Novel Therapeutic Strategies in Asthma-Chronic Obstructive Pulmonary Disease Overlap

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KEYWORDS

• Asthma • ACO • COPD • Dysbiosis • Inflammation • Mucus • Therapies
• Remodeling

KEY POINTS

- Precision medicine can be achieved by targeting specific phenotypes where asthma and COPD overlap.
- Many agents show promise in ameliorating type 2 eosinophilic inflammation and are progressing through clinical trials; however, novel therapies targeting neutrophilic inflammation have been less successful.
- Specific biomarkers are required to identify those likely to benefit from antimicrobial interventions in airways disease.
- Therapeutic agents targeting inflammation may have a positive impact on airway remodeling or mucous hypersecretion; however, further studies in larger numbers are required to evaluate both specific agents in current development and novel approaches.

INTRODUCTION

Heterogeneity is well recognized in airways diseases like asthma and chronic obstructive pulmonary disease (COPD), and characterization of distinct phenotypes has highlighted where pathologic processes overlap. Asthma-COPD overlap (ACO) has been used to describe individuals with clinical features of both diseases. More specificity, however, is required because treatments are increasingly targeted to specific disease traits and established biomarkers rather than traditional disease labels. The underpinning mechanisms for many of the novel therapies within are common and likely to be effective in the correctly identified individual, irrespective of a disease label such as asthma, COPD, or ACO.

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In this article, the authors discuss novel therapeutic agents according to several phenotypes recognized in both asthma and COPD, including the more widely established T2 eosinophilic inflammation, particularly noted in asthma, as well as other pathways such as neutrophilic inflammation and dysbiosis more commonly reported in COPD. Specifically, the following treatment topics are reviewed (Fig. 1):

- T2-mediated, eosinophilic inflammation
- Non-T2 (neutrophilic) inflammation
- Dysbiosis
- Mucous hypersecretion
- Airways remodeling

T2 Eosinophilic Inflammation

T2-mediated eosinophilic inflammation is the most common inflammatory endotype in asthma and may be underestimated due to the suppressive effects of treatment, with only 5% of patients persistently "T2-low" following T2 biomarker-based corticosteroid optimization.[1] Inflammation in COPD is more commonly Th1 mediated and neutrophilic; however, sputum eosinophilia is recorded in 10% to 40% of patients.[2]

Eosinophilic inflammation has been the recent focus of pharmacotherapy in asthma, with multiple agents now licensed or in development; however, there are currently no licensed T2 biologics available for use in COPD.

ANTI-IMMUNOGLOBULIN E

Omalizumab is approved for use in children and adults with moderate-to-severe asthma and proven aeroallergen sensitization. Omalizumab reduces circulating immunoglobulin E (IgE) in the blood and interstitial space and inhibits IgE binding to high- and low-affinity receptors on mast cells, basophils, and dendritic cells. Clinically, omalizumab reduces asthma exacerbations and oral corticosteroid dependence.[3]

Data suggest that atopy is present in roughly one-third of patients with COPD[4]; however, it is associated with a lower risk of acute exacerbation. Independent of allergic status, upregulation of the high-affinity FcεRI receptors on plasma dendritic cells implicated in the asthmatic response to omalizumab has also been demonstrated in severe COPD[5] indicating that selected patients with COPD could benefit from anti-IgE treatment.

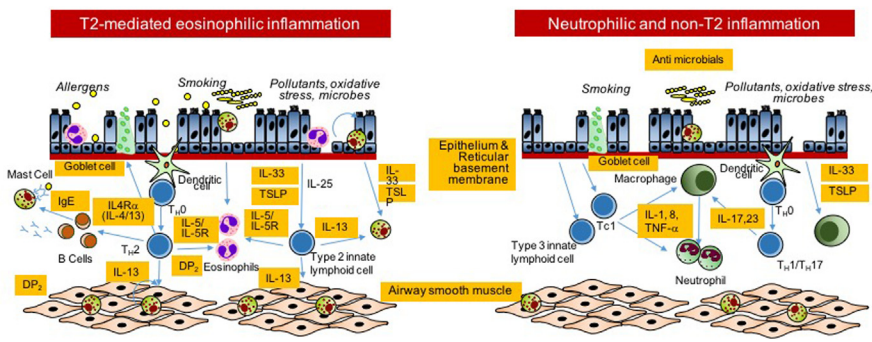

Fig. 1. Inflammatory pathways and therapeutic targets in airways disease. RBM, Reticular basement membrane.

Although omalizumab use in COPD has not been studied, small studies in allergic asthma with comorbid COPD, consistent with ACO, suggest a positive impact. A post-hoc analysis of Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) evaluated ~50 patients with ACO, based on 2 different definitions: indicating similar improvements in exacerbations and asthma control compared with those observed in asthmatic subjects without ACO.[6] Similarly, data from the Australian Xolair Registry reported that 17 patients with ACO demonstrated improvements in asthma control and quality of life compared with those with no COPD, although associated improvements in forced expiratory volume in 1 second (FEV_1) were not observed in this subgroup.[7] A further analysis examined the response to omalizumab in subgroups of asthma with and without fixed airflow obstruction (FAO), demonstrating a positive impact on exacerbations in those with high but not low bronchodilator reversibility (BDR) in both of these groups, whereas improvements in FEV_1 were observed only in those with high BDR and absent FAO.[8]

ANTI-INTERLEUKIN-5/5R

Interleukin (IL)-5 is produced by T-helper type 2 lymphocytes, innate lymphoid type 2 cells, and eosinophils and is a key cytokine involved in recruitment, maturation, activation, and survival of eosinophils. Biological agents are available targeting both IL-5 and the IL-5 receptor. In severe eosinophilic asthma, these agents have consistently reduced acute exacerbation rates and successfully allowed reduction of oral corticosteroid burden.[9–15] Sputum IL-5 levels are elevated in eosinophilic COPD[16] suggesting that targeting this pathway could be of clinical benefit.

