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What effect does asthma treatment have on airway remodeling? Current perspectives

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Airway remodeling, or structural changes of the airway wall arising from injury and repair, plays an important role in the pathophysiology of asthma. Remodeling is characterized as structural changes involving the composition, content, and organization of many of the cellular and molecular constituents of the bronchial wall. These structural changes can include epithelial injury, subepithelial thickening/fibrosis, airway smooth muscle hyperplasia, goblet cell hypertrophy and hyperplasia, and angiogenesis. Historically, these changes are considered a consequence of long-standing airway inflammation. Recent infant and child studies, however, suggest that remodeling occurs in parallel with inflammation in asthmatic subjects. Despite advancements in the recognition of key cellular and molecular mechanisms involved in remodeling, there remains a paucity of information about which treatments or interactions are most likely to regulate these processes. Furthermore, it is unclear as to when is the best time to initiate treatments to modify remodeling, which components to target, and how best to monitor interventions on remodeling. Indeed, inhaled corticosteroids, which are generally considered to have limited influence on remodeling, have been shown to be beneficial in studies in which the dose and duration of treatment were increased and prolonged, respectively. Moreover, several studies have identified the need to identify novel asthma indices and phenotypes that correlate with remodeling and, as a consequence, might specifically respond to new therapies, such as anti-IgE, anti-IL-5, and anti-TNF- α mAbs. Our review will evaluate the development of remodeling in asthmatic subjects and the effects of treatment on these processes. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: *Asthma, asthma treatment, remodeling, corticosteroids, inflammation, anti-IgE, omalizumab, anti-TNF- α , golimumab, anti-IL-5, mepolizumab*

Abbreviations used

AHR: Airway hyperresponsiveness
 ASM: Airway smooth muscle
 ECM: Extracellular matrix
 ICS: Inhaled corticosteroid
 LABA: Long-acting β_2 -agonist
 MMP: Matrix metalloproteinase
 RBM: Reticular basement membrane
 TIMP: Tissue inhibitor of metalloproteinases
 VEGF: Vascular endothelial growth factor

Airway remodeling in asthmatic subjects represents a complex multicellular process that leads to structural changes involving the composition, content, and organization of many of the cellular and molecular constituents of the bronchial wall.¹ These structural changes, which have been proposed to result in lower lung function, include epithelial injury, subepithelial fibrosis, airway smooth muscle (ASM) hyperplasia, goblet cell hypertrophy and hyperplasia, and angiogenesis (Fig 1), although their specific expression in individual patients is variable in terms of onset and severity. Although there is focus on “remodeling” as a factor in the accelerated and progressive loss in lung function, it is important to point out that physiologic abnormalities in asthmatic subjects (eg, air trapping) might be another significant factor in the decreased levels of lung function seen in asthmatic subjects.² Despite these significant and important contributions, the scope of the following review will be limited to the histopathologic abnormalities associated with airway remodeling in asthmatic subjects.

Airway remodeling has been considered to result in an accelerated and progressive loss of lung function in some asthmatic subjects. However, it should be emphasized that remodeling in asthmatic subjects refers to a series of histopathologic changes and not necessarily to any clinically measurable outcome. Therefore although there is an enormous body of literature associating remodeling with loss of lung function, there remains no definitive proof of this causation. Nonetheless, available evidence would suggest causation, as discussed broadly in this review, and the issue of this relationship remains significant enough to warrant ongoing research to understand airway remodeling and pathophysiologic mechanisms to promote the development of therapies to attenuate remodeling. Given this background, it is our premise that remodeling, whether structural or physiological in origin, is a component of asthma in some patients and is of interest and importance to the basic mechanisms of both the disease and the therapy used to either prevent or attenuate it.

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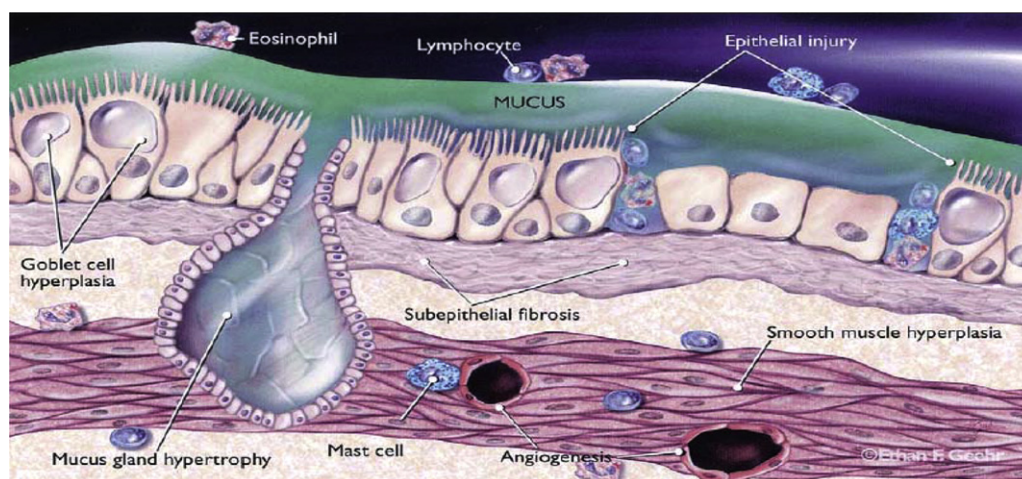


