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REVIEW

Biologics and airway remodeling in asthma: early, late, and potential preventive effects

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Abstract

Although airway remodeling in severe and/or fatal asthma is still considered irreversible, its individual components as a cause of clinical symptoms and/or lung function changes remain largely unknown. While inhaled glucocorticoids have not consistently been shown to affect airway remodeling, biologics targeting specific pathways of airway inflammation have been shown to improve lung function, mucus plugging, and airway structural changes that can exceed those seen with glucocorticoids. This superiority of biologic treatment, which cannot be solely explained by insufficient doses or limited durations of glucocorticoid therapies, needs to be further explored. For this field of research, we propose a novel classification of the potential effects of biologics on airway remodeling into three temporal effects: *early effects* (days to weeks, primarily modulating inflammatory processes), *late effects* (months to years, predominantly affecting structural changes), and potential *preventive effects* (outcomes of early treatment with biologics). For the identification of potential *preventive effects* of biologics, we call for studies exploring the impact of early biological treatment on airway remodeling in patients with moderate-to-severe asthma, which should be accompanied by a long-term evaluation of clinical parameters, biomarkers, treatment burden, and socioeconomic implications.

KEYWORDS
asthma treatment, biologics, remodeling

1 | PREMISE

In the context of a recent classification which includes biologics in the treatment of asthma among the disease-modifying anti-asthmatic drugs (DMAADs),[1] this viewpoint examines the disease-modifying potential of biologics beyond that of achieving remission by controlling symptoms, avoiding exacerbations, and the need for systemic glucocorticoids. Prior to the introduction of biologics, persistent fixed airflow obstruction (FAO) in severe asthma, unresponsive to oral glucocorticoids (OCS), was attributed

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to permanent structural changes in the airways. Although ill-defined in terms of structural and/or pathophysiological alterations, these changes were frequently referred to as "airway remodeling" (AiRem). Its pathobiological relevance in asthma was first described in 1992[2] and later referred to as "structural consequences of airway inflammation in asthma",[3] underscoring its presumed irreversible nature. Autopsy studies of fatal asthma cases have documented various histological alterations, including epithelial damage, reticular basement membrane (RBM) thickening, goblet cell hyperplasia/metaplasia, mucus plugging, airway smooth muscle (ASM) hyperplasia, altered extracellular matrix composition, and increased inflammatory angiogenesis in both large and small airways.[4–6] Moreover, airway inflammation is characterized by prominent infiltration of eosinophils, mast cells, and neutrophils.[7–9] Based on the multifactorial pathogenetic heterogeneity of AiRem, the underlying mechanisms, as well as personalized approaches to target different components of AiRem, remain challenging to address.[10]

Clinical observations suggest that AiRem can be differentiated into two major components:

1. An inflammatory component characterized by persistent airway infiltration/activation of immune cells, including eosinophils, mast cells, monocytes/macrophages, basophils, and neutrophils, associated with mucosal oedema and mucus plugs.[11,12] This component contributes to airway alterations not only due to their proinflammatory effects but also due to steric changes caused by their mere accumulation.[13]
2. A structural component characterized by epithelial and connective tissue changes involving fibroblast/myofibroblast transition, ASM hypertrophy/hyperplasia, RBM thickening, goblet cell hyperplasia/metaplasia, angiogenesis, increased sensory nerve endings, and altered neuronal function.[12,14–17] The combination of inflammatory and structural changes in AiRem provides the basis of what manifests as FAO in clinical settings.[12]

Currently available biologics which target IgE, interleukin (IL)-5/IL-5Rα, IL-4Rα, and the alarmin thymic stromal lymphopoietin (TSLP) as well as IL-25 and IL-33 interfere with specific mechanisms relevant to the pathogenesis of both components of AiRem mentioned above. For instance, IgE contributed to AiRem by inducing human ASM cell proliferation[18] and by stimulating the production of several cytokines (e.g., IL-13 and IL-4) and chemokines (e.g., CXCL8) from mast cells.[19,20] IL-5 induced subepithelial and peribronchial fibrosis by recruiting and activating eosinophils, which are a major source of TGF-β.[21,22] In a preclinical study, treatment of wild-type mice with neutralizing anti-IL-5 antibody almost completely prevented allergen-induced subepithelial and peribronchial fibrosis.[22] Similarly, IL-4 stimulated ASM cells with increased actin and collagen synthesis and TGF-β release by the airway epithelium,[23,24] IL-13 disrupted epithelial integrity,[25] promoted TGF-β release from airway epithelial cells, stimulated airway fibrosis[23] through the action of matrix metalloproteinases (MMPs),[26] and enhanced goblet cell metaplasia.[27–29] In a mouse model of asthma, anti-IL-13 antibody suppressed airway inflammation and remodeling.[30] TSLP promoted AiRem by activating dendritic cells, eosinophils,[31] mast cells,[32] and human lung macrophages.[33,34] TSLP also activated lung fibroblasts, which produce extracellular matrix (ECM) molecules such as collagen type I and MMP-1.[35] TSLP induced the release of vascular endothelial growth factor (VEGF)-A, the most potent angiogenic factor, from human lung macrophages.[34] This alarmin also induced epithelial-mesenchymal transition (EMT) in airway epithelial cells.[36] In a mouse model of allergic asthma induced by chronic exposure to house dust mites (HDM), neutralization of TSLP inhibited AiRem.[37] Additionally, microRNA-19b reduced AiRem by inhibiting Stat3 signaling through TSLP downregulation in a mouse model of asthma.[38] Administration of an anti-TSLP mAb decreased airway structural changes by reducing MMP, TGF-β, and connective tissue growth factor in AiRem in ovalbumin-challenged (OVA) mice.[39] IL-33 increased the production of collagen and fibronectin-1 in lung fibroblasts contributing to AiRem.[40,41] In a mouse asthma model, neutralization of the IL-33 pathway improved several aspects of AiRem and lung function.[42] IL-25 stimulated lung fibroblast proliferation[43] and collagen production.[44] IL-25 contributed to AiRem by inducing airway angiogenesis in mouse asthma models.[44,45] Finally, the combined blockade of IL-25, IL-33, and TSLP more effectively inhibited AiRem in a mouse model of asthma compared to blocking each cytokine individually.[42]