Benralizumab in COPD: In an initial phase 2a trial in eosinophilic COPD, treatment did not meet the primary end point of reducing exacerbation rates. However, reduction in sputum eosinophils was associated with a significant improvement in FEV_1 and there was a trend toward reduced exacerbations in those with higher blood eosinophils, suggesting treatment could be beneficial in some.[17] The subsequent phase 3 trial found no significant reduction in exacerbation rate despite substantial depletion of sputum and blood eosinophils.[18] Further analysis was performed, aiming to identify the population of subjects with COPD most likely to benefit from treatment, with the greatest treatment effect in those with blood eosinophils greater than or equal to 220 cells/μL, particularly in the presence of increased exacerbation frequency and severe airflow obstruction (FEV_1 <40%).[19] Another trial of benralizumab for acute exacerbations of eosinophilic airways disease, including both subjects with asthma and COPD, is ongoing.[20]

Mepolizumab in COPD: Two phase 3 trials (Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients (METREX) and Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients Characterized by Eosinophil Level (METREO)) evaluated the impact of anti-IL-5 on COPD exacerbation rates in subjects who were uncontrolled despite triple therapy.[21] Outcomes were assessed across a range of baseline blood eosinophil counts. In eosinophilic COPD, moderate and severe exacerbation rates were reduced by 18% and 20%, respectively, whereas no benefit was observed in those who were noneosinophilic. The phase 3 Mepolizumab as Add-on Treatment IN Participants With COPD Characterized by Frequent Exacerbations and Eosinophil Level (MATINEE)[22] trial is recruiting subjects with eosinophilic COPD who are persistent exacerbators with an elevated blood eosinophil count at baseline (≥300 cells/μL) and will assess the effect on annualized exacerbation rates. The Mepolizumab for COPD Hospital Eosinophilic

Admissions Pragmatic Trial (COPD-HELP) trial is also evaluating the effect of mepolizumab on acute exacerbations of COPD.[23]

TARGETING INTERLEUKIN-4/13

Despite being an integral T2 cytokine, therapies targeting IL-13 alone in asthma have failed to meet the primary end point of reducing asthma exacerbations, and development has ceased.[24,25] The efficacy of lebrikizumab was examined in patients with moderate-to-severe COPD and a history of exacerbations but did not reduce exacerbations,[26] and development has ceased.

The monoclonal antibody dupilumab targets IL-4Rα, blocking downstream activity in both IL-13 and IL-4 pathways. In asthma, this has led to significant clinical improvements both with regard to exacerbation rates and physiology.[27] Consequently, this agent is being evaluated in moderate-to-severe COPD with evidence of T2 inflammation.[28]

Targeting Epithelial Cytokines

The epithelial cytokines IL-25, IL-33, and Thymic stromal lymphopoietin perpetuate T2 inflammation via downstream effects on various cells including Th2 cells, innate lymphoid cells, and dendritic cells. Therapies targeting these upstream mediators are more advanced in asthma but are now in trials for appropriate subgroups of patients with COPD.

Interleukin-33: IL-33 is a member of the IL-1 family and signals via the ST2 pathway to promote Th2 immunity and inflammation. IL-33 levels are increased in asthma with bronchial epithelial cells as an important source. A role in asthma pathophysiology is supported by genome association studies.[29,30] A phase 2a clinical trial of anti-IL-33 in asthma was positive for a reduction in loss of control events.[31]

IL-33 levels and levels of the soluble ST2 receptor are also known to be increased in COPD, with IL-33 levels correlating positively with blood eosinophil count[32] and associated with an increased risk of exacerbation. Rabe and colleagues[33] demonstrated that the genetic risk of COPD is reduced by loss-of-function mutation in the IL-33 gene. The investigators subsequently randomized 343 patients with COPD to itepekimab or placebo. Although the study was negative overall, subgroup analysis revealed that exacerbations were reduced and FEV_1 improved in former smokers, whereas therapy had no impact on clinical outcomes in those who continued to smoke.[33] Phase 3 trials will aid understanding of whether this represents a therapeutic option in certain patients.

Targeting the ST2 receptor has also shown promise. In a phase 2 trial in asthma, the ST2 receptor antagonist, astegolimab, significantly reduced acute exacerbations, including in those with blood eosinophils less than 300 cells/μL.[34] A similar phase 2a trial has recently been published in COPD, although it did not meet statistical significance.[35] Subgroup analysis indicated that effects were greatest in those with blood eosinophil counts less than 170 cells/μL and exploring the effects of treatment on other exacerbation drivers, such as respiratory viral infection, may help to clarify these effects in future.

TSLP: TSLP is another epithelial cytokine that is elevated in asthma. A mechanistic trial in severe asthma showed that the anti-TSLP agent tezepelumab successfully attenuates eosinophilic inflammation in the airway submucosa,[36] whereas concurrent phase 3 clinical trials reported a significant reduction in acute exacerbations and improvement in other clinical outcomes.[37]

Targeting TSLP in COPD is being studied in the Tezepelumab COPD Exacerbation Study (COURSE) trial, a phase 2a multicenter randomized controlled trial to assess the effect of tezepelumab on moderate or severe exacerbation rate ratios.[38]

OTHERS

DP_2: Selective DP_2 inhibitors were an attractive prospect for targeting eosinophilic inflammation in airways disease due to expression of the receptor on key inflammatory cells, and involvement in regulating both allergic and non-allergic pathways.[39] However, phase 2 data demonstrating significant reductions in airway eosinophilia in asthma[40] were not reflected in 4 further phase 3 trials.[41,42] Earlier studies of another DP_2 antagonist, AZD1981, in COPD had been negative, with no significant impact on FEV_1 or Clinical COPD Questionnaire scores.[43]

SB010 (GATA3 inhibitor): GATA3 is an integral transcription factor directly involved in Th2 differentiation and initial expression of T2 cytokines.[44] The inhaled DNA enzyme SB010 cleaves GATA3 mRNA and has been shown to attenuate Th2 inflammatory responses in both asthma[45] and eosinophilic COPD.[46] Drug development remains ongoing. It has also been suggested that sirtuin 6 activators could decrease the T2 immune response through decreased acetylation of GATA3.[47,48]

Dexpramipexole: Dexpramipexole is an oral, synthetic aminobenzothiazole initially developed as treatment of amyotrophic lateral sclerosis. Despite failing to meet phase 3 outcomes in this area, a significant and targeted depletion of blood eosinophils in subjects receiving the drug was observed during the development program, related to inhibition of eosinophil maturation. Subsequent positive studies in hypereosinophilic syndrome[49] and chronic rhinosinusitis with nasal polyps[50] have led to extension of clinical trials into asthma. A phase 2 trial in moderate-to-severe eosinophilic ($\geq 0.3 \times 10^9$/L) asthma reported that 300 mg dexpramipexole led to an 80% decrease in blood eosinophils with an associated trend toward improvement in FEV_1,[51] indicating a potential benefit in other eosinophilic airways diseases such as eosinophilic COPD.

Non-T2 Inflammation, T1/17, and Neutrophilic Inflammation

Neutrophilic inflammation is well recognized as the predominant inflammatory characteristic of COPD but is also a recognized phenotype of asthma, so it is of relevance to those with ACO. However, to date interventions to target neutrophilic inflammation have been disappointing and none are currently or imminently licensed. A summary of trialed therapies, both past and ongoing, are described in **Table 1**.

Airways Dysbiosis

The development of culture-independent techniques for in-depth characterization of airway ecology means this is an evolving field. It is known that some clinical outcomes, such as exacerbations, in airways disease relate to bacterial, viral, or fungal airway infection, and that these may or may not be associated with a chronically altered airway ecology. Understanding the relationship between airway organisms and inflammation is likely to indicate several novel therapeutic targets in future, irrespective of disease label.

