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### **Asthma and COPD: Similarities and Differences**

A simplistic description of pathophysiologic differences between asthma and chronic obstructive pulmonary disease (COPD) portrays asthma characterized by eosinophilic airway inflammation and COPD by neutrophilic airway inflammation. While this is the case as a broad characterization, the picture may be less specific in an individual patient. Airway remodelling and inflammation occur in both asthma and COPD, with differences varying from patient to patient in patterns of inflammation, lung structures affected by inflammatory processes, and the anatomic sites at which airway remodelling occurs.

Differences between asthma and COPD can be characterized by clinical phenotype and inflammatory phenotype:

#### *Clinical Phenotype Differences*

- COPD—FEV<sub>1</sub> decline largely irreversible, airway hyperresponsiveness variable, lung parenchyma damaged or destroyed, response to bronchodilator and inhaled corticosteroid therapy variable.
- Asthma—airflow limitation reversible, airway hyperresponsiveness significant, lung parenchyma unharmed except in some severe asthma in smoking patients, responds well to inhaled corticosteroid therapy.

#### *Inflammatory Phenotype Differences*

- COPD—neutrophils, macrophages, CD8<sup>+</sup> T lymphocytes, eosinophils.
- Asthma—eosinophils, mast cells, CD4<sup>+</sup> T lymphocytes, macrophages.

Expression of many cytokines such as interleukins and tumor necrosis factor-alpha (TNF-alpha) has been identified in airways of both diseases in varying proportion. The varying presence of eosinophils and neutrophils in asthma and COPD is demonstrated in conditions that can be characterized as non-eosinophilic asthma and eosinophilic bronchitis. Perhaps only about 50% of asthma cases are wholly attributable to eosinophilic airway inflammation; neutrophilic inflammation may also be present, possibly induced by factors such as bacterial infection or environmental air pollution.

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Eosinophilic bronchitis has been identified in patients with COPD who had sputum eosinophilia; the presence of eosinophils in bronchitis may be associated with the intensity of the inflammatory process.<sup>1</sup> Overlap in airway eosinophils and neutrophils is observed in exacerbations of both COPD and asthma.<sup>2</sup>

The concept of clear differences between asthma and COPD in reversibility of airflow limitation has been replaced by recognition that a proportion of patients with severe asthma may develop fixed airflow limitation that resembles the irreversible airflow limitation of COPD.

Studies and experience have also demonstrated that acute short-term response to inhaled beta<sub>2</sub>-adrenergic agonists does not reliably differentiate asthma and COPD in spirometric reading alone.<sup>3</sup> Spirometry can reliably assess risk for mortality in both asthma and COPD on the basis of maximum attainable FEV<sub>1</sub>.<sup>4</sup>

Effects of long-term tobacco smoking are clearly seen in COPD and are associated with greater risk of mortality in asthma patients. Decline in lung function also occurs with aging; the greatest and earliest decline is seen in patients with long smoking histories as they age.<sup>5</sup>

Damage to lung parenchyma in COPD and severe asthma is observed and quantified on high-resolution computed tomography (HRCT). Elastase score may be significantly associated with HRCT scan score in both COPD and severe asthma but not in patients with mild asthma.<sup>6</sup> That smoking is pathogenic in both asthma and COPD is demonstrated on HRCT images of smoking and nonsmoking asthma patients.<sup>6</sup>

Tobacco smoking can substantially alter physiologic differences between asthma and COPD. In asthmatic smokers, there may be a continuum of parenchymal damage that can result in emphysemic changes. Smoking may also influence response to inhaled corticosteroid (ICS) therapy in both asthma and COPD.

The presence or nonpresence of asthma in stable COPD can influence response to a trial of ICS.<sup>8</sup> A mechanism of corticosteroid resistance has been proposed for COPD, severe asthma, and asthma in

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smokers.<sup>9</sup> Smoking contributes to disease severity. As disease becomes more severe and use of ICS increases, the pattern of inflammation in asthma and COPD becomes more similar.

A clinical overlap in asthma and COPD has been described as a continuum of what is fundamentally the same condition. This was proposed in 1961 by Dutch investigators and has become known as the Dutch Hypothesis.<sup>10</sup> The investigators based their conclusions on a comparison of natural history, signs, laboratory findings, and treatment response. The Dutch Hypothesis proposes that:

- Various forms of obstructive lung disease have overlapping features; clinical features defining a specific phenotype is suggested by symptoms, presence of allergy, respiratory mechanics, and bronchial hyperresponsiveness (BHR);
- The natural history of asthma and COPD overlap, and one form of obstructive lung disease (asthma) may evolve into another (COPD); and,
- The development of obstructive lung disease is based on inflammation and BHR, endogenous host factors largely hereditary in nature, and modulating exogenous (environmental) factors.

Debate about the Dutch Hypothesis and its components has been ongoing more than 40 years; none of the components of the Dutch Hypothesis has been conclusively disproven.

Guidelines for treatment of asthma and COPD have taken note of overlapping features such as inflammation. Increasing attention has been paid to overlap of inflammatory features of both diseases. BHR is seen in both diseases, and a correlation has been shown between BHR and mortality.<sup>11</sup> Atopy, often a factor in BHR, is associated with accelerated decline in FEV<sub>1</sub>.

In a range of patients with asthma and COPD seen in clinical practice, clinical features such as wheezing, cough with or without sputum production, and airway remodelling may strongly overlap—even in the same patient. Inflammation is the central factor in development of both diseases, and antiinflammatory therapy is most likely to improve symptoms, reduce BHR, improve airway function, and reduce or prevent exacerbations.