2 | AIRWAY INFLAMMATION AND REMODELING

Type (T) 2 inflammation has been postulated to be involved in AiRem development in patients with severe asthma.[46] The contribution of eosinophilic inflammation to AiRem varies between allergic and eosinophilic or intrinsic asthma, with the latter expressing higher levels of T2-markers[1] and a more difficult-to-treat phenotype.[47] Activated eosinophils and mast cells induce AiRem by stimulating the proliferation of ASM cells and the release of TGF-β, cationic proteins, and cytokines.[48,49] Blood eosinophils are associated with airflow obstruction and enhanced lung function decline, independently of asthma or smoking.[50] Moreover, in a large longitudinal study, blood eosinophils were associated with the risk of developing obstructive lung disease.[51] A recent study identified IL-5Rα expression in lower airway fibroblasts from healthy individuals and patients with asthma, suggesting a potential pathogenic role of IL-5 in fibrosis and AiRem. This observation expands the scope of IL-5 biology beyond its effects on eosinophils, suggesting that IL-5 inhibition could offer a therapeutic pathway to prevent, mitigate, or even reverse AiRem.[52] Accordingly, it could be postulated that any sustained reduction in peripheral blood eosinophil levels, and consequently in the airways, might lead to a reduction in the progressive decline of lung function. Similarly, elevated FeNO levels have been associated with a progressive decline in lung function[53]; however, it remains unclear to what extent elevated FeNO levels contribute to this decline or whether they are merely a consequence of underlying airway inflammation. Thus, as yet there is only circumstantial evidence that

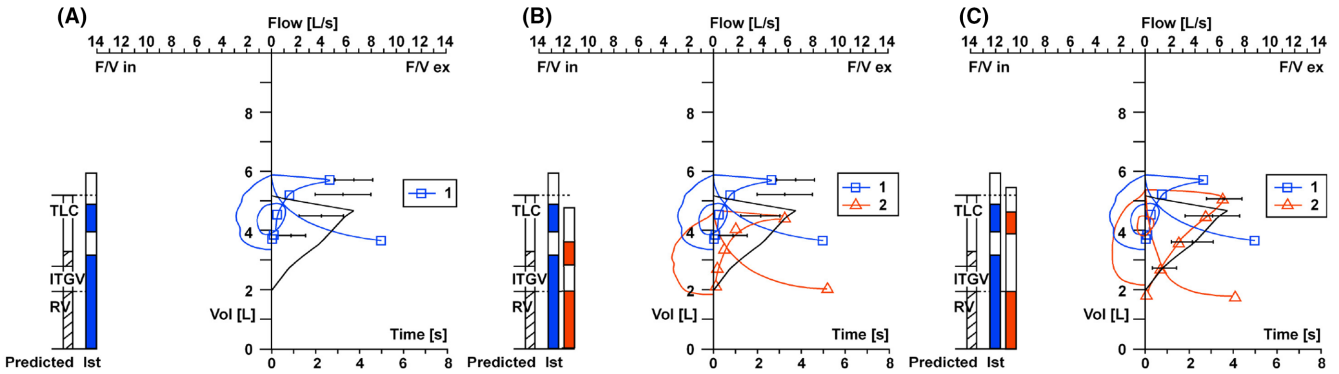

FIGURE 1 (A) FEV_1 (1.3 L [49% predicted]) in a patient with severe asthma and repeated severe OCS-dependent exacerbations despite maintenance treatment with oral prednisolone (5 mg/day per os) prior to biologics. (B) The red lines show the FEV_1 improvement (1.6 L [61% predicted]) after seven courses of mepolizumab (100 mg s.c./4 weeks) without prednisolone. (C) The red lines show FEV_1 improvement [FEV_1 2.8 L (105% predicted)] after five courses of reslizumab (3 mg/kg IV/4 weeks) without prednisolone. F/V ex, flow/volume during expiration; F/V in, flow/volume during inspiration; ITGV, intrathoracic gas volume; RV, residual volume; TLC, total lung capacity; Vol, volume.

as therapeutic interventions biologics can achieve these outcomes. Therefore, studies such as the ongoing ATLAS trial (clinicaltrials.gov identifier NCT05097287) will be instrumental in evaluating the long-term effects of biologics on preventing or slowing lung function decline. The ATLAS trial will assess whether dupilumab can prevent or slow lung function decline over a 3-year period, focusing on patients with elevated FeNO levels.[54]

The contribution of non-T2 inflammation to AiRem remains controversial.[55–58] Dendritic cells activated by TSLP drive the differentiation of naïve T-cells into a Th17 phenotype,[59] which enhances neutrophilic inflammation and fibrotic matrix accumulation that correlate with TGF-β expression.[60,61] However, in the absence of T2 inflammation, the diagnosis of asthma needs to be questioned.[62] Accordingly, the pathobiology of what is defined as "T2-low" asthma remains unclear and might include patients in whom asthma is unlikely but also those with spontaneously (i.e., infections) or pharmacologically (i.e., glucocorticoids) suppressed T2-markers.

3 | GLUCOCORTICOIDS AND AIRWAY REMODELING

Although inhaled glucocorticoids (ICS) have been shown to downregulate some mediators (i.e., tenascin) involved in airway structural changes, other aspects such as RBM thickening, remain unchanged.[63–66] Intramuscular glucocorticoids do not improve FEV_1 in approximately 80% of patients with severe asthma,[67] and rescue OCS in patients already treated with high dose ICS/LABA only partly improve lung function.[68] Finally, pharmacologic treatment might paradoxically contribute to AiRem: β_2-agonists can increase neurotrophin levels in patients with asthma,[69] potentially augmenting the autonomous nervous system's hyperresponsiveness.[70]

In contrast, biologics have been shown to improve airflow obstruction unresponsive to OCS in a substantial percentage of patients with severe asthma.[71–76] Benralizumab,[77] mepolizumab,[78,79] and dupilumab[71,80] improve lung function and reduce the frequency of exacerbations despite an average reduction of their OCS dose of approximately 75%.