Macrolide therapy

Long-term macrolide therapy is a well-established therapy in COPD[52] and should be considered in moderate-to-severe asthma[53,54] wherein the benefits are thought to outweigh the risks. Although many patients currently benefit from this therapy, appropriate patient selection will help to reduce the wider public health risks from antibiotic

Table 1
Key trials of therapies targeting mediators of non-T2 inflammation in airways disease

Target	Evidence in Asthma	Evidence in COPD	Current Perspective for ACO
TNF-α	Increased rates of malignancy in the treatment group[97] (golimumab)	No impact on health status, lung function, or physical activity including in subgroups selected by elevated baseline TNF or CRP Concern for increased rates of malignancy[98] (infliximab)	Despite use in other conditions, the unacceptable adverse event profile has prevented use of anti-TNF agents in airways disease
IL-1	Improved late-phase allergen response[99] (canakinumab) Agents targeting the NLRP3 inflammasome have reduced airway inflammation and airway hyperresponsiveness in animal models[104]	Reduced blood neutrophils and CRP but no effect on exacerbation rates or quality of life (MEDI8968)[100] No impact on lung function (canakinumab)[101]	Further trials of canakinumab in asthma have been halted due to the SARS-CoV-2 pandemic[102] Many NLRP3 inhibiting agents are in early-phase development; however, RRx-001 (an oncological treatment) potently inhibits NLRP3 without significant safety concerns and is in phase 3 clinical trials[103]; this could potentially be of benefit in airways disease
IL-6	No effect on late-phase allergen response in mild asthma, although participants were unselected and predominantly T2 high (tocilizumab)[105]	No clinical trial data	Although no studies are currently in progress, specific asthma and COPD phenotypes have been linked to IL-6 trans-signalling, so there may be a basis for targeting IL-6 in selected groups in future

IL-17	No impact on asthma control, asthma symptoms, or lung function (brodalumab).[106] Follow-up trials refuted any benefit in subjects with high bronchodilator reversibility[107]	No impact on lung function, symptom scores, and rescue medication use. No measurement made of biological mediators limiting ability to examine effects in specific endotypes (CNTO 6785)[109]	Considerable interest remains in the Th17 pathway as a key mediator of neutrophilic inflammation in airways disease, and early studies in animal models suggest that this pathway could also be targeted, for example, through the Th17 transcription factor RORγt[110] Further characterization of this pathway and the relationships with other inflammatory pathways may indicate whether IL-17-targeted therapies could improve outcomes in selected patiemts with airways disease
IL-23	No improvement in lung function or asthma control in T2-low, uncontrolled moderate-to-severe asthma (CJM112)[108] Despite evidence for a biological effect, median time to asthma worsening increased in the treatment group (risankizumab)[111]	No reported clinical trials of anti-IL23 in COPD	
CXCR2	No effect on severe exacerbations, lung function, symptoms, or quality of life in subjects with low blood eosinophils and IgE (AZD5069)[112]	Improved FEV_1 particularly in smokers, but high rates of treatment discontinuation due to neutropenia and increased infections on continued monitoring (navarixin)[113] Improved patient-reported dyspnoea outcomes in a small study (anti-IL8)[114]	The role of CXCR2 in regulation of neutrophil extracellular trap formation[115] presents the opportunity to refine the use of anti-CXCR2 in specific disease phenotypes of severe asthma and COPD
Kinase inhibitors: PI3K	Reduced sputum proinflammatory cytokines but no impact on clinical outcomes (nemiralisib)[116]	Evidence of reduced inflammation and improved time to recovery when given at time of acute exacerbation; however, no improvement in FEV_1 and no effect on future exacerbations (nemiralisib)[117–119]	Multiple kinases drive inflammation and remodeling in the lung and therefore represent potential therapeutic strategies in both asthma and COPD; however, off-target effects and lack of specificity have been some of the issues stalling development. Agents targeting JAK1 and spleen tyrosine kinases remain in early-phase development[120–122]
P38 MAPK	No reported trials in asthma	Well tolerated but no effect on exercise tolerance or lung function including in subgroups without eosinophilia (losmapimod)[123–125]	

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Table 1
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Target	Evidence in Asthma	Evidence in COPD	Current Perspective for ACO
PDE3/4	Improvement in lung function in asthma but not progressed in clinical trials (roflumilast)[126]	Roflumilast a currently licensed therapy recognized to have some positive impact on FEV_1 and exacerbations; however, poorly tolerated due to gastrointestinal and psychiatric adverse effects associated with treatment[127]	Although roflumilast is already licensed in COPD, the side effect profile has limited use. Development of agents delivered directly to the respiratory tract may minimize the systemic effects
	Inhaled PDE4 reduces the late-phase allergen response (CHF6001)[129]	Inhaled PDE3/4 inhibitors reduce inflammation and improve FEV_1 (ensifentrine)[130,131]	Attenuation of Th1 cytokines indicates there may be specific populations within airways disease more likely to benefit[128]

Abbreviations: CRP, C-reactive protein; CXCR2, C-X-C motif chemokine receptor 2; JAK1, Janus kinase 1; MAPK, mitogen-activated protein kinase; NLRP3, NLR family pyrin domain containing 3; PDE, phosphodiesterase; PI3K, phosphoinositide 3 kinase; RORγt, RAR-related orphan receptor gamma; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T2, type 2 inflammation; TNF, tumor necrosis factor.

resistance[55]; therefore identifying the target population most likely to respond remains an unmet clinical need.

In asthma, Brusselle and colleagues[56] indicated that the benefits of macrolide therapy were observed in noneosinophilic subgroups only; however, this was refuted by the Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES) trial, which reported benefits independent of inflammatory status,[57] although subgroup analysis demonstrated maximal effects in those with positive bacterial cultures. Posthoc analysis of the AMAZES trial has, however, suggested that airway abundance of *Haemophilus influenzae* predicts response to azithromycin therapy.[58] At present, widely accessible biomarkers of dysbiosis are not available; however, in future it is likely that these will be useful to indicate those most likely to benefit. In COPD, the Gammaproteobacteria to Firmicutes ratio (γP:F) has shown promise in identifying those likely to benefit from antimicrobials in the context of acute exacerbation.[59]

Probiotics and prebiotics

Probiotics are live microorganisms that confer health benefits on their recipient host and include the genera *Lactobacillus* and *Bifidobacteria.* Prebiotics are indigestible carbohydrates metabolized by gut bacteria but not host cells, thereby stimulating growth and/or activity of beneficial organisms. These strategies have been used in asthma with the aim of modulating the gut microbiome to achieve an antiinflammatory effect.[60] Probiotics have demonstrated mixed success in terms of improving clinical outcomes in asthma but remain in clinical trials. A current trial in COPD is seeking to ascertain whether modulating the lower respiratory microbiome will reduce exacerbations in moderate-to-very severe COPD, comparing an oral probiotic intervention with inhalation of amikacin, combined administration of the influenza and pneumococcal vaccine, and current standard of care.[61]

