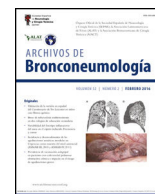




ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Review Article

Airway Remodeling in Asthma: Mechanisms, Diagnosis, Treatment, and Future Directions

Angelica Tiotiu^{a,b,*}, Paschalis Steiropoulos^c, Silviya Novakova^d, Denislava Nedeva^e,
Plamena Novakova^f, Herberto Chong-Neto^g, Guillermo Guidos Fogelbach^h, Krzysztof Kowalⁱ

^a Department of Pulmonology, University Hospital Saint-Luc, Brussels, Belgium

^b Pole Pneumology, ENT, and Dermatology – LUNS, Institute of Experimental and Clinical Research (IREC), UCLouvain, Brussels, Belgium

^c Department of Pulmonology, Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, Alexandroupolis, Greece

^d Department of Allergology, University Hospital “Sv. Georgi” Plovdiv, Bulgaria

^e Clinic of Asthma and Allergology, UMBAL Alexandrovska, Medical University Sofia, Sofia, Bulgaria

^f Department of Allergy, Medical University Sofia, Sofia, Bulgaria

^g Division of Allergy and Immunology, Complexo Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, Brazil

^h School of Medicine, ENMH, Instituto Politecnico Nacional, Mexico City, Mexico

ⁱ Department of Experimental Allergology and Immunology and Department of Allergology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland

ARTICLE INFO

Article history:

Received 28 July 2024

Accepted 20 September 2024

Available online xxx

Keywords:

Airway remodeling

Mechanisms

Diagnosis

Therapeutic approaches

ABSTRACT

Airway remodeling (AR) with chronic inflammation, are key features in asthma pathogenesis. AR characterized by structural changes in the bronchial wall is associated with a specific asthma phenotype with poor clinical outcomes, impaired lung function and reduced treatment response. Most studies focus on the role of inflammation, while understanding the mechanisms driving AR is crucial for developing disease-modifying therapeutic strategies.

This review paper summarizes current knowledge on the mechanisms underlying AR, diagnostic tools, and therapeutic approaches. Mechanisms explored include the role of the resident cells and the inflammatory cascade in AR. Diagnostic methods such as bronchial biopsy, lung function testing, imaging, and possible biomarkers are described. The effectiveness on AR of different treatments of asthma including corticosteroids, leukotriene modifiers, bronchodilators, macrolides, biologics, and bronchial thermoplasty is discussed, as well as other possible therapeutic options.

AR poses a significant challenge in asthma management, contributing to disease severity and treatment resistance. Current therapeutic approaches target mostly airway inflammation rather than smooth muscle cell dysfunction and showed limited benefits on AR. Future research should focus more on investigating the mechanisms involved in AR to identify novel therapeutic targets and to develop new effective treatments able to prevent irreversible structural changes and improve long-term asthma outcomes.

© 2024 SEPAR. Published by Elsevier España, S.L.U. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Introduction

Asthma is a chronic airway inflammatory disease characterized by typical respiratory symptoms (cough, wheeze, chest tightness, shortness of breath) that vary over time and in intensity associated with variable expiratory airflow limitation. In some patients with long-lasting asthma, airflow obstruction becomes persistent and incompletely reversible due to pathological airway remodeling (AR).^{1,2}

AR is a complex feature of asthma that involves long-term changes of airway architecture such as hyperplasia of the smooth muscles, subepithelial collagen deposition with increased thickness of the reticular basement membrane (RBM), disruption of the epithelial barrier integrity with metaplasia of goblet cells inducing mucus hyperproduction, and angiogenesis.^{3,4} AR pathogenesis is not fully understood. Until recently, it was thought that it is caused by chronic airway inflammation.⁵ However, AR is not only a feature of late-onset asthma, because structural changes were found in bronchial biopsies from pre-school children with severe wheezing and a murine model with neonatal inhaled allergen-disease.^{6–8} These findings suggest that AR may occur early in the disease, and could be a triggering process, rather than a secondary event.^{9,10} A

* Corresponding author.
E-mail address: angelica.tiotiu@yahoo.com (A. Tiotiu).

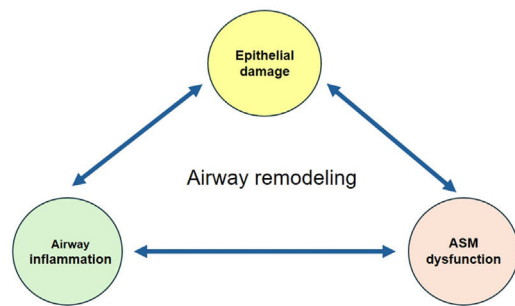


Fig. 1. Main contributors to airway remodeling in asthma. ASM: airway smooth muscle.

genetic predisposition is also suggested.⁴ AR is associated with poor clinical outcomes, impaired lung function, lower response to treatment, and altered quality of life (measured by Asthma Quality of Life Questionnaire – AQLQ) in asthma patients.¹¹ Even though the degree of remodeling correlates with asthma severity, alterations of the bronchial wall are also present in mild disease.^{12,13} Like inflammation, AR in asthma is heterogeneous, varies between individuals, and may contribute to asthma phenotypes and endotypes.¹⁴

As the presence of AR is associated with more severe asthma (SA) and poor response to treatment, targeting this component of the disease with early diagnosis and prevention could improve clinical outcomes and patients' AQLQ score.¹³ This review summarizes current knowledge on the mechanisms underlying AR in asthma, the diagnostic tools, the clinical phenotypes and the possible therapeutic approaches in the aspect of personalized medicine.

Mechanisms

AR is the result of complex interaction between the airway resident cells (epithelial cells, smooth muscle cells, fibroblasts, neuronal cells, endothelial cells), the inflammatory cells (dendritic cells – DCs, eosinophils, neutrophils, mast cells – MCs, macrophages, lymphocytes and innate lymphoid cells – ILC), and many humoral components (cytokines, enzymes, and growth factors)^{2,7,10} (Figs. 1 and 2).

AR as Secondary Event of Inflammation

According to the “inflammatory theory”, the airway epithelial cells (AECs) are the “initiators” of the process.^{10,15} Following exposure to allergens, microbial proteins, and air pollutants, injured AECs release alarmins (e.g. IL-33, IL-25, TSLP) that activate DCs, ILC2, T helper 2 lymphocytes (Th2), MCs, and macrophages, which contribute to downstream inflammation.^{5,15} In addition, environmental injuries may induce AECs apoptosis, with paracrine secretion of transforming growth factor- β (TGF- β) which initiates tissue regeneration to restore homeostasis. However, persistent, and prolonged tissue stimulation by growth factors can lead to pathological AR seen in asthma.¹⁰

The alarmins could directly induce collagen production by lung fibroblasts. IL-25 promotes lung fibroblasts proliferation while IL-33 induces the expression of fibronectin. The consequent accumulation of extracellular matrix (ECM) proteins leads to subepithelial RBM thickening that occurs early in the pathogenesis of asthma.¹⁵

The three alarmins promote eosinophilic inflammation by activating ILC2 and Th2 via DCs, both sources of IL-4, and IL-13, that increase mucus production, collagen synthesis and deposition, airway smooth muscle (ASM) cell contraction and proliferation, and fibroblast-to-myofibroblast transition (FMT).^{15,16} Eosinophils

release various mediators including TGF- β that can directly activate the AECs and mesenchymal cells.¹⁵ Alarmins trigger the production of TGF- β by macrophages and stimulate ASM proliferation. Activated macrophages release matrix metalloproteinases (MMPs) that can alter the ECM structure.^{10,15} During allergic response, MCs secrete mediators (e.g. histamine, prostaglandin D₂, tryptase), cytokines (e.g. TSLP, IL-33, IL-13), and vascular growth factors that induce fibroblast, endothelial, and epithelial cell proliferation promoting AR.¹³ In non-allergic asthma, AECs stimulate the production of Th17 cytokines inducing neutrophilic inflammation and TGF- β production with accumulation of fibrotic matrix components. The immune cells are “amplifiers” of AR.¹⁰

The epithelial–mesenchymal transition (EMT), a key feature of AR, is a biological process allowing AECs to assume a mesenchymal cell phenotype. That includes increased migratory capacity, invasiveness, resistance to apoptosis, and production of ECM components, contributing to airway wall fibrosis.¹⁰ This process is upregulated by growth factors (e.g. TGF- β), cytokines and mediators (e.g. IL-4, IL-24, MMPs) secreted by resident and inflammatory cells.^{17–21}

Subepithelial fibrosis is mediated by submucosal resident fibroblasts that proliferate and differentiate into myofibroblasts through the process of FMT. Myofibroblasts are mesenchymal cells with contractile and secretory abilities (e.g. collagen, fibronectin, MMPs, growth factors). TGF- β plays a central role in the induction of FMT in asthma, but interleukins (e.g. IL-4, IL-5, IL-13, IL-17, IL-25, IL-33), chemokines (eotaxin, periostin), as well as mechanical forces and ECM proteins could also influence this process.²²

ASM mass is increased in both large and small airways in asthma due to cells hyperplasia. The ASM layer thickness correlates positively with the severity of asthma. Additional immigration of myofibroblasts contributes to the rise of ASM layer. These processes are triggered by growth factors (e.g. TGF- β), cytokines (e.g. TSLP), components of the ECM, and chemokines.²³ ASM cells from asthma patients exhibit increased metabolism, and proliferation which can lead to changes in mechanical capabilities, increased airway stiffness, and the formation of mucosal folds.¹⁴ ASM cells can also contribute to airway inflammation through the release of cytokines and chemokines (e.g. IL-5, IL-13, eotaxin), regulate ECM via the secretion of MMPs, collagen type I, and perlecan, which in turn, may promote the ASM proliferation. MCs infiltration is increased in ASM in asthma patients, and their number correlates with the degree of airway hyperresponsiveness (AHR).¹³ In this model, fibroblasts and ASM cells are “effectors” of AR in asthma.¹⁰

AR as Primary Event

ASM is the cell responsible for generation of airway tone and contraction. Enhanced contractility of ASM was found in asthma patients due to abnormalities of calcium homeostasis and/or sensitization and altered airway innervation. Increased ASM contractility contributes to AHR.²⁴ AR might be initiated in the absence of inflammation, following bronchoconstriction in response to stimuli.^{2,7} During bronchoconstriction, the airway epithelium is subjected to excessive mechanical forces causing AECs damage that leads to previous described effects contributing to AR (e.g. release of TGF- β promoting subepithelial fibrosis by fibronectin collagen type III and V deposition, FMT, ASM cells hyperplasia and mucus hypersecretion due to goblet cell metaplasia). Bronchoconstriction stimulates epithelium to release IL-6, IL-8, and monocyte chemoattractant protein-1, which act as mitogens for ASM cells.¹³ Several data suggests that mitochondrial dysfunction could play a role in ASM remodeling in asthma.^{8,25}

