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Patient response and remission in respiratory disease: Special focus on severe asthma and chronic obstructive pulmonary disease

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Abstract

Over the past decades, monoclonal antibodies have been playing a pivotal role in the treatment of chronic inflammatory airway diseases. Currently, ample data are available on the efficacy and safety of biologics in asthma from randomized controlled trials and open-label trials; conversely, limited data are available on the use of biologics in chronic obstructive pulmonary disease. In this context, once the fundamental role of inhaled corticosteroid/long-acting β2-agonist/long-acting muscarinic antagonist therapy is established, clinical response and disease remission, based on clinical and functional response parameters such as oral corticosteroid need, annual exacerbation rates, and lung function, are the key factors driving the clinical and therapeutic management. This narrative review has summarized the literature data from randomized controlled trials and

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real-life experience on currently available biologics in asthma and chronic obstructive pulmonary disease. The role of inhaled corticosteroid, long-acting β2-agonist, and long-acting muscarinic antagonist therapy has been further investigated with a particular focus on drug-free concept.

Keywords
Asthma, chronic obstructive pulmonary disease, eosinophils, type 2 inflammatory diseases, type 2 lower inflammatory airway diseases, patient response, patient remission, biologics

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Introduction

Biologics are currently widely used in severe asthma as add-on therapy to high-dose inhaled corticosteroid (ICS), long-acting β2-agonist (LABA), and long-acting muscarinic antagonist (LAMA) therapy. Biologics have been proven to reduce the burden of asthma exacerbations and the use of oral corticosteroids (OCS) in patients with severe asthma; as such, they have enabled a precision medicine approach, thus reinvigorating the debate on remission achievement and maintenance in patients with asthma.[1]

Biologics have also been investigated in chronic obstructive pulmonary disease (COPD), and biologics that selectively target and block eosinophilic pathways have shown positive results in terms of reducing the rate of exacerbation and improving health status. In 2023, an expert consensus group defined asthma remission as the absence of OCS need, symptoms, exacerbations or attacks, and pulmonary function stability as well as defined partial clinical remission as the absence of OCS need and fulfillment of two of the following three criteria: absence of symptoms, absence of exacerbations or attacks, and absence of pulmonary stability.[2] The background therapy remains controversial.

In this review, we summarized the literature data from randomized controlled trials (RCTs) and real-life experiences on currently available biologic therapies in severe asthma and COPD, with a particular focus on clinical and functional parameters of response and eventually disease remission. The roles of ICS and LAMA have been further investigated with a focus on drug-free concept. This narrative review is guided by the Scale of Assessment for Narrative Review Articles (SANRA).[3]

Anti-immunoglobulin (Ig) E treatment

Omalizumab, a humanized IgG1 monoclonal antibody (mAb) that binds to IgE with high affinity, is the first biological drug approved for the treatment of moderate-to-severe allergic asthma. Add-on therapy with omalizumab has proven efficacy in IgE-mediated asthma inadequately controlled by high-dose ICS/LABA in both children and adults.

In several randomized, double-blind placebo-controlled trials, omalizumab has shown to reduce the rate of asthma exacerbations from 25% to 58%, thereby increasing forced expiratory volume in one second (FEV_1) and improving quality of life (QoL) in patients with severe IgE-mediated asthma.[4–7]

INNOVATE, a pivotal phase 3 randomized, double-blind placebo-controlled study, showed a reduction of 26% in asthma exacerbations and a gain in lung function (improvements in FEV_1 were 190 mL in omalizumab group vs. 96 mL in the placebo group). Moreover, asthma symptom control and QoL improved in the omalizumab group.[8]

Omalizumab reduced asthma symptoms and asthma exacerbations (approximately 19%) in children, adolescents, and young adults with persistent allergic asthma in a 60-week randomized, double-blind, placebo--controlled, parallel-group multicenter trial.[9] The EXTRA study evaluated the effects of 48-week omalizumab vs. placebo treatment in patients with inadequately controlled severe allergic asthma according to three different biomarkers (fractional exhaled nitric oxide (FeNO) level, blood eosinophil count (BEC), and serum periostin level at baseline), demonstrating a greater reduction in asthma exacerbations in high versus low subgroups for all three biomarkers.[10]

Based on a post hoc analysis of the EXTRA study, omalizumab reduced exacerbations to a greater extent than placebo in patients with high bronchodilator responsiveness, regardless of the presence of fixed airflow obstruction and improved FEV_1 in patients with high responsiveness without fixed airflow obstruction.[11] In a 1-year, randomized open-label study, the add-on therapy with omalizumab significantly reduced the annual asthma exacerbation rate (59%) and improved FEV_1 (71% vs. 60%; $P < 0.001$) and asthma symptoms in patients with moderate-to-severe allergic IgE-mediated asthma.[12]

Long-term treatment with omalizumab has been shown to be safe and well-tolerated in both adults and children with allergic asthma.[13,14] Omalizumab is also the best studied biologic in pregnancy and lactation, with reassuring available safety data.[15]

Anti-interleukin (IL)-5 treatment

Mepolizumab, a humanized IgG1 mAb that binds to free IL-5 and impedes interaction with its receptor, is the first approved biologic in severe eosinophilic asthma. Mepolizumab prevents activation, maturation, and survival of blood eosinophils, thus causing a decrease in BEC.

Phase 2 and 3 studies showed a significant reduction in asthma exacerbations of approximately 50%,[16–18] improvement in asthma control and QoL,[16,17,19] and improvement in FEV_1 of approximately 100 mL.[17] In patients receiving maintenance OCS therapy, a reduction in OCS dose of 50% was achieved.[16] These data confirmed a favorable safety profile of the drug, which is currently approved for self-administration among adults and children older than 6 years.