Phage therapy

Bacteriophages are natural biological entities that kill bacteria with species-specific precision, indicating a promising strategy to target pathogens known to be implicated in chronic lung diseases. Although bacteriophages were discovered over a century ago, there has been renewed interest recently in view of increasing antibiotic resistance and slowed development of new antibiotic agents.[62] In COPD, bacteriophage abundance decreased during viral infection, suggesting a possible mechanism for increased susceptibility to bacterial infection in this context.[63] Virome study in asthma also indicates that bacteriophage abundance was severely reduced compared with healthy controls, and correlated with ACT and FEV_1.[64] Clinical trials in obstructive airways disease are awaited; however, in preclinical studies of chronic lung infection, phage therapy was shown to be efficacious against *Pseudomonas aeruginosa*.[65]

Antifungal and antiviral interventions

Viral infection, particularly rhinovirus, is a well-recognized etiological factor in exacerbations and is associated with suboptimal interferon responses. Although a trial of inhaled interferon-β did not improve asthma control questionnaire-6 scores in those with asthma with acquired viral infection, analysis of the subgroup with moderate-to-severe disease demonstrated a significant improvement compared with placebo.[66] In vitro bronchial epithelial cells pretreated with azithromycin had an augmented interferon response when infected with rhinovirus,[67] suggesting that the positive effects observed in clinical trials in asthma and COPD may relate to the effect on viral immunity; however, whereas studies of azithromycin in acute exacerbations of COPD

trended toward reducing treatment failure,[68] studies in acute exacerbations of asthma were negative, albeit potentially underpowered.[69]

The clinical significance of fungal infection in COPD is incompletely understood, and likely to be underestimated; however, *Aspergillus* spp are isolated in ~15% at exacerbation and follow-up, with hypersensitivity to *Aspergillus* reported in 8% to 15%, associated with reduced lung function.[70] It is unknown whether antifungal therapies may improve lung function in COPD, and treatment is only recommended where there is a concurrent diagnosis of fungal lung disease. Fungal sensitization is more common in severe asthma, reported in up to 50%[71]; however, to date antifungal treatment in severe asthma not meeting criteria for allergic bronchopulmonary aspergillosis has not been efficacious in reducing severe exacerbations or improving quality of life.[72]

Mucous Hypersecretion

Mucus is an aqueous solution of lipids, proteins, and mucins. Mucins are encoded by MUC genes and synthesized in goblet cells and submucosal glands.[73]

In asthma, mucous hypersecretion is linked to overexpression of the cytokine IL-13, which increases the number of goblet cells in the airway. Studies in COPD have linked goblet cell hyperplasia and mucin production to activation of the epidermal growth factor receptor (EGFR) cascade.

Several mucolytic agents are licensed for use in airways disease; however, development of novel agents to inhibit mucin synthesis has been limited by lack of both efficacy and selectivity resulting in poor tolerance (eg, targeting EGFR[74] and MAPK13[75]). Bio-11006, an agent aiming to reduce mucin secretion via inhibition of myristoylated alanine-rich C-kinase substrate (MARCKS), remains in development for COPD having demonstrated an improvement in mucous hypersecretion with associated increase in lung function in an initial phase 2 trial[76]; however, there are no active trials in asthma at present.

Several bronchoscopic techniques have been proposed for the treatment of chronic bronchitis, characterized by increased mucous production and goblet cell hyperplasia. The RejuvenAir System (CSA Medical, Inc. Lexington, MA) metered cryospray aims to destroy hyperplastic goblet cells and excessive airway mucous glands with topical liquid nitrogen spray. Small studies have demonstrated the technique to be safe,[77] and further trials assessing the effects of treatment on acute exacerbations (NCT03893370) and goblet cell density (NCT03892694) are ongoing. In bronchial rheoplasty, the RheOx catheter delivers bursts of high-frequency electrical energy to the airway using a monopolar electrode, targeting abnormal goblet cells and glands. Despite some early serious adverse events (SAEs), this technique reduced goblet cell hyperplasia score and improved patient-reported outcomes at 12 months.[78] These bronchoscopic techniques have not yet been trialed in patients with asthma, or evaluated subgroups with features of ACO.

Targeting mucin synthesis or secretion in airways disease will require development of agents with greater selectivity. Other novel approaches have been proposed further, such as lysis of occlusive mucous plugs in the context of acute clinical deterioration.[79]

Airways Remodeling

Airway remodeling occurs in both asthma and COPD, affecting both small and large airways in asthma and predominantly small airways in COPD. Common remodeling features include loss of epithelial integrity, mucous hypersecretion, increased airway smooth muscle (ASM) mass, and alterations to levels of extracellular matrix proteins and airway microvasculature. Inflammation is closely linked to remodeling, and one

approach is to target the inflammatory pathways responsible for structural changes in the airway. Physiologic changes including airflow limitation and airway hyperresponsiveness occur in both conditions to differing degrees.[80]

Targeting airway smooth muscle

Therapies targeting ASM have been more extensively studied in asthma because ASM area in COPD airways is similar to that in healthy smokers and nonsmokers, although with increased localization of neutrophils.[81] The anti-DP_2 agent, fevipiprant, reduced ASM mass compared with placebo[82] with computational modeling indicating that both attenuation of eosinophilic inflammation and decreased myofibroblast recruitment were responsible; however, as discussed earlier, this agent is no longer in development for asthma or COPD. Other biologic agents in asthma have not reported reductions in ASM compared with placebo,[36,82,83] and indeed a recent cluster analysis based on fluctuations in lung function in asthma and COPD suggests that remodeling is not directly related to T2 inflammation.[84]

Bronchial thermoplasty (BT) in severe asthma involves pulsed application of radiofrequency energy to the airway wall via a bronchoscopically inserted catheter and led to improvements in exacerbations and hospitalizations in clinical trials.[85,86] The positive impacts reported following BT are thought to relate to reduction in ASM as a direct response to heat; however, biopsy studies have shown an improvement in epithelial integrity post-BT, and mathematical modeling suggests that other mechanisms may contribute to ASM reduction.[87] Small retrospective studies of BT in subjects with ACO and severe asthma with smoking history suggest that a benefit is still observed in these groups; however, further data are required.[88–91] In COPD, targeted lung denervation aims to disrupt parasympathetic nerve transmission to and from the lung through the application of radiofrequency energy via a dual cooled catheter, reducing ASM contraction and mucous production and increasing acetylcholine production. The Targeted Lung Denervation for Patients With Moderate to Severe COPD-2 (AIRFLOW-2) trial indicated that those receiving treatment experienced fewer events, and were less likely to be hospitalized for COPD exacerbation, than those in the sham procedure group.[92] The AIRFLOW-3 trial will study the technique in a larger number of subjects.[93–95]