Normal airway epithelium

Airway remodeling

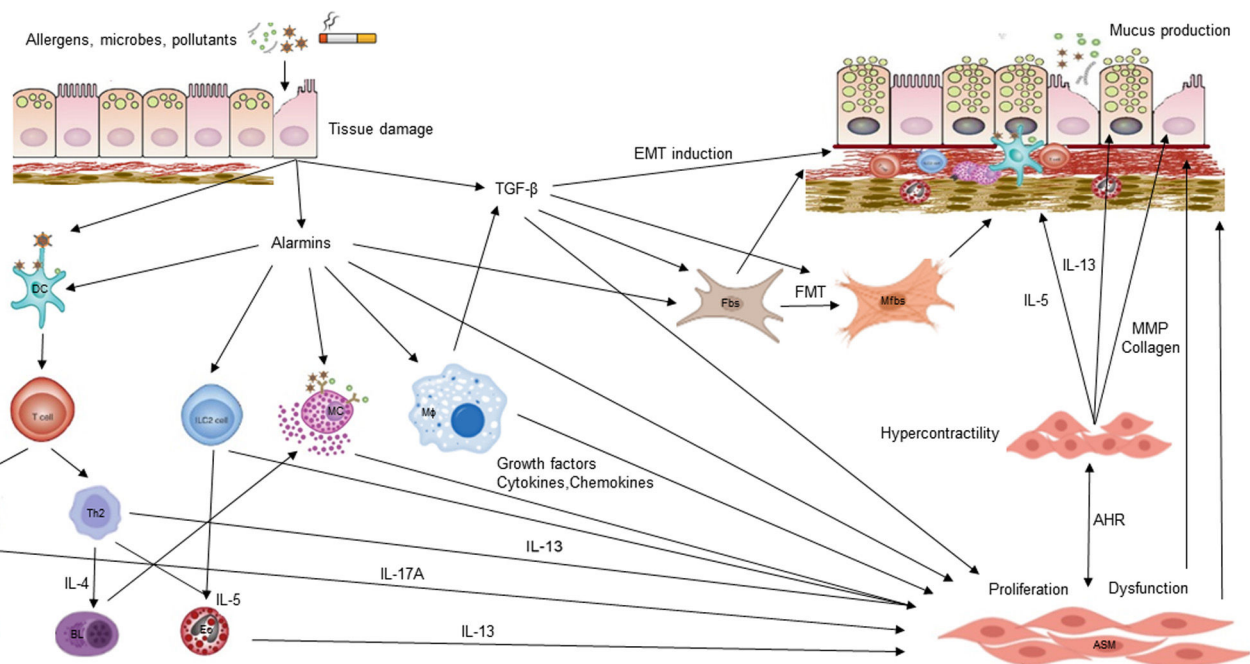


Fig. 2. Mechanisms involved in asthma airway remodeling. AHR: airway hyperresponsiveness, ASM: airway smooth muscle, BL: B lymphocyte, DC: dendritic cell, Eo: eosinophil, EMT: epithelial mesenchymal transition, Fbs: fibroblast, FMT: fibroblast–myofibroblast transition, IL: interleukin, ILC2: innate lymphoid cell type 2, Mφ: macrophage, MC: mast cell, MMP: matrix metallo-proteinase, Mfbs: myofibroblast, Ne: neutrophil, Th2: T helper 2 cell, Th17: T helper 17 cell, TGF-β: transforming growth factor beta.

Diagnosis Tools

Bronchial Biopsy

The gold standard of AR diagnosis requires bronchial biopsy by fiberoptic bronchoscopy allowing to the direct examination of the tissue (Fig. 4). However, this method is invasive and reflects mostly the proximal airways rather than small airways, so it is not recommended to be performed routinely in clinical practice.^{2,10} A recent study in asthma adults identified different clusters according to the structural changes on bronchial biopsies. The cluster with high ASM mass (19% of studied patients) was characterized by sputum eosinophilia, elevated total serum IgE levels, increased prevalence of positive skin test for *Aspergillus* sp, low lung function, important AHR, and moderate therapeutic pressure. The particularities of the cluster with high RBM thickness (31% of patients) were: increased prevalence of atopy, high total serum IgE levels, sputum eosinophilia, moderate decrease in lung function, elevated exhaled fraction of nitric oxide (FeNO) despite maximal daily doses of inhaled corticosteroids (ICS), and great AHR.²⁶ Asthma patients with ASM area > 26.6% had worse asthma control, high rate of exacerbations per year and increased weekly use of reliever medication.²⁵

Biomarkers

Currently there are no specific biomarkers for the assessment of AR in clinical practice. Blood eosinophilia was identified as a risk factor for airflow obstruction in asthma and predictive for enhanced longitudinal decline in lung function.²⁷ Clinical studies showed increased levels of eosinophils in blood, sputum, and bronchoalveolar lavage fluid in patients with irreversible airway obstruction (IRAO) compared to those with reversible airway obstruction.^{28,29} FeNO, another biomarker of T2-asthma, is correlated with greater

AHR in asthmatic children and adults.²⁷ Elevated serum levels of periostin were found in asthma adults with fixed and more severe airflow obstruction, while its expression in bronchial biopsies is associated with enhanced lung function decline.^{27–29} Serum periostin seems to be more useful than blood eosinophils or FeNO for assessing AR in asthmatics, even in those well-controlled.^{30,31} Patients with IRAO have high serum levels of fibrinogen and TGF-β, but their potential as biomarkers of AR should be better investigated.^{28,29}

Lung Function Tests

Asthma diagnosis is usually confirmed when evidence of variable expiratory airflow limitation assessed by spirometry or measure of Peak Expiratory Flow (PEF), over time, and in magnitude. Spirometry testing allowed to the measure of the forced expiratory volume per second (FEV₁) and the ratio of FEV₁ to forced vital capacity (FEV₁/FVC). Decrease of these parameters indicates expiratory airflow limitation. Responsiveness (previously called “reversibility”) should be tested if suspicion of asthma. Improvement from baseline in FEV₁ or FVC by ≥12% and 200 mL, measured within minutes after inhalation of rapid-acting bronchodilator, or weeks after the introduction of ICS was considered longtime as a positive responsiveness test, but recently the cut-off has been changed by >10% of the patient’s predicted value. Sometimes, a bronchial provocation test is needed to assess AHR.¹

Some asthma patients develop IRAO (FEV₁/FVC < 0.7 and FEV₁ < 80%) due to the presence of AR.^{24,25} They have a particular clinical phenotype of “asthma with persistent airflow limitation”¹ (Fig. 3). IRAO is present in 55–60% of patients with SA.¹⁰

PEF measurement is not useful for the diagnosis of AR. Spirometry assesses the severity of airflow obstruction, but it not directly detects AR. However, certain spirometry findings like the persistent airflow limitation despite treatment, the reduced lung function,

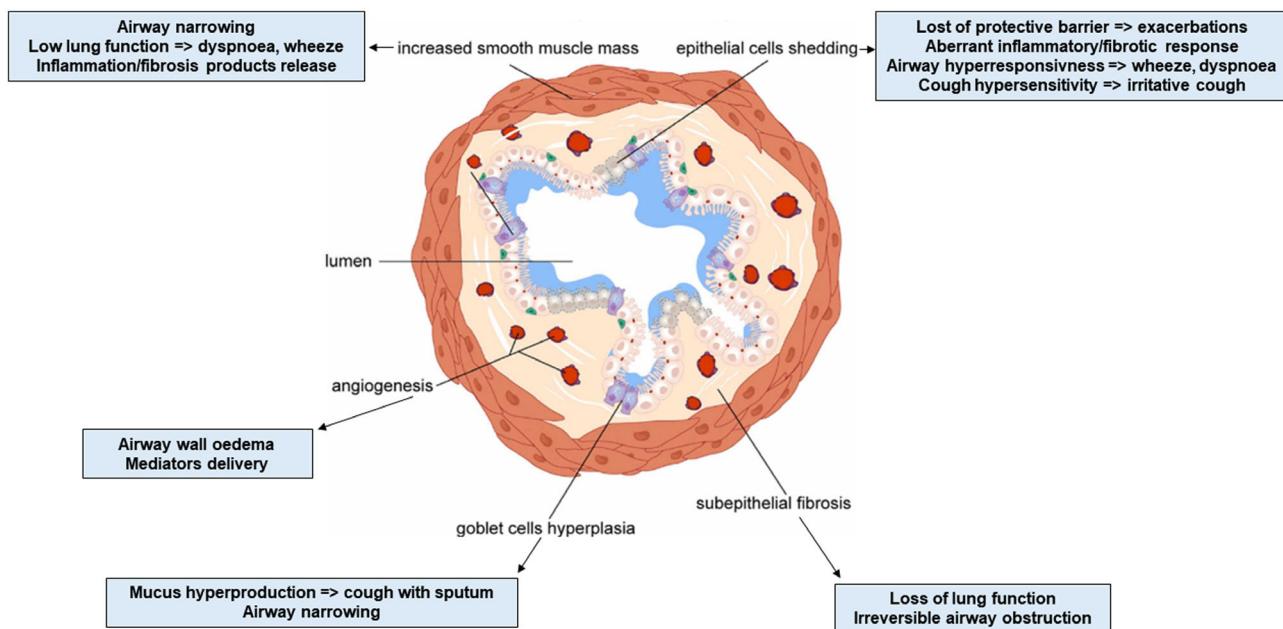


Fig. 3. Main structural airway remodeling features correlated with clinical characteristics of asthma.