In a post hoc meta-analysis of data from the phase 3 RCTs MENSA and MUSCA, mepolizumab reduced the rate of clinically significant exacerbations by 49%–63% and improved lung function and asthma symptom control (St. George's Respiratory Questionnaire (SGRQ) total score and Asthma Control Questionnaire-5 (ACQ-5) score) regardless of the age at asthma onset, lung function, airway reversibility, and allergen sensitivities at baseline.[20]

A decrease in OCS dose and exacerbation reduction have also been confirmed by real-life observations, such as the REALITI-A study[21] and the study by Harrison et al.,[22] respectively. Reslizumab, an anti–IL-5 directed mAb, has shown significant reduction of sputum eosinophils and improvements in airway function and asthma control, compared with placebo. Considerably larger improvements in FEV_1, ACQ-7, rescue Short Acting Beta Agonists use, and forced vital capacity (FVC) have been observed in the subgroup of patients with an eosinophil count $\geq$400

cells/μL, compared with the placebo group.[23–25]

Anti–IL-5 receptor treatment

Benralizumab is a fucosylated fully humanized IgG1k mAb that targets the IL-5 receptor α-chain. This binding results in subsequent inhibition of IL-5–mediated activation of the receptor.[26] The deletion of fucose residues enhances the interaction of benralizumab with its binding site and strongly induces antibody-dependent cell-mediated cytotoxicity by natural killer cells, markedly reducing eosinophils and other IL-5 receptor-positive cells, such as progenitors of eosinophils, basophils, and type 2 innate lymphoid cells.[27] During the WINDWARD development program, two phase 3 RCTs (CALIMA and SIROCCO) evaluated the efficacy of benralizumab in patients with BEC $\geq$300 and $<$300/μL.[28,29] In the first study, benralizumab reduced asthma exacerbations by 36% and 28% in the every 4-week (Q4W) and 8-week (Q8W) groups, respectively, compared with the placebo group with high BEC. In the SIROCCO study, patients with high BEC treated with benralizumab Q4W and Q8W showed reduced exacerbation rate by 45% and 51%, respectively, compared with placebo. In the low BEC subgroup, benralizumab Q8W reduced the exacerbation rate by 17% in the benralizumab group compared with placebo.

A pooled analysis of SIROCCO and CALIMA RCTs indicated that patients with both high BEC ($\geq$300 or $\geq$450/μL) and a history of three or more exacerbations showed higher improvements in the annual exacerbation rate.[30] The phase 3 ZONDA RCT evaluated changes in OCS dose during 28 weeks of benralizumab treatment.[31] Benralizumab showed a 50% reduction in prednisone dose, including the placebo effect. Examination of the secondary endpoints revealed that the administration of benralizumab Q8W reduced the annual rate of exacerbations by 70% compared with placebo ($P < 0.001$). No significant effect on FEV_1 was found at the end of the study.

A post hoc analysis examined the rate of clinical remission among the SIROCCO/CALIMA or ZONDA RCT population[32]; in the SIROCCO/CALIMA study, 14.5% of benralizumab-treated patients and 7.7% of placebo-treated patients achieved clinical remission at 12 months, whereas in the ZONDA study, 22.5% of the benralizumab active treatment group achieved clinical remission compared with 7.5% of the placebo arm. A subsequent open-label, single-arm multicenter study (PONENTE) had the following main endpoint: the proportion of patients for whom it was possible to avoid prolonged daily use of OCS for at least 4 weeks and the proportion of patients for whom it was possible to achieve weaning from OCS or a prednisone/prednisolone dose of $\leq$5 mg for at least 4 weeks if the reason for complete discontinuation was adrenocortical insufficiency.[33] Based on the analysis, 63% of the patients were weaned from OCS, and 82% eliminated OCS use or reached a dose of 5 mg or lower if the reason for incomplete elimination was adrenocortical insufficiency. Considering subgroups, OCS dose reductions were achieved regardless of BEC, baseline OCS dose, or duration of OCS treatment. An important finding was the prevalence of adrenocortical insufficiency, detected in 60% of patients in the first evaluation and in 38% 3 months later. A 2017 Cochrane review revealed a significant reduction in asthma exacerbations in patients treated with benralizumab regardless of baseline BEC, although the maximal effect was obtained in the subgroup with BEC $\geq$300/μL. However, these exacerbations were present only in this subpopulation of patients with significant improvements in lung function and QoL.[34] Finally, the

long-term open-label MELTEMI extension study confirmed that benralizumab maintains a high safety and efficacy profile until 5 consecutive years of treatment.[35]

Anti–IL-4/IL-13 treatment

Dupilumab is a fully humanized anti–IL-4 receptor α mAb blocking both IL-4 and IL-13 signaling. The blockage of IL-4 and IL-13 limits the type 2 (T2) immune response with effects on different cellular types, such as eosinophils, basophils, and mast cells, which play a key role in inducing T2 inflammation, clinical symptoms, and tissue damage.

