



Perspectives

Asthma—chronic obstructive pulmonary disease overlap syndrome

What we know and what we need to find out

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Introduction

The burgeoning literature on asthma phenotypes and endotypes continues to deepen our understanding of asthma and our appreciation of the complexity of this heterogeneous syndrome. Physicians in practice have long encountered patients who have features of asthma and chronic obstructive pulmonary disease (COPD). Thus, we should not be surprised that there is a new category called asthma-COPD overlap syndrome (ACOS).

Consider the following patients. A 45-year-old, nonsmoking woman with a history of moderate persistent asthma and allergies since childhood seeks treatment. She has numerous exacerbations, and her spirometry reveals chronic airflow limitation despite asthma therapy. Alternatively, you see a 58-year-old man with a 45-pack-year tobacco history and previously diagnosed emphysema. He is allergic to his cat, and his spirometry reveals chronic airflow limitation with partial reversibility after receiving short-acting bronchodilators.

Such patients bring to mind the possibility of an overlap syndrome. In clinical practice, separating asthma from COPD can be difficult, particularly in the older patient who is a smoker. The term ACOS has been proposed in guidelines to describe this understudied

group of individuals. No definition for ACOS currently exists because ACOS, like asthma and COPD, likely represents a spectrum of disease and distinct clinical phenotypes; therefore, no single definition will be precise and clinically meaningful. We explore controversies regarding this term and limitations in the clinical utility of our current classification schemes. Patients with ACOS unfortunately have a more turbulent clinical course than those with asthma or COPD alone. Despite this, firm treatment guidelines and algorithms do not exist for this population (because they have largely been excluded from asthma and COPD trials in the past). Instead, clinical decision making is shaped by our overall impression of the patients (are their conditions more COPD-like or more asthma-like?), an approach that has obvious limitations.

What has emerged with certainty is that overlap between asthma and COPD is a clinical reality and that further investigation is warranted regarding its pathophysiology, severity, prognosis, environmental influences, and treatment. Our efforts to dissect, identify, and study this syndrome and identify phenotypes are crucial to the goal of providing precision medicine with targeted therapeutics to optimize clinical outcomes. In this review, we summarize the existing literature regarding ACOS and explore emerging approaches, treatment options, and areas for future study.

Definitions of Asthma, COPD, and ACOS

Asthma is a chronic inflammatory disease of the small and large airways that typically presents in childhood or young adulthood and is commonly seen in patients with concomitant allergic illness. That said, asthma may present at any age. Asthma is characterized by inflammation of the airways, reversible obstruction, and bronchial hyperresponsiveness to external stimuli. Asthma is a heterogeneous syndrome that manifests as different clinical phenotypes (eg, exercise-induced asthma, aspirin-exacerbated respiratory

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disease).¹ Thus, it is not surprising that although lung function typically returns to normal between episodes in most patients with asthma, a subset loses reversibility over time.

COPD is also an inflammatory disease of the airway, mostly of the small airways, that is generally diagnosed in older patients who have a history of tobacco smoking. Two main phenotypes are chronic obstructive bronchitis and emphysema, which involves destruction of the lung architecture. COPD is typically progressive despite treatment, and patients have persistent airflow limitation with hyperinflation of the lungs and frequent extrapulmonary comorbidities.

Some patients purely fit one diagnosis. However, distinguishing between the 2 can often be difficult, particularly in older patients who are smokers. This difficulty is attributable to overlapping features and an unclear and variable picture of the underlying mechanism(s) of disease onset and progression and is further complicated by the myriad ways in which these patients can present.

There is mounting evidence that some patients with COPD have features that resemble asthma, with evidence of T_H2-mediated inflammation, atopy, bronchial hyperresponsiveness, or significant and sometimes marked reversibility seen with use of a bronchodilator. In addition, some patients with asthma and no risk factors for COPD develop permanent structural changes in the lung (airway remodeling) and an irreversible decline in forced expiratory volume in 1 second (FEV₁). The remodeling process is often accompanied by an increase in symptoms and a decrease in bronchodilator responsiveness. Such patients have persistent airflow limitation (postbronchodilator ratio of FEV₁ to forced vital capacity <0.7), raising the possibility of ACOS. The presence of fixed airflow obstruction itself is not sufficient to meet criteria for ACOS because it may be inconsistent over time and fixed airflow obstruction may be a feature of asthma, particularly if it is suboptimally treated.^{2,3} Therefore, discerning between these disease processes is important based on a constellation of phenotypic characteristics.