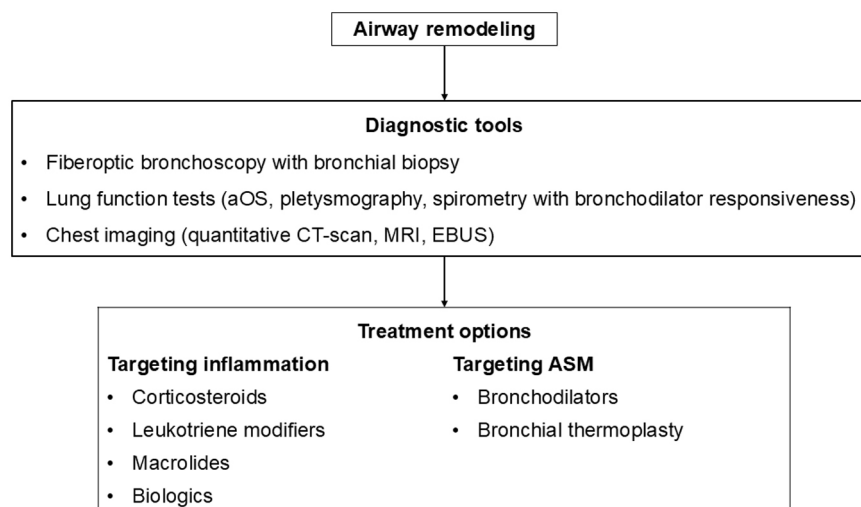


Fig. 4. Summary of current diagnostic tools and therapeutic options of airway remodeling in asthma. aOS: airway oscillometry, CT: computed tomography, MRI: magnetic resonance imaging, EBUS: endobronchial ultrasound.

and the decreased responsiveness to bronchodilator medications may suggest the presence of AR in severe or long-standing asthma. Spirometry is useful for monitoring disease progression in asthma, including AR development over time, and helps physicians to prevent this feature by adjusting the treatment.¹ In addition to spirometry, the plethysmography assesses the airway resistance (Raw) directly related to AR and the presence of indirect signs of airway obstruction such as pulmonary hyperinflation.^{29,32,33} The bronchial lumen area correlates directly with bronchial obstruction parameters (FEV₁, forced mid-expiratory flow FEF₂₅₋₇₅) and inversely with residual volume and Raw.³³ Airway oscillometry (aOS) is particularly useful in asthma. By measuring Raw, reactance, and impedance across a range of frequencies, aOS provides a more comprehensive evaluation of airway function compared to traditional spirometry. Increased Raw and respiratory impedance correlate with the degree of AR in asthma and could detect early changes in airway function even before airflow limitation.³⁴ Oscillometry bronchodilator response also seems more sensitive than

those assessed by spirometry and should be performed before labeling people with the term IRAO.³⁵ Persistent AHR has been identified as a risk factor for longitudinal decline of FEV₁ in asthmatics even in those well-controlled by ICS.³⁶ Early identification of AHR by bronchial provocation tests allows for timely therapeutic intervention and prevention of AR.¹

Several factors were identified as associated with IRAO such as male gender, long disease duration, cigarette smoking, uncontrolled asthma, sputum eosinophils and neutrophils, and high therapeutic pressure including oral corticosteroids (OCS). An Asthma Control Questionnaire score of 2.36 could identify IRAO with a high sensitivity (72%) and specificity (77%).²⁸

Imaging

Routinely performed chest X-ray examination is not helpful to evaluate AR in asthma patients. Its clinical value is restricted to

identify asthma complications or concomitant disorders such as pneumonia or pneumothorax.

The airways have been reliably examined with computed tomography (CT) scans from more than 20 years.^{37,38} Since its introduction, multidetector computed tomography (MDCT) has proved to be particularly useful in the evaluation of AR in asthmatic patients.^{39–41} By applying minimal radiation levels, the new-generation MDCT provides better resolution than helical CT with acquisition of multiple cross-sectional slices as thin as 0.60–0.75 mm without interslice gaps, in shorter time, during inspiratory and expiratory phases, with the possibility to extract quantitative data.^{42–45} Quantitative CT (qCT) can evaluate bronchial thickness (lumen diameter – LD and area – LA, bronchial wall thickness – WT and area – WA), the presence of mucous plugs in the airways, lung hyperinflation and air trapping (e.g. identification of low-attenuation areas, measure of lung density).^{39,46–49} The features of AR observed in qCT images show strong correlations with pathological and functional examinations.^{29,50,51} Analysis of qCT allowed to identify distinct asthma phenotypes with different clinical outcomes. The more advanced AR on qCT is associated with low lung function, high exacerbation rate, and worse response to standard therapy.^{29,47,52} Mucus plugging on CT-scan is linked to T2-inflammation, more severe asthma, frequent exacerbations and poor lung function.^{53,54} Positive correlations were found between WA% \geq 50% on CT-scan and increased peripheral resistance and reactivity measured by aOS.⁵⁵ Recent longitudinal studies demonstrated that qCT can help in selecting asthmatics prone to irreversible loss of lung function with time and assist in the evaluation of response to biologics, becoming a useful diagnostic tool for personalized medicine in asthma management.^{46,56,57}

Compared to CT-scan, magnetic resonance imaging (MRI) provides superior soft-tissue contrast, without patient radiation exposure.^{58,59} Fast imaging protocols are based on breath hold acquisitions or triggering/gating to compensate for motion artifacts.⁵⁹ However, MRI has lower spatial resolution than qCT, so non-contrast-enhanced MRI is not very useful for the evaluation of subtle changes in airway structure seen in asthma patients.⁵⁸ The application of hyperpolarized gases with MRI allows to direct assessment of ventilation heterogeneity and quantitative measurement of terminal airway, that correlate with AR. Serial imaging can evaluate disease progression and response to therapy over time.^{58–60}

The endobronchial ultrasound technique (EBUS) is also useful for the assessment of AR in asthma patients.⁶¹ EBUS allows the detailed analysis of the bronchial wall structures distinguishing different layers. The inner layers contain the epithelium, submucosa, and ASM while the outer layers correspond to cartilage.^{61,62} In distal no cartilaginous airways EBUS can visualize the three layers of the bronchial wall.⁶² The EBUS may be useful for asthma patients to evaluate wall changes after bronchial thermoplasty (BT).⁶³ However, EBUS is an invasive method, requires an expert bronchoscopy skill, and allows for local evaluation of the airways.

The role of other imaging methods such as optical coherence tomography or positron emission tomography in the evaluation of AR should be determined.^{60,64}

Treatment

Corticosteroids

Corticosteroids are the cornerstone of treatment in asthma.¹ Several clinical data showed that inhaled corticosteroids (ICS) decreased RBM thickness and collagen type III deposition in bronchial biopsies in asthma patients if administered for more than 6-weeks.^{65–68} A greater effect was observed after 2-years of treatment with a high-dose of budesonide, suggesting a possible

dose-dependent, long-term effect.⁶⁸ This benefit was not confirmed by all studies with ICS, neither after 2-weeks treatment with OCS.^{69–72}

The data about the effect of corticosteroids on the airway epithelial damage are also divergent. Several experimental studies suggested that corticosteroids may contribute to AR by inducing AECs apoptosis, while others demonstrated that this treatment restored the integrity of epithelial cell monolayers through the redistribution of tight junction proteins.^{73–75} Bronchial biopsies from asthmatics treated 10-years with ICS showed a significant decrease in the number of inflammatory cells, with small focal areas with non-ciliated cells and persistence of squamous cell metaplasia in some patients, suggesting partial recovery of epithelial damage.⁷⁶

In an animal model, a single dose administration of beclomethasone caused acceleration of the mucus release from goblet cells probably due to overstimulation.⁷⁷ Other clinical and experimental studies from asthma patients treated longer time with ICS demonstrated an increase in the number of ciliated cells and a reduction of goblet cell hyperplasia suggesting a possible time-dependent effect.^{78,79}

On asthma patients, a 6-months treatment with inhaled beclomethasone dipropionate decreased both vessel number and percent vascularity within the lamina propria, modifications associated with changes in collagen III thickness.⁸⁰ Another study showed a significant reduction in the vascular component of AR only in asthma patients receiving high-dose inhaled fluticasone propionate after 6-weeks of treatment.⁸¹

Despite undeniable evidence of ICS effectiveness on reducing AHR, the therapeutic index is not the same for all products and some asthma patients under treatment continue to have airflow obstruction.^{65,69,82–84} In addition, the long-term use of high-dose ICS is associated with potential systemic side effects.⁸⁵

Beta-agonists

Beta-agonists are vital for alleviating asthma symptoms by relaxing ASM.¹ Experimental data suggests that long acting β_2 -agonists (LABA) have no impact on ASM cells hyperplasia in asthma patients, but the association ICS-LABA decreased goblet cell metaplasia.^{86,87} A clinical study showed that salmeterol addition in asthmatics already receiving ICS, reduced vessels density in lamina propria after 3-months of treatment.⁸⁸

Anticholinergics

Studies on animal models suggested that tiotropium administration could reduce AHR, mucus production, thickness of ASM, subepithelial fibrosis, and goblet cell metaplasia.^{89–91} Several clinical data showed that addition of tiotropium in asthma patients treated with ICS-LABA significantly decreased airway WA and WT on CT-scan ($p < 0.05$ for both), and improved airflow obstruction, while glycopyrronium offers a better protection against methacholine-induced bronchoconstriction than placebo ($p < 0.002$).^{92–94}

Leukotriene Modifiers

In animal models, leukotrienes receptor antagonists (LTRA) showed a positive impact on AHR, goblet cell hyperplasia, EMT, subepithelial fibrosis, ASM hyperplasia by inhibiting TGF- β signaling.^{95–101} Zileuton, a leukotriene synthesis inhibitor, reduced ASM mass and ECM deposition in an animal model.¹⁰² LTRA improve AHR in asthma patients.^{103,104} Several clinical data showed that 8-weeks treatment with montelukast prevents AR by decreasing collagen deposition in airways in asthmatic

children, and myofibroblast count in adults with mild atopic asthma.^{98,105}

Macrolides

Macrolides are antibiotics recognized for their anti-inflammatory properties, that can reduce exacerbation rate in SA.¹⁰⁶ Experimental data suggested that azithromycin administration decreases AECs apoptosis, attenuates goblet cell hyperplasia, suppresses EMT, reduces AHR, proliferation and viability of ASM cells.^{107–114} Both roxithromycin and azithromycin inhibit vascular endothelial growth factor induced ASM cell proliferation in vitro.^{115,116} A clinical trial showed that 8-months treatment with azithromycin (250 mg three days a week) increased LA in patients with SA on CT-scan without significant change of the WT versus placebo.¹¹⁷

Biologics

Biologics, humanized antibodies used as add-on treatment in patients with SA, showed also benefits on AR.