In a phase 2a randomized, placebo-controlled double-blind clinical trial, add-on therapy with dupilumab (300 mg once weekly) showed efficacy in patients with moderate-to-severe uncontrolled eosinophilic asthma who had BEC $\geq$300/μL.[36] In the phase 2b DRI trial, dupilumab administration (200 mg every 2 weeks (Q2W) or 300 mg Q2W or 200 mg every 4 week (Q4W) or 300 mg Q4W) led to improved lung function, reducing the rate of severe exacerbations and FeNO levels in all dupilumab-treated groups compared with placebo, irrespective of baseline BEC.[37]

In the LIBERTY ASTHMA QUEST phase 3 randomized, placebo-controlled double-blind clinical trial, dupilumab administered subcutaneously (200 or 300 mg Q2W) after loading doses has been demonstrated to reduce the annual severe asthma exacerbations and improve lung function (FEV_1) in patients with moderate-to-severe uncontrolled asthma, compared with placebo. The results were more evident in patients with increased baseline BEC and FeNO levels.[38]

Moreover, in the LIBERTY ASTHMA VENTURE phase 3 trial, add-on therapy with dupilumab (300 mg Q2W) significantly reduced the use of oral glucocorticoids in patients with glucocorticoid-dependent severe asthma, irrespective of baseline BEC.[39] Treatment with dupilumab, compared with placebo, avoided the loss of post-bronchodilator lung function, suggesting protection from airway remodeling.[40]

The long-term open-label study TRAVERSE explored the safety and efficacy of dupilumab (300 mg Q2W) in adults and adolescents with moderate-to-severe corticosteroid-dependent asthma who had participated in a previous phase 2 or phase 3 randomized, placebo-controlled double-blind clinical trial, demonstrating effectiveness in reducing asthma exacerbations and improving lung function and asthma control. Moreover, dupilumab has been shown to have a favorable profile in terms of safety.[41]

Anti-thymic stromal lymphopoietin (TSLP) treatment

Tezepelumab, a fully humanized IgG2λ, is the first and only approved mAb that specifically inhibits TSLP. By targeting TSLP, which is an epithelial cytokine, tezepelumab acts on the top of the inflammatory cascade. Currently, it is the only molecule that could be used in both T2 and non-T2 asthma phenotypes.[42]

In the phase 2b study PATHWAY, tezepelumab administered at 210 mg Q4W significantly reduced exacerbations (71%), improved lung function (FEV_1 increase >100 mL), and reduced OCS dose by 60% in adults with severe uncontrolled asthma.[43] In the phase 3 NAVIGATOR study, tezepelumab (210 mg Q4W) reduced asthma exacerbations over 52 weeks in both allergen-sensitized patients with BEC $\geq$300 cells/μL (71%) and patients with BEC $\geq$300 cells/μL and FeNO levels $\geq$25 ppb (77%). Moreover, a 41% reduction of asthma exacerbations has been observed in patients with a T2-low asthma phenotype (BEC <300/μL),

and a 45% reduction has been observed in patients with a non-T2 phenotype (nonallergic, BEC <150/μL, FeNO level <25 ppb). Tezepelumab has been shown to improve lung function, as indicated by FEV_1; asthma control; FeNO level; and levels of serum biomarkers such as eosinophils, total IgE, IL-4, IL-5, and IL-13.[44]

In the phase 3 trial SOURCE, tezepelumab showed a nonsignificant difference in OCS-sparing effect at 48 weeks compared with placebo.[45] DESTINATION, a long-term safety and tolerability placebo-controlled phase 3 study, showed the positive benefit–risk profile of tezepelumab over 104 weeks.[46] Tezepelumab has been approved by the Food and Drug Administration (FDA) in 2021 and by European Medicine Agency in 2022 as an add-on maintenance treatment for patients aged >12 years with severe asthma whose condition remains uncontrolled despite high ICS dose and another controller (such as LABA or LAMA).

Treatment response in asthma

Asthma treatments have deeply evolved over the past centuries, and the availability of mAbs targeting cytokines or cytokine receptors, which are involved in the inflammatory pathways of different asthma pheno-endotypes, has led to a new era of treatment, particularly for severe asthma. By targeting the specific immunopathological mechanisms underlying asthma, biologics have paved the way to the concept of disease-modifying antiasthmatic drugs, as recently proposed by Lommatzsch et al.,[47] which aim to modify the course of asthma and possibly modulate or prevent airway remodeling. Similarly, the primary endpoints of RCTs have changed, shifting from FEV_1 improvements to asthma exacerbation reduction as clinical outcomes for asthma treatments. Thus, in a precision medicine approach for treating asthma, an ideal definition of asthma remission should be based on the absence of symptoms, absence of exacerbation, and no need for OCS, along with stable lung function. Recently, clinical remission has been proposed as a novel outcome measure to evaluate treatment efficacy and effectiveness.

The concept of "super-responders" has been introduced in biologic-treated severe asthma. Although various definitions have been proposed, the lack of asthma exacerbations and the discontinuation of OCS after 1 year of biologic treatment have been recognized as common features of super-responders; asthma control improvement, FEV_1 increase, and the absence of exacerbations after a 1-year course have been also considered.[48]

Omalizumab, which was approved in 2003, was the first biologic therapy for patients with severe asthma, as several RCTs demonstrated a reduction of asthma exacerbations as well as an increase in QoL and asthma control. In terms of lung function, improvements were modest, demonstrating improved morning peak expiratory flow[5,6,8] as well as slightly improved FEV_1.[5] The proportion of responding patients was 60%–90% in several real-life studies, with a mean reduction in annual exacerbations of >50%, an increase in asthma control test (ACT) score of approximately 5 points, and OCS reduction of approximately 50%; however, beneficial effects on lung function were less evident.[49–51]

In phase 2 and 3 studies, patients with severe eosinophilic asthma (BEC > 150/μL) on high-dose ICS therapy plus another controller treated with mepolizumab showed reduced asthma exacerbations of approximately 50%,[15–17] improved asthma control and QoL,[16,18,19] and increase in FEV_1 of approximately 100 mL.[17] In patients with maintenance OCS therapy, a reduction of OCS dose of 50% was achieved.[16] Real-life studies have confirmed the following RCT data: a strong reduction in OCS dose, with

a decrease from 10 to 5 mg/day, or OCS treatment discontinuation (30% of patients) has been shown in two analyses derived from the global, prospective, observational REALITI-A cohort of patients with severe eosinophilic asthma treated with mepolizumab. Furthermore, the majority of patients had a reduction in exacerbations of >50%[21,22,52]