FIG 1. Integrative model of the components of airway remodeling. In asthmatic patients airway inflammation, epithelial and goblet cell phenotype alterations, subepithelial fibrosis (eg, reticular basement membrane in the text), excess mucus secretion, smooth muscle cell hypertrophy and hyperplasia, and angiogenesis are present. Copyright 2003, Ethan F. Geer. Reproduced from Lazaar et al.⁹⁹

Historically, remodeling was attributed to the consequences of longstanding and persistent inflammation, as well as a subsequent dysfunctional injury and repair mechanism.³ Because chronic inflammation is considered a driving force behind airway injury and repair, it has been proposed that asthma treatments, which might specifically and effectively target airway inflammation, would also affect the remodeling process, particularly if prescribed in sufficiently high doses and for a sufficient duration.⁴ Additionally, it has been believed that the use of anti-inflammatory medications early in the expression of asthma would attenuate inflammation and, consequently, prevent remodeling and the resultant accelerated decrease in lung function. Finally, it has been believed that effective use of anti-inflammatory medications might reverse existing airway remodeling and thus improve lung function.⁴

An apparent lack of effectiveness of traditional therapies to attenuate inflammation (eg, inhaled corticosteroids [ICSs]), especially in those with severe asthma and children with the finding of early changes in airway histopathology, have questioned the concept that “persistent inflammation leads to remodeling.”⁵ Specifically, there is mounting histologic evidence that the presence of remodeling, such as epithelial loss, reticular basement membrane (RBM) thickening, and angiogenesis, might occur as early as 4 years of age in asthmatic subjects.⁶⁻⁸ However, airway remodeling was not demonstrated in “asthmatic” infants at 1 year of age,⁹ suggesting that remodeling can occur in parallel, rather than in sequence, with inflammation and might be a component of the natural history of asthma for some patients.⁶

Although the pathogenesis of airway remodeling in asthmatic subjects remains in question, the clinical consequences are better appreciated. Airway remodeling has been implicated as playing a role in persistent airway hyperresponsiveness (AHR),¹⁰ excessive airflow narrowing,¹¹ and ultimately fixed airflow obstruction, especially in subjects with severe asthma.¹² The clinical consequences of persistent airflow obstruction can be dramatic and irreversible and, as such, imply a need to develop new therapeutic approaches or interventions to specifically target

components of airway remodeling to either prevent or reverse these processes.

Unfortunately, such a proposal is easier said than done with current treatments. First, it is unclear which components of remodeling should be targeted and at what point in the natural history of asthma such treatments should be initiated to achieve the best results. Second, it is unclear whether all components of remodeling are actually detrimental to the pathophysiology of asthma. For example, asthmatic airways might become “stiffer” because of remodeling (eg, fibrosis), and these changes might actually counteract excessive airway narrowing.¹ Therefore developing a treatment directed toward a specific aspect of airway remodeling, the physiologic consequence of which might ultimately have been of benefit in asthmatic subjects, might be counterproductive. As a result, it is necessary to have a more clear understanding of the clinical consequences of specific components of remodeling. There is also uncertainty as to whether certain aspects of remodeling determine asthma severity and its progression.¹³ Finally, there is a need to better understand which asthma indices correlate with detrimental components of airway remodeling and which aspects might best direct the treatment of remodeling to attenuate its progression to irreversible airflow obstruction.

The following review summarizes current interventions in asthmatic subjects and their effects on aspects of airway remodeling. The majority of experience to date involves the effects of corticosteroids, and as such, our review will focus largely on the influence of corticosteroid treatment on remodeling. Although more limited, we will also review the experiences with other interactions, such as anti-IgE, anti-IL-5, and anti-TNF- α , on airway remodeling.

WHAT ARE THE EFFECTS OF CORTICOSTEROIDS ON AIRWAY REMODELING?

Corticosteroids, either inhaled (ICSs) or systemic (oral corticosteroids), modulate acute and chronic inflammation in asthmatic subjects, particularly in those with milder disease, and have

broad pharmacologic actions.^{14,15} Consequently, glucocorticoids are considered the therapeutic mainstay for chronic asthma and its underlying inflammation. Indeed, as a result of the “chronic inflammation leads to remodeling” paradigm, corticosteroids have long played a central role in interventional studies to assess the effect of treatment on airway remodeling in asthmatic subjects. However, the aforementioned recent childhood airway studies have cast doubt on this model. New evidence suggests remodeling might arise from asthma exacerbations and not chronic inflammation,⁵⁻⁸ and these events ultimately lead to an exaggerated decrease in lung function.^{16,17} These observations imply that airway remodeling might be due to worsening of airway inflammation associated with asthma exacerbations and support the paradigm that inflammation and remodeling occur in concert.¹⁶

For example, the Inhaled Steroid Treatment As Regular Treatment trial found that the decrease in lung function associated with exacerbations might be attenuated by ongoing treatment with low-dose ICSs.¹⁷ These clinical findings and those of Bai et al¹⁶ indicate that corticosteroids might affect remodeling, especially if administered during critical periods of asthma development and airway injury (ie, exacerbations). Therefore to appreciate the role and contribution of remodeling to asthma and the effects of treatment on these processes, our discussion will focus on individual aspects of remodeling and the effects of medication on these airway features. Although our discussion might focus on individual components of remodeling and the effects of treatment, it is more likely that the repair process involves multiple changes at the same time, and if an intervention is beneficial, the improvement might represent a broad-based effect.