As mentioned, no definition of ACOS currently exists. The recent Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) report on ACOS put forth the following description: "Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD."⁴ ACOS remains somewhat of a controversial term, with some experts voicing concern that an umbrella term such as this is an oversimplification and that ACOS comprises a spectrum of diseases and phenotypes.⁵

The GINA/GOLD authors acknowledge that ACOS likely consists of multiple phenotypes and that one of the main aims of this diagnostic category is to raise awareness about the overlap syndrome and highlight the need for further study. They offer the following practical approach in identifying such patients.

1. Establish the presence of chronic airways disease.
2. Determine if there are features clearly suggestive of either asthma or COPD or whether there are an equal number of features of both, suggesting ACOS.
3. Perform lung function testing with lung volumes and diffusion capacity

In addition, the GINA/GOLD documents offers a table of typical features of asthma and typical features of COPD that may be useful to the reader; an equal number of features of each disease may suggest an overlap syndrome.

Prevalence and Natural History of ACOS

Given that a clear definition does not exist, it is not surprising that the prevalence of ACOS remains unknown. It has been cited to

range from as low as 15% to as high as 55% in those with obstructive lung disease.⁴ It is a highly age-dependent diagnosis, with the diagnosis more likely to be made in a population of older patients or in those who smoke.

Despite the uncertainty surrounding ACOS criteria, there is recognition that patients with features of asthma and COPD tend to have a worse clinical course. These patients have fixed airflow obstruction, poor quality of life, a more rapid decline in lung function, and higher mortality compared with those with asthma or COPD.^{4,6,7} As such, they are frequent consumers of health care resources, and costs associated with caring for such patients are high.

A large retrospective study was recently performed in the Balearic Islands, Spain, to better characterize ACOS in real life.⁸ Investigators compared patients with ACOS (n = 5,093) and those with COPD (n = 22,778) and found that patients with ACOS were more frequently female and younger, had less smoking exposure, and had higher rates of certain comorbidities, such as anxiety, gastroesophageal reflux disease, and osteoporosis. Hospitalization risk was associated with the presence of cardiovascular diseases. Further data regarding prognosis are provided by a recent large study of 8,382 participants from the Copenhagen City Heart Study. Investigators found that patients with ACOS and late-onset asthma had higher rates of FEV₁ decline and exacerbations, with poorer prognosis compared with other groups.⁹

Cosio et al¹⁰ examined a cohort of patients with COPD to look for features of asthma and found 125 patients who fulfilled the criteria for ACOS. These patients were predominantly male, and most were receiving inhaled corticosteroids (ICSs). Interestingly, they found that these patients had better 1-year prognosis than clinically similar patients with COPD alone. These studies reveal a significant disparity in findings concerning the spectrum of illnesses described by the term ACOS and reinforce the need to better define and stratify this/these illness(es).

Overlapping Mechanisms of Disease

The overlap that is seen clinically is likely related to the overlap in the underlying inflammatory pathophysiologic mechanisms of the disease. In addition, overlap is seen in clinical manifestations of obstructive lung disease, such as bronchial hyperreactivity and reversibility with bronchodilators (which has more commonly been associated solely with asthma in the past).

Asthma phenotypes are largely believed to be an eosinophilic T_H2-driven cytokine pattern of inflammation. However, some patients with asthma are refractory to T_H2-targeted therapeutics, and these patients often have the most severe or recalcitrant disease, indicating a neutrophilic or pauci-granulocytic pattern of inflammation.

COPD, on the other hand, has traditionally been viewed primarily as a neutrophilic inflammatory process of the airways. However, increasing attention has been given to evidence that suggests that some of these patients have T_H2 inflammation. This finding is exemplified by the fact that eosinophils (in the sputum, bronchoalveolar lavage, and lung tissue) have been reported in 15% to 40% of patients with stable COPD.^{11,12} In fact, in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, 37.4% of the 1,483 patients with COPD had persistent blood eosinophilia during the 3-year follow-up period.¹³ Furthermore, the presence of sputum or blood eosinophilia may have important therapeutic implications regarding the decision to add on therapy with ICSs.