Novel remodeling targets

Several novel bronchodilator targets are in preclinical development and may demonstrate efficacy in asthma, COPD, and ACO in future; these include the selective phosphodiesterase inhibitors discussed in see **Table 1**, bitter taste receptor agonists, E-prostanoid receptor 4 agonists, Rho kinase inhibitors, calcilytics, agonists of peroxisome proliferator-activated receptor-γ, agonists of relaxin receptor 1, soluble guanylyl cyclase activators, and pepducins.[96]

With increasing recognition of heterogeneity in asthma and COPD, characterization of underlying disease mechanisms has highlighted numerous potential therapeutic targets. Agents directed toward these may have benefit only in specific subgroups, although pathways may be common across asthma and COPD, and future clinical trials will need to carefully select both appropriate subjects for inclusion and clinical outcome measures to ensure that the effects of new treatments can be interpreted with confidence. The lack of a clear definition for ACO increases the complexity of performing prospective clinical trials in this group; however, where evidence is consistent across phenotype-specific populations in asthma and COPD, extrapolation may be possible.

As there is increasing success in outcomes such as reducing exacerbations across airways disease, focus should shift to other treatment goals where current agents

have demonstrated less success, although the contribution of extrathoracic factors such as obesity, deconditioning, and comorbidities may play a significant role here. Expectations will then need to be raised further to include cure and disease prevention.

SUMMARY

Novel therapeutic options in asthma, COPD, and ACO have started to come into clinical practice over the last decade, initially targeting anti-IL-5 pathways, but will continue to expand and indications widen. The specificity of treatment group, alongside relatively expensive cost, means they are likely to remain specialist interventions requiring phenotypic workup; this makes their application in ACO more challenging but does mean careful patient characterization and workup is needed to ensure the right patient receives the right therapy.

To date, most therapies have targeted T2 inflammation and eosinophil-driven disease, with limited success in antineutrophilic interventions. Other pathways, such as dysbiosis, mucous hypersecretion, and airways remodeling provide considerable opportunities for increased therapeutic targets over the next 15 years.

CLINICS CARE POINTS

- Targeted therapies are unlikely to be licensed in ACO due to the lack of formal diagnostic criteria; this could potentially limit access where there is a potential benefit for patients.
- Standalone trials, or posthoc analyses of interventions in subgroups with specific treatable traits like fixed airflow obstruction, but without disease labels, could provide evidence to support the use of targeted therapies in certain groups.
- We suggest that when assessing a patient for specific therapeutic strategies, clinicians could clearly identify and document the mechanism or treatable trait that a therapy will target rather than utilizing broad disease labels, such as ACO, for example, "eosinophilic airway inflammation with recurrent exacerbations" or "recurrent lower respiratory tract infections with growth of *Haemophilus influenzae* in sputum."
- Although patients with ACO may have wider-ranging disease features, it is important to acknowledge that they may still demonstrate features consistent with the inclusion criteria of clinical trials of targeted therapies in either asthma or COPD that justify the use of these agents.

DISCLOSURE

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REFERENCES

1. Heaney LG, Busby J, Hanratty CE, et al. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. Lancet Respir Med 2021;9(1):57–68.

2. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. Ther Adv Chronic Dis 2016;7(1):34–51.
3. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014;1:CD003559.
4. Putcha N, Fawzy A, Matsui EC, et al. Clinical Phenotypes of Atopy and Asthma in COPD: A Meta-analysis of SPIROMICS and COPDGene. Chest 2020;158(6): 2333–45.
5. Stoll P, Bähker A, Ulrich M, et al. The dendritic cell high-affinity IgE receptor is overexpressed in both asthma and severe COPD. Clin Exp Allergy 2016; 46(4):575–83.
6. Hanania NA, Chipps BE, Griffin NM, et al. Omalizumab effectiveness in asthma-COPD overlap: Post hoc analysis of PROSPERO. J Allergy Clin Immunol 2019; 143(4):1629–33.e2.
7. Maltby S, Gibson PG, Powell H, et al. Omalizumab Treatment Response in a Population With Severe Allergic Asthma and Overlapping COPD. Chest 2017; 151(1):78–89.
8. Hanania NA, Fortis S, Haselkorn T, et al. Omalizumab in Asthma with Fixed Airway Obstruction: Post Hoc Analysis of EXTRA. J Allergy Clin Immunol Pract 2022;10(1):222–8.
9. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380(9842):651–9.
10. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371(13):1189–97.
11. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014;371(13):1198–207.
12. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3(5):355–66.
13. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388(10056):2115–27.
14. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388(10056):2128–41.
15. Nair P, Wenzel S, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med 2017;376(25):2448–58.
16. Bafadhel M, McCormick M, Saha S, et al. Profiling of sputum inflammatory mediators in asthma and chronic obstructive pulmonary disease. Respiration 2012; 83(1):36–44.
17. Brightling CE, Bleecker ER, Panettieri RA Jr, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med 2014; 2(11):891–901.
18. Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for the Prevention of COPD Exacerbations. N Engl J Med 2019;381(11):1023–34.

19. Criner GJ, Celli BR, Singh D, et al. Predicting response to benralizumab in chronic obstructive pulmonary disease: analyses of GALATHEA and TERRANOVA studies. Lancet Respir Med 2020;8(2):158–70.
20. ClinicalTrials.gov. Acute Exacerbations Treated With BenRAlizumab (The ABRA Study) (ABRA). 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04098718. Accessed 17 Sept 2021.
21. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. N Engl J Med 2017;377(17):1613–29.
22. ClinicalTrials.gov. Mepolizumab as Add-on Treatment IN Participants With COPD Characterized by Frequent Exacerbations and Eosinophil Level (MATINEE). 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04133909. Accessed 3 Dec 2021.
23. ClinicalTrials.gov. Mepolizumab for COPD Hospital Eosinophilic Admissions Pragmatic Trial (COPD-HELP). 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04075331. Accessed December 3 2021.
24. Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. Lancet Respir Med 2016;4(10):781–96.
25. Panettieri RA Jr, Sjöbring U, Péterffy A, et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. Lancet Respir Med 2018;6(7):511–25.
26. Yousuf A, Ibrahim W, Greening NJ, et al. T2 Biologics for Chronic Obstructive Pulmonary Disease. J Allergy Clin Immunol Pract 2019;7(5):1405–16.
27. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med 2018;378(26):2486–96.
28. ClinicalTrials.gov. Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate-to-severe COPD With Type 2 Inflammation (BOREAS). 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03930732. Accessed 3 Dec 2021.
29. Aneas I, Decker DC, Howard CL, et al. Asthma-associated genetic variants induce IL33 differential expression through an enhancer-blocking regulatory region. Nat Commun 2021;12(1):6115.
30. Ketelaar ME, Portelli MA, Dijk FN, et al. Phenotypic and functional translation of IL33 genetics in asthma. J Allergy Clin Immunol 2021;147(1):144–57.
31. Wechsler ME, Ruddy MK, Pavord ID, et al. Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma. N Engl J Med 2021;385(18):1656–68.
32. Kim SW, Rhee CK, Kim KU, et al. Factors associated with plasma IL-33 levels in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2017;12:395–402.
33. Rabe KF, Celli BR, Wechsler ME, et al. Safety and efficacy of itepekimab in patients with moderate-to-severe COPD: a genetic association study and randomised, double-blind, phase 2a trial. Lancet Respir Med 2021;9(11):1288–98.
34. Kelsen SG, Agache IO, Soong W, et al. Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: A randomized clinical trial. J Allergy Clin Immunol 2021;148(3):790–8.
35. Yousuf AJ, Mohammed S, Carr L, et al. Late Breaking Abstract - Astegolimab, an anti-ST2, in chronic obstructive pulmonary disease - COPD-ST2OP: a phase IIa, placebo-controlled trial. Eur Respir J 2021;58(suppl 65):RCT206.