In vitro administration of the anti-IgE antibody, omalizumab, prevented ASM cell proliferation, collagen and fibronectin deposition in allergic asthma.^{118,119} Clinical data showed that 16-weeks treatment with omalizumab decreased airway WT on CT-scan in patients with SA.^{120,121} Effectively, a significant reduction in RBM thickness and fibronectin accumulation was found on bronchial biopsies from patients with severe allergic asthma after 12-months treatment with omalizumab.^{122,123} The decrease of fibronectin deposition in bronchial mucosa was associated with an improvement in asthma control and AQLQ.¹²³ Experimental and clinical studies demonstrated that omalizumab administration inhibited AHR in allergic asthma.^{124–126}

Biologics targeting IL-5 (mepolizumab) and its receptor α (benralizumab) showed positive impact on AR. One-year treatment with mepolizumab significantly decreased airway WA on CT-scan in patients with refractory eosinophilic asthma.¹²⁷ Mepolizumab reduced expression of ECM proteins (e.g. tenascin, lumican, procollagen III) and of TGF- β 1 by eosinophils in bronchial biopsies from patients with mild atopic asthma, after 3-months of treatment.¹²⁸ Preliminary results from the MESILICO study showed that one-year treatment with mepolizumab significantly decreased RBM thickness, ASM area, and extent of epithelial damage in patients with late-onset, severe eosinophilic asthma and fixed airflow obstruction.¹²⁹ Benralizumab reduced the number of tissue myofibroblasts and ASM mass in bronchial biopsies from patients with severe eosinophilic asthma after 3-months of treatment.¹³⁰ Decrease in mucus plugs and ventilation defects were observed on functional imaging already at day 28 after benralizumab injection in patients with severe eosinophilic asthma, and the early response persisted 2.5-years later, alongside significantly improved asthma control.^{131–133} Both mepolizumab and benralizumab suppressed the AHR induced by histamine in an experimental study, but this benefit was confirmed only for benralizumab in clinical setting.^{127,134–136}

Experimental data showed that IL-4 receptor α blockade by dupilumab decreased AHR, mucus production, and vascular permeability in the airways.^{137,138} A prospective clinical study proved that 48-weeks treatment with dupilumab reduced mucus score and airway WT on CT-scan in patients with uncontrolled moderate-to-severe asthma. The decrease in mucus score was associated with improvement of asthma control, AQLQ, and airway obstruction.¹³⁹

Tezepelumab, an anti-TSLP antibody, showed benefits on AR in a murine model of asthma by reducing collagen deposition, goblet cell hyperplasia, TGF- β levels in the airways, and AHR to methacholine.¹⁴⁰ However, a recent randomized clinical trial failed

to prove a significant effect of tezepelumab after 28-weeks of treatment on AR assessed by bronchial biopsies, CT-scan and IOS in patients with moderate-to-severe asthma compared to placebo.¹⁴¹ Other clinical data demonstrated a decrease of AHR to mannitol after at least 12-weeks of treatment by tezepelumab versus placebo, and a reduction of occlusive mucus plugs on CT-scan after 28-weeks of treatment.^{141–143} The last effect was correlated with the improvement in FEV₁.¹⁴³

Other Medications

Adding six standardized quality house dust mite sublingual immunotherapy to standard pharmacotherapy in patients with allergic asthma and rhinitis for 48-weeks significantly decreased airway WA and WT with increase in LA on CT-scan.¹⁴⁴ Fevipirant, a prostaglandin D₂ type 2 receptor antagonist, administered 12-weeks reduced ASM mass on bronchial biopsies in asthma patients by decreasing airway eosinophilia with concomitant diminished recruitment of myofibroblasts and fibrocytes to the ASM bundle.¹⁴⁵ Increasing number of studies are focusing on potential therapies that could reduce ASM hypercontractility and AHR by improving abnormalities in calcium homeostasis and in airway innervation.²⁴ A clinical trial showed that gallopamil, a calcium channel blocker, administered for one year, reduces ASM area on bronchial biopsies and normalized ASM thickness on CT-scan.¹⁴⁶

Bronchial Thermoplasty

BT, an endoscopic treatment using radiofrequency energy, is the only therapy that lastingly decreased AR in 60% of adults with SA.^{1,147} Besides the reduction in ASM mass, RBM thickening, submucosal nerves, and epithelium neuroendocrine cells, BT induces an ECM rearrangement with increase in tissue area occupied by collagen but a less dense fiber organization.^{147–151} BT decreased AR by modifying the secretion of epithelium-derived heat shock proteins that improve AECs regeneration with negative impact on fibroblasts and ASM cells proliferation without affecting vasculature.^{147–149,152,153} Histological parameters were associated with improvement of asthma control, AQLQ, lung function, and reduction of the exacerbation rate.^{151,154–156} If the response to BT seems to be independent of the bronchodilator responsiveness, the patients with FEV₁ < 80% have a greater reduction in ASM mass after treatment compared to those with higher FEV₁.^{156,157} The reduction in ASM mass by BT becomes visible after 3-months of treatment and could persist > 10 years after the procedure.^{5,151,158}

Conclusion

AR and chronic inflammation are critical components in asthma pathogenesis. Recognizing that AR may occur early in the disease and not simply as consequence of the inflammation is crucial to developing novel therapeutic strategies in asthma. AR is associated with a specific clinical phenotype of asthma. Understanding the complex mechanisms driving AR is mandatory to identify different pathological endotypes and for developing new therapies in asthma.

Advances in imaging techniques offer the possibility for an objective assessment of AR in the whole respiratory tract in asthmatics by broadly accessible, noninvasive, and highly reproducible tools. Imaging and lung function testing help clinicians to early detect and accurately evaluate the presence of AR in asthma patients.

Most of current therapies of asthma showed limited effects on AR because they are targeting inflammation and not ASM dysfunction. Even BT which acts directly on ASM mass showed benefits only

in a selected population. Potential targets causing ASM cell dysfunction were identified, and medications are under study, but more efforts should be deployed on this research way to find effective treatments of AR in asthma.

Funding Source

None.

Conflict of Interest

A.T. received honoraria as speaker for educational events from AstraZeneca, BMS, GSK, and Sanofi; as member of Advisory Board from AstraZeneca and Sanofi; support for attending meetings from AstraZeneca and Sanofi.

P.S. received honoraria as speaker from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Elpen, Guidotti, Menarini, Specialty Therapeutics; support for attending meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Elpen, Guidotti, Menarini, Specialty Therapeutics.

S.N. and G.G. have no conflict of interest to declare.

D.N. received honoraria as speaker from AstraZeneca, Berlin Chemie, Takeda, Chiesi and support for attending meetings from AstraZeneca and Stallergen.

P.N. received honoraria as speaker from Berlin Chemie, Chiesi.

H.C.N. received consulting fees from AstraZeneca, Sanofi; honoraria as speaker from AstraZeneca, Sanofi.

K.K. received royalties from UpToDate, honoraria as speaker from ALK Abello, Aurovitas Pharma, AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, EMMA MDT, Stallergenes.

Artificial Intelligence Involvement

None.