Accordingly, the definition of FAO should no longer be defined by an unresponsiveness to OCS, but rather on pathobiological assessments. The dichotomy between inflammatory and functional changes refractory to OCS and the seemingly irreversible sequelae of airway structural changes needs to be reevaluated in the biological era. Unfortunately, but understandably from an ethical point of view, there are no direct comparative studies between biologics and OCS. Moreover, the clinical impression that remission achieved by biologics exceeds that achievable with OCS may be influenced by the tapering of OCS dosage during the observation period. This practice might lead to inadequate dosing of OCS, as it represents a compromise between suppressing inflammation and patients' willingness to adhere to the treatment.

4 | EVIDENCE FOR THE EFFECTS OF BIOLOGICS ON AIRWAY REMODELING

The current hypothesis holds that FAO in asthma, particularly in nonsmokers, is at least partially linked to AiRem driven by persistent airway inflammation.[81,82] AiRem refers to pathologic alterations of the airway wall that have been documented in patients with different asthma severity and age and involve both large and small airways.[82] Parenchymal and vascular remodeling may also contribute to FAO and longitudinal decline in FEV_1.[81] Thus, AiRem affects the "whole lung", with functional and structural changes in the airways and lung parenchyma (e.g., loss of lung tissue elasticity and alveolar damage) leading to FAO.[81]

A reduction in the rate of asthma exacerbations has been the primary endpoint in all clinical studies with biologics in severe asthma since the INNOVATE trial for omalizumab.[83] Clinical experience as well as real-life studies suggest that biologics can normalize airway patency in a substantial percentage of patients, even if FEV_1 impairment was poorly or unresponsive to inhaled bronchodilators, ICS,

and OCS. In the past, these patients' airflow obstruction had been labeled as "fixed" or "nonresponsive" even to OCS and was, therefore, allegedly due to irreversible structural changes. Figure 1 exemplifies the normalization of lung function after biologics treatment in a patient with severe eosinophilic asthma, challenging the notion of irreversibility and highlighting the disease-modifying potential of biologics.

These clinical observations have never been formally analyzed in randomized clinical trials (RCT). However, the term "super-responder" has been introduced[84] to define patients treated with biologics who achieve no further exacerbations. This definition, which varies across the studies discussed below, does not address the newer and overarching concept of remission, which refers to few or no symptoms, no requirement for OCS, absence of asthma exacerbations, and stable lung function for a period of 12 months.[1]

Indirect evidence suggests that lung function impairment unresponsive to glucocorticoids, and therefore considered "irreversible", can improve with biologics.[85] The latter study defined "super-responders" as patients without exacerbations, OCS withdrawal, and few or no asthma symptoms (ACT score ≥ 20 and ACQ score < 1.5). Accordingly, 47% of patients on benralizumab, 58% on mepolizumab, and 61% on omalizumab achieved such improvements in FEV_1.[85]

Stopping omalizumab after long-term treatment led to a recurrence of asthma exacerbation in 52.3% of patients within a year, while asthma control was maintained in 47.7% of patients.[86] Obviously, this circumstantial evidence is only suggestive of possible anti-remodeling effects but needs further investigation. Similarly, in patients with severe asthma whose treatment with mepolizumab was discontinued after 3 years, worsening of lung function and exacerbations occurred earlier and more frequently compared to those who had not discontinued mepolizumab. However, a substantial proportion of the latter remained in remission, suggesting long-term benefits which could be attributed not only to anti-inflammatory but also to anti-remodeling effects.[87] Characteristics and biomarkers of "super-responders" to biologics have not been identified but should become a priority of future prospective studies.

In a real-life study, patients treated with mepolizumab, who discontinued OCS without exacerbations, did not show any FEV_1 improvements,[88] while in a similar study, patients on benralizumab showed a significant increase in FEV_1 despite a reduction in OCS.[89] Notably, "super-responders" to benralizumab had lower baseline FEV_1 values but higher doses of OCS compared to responders, supporting the assumption that airflow obstruction responded to benralizumab better than to OCS. In another observational study conducted in patients with frequent exacerbations (median 3 OCS courses/year) and a mean FEV_1 of 57% predicted, mepolizumab treatment increased FEV_1 despite a reduction in OCS.[90]

"Super-responders", defined as patients with no residual disease manifestation after a 2-year treatment with anti-IL-5/IL-5Rα antibodies (mepolizumab, reslizumab, and benralizumab), had a greater improvement in FEV_1 than those with partial or no response, despite a complete withdrawal of OCS.[91] In a previous RCT conducted in patients on maintenance OCS, mepolizumab improved FEV_1 despite a mean reduction in OCS of 50%.[79] Similarly, benralizumab showed an increase in FEV_1 after 20 weeks of treatment despite a 75% reduction in maintenance OCS dose.[89] Moreover, it has been shown that lung function impairment poorly responsive to β_2-agonists in severe asthma might predict a better response to reslizumab.[92]

The addition of the IL-4Rα blocker dupilumab to maintenance OCS led to a sustained FEV_1 improvement despite an average 70% reduction in the maintenance dose of OCS.[93] These findings suggest that this biologic is superior to conventional asthma treatment, including OCS, to maintain airway patency. Rapid lung function improvement has also been described in patients with uncontrolled, moderate-to-severe asthma treated with dupilumab.[94]

Tezepelumab, which blocks the activity of TSLP,[95] rapidly improved lung function, reduced airway submucosal eosinophils, and biomarkers of AiRem (i.e., matrix metalloproteinase (MMP)-10 and MMP-3) in a broad population of patients with severe, uncontrolled asthma.[96,97] Lung function parameters improved at week two and were sustained over 52 weeks.[96]