In the SIROCCO trial, benralizumab Q8W reduced the annual exacerbation rate by 51%, increased FEV_1 by >150 mL, and improved asthma symptom scores in patients with a BEC >300/μL.[25] Similar results were obtained in the randomized, double-blind placebo-controlled phase 3 study CALIMA.[24] In their extension trial BORA, the previously reported improvements in annual asthma exacerbations and lung function were maintained, with no new safety signals.[53] The ZONDA trial showed the effect of benralizumab on patients with OCS-dependent severe asthma, which could reduce OCS dose by 75%, and >50% of patients completely discontinued OCS. No effect on lung function has been obtained; however, asthma exacerbations considerably reduced.[31] Several real-life studies on benralizumab in patients with severe asthma confirmed the findings of RCTs and revealed greater lung function improvements compared with those reported in CALIMA and SIROCCO, with FEV_1 increases ranging from 300 to 600 mL.[54–59]

The phase 3 LIBERTY ASTHMA QUEST trial demonstrated a significant reduction in annualized asthma exacerbations and an increase in FEV_1 in patients with moderate-to-severe asthma treated with dupilumab versus placebo. The baseline BEC was >150/μL and FeNO level was >25 ppb.[38] The phase 3 trial LIBERTY ASTHMA VENTURE focused on OCS-dependent patients, demonstrating the reduction of asthma exacerbations and OCS intake, with more than half of the patients being able to discontinue OCS treatment.[39] Several multicenter retrospective real-life studies confirmed the observed results of RCTs, reporting significant increases in ACT score and FEV1, with a strong decrease in OCS dose and annual exacerbations.[60–62]

Tezepelumab (210 mg Q4W) was effective in reducing annual asthma exacerbations, increasing FEV_1, and improving asthma control in the phase 3 NAVIGATOR trial, independently from T2 biomarker status[63]; however the OCS-sparing study SOURCE failed to demonstrate a significant improvement in OCS dose reduction with tezepelumab compared with placebo.[45] Currently, no real-life data are available for tezepelumab.

Treatment response in COPD

Early studies on biologics in COPD targeted neutrophils and proinflammatory cytokines with negative results.[64,65] In light of these experiences, the most recent RCTs have targeted eosinophilic inflammatory pathways in subgroups with increased eosinophils. Extending observations from asthma to COPD has led to the concrete hypothesis that biologics that target and block eosinophils could have had positive results in terms of reducing the rate of exacerbations and improving health status. In the largest biologic RCTs in COPD conducted to date, Pavord et al.[66] evaluated the efficacy and safety of mepolizumab in moderate-to-very severe COPD (METREX and METREO). In the former study, patients were randomized to receive 100 mg mepolizumab or placebo (n = 836), while patients in the latter study received 100 mg or 300 mg of mepolizumab or placebo (n = 674) Q4W for 52 consecutive weeks of treatment. The two studies differed in the eosinophilic phenotype of patients. METREX had recruited both patients with eosinophilia (defined as eosinophil counts of 150/μL at screening or 300/μL in the previous year) and without (defined

as eosinophil counts <150/μL at screening or <300/μL in the previous year), while METREO included only patients with blood eosinophilia. In METREX, there was no overall difference in exacerbations between the two groups. An 18% reduction in moderate or severe exacerbations was observed in the eosinophilic subgroup in the mepolizumab group versus placebo (1.40 exacerbations per year compared with 1.71 per year). In METREO, the average annual rates of moderate or severe exacerbations were 1.19 per year in the 100 mg mepolizumab group, 1.27 per year in the 300 mg mepolizumab group, and 1.49 per year in the placebo group. The two doses showed no significant improvement compared with placebo (100 mg, rate ratio: 0.80; adjusted $P = 0.07$; 300 mg, rate ratio: 0.86; adjusted $P = 0.14$). No additional results were obtained with the highest dose of mepolizumab. Regarding secondary endpoints, time to first moderate or severe exacerbation was significantly longer with mepolizumab than with placebo in the eosinophilic subgroup in METREX (192 vs. 141 days; adjusted $P = 0.04$). Mepolizumab showed no significant impact on lung function and health status compared with placebo, and fortunately, no differences in adverse events were observed. Although mepolizumab was the first mAb showing a significant reduction in the rate of exacerbations in patients with eosinophilic COPD, the extent of this benefit has not been considered adequately by the FDA for the use of mepolizumab for COPD.

In a 52-week phase 2a RCT of benralizumab in 101 patients with moderate–to-severe COPD, the primary outcome measure of reduction in the annual rate of acute exacerbations was not achieved despite a reduction in eosinophilic inflammation.[67] There was an improvement in FEV_1 in patients who received benralizumab, but no differences in health status were observed. In a post hoc analysis in patients with sputum eosinophil count of >2% and BEC ≥250/μL, greater improvement in lung function and health status was observed along with a numerical reduction in exacerbations. There was no difference in the rate of adverse events. Moreover, in this case, the results confirmed a greater efficacy in the subgroup with higher BEC. Unfortunately, benralizumab failed to meet the primary endpoint of annual COPD exacerbation rate for patients with a baseline BEC ≥220/μL. Interestingly, the effect size was smaller in studies on mepolizumab and benralizumab than in studies on severe asthma, and the magnitude of the benefit is directly related to the intensity of inflammatory eosinophilia and BEC.[66,67]