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Differentiating asthma from COPD in clinical practice is not necessarily simple and straight-forward. Both are relatively common respiratory conditions with prevalence of about 8.0% in the United States. COPD has a much higher risk for disease-associated mortality. If the physician's focus is not on immediate, acute symptoms, clinical features can be useful in differentiating the diseases. Differentiation can be more difficult when there is overlap of clinical features in an individual patient. Grossly apparent features can strongly suggest a diagnosis—for example, symptomatic airflow limitation in a patient over age 45 with a long smoking history strongly indicates COPD. Age of onset is a major clinical indicator; onset in childhood is indicative of asthma, onset in early adulthood or middle-age is more common in COPD.

Biases that may influence diagnosis include:

- Asthma is regarded as a more treatable disease and more is known about treatments that are effective; more molecular targets have been identified for asthma pharmacotherapy.
- COPD is more likely to be regarded as a disease more common in men than in women, a bias that may shift suspicion toward an erroneous diagnosis.

A trial of bronchodilator therapy may provide some insight for diagnosis; asthma symptoms are usually very responsive to bronchodilator therapy, COPD symptoms to a lesser degree. The primary respiratory complaint also can be indicative; chest tightness and wheeze are dominant complaints in asthma, dyspnea on physical exertion a dominant complaint in COPD. COPD is more likely to have comorbidities—*eg*, cardiovascular disease, muscle weakness, depression/anxiety.

Over a period of time, the COPD patient is likely to be a more frequent user of medical services than an asthma patient—*eg*, emergency department visits, hospitalizations for exacerbations.<sup>12</sup>

The most dependable and most frequently used drugs are the same for asthma and COPD—beta<sub>2</sub>-adrenergic agonists, long-acting beta<sub>2</sub>-adrenergic agonists (LABA), anticholinergics, and ICS. The earlier and more frequent use of ICS has increased as the role of inflammation in both diseases is better understood.

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Even when COPD is correctly diagnosed, treatment may be less effective than results expected for asthma treatment. Few disease-modifying drugs are available for use in COPD, in part because fewer molecular targets for pharmacotherapy have been identified for COPD. The existence of multiple COPD phenotypes has not been well recognized and is not noted in design of clinical trials, even though it has been shown that disease phenotype can influence therapeutic response. Regulatory approval of drugs to treat COPD may be slowed by lack of well-defined endpoints for COPD therapy trials.

A number of new drugs directed at novel molecular targets are under development for treatment of asthma and COPD.

#### *Asthma Drugs in Development*

A number of ultralong acting beta<sub>2</sub>-adrenergic agonists are in development. Indacaterol appears likely to be first, or one of the first to be approved for treatment of asthma.<sup>13,14</sup>

Inflammation-modifying drugs under development include once-daily ICS and LABA/ICS combinations. These drugs may to some degree address the as-yet unmet need of effectively controlling airway inflammation in patients with varying genetic factors, body mass index, and smoking histories. An effective drug should also be effective in treating poorly controlled asthma.

Phosphodiesterase 4 (PDE 4) inhibitors, approved for use in treating other diseases, are under investigation for use in modifying the allergic/inflammatory response in asthma. Criticism that the effect of PDE 4 inhibitors is basically no different from that of theophylline has been addressed by showing that they are uniquely different drugs.<sup>15</sup>

Other agents in development for treating asthma include:

- Calcineurin inhibitors;
- Interleukin-4 inhibitors;

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- Cytokine (TNF-alpha, IL-2) inhibitors; and,
- Regulatory T cell inducers.

### *COPD Drugs in Development*

The number and type of drugs under development to treat COPD are fewer than those in development to treat asthma. COPD is less well characterized and fewer molecular targets are well defined.

Ultra-LABA, long-acting anticholinergics, and combination LABA and long-acting muscarinic antagonists (LAMA) are in development to treat COPD. The PDE 4 inhibitor roflumilast has shown promising results in clinical trial.<sup>16</sup> Treatment with a TNF-alpha has also shown promising results.<sup>17</sup> Other therapeutic strategies in development include IL-8 neutralization with a monoclonal antibody and proteinase inhibition.

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### Standard of Practice

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Asthma and chronic obstructive pulmonary disease (COPD) are obstructive airway diseases frequently seen in clinical practice. While they are defined as distinct and separate entities in common medical usage, a picture of overlapping pathophysiology and clinical features is emerging in medical literature. The most significant pathogenic feature shared by the two diseases is airway inflammation. Treatment of airway inflammation has become a crucial target of asthma and COPD pharmacotherapy.

More is known about asthma than about COPD in terms of macro- and molecular pathophysiology, clinical presentation, and response to pharmacotherapy. Perhaps because COPD is less well understood, it is more likely than asthma to go unrecognized, and to be erroneously treated or under-treated. Misdiagnosis of COPD as asthma is known to occur in clinical practice.

Both asthma and COPD are chronic diseases that require treatment as such, with appropriate attention to prevention and management of acute symptoms. The clinical course of the diseases is very different over the long term. Unlike asthma, COPD is a relentlessly progressive disease with increasing risk for mortality as lung function irreversibly declines.

Pharmacotherapy for the two diseases relies upon the same drugs—beta<sub>2</sub>-adrenergic agonists, acetylcholine, and inhaled corticosteroids—with different patterns of use in various stages of disease. Because long-term inhaled tobacco smoke is identified as the most important cause of COPD, smoking cessation is regarded as essential to treatment of COPD. While smoking cessation does not reverse airflow obstruction, it can contribute importantly to slowing the progressive decline of lung function.

A long-standing hypothesis proposes that asthma and COPD are not separate entities, but are rather somewhat different presentations of obstructive lung disease with an inflammatory diathesis. While debate about this hypothesis goes on, the basic premise of commonality of pathophysiology may help clinicians better understand rationale for effective therapy.