Mucus plugging which has been described as localized and persistent[98] significantly contributes to symptom severity and exacerbations in asthma, correlating with airway obstruction and T2 inflammation. Biologics have shown effectiveness in reducing mucus plugs and improving airway obstruction in severe asthma.[99,100] In particular, benralizumab, dupilumab, mepolizumab, and most recently tezepelumab have been associated with a reduction in mucus plugs in the airways of patients with severe asthma.[101–105] Benralizumab significantly reduced the number of mucus plugs, which were associated with sputum eosinophils.[103] Dupilumab reversed airway mucus hypersecretion, as evidenced by reduced mucus score, and imaging aspects of AiRem (e.g., airway wall area) in patients with moderate-to-severe asthma.[106] Tezepelumab has been shown to reduce mucus plug scores and improve lung function in adults with moderate-to-severe asthma.[104]

In recent years, high-resolution computed tomography (HRCT) and magnetic resonance imaging (MRI) have emerged as noninvasive techniques to examine various aspects of AiRem.[107] Two studies reported that omalizumab reduced airway wall thickness[108] and airway wall area corrected for body surface[109] assessed by HRTC. In two studies conducted[110,111] on AiRem using HRCT, it was found that mepolizumab treatment resulted in a greater change in pre-/post-treatment luminal area compared to the placebo group. In addition, mepolizumab reduced bronchial wall thickness, as evaluated by endobronchial ultrasound (EBUS).[112] In a phase 2 study, tezepelumab improved the CT scan-determined lumen area across airway generations.[97] In uncontrolled eosinophilic asthma, early ventilation defect responses at 4 weeks after benralizumab persisted at 2.5 years, along with marked improvements in mucus scores.[113] Future studies, such as the BURAN study (NCT05552508) for benralizumab and FUNLUM study (NCT04512521) for mepolizumab, are needed to evaluate the effects of these biologics on airway structure and dynamics through functional respiratory imaging (FRI), a new technique for detailed 3D lung analysis.[114] Overall, studies using CT and

MRI in asthma have the potential to noninvasively address some structural and functional changes in airways and pulmonary vessels associated with disease severity. These techniques will be useful in assessing the effects of biologics on AiRem, and possibly differentiating between reversible and potentially irreversible changes.

5 | PROPOSAL FOR A CLASSIFICATION OF THE POTENTIAL EFFECTS OF BIOLOGICS ON AIRWAY REMODELING

There is increasing evidence that biologics can improve lung function, inflammatory, and/or structural alterations, "traditionally" referred to as AiRem.[12,46] The underlying mechanisms and specific predictors of the biologics' effects on various aspects of AiRem are still largely unknown. Future investigations, including studies using novel technologies (e.g., single-cell mRNA sequencing of airway biopsies), should investigate the effects of different biologics on distinct components (inflammatory/immune and structural) of AiRem in patients with asthma. In proposing a classification of the potential effects of biologics on AiRem, we categorize these effects into early, late, and preventive. It's imperative to clarify that while early and late effects are supported by emerging evidence showcasing biologics' impact on lung function and on inflammatory and structural changes, the "preventive effects" represent a forward-looking hypothesis. This distinction aims to underscore the nascent yet promising area of preventive potential, which, despite its current lack of direct evidence, encourages a pivotal direction for future research.

Figure 2 schematically illustrates the mechanisms of action of different biologics and their immunological and cellular targets in the context of airway remodeling. The red lines represent the potential mechanisms responsible for early effects, while the blue lines for late effects.

Figure 3 Proposed classification of the early, late, and potential preventive effects of biologics on airway remodeling in asthma.

5.1 | Early effects of biologics

Early effects of biologics on inflammatory events of AiRem are observed within days or weeks of starting treatment. Dupilumab has a fast onset of action on different T2 inflammatory disorders, including severe asthma, leading to FEV_1 improvements within 2 weeks after the first administration, maintained throughout the treatment.[71,121,124,144] Similar rapid effects occur in patients with chronic rhinosinusitis with nasal polyps (CRSwNP), where dupilumab reduced polyps' size (NPS-Nasal Polyp Score) within 2 weeks.[145] This was also confirmed for benralizumab in a real-life study.[146]

FEV_1 improvements after a single administration of benralizumab have been observed within 28 days,[125,147,148] possibly also due in part to a reduction in peripheral airway mucus plugs. A significant change in mean predicted FEV_1 and FEV_1% was observed after 1 month of mepolizumab treatment.[122] Moreover, mepolizumab improved small airway function after the first administration.[149] A post hoc analysis demonstrated lung function improvement in patients with moderate-to-severe allergic asthma treated with omalizumab as early as 16 weeks.[123] Tezepelumab demonstrated significant FEV_1 improvements as early as week 2 and was sustained for the duration of the trial.[150] Itepekimab, which blocks IL-33 activity, has been shown to improve pre-bronchodilator FEV_1 as early as 4 weeks of treatment.[126] Additionally, tozorakimab is a novel mAb that inhibits IL-33 activity via both the ST2 and the receptor for advanced glycation end products–epidermal growth factor receptor complex signaling pathways. Although its effects on AiRem in asthma have not been studied, the broader context of IL-33 inhibition suggests potential improvements in lung function and certain features of AiRem. Figure 3 schematically illustrates a proposed classification of the early, late, and potential preventive effects of biologics on airway remodeling in asthma.