A substantial reduction of T2 inflammation was achieved with dupilumab, owing to the inhibition of both IL-13 and IL-4 effects, with a likely greater effect on mucus and airway smooth muscle,[68] which led to superior outcomes with the use of this mAb in COPD. The 52-week, phase 3, multicenter double-blind trial BOREAS enrolled 939 patients with COPD and a BEC of ≥300/μL.[69] Add-on treatment with dupilumab (300 mg Q2W administered subcutaneously) resulted in a significant reduction in the incidence of COPD exacerbations (0.78 with dupilumab and 1.10 without; $P < 0.001$), improved lung function (FEV_1 increased from baseline by a least-squares mean of 160 mL in the treatment arm and 77 mL in the placebo group; $P < 0.001$) and health status, and less severe respiratory symptoms compared with placebo. In the BOREAS study, a specific subgroup of patients with COPD and a BEC of ≥300/μL who had a mean age of 65 years was selected. Elevated circulating levels of eosinophils in patients with COPD are not only known to identify individuals at greatest risk of exacerbations but are also most likely to have a response to the preventive effects of ICS.[70] Therefore, the results of the BOREAS trial cannot be

generalized to all patients with COPD, and further studies will be needed to evaluate eventual clinical effects in patients with lower BEC. It is equally important to highlight that these effects have been observed when dupilumab treatment was added to triple inhaled therapy. This in turn reduces exacerbations and improves COPD symptoms, regardless of the level of circulating eosinophils.[71]

In a phase 3, double-blind randomized trial (NOTUS) involving patients with COPD and a BEC $\geq$300/μL, dupilumab (300 mg Q2W) showed a significant reduction of exacerbations and improvements in the lung function compared with placebo[72] COURSE was a double-blind, randomized, placebo-controlled, phase 2a trial in which patients with COPD received tezepelumab (420 mg) or placebo subcutaneously Q4W for up to 52 weeks. However, the reduction in the annual rate of moderate or severe COPD exacerbations was not significant in the tezepelumab group versus placebo.[73]

In the future, it will be necessary to conduct post hoc analyses with the aim of directing future investigations to refine the selection of target patients. It is also possible that the diagnosis and treatment of COPD at an early age can provide better results, as indicated by the recently released Global Initiative for Chronic Obstructive Lung disease report (GOLD).[74] Table 1 summarizes RCTs evaluating the efficacy of currently available biologics as add-on therapy in uncontrolled asthma and COPD.

OCS and ICS sparing

Drug-free concept in severe asthma

Currently, ICS plays a central role in asthma treatment; however, as ICS therapy does not change the underlying pathophysiology of asthma, additional treatment should be considered. Based on the successful development of disease-modifying treatments in other settings, an achievable and pragmatic goal of asthma therapy is disease remission or prevention. New therapeutic options such as biologics potentially demonstrate a disease-modifying action. Currently, however, these data have been observed in studies based on small sample sizes and of short duration.[75] The European Academy of Allergy and Clinical Immunology guidelines for the use of biologic therapies in severe asthma have stated that based on the available evidence, none of the currently available biologics have demonstrated true disease-modifying effects and all have shown declines in efficacy soon after discontinuation.[76] A large body of data accumulated over the years from RCTs and real-world evidence suggests that the therapeutic effects of different biologic agents in severe asthma are maintained in most patients only during treatment. In other words, the interruption of treatment involves the worsening of asthma control in an almost systematic way, with recurrence of exacerbations and the frequent need for bursts of OCS.[77,78] There are similar data and clinical experiences with ICS in patients with less severe disease.[79] By extending the concept of disease-modifying agents from rheumatic diseases to asthma, effective treatment with ICS or biologics capable of leading to disease remission (defined as the absence of asthma symptoms, optimization or stabilization of lung function, and weaning from OCS) could be defined similarly.[80] However, the definition of a disease-modifying drug can be used in two ways, asthma remission on treatment and asthma remission without treatment (as occurs in the case of allergen immunotherapy).[81,82] As mentioned previously, most of the evidence converges on the concept that currently available asthma medications (including mAbs) have a disease-modifying effect only on treatment. Studies on large case series support these

Table 1. Summary of RCTs evaluating the efficacy of currently available biologics as add-on therapy in uncontrolled asthma and COPD.

RCT	Intervention type	Population	Outcomes
Busse et al. 2001[5]	Omalizumab (SC) or placebo every 2 or 4 weeks calculated based on body weight and baseline serum IgE levels	Severe atopic asthma	· From 41% (steroid-reduction phase) to 48% (stable-steroid phase) ↓ rate of exacerbations · 4.33% ↑ pre-bronchodilator FEV_1
Solèr et al. 2001[6]	Omalizumab (SC) or placebo every 2 or 4 weeks for 28 weeks calculated based on body weight and baseline serum IgE levels	Moderate-to-severe atopic asthma	· 52% (steroid-reduction phase) to 58% (stable-steroid phase) ↓ rate of exacerbations · ↑ Pre-bronchodilator FEV_1 (mL)
Humbert et al. 2005[8] (INNOVATE)	Omalizumab (SC) or placebo every 2 or 4 weeks for 28 weeks calculated based on body weight and baseline serum IgE levels	Inadequately controlled severe persistent asthma	· 26% ↓ rate of exacerbations · 94 ↑ pre-bronchodilator FEV_1 (mL)
Busse et al. 2011[9] (ICATA)	Omalizumab (SC) or placebo every 2 or 4 weeks for 60 weeks calculated based on body weight and baseline serum IgE levels	Persistent allergic asthma (6 to 20 years of age)	· 18.5% ↓ rate of exacerbations · No changes in FEV_1
Hanania et al. 2011[4]	Omalizumab (SC) or placebo every 2 or 4 weeks for 48 weeks calculated based on body weight and baseline serum IgE levels	Inadequately controlled severe persistent asthma	· 25% ↓ rate of exacerbations
Hanania et al. 2013[10] (EXTRA)	Omalizumab (SC) or placebo every 2 or 4 weeks for 48 weeks calculated based on body weight and baseline serum IgE levels	Uncontrolled severe persistent allergic asthma	· 53% (FeNO $\geq$ 19.5 ppb) ↓ rate of exacerbations · 32% (BEC $\geq$ 260/μL) ↓ rate of exacerbations · 30% (periostin $\geq$ 50 ng/mL) ↓ rate of exacerbations
Pavord et al. 2012[18] (DREAM)	Mepolizumab (75, 250, or 750 mg IV) or placebo every 4 weeks for 13 doses	Severe uncontrolled refractory eosinophilic asthma	· From 39% (250 mg) to 48% (75 mg) to 52% (750 mg) ↓ rate of exacerbations · No changes in the pre-bronchodilator FEV_1
Bel et al. 2014[16] (SIRIUS)	Mepolizumab (100 mg SC) or placebo every 4 weeks for 24 weeks	Severe eosinophilic asthma patients receiving daily OCS	· 50% ↓ OCS · 32% ↓ rate of exacerbations