According to the GINA/GOLD guidelines, patients with ACOS may have eosinophils and/or neutrophils in the sputum.⁴ Ghebre et al¹⁴ used cluster analysis with sputum from patients with obstructive lung disease and found 3 clusters: asthma predominant

(eosinophilic), COPD predominant (mixed eosinophils and neutrophils), and ACOS (neutrophils). This finding highlights the need for further studies of the inflammatory milieu present in ACOS. In both asthma and COPD, clearly there is heterogeneity in mucosal inflammation, and this manifests as various phenotypes and subphenotypes of disease that have implications regarding predictability of therapeutic intervention. Predetermining the phenotype has the downstream effect of potentially improving therapeutic outcomes.

Bronchial hyperresponsiveness, a hallmark of asthma, has been documented in up to 60% of patients with COPD.¹⁵ Studies suggest that the presence of bronchial hyperresponsiveness is actually associated with a more rapid decline in FEV₁ in patients with COPD.¹⁶ Reversibility of airway obstruction as well has classically been associated with asthma, yet patients with COPD with persistent airflow limitation may indeed have some degree of reversibility when given bronchodilators, with up to 50% demonstrating reversibility.¹⁷ Likewise, atopy is seen in up to 30% of patients with COPD.¹⁸ It is important to identify such classic asthma features in patients with COPD because these represent components of their disease that are treatable.

Airway reversibility is considered a hallmark of asthma. However, not all patients with asthma have full reversibility; in fact, many lose reversibility over time as a consequence of airway remodeling. In those with fixed obstructive patterns, the pathogenesis involves epithelial damage, collagen deposition, smooth muscle hyperplasia and hypertrophy, increased smooth muscle mass, mucous gland hypertrophy, and angiogenesis. Currently, there are no clear indicators that predict which asthma cases will progress to a COPD-like phenotype with fixed airway obstruction, and it would appear that no available therapy prevents this potential decay.

Factors Influencing Overlap Phenotype

In addition to the underlying mechanisms of inflammatory disease, there are numerous environmental factors that may influence the overlap phenotype. These exposures, which may modify genetic risk, include smoking, infections, exposure to inhalable pollutants, and diet. Two of the best studied of these triggers are discussed below.

Smoking

Smoking is a habit commonly seen in the asthmatic population. This is clearly seen in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, a large, 3-year, multicenter observational cohort study of patients with difficult-to-treat or severe asthma. Of the 3,489 adults in the study, 4.3% were current smokers, but 32% reported a prior smoking history.¹⁹ Although tobacco exposure is clearly a key etiologic driver of COPD, it is not known whether smoking contributes to irreversible airway remodeling in patients with asthma. Even in COPD, the decline in lung function that is seen in patients with similar tobacco exposure is highly variable. Lange et al²⁰ looked at 3 large COPD cohorts and found that the trajectory of lung function decline in patients with COPD varies, with approximately half of patients following a trajectory of rapid FEV₁ decline.

Research reveals that individuals with asthma who smoke have increased symptoms and impaired corticosteroid responsiveness compared with nonsmokers with asthma.^{21,22} Likewise, active smokers additionally have a more rapid annual rate of lung function decline, which may be mitigated by smoking cessation. A British study by Chaudhuri et al²³ found that 6 weeks after quitting smoking, individuals with asthma had improved lung function and decreased sputum neutrophilia compared with those who continued to smoke. In the Smoking Modulates Outcomes of

Glucocorticoid Therapy (SMOG) study, Lazarus et al²⁴ found that smokers with mild asthma had a blunted response to ICSs but not to montelukast, providing further evidence that smoking may be important when considering therapeutic effectiveness of various treatment options. It is unclear at this time if smoking individuals with asthma who progress to ACOS represent the same phenotype as nonsmokers. Presumably, long-term exposure to noxious stimuli may stimulate different pathophysiologic processes than allergenic stimuli. Further study is needed regarding the effect of smoking on asthma and optimal therapy in this subgroup, which is generally excluded from participation in clinical trials in asthma.

Air Pollution

Exposure to air pollution has been linked to the development of asthma and COPD, but its effect on ACOS is unknown. One recent Canadian study that addressed the question of whether air pollution is a risk factor for the progression of asthma to COPD found that patients with ACOS (n = 630), derived from a large group of adults with asthma (n = 6,040), had later onset of asthma and greater morbidity and mortality.²⁵ Moreover, study participants with higher cumulative exposure to fine particulate matter and ozone had nearly a 3-fold greater odds of developing ACOS. This finding reinforces that noxious exposures beyond cigarette smoke may contribute to the development of ACOS.