5.2 | Late effects of biologics

The evidence for a therapeutic effect of biologics on structural changes in asthma that revert after prolonged treatment is still circumstantial and requires further investigation. In analogy, atopic dermatitis, which causes hyperplastic epidermis, prominent hyperkeratosis, minimal spongiosis, and infiltration of immune cells (i.e., dendritic, Th1, Th2, and pro–B cells) can respond to dupilumab with almost complete restoration of previously damaged and scarred skin lesions.[136,137] This reversal of skin structural changes induced by a biologic in severe atopic dermatitis was neither anticipated nor observed with any previous treatment, especially not with systemic or topical glucocorticoids. Accordingly, these effects have been attributed to direct or indirect effects of dupilumab on skin remodeling.[136,137] Similarly, in eosinophilic esophagitis (EoE), dupilumab has been shown to improve aspects related to structural remodeling, as evidenced by the reduction in peak oesophageal intraepithelial eosinophil count, Endoscopic Reference Score (EREFS), as well as Histologic Scoring System (HSS) versus placebo.[138] There is increasing evidence that similar effects might occur in asthma. Late effects of biologics might modify some of the structural changes of AiRem which occur in severe asthma, with these changes becoming evident over the course of several months or even years of therapy.[12] Initial studies of the biologics' effects on AiRem were performed in vivo on bronchial biopsies.[63] Although such invasive investigations are not part of any routine assessment of the effects of antiasthmatic treatments, noninvasive imaging techniques (HRCT and nuclear magnetic resonance [NMR]) might in the future be useful to indirectly document the effects of biologics on AiRem in asthma.[81,93,151] Accordingly, it has been reported that omalizumab reduced airway wall thickening and sputum eosinophil numbers in patients with asthma.[108] Similar effects on RBM thickening were reported in biopsies of patients with severe asthma.[152] Moreover, omalizumab reduced basal lamina thickness and fibronectin deposits in the bronchial mucosa of severe allergic asthmatics.[120] In vitro

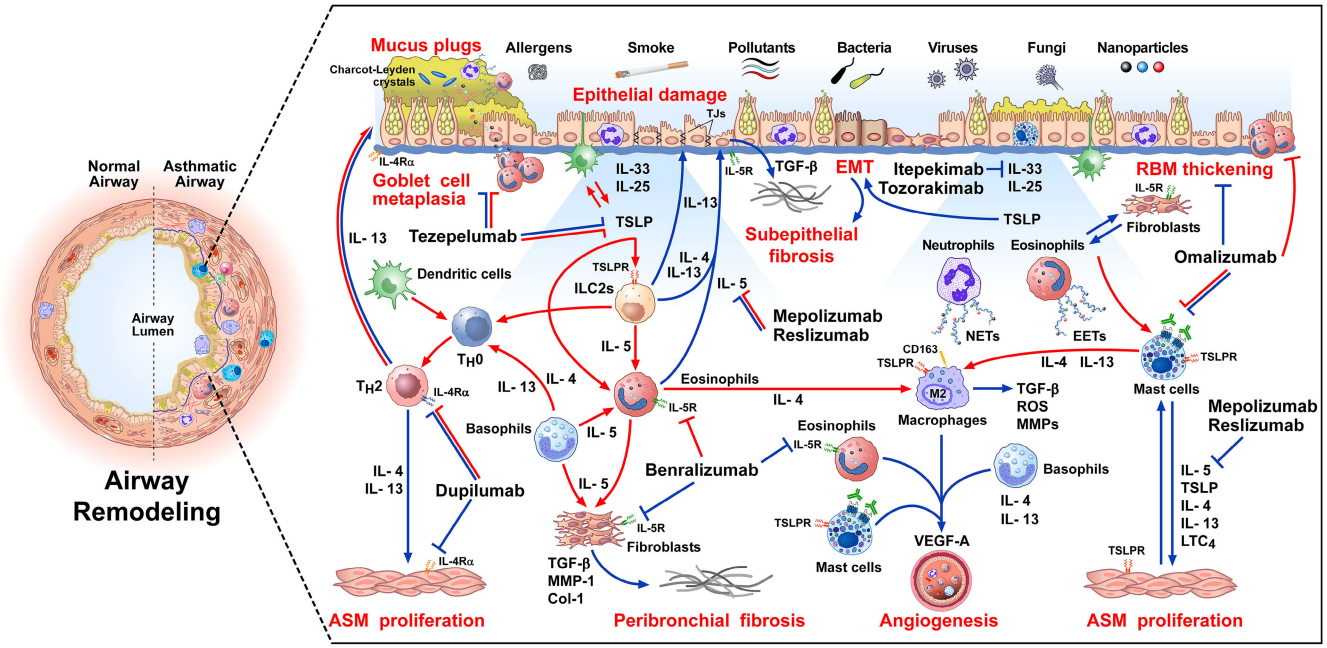

FIGURE 2 The figure schematically illustrates the complex mechanisms involved in airway remodeling (AiRem) in asthma. The figure also highlights the effects of various biological therapies in modulating these processes. The left side of the figure shows a normal airway compared to an asthmatic airway, which is characterized by inflammatory and structural changes such as epithelial damage, goblet cell metaplasia, mucus plugging, reticular basement thickening (RBM), airway smooth muscle (ASM) proliferation, subepithelial and peribronchial fibrosis, and increased angiogenesis. Several environmental factors (e.g., allergens, smoke, pollutants, microbial compounds, and nanoparticles) cause epithelial damage, leading to the release of alarmins (i.e., TSLP, IL-33, and IL-25). These cytokines activate a broad spectrum of innate (e.g., ILC2s) and adaptive (e.g., Th2 cells) immune cells, which promote airway inflammation and remodeling through the production of IL-4, IL-5, and IL-13.[115] TSLP plays a central role in AiRem by activating dendritic cells, eosinophils,[31] mast cells,[32] and human lung macrophages.[33,34] TSLP also stimulates lung fibroblasts to produce extracellular matrix (ECM) components, promoting peribronchial fibrosis.[35] In addition, TSLP induces the release of vascular endothelial growth factor (VEGF)-A, the most potent angiogenic factor, from lung macrophages,[34] and triggers epithelial-mesenchymal transition (EMT).[36] Tezepelumab, a human monoclonal antibody (mAb) that blocks TSLP, interferes with the activation of upstream and downstream inflammatory pathways, which contribute to goblet cell hyperplasia, mucus plugging, EMT, and angiogenesis. Dupilumab, an IL-4Rα mAb antagonist, blocks both IL-4 and IL-13 signaling. IL-4 promotes ASM proliferation by increasing Actin and collagen synthesis and enhancing TGF-β release from the airway epithelium.[23,24] IL-13 disrupts epithelial integrity[25] and promotes TGF-β release from airway epithelial cells, stimulating airway fibrosis[26] through the action of matrix metalloproteinases (MMPs). IL-13 also enhances goblet cell metaplasia, contributing to mucus production and airway obstruction.[23,27,29] Dupilumab reduces mucus hypersecretion and goblet cell metaplasia[106] and modulates ASM responses.[116] Mepolizumab and reslizumab block IL-5, which plays a critical role in subepithelial and peribronchial fibrosis by recruiting and activating eosinophils, which are major sources of TGF-β.[21,22] Mepolizumab reduces ASM proliferation and prevents IL-5-mediated epithelial damage and fibrosis.[117,118] Benralizumab, by targeting IL-5Rα, induces eosinophil depletion, thereby mitigating eosinophil-driven AiRem. Benralizumab also reduces mucus plugging[103] and ASM proliferation.[119] Omalizumab, which targets IgE, reduces RBM thickening and fibronectin deposits in the bronchial mucosa.[120] Itepekimab and Tozorakimab, interfering with IL-33 signaling, may reduce AiRem by inhibiting TGF-β pathways, although their role in clinical practice is still being evaluated. IL-33 increases the production of collagen and fibronectin-1 in lung fibroblasts, contributing to subepithelial and peribronchial fibrosis.[40] Red lines indicate inflammatory mechanisms targeted by biologics in early intervention, while blue lines represent the modulation of structural changes in the late phase of treatment. ASM, airway smooth muscle; Col-1, collagen-1; EMT, epithelial-mesenchymal transition; IL, interleukin; IL-5R, interleukin-5 receptor; ILC2, innate lymphoid cell type 2; LTC_4, leukotriene C_4; MMP, matrix metalloproteinase; RBM, reticular basement thickness; ROS, reactive oxygen species; TGF, transforming growth factor; T_H, T helper lymphocyte; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