(continued)

Table 1. Continued.

RCT	Intervention type	Population	Outcomes
Ortega et al. 2014[17] (MENSA)	Mepolizumab (75 mg IV or 100 mg SC) or placebo every 4 weeks for 32 weeks	Severe eosinophilic asthma	· From 47% (SC) to 53% (IV) ↓ rate of exacerbations · 98 (SC) to 100 (IV) ↑ pre-bronchodilator FEV_1 (mL)
Chupp et al. 2017[19] (MUSCA)	Mepolizumab (100 mg SC) or placebo every 4 weeks for 24 weeks (last dose at 20 weeks)	Severe eosinophilic asthma	· 120 ↑ pre-bronchodilator FEV_1 (mL)
FitzGerald et al. 2016[28] (CALIMA)	Benralizumab (30 mg SC) or placebo either every 4 weeks or every 4 weeks for the first 3 doses and then every 8 weeks or placebo for 56 weeks	Severe uncontrolled eosinophilic asthma	· 28% (Q8W) to 36% (Q4W) ↓ rate of exacerbations (BEC $\geq$ 300/μL) · 116 (Q8W) to 125 (Q4W) ↑ pre-bronchodilator FEV_1 (mL) (BEC $\geq$ 300/μL)
Bleecker et al. 2016[29] (SIROCCO)	Benralizumab 30 mg (SC) or placebo either every 4 weeks or every 4 weeks for the first 3 doses and then every 8 weeks or placebo for 48 weeks	Severe uncontrolled eosinophilic asthma	· 45% (Q4W) to 51% (Q8W) ↓ rate of exacerbations (BEC $\geq$ 300/μL) · 106 (Q4W) to 159 (Q8W) ↑ pre-bronchodilator FEV_1 (mL) (BEC $\geq$ 300/μL)
Nair et al. 2017[31] (ZONDA)	Benralizumab 30 mg (SC) or placebo either every 4 weeks or every 4 weeks for the first 3 doses and then every 8 weeks for 24 weeks	Severe uncontrolled eosinophilic asthma receiving daily OCS	· 75% ↓ OCS · 55% (Q4W) to 70% (Q8W) ↓ rate of exacerbations · 222 (Q8W) to 256 (Q4W) ↑ pre-bronchodilator FEV_1 (mL; week 20), no significant changes at week 24
Wenzel et al. 2013[36] (EXPEDITION)	Dupilumab (300 mg SC) or placebo once weekly for 12 weeks	Moderate-to-severe uncontrolled asthma	· 87% ↓ rate of exacerbations · 270 ↑ pre-bronchodilator FEV_1 (mL)
Wenzel et al. 2016[37] (DRI)	Dupilumab 200 mg (loading dose, 400 mg) or 300 mg (loading dose, 600 mg) (SC) every 2 weeks or dupilumab 200 mg (loading dose, 400 mg) or 300 mg (loading dose, 600 mg) (SC) every 4 weeks or placebo for 24 weeks	Moderate-to-severe uncontrolled asthma	· From 16.6% to 17.3% (overall population); from 22.9% to 24.9% (BEC $\geq$ 300/μL, from 12.6% to 13.4% (BEC $<$ 300/μL) ↑ pre-bronchodilator FEV_1 37.2% (300 mg Q4W); 42.9% (200 mg Q4W); 59.9% (300 mg Q2W) to 67.6% (200 mg Q2W) ↓ rate of exacerbations

(continued)

Table 1. Continued.