Reticular basement membrane thickening

Many factors contribute to remodeling. A prominent feature of remodeling is subepithelial fibrosis, which consists of subepithelial lamina reticularis thickening underneath the true basement membrane and is referred to as reticular basement membrane thickening. RBM thickening is a characteristic feature of airway remodeling (Fig 1). It is important to note that the true basement membrane (ie, basal lamina of the bronchial epithelium) is not affected in asthma; rather, when the phrase basement membrane thickening is used, it most often refers to a thickening of the RBM and involves the replacement of a typically loose network of collagen fibrils with a dense network of collagen (type I and III), laminin, tenascin, fibronectin, and proteoglycans.^{18,19} RBM thickening is one of the most commonly studied components of remodeling, in part because of the relative ease of access to airway tissue with bronchoscopy, with samples retrieved predominantly from the large airways.

The primary cellular and molecular mechanisms of RBM thickening/subepithelial fibrosis are thought to arise from an imbalance between synthesis and degradation of matrix components by key effector cells (eg, fibroblasts, myofibroblasts, and eosinophils).²⁰ Under normal conditions, matrix metalloproteinases (MMPs), which regulate the deposition of collagen, and tissue inhibitors of metalloproteinases (TIMPs), which prevent this process, are in equilibrium. In asthmatic subjects increased levels, activity, or both of MMPs are common and can occur after allergen challenge,²¹ during asthma exacerbations, and in subjects with severe asthma.²⁰ Interestingly, increased levels of TIMPs

are also found in asthmatic subjects with increased airway fibrosis, which suggests that remodeling might also be the consequence of excessive repair.²⁰

TGF- β is considered a key mediator in remodeling and is synthesized by airway cells, epithelial cells, fibroblasts, and eosinophils.²² TGF- β induces TIMP-1 to stimulate fibroblasts to produce extracellular matrix (ECM) proteins and promotes myofibroblasts to produce collagen.²² Furthermore, TGF- β expression correlates with the degree of subepithelial fibrosis and is significantly increased in subjects with severe asthma with associated eosinophilia.^{22,23}

RBM thickening is associated with many pathophysiologic features of asthma, can be found in subjects with all degrees of asthma severity,^{24,25} and correlates directly with airflow obstruction^{24,26} and AHR.²⁷ Changes in RBM, in contrast, are negatively correlated with airway distensibility.^{12,28} Furthermore, RBM thickening has not been demonstrated in symptomatic infants with reversible airway obstruction,⁹ whereas it is found in older children with more severe asthma.⁸ These findings suggest that RBM thickening occurs once the asthma process is started. The resulting subepithelial fibrosis increases airway narrowing by reducing airway elastance and generating a greater force of contraction as the bulk of ASM increases.²⁹

The clinical implications of attenuating or preventing subepithelial fibrosis are significant, but the effects associated with corticosteroid treatment are poorly understood and, at times, conflicting (Table I).³⁰⁻⁴³ On the positive side, for example, Sont et al³⁰ reported important and perhaps unique outcomes when they evaluated the effects of ICSs on airway remodeling. In a randomized, prospective, parallel trial of 75 adults with mild-to-moderate asthma, these investigators³⁰ designed a study to determine whether a treatment strategy that was directed to reduce AHR versus guideline-based treatment alone (reference strategy; ie, symptom based) would lead to improved asthma control and reduced chronic airway inflammation. To assess the latter aspect and as an index of remodeling, the investigators also assessed RBM thickness at baseline and after 2 years of treatment. At baseline, both the AHR and reference strategy groups had similarly increased thickness of the subepithelial reticular layer. After 2 years of treatment, the AHR strategy group had 1.8-fold reduction in mild exacerbations, had significantly increased FEV₁, and, relevant to our discussion, demonstrated a greater reduction in RBM thickness (Fig 2, A) compared with the reference group. This latter finding suggests that a more aggressive dose of ICS (approximately 400 μ g/d greater in the AHR strategy group) could reverse components of airway remodeling.³⁰ In addition, bronchial biopsy specimens showed a significant decrease in airway eosinophil numbers, suggesting that AHR might serve as a surrogate marker of airway inflammation and remodeling in asthmatic subjects and that eosinophils might be a component of these airway changes (Fig 2, B). The findings of Sont et al³⁰ suggest that remodeling or some of its components respond to ICSs, but to achieve these effects, a larger dose and long-term administration are necessary to achieve this outcome.

Subsequently, Ward et al³¹ evaluated the relationships between spirometric indices, airway inflammation, airway remodeling, and AHR before and after treatment with a high dose of fluticasone propionate (1500 μ g/d). Creating a model from cross-sectional data, this double-blind, randomized, placebo-controlled, parallel study found that although airway inflammation was an important

TABLE I. Summary of the main studies demonstrating corticosteroids' effects on RBM thickness