incubation of ASM cells with omalizumab prevented mesenchymal cell proliferation and accumulation of collagen and fibronectin induced by IgE-containing serum from asthmatic patients.[139] The latter findings might explain some of the in vivo effects of omalizumab on AiRem.

Examination of bronchial biopsies of patients with mild asthma before and after mepolizumab[117] showed a reduction in bronchial eosinophil numbers, airway TGF-β1$^+$ eosinophils, RBM thickness, and tenascin immunoreactivity as well as TGF-β1 concentration in bronchoalveolar lavage fluid. In the MESILICO study, mepolizumab treatment was associated with a significant reduction (mean 27%) in ASM area and improved FEV_1. These findings suggest that changes associated with structural remodeling might indeed be reversible.[12,117,118]

Benralizumab reduces eosinophil infiltration in the airway mucosa/submucosa and sputum.[153] Moreover, benralizumab leads to

Effects of Biologics on Airway Remodeling

Early effects

On Inflammatory changes unresponsive to glucocorticoids

- FEV_1 [a]
- Airway eosinophil infiltration [b]
- Eosinophil cationic protein deposition [c]
- Small airway obstruction [d]
- Mucus plugging [e]
- T-cell infiltration [f]
- Neurotrophin release [g]
- IL-13 / IL-4 dependent T-cell activation [h]
- Cytokine release / action (IL-5, IL-4 / 13) [i]
- IgE-mediated inhibition of IFN - γ - release by pDCs [j]

Late effects

On anatomical / histological / functional changes

- FEV_1 [k]
- Airway eosinophil infiltration [l]
- Myofibroblast activation [m]
- RBM thickening [n]
- ASM hypertrophy / hyperplasia [o]
- ECM deposition [p]
- Tenascin expression [q]
- Neuronal remodeling [r]

Preventive effects

(To be demonstrated)

- Progression to chronic asthma [s]
- Development of secondary structural changes [t]
- Progressive loss of pulmonary function [u]
- Requirement for chronic long-term treatment [v]

