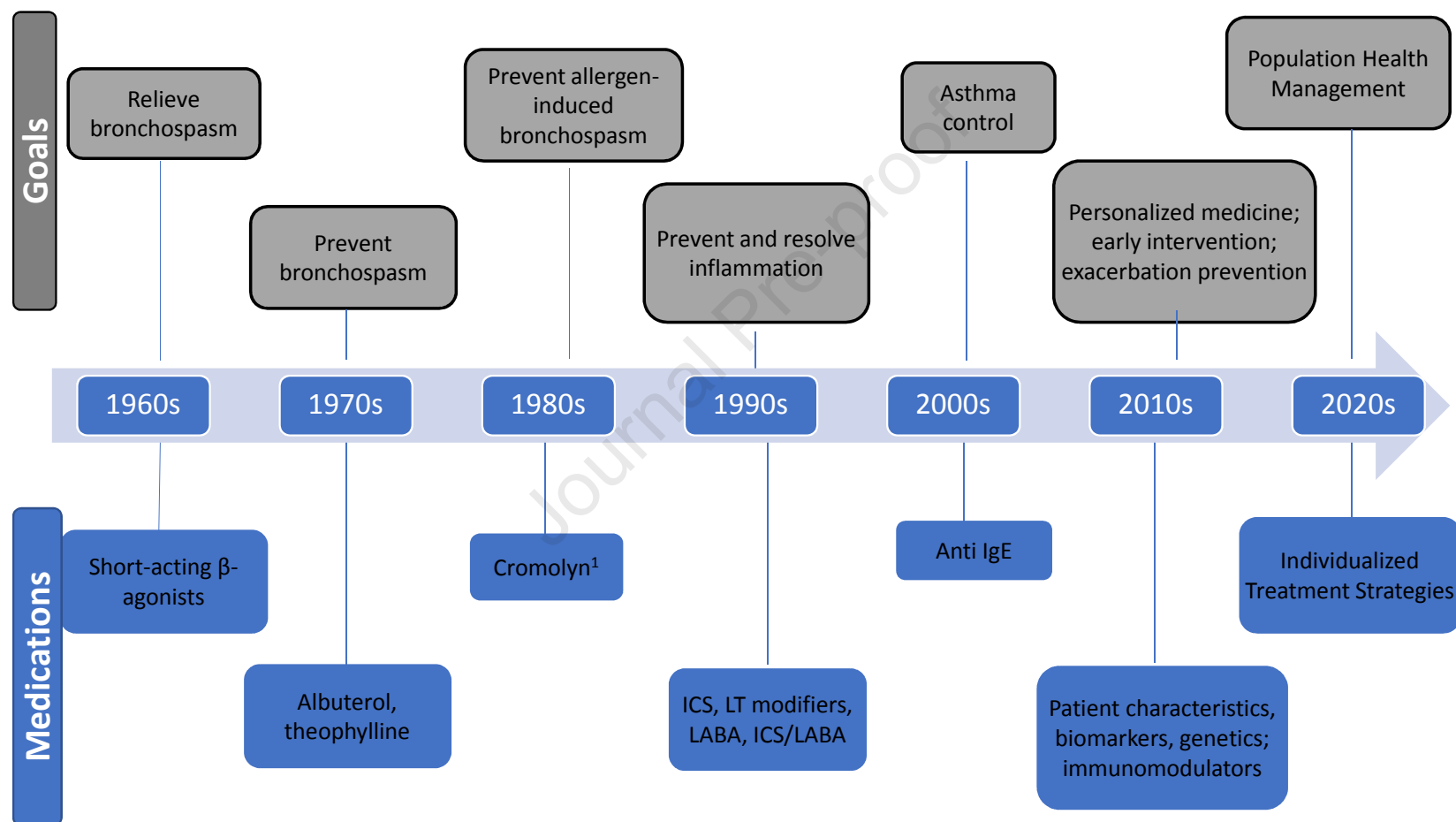
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Evolving Patterns in Asthma Management



Clinical Remission on Treatment

For ≥ 12 months:

- Sustained absence of significant asthma symptoms based on validated instrument, **and**
- Optimization and stabilization of lung function, **and**
- Patient and HCP agreement regarding disease remission, **and**
- No use of systemic corticosteroid therapy for exacerbation treatment or long-term disease control

Clinical Remission off Treatment

Same criteria maintained without asthma treatment for ≥ 12 months

Complete Remission on Treatment

Clinical remission plus the following:

- Current, objective evidence of the resolution of previously documented asthma-related inflammation (eg, reduced blood or sputum eosinophil counts, FENO, and/or other relevant measures), **and**
- In appropriate research settings: Current negative bronchial hyperresponsiveness

Complete Remission off Treatment

Same criteria maintained without asthma treatment for ≥ 12 months