RCT	Intervention type	Population	Outcomes
Castro et al. 2018[38] (LIBERTY ASTHMA QUEST)	Dupilumab 200 mg (loading dose, 400 mg) or 300 mg (loading dose, 600 mg) (SC) or placebo every 2 weeks for 52 weeks	Uncontrolled asthma	· 47.7% ↓ rate of exacerbations · 140 ↑ pre-bronchodilator FEV_1 (mL)
Rabe et al. 2018[39] (LIBERTY ASTHMA VENTURE)	Dupilumab 300 mg (loading dose, 600 mg) (SC) or placebo every 2 weeks for 24 weeks	Severe OCS-treated asthma	· 70%↓ OCS · 59% ↓ rate of exacerbations · 220 ↑ pre-bronchodilator FEV_1 (mL; week 20)
Corren et al. 2017[43] (PATHWAY)	Tezepelumab (70 mg SC) or 210 mg every 4 weeks or 280 mg or placebo every 2 weeks for 52 weeks	Severe uncontrolled asthma	· 62% (70 mg); 66% (280 mg) to 71% (210 mg) ↓ rate of exacerbations · 48% (70; 280 mg) to 60% (210 mg) ↓ OCS · 120 (70 mg); 130 (210 mg) to 150 (280 mg) ↑ pre-bronchodilator FEV_1 (mL)
Wechsler et al. 2020[45] (SOURCE)	Tezepelumab (210 mg SC) or placebo every 4 weeks for 48 weeks	Severe uncontrolled asthma	· No changes in OCS
Menzies-Gow et al. 2023[44] (NAVIGATOR)	Tezepelumab (210 mg SC) or placebo every 4 weeks for 52 weeks	Severe, uncontrolled asthma	· 56 % ↓ rate of exacerbations · 130↑ pre-bronchodilator FEV_1 (mL)
Brightling et al. 2014[67]	Benralizumab 100 mg (SC) or placebo every 4 weeks for the first 3 doses and then every 8 weeks for 48 weeks	Moderate-to-severe COPD	· No changes in the rate of exacerbations · 130 ↑ pre-bronchodilator FEV_1 (mL; week 20)
Pavord et al. 2017[66] (METREX)	Mepolizumab (100 mg SC) or placebo every 4 weeks for 52 weeks (last dose at 48 weeks)	Frequently exacerbating COPD	· 18% ↓ rate of exacerbations (BEC $\geq$150/μL) · No changes in FEV_1
Pavord et al. 2017[66] (METREO)	Mepolizumab (100 mg or 300 mg SC) or placebo every 4 weeks for 52 weeks (last dose at 48 weeks)	Frequently exacerbating COPD	· No significant changes in the rate of exacerbations and FEV_1
Bhatt et al. 2023[69] (BOREAS)	Dupilumab (300 mg SC) or placebo every 2 weeks for 52 weeks	Moderate-to-severe COPD	· 30% ↓ rate of exacerbations · 83↑ pre-bronchodilator FEV_1 (mL)
Bhatt et al. 2024[72] (NOTUS)	Dupilumab 300 mg (SC) or placebo every 2 weeks for 52 weeks	Moderate-to-severe COPD	· 44% ↓ rate of exacerbations · 160↑ pre-bronchodilator FEV_1 (mL)

BEC: blood eosinophil count; COPD: chronic obstructive pulmonary disease; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; IV: intravenous; OCS: oral corticosteroid; RCTs: randomized controlled trials; SC: subcutaneously.

conclusions, highlighting how most patients who discontinue biologics have a higher risk of exacerbations and worse clinical outcomes.[76,83] Notably, based on real-world evidence regarding subsets of patients who reached highly well-controlled conditions during therapy with biological agents, who are considered super-responders, some authors have proposed algorithms for the suspension of biological agents in this subset of patients.[84] Obviously, this type of proposal and the related interruption criteria need validation and refinement through further extensive studies, considering the limited number of supporting evidence. The efficacy of mAbs in terms of reducing dosage of asthma usual care drugs such as ICS and OCS is considerably more established. A Cochrane systematic review confirmed that omalizumab allows not only an approximately 25% reduction in asthma exacerbation rates but also a substantial reduction in maintenance doses of ICS.[85] Other data support the evidence that dupilumab reduces severe exacerbations and improves lung function and asthma control in subsets of patients with T2 asthma who received high-dose ICS at baseline, also allowing for an ICS-sparing effect.[86] Recently, a phase 4, randomized, open-label active-controlled study (SHAMAL)[87] demonstrated that patients controlled on benralizumab can exhibit meaningful reductions in ICS therapy doses while maintaining asthma control. Overall, 110 (92%) patients reduced their ICS–formoterol dose: 18 (15%) to medium dose, 20 (17%) to low dose, and 72 (61%) to as-needed dose only. In 113 (96%) patients, reductions were maintained to week 48, and 91% of the patients in the reduction group did not exhibit exacerbations during tapering.

There exists ample and strong evidence regarding the OCS-sparing effect of biologics. The current mAbs have been shown to exert an OCS-sparing effect in RCTs, paving the way for overcoming OCS dependence in severe asthma.[88] In patients in whom OCS resistance or dependence is demonstrated by high daily doses, the current pharmacologic armamentarium based on the use of biological agents effectively allows the reversal of OCS dependence, with many cases exhibiting weaning from OCS therapy or >50% reduction in baseline maintenance dose.[89–91]

Patients with severe asthma present with various comorbidities, and some of them can complicate asthma treatment and considerably increase the risk of poor asthma-related outcomes. Asthma comorbidities have been classified into three categories, including those related to T2 inflammation, those potentially due to chronic OCS exposure, and those that could mimic or worsen asthma symptoms. Overlapping of the comorbidities is common. According to the latest data from the International Severe Asthma Registry,[92] some comorbidities are more prevalent than others (e.g. rheumatoid arthritis, obesity, and gastroesophageal reflux disease), and >50% of patients with severe asthma present with at least three comorbidities. A marked variability was observed between countries in the prevalence of comorbidities, probably due to a heterogeneity in reporting methodology, misclassification, or demographic variability between countries. Nonetheless, the study underlined the need to evaluate comorbidities in the real world through standardized tools, given the impact of comorbidities on clinical outcomes, namely, exacerbations, OCS use, and disease control, which are the same outcomes used to define response to therapy and remission.

Drug-free concept in COPD and the anti-inflammatory effect of LAMA

The latest GOLD 2023 report[93] defines COPD as a heterogeneous lung condition characterized by chronic respiratory

symptoms due to abnormalities of the airways that cause persistent or progressive airflow obstruction, indicating that inhaled therapy is the cornerstone of treatment. Thus, COPD is strictly associated with pharmacological treatment using inhalers to reduce symptoms, exacerbations, and slow the lung functional decline.

However, the proven efficacy of inhalers leads us to the question of whether COPD can be cured and not only treated. To date, the concept of drug-free remission in COPD has never been analyzed, although the scientific literature depicts interesting scenarios in other conditions such as asthma, rheumatoid arthritis, or type II diabetes.