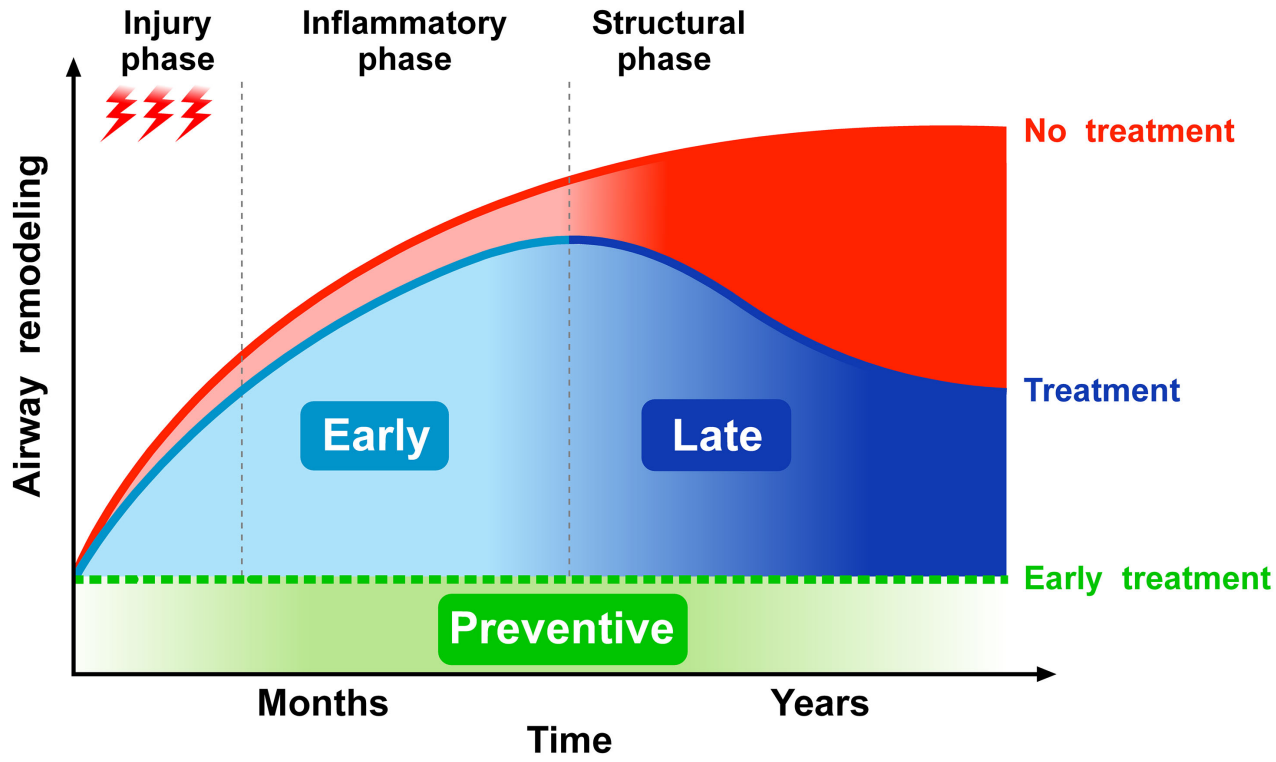

FIGURE 3 Early effects: Evidence of improvements in lung function and reduction in inflammation shortly after biologics' initiation illustrate the rapid benefits of targeting specific inflammatory pathways (a[94,95,113,121–126]; b[127]; c[128]; d[129]; e[130]; f[127]; g[131]; h[132,133]; i[134]; j[135]). Late effects: Analogous to observed outcomes in conditions like atopic dermatitis[136,137] and eosinophilic oesophagitis,[138] biologics may also impact long-term structural changes within the airways, suggesting a potential for reversing or ameliorating established AiRem (k[79,85,89–91,93,96]; l[127]; m[52]; n[117,120]; o[118,119,139]; p[117]; q[117]; r[140]). Potential preventive effects: This represents an emerging research domain, emphasizing the potential of biologics to prevent the onset or progression of AiRem. Although empirical evidence is presently limited in this area, it is identified as a vital avenue for future research aimed at elucidating the comprehensive effects of biologics on the asthma disease trajectory (s[141]; t[12]; u[142]; v[143]). It is important to note that the studies regarding the early and late effects of biologics are essentially based on adults with severe asthma. Further research is needed to evaluate early, late, and potential preventive effects of biologics in pediatric cohorts. ASM, airway smooth muscle; ECM, collagen and extracellular matrix; FEV_1, forced expiratory volume in 1 s; IFN, interferon; IL, interleukin; pDC, plasmacytoid dendritic cell; RBM, reticular basement membrane.

a reduction in ASM mass in severe eosinophilic asthma patients.[119] Indices of airway caliber (R5 and R20) measured by oscillometry improved after 4 weeks of treatment with benralizumab despite unchanged spirometry values, suggesting that oscillometric parameters may be more sensitive to detect changes in the small airways than conventional spirometry.[154]

Further evidence for the effects of biologics on lung function and airway structural changes has been provided through functional respiratory imaging. In the VESTIGE study (NCT04400318), dupilumab reduced airway inflammation and mucus plugging, which led to improved airway volume and flow.[155] In addition, dupilumab improved ventilation heterogeneity measured by magnetic resonance imaging (MRI), suggesting its role in modulating different aspects of airway obstruction.[156] Blocking of IL-4Rα has also been shown to improve CT-derived measures of pulmonary vascular volume.[157] In a placebo-controlled RCT, it was demonstrated that dupilumab reduces CT biomarkers of airway mucus, gas trapping, and remodeling, thereby improving ventilation as assessed by MRI and measures of small airway function via oscillometry in patients with severe asthma.[158] In a mouse model, blocking IL-4Rα was found to inhibit the entry of eosinophils into lung tissue by reducing chemotaxis and endothelial activation. Moreover, IL-4Rα blockade prevents house dust mite (HDM)-induced epithelial barrier dysfunction, tissue remodeling, and lung function decline.[133]

In the phase 2 CASCADE study performed in moderate-to-severe asthma patients, tezepelumab increased CT scan-determined lumen area across airway generations.[97] In addition, there was a numerical but statistically nonsignificant improvement in RBM thickening, epithelial damage, and denudation. Future studies evaluating the "late effects" of biologics on AiRem should be performed at later time points in the course of treatment and/or in larger cohorts of patients with different asthma phenotypes. Moreover, there is a need to study the late effects of each biologic on AiRem. The results arising from these studies will contribute to our understanding of the underlying mechanisms of different aspects of AiRem. These findings will form the basis for even better targeted, personalized therapies of severe asthma.

5.3 | Potential preventive effects of biologics

Preventive effects of biologics on AiRem represent a promising yet unexplored avenue in asthma management. There is growing evidence suggesting that modulating early inflammatory cascades with biologics could limit the progression of airway fibrosis.[12] Biopsy studies conducted in young children suggest that AiRem might be an early event in asthma development, preceding the onset of symptoms.[159–162] However, clinical studies on the preventive effects of biologics in asthma and/or AiRem development are lacking, particularly in the pediatric population. Early intervention with biologics may be beneficial in altering the disease trajectory from its inception, not only in pediatric populations but also in adults. Pediatric and adult studies targeting early intervention could provide valuable insights into the long-term outcomes of asthma management. Furthermore, upstream inhibition of inflammatory cascades (e.g., anti-alarmins) but also direct inhibition of specific immunological/inflammatory pathways (IgE, cytokines, and immune cells) can interfere with the progression of airway fibrosis.[21,22,27,28] Based on these findings, it can be reasonably hypothesized that early intervention with biologics blocking these initial events may be useful in preventing asthma or the progression of milder forms into more severe diseases. Moreover, such early intervention could potentially prevent both functional as well as structural aspects of AiRem (Figure 3).

This would include the prevention of cytotoxic effects of eosinophil-derived mediators leading to fibrosis (e.g., eosinophilic endomyocardial fibrosis),[163,164] but also the steric effects of eosinophil accumulation in airway walls, including mucus plugging. Similarly, the use of anti-IL-5 mAbs for eosinophilic diseases[165] possibly suggests these biologics as first-line treatment in eosinophilic inflammatory diseases, including asthma, as recently suggested.[166]

TABLE 1 Outstanding pathophysiological and therapeutic questions.

Research domain	Outstanding questions	Clinical and research implications
Early intervention with biologics	At which disease stage is intervention most effective in modifying disease progression?	Identifying critical windows and patient profiles for early biologic therapy to prevent or reverse AiRem.
Long-term and preventive effects	Can biologics prevent the progression to chronic asthma and halt secondary structural changes?	Evaluating the potential disease-modifying effects of biologics by preventing structural changes and minimizing long-term treatment needs.
Pediatric asthma and airem	How does early biologic treatment impact the development and progression of AiRem in pediatric asthma?	Assessing safety, efficacy, and long-term outcomes of biologic treatments in children to guide early intervention strategies.
Stratification for airem prevention	Which biomarkers or clinical indicators can predict the development of AiRem and response to biologic therapy?	Developing biomarkers and predictive models for early identification of patients at risk of AiRem who may benefit from targeted biologic interventions.
Biologics vs. conventional therapies	How do biologics compare to conventional treatments in preventing or reversing AiRem?	Direct comparison studies to clarify the superiority of biologics in modifying disease progression and structural changes.
T2 and non-T2 asthma and airem	What is the impact of biologics on AiRem across T2-high and non-T2 asthma phenotypes?	Expanding research to understand the therapeutic potential of biologics on AiRem in various asthma phenotypes, including non-T2 inflammation.
Emerging targets for airem	What novel targets for biologic therapy have the potential to address AiRem more effectively?	Investigating new biologic agents and their mechanisms of action with the potential to specifically target and alter AiRem processes.

TABLE 2 Ongoing clinical trials evaluating the reversing effects of biologics on airway remodeling in asthma.

Biologic	Clinical trial identifier	Phase	Population	Primary outcomes	Duration	Status
Dupilumab	NCT04400318 (VESTIGE)	Phase 4	Adults with severe asthma	Effect of dupilumab on lung inflammation and related changes in airway volumes detectable by functional respiratory imaging	Minimum 29 weeks and up to 41 weeks	Completed
Mepolizumab	NCT04612556 (MESILICO)	Phase 4	Adults with severe asthma	Any improvement in airway remodeling after 156 weeks of treatment	3 years	Active, not recruiting
Mepolizumab	NCT03797404 (REMOMEPO)	Phase 4	Adults with severe asthma	Changes in RBM thickening, in ASM area after 6 months and 12 months of mepolizumab treatment	12 months	Completed
Mepolizumab	NCT05708300 (CALIOPI)	Phase 4	Adults with severe asthma and CRSwNPs	Evaluation of the airway remodeling in various anatomic locations of the airways (nose, bronchus) at baseline-before treatment initiation and after 156 weeks of mepolizumab treatment.	3 years	Recruiting
Benralizumab	NCT04365205 (BENRAMOD)	Phase 4	Adults with severe asthma	Number of bronchial smooth muscle (BSM) cells obtained from severe asthmatics measured in vitro using BrdU incorporation.	12 months	Recruiting
Benralizumab	NCT03953300 (CHINOOK)	Phase 4	Adults with severe asthma	The change in eosinophil numbers expressed as number/mm^2 in submucosa as measured by major basic protein (MBP) staining in endobronchial biopsies	1 year	Recruiting
Benralizumab	NCT06288516 (BREATH)	Phase 4	Adults with severe asthma	Any improvement in airway remodeling after 52 weeks of treatment	12 months	Recruiting
Tezepelumab	NCT05651841 (REVERT)	Phase 4	Adults with severe asthma	Comparison on CT-scan in the change in mean percentage bronchial wall area (%WA) at the B1 and B8 bronchi, generations 3, 4, and 5	12 months	Recruiting

It is critical to recognize that not all individuals with mild or moderate asthma will develop severe asthma or AiRem. Therefore, studies on cohorts such as The Mild/Moderate Asthma Network in Italy (MANI) are needed to understand individual patients' trajectories and their risk factors.[167] Furthermore, the use of canonical (e.g., blood eosinophil counts and FeNO levels) and the identification of novel biomarkers predictive of severe asthma could play a critical role in optimizing the use of biologics in preventive strategies. These efforts could help stratify patients at risk of severe asthma and/or AiRem, guiding early biologic interventions more efficiently.

Based on the previous observations, existing biologics as well as those in development, offer a challenging opportunity to also study early treatment (GINA Step 3 or even 2) of asthma with biologics. These strategies could prevent or limit not only the side effects of OCS but also the structural changes resulting from longstanding uncontrolled airway inflammation. Future studies should aim to prevent the onset of AiRem, taking into account the cost-effectiveness of early treatment with biologics, potentially at lower doses or different schedules. The inclusion of predictive modeling and risk stratification, as pursued by MANI,[167] could guide the judicious selection of patients for these preventive interventions.

6 | CONCLUSION

Our proposal concerning the effects of biologics on AiRem aligns with the evolving perspective of considering biologics as disease-modifying anti-asthmatic drugs.[1] Table 1 outlines key unanswered questions about biologics and AiRem in asthma, emphasizing the need for further research to clarify their impact on AiRem. This research is crucial for identifying the potential preventive effects of biologics and involves exploring the impact of early biological treatment on AiRem. We advocate for studies leveraging cutting-edge technologies and imaging techniques to investigate the role of biologics in mitigating AiRem among patients with moderate-to-severe asthma. Currently, several clinical trials are evaluating the REVERSING effect of biologics on AiRem. These include dupilumab (NCT04400318), mepolizumab (NCT04612556, NCT03797404, and NCT05708300), benralizumab (NCT04365205, NCT03953300, and NCT06288516), and tezepelumab (NCT05651841) (Table 2). Future research should include both short- and long-term evaluations of clinical outcomes, biomarkers, treatment burden, and socioeconomic implications.

AUTHOR CONTRIBUTIONS

GV, GWC, and JCV wrote the first draft of the manuscript. GV, RP, ML, GB, FB, GWC, and JCV reviewed and modified the manuscript. All authors contributed to the refinement of the final version and agreed to the decision to submit for publication.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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