References

- Global Initiative for Asthma. <https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Main-Report-WMS-1.pdf> [accessed 18.5.24].
- Fehrenbach H, Wagner C, Wegmann M. Airway remodeling in asthma: what really matters. *Cell Tissue Res*. 2017;367:551–69. <http://dx.doi.org/10.1007/s00441-016-2566-8>.
- Joseph C, Tatler AL. Pathobiology of airway remodeling in asthma: the emerging role of integrins. *J Asthma Allergy*. 2022;15:595–610. <http://dx.doi.org/10.2147/JAA.S267222>.
- Samitas K, Carter A, Kariyawasam HH, Xanthou G. Upper and lower airway remodelling mechanisms in asthma, allergic rhinitis and chronic rhinosinusitis: the one airway concept revisited. *Allergy*. 2018;73:993–1002. <http://dx.doi.org/10.1111/all.13373>.
- Jendzjowsky N, Laing A, Malig M, Matyas J, de Heuvel E, Dumonceaux C, et al. Long-term modulation of airway remodelling in severe asthma following bronchial thermoplasty. *Eur Respir J*. 2022;59:2100622. <http://dx.doi.org/10.1183/13993003.00622-2021>.
- Lezmi G, Gosset P, Deschildre A, Abou-Taam R, Mahut B, Beydon N, et al. Airway remodeling in preschool children with severe recurrent wheeze. *Am J Respir Crit Care Med*. 2015;192:164–71. <http://dx.doi.org/10.1164/rccm.201411-1958OC>.
- Saglani S, Lloyd CM. Novel concepts in airway inflammation and remodelling in asthma. *Eur Respir J*. 2015;46:1796–804. <http://dx.doi.org/10.1183/13993003.01196-2014>.
- Beaufils F, Esteves P, Enaud R, Germande O, Celle A, Marthan R, et al. Mitochondria are involved in bronchial smooth muscle remodeling in severe preschool wheezers. *J Allergy Clin Immunol*. 2021;148:645–51.e11. <http://dx.doi.org/10.1016/j.jaci.2021.03.027>.
- Berankova K, Uhlik J, Honkova L, Pohunek P. Structural changes in the bronchial mucosa of young children at risk of developing asthma. *Pediatr Allergy Immunol*. 2014;25:136–42. <http://dx.doi.org/10.1111/pai.12119>.
- Hough KP, Curtiss ML, Blain TJ, Liu RM, Trevor J, Deshane JS, et al. Airway remodeling in asthma. *Front Med*. 2020;7:191. <http://dx.doi.org/10.3389/fmed.2020.00191>.
- Bergeron C, Tulic MK, Hamid Q. Airway remodelling in asthma: from benchside to clinical practice. *Can Respir J*. 2010;17:e85–93. <http://dx.doi.org/10.1155/2010/318029>.
- Wilson SJ, Rigden HM, Ward JA, Laviolette M, Jarjour NN, Djukanović R. The relationship between eosinophilia and airway remodelling in mild asthma. *Clin Exp Allergy*. 2013;43:1342–50. <http://dx.doi.org/10.1111/cea.12156>.
- Varricchi G, Ferri S, Pepys J, Poto R, Spadaro G, Nappi E, et al. Biology and airway remodeling in severe asthma. *Allergy*. 2022;77:3538–52. <http://dx.doi.org/10.1111/all.15473>.
- Hsieh A, Assadina N, Hackett TL. Airway remodeling heterogeneity in asthma and its relationship to disease outcomes. *Front Physiol*. 2023;14:1113100. <http://dx.doi.org/10.3389/fphys.2023.1113100>.
- Nedeva D, Kowal K, Mihaicuta S, Guidos Fogelbach G, Steiropoulos P, Jose Chong-Neto H, et al. Epithelial alarmins: a new target to treat chronic respiratory diseases. *Expert Rev Respir Med*. 2023;17:773–86. <http://dx.doi.org/10.1080/17476348.2023.2262920>.
- Pelaia C, Vatrella A, Gallelli L, Terracciano R, Navalesi P, Maselli R, et al. Dupilumab for the treatment of asthma. *Expert Opin Biol Ther*. 2017;17:1565–72. <http://dx.doi.org/10.1080/14712598.2017.1387245>.
- Tan QY, Cheng ZS. TGFβ1-Smad signaling pathway participates in interleukin-33 induced epithelial-to-mesenchymal transition of a549 cells. *Cell Physiol Biochem*. 2018;50:757–67. <http://dx.doi.org/10.1159/000494241>.
- Cai LM, Zhou YQ, Yang LF, Qu JX, Dai ZY, Li HT, et al. Thymic stromal lymphopoietin induced early stage of epithelial-mesenchymal transition in human bronchial epithelial cells through upregulation of transforming growth factor beta 1. *Exp Lung Res*. 2019;45:221–35. <http://dx.doi.org/10.1080/01902148.2019.1646841>.
- Ojaku CA, Yoo EJ, Panettieri RA. Transforming growth factor β1 function in airway remodeling and hyperresponsiveness. The missing link? *Am J Respir Cell Mol Biol*. 2017;56:432–42. <http://dx.doi.org/10.1165/rcmb.2016-0307TR>.
- Osei ET, Booth S, Hackett TL. What have in vitro co-culture models taught us about the contribution of epithelial-mesenchymal interactions to airway inflammation and remodeling in asthma? *Cells*. 2020;9:1694. <http://dx.doi.org/10.3390/cells9071694>.
- Feng KN, Meng P, Zou XL, Zhang M, Li HK, Yang HL, et al. IL-37 protects against airway remodeling by reversing bronchial epithelial-mesenchymal transition via IL-24 signaling pathway in chronic asthma. *Respir Res*. 2022;23:244. <http://dx.doi.org/10.1186/s12931-022-02167-7>.
- Michalik M, Wójcik-Pszczola K, Paw M, Wnuk D, Koczurkiewicz P, Sanak M, et al. Fibroblast-to-myofibroblast transition in bronchial asthma. *Cell Mol Life Sci*. 2018;75:3943–61. <http://dx.doi.org/10.1007/s00018-018-2899-4>.
- Rosethorne EM, Charlton SJ. Airway remodeling disease: primary human structural cells and phenotypic and pathway assays to identify targets with potential to prevent or reverse remodeling. *J Exp Pharmacol*. 2018;10:75–85. <http://dx.doi.org/10.2147/JEP.S159124>.
- Khalifaoui L, Pabelick CM. Airway smooth muscle in contractility and remodeling of asthma: potential drug target mechanisms. *Expert Opin Ther Targets*. 2023;27:19–29. <http://dx.doi.org/10.1080/14728222.2023.2177533>.
- Girodet PO, Allard B, Thumerel M, Begueret H, Dupin I, Ousova O, et al. Bronchial smooth muscle remodeling in nonsevere asthma. *Am J Respir Crit Care Med*. 2016;193:627–33. <http://dx.doi.org/10.1164/rccm.201507-1404OC>.
- Siddiqui S, Shikotra A, Richardson M, Doran E, Choy D, Bell A, et al. Airway pathological heterogeneity in asthma: visualization of disease microclusters using topological data analysis. *J Allergy Clin Immunol*. 2018;142:1457–68. <http://dx.doi.org/10.1016/j.jaci.2017.12.982>.
- Tiotiu A. Biomarkers in asthma: state of the art. *Asthma Res Pract*. 2018;4:10. <http://dx.doi.org/10.1186/s40733-018-0047-4>.
- Graff S, Brimont N, Moermans C, Henket M, Paulus V, Guissard F, et al. Clinical and biological factors associated with irreversible airway obstruction in adult asthma. *Respir Med*. 2020;175:106202. <http://dx.doi.org/10.1016/j.rmed.2020.106202>.
- Kozlik P, Zuk J, Bartyzel S, Zarychta J, Okon K, Zareba L, et al. The relationship of airway structural changes to blood and bronchoalveolar lavage biomarkers, and lung function abnormalities in asthma. *Clin Exp Allergy*. 2020;50:15–28. <http://dx.doi.org/10.1111/cea.13501>.
- Mansur AH, Srivastava S, Sahal A. Disconnect of type 2 biomarkers in severe asthma: dominated by FeNO as a predictor of exacerbations and periostin as predictor of reduced lung function. *Respir Med*. 2018;143:31–8. <http://dx.doi.org/10.1016/j.rmed.2018.08.005>.
- Takahashi K, Meguro K, Kawashima H, Kashiwakuma D, Kagami SI, Ohta S, et al. Serum periostin levels serve as a biomarker for both eosinophilic airway inflammation and fixed airflow limitation in well-controlled asthmatics. *J Asthma*. 2019;56:236–43. <http://dx.doi.org/10.1080/02770903.2018.1455855>.
- Gibson GJ. Pulmonary hyperinflation a clinical overview. *Eur Respir J*. 1996;9:2640–9. <http://dx.doi.org/10.1183/09031936.96.09122640>.
- Fuso L, Macis G, Condoluci C, Sbarra M, Contu C, Conte EG, et al. Impulse oscillometry and nitrogen washout test in the assessment of small airway dysfunction in asthma: correlation with quantitative computed tomography. *J Asthma*. 2019;56:323–31. <http://dx.doi.org/10.1080/02770903.2018.1452032>.
- Karayama M, Inui N, Mori K, Kono M, Hozumi H, Suzuki Y, et al. Respiratory impedance is correlated with airway narrowing in asthma using three-dimensional computed tomography. *Clin Exp Allergy*. 2018;48:278–87. <http://dx.doi.org/10.1111/cea.13083>.
- Chan R, Lipworth BJ. Oscillometry bronchodilator response in adult moderate to severe eosinophilic asthma patients: a prospective cohort study. *Clin Exp Allergy*. 2022;52:1118–20. <http://dx.doi.org/10.1111/cea.14185>.
- Ohkura N, Fujimura M, Tokuda A, Furusho S, Abo M, Katayama N. Evaluation of airway hyperresponsiveness and exhaled nitric oxide as risk factors