To date, there is no expert consensus in drug-free remission concept in COPD such as asthma[81] where remission is defined by the absence of respiratory symptoms for 12 months after discontinuing drugs, along with a reduction of inflammation and decline in lung function.

We may assume that features of a drug-free clinical remission in COPD should include 12 months of absence of symptoms, the same decline in the lung function of healthy controls, radiological stability of emphysema, and no acute exacerbations of COPD over 12 months.

According to the 2023 GOLD Report, patients with symptomatic COPD must be defined as those with a modified Medical Research Council (mMRC) score $\geq$2 or a COPD Assessment Test (CAT) score $\geq$10. In parallel to the drug-free and clinical remission concepts, the concept of treatment response in COPD should be considered. Patients with COPD may be considered controlled if minimal or no symptoms, no exacerbations, and no impairment in QoL occur during follow-up, due to the correct treatment administered.[94]

Inhalers have a significant impact on primary respiratory outcomes of symptom burden such as the reduction of mMRC/CAT[95] or other QoL scores such as the SGRQ,[96] although the off-treatment scores remain unpredictable to date. Besides inhalers, GOLD Report pointed out that "Group A" is already showing a COPD diagnosis using a FEV_1/FVC fixed ratio of $<$0.70 with poor respiratory symptoms regardless of inhalation treatment.

LAMA is a pivotal drug in COPD and an important approved treatment in GINA step 4 and 5 when severe asthma occurs. COPD and asthma share airflow obstruction, although such disorders are characterized by different pathophysiological pathways (hyperinflation vs. airway hyperresponsiveness) or bronchospasm triggers.[97]

LAMA treatment modulates airway contractility by blocking the muscarinic acetylcholine receptors (AchRs) M1–M2–M3 located in the airway smooth muscle of the lung bronchial tree.[98] Interestingly, in vitro anti-inflammatory effect of LAMAs have been well-described for tiotropium, aclidinium, and glycopyrronium with regard to significant effect on neutrophilic macrophage-1 antigen or chemokine expression, leading to further in vivo investigations.[99] Moreover, anti-inflammatory effects of muscarinic receptor antagonists have been described in laboratory mammals, showing that the number of neutrophils and macrophages in bronchoalveolar lavage fluid can be affected by LAMAs.[100] Thus, increasing evidence has indicated that LAMAs can affect respiratory diseases via an anti-inflammatory mechanism by blocking AchRs expressed on inflammatory cells or epithelial cells.[101,102]

The clinical effect of LAMAs in reducing the risk of COPD acute exacerbation has been confirmed by recent evidence showing that LAMA in stable COPD led to a lower incidence of exacerbations than LABA.[103] Furthermore, inflammatory cascade in lung diseases, especially COPD, can be influenced by LAMAs, reducing mucus

secretion via M3 AchR modulation, and could play a key role in lung microbiota.[104]

Therefore, LAMA treatment demonstrates its efficacy not only through the notorious modulation of airway obstruction by blocking the muscarinic AchRs but also through anti-inflammatory pathways leading to protective effects against the risk of exacerbation or lung function decline.

Discussion and conclusions

Taken together, all data from RCTs and real-life observations confirm that mAbs have a significantly favorable impact on clinical and functional outcomes in severe asthma, paving the way for the emerging concepts of disease-modifying drugs and disease remission. In a patient-centered approach, an ideal definition of asthma remission should be based on the absence of symptoms and exacerbations and no need for OCS, along with stable lung function. Thus, clinical remission has been proposed as a novel outcome measure to evaluate treatment efficacy and effectiveness.

If substantial evidence has demonstrated that biologics allow OCS reduction or even discontinuation, emerging data propose that ICS sparing is similarly possible in patients with well-controlled asthma. Nonetheless, given the impact of comorbidities on clinical outcomes such as exacerbations, OCS use, and disease control, a systematic evaluation of comorbidities during routine asthma review, possibly through standardized tools, and a multidisciplinary and holistic approach to asthma management are recommended. Considering predictors of treatment response in asthma, recent evidence demonstrates that a shorter duration of disease, less severe impairment, and a lower body mass index are remission predictors in patients receiving biologic therapy.[105,106]

Biologic treatment should not be delayed if remission is the goal, and complete remission should be pursued for all patients with asthma. Partial remission or sustained symptom control could be considered acceptable in patients with a negative predictor of treatment response or airway remodeling; however, even if these concepts could better answer the clinical needs from a practical perspective, complete remission remains the desirable target for all patients with asthma. The treat-to-target approach aims to achieve disease remission, imposing a deeper and more accurate understanding of the critical causal mechanisms and endotypes to generate real-life–changing benefits for patients.[107]

It has been hypothesized that different levels of therapeutic success are appropriate for different patient phenotypes, highlighting the importance of different inflammatory profiles.[108] This aspect is crucial in patients with COPD who are currently considered very distant from the possibility of reaching the remission status. Based on the increasing confirmed evidence on patients with asthma, better endo-phenotyping is central to these patients and could be anticipated in clinical practice, paving the way for biologic treatment access, disease-modifying possibility, symptom control, and disease stability.[109–111] Currently, a pragmatic approach is needed to better define how long it takes for remission to be considered sustained, which may help determine the role of comorbidities in reaching the status of disease remission. The evaluation of eventual biomarkers of remission in asthma treatment can help predict whether this goal can be maintained after cessation of biological treatment, which is an important unmet need and should be explored in further research.

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Author contributions

SC, FM, IB, PVM, FL, and FM were involved in conceptualizing the idea and writing the main manuscript. IB prepared the table. CC was involved in revision and production of the final version of the manuscript.

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