36. Diver S, Khalfaoui L, Emson C, 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(11):1299–312.
37. Menzies-Gow A, Colice G, Griffiths JM, et al. NAVIGATOR: a phase 3 multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res 2020;21(1):266.
38. ClinicalTrials.gov. Tezepelumab COPD Exacerbation Study (COURSE). 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04039113. Accessed 3 Dec 2021.
39. Brightling CE, Brusselle G, Altman P. The impact of the prostaglandin D(2) receptor 2 and its downstream effects on the pathophysiology of asthma. Allergy 2020;75(4):761–8.
40. Gonem S, Berair R, Singapuri A, et al. Fevipiprant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial. Lancet Respir Med 2016;4(9):699–707.
41. Castro M, Kerwin E, Miller D, et al. Efficacy and safety of fevipiprant in patients with uncontrolled asthma: Two replicate, phase 3, randomised, double-blind, placebo-controlled trials (ZEAL-1 and ZEAL-2). EClinicalMedicine 2021;35:100847.
42. Brightling CE, Gaga M, Inoue H, et al. Effectiveness of fevipiprant in reducing exacerbations in patients with severe asthma (LUSTER-1 and LUSTER-2): two phase 3 randomised controlled trials. Lancet Respir Med 2021;9(1):43–56.
43. Snell N, Foster M, Vestbo J. Efficacy and safety of AZD1981, a CRTH2 receptor antagonist, in patients with moderate to severe COPD. Respir Med 2013;107(11):1722–30.
44. Bowen H, Kelly A, Lee T, et al. Control of cytokine gene transcription in Th1 and Th2 cells. Clin Exp Allergy 2008;38(9):1422–31.
45. Krug N, Hohlfeld JM, Kirsten AM, et al. Allergen-induced asthmatic responses modified by a GATA3-specific DNAzyme. N Engl J Med 2015;372(21):1987–95.
46. Greulich T, Hohlfeld JM, Neuser P, et al. A GATA3-specific DNAzyme attenuates sputum eosinophilia in eosinophilic COPD patients: a feasibility randomized clinical trial. Respir Res 2018;19(1):55.
47. Jang HY, Gu S, Lee SM, et al. Overexpression of sirtuin 6 suppresses allergic airway inflammation through deacetylation of GATA3. J Allergy Clin Immunol 2016;138(5):1452–5.e13.
48. Ma K, Lu N, Zou F, et al. Sirtuins as novel targets in the pathogenesis of airway inflammation in bronchial asthma. Eur J Pharmacol 2019;865:172670.
49. Panch SR, Bozik ME, Brown T, et al. Dexpramipexole as an oral steroid-sparing agent in hypereosinophilic syndromes. Blood 2018;132(5):501–9.
50. Laidlaw TM, Prussin C, Panettieri RA, et al. Dexpramipexole depletes blood and tissue eosinophils in nasal polyps with no change in polyp size. Laryngoscope 2019;129(2):E61–6.
51. ClinicalTrials.gov. Dexpramipexole Dose-Ranging Biomarker Study in Subjects With Eosinophilic Asthma (AS201). 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04046939. Accessed 17 Sept 2021.
52. Herath SC, Normansell R, Maisey S, et al. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev 2018;10(10):Cd009764.

53. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Scientific Report 2021. Available at: https://ginasthma.org/gina-reports/.
54. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2020;55(1):1900588.
55. Taylor SL, Leong LEX, Mobegi FM, et al. Long-Term Azithromycin Reduces Haemophilus influenzae and Increases Antibiotic Resistance in Severe Asthma. Am J Respir Crit Care Med 2019;200(3):309–17.
56. Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax 2013;68(4):322–9.
57. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet 2017;390(10095):659–68.
58. Taylor SL, Ivey KL, Gibson PG, et al. Airway abundance of Haemophilus influenzae predicts response to azithromycin in adults with persistent uncontrolled asthma. Eur Respir J 2020;56(4):2000194.
59. Haldar K, Bafadhel M, Lau K, et al. Microbiome balance in sputum determined by PCR stratifies COPD exacerbations and shows potential for selective use of antibiotics. PLoS One 2017;12(8):e0182833.
60. Chung KF. Airway microbial dysbiosis in asthmatic patients: A target for prevention and treatment? J Allergy Clin Immunol 2017;139(4):1071–81.
61. Hua JL, Hu WP, Zuo YH, et al. Prevention of Acute Exacerbation in Subjects with Moderate-to-very Severe COPD by Modulating Lower Respiratory Microbiome: Protocol of a Prospective, Multicenter, Randomized Controlled Trial. Int J Chron Obstruct Pulmon Dis 2020;15:2985–90.
62. Nale JY, Clokie MR. Preclinical data and safety assessment of phage therapy in humans. Curr Opin Biotechnol 2021;68:310–7.
63. van Rijn AL, van Boheemen S, Sidorov I, et al. The respiratory virome and exacerbations in patients with chronic obstructive pulmonary disease. PLoS One 2019;14(10):e0223952.
64. Choi S, Sohn KH, Jung JW, et al. Lung virome: New potential biomarkers for asthma severity and exacerbation. J Allergy Clin Immunol 2021;148(4):1007–15.e9.
65. Waters EM, Neill DR, Kaman B, et al. Phage therapy is highly effective against chronic lung infections with Pseudomonas aeruginosa. Thorax 2017;72(7):666–7.
66. Djukanovic R, Harrison T, Johnston SL, et al. The effect of inhaled IFN-beta on worsening of asthma symptoms caused by viral infections. A randomized trial. Am J Respir Crit Care Med 2014;190(2):145–54.
67. Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. Eur Respir J 2010;36(3):646–54.
68. Vermeersch K, Gabrovska M, Aumann J, et al. Azithromycin during Acute Chronic Obstructive Pulmonary Disease Exacerbations Requiring Hospitalization (BACE). A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial. Am J Respir Crit Care Med 2019;200(7):857–68.
69. Johnston SL, Szigeti M, Cross M, et al. Azithromycin for Acute Exacerbations of Asthma : The AZALEA Randomized Clinical Trial. JAMA Intern Med 2016;176(11):1630–7.