- for airway remodeling in patients with stable asthma. *Allergy Asthma Proc.* 2009;30:419–23, <http://dx.doi.org/10.2500/aap.2009.30.3253>.
37. Niimi A, Matsumoto H, Amitani R, Nakano Y, Mishima M, Minakuchi M, et al. Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. *Am J Respir Crit Care Med.* 2000;162:1518–23, <http://dx.doi.org/10.1164/jrccm.162.4.9909044>.
38. Little SA, Sproule MW, Cowan MD, Macleod KJ, Robertson M, Love JG, et al. High resolution computed tomographic assessment of airway wall thickness in chronic asthma: reproducibility and relationship with lung function and severity. *Thorax.* 2002;57:247–53, <http://dx.doi.org/10.1136/thorax.57.3.247>.
39. Aysola RS, Hoffman EA, Gierada D, Wenzel S, Cook-Granroth J, Tarsi J, et al. Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. *Chest.* 2008;134:1183–91, <http://dx.doi.org/10.1378/chest.07-2779>.
40. Castro M, Fain SB, Hoffman EA, Gierada DS, Erzurum SC, Wenzel S, et al. Lung imaging in asthmatic patients: the picture is clearer. *J Allergy Clin Immunol.* 2011;128:467–78, <http://dx.doi.org/10.1016/j.jaci.2011.04.051>.
41. Jarjour NN, Erzurum SC, Bleecker ER, Calhoun WJ, Castro M, Comhair SAA, et al. Severe asthma: lessons learned from the national heart, lung, and blood institute severe asthma research program. *Am J Respir Crit Care Med.* 2012;185:356–62, <http://dx.doi.org/10.1164/rccm.201107-1317PP>.
42. Kalra MK, Maher MM, D'Souza R, Saini S. Multidetector computed tomography technology: current status and emerging developments. *J Comput Assist Tomogr.* 2004;28:S2–6, <http://dx.doi.org/10.1097/01.rct.0000120857.80935.bd>.
43. Newell JD, Fuld MK, Allmendinger T, Sieren JP, Chan KS, Guo J, et al. Very low-dose (0.15 mGy) chest CT protocols using the COPDGene 2 test object and a third-generation dual-source CT scanner with corresponding third-generation iterative reconstruction software. *Invest Radiol.* 2015;50:40–5, <http://dx.doi.org/10.1097/RLI.0000000000000093>.
44. Sundaram B, Chughtai AR, Kazerooni EA. Multidetector high-resolution computed tomography of the lungs: protocols and applications. *J Thorac Imaging.* 2010;25:125–41, <http://dx.doi.org/10.1097/RTI.0b013e3181d9ca37>.
45. Chen-Mayer HH, Fuld MK, Hoppel B, Judy PF, Sieren JP, Guo J, et al. Standardizing CT lung density measure across scanner manufacturers. *Med Phys.* 2017;44:974–85, <http://dx.doi.org/10.1002/mp.12087>.
46. Krings JG, Goss CW, Lew D, Samant M, McGregor MC, Boomer J, et al. Quantitative CT metrics are associated with longitudinal lung function decline and future asthma exacerbations: results from SARP-3. *J Allergy Clin Immunol.* 2021;148:752–62, <http://dx.doi.org/10.1016/j.jaci.2021.01.029>.
47. Choi S, Hoffman EA, Wenzel SE, Castro M, Fain SB, Jarjour NN, et al. Quantitative assessment of multiscale structural and functional alterations in asthmatic populations. *J Appl Physiol.* (1985). 2015;118:1286–98, <http://dx.doi.org/10.1152/japplphysiol.01094.2014>.
48. Zhang X, Xia T, Lai Z, Zhang Q, Guan Y, Zhong N. Uncontrolled asthma phenotypes defined from parameters using quantitative CT analysis. *Eur Radiol.* 2019;29:2848–58, <http://dx.doi.org/10.1007/s00330-018-5913-1>.
49. Tang M, Elicker BM, Henry T, Gierada DS, Schiebler ML, Huang BK, et al. Mucus plugs persist in asthma, and changes in mucus plugs associate with changes in airflow over time. *Am J Respir Crit Care Med.* 2022;205:1036–45, <http://dx.doi.org/10.1164/rccm.202110-2265OC>.
50. Hartley RA, Barker BL, Newby C, Pakkai M, Baldi S, Kajekar R, et al. Relationship between lung function and quantitative computed tomographic parameters of airway remodeling, air trapping, and emphysema in patients with asthma and chronic obstructive pulmonary disease: a single-center study. *J Allergy Clin Immunol.* 2016;137:1413–22e12, <http://dx.doi.org/10.1016/j.jaci.2016.02.001>.
51. Berair R, Hartley R, Mistry V, Sheshadri A, Gupta S, Singapuri A, et al. Associations in asthma between quantitative computed tomography and bronchial biopsy-derived airway remodelling. *Eur Respir J.* 2017;49:1601507, <http://dx.doi.org/10.1183/13993003.01507-2016>.
52. Kim S, Choi S, Kim T, Jin KN, Cho SH, Lee CH, et al. Phenotypic clusters on computed tomography reflects asthma heterogeneity and severity. *World Allergy Organ J.* 2022;15:100628, <http://dx.doi.org/10.1016/j.waojou.2022.100628>.
53. Chan R, Duraikannu C, Lipworth B. Clinical associations of mucus plugging in moderate to severe asthma. *J Allergy Clin Immunol Pract.* 2023;11:195–9e2, <http://dx.doi.org/10.1016/j.jaip.2022.09.008>.
54. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest.* 2018;128:997–1009, <http://dx.doi.org/10.1172/JCI95693>.
55. Chan R, Duraikannu C, Thouseef MJ, Lipworth B. Impaired respiratory system resistance and reactance are associated with bronchial wall thickening in persistent asthma. *J Allergy Clin Immunol Pract.* 2023;11:1459–62e3, <http://dx.doi.org/10.1016/j.jaip.2022.12.040>.
56. Hayashi Y, Tanabe N, Matsumoto H, Shimizu K, Sakamoto R, Oguma T, et al. Associations of fractional exhaled nitric oxide with airway dimension and mucus plugs on ultra-high-resolution computed tomography in former smokers and nonsmokers with asthma. *Allergol Int.* 2024, <http://dx.doi.org/10.1016/j.alit.2024.01.013>. S1323–8930(24)00015–7.
57. Tsuge M, Ikeda M, Kondo Y, Tsukahara H. Severe pediatric asthma with a poor response to omalizumab: a report of three cases and three-dimensional bronchial wall analysis. *J Int Med Res.* 2020;48:3000605211070492, <http://dx.doi.org/10.1177/03000605211070492>.
58. Biederer J. MR imaging of the airways. *Br J Radiol.* 2023;96:20220630, <http://dx.doi.org/10.1259/bjr.20220630>.
59. Sodhi KS, Ciet P, Vasanawala S, Biederer J. Practical protocol for lung magnetic resonance imaging and common clinical indications. *Pediatr Radiol.* 2022;52:295–311, <http://dx.doi.org/10.1007/s00247-021-05090-z>.
60. Ash SY, Diaz AA. The role of imaging in the assessment of severe asthma. *Curr Opin Pulm Med.* 2017;23:97–102, <http://dx.doi.org/10.1097/MCP.0000000000000341>.
61. Górka K, Gross-Sondej I, Górka J, Stachura T, Polok K, Celejewska-Wójcik N, et al. Assessment of airway remodeling using endobronchial ultrasound in asthma-COPD overlap. *J Asthma Allergy.* 2021;14:663–74, <http://dx.doi.org/10.2147/JAA.S306421>.
62. Soja J, Grzanka P, Śladek K, Okoń K, Ćmiel A, Mikoś M, et al. The use of endobronchial ultrasonography in assessment of bronchial wall remodeling in patients with asthma. *Chest.* 2009;136:797–804, <http://dx.doi.org/10.1378/chest.08-2759>.
63. Soja J, Górka K, Gross-Sondej I, Jakiela B, Mikrut S, Okoń K, et al. Endobronchial ultrasound is useful in the assessment of bronchial wall changes related to bronchial thermoplasty. *J Asthma Allergy.* 2023;16:585–95, <http://dx.doi.org/10.2147/JAA.S404254>.
64. Xie H, Zhao Z, Zhang W, Li L. Quantitative analysis of lung function and airway remodeling using ventilation/perfusion single photon emission tomography/computed tomography and HRCT in patients with chronic obstructive pulmonary disease and asthma. *Ann Nucl Med.* 2023;37:504–16, <http://dx.doi.org/10.1007/s12149-023-01848-7>.
65. Ward C, Pais M, Bish R, Reid D, Feltis B, Johns D, et al. Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. *Thorax.* 2002;57:309–16, <http://dx.doi.org/10.1136/thorax.57.4.309>.
66. Olivieri D, Chetta A, Del Donno M, Bertorelli G, Casalini A, Pesci A, et al. Effect of short-term treatment with low-dose inhaled fluticasone propionate on airway inflammation and remodeling in mild asthma: a placebo-controlled study. *Am J Respir Crit Care Med.* 1997;155:1864–71, <http://dx.doi.org/10.1164/jrccm.155.6.9196087>.
67. Trigg CJ, Manolitsas ND, Wang J, Calderón MA, McAulay A, Jordan SE, et al. Placebo-controlled immunopathologic study of four months of inhaled corticosteroids in asthma. *Am J Respir Crit Care Med.* 1994;150:17–22, <http://dx.doi.org/10.1164/jrccm.150.1.8025745>.
68. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med.* 1999;159:1043–51, <http://dx.doi.org/10.1164/jrccm.159.4.9806052>.
69. Boulet LP, Turcotte H, Laviolette M, Naud F, Bernier MC, Martel S, et al. Airway hyperresponsiveness, inflammation, and subepithelial collagen deposition in recently diagnosed versus long-standing mild asthma. Influence of inhaled corticosteroids. *Am J Respir Crit Care Med.* 2000;162:1308–13, <http://dx.doi.org/10.1164/jrccm.162.4.9910051>.
70. Jeffery PK, Godfrey RW, Adroldi E, Nelson F, Rogers A, Johansson SA. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. A quantitative light and electron microscopic study. *Am Rev Respir Dis.* 1992;145:890–9, <http://dx.doi.org/10.1164/jrccm.145.4.Pt.1.890>.
71. Chakir J, Shannon J, Molet S, Fukakusa M, Elias J, Laviolette M, et al. Airway remodeling-associated mediators in moderate to severe asthma: effect of steroids on TGF-beta, IL-11, IL-17, and type I and type III collagen expression. *J Allergy Clin Immunol.* 2003;111:1293–8, <http://dx.doi.org/10.1067/mai.2003.1557>.
72. Bergeron C, Hauber HP, Gotfried M, Newman K, Dhanda R, Servi RJ, et al. *J Allergy Clin Immunol.* 2005;116:983–9, <http://dx.doi.org/10.1016/j.jaci.2005.07.029>.
73. Dorscheid DR, Wojcik KR, Sun S, Marroquin B, White SR. Apoptosis of airway epithelial cells induced by corticosteroids. *Am J Respir Crit Care Med.* 2001;164:1939–47, <http://dx.doi.org/10.1164/jrccm.164.12.103013>.
74. White SR, Dorscheid DR. Corticosteroid-induced apoptosis of airway epithelium: a potential mechanism for chronic airway epithelial damage in asthma. *Chest.* 2002;122:2785–84S, <http://dx.doi.org/10.1378/chest.122.6.suppl.2785>.
75. Sekiyama A, Gon Y, Terakado M, Takeshita I, Kozu Y, Maruoka S, et al. Glucocorticoids enhance airway epithelial barrier integrity. *Int Immunopharmacol.* 2012;12:350–7, <http://dx.doi.org/10.1016/j.intimp.2011.12.006>.
76. Lundgren R, Söderberg M, Hörstedt P, Stenling R. Morphological studies of bronchial mucosal biopsies from asthmatics before and after ten years of treatment with inhaled steroids. *Eur Respir J.* 1988;1:883–9.
77. Uhlík J, Vajner L, Adásková J, Konrádová V. Effect of inhalation of single dose of beclomethasone on airway epithelium. *Ultrastruct Pathol.* 2007;31:221–32, <http://dx.doi.org/10.1080/01913120701425951>.
78. Laitinen LA, Heino M, Laitinen A, Kava T, Haahela T. Damage of the airway epithelium and bronchial reactivity in patients with asthma. *Am Rev Respir Dis.* 1985;131:599–606, <http://dx.doi.org/10.1164/arrd.1985.131.4.599>.
79. Lu W, Lillehoj EP, Kim KC. Effects of dexamethasone on Muc5ac mucin production by primary airway goblet cells. *Am J Physiol Lung Cell Mol Physiol.* 2005;288:L52–60, <http://dx.doi.org/10.1152/ajplung.00104.2004>.
80. Hoshino M, Takahashi M, Takai Y, Sim J, Aoiike N. Inhaled corticosteroids decrease vascularity of the bronchial mucosa in patients with asthma. *Clin Exp Allergy.* 2001;31:722–30, <http://dx.doi.org/10.1046/j.1365-2222.2001.01071.x>.
81. Chetta A, Zanini A, Foresi A, Del Donno M, Castagnaro A, D'Ippolito R, et al. Vascular component of airway remodeling in asthma is reduced

