Biologic Therapy in Chronic Obstructive Pulmonary Disease

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KEYWORDS

• Biologic therapy • COPD • TNF-alpha • IL-5 • Exacerbation

KEY POINTS

- Chronic obstructive pulmonary disease (COPD) has a broader array of mechanisms implicated in its pathogenesis than many other respiratory disorders, including asthma. Accordingly, a broad array of selective biologic agents have been proposed as potential therapies for COPD.
- Antineutrophil approaches have a clear rationale, but the overall experience with strategies that block neutrophil influx and activation has been disappointing. The redundant mechanisms that underlie these critical host defenses may be a partial explanation for these results.
- The more recent understanding of the contribution of eosinophils in COPD, particularly in exacerbation, has raised the possibility that agents that affect eosinophil recruitment and activation may also have a role in COPD, especially in the setting of exacerbation. These studies, although promising, have yet to provide compelling data in support of their use in COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[1] It is a global medical problem with a lifetime risk of development estimated to be around 25%.[2] In developed countries, the biggest risk factor for development of COPD is cigarette smoking, whereas indoor pollutants are the major cause in lower-income, developing nations. The economic burden is large, with attributed costs for hospitalizations, loss of productivity, and disability, in addition to chronic medical care. In the

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United States the estimated direct costs of COPD are $29.5 billion and indirect costs $20.4 billion.[1] Current treatment options are aimed primarily at symptom control with bronchodilation and include long-acting beta agonists and antimuscarinics. Inhaled corticosteroids are indicated in severe COPD (Global initiative for Obstructive Lung Disease (GOLD) stage III and above); however, they are not always effective in controlling symptoms and exacerbations. At present, there are no therapies approved that substantively reduced the inflammatory process and or prevent progression of disease.

The defining characteristic of COPD, chronic airflow limitation, is caused by several mechanisms. Small airway disease is mediated by chronic inflammation leading to airway fibrosis, structural changes, and increased resistance. This process is coupled with parenchymal destruction causing loss of alveolar attachments to the small airways and decrease of lung elastic recoil.[1] Together, these changes diminish the ability of the airway to stay open during expiration, and contribute to dynamic airway collapse. Historically, the inflammation leading to these alterations has been described as type 1 inflammation with neutrophilic predominance; however, recently more evidence has been published about the role of eosinophils in stable COPD.[3] As described in a review by Barnes,[4] inhaled irritants such as cigarette smoke activate airway epithelial cells and macrophages to release tumor necrosis factor (TNF)-α and neutrophil and monocyte chemotactic factors including CC Ligand 2 (CCL2), CXC Ligand 1 (CXCL1), and CXCL8. These mediators attract inflammatory cells, such as Th1 cells, cytotoxic T lymphocytes, and Th17, as well as neutrophils and monocytes, to the site of injury, where they release proteases and other inflammatory mediators and cause elastin degradation leading to emphysema and also increased mucus secretion.[5] The inflammasome also plays a role in the pathogenesis of COPD. Cigarette smoke and microbes can activate pathogen-associated molecular patterns and damage-associated molecular patterns, which activate inflammasomes. This process in turn initiates a cascade of events that result in the recruitment and cleavage of pro–caspase-1 into active caspase-1 molecules, which then mediate the cleavage of pro–interleukin (IL)-1β into its active form IL-1β.[6] IL-1β activates macrophages to secrete inflammatory cytokines and chemokines and the cycle of inflammation and neutrophilic infiltration continues.[4]

Although the role of neutrophilic inflammation is well accepted, emerging evidence suggests a role for eosinophilic or type 2 inflammation in COPD as well. As recently reviewed, eosinophils are recruited to the lung by a multistep process mainly directed by Th2 cytokines.[7] After being released from the bone marrow under the influence of IL-5, eosinophils are directed to the lung via several steps. Lung epithelial cell expression of vascular cell adhesion molecule-1 is induced by local expression of IL-4 and IL-13, which allows for eosinophil binding via VLA-4 and P-selectin. In addition, chemokines, like eotaxin, secreted by airway cells, activate the chemokine receptor CCR3 on eosinophils, further attracting eosinophils into lung tissue. Once present, eosinophil survival in tissue is mediated by local production of IL-5 and granulocyte-macrophage colony-stimulating factor. Release of eosinophilic specific basic proteins, like major basic protein and eosinophilic cationic protein, cause direct injury to lung tissue, and the release of other preformed mediators and proinflammatory cytokines contributes to ongoing inflammation. In addition, IL-33 stimulation of group 2 innate lymphoid cells (ILC2), which are potent producers of IL-5 and IL-13, may contribute to eosinophilic type II inflammation in COPD.[8,9] This article discusses the use of biologic agents to target these inflammatory pathways in the treatment of COPD.