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Inflammation in COPD: Implications for Management

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is recognized by the Global Initiative for Chronic Obstructive Lung Disease guidelines as an inflammatory disease state, and treatment rationales are provided accordingly. However, not all physicians follow or are even aware of these guidelines. Research has shown that COPD inflammation involves multiple inflammatory cells and mediators and the underlying pathology differs from asthma inflammation. For these reasons, therapeutic agents that are effective in asthma patients may not be optimal in COPD patients. COPD exacerbations are intensified inflammatory events compared with stable COPD. The clinical and systemic consequences believed to result from the chronic inflammation observed in COPD suggest that inflammation intensity is a key factor in COPD and exacerbation severity and frequency. Although inhaled corticosteroids are commonly used and are essential in asthma management, their efficacy in COPD is limited, with only a modest effect at reducing exacerbations. The importance of inflammation in COPD needs to be better understood by clinicians, and the differences in inflammation in COPD versus asthma should be considered carefully to optimize the use of anti-inflammatory agents.
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Chronic obstructive pulmonary disease (COPD) is a health problem of global importance and rising prevalence. COPD results in approximately 5% of total deaths worldwide, is the fourth leading cause of death in the world,[1] and is expected to become third by 2020.[2] In fact, chronic diseases of the lower respiratory tract, including COPD, are already reported as the third leading cause of death in the US.[3]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles or gases.[4] Although cigarette smoke is the most common risk factor for COPD development, the role of biomass smoke exposure in causing COPD is increasingly appreciated.[4] COPD can be complicated by frequent exacerbations, defined as acute events characterized by respiratory symptom worsening that is beyond normal day-to-day variations and that may lead to a change in medication.[4] The inflammation seen in stable COPD changes and is enhanced during exacerbations. Like COPD, asthma also is characterized by inflammation and airflow limitation.[5] While inflammatory patterns in COPD and asthma differ, to date those differences are not diagnostic.

Because most COPD patients are treated in primary care settings,[6] COPD management imposes a large burden on primary care physicians and other clinicians. Several guidelines assist with COPD diagnosis and management (eg, GOLD, American Thoracic Society/European Respiratory Society, and International Primary Care Respiratory Group guidelines).[4,7,8] While such publications define COPD as an inflammatory disease, there are no specific recommendations on the assessment and targets for reduction in inflammation, as these are not established. Nevertheless, inflammation control is the rationale behind the use of some medications for both COPD and asthma, and a clear under-

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standing of current concepts is key to appropriate pharmacotherapy in these disorders.

This article will describe the characteristics and impact of lung inflammation in stable COPD and COPD exacerbations, correlating inflammation with clinical outcomes. In addition, the differences and similarities in inflammatory mechanisms in COPD and asthma will be highlighted to facilitate understanding of the rational use of anti-inflammatory agents in each condition.

CLINICAL SIGNIFICANCE

- Chronic obstructive pulmonary disease (COPD) is an inflammatory disease, and lung and systemic inflammation intensifies during most COPD exacerbations.
- The characteristics of lung inflammation in COPD differ from lung inflammation in asthma, impacting treatment decisions.
- Anti-inflammatory therapy is not currently first-line COPD therapy and requires careful consideration to optimize the use of anti-inflammatory agents in COPD.

INFLAMMATION IN COPD

Stable Disease

Chronic inflammation in the small airways and lung parenchyma of COPD patients has been demonstrated by tissue biopsies, sputum analyses, and postmortem samples.[9-11] In COPD, repeated exposure to noxious particles, usually tobacco smoke, can trigger a distinct inflammatory cascade (**Figure**)[5,12] in the small airways and lung parenchyma involving several different cell types (eg, neutrophils, macrophages, lymphocytes) and inflammatory mediators (eg, growth factors, cytokines, chemokines, proteinases) (**Table 1**).[5,13,14] Increased lung proteinase production and alveolar septal cell apoptosis together lead to destruction of alveolar structures (emphysema). Proteinases also promote mucus hypersecretion by increasing goblet cell numbers and causing enlargement of the large airway submucosal glands. Connective tissue deposition around the small airways leads to narrowing of the small airway walls (obstructive bronchiolitis).[5,15]