- by high dose of fluticasone. *Am J Respir Crit Care Med*. 2003;167:751–7, <http://dx.doi.org/10.1164/rccm.200207-7100C>.
82. Phelan PD, Robertson CF, Olinsky A. The Melbourne asthma study: 1964–1999. *J Allergy Clin Immunol*. 2002;109:189–94, <http://dx.doi.org/10.1067/mai.2002.120951>.
83. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med*. 2003;349:1414–22, <http://dx.doi.org/10.1056/NEJMoa022363>.
84. Daley-Yates P, Brealey N, Thomas S, Austin D, Shabbir S, Harrison T, et al. Therapeutic index of inhaled corticosteroids in asthma: a dose–response comparison on airway hyperresponsiveness and adrenal axis suppression. *Br J Clin Pharmacol*. 2021;87:483–93, <http://dx.doi.org/10.1111/bcp.14406>.
85. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. *Respir Med*. 2006;100:1307–17, <http://dx.doi.org/10.1016/j.rmed.2005.11.020>.
86. Qi Y, Fang L, Stolz D, Tamm M, Roth M. Long acting β_2 -agonist's activation of cyclic AMP cannot halt ongoing mitogenic stimulation in airway smooth muscle cells. *Pulm Pharmacol Ther*. 2019;56:20–8, <http://dx.doi.org/10.1016/j.pupt.2019.03.005>.
87. Lachowicz-Scroggins ME, Finkbeiner WE, Gordon ED, Yuan S, Zlock L, Bhakta NR, et al. Corticosteroid and long-acting β -agonist therapy reduces epithelial goblet cell metaplasia. *Clin Exp Allergy*. 2017;47:1534–45, <http://dx.doi.org/10.1111/cea.13015>.
88. Orsida BE, Ward C, Li X, Bish R, Wilson JW, Thien F, et al. Effect of a long-acting beta2-agonist over three months on airway wall vascular remodeling in asthma. *Am J Respir Crit Care Med*. 2001;164:117–21, <http://dx.doi.org/10.1164/ajrccm.164.1.2006003>.
89. Ohta S, Oda N, Yokoe T, Tanaka A, Yamamoto Y, Watanabe Y, et al. Effect of tiotropium bromide on airway inflammation and remodelling in a mouse model of asthma. *Clin Exp Allergy*. 2010;40:1266–75, <http://dx.doi.org/10.1111/j.1365-2222.2010.03478.x>.
90. Kang JY, Rhee CK, Kim JS, Park CK, Kim SJ, Lee SH, et al. Effect of tiotropium bromide on airway remodeling in a chronic asthma model. *Ann Allergy Asthma Immunol*. 2012;109:29–35, <http://dx.doi.org/10.1016/j.anai.2012.05.005>.
91. Gosens R, Gross N. The mode of action of anticholinergics in asthma. *Eur Respir J*. 2018;52:1701247, <http://dx.doi.org/10.1183/13993003.01247-2017>.
92. Hoshino M, Ohtawa J, Akitsu K. Effects of the addition of tiotropium on airway dimensions in symptomatic asthma. *Allergy Asthma Proc*. 2016;37:147–53, <http://dx.doi.org/10.2500/aap.2016.37.3991>.
93. Hoshino M, Akitsu K, Ohtawa J. Comparison between montelukast and tiotropium as add-on therapy to inhaled corticosteroids plus a long-acting β_2 -agonist in for patients with asthma. *J Asthma*. 2019;56:995–1003, <http://dx.doi.org/10.1080/02770903.2018.1514047>.
94. Hansel TT, Neighbour H, Erin EM, Tan AJ, Tennant RC, Maus JG, et al. Glycypirrolate causes prolonged bronchoprotection and bronchodilatation in patients with asthma. *Chest*. 2005;128:1974–9, <http://dx.doi.org/10.1378/chest.128.4.1974>.
95. Wang CG, Du T, Xu LJ, Martin JG. Role of leukotriene D4 in allergen-induced increases in airway smooth muscle in the rat. *Am Rev Respir Dis*. 1993;148:413–7, <http://dx.doi.org/10.1164/ajrccm.148.2.413>.
96. Henderson WR, Tang LO, Chu SJ, Tsao SM, Chiang GKS, Jones F, et al. A role for cysteinyl leukotrienes in airway remodeling in a mouse asthma model. *Am J Respir Crit Care Med*. 2002;165:108–16, <http://dx.doi.org/10.1164/ajrccm.165.1.2105051>.
97. Muz MH, Deveci F, Bulut Y, Ilhan N, Yekeler H, Turgut T. The effects of low dose leukotriene receptor antagonist therapy on airway remodeling and cysteinyl leukotriene expression in a mouse asthma model. *Exp Mol Med*. 2006;38:109–18, <http://dx.doi.org/10.1038/emmm.2006.14>.
98. Kelly MM, Chakir J, Vethanayagam D, Boulet LP, Laviolette M, Gauldie J, et al. Montelukast treatment attenuates the increase in myofibroblasts following low-dose allergen challenge. *Chest*. 2006;130:741–53, <http://dx.doi.org/10.1378/chest.130.3.741>.
99. Hur J, Kang JY, Rhee CK, Kim YK, Lee SY. The leukotriene receptor antagonist pranlukast attenuates airway remodeling by suppressing TGF- β signaling. *Pulm Pharmacol Ther*. 2018;48:5–14, <http://dx.doi.org/10.1016/j.pupt.2017.10.007>.
100. Ueno H, Koya T, Takeuchi H, Tsukioka K, Saito A, Kimura Y, et al. Cysteinyl leukotriene synthesis via phospholipase A2 group IV mediates exercise-induced bronchoconstriction and airway remodeling. *Am J Respir Cell Mol Biol*. 2020;63:57–66, <http://dx.doi.org/10.1165/rcmb.2019-0325OC>.
101. Chen HC, Chiou HYC, Tsai ML, Chen SC, Lin MH, Chuang TC, et al. Effects of montelukast on arsenic-induced epithelial–mesenchymal transition and the role of reactive oxygen species production in human bronchial epithelial cells. *Front Pharmacol*. 2022;13:877125, <http://dx.doi.org/10.3389/fphar.2022.877125>.
102. Chen WJ, Liaw SF, Lin CC, Lin MW, Chang FT. Effects of zileuton on airway smooth muscle remodeling after repeated allergen challenge in brown Norway rats. *Respir Int Rev Thorac Dis*. 2013;86:421–9, <http://dx.doi.org/10.1159/000353427>.
103. Horwitz RJ, McGill KA, Busse WW. The role of leukotriene modifiers in the treatment of asthma. *Am J Respir Crit Care Med*. 1998;157:1363–71, <http://dx.doi.org/10.1164/ajrccm.157.5.9706059>.
104. Montuschi P. Role of leukotrienes and leukotriene modifiers in asthma. *Pharm Basel Switz*. 2010;3:1792–811, <http://dx.doi.org/10.3390/ph3061792>.
105. Tenero L, Piazza M, Sandri M, Azzali A, Chinellato I, Peroni D, et al. Effect of montelukast on markers of airway remodeling in children with asthma. *Allergy Asthma Proc*. 2016;37:77–83, <http://dx.doi.org/10.2500/aap.2016.37.3978>.
106. Brusselle GG, Vanderstichele C, Jordens P, Deman R, Slabbynck H, Ringoet V, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax*. 2013;68:322–9, <http://dx.doi.org/10.2500/aap.2016.37.3978>.
107. Stamatou R, Paraskeva E, Boukas K, Gourgoulisanis KI, Molyvdas PA, Hatziefthimiou AA. Azithromycin has an antiproliferative and autophagic effect on airway smooth muscle cells. *Eur Respir J*. 2009;34:721–30, <http://dx.doi.org/10.1183/09031936.00089407>.
108. Stamatou R, Boukas K, Paraskeva E, Molyvdas PA, Hatziefthimiou A. Azithromycin reduces the viability of human bronchial smooth muscle cells. *J Antibiot (Tokyo)*. 2010;63:71–5, <http://dx.doi.org/10.1038/ja.2009.125>.
109. Zhao X, Yu FQ, Huang XJ, Xu BY, Li YL, Zhao XY, et al. Azithromycin influences airway remodeling in asthma via the PI3K/Akt/MTOR/HIF-1 α /VEGF pathway. *J Biol Regul Homeost Agents*. 2018;32:1079–88.
110. Liu Y, Pu Y, Li D, Zhou L, Wan L. Azithromycin ameliorates airway remodeling via inhibiting airway epithelium apoptosis. *Life Sci*. 2017;170:1–8, <http://dx.doi.org/10.1016/j.lfs.2016.11.024>.
111. Wu L, Yin J, Zhang Q, Wang M, Dai W, Zhou J, et al. Azithromycin induces apoptosis in airway smooth muscle cells through mitochondrial pathway in a rat asthma model. *Ann Transl Med*. 2021;9:1181, <http://dx.doi.org/10.21037/atm-21-3478>.
112. Kang JY, Jo MR, Kang HH, Kim SK, Kim MS, Kim YH, et al. Long-term azithromycin ameliorates not only airway inflammation but also remodeling in a murine model of chronic asthma. *Pulm Pharmacol Ther*. 2016;36:37–45, <http://dx.doi.org/10.1016/j.pupt.2015.12.002>.
113. Donovan GM, Wang KCW, Shamsuddin D, Mann TS, Henry PJ, Larcombe AN, et al. Pharmacological ablation of the airway smooth muscle layer–mathematical predictions of functional improvement in asthma. *Physiol Rep*. 2020;8:e14451, <http://dx.doi.org/10.14814/phy2.14451>.
114. Pu Y, Liu Y, Liao S, Miao S, Zhou L, Wan L. Azithromycin ameliorates OVA-induced airway remodeling in Balb/c mice via suppression of epithelial-to-mesenchymal transition. *Int Immunopharmacol*. 2018;58:87–93, <http://dx.doi.org/10.1016/j.intimp.2018.03.016>.
115. Pei QM, Jiang P, Yang M, Qian XJ, Liu JB, Kim SH. Roxithromycin inhibits VEGF-induced human airway smooth muscle cell proliferation: opportunities for the treatment of asthma. *Exp Cell Res*. 2016;347:378–84, <http://dx.doi.org/10.1016/j.yexcr.2016.08.024>.
116. Willems-Widyastuti A, Vanaudenaerde BM, Vos R, Dilisen E, Verleden SE, De Vleeschauwer SI, et al. Azithromycin attenuates fibroblast growth factors induced vascular endothelial growth factor via p38(MAPK) signaling in human airway smooth muscle cells. *Cell Biochem Biophys*. 2013;67:331–9, <http://dx.doi.org/10.1007/s12013-011-9331-0>.
117. Sadeghdoust M, Mirsadrade M, Aligolghasemabadi F, Khakzad MR, Hashemi Attar A, Naghibi S. Effect of azithromycin on bronchial wall thickness in severe persistent asthma: a double-blind placebo-controlled randomized clinical trial. *Respir Med*. 2021;185:106494, <http://dx.doi.org/10.1016/j.rmed.2021.106494>.
118. Roth M, Zhao F, Zhong J, Lardinois D, Tamm M. Serum IgE induced airway smooth muscle cell remodeling is independent of allergens and is prevented by omalizumab. *PLOS ONE*. 2015;10:e0136549, <http://dx.doi.org/10.1371/journal.pone.0136549>.
119. Roth M, Zhong J, Zumkeller C, S'ng CT, Goulet S, Tamm M. The role of IgE-receptors in IgE-dependent airway smooth muscle cell remodelling. *PLoS ONE*. 2013;8:e56015, <http://dx.doi.org/10.1371/journal.pone.0056015>.
120. Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. *Respiration*. 2012;83:520–8, <http://dx.doi.org/10.1159/000334701>.
121. Tajiri T, Niimi A, Matsumoto H, Ito I, Oguma T, Otsuka K, et al. Comprehensive efficacy of omalizumab for severe refractory asthma: a time-series observational study. *Ann Allergy Asthma Immunol*. 2014;113:470–5.e2, <http://dx.doi.org/10.1016/j.anai.2014.06.004>.
122. Riccio AM, Dal Negro RW, Micheletto C, De Ferrari L, Folli C, Chiappori A, et al. Omalizumab modulates bronchial reticular basement membrane thickness and eosinophil infiltration in severe persistent allergic asthma patients. *Int J Immunopathol Pharmacol*. 2012;25:475–84, <http://dx.doi.org/10.1177/0394633201202500217>.
123. Zastrzeżyńska W, Przybyszowski M, Bazan-Socha S, Gawlewicz-Mroccka A, Sadowski P, Okoń K, et al. Omalizumab may decrease the thickness of the reticular basement membrane and fibronectin deposit in the bronchial mucosa of severe allergic asthmatics. *J Asthma*. 2020;57:468–77, <http://dx.doi.org/10.1080/02770903.2019.1585872>.
124. Kang JY, Kim JW, Kim JS, Kim SJ, Lee SH, Kwon SS, et al. Inhibitory effects of anti-immunoglobulin E antibodies on airway remodeling in a murine model of chronic asthma. *J Asthma*. 2010;47:374–80, <http://dx.doi.org/10.3109/02770901003801972>.
125. Berger P, Scotto-Gomez E, Molimard M, Marthan R, Le Gros V, Tunon-de-Lara JM. Omalizumab decreases nonspecific airway hyperresponsiveness in vitro. *Allergy*. 2007;62:154–61, <http://dx.doi.org/10.1111/j.1398-9995.2006.01243.x>.
126. Prieto L, Gutiérrez V, Colás C, Tabar A, Pérez-Francés C, Bruno L, et al. Effect of omalizumab on adenosine 5'-monophosphate responsiveness in subjects with allergic asthma. *Int Arch Allergy Immunol*. 2006;139:122–31, <http://dx.doi.org/10.1159/000090387>.

127. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360:973–84. <http://dx.doi.org/10.1056/NEJMoa0808991>.
128. Flood-Page P, Menzies-Gow A, Phipps S, Ying S, Wangoo A, Ludwig MS, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest*. 2003;112:1029–36. <http://dx.doi.org/10.1172/JCI17974>.
129. Domvri K, Tsiouprou I, Bakakos P, Rovina N, Stiropoulos P, Voulgaris A, et al. Effect of Mepolizumab on airways remodeling in patients with late-onset severe eosinophilic asthma and fixed obstruction (preliminary data of the MESILICO study). *Eur Respir J* 62 (Suppl. 67). Available from: <https://erj.ersjournals.com/content/62/suppl.67/OA3152> [accessed 19.5.24].
130. Chachi L, Diver S, Kaul H, Rebelatto MC, Boutrin A, Nisa P, et al. Computational modelling prediction and clinical validation of impact of benralizumab on airway smooth muscle mass in asthma. *Eur Respir J*. 2019;54:1900930. <http://dx.doi.org/10.1183/13993003.00930-2019>.
131. McIntosh MJ, Kooner HK, Eddy RL, Jeimy S, Licskai C, Mackenzie CA, et al. Asthma control, airway mucus, and 129Xe MRI ventilation after a single benralizumab dose. *Chest*. 2022;162:520–33. <http://dx.doi.org/10.1016/j.chest.2022.03.003>.
132. McIntosh MJ, Kooner HK, Eddy RL, Wilson A, Serajeddini H, Bhalla A, et al. CT mucus score and 129Xe MRI ventilation defects after 2.5 years' anti-IL-5Rα in eosinophilic asthma. *Chest*. 2023;164:27–38. <http://dx.doi.org/10.1016/j.chest.2023.02.009>.
133. Sakai N, Koya T, Murai Y, Tsubokawa F, Tanaka K, Naramoto S, et al. Effect of benralizumab on mucus plugs in severe eosinophilic asthma. *Int Arch Allergy Immunol*. 2023;184:783–91. <http://dx.doi.org/10.1159/000530392>.
134. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med*. 2003;167:199–204. <http://dx.doi.org/10.1164/rccm.200208-789OC>.
135. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet*. 2000;356:2144–8. [http://dx.doi.org/10.1016/S0140-6736\(00\)03496-6](http://dx.doi.org/10.1016/S0140-6736(00)03496-6).
136. Chan R, RuiWen Kuo C, Jabbal S, Lipworth BJ. Eosinophil depletion with benralizumab is associated with attenuated mannitol airway hyperresponsiveness in severe uncontrolled eosinophilic asthma. *J Allergy Clin Immunol*. 2023;151:700–5.e10. <http://dx.doi.org/10.1016/j.jaci.2022.10.028>.
137. Manson ML, Sjöholm J, James A, Johnsson AK, Bergman P, Al-Ameri M, et al. IL-13 and IL-4, but not IL-5 nor IL-17A, induce hyperresponsiveness in isolated human small airways. *J Allergy Clin Immunol*. 2020;145:808–17.e2. <http://dx.doi.org/10.1016/j.jaci.2019.10.037>.
138. Scott G, Asrat S, Allinne J, Keat Lim W, Nagashima K, Birchard D, et al. IL-4 and IL-13, not eosinophils, drive type 2 airway inflammation, remodeling and lung function decline. *Cytokine*. 2023;162:156091. <http://dx.doi.org/10.1016/j.cyto.2022.156091>.
139. Tajiri T, Suzuki M, Nishiyama H, Ozawa Y, Kurokawa R, Takeda N, et al. Efficacy of dupilumab for airway hypersecretion and airway wall thickening in patients with moderate-to-severe asthma: a prospective, observational study. *Allergol Int*. 2024;73:406–15. <http://dx.doi.org/10.1016/j.alit.2024.02.002>.
140. Chen ZG, Zhang TT, Li HT, Chen FH, Zou XL, Ji JZ, et al. Neutralization of TSLP inhibits airway remodeling in a murine model of allergic asthma induced by chronic exposure to house dust mite. *PLoS ONE*. 2013;8:e51268. <http://dx.doi.org/10.1371/journal.pone.0051268>.
141. Diver S, Khalfaoui L, Emson C, Wenzel SE, Menzies-Gow A, Wechsler ME, et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med*. 2021;9:1299–312. [http://dx.doi.org/10.1016/S2213-2600\(21\)00226-5](http://dx.doi.org/10.1016/S2213-2600(21)00226-5).
142. Sverrild A, Hansen S, Hvidtfeldt M, Clausson CM, Cozzolino O, Cerps S, et al. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). *Eur Respir J*. 2022;59:2101296. <http://dx.doi.org/10.1183/13993003.01296-2021>.
143. Nordenmark LH, Hellqvist Å, Emson C, Diver S, Porsbjerg C, Griffiths JM, et al. Tezepelumab and mucus plugs in patients with moderate-to-severe asthma. *NEJM Evid*. 2023;2. <http://dx.doi.org/10.1056/EVIDoa2300135>. EVI-Doa2300135.
144. Hoshino M, Akitsu K, Kubota K. Effect of sublingual immunotherapy on airway inflammation and airway wall thickness in allergic asthma. *J Allergy Clin Immunol Pract*. 2019;7:2804–11. <http://dx.doi.org/10.1016/j.jaip.2019.06.003>.
145. Saunders R, Kaul H, Berair R, Gonen S, Singapuri A, Sutcliffe AJ, et al. DP2 antagonism reduces airway smooth muscle mass in asthma by decreasing eosinophilia and myofibroblast recruitment. *Sci Transl Med*. 2019;11. <http://dx.doi.org/10.1126/scitranslmed.aao6451>, eao6451.
146. Girodet PO, Dournes G, Thumerel M, Begueret H, Santos PD, Ozier A, et al. Calcium channel blocker reduces airway remodeling in severe asthma. A proof-of-concept study. *Am J Respir Crit Care Med*. 2015;191:876–83. <http://dx.doi.org/10.1164/rccm.201410-1874OC>.
147. Fang L, Li J, Papakonstantinou E, Karakioulaki M, Sun Q, Schumann D, et al. Secreted heat shock proteins control airway remodeling: evidence from bronchial thermoplasty. *J Allergy Clin Immunol*. 2021;148:1249–61.e8. <http://dx.doi.org/10.1016/j.jaci.2021.02.022>.
148. Salem IH, Boulet LP, Biardel S, Lampron N, Martel S, Laviolette M, et al. Long-term effects of bronchial thermoplasty on airway smooth muscle and reticular basement membrane thickness in severe asthma. *Ann Am Thorac Soc*. 2016;13:1426–8. <http://dx.doi.org/10.1513/AnnalsATS.201603-182LE>.
149. Chakir J, Haj-Salem I, Gras D, Joubert P, Beaudoin ÉL, Biardel S, et al. Effects of bronchial thermoplasty on airway smooth muscle and collagen deposition in asthma. *Ann Am Thorac Soc*. 2015;12:1612–8. <http://dx.doi.org/10.1513/AnnalsATS.201504-208OC>.
150. Wijsman PC, Goorsenberg AWM, Keijzer N, d'Hooghe JNS, Ten Hacken NHT, Shah PL, et al. Airway wall extracellular matrix changes induced by bronchial thermoplasty in severe asthma. *J Allergy Clin Immunol*. 2024;153:435–46.e4. <http://dx.doi.org/10.1016/j.jaci.2023.09.035>.
151. Pretolani M, Bergqvist A, Thabut G, Dombret MC, Knapp D, Hamidi F, et al. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: clinical and histopathologic correlations. *J Allergy Clin Immunol*. 2017;139:1176–85. <http://dx.doi.org/10.1016/j.jaci.2016.08.009>.
152. Sun Q, Fang L, Roth M, Tang X, Papakonstantinou E, Zhai W, et al. Bronchial thermoplasty decreases airway remodelling by blocking epithelium-derived heat shock protein-60 secretion and protein arginine methyltransferase-1 in fibroblasts. *Eur Respir J*. 2019;54:1900300. <http://dx.doi.org/10.1183/13993003.00300-2019>.
153. Ichikawa T, Panariti A, Audousseau S, Mogas AK, Olivenstein R, Chakir J, et al. Effect of bronchial thermoplasty on structural changes and inflammatory mediators in the airways of subjects with severe asthma. *Respir Med*. 2019;150:165–72. <http://dx.doi.org/10.1016/j.rmed.2019.03.005>.
154. Goorsenberg AWM, d'Hooghe JNS, Srikanthan K, Ten Hacken NHT, Weersink EJM, Roelofs JJTH, et al. Bronchial thermoplasty induced airway smooth muscle reduction and clinical response in severe asthma. The TAsMA randomized trial. *Am J Respir Crit Care Med*. 2021;203:175–84. <http://dx.doi.org/10.1164/rccm.201911-2298OC>.
155. Goorsenberg AWM, d'Hooghe JNS, Slats AM, van den Aardweg JG, Annema JT, Bonta PI. Resistance of the respiratory system measured with forced oscillation technique (FOT) correlates with bronchial thermoplasty response. *Respir Res*. 2020;21:52. <http://dx.doi.org/10.1186/s12931-020-1313-6>.
156. d'Hooghe JNS, Goorsenberg AWM, Ten Hacken NHT, Weersink EJM, Roelofs JJTH, Mauad T, et al. Airway smooth muscle reduction after bronchial thermoplasty in severe asthma correlates with FEV₁. *Clin Exp Allergy*. 2019;49:541–4. <http://dx.doi.org/10.1111/cea.13365>.
157. Langton D, Ing A, Fielding D, Wang W, Plummer V, Thien F. Bronchodilator responsiveness as a predictor of success for bronchial thermoplasty. *Respiology*. 2019;24:63–7. <http://dx.doi.org/10.1111/resp.13375>.
158. Gagnon PA, Côté A, Klein M, Biardel S, Laviolette M, Godbout K, et al. The reduction of airway smooth muscle by bronchial thermoplasty stands the test of time. *ERJ Open Res*. 2023;9:00024–2023. <http://dx.doi.org/10.1183/23120541.00024-2023>.