70. Leung JM, Tiew PY, Mac Aogáin M, et al. The role of acute and chronic respiratory colonization and infections in the pathogenesis of COPD. Respirology 2017; 22(4):634–50.
71. O'Driscoll BR, Powell G, Chew F, et al. Comparison of skin prick tests with specific serum immunoglobulin E in the diagnosis of fungal sensitization in patients with severe asthma. Clin Exp Allergy 2009;39(11):1677–83.
72. Agbetile J, Bourne M, Fairs A, et al. Effectiveness of voriconazole in the treatment of Aspergillus fumigatus-associated asthma (EVITA3 study). J Allergy Clin Immunol 2014;134(1):33–9.
73. Ha EV, Rogers DF. Novel Therapies to Inhibit Mucus Synthesis and Secretion in Airway Hypersecretory Diseases. Pharmacology 2016;97(1–2):84–100.
74. Woodruff PG, Wolff M, Hohlfeld JM, et al. Safety and efficacy of an inhaled epidermal growth factor receptor inhibitor (BIBW 2948 BS) in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;181(5):438–45.
75. Alevy YG, Patel AC, Romero AG, et al. IL-13-induced airway mucus production is attenuated by MAPK13 inhibition. J Clin Invest 2012;122(12):4555–68.
76. Van As A, Kraft M, Hanania NA, et al. Inhibition of airway mucus hypersecretion and inflammation with bio-11006, A novel dual action drug, results in improvement of indices of bronchitis and lung function in chronic obstructive pulmonary disease (COPD), 2011. American Thoracic Society Congress; 2011. Colorado Convention Center: American Journal of Respiratory and Critical Care Medicine; 2011.
77. Garner JL, Shaipanich T, Hartman JE, et al. A prospective safety and feasibility study of metered cryospray for patients with chronic bronchitis in COPD. Eur Respir J 2020;56(6):2000556.
78. Valipour A, Fernandez-Bussy S, Ing AJ, et al. Bronchial Rheoplasty for Treatment of Chronic Bronchitis. Twelve-Month Results from a Multicenter Clinical Trial. Am J Respir Crit Care Med 2020;202(5):681–9.
79. Dunican EM, Watchorn DC, Fahy JV. Autopsy and Imaging Studies of Mucus in Asthma. Lessons Learned about Disease Mechanisms and the Role of Mucus in Airflow Obstruction. Ann Am Thorac Soc 2018;15(Suppl 3):S184–91.
80. Liu G, Philp AM, Corte T, et al. Therapeutic targets in lung tissue remodelling and fibrosis. Pharmacol Ther 2021;225:107839.
81. Baraldo S, Turato G, Badin C, et al. Neutrophilic infiltration within the airway smooth muscle in patients with COPD. Thorax 2004;59(4):308–12.
82. Saunders R, Kaul H, Berair R, et al. Fevipiprant reduces airway smooth muscle mass in asthmatics via PGD2 receptor antagonism. Eur Respir J 2017;50(suppl 61):OA283.
83. Chachi L, Diver S, Kaul H, et al. Computational modelling prediction and clinical validation of impact of benralizumab on airway smooth muscle mass in asthma. Eur Respir J 2019;54(5):1900930.
84. Delgado-Eckert E, James A, Meier-Girard D, et al. Lung function fluctuation patterns unveil asthma and COPD phenotypes unrelated to type 2 inflammation. J Allergy Clin Immunol 2021;148(2):407–19.
85. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med 2010; 181(2):116–24.
86. Wechsler ME, Laviolette M, Rubin AS, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol 2013;132(6):1295–302.

87. Chernyavsky IL, Russell RJ, Saunders RM, et al. In vitro, in silico and in vivo study challenges the impact of bronchial thermoplasty on acute airway smooth muscle mass loss. Eur Respir J 2018;51(5):1701680.
88. Hu SY, Long F, Long L, et al. [Analysis of the clinical efficacy and safety of bronchial thermoplasty in the treatment of patients with severe asthma and asthma-chronic obstructive pulmonary disease overlap]. Zhonghua Yi Xue Za Zhi 2021; 101(15):1071–6.
89. Otoshi R, Baba T, Aiko N, et al. Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma with Smoking History: A Single-Center Experience. Int Arch Allergy Immunol 2020;181(7):522–8.
90. Slebos DJ, Klooster K, Koegelenberg CF, et al. Targeted lung denervation for moderate to severe COPD: a pilot study. Thorax 2015;70(5):411–9.
91. Valipour A, Asadi S, Pison C, et al. Long-term safety of bilateral targeted lung denervation in patients with COPD. Int J Chron Obstruct Pulmon Dis 2018;13: 2163–72.
92. Slebos DJ, Shah PL, Herth FJF, et al. Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe Chronic Obstructive Pulmonary Disease (AIRFLOW). A Multicenter Randomized Controlled Clinical Trial. Am J Respir Crit Care Med 2019;200(12):1477–86.
93. Slebos DJ, Degano B, Valipour A, et al. Design for a multicenter, randomized, sham-controlled study to evaluate safety and efficacy after treatment with the Nuvaira® lung denervation system in subjects with chronic obstructive pulmonary disease (AIRFLOW-3). BMC Pulm Med 2020;20(1):41.
94. Zakarya R, Chan YL, Rutting S, et al. BET proteins are associated with the induction of small airway fibrosis in COPD. Thorax 2021;76(7):647–55.
95. Tian B, Hosoki K, Liu Z, et al. Mucosal bromodomain-containing protein 4 mediates aeroallergen-induced inflammation and remodeling. J Allergy Clin Immunol 2019;143(4):1380–94.e9.
96. Cazzola M, Rogliani P, Matera MG. The future of bronchodilation: looking for new classes of bronchodilators. Eur Respir Rev 2019;28(154).
97. Wenzel SE, Barnes PJ, Bleecker ER, et al. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma. Am J Respir Crit Care Med 2009;179(7):549–58.
98. Rennard SI, Fogarty C, Kelsen S, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;175(9):926–34.
99. Pascoe S, Kanniess F, Bonner J, et al. A monoclonal antibody to IL-1B attenuates the late asthmatic response to antigen challenge in patients with mild asthma. Suppl. 5028. Eur Respir J; 2006. p. 752. European Respiratory Journal.
100. Calverley PMA, Sethi S, Dawson M, et al. A randomised, placebo-controlled trial of anti-interleukin-1 receptor 1 monoclonal antibody MEDI8968 in chronic obstructive pulmonary disease. Respir Res 2017;18(1):153.
101. Rogliani P, Calzetta L, Ora J, et al. Canakinumab for the treatment of chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2015;31:15–27.
102. Osei ET, Brandsma CA, Timens W, et al. Current perspectives on the role of interleukin-1 signalling in the pathogenesis of asthma and COPD. Eur Respir J 2020;55(2).
103. Oronsky B, Reid TR, Larson C, et al. REPLATINUM Phase III randomized study: RRx-001 + platinum doublet versus platinum doublet in third-line small cell lung cancer. Future Oncol 2019;15(30):3427–33.