Effect on RBM	Study	Summary
Studies demonstrating reduction in thickness of RBM	Sont et al ³⁰	Two years of high-dose ICSs demonstrated a mean difference in RBM thickness of 1.7 μ m compared with that seen with standard treatment in 75 patients by using a treatment strategy targeting AHR. Versus the standard treatment group, the AHR treatment group received approximately 400 μ g more of ICSs per day (approximately 800 μ g/d). ³⁰
	Ward et al ³¹	Decrease in RBM thickness after 12 months of high-dose FP (750 μ g twice daily) of 1.9 μ m from baseline (10.1 μ m $\rightarrow$ 8.2 μ m). ³¹
	Hoshino et al ^{32,33}	Six months of BDP, 800 μ g/d, resulted in a decrease in RBM from 11.3 to 8.4 μ g compared with no change for placebo ³² ; 6 months of high-dose BDP (400 μ g twice daily) vs placebo resulted in decrease in RBM thickness from 8.18 μ m $\rightarrow$ 5.93 μ m) in the BDP group. ³³
	Chetta et al ³⁴ ; Olivieri et al ³⁵	High-dose FP (500 μ g twice daily) resulted in a significant decrease in RBM after 6 weeks (9.7 μ m $\rightarrow$ 8.4 μ m) vs low-dose FP (100 μ g twice daily). ³⁴ There was a reduction in RBM with 250 μ g of FP twice daily. ³⁵
	Laitinen et al ³⁶ ; Trigg et al ³⁷ ; Hoshino et al ³⁸	There is a decrease in tenascin expression in RBM with BD. ³⁶ There is a decrease in the thickness of type III collagen in RBM with BDP. ³⁷ There is a decrease in type III collagen expression and MMP-9 with BDP. ³⁸
Studies that found no change in RBM thickness	Jeffery et al ³⁹	Low-dose BD (200 μ g twice daily) or terbutaline compared with subjects receiving long-term ICSs (average, 3.7 years) or healthy control subjects found no effect on RBM after 4 weeks of treatment in all groups compared with control subjects. ³⁹
	Boulet et al ⁴⁰	Eight weeks of high-dose FP (1000 μ g/d) in subjects with recently diagnosed and long-standing asthma found no change in type I and III collagen deposition. ⁴⁰
	Bergeron et al ⁴¹	Six weeks of flunisolide was unable to modulate collagen deposition in the central and small airways or TGF- β expression in 12 patients. ⁴¹
	Lundgren et al ⁴² ; Laursen et al ⁴³	Ten years of daily ICSs in 6 subjects with severe asthma ⁴² and 7-15 months of high-dose BD (1600 μ g/d) in 10 asthmatic subjects ⁴³ resulted in no change in collagen fibril distribution.

BD, Budesonide; BDP, beclomethasone dipropionate; FP, fluticasone propionate.

predictor for AHR, changes associated with remodeling represented a stronger association.³¹ In addition, RBM thickness was decreased in the fluticasone propionate-treated group but only after 12 months of treatment (Fig 3). Their data also demonstrated that two thirds of the improvement in AHR was associated with a reduction in indices of airway remodeling. This study³¹ was the first, to our knowledge, to dissect the relative contributions of airway inflammation and remodeling to AHR and to elucidate the temporal improvements in these parameters with ICS treatment. Interestingly, significant improvement in symptoms, pulmonary function, and airway inflammation were seen within 3 months of treatment; however, no effect on RBM thickness or AHR was noted by that time (Fig 3). On the basis of the present recommendations in management guidelines, it is likely that ICS doses would have been decreased because symptoms and lung function have improved, potentially missing an opportunity to attenuate airway remodeling and AHR noted with longer treatment.³¹

The observations by Sont et al³⁰ and Ward et al,³¹ as well as others (Table I)^{32-38,44-46} suggest that the corticosteroid dose and its duration of administration are important considerations when evaluating the effects of treatment on remodeling. These studies also suggest that some aspects of remodeling might be reversible and that current treatment end points (ie, symptoms alone) might not be fully informative on what approaches are needed to modify airway remodeling.

In contrast, Chakir et al⁴⁷ found no decrease in the amount of collagen deposition or increased TGF- β expression in subjects

with a broad range of asthma severity after 2 weeks of oral corticosteroids. Indeed, many studies have also demonstrated no effects on RBM thickening by ICSs (Table I).³⁹⁻⁴³ However, it has been argued that a lack of response to corticosteroids in these studies might be the result of small numbers of subjects.^{31,48} Ultimately, studies that will assess novel markers of asthma activity with indices predictive of remodeling are needed.³¹

ASM hyperplasia

Increased ASM mass has been believed to account for most of the functional contribution of airway remodeling to the pathophysiology of AHR.^{10,49} Increased ASM mass and myofibroblast numbers in the proximal airways have been an aspect of remodeling that, thus far, appears to discriminate severe asthma from milder forms of the disease.⁴⁹⁻⁵¹ In support of this association, analyses of postmortem tissue from subjects with severe asthma have demonstrated an apparent increase in ASM mass.⁵²⁻⁵⁴

Corticosteroids are hypothesized to decrease ASM mass by acting directly on these cells and indirectly through a modulation of chemokine and cytokine generation.⁵⁵ Corticosteroids inhibit some, but not all, growth factor-induced proliferation of ASM cells.⁵⁵ In asthmatic subjects ASM mitogenesis and growth have been found to be resistant to glucocorticoids *in vitro*.⁵⁶ Although ICSs reduce ASM mass and thickness in rat models of chronic asthma,⁵⁷ a recent study of the human airway by Kelly et al⁴⁹ found that ASM area was decreased by budesonide (400 μ g twice daily) in 14 asthmatic subjects who had undergone