Need for Identification of ACOS Phenotypes

As noted earlier, there is no clear definition for ACOS because it probably represents a syndrome of multiple phenotypes that needs further study and better stratification. In all likelihood, the patient with allergies and lifelong asthma who develops fixed airflow obstruction is different from the smoker with emphysema who has some features of atopy and asthma. Studies to characterize the natural history and prognosis will likely need to prestratify individuals based on asthma or COPD being the predominant and preceding illness. A similar approach to that used to identify asthma phenotypes, such as study of inflammatory markers and application of nonbiased clustering models, will likely be helpful in studying ACOS phenotypes in the future.^{26–28}

Therapeutic Approaches

Currently, no firm treatment recommendations exist for patients with ACOS. Instead, our overall impression of the patient having more asthma-like or COPD-like disease guides our clinical decision making. These patients historically have been excluded from clinical trials (eg, cigarette smoking being an exclusion in an asthma study and a history of asthma being exclusionary for a COPD study); as such, physicians are left to choose a treatment approach without substantiated evidence of efficacy in this group. That said, there are reasonable default approaches that may be considered. Good practice, alongside therapeutic options, includes the treatment of modifiable risk factors, such as smoking cessation, pulmonary rehabilitation when indicated, and vaccinations to prevent infection (such as influenza and pneumococcal pneumonia).

ICSs and Bronchodilators

As noted in a review article by Postma et al,¹¹ the recommended default position in these patients with overlap disease is to start therapy for asthma, usually with an ICS. Step-up therapy often includes the addition of a long-acting β -agonist (LABA) or long-acting muscarinic antagonist (LAMA) alone or in combination, perhaps earlier in the treatment algorithm than would be considered for asthma alone. Leukotriene modifiers may be of value in those with atopy. Given the debate of LABA safety in patients with asthma, the presence of an asthmatic component warrants concomitant use of

ICS with LABA therapy. One of the concerns raised about this approach is the potential to overuse ICSs in patients with COPD, who may experience adverse effects, such as pneumonia.²⁹

Because there have been no studies directly examining therapeutic intervention in ACOS, we are left with exploring the COPD and asthma literature with inference into potential efficacy in ACOS. Pascoe et al³⁰ performed a post-hoc analysis of data from 2 replicate, randomized, double-blind trials of 12 months' duration in which once-a-day vilanterol, 25 μ g, was compared with 25 μ g of vilanterol plus 50 μ g, 100 μ g, or 200 μ g of fluticasone furoate in patients with moderate-to-severe COPD and a history of 1 or more exacerbations in the previous year. They compared exacerbation rates between 2 baseline eosinophil cell count strata (<2% and $\geq$ 2%) and found that the short-term benefits of ICSs for patients with COPD are greater in those with evidence of a T_H2 high phenotype as indicated by elevated blood eosinophil counts compared with those without.³⁰ Likewise, a study by Siddiqui et al³¹ found that peripheral blood eosinophilia in patients with COPD was associated with a favorable response to inhaled ICS and LABA therapy. However, others have reported benefits of ICS therapy in patients with COPD only when higher peripheral eosinophil cut points (eg, $\geq$ 4% or $\geq$ 300/ μ L) were present.³² Although further study is needed, one can surmise similar possible efficacy in patients with ACOS.

In addition, LAMAs, mostly used for patients with COPD in the past, have established a therapeutic role in step-up therapy for patients with asthma. In a 3-way, double-blind, triple-dummy crossover trial of 210 patients with asthma, the addition of tiotropium to a LABA and ICS combination improved symptoms and lung function in patients with uncontrolled asthma.³³

As we await formal study of pharmacologic agents in patients with ACOS, it is reasonable to consider the early addition of a LABA and/or a LAMA to an ICS in the ACOS population. However, potential adverse effects of each of these agents should be considered when choosing therapy.

Potential Future Therapies

Biologic therapies are emerging as an important therapeutic consideration for patients with poorly controlled moderate to severe asthma. The current biologics available and in the pipeline mainly target T_H2-mediated disease. Such medications include anti-IgE, anti-interleukin 5, anti-interleukin 5 receptor, and others. The use of biologics in patients with overlap of asthma and COPD has not been studied.

Studies have also examined the potential role of biologics in COPD, but this literature is nowhere near as robust as that for T_H2 asthma. In a randomized, placebo-controlled trial of patients with moderate to severe COPD and eosinophilia (n = 50 placebo, n = 51 benralizumab), using a cut point of 200 to 300/ μ L, numeric (but nonsignificant) improvements in exacerbations and FEV₁ were found in the benralizumab group compared with placebo, suggesting this may warrant further research.³⁴ No such studies have been performed in the ACOS group.

Given cost and other considerations with biologic therapies, it will be important to tailor treatment and preselect patients most likely to have a good therapeutic response. Ideally, an easily measured biomarker, such as blood eosinophils, would help stratify patients most likely to benefit from a particular anticytokine therapy.

Studies of other drugs, such as roflumilast (a phosphodiesterase type 4 antagonist), reveal some potential efficacy in patients with asthma and COPD. In a randomized, double-blind, placebo-controlled study of 64 patients with moderate-to-severe asthma inadequately controlled with ICS and LABA therapy, the addition of roflumilast plus montelukast resulted in a statistically significant

improvement in FEV₁ at 4 weeks vs montelukast alone.³⁵ Similarly, studies of roflumilast in COPD have found significant reductions in exacerbations when added to other therapy, but further study is needed to evaluate its efficacy in patients with asthma alone and those with ACOS.^{36,37}

Prevention

Ultimately, it would be helpful to be able to identify those patients with asthma who are at particular risk of experiencing airway remodeling and progression to fixed airway obstruction. Currently, it is difficult to identify which patients will experience the consequences of airway remodeling because no strong clinical predictors exist. Although early studies indicated that early intervention with ICSs could potentially halt this process, currently there is no convincing evidence that asthma therapies can prevent the remodeling process.³⁸ In the Childhood Asthma Management Program (CAMP) study, treatment with budesonide or nedocromil for 4 to 6 years did not improve lung function.³⁹ A subsequent analysis of this cohort of patients found that 25.7% of children, despite treatment with ICSs, had a significant decline in post-bronchodilator FEV₁.⁴⁰ In the full 5-year follow-up study of the Steroid Treatment as Regular Therapy (START) trial, post-bronchodilator FEV₁ declined by a mean of 2.22%, regardless of treatment with low-dose ICSs or placebo.^{41,42} More recently, McGeachie et al⁴³ examined predictors of abnormal lung function growth and decline and found that childhood impairment of lung function and male sex were significant predictors. Identifying patients with asthma who will progress to fixed obstruction and ACOS may be a group who would benefit from trials of novel targeted therapeutics in an attempt to prevent this loss.

Current Limitations and Unmet Needs

The recent attention received by ACOS in the medical literature is a good starting point in the further investigation of this syndrome. Patients with overlap syndrome rightfully deserve dedicated study in clinical trials, especially so given their relatively high morbidity and health care use. As noted earlier, ACOS is likely a spectrum of diseases. As we explore this illness, we will likely stratify this group into multiple subsets and find that some patients with asthma and a COPD phenotype may benefit from early addition of LABAs or LAMAs to ICS therapy, and some patients with COPD and the T_H2 high phenotype may benefit from the early addition of ICSs to LABAs or LAMAs. Continued efforts to identify clinical phenotypes that predict therapeutic responsiveness will pave the way for personalized, tailored therapy for patients with overlap syndromes.

References

- [1] Desai M, Oppenheimer J. Elucidating asthma phenotypes and endotypes: progress towards personalized medicine. *Ann Allergy Asthma Immunol*. 2016; 116:394–401.
- [2] Tashkin DP, Chipps BE, Trudo F, Zangrilli JG. Fixed airflow obstruction in asthma: a descriptive study of patient profiles and effect on treatment responses. *J Asthma*. 2014;51:603–609.
- [3] Tashkin DP, Moore GE, Trudo F, DePietro M, Chipps BE. Assessment of consistency of fixed airflow obstruction status during budesonide/formoterol treatment and its effects on treatment outcomes in patients with asthma. *J Allergy Clin Immunol Pract*. 2016;4:705–712.
- [4] Diagnosis of Diseases of Chronic Airflow Limitation: Asthma COPD and Asthma-COPD Overlap Syndrome (ACOS). 2015. www.ginasthma.org. Accessed September 1, 2016.
- [5] Cazzola M, Rogliani P. Do we really need asthma-chronic obstructive pulmonary disease overlap syndrome? *J Allergy Clin Immunol*. 2016;138: 977–983.
- [6] Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax*. 2009;64:728–735.
- [7] Kauppi P, Kupiainen H, Lindqvist A, et al. Overlap syndrome of asthma and COPD predicts low quality of life. *J Asthma*. 2011;48:279–285.