104. Williams EJ, Negewo NA, Baines KJ. Role of the NLRP3 inflammasome in asthma: Relationship with neutrophilic inflammation, obesity, and therapeutic options. J Allergy Clin Immunol 2021;147(6):2060–2.
105. Revez JA, Bain LM, Watson RM, et al. Effects of interleukin-6 receptor blockade on allergen-induced airway responses in mild asthmatics. Clin Transl Immunol 2019;8(6):e1044.
106. Busse WW, Holgate S, Kerwin E, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. Am J Respir Crit Care Med 2013; 188(11):1294–302.
107. ClinicalTrials.gov. Study of Efficacy and Safety of Brodalumab Compared With Placebo in Inadequately Controlled Asthma Subjects With High Bronchodilator Reversibility. 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT01902290. Accessed 3 Dec 2021.
108. ClinicalTrials.gov. Study to Assess the Efficacy and Safety of CJM112 in Patients With Inadequately Controlled Severe Asthma. 2021. Available at: https://clinicaltrials.gov/ct2/show/study/NCT03299686. Accessed 3 Dec 2021.
109. Eich A, Urban V, Jutel M, et al. A Randomized, Placebo-Controlled Phase 2 Trial of CNTO 6785 in Chronic Obstructive Pulmonary Disease. COPD 2017;14(5): 476–83.
110. Whitehead GS, Kang HS, Thomas SY, et al. Therapeutic suppression of pulmonary neutrophilia and allergic airway hyperresponsiveness by a RORγt inverse agonist. JCI Insight 2019;5(14):e125528.
111. Brightling CE, Nair P, Cousins DJ, et al. Risankizumab in Severe Asthma - A Phase 2a, Placebo-Controlled Trial. N Engl J Med 2021;385(18):1669–79.
112. O'Byrne PM, Metev H, Puu M, et al. Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2016;4(10):797–806.
113. Rennard SI, Dale DC, Donohue JF, et al. CXCR2 Antagonist MK-7123. A Phase 2 Proof-of-Concept Trial for Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2015;191(9):1001–11.
114. Mahler DA, Huang S, Tabrizi M, et al. Efficacy and safety of a monoclonal antibody recognizing interleukin-8 in COPD: a pilot study. Chest 2004;126(3): 926–34.
115. Uddin M, Watz H, Malmgren A, et al. NETopathic Inflammation in Chronic Obstructive Pulmonary Disease and Severe Asthma. Front Immunol 2019;10:47.
116. Khindri S, Cahn A, Begg M, et al. A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Crossover Study To Investigate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Repeat Doses of Inhaled Nemiralisib in Adults with Persistent, Uncontrolled Asthma. J Pharmacol Exp Ther 2018;367(3):405–13.
117. Cahn A, Hamblin JN, Begg M, et al. Safety, pharmacokinetics and dose-response characteristics of GSK2269557, an inhaled PI3Kδ inhibitor under development for the treatment of COPD. Pulm Pharmacol Ther 2017;46:69–77.
118. Cahn A, Hamblin JN, Robertson J, et al. An Inhaled PI3Kδ Inhibitor Improves Recovery in Acutely Exacerbating COPD Patients: A Randomized Trial. Int J Chron Obstruct Pulmon Dis 2021;16:1607–19.
119. Fahy WA, Homayoun-Valiani F, Cahn A, et al. Nemiralisib in Patients with an Acute Exacerbation of COPD: Placebo-Controlled, Dose-Ranging Study. Int J Chron Obstruct Pulmon Dis 2021;16:1637–46.

120. Braithwaite IE, Cai F, Tom JA, et al. Inhaled JAK inhibitor GDC-0214 reduces exhaled nitric oxide in patients with mild asthma: A randomized, controlled, proof-of-activity trial. J Allergy Clin Immunol 2021;148(3):783–9.
121. Li S, Hui Y, Yuan J, et al. Syk-Targeted, a New 3-Arylbenzofuran Derivative EAPP-2 Blocks Airway Inflammation of Asthma-COPD Overlap in vivo and in vitro. J Inflamm Res 2021;14:2173–85.
122. Ramis I, Otal R, Carreño C, et al. A novel inhaled Syk inhibitor blocks mast cell degranulation and early asthmatic response. Pharmacol Res 2015;99:116–24.
123. Watz H, Barnacle H, Hartley BF, et al. Efficacy and safety of the p38 MAPK inhibitor losmapimod for patients with chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2014;2(1):63–72.
124. Marks-Konczalik J, Costa M, Robertson J, et al. A post-hoc subgroup analysis of data from a six month clinical trial comparing the efficacy and safety of losmapimod in moderate-severe COPD patients with ≤2% and >2% blood eosinophils. Respir Med 2015;109(7):860–9.
125. Pascoe S, Costa M, Marks-Konczalik J, et al. Biological effects of p38 MAPK inhibitor losmapimod does not translate to clinical benefits in COPD. Respir Med 2017;130:20–6.
126. Luo J, Yang L, Yang J, et al. Efficacy and safety of phosphodiesterase 4 inhibitors in patients with asthma: A systematic review and meta-analysis. Respirology 2018;23(5):467–77.
127. Janjua S, Fortescue R, Poole P. Phosphodiesterase-4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2020;5(5):Cd002309.
128. Southworth T, Kaur M, Hodgson L, et al. Anti-inflammatory effects of the phosphodiesterase type 4 inhibitor CHF6001 on bronchoalveolar lavage lymphocytes from asthma patients. Cytokine 2019;113:68–73.
129. Singh D, Leaker B, Boyce M, et al. A novel inhaled phosphodiesterase 4 inhibitor (CHF6001) reduces the allergen challenge response in asthmatic patients. Pulm Pharmacol Ther 2016;40:1–6.
130. Singh D, Beeh KM, Colgan B, et al. Effect of the inhaled PDE4 inhibitor CHF6001 on biomarkers of inflammation in COPD. Respir Res 2019;20(1):180.
131. Singh D, Lea S, Mathioudakis AG. Inhaled Phosphodiesterase Inhibitors for the Treatment of Chronic Obstructive Pulmonary Disease. Drugs 2021;81(16):1821–30.