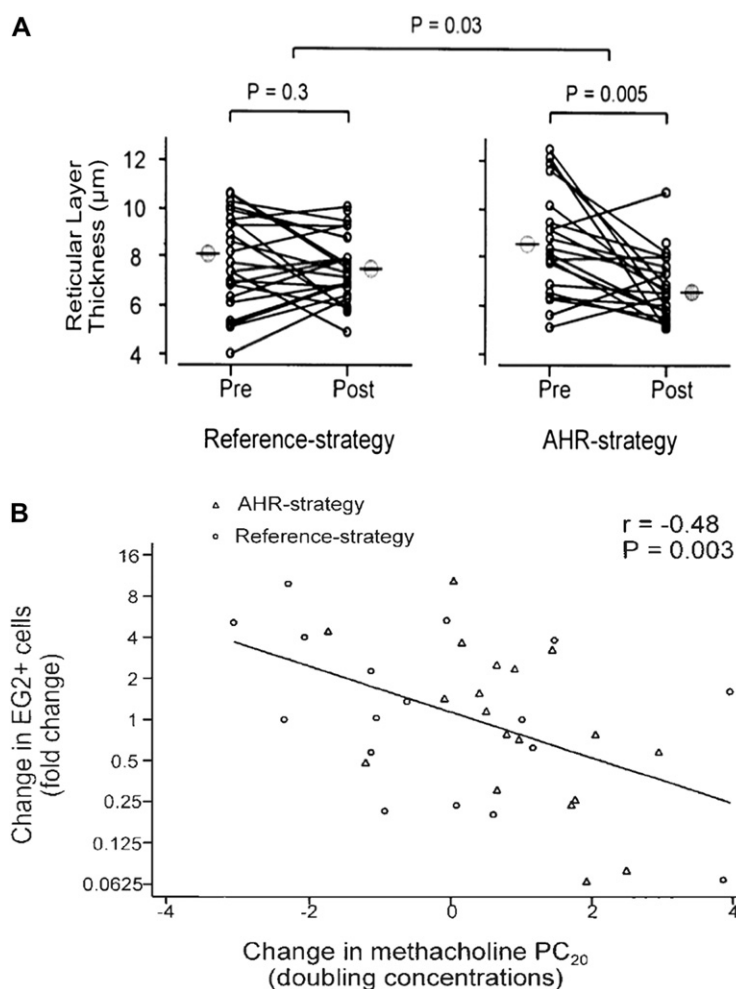


FIG 2. **A**, Individual changes in reticular layer thickness beneath the epithelium in bronchial biopsy specimens before and after 2 years of treatment according to the reference and AHR strategies. Bars indicate mean values at the visits for both strategies. There was a significant decrease in reticular layer thickness within the AHR strategy group, which was significantly greater than in the reference strategy group. Excerpted from Sont et al.³⁰ **B**, Relationship between changes in EG2⁺ eosinophils and changes in methacholine PC₂₀ values during 2 years of treatment according to the reference and AHR strategies. The greater the decrease in the number of EG2⁺ eosinophils, the greater the improvement in AHR to inhaled methacholine. Excerpted from Sont et al.³⁰

allergen challenge and bronchial biopsy 24 hours after challenge, whereas allergen-induced myofibroblast increases were not attenuated. From the results of this study, it was hypothesized that myocytes dedifferentiate into myofibroblasts and then migrate into the submucosa, thus explaining both the increase in myofibroblasts and the decrease in ASM area. It can also be postulated from these results that myofibroblasts affect AHR by altering the ECM and also by contracting and stiffening the airway wall.⁴⁹ The increase in myofibroblast numbers and the decrease in ASM area by budesonide also corroborate the aforementioned *in vitro* study, which demonstrated glucocorticoid-resistant ASM mitogenesis and growth.⁵⁶ Of note, in the study by Kelly et al,⁴⁹ combination therapy with budesonide/formoterol (400/12 μg twice daily) significantly attenuated myofibroblast numbers while preventing a decrease in the ASM area. These findings suggest that combination therapy might have a greater anti-inflammatory and antiremodeling effect than ICS monotherapy, an effect that will be discussed later.⁴⁹

Bronchial epithelial damage and detachment

Epithelial cell damage and detachment are thought to relate to the fragility of these cells and have long been considered a characteristic feature of airway inflammation and remodeling in asthmatic subjects.⁵⁸ Others, however, suggest that these changes are an artifact arising from the bronchoscopic procedure and biopsy. Given repeated observations of increased epithelial cell detachment in postmortem tissues, bronchoalveolar lavage fluid, and sputum from asthmatic subjects, these findings appear to be part of asthma.⁵⁹ What is also becoming increasingly apparent is that a structurally and functionally abnormal epithelial cell likely plays a central role in remodeling in asthmatic subjects because of its location at the interface of host-environment interactions.⁶⁰

Controversy still exists on the effects of corticosteroids on bronchial epithelial injury.¹ Some *in vitro* studies have shown that corticosteroids induce apoptosis of airway epithelium^{61,62} and prolong the repair process after repeated episodes of epithelial