COPD progression is associated with increasing neutrophil numbers in the conducting airway lumen and perhaps in the airway walls.[16] Macrophages are elevated in the small airways and parenchyma, correlating directly with emphysema severity. CD8+ lymphocytes are found in the airway walls of emphysematous areas and in large and small airways and peripheral smooth muscle.[16] In COPD, inflammatory cell activation changes levels of growth factors, cytokines, metalloproteinases, and serine proteinases. These changes are believed to lead to mucus hypersecretion, extracellular matrix degradation (especially degradation of lung elastin), and injury to alveolar epithelial cells, leading to emphysematous changes. Small airway narrowing results from fibroblast activation and proliferation in the small airways, leading to collagen deposition. CD8+ lymphocytes may contribute to emphysema by releasing ligands that activate macrophages and by releasing perforins and granzymes that may damage lung epithelial cells.[16] Although smoking cessation slows COPD progression, inflammation persists despite removal of the noxious irritants.[17]

Exacerbations

COPD exacerbations represent a further amplification of the inflammatory process in the lung. Exacerbations are triggered by one or more of bacterial infections, viral infections, or environmental pollutants,[18] although in one third of severe exacerbations, no trigger is identifiable.[4] Pulmonary embolism also may contribute to exacerbations, as approximately 25% of patients hospitalized for an acute exacerbation of COPD may have a pulmonary embolism.[19] Compared with patients who experience exacerbations infrequently, those who experience frequent exacerbations have increased inflammation during stable disease, suggesting a correlation between inflammation levels and exacerbation frequency.[20] However, there is considerable overlap in the severity of inflammatory measures, limiting the current use of inflammation as a biomarker to identify individuals with frequent exacerbations. Augmented inflammatory responses during COPD exacerbations result in cascades of increased lung inflammatory cell numbers and inflammatory cell mediator release, enhancing the pathological process associated with lung function loss (**Table 1**).[5,18] Neutrophils, lymphocytes, and eosinophils are increased in the airways during exacerbations.[21] Inflammatory mediators such as neutrophil chemoattractants (interleukin [IL]-8 and leukotriene-B4), neutrophil degranulation products (including myeloperoxidase), systemic inflammation markers (IL-6 and C-reactive protein [CRP]), and chemokines (eotaxin and regulated upon activation, normal T-cell expressed, and secreted [RANTES]) are increased compared with stable COPD,[22,23] and imbalances occur between proteinase and proteinase inhibitors.[24]

Eosinophilic inflammation seems to be characteristic of viral exacerbations, whereas neutrophils and neutrophil-derived mediators are noted with both viral and bacterial exacerbations.[25,26] Exacerbations associated with bacterial strains new to the patient correspond to more intense airway and systemic inflammation compared with those associated with preexisting strains and nonbacterial episodes.[26] Exacerbations associated with preexisting strains of bacteria have an inflammatory profile similar to pathogen-negative exacerbations, suggesting that preexisting bacterial strains were not the causative agents.