- [8] van Boven JF, Román-Rodríguez M, Palmer JF, Toledo-Pons N, Cosío BG, Soriano JB. Comorbidity, pattern, and impact of asthma-COPD overlap syndrome in real life. *Chest*. 2016;149:1011–1020.
- [9] Lange P, Çolak Y, Ingebrigtsen TS, Vestbo J, Marott JL. Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis. *Lancet Respir Med*. 2016;4:454–462.
- [10] Cosío BG, Soriano JB, López-Campos JL, et al. Defining the asthma-COPD overlap syndrome in a COPD cohort. *Chest*. 2016;149:45–52.
- [11] Postma DS, Rabe KF. The asthma-COPD overlap syndrome. *N Engl J Med*. 2015;373:1241–1249.
- [12] Barker BL, Brightling CE. Phenotyping the heterogeneity of chronic obstructive pulmonary disease. *Clin Sci (Lond)*. 2013;124:371–387.
- [13] Singh D, Kolsam U, Brightling CE, et al. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J*. 2014;44:1697–1700.
- [14] Ghebre MA, Bafadhel M, Desai D, et al. Biological clustering supports both “Dutch” and “British” hypotheses of asthma and chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2015;135:63–72.
- [15] Tashkin DP, Altose MD, Bleecker ER, et al. The Lung Health Study Research Group. The lung health study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. *Am Rev Respir Dis*. 1992;145:301–310.
- [16] Tashkin DP, Altose MD, Connett JE, Kanner RE, Lee WW, Wise RA. The Lung Health Study Research Group. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1996;153:1802–1811.
- [17] Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543–1554.
- [18] Jamieson DB, Matsui EC, Belli A, et al. Effects of allergic phenotype on respiratory symptoms and exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;188:187–192.
- [19] Chipps BE, Zeiger RS, Borish L, et al. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol*. 2012;130:332–342.e310.
- [20] Lange P, Celli B, Agustí A. Lung-function trajectories and chronic obstructive pulmonary disease. *N Engl J Med*. 2015;373:1575.
- [21] Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax*. 2002;57:226–230.
- [22] Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med*. 2003;168:1308–1311.
- [23] Chaudhuri R, Livingston E, McMahon AD, et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. *Am J Respir Crit Care Med*. 2006;174:127–133.
- [24] Lazarus SC, Chinchilli VM, Rollings NJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med*. 2007;175:783–790.
- [25] To T, Zhu J, Larsen K, et al. Progression from asthma to chronic obstructive pulmonary disease, is air pollution a risk factor? *Am J Respir Crit Care Med*. 2016;194:429–438.
- [26] Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2010;181:315–323.
- [27] Siroux V, Basagaña X, Boudier A, et al. Identifying adult asthma phenotypes using a clustering approach. *Eur Respir J*. 2011;38:310–317.
- [28] Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008;178:218–224.
- [29] Suissa S, Dell’Aniello S, Ernst P. Long-acting bronchodilator initiation in COPD and the risk of adverse cardio-pulmonary events: a population-based comparative safety study. *Chest*. 2017;151:60–67.
- [30] Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med*. 2015;3:435–442.
- [31] Siddiqui SH, Guasconi A, Vestbo J, et al. Blood Eosinophils: A biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;192:523–525.
- [32] Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med*. 2016;4:390–398.
- [33] Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med*. 2010;363:1715–1726.
- [34] Brightling CE, Bleecker ER, Panettieri RA, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. *Lancet Respir Med*. 2014;2:891–901.
- [35] Bateman ED, Goehring UM, Richard F, Watz H. Roflumilast combined with montelukast versus montelukast alone as add-on treatment in patients with moderate-to-severe asthma. *J Allergy Clin Immunol*. 2016;138:142–149.e148.
- [36] Bateman ED, Rabe KF, Calverley PM, et al. Roflumilast with long-acting β_2 -agonists for COPD: influence of exacerbation history. *Eur Respir J*. 2011;38:553–560.
- [37] Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multi-centre randomised controlled trial. *Lancet*. 2015;385:857–866.
- [38] Hahtela T, Järvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med*. 1994;331:700–705.
- [39] The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med*. 2000;343:1054–1063.
- [40] Covar RA, Spahn JD, Murphy JR, Szefer SJ, Group CAMPR. Progression of asthma measured by lung function in the childhood asthma management program. *Am J Respir Crit Care Med*. 2004;170:234–241.
- [41] Busse WW, Pedersen S, Pauwels RA, et al. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol*. 2008;121:1167–1174.
- [42] Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet*. 2003;361:1071–1076.
- [43] McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med*. 2016;374:1842–1852.