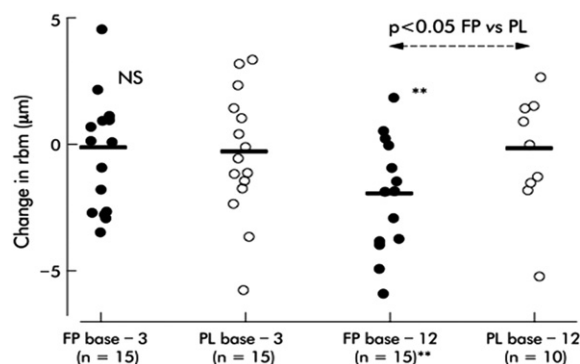


FIG 3. Comparison of changes in RBH thickness for fluticasone propionate (FP; solid circles) and placebo (PL; open circles) at 3 and 12 months' treatment. *** $P < .01$, 12-month FP versus baseline; $P < .05$ versus placebo. Reproduced from Ward et al.³¹

injury.^{1,63} However, in guinea pigs who have denuded tracheal epithelium, repair was found to occur in the presence of corticosteroids.⁶⁴

In asthmatic subjects there is an increase in the number of ciliated bronchial epithelial cells after 3 months of budesonide treatment.³⁶ Additionally, in a retrospective study with lung tissue from asthmatic subjects, the epithelium appeared to be partially restored after 10 years of ICS use.⁴² After these observations, it is likely that long-term prospective interventional studies will be needed to more fully evaluate the effects of corticosteroids on airway epithelial damage and remodeling.

Goblet cell metaplasia/mucus hypersecretion

The contribution of goblet cell metaplasia and mucus hypersecretion to asthma remains under investigation. Excessive production and secretion of mucus can occlude the airways and, consequently, reduce lung function.⁶⁵ In severe episodes of asthma, large amounts of mucus plug are present in the airways, as has been frequently noted at autopsy.⁶⁶ Although there are limited studies on therapeutic interventions on goblet cell number and function, De Kluiver et al⁶⁷ noted a decrease in the number of airway goblet cells after just 2 weeks of low-dose inhaled budesonide (400 μ g once daily). Additionally, in a rat model of allergic inflammation, ICSs reduced the degree of goblet cell metaplasia.⁵⁷

Vascular remodeling

Increased size, engorgement, number, and permeability of blood vessels within the airway wall can lead to edema, amplified inflammation, and increased airway wall thickness. Vascular remodeling in asthmatic subjects can result from increased angiogenesis, which is mediated by vascular endothelial growth factor (VEGF).⁶⁸ ICSs can affect vascular remodeling in asthmatic subjects through a number of mechanisms, including vasoconstriction, alteration of chronic airway inflammation, inhibition of proangiogenic cytokines/chemokines production (eg, IL-8, GM-CSF, and TNF- α), suppression of immune cell functions (eg, basophils, eosinophils, and mast cells) that express proangiogenic molecules, and, perhaps most importantly, reduced expression of VEGF.⁶⁸ In asthmatic subjects the use of higher doses of ICS was found to inversely correlate with airway vascularity. For

example, studies using high dose inhaled beclomethasone dipropionate (800-1500 μ g/d)^{52,69} or fluticasone dipropionate (1000 μ g/d)³⁴ decreased vascular-associated remodeling. Additionally, Feltis et al⁷⁰ found that when 1500 μ g of fluticasone dipropionate was administered daily to corticosteroid-naïve asthmatic patients for 3 months, subepithelial vascularity and VEGF expression decreased.

WHAT IS THE EFFECT OF COMBINATION TREATMENT WITH ICS AND LONG-ACTING β_2 -AGONISTS ON REMODELING?

Burgess et al⁷¹ found that neither ICS nor long-acting β_2 -agonist (LABA) monotherapy inhibited TGF- β -stimulated release of ECM proteins and cytokines in an *in vitro* model. However, another recent *in vitro* study found that combination treatment with LABAs and ICSs versus monotherapy with either ICSs or LABAs was superior in regulating excessive matrix production in human fibroblast cultures.²⁰ Wang et al⁷² demonstrated decreases in MMP-9, TIMP-1, and TGF- β levels in sputum samples and decreased airway wall thickness, as assessed by means of high-resolution computed tomography with ICS/LABA treatment. A 52-week parallel-group, randomized, double-blind study⁷³ compared the effects of budesonide/formoterol (200/6 μ g twice daily) taken as needed versus daily budesonide/formoterol (800/12 μ g twice daily) in 17 symptomatic asthmatic subjects. RBM thickness significantly decreased in both treatment groups, and changes were equivalent. At baseline, however, neither group had significantly increased RBM thickness, suggesting that the subjects in this study had milder disease.⁷³ Overall, these findings are promising, but it should be noted that there is an absence of studies comparing combination therapy versus ICSs alone on human airway remodeling. Nonetheless, these findings suggest a possible advantage with combination therapy to affect remodeling while potentially minimizing the ICS dose as well. There is also interest in the possibility that β -adrenergic agents could affect aspects of remodeling that might arise as a consequence of repetitive bronchoconstriction and might stimulate ASM generation of collagen deposits through compressive mechanical forces.⁷⁴

WHAT IS THE EFFECT OF OMALIZUMAB ON REMODELING?

IgE contributes to the pathophysiology of allergic diseases by attaching to mast cells and regulating its mediator release. These mediators can then initiate a cascade of inflammation involving B and T lymphocytes, eosinophils, fibroblasts, ASM, and epithelial cells, which then results in the release of a multitude of cytokines and chemokines to intensify airway inflammation, symptoms, and possibly remodeling.⁷⁵

Omalizumab is a recombinant humanized IgG₁ mAb that binds to the Fc portion of free IgE to prevent its attachment to the Fc ϵ receptor of mast cells, basophils, and dendritic cells. This action decreases circulating IgE levels, which in turn downregulates IgE receptor expression.⁷⁶ Although omalizumab reduces airway inflammation, there is little evidence to suggest an effect on airway remodeling. Huang et al,⁷⁷ however, demonstrated that omalizumab inhibits proinflammatory cytokines and growth factor generation, most notably TNF- α and TGF- β , in human bronchial epithelial cell cultures. In addition, Zietkowski et al⁷⁵ found

that subjects with severe persistent allergic asthma who were treated for 1 year with omalizumab had decreased levels of endothelin-1 in exhaled breath condensates, as well as an improvement in lung function. Endothelin-1 and other cytokines are growth factors for bronchial subepithelial myofibroblasts, which might contribute to airway remodeling. There are few clinical studies with omalizumab to show significant improvements in lung function.^{76,78} If changes in lung function (eg, FEV₁) occur, they are usually modest (ie, 2% to 5%).⁷⁸ In contrast, Zietkowski et al⁷⁵ found an improvement of approximately 17% in FEV₁ values. However, this was an unblinded study with a small number of subjects (n = 19). Nonetheless, their results suggest that prolonged use of anti-IgE in a selected patient population (eg, one with significant eosinophilic inflammation) might limit ongoing airway remodeling.

WHAT IS THE EFFECT OF MEPOLIZUMAB (ANTI-IL-5) ON REMODELING?

Eosinophils play a role in airway remodeling in asthmatic subjects.^{30,31} RBM thickening has been associated with increased numbers of eosinophils in the bronchial mucosa.³⁰ Eosinophils also produce several mediators and cytokines (ie, TGF- β , VEGF, MMP-9, TIMP-1, and IL-13) that are capable of stimulating matrix remodeling.⁷⁹ Interestingly, eosinophil-deficient mice are protected from peribronchiolar collagen deposition and increases in ASM; however, increases in AHR and mucus secretion still followed allergen challenge in these animals.⁸⁰ The authors posited that eosinophils contribute substantially to airway remodeling but are not obligatory for allergen-induced lung dysfunction.⁸⁰

IL-5 promotes terminal differentiation, bone marrow release, and survival of eosinophils. Consequently, anti-IL-5 therapies have undergone extensive evaluation in asthma. Flood-Page et al⁷⁹ found that treating asthmatic patients with mepolizumab decreased airway tissue eosinophil numbers by approximately 50%, as well as the expression of tenascin, lumican, and procollagen III, in the bronchial RBM; eosinophil mRNA TGF- β 1 and overall concentrations of TGF- β 1 in bronchoalveolar lavage fluids were also decreased. However, lung functions were not affected, possibly reflecting the duration of treatment or the possibility that these eosinophil-associated findings do not result in a loss of lung function, despite having features of airway remodeling.⁷⁹

Early clinical trials in asthmatic subjects with mepolizumab have shown little to no effect on symptoms, lung function, or prevention of exacerbations.⁸¹ Recently, however, 2 randomized, placebo-controlled, parallel-group studies of mepolizumab were conducted in highly selected subpopulations of asthmatic subjects with severe exacerbation-prone disease who were also refractory to asthma control with high doses of corticosteroids and had persistent airway eosinophilia.^{82,83} In these studies mepolizumab significantly reduced exacerbation rates in patients with persistent eosinophilic asthma (defined as sputum eosinophilia >3% despite treatment with ICSs, systemic corticosteroids, or both). Moreover, Nair et al⁸³ found a small but significant improvement in FEV₁ with mepolizumab. Also of interest, Haldar et al⁸² found a significant improvement in the airway wall area and total airway area when evaluated by means of computed tomographic scans. These findings suggest that anti-IL-5 can improve the features of airway remodeling in selected patient

populations; however, other than the computed tomographic findings,⁸² there remain limited human airway studies that demonstrate that anti-IL-5 affects the histopathological components of remodeling.⁷⁹

WHAT ARE THE EFFECTS OF ANTI-TNF- α ON REMODELING?

There is limited evidence that therapies against TNF- α are effective in subjects with severe asthma. However, in addition to promoting airway inflammation and AHR, TNF- α might play a central role in airway remodeling and induce glucocorticoid resistance, myocyte proliferation, vascular remodeling, and stimulation of fibroblast growth and maturation into myofibroblasts by promoting TGF- β expression.^{84,85} Patients with treatment-refractory asthma have an upregulation of their TNF- α axis.⁸⁶ Initial enthusiasm for TNF- α blockade occurred after a clinical study using 10 weeks of etanercept by Berry et al⁸⁶ found a decrease in AHR, as well as improved quality of life and lung function.

Unfortunately, a larger, randomized, double-blind, placebo-controlled study⁸⁷ of golimumab (mAb against TNF- α) tempered these expectations. This phase 2 study randomized 309 subjects with severe and uncontrolled asthma to either placebo or golimumab for 1 year in addition to the usual treatment. No significant differences were observed in lung function or exacerbation rates through 24 weeks of treatment, but the study was prematurely terminated at that time because of an unacceptable risk/benefit profile (increased serious adverse events, including increased serious infections, malignancies, and 1 death).⁸⁷ Interestingly, Wenzel et al⁸⁷ found patients with reversible airflow obstruction at enrollment had a significantly improved response to golimumab therapy, as reflected by a decrease in exacerbations, thus suggesting that patients with fixed airway disease represent a phenotype that is less responsive to anti-TNF agents. In the absence of human studies specifically examining airway tissue, there is little evidence that anti-TNF agents affect remodeling in asthmatic subjects.

WHAT EFFECTS DO LEUKOTRIENE MODIFIERS, ANTICHOLINERGICS, AND TYROSINE KINASE INHIBITORS HAVE ON REMODELING?

Although an extensive discussion of all treatments is beyond the scope of this article, to be more inclusive, it is helpful to briefly highlight the role of leukotriene modifiers, anticholinergics, and tyrosine kinase inhibitors in airway remodeling. Most of these observations lack human studies for confirmation.

Leukotriene modifiers suppress eosinophilic infiltration and eosinophil numbers in peripheral blood, sputum, and bronchoalveolar lavage fluid samples, as well as improving AHR and lung function.⁸⁸⁻⁹⁰ Using a murine model, Henderson et al⁹¹ demonstrated a reduction in airway eosinophilic infiltration and goblet cell metaplasia, as well as a reversal in the established increase in ASM mass and subepithelial collagen deposition with montelukast. Muz et al⁹² were also able to replicate similar results in a murine model and additionally demonstrated a marked reduction in epithelial desquamation of airways when treated with montelukast compared with that seen in untreated control subjects.

Acetylcholine has also been implicated as an additional culprit in airway remodeling because prolonged cholinergic stimulation

enhances ASM contractile protein expression, promitogenic cell proliferation, and release of inflammatory mediators.^{93,94} Anticholinergics, such as ipratropium and tiotropium, have already established treatment roles in chronic obstructive pulmonary disease and possibly asthma.⁹⁵ Using a guinea-pig model, Bos et al⁹³ found complete inhibition of allergen-induced mucous gland hypertrophy, as well as a partial suppression of ASM thickening, contractile protein expression, airway eosinophilia, and goblet cell MUC5AC expression with tiotropium use. These results were replicated in a murine model that showed significantly decreased goblet cell metaplasia, ASM thickening, and airway fibrosis, as well as decreased T_H2 cytokine levels, including TGF- β levels in bronchoalveolar lavage fluid, which clinically resulted in abrogation of AHR.⁹⁶

Although tyrosine kinase inhibitors (eg, erlotinib and imatinib) have documented efficacy in tumor-associated angiogenesis, their role in asthma is not clearly established. Kung et al⁹⁷ explored the effects of erlotinib in allergen-sensitized Brown Norway rats and found decreased collagen deposition surrounding the airways, decreased smooth muscle thickening, and decreased peribronchial vascularization in treated animals. Additionally, levels of inflammatory T_H2 cytokines, including IL-4, IL-5, IL-10, and IL-13, as well as TNF- α and TGF- β , were substantially decreased in the erlotinib-treated group, along with improved bronchial hyperresponsiveness.⁹⁷ Nearly identical results were noted with imatinib in a study with ovalbumin-sensitized mice.⁹⁸ As such, these therapeutics merit prospective testing in human subjects and deserve further consideration in the management of airway remodeling.

CONCLUSIONS

Airway remodeling is a complex and incompletely defined process in asthmatic subjects that might contribute to pathophysiology, progression of airflow obstruction, and ultimately treatment responsiveness. Understanding which components of remodeling contribute to various physiologic consequences of asthma remains an important tenet of future pathophysiological, diagnostic, and therapeutic approaches. Additionally, there must be human studies to assess the effects of higher dosing and longer duration of ICSs with or without LABAs while identifying key indices and/or biomarkers that might serve as surrogates of airway remodeling in asthmatic subjects. For example, little is known about the long-term side effects (eg, hypothalamic-pituitary axis suppression and bone metabolism impairment) of the significantly higher doses of ICSs mentioned in this review. Once key indices related to remodeling are identified, additional outcomes research is needed to provide a context to the health care professional on how remodeling and the decision-making process to attenuate remodeling relates to the 2 current tenets of asthma treatment: future risk and impairment. Finally, although there have been advancements on the cellular and molecular mechanisms involved in airway remodeling with current treatments, there is a need to assess the developmental aspects of unique therapies that specifically target these pathways, and this is an example of where a personalized medicine approach might lead to greater beneficial effects. Ultimately, the advent of such therapies would achieve a new component of treatment: the prevention of the progressive loss of lung function that occurs in some asthmatic subjects.

What do we know?

- Airway remodeling in asthmatic subjects represents complex multicellular processes that include structural changes, such as epithelial injury, subepithelial fibrosis, ASM hyperplasia, goblet cell hypertrophy and hyperplasia, and angiogenesis, which can lead to irreversible airflow obstruction.
- Infant and childhood airway studies have begun to challenge the accepted paradigm that chronic inflammation leads to structural remodeling in asthmatic subjects and suggest that remodeling and inflammation occur in parallel during the evolution of asthma.
- Although remodeling has been considered irreversible, the use of ICSs in higher doses and for a longer duration has shown improvement in these airway changes.

What is still unknown?

- Defining the conditions that promote the development of airway remodeling in asthma.
- Establishing individual components of airway remodeling that contribute to the clinical manifestations of asthma.
- Ascertaining whether all remodeling is detrimental to asthma.
- Identifying the components of remodeling that should be targeted and at what point in the natural history of treatment they should be initiated to achieve the best results.

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