CHEST

New Anti-Eosinophil Drugs for Asthma and COPD

Targeting the Trait!

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Asthma and COPD are prevalent chronic inflammatory airway diseases that are responsible for a large global disease burden. Both diseases are complex and heterogeneous, and they are increasingly recognized as overlapping syndromes that may share similar pathophysiologic mechanisms and treatable traits. Eosinophilic airway inflammation is considered the most influential treatable trait of chronic airway disease, and over the last decade, several monoclonal antibodies and small molecule therapies have been developed to target this trait. These include monoclonal antibodies against IL-5 or IL-5 receptor alpha (mepolizumab, reslizumab, and benralizumab), IL-13 (lebrikizumab and tralokinumab), IL-4 receptor alpha (dupilumab), IgE (omalizumab), and anti-thymic stromal lymphopoietin (tezepelumab) and small molecule therapies such as prostaglandin D_2 blockers (fevipiprant and timapiprant). Although these novel biologic agents have shown promising results in many patients with asthma and COPD who have eosinophilic airway inflammation, it is evident that not all patients respond equally well, despite similar clinical, functional, and inflammatory characteristics. This heterogeneity in treatment response is probably related to different molecular pathways or endotypes leading to eosinophilic airway inflammation, including adaptive immune pathways mediated by T helper 2 cells and innate immune pathways mediated by innate lymphoid cells. The relative contribution of these pathways in asthma and COPD is not yet clarified, and there are currently no reliable biomarkers that represent the various pathways. Therefore, there is an urgent need for easily measurable and reproducible biomarkers that are linked to underlying pathophysiologic disease mechanisms and can predict and monitor responses to novel biologic agents.

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Asthma and COPD are prevalent chronic inflammatory airway diseases that are responsible for a large global disease burden.[1] Both asthma and COPD are complex and heterogeneous, and they are increasingly considered as overlapping syndromes that may present with similar symptoms and share similar pathobiologic mechanisms.[2] Due to this complex heterogeneity, the management of asthma and COPD still poses a significant health problem in a large proportion of patients,

ABBREVIATIONS: CRTH2 = chemoattractant receptor-homologous molecules expressed on Th2 cells; FeNO = fraction of exhaled nitric oxide; ILC2 = type 2 innate lymphoid cells; Rα = receptor alpha; Th2 = T helper 2; TSLP = thymic stromal lymphopoietin

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despite the existence of effective treatments. Thus, clinical researchers have proposed deconstruction of chronic airway diseases into individual traits that can be measured and modified ("treatable traits").[3] Instead of using the "one size fits all" approach that is advocated in current guidelines, targeting the key mechanism seems to be more appropriate, particularly in patients who do not respond to the initial treatment recommendation.[4]

Eosinophilic Airway Inflammation: A Principal Trait

Eosinophilic airway inflammation has shown to be one of the most influential traits in chronic airways disease. Stratification of patients according to markers of eosinophilic airway inflammation has led to the identification of patients at risk of adverse outcomes,[5] and treatment guided by markers of eosinophilic airway inflammation has resulted in better health outcomes.[6] However, many patients, in particular adults with severe disease, have persistent eosinophilic airway inflammation.[7] These patients experience frequent exacerbations, and they often depend on the chronic use of oral corticosteroids with associated serious adverse effects.[8] Not surprisingly, targeting eosinophilic airway inflammation has been the basis of recent new drug development. Several anti-eosinophilic drugs are now approved for asthma, and there is increasing evidence of beneficial effects in patients with COPD as well.[9]

The present article discusses the pathobiologic role of eosinophils in asthma and COPD, and the effects of anti-eosinophil drugs in patients for whom no effective and safe treatment has been available previously.

Role of Eosinophils in Asthma and COPD

Eosinophils are granulocytes derived from common myeloid progenitors in the bone marrow. The maturation of eosinophil progenitors depends largely on cytokines such as IL-3, IL-5, and granulocyte macrophage-colony stimulating factor. Of these cytokines, IL-5 is the most critical for eosinophil proliferation, differentiation, and activation.[10] Under normal circumstances, eosinophils constitute only 1% to 2% of the total WBC pool. Their physiologic role is multifaceted and not fully understood. Traditionally regarded as having a homeostatic role in the defense against helminth parasitic infections, these cells are now known to contribute to multiple phases of both innate and adaptive immune responses and tissue repair processes. In eosinophilic lung diseases, including asthma, eosinophils are increased in blood and tissue, with the degree of eosinophilia generally correlating with disease severity.[11] Elevated percentages of eosinophils in sputum and blood from patients with asthma are associated with frequent exacerbations and fixed airflow limitation,[7] and patients who die of asthma exhibit an intense eosinophilic airway infiltrate.[12] However, the most convincing evidence that eosinophils play a critical role in the pathogenesis and severity of asthma comes from studies with anti-eosinophil drugs, showing marked reductions in asthma exacerbations, and sparing of chronic oral corticosteroid use in the subgroup of patients with severe disease.[13]

In COPD, airway inflammation has been shown to be predominantly neutrophilic, but increased percentages of sputum eosinophils can be observed in 30% to 40% of patients with COPD, both during stable periods and acute exacerbations.[14,15] The pathogenetic role of eosinophils in COPD is less clear than in asthma, but it has been shown that increased eosinophil counts in sputum or blood predict a clinical response to inhaled and oral corticosteroids.[14,16] Eosinophilic airway inflammation in COPD is associated with an increased risk of exacerbations,[17] and recent evidence has shown that elevated blood eosinophil counts in severe COPD exacerbations are associated with a $>$ 3-fold increase in readmission rate.[15] In addition, a management strategy that aimed to minimize eosinophilic airway inflammation in patients with COPD has been shown to reduce severe exacerbations by 62%.[18] The definitive answer on the importance of eosinophils in the pathogenesis of COPD has to come from large intervention studies with anti-eosinophil drugs, which are now underway.

Molecular Pathways of Eosinophilic Airway Inflammation

Different molecular pathways may lead to eosinophilic airway inflammation in patients with chronic airways disease (Fig 1).[19,20] Airway epithelial cells exposed to damaging insults such as allergens, viruses, fungi, and pollutants release "alarmin" cytokines (IL-33, IL-25, and thymic stromal lymphopoietin [TSLP]). These alarmins, on the one hand, can initiate an adaptive immune response through dendritic cells that stimulate naive T cells to differentiate into T helper 2 (Th2) cells. Th2 cells produce IL-5, IL-13, and IL-4, the latter driving IgE synthesis by B cells. On the other hand, alarmins can also activate the innate immune system by stimulating type 2 innate lymphoid cells (ILC2), which are also capable of producing large amounts of "type 2"