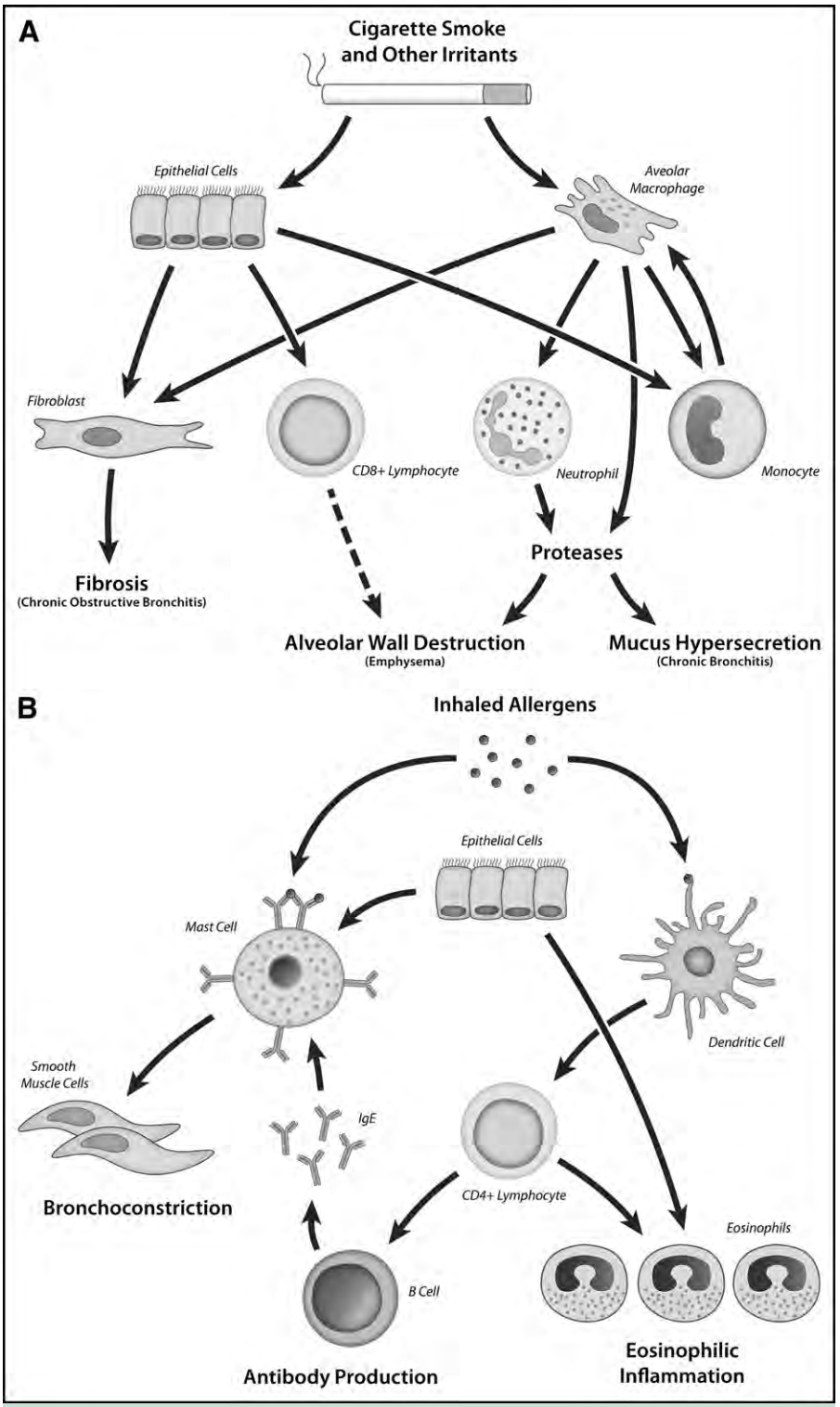

Figure (**A**) Inflammatory cascade of chronic obstructive pulmonary disease (COPD). Adapted with permission from the American College of Chest Physicians.[12] (**B**) Inflammatory cascade of asthma. Adapted by permission from Macmillan Publishers Ltd: *Nature Reviews Immunology*, 2008.[5]

Table 1 Comparison between Patterns of Inflammation in Asthma and COPD

	Asthma			COPD		
	Mild	Severe	Exacerbation	Mild	Severe	Exacerbation
Neutrophils	0	++	++++	++	+++	++++
Eosinophils	+	++	+++	0	0	+
Mast cells	++	+++	+++?	0	0	?
Macrophages	+	+	?	+++	++++	++++
T cells	T_H2 cells: ++ iNKT cells: ?	T_H1 cells: + T_H2 cells: + T_C1 cells: + T_C2 cells: +? T_H17 cells: ?	?	T_C1 cells: +	T_H1 cells: + T_C1 cells: + T_H17 cells: ?	?
B cells	IgE producing	IgE producing	?	+	+++	?
Dendritic cells	+	?	?	+?	+?	?
Chemokines	CCL11: +	CXCL8: +	CXCL8: ++	CXCL8: + CXCL1: + CCL2: +	CXCL8: ++	CXCL8: +++
Cytokines	IL-4: ++ IL-5: ++ IL-13: ++	TNF: ++	?	TNF: +	TNF: ++	TNF: +++
Lipid mediators	LTD_4: ++ PGD_2: +	LTB_4: ++ PGD_2: +	?	LTB_4: +	LTB_4: ++	LTB_4: +++
Oxidative stress	0	++	+++	++	+++	++++
Steroid response	++++	++	+	0	0	0

0 = no response; + to ++++ = magnitude scale; ? = uncertain; CCL = CC-chemokine ligand; COPD = chronic obstructive pulmonary disease; CXCL = CXC-chemokine ligand; IL = interleukin; iNKT = invariant natural killer T; LTB_4 = leukotriene B_4; LTD_4 = leukotriene D_4; PGD2 = prostaglandin D2; T_C = cytotoxic T; T_H = T helper; TNF = tumor necrosis factor.

Adapted by permission of Macmillan Publishers Ltd: *Nature Reviews Immunology*, 2008.[5]

DIFFERENCES IN INFLAMMATION BETWEEN COPD AND ASTHMA

Stable Disease

Both COPD and asthma involve bronchial inflammation and airflow limitation; however, inflammatory processes of these diseases differ (**Table 1**, **Figure**).[5,12] In the tracheobronchial lumen of COPD patients, neutrophils are increased substantially over macrophages, while in asthma patients, the characteristic inflammatory process involves eosinophils. In most COPD patients, eosinophils are not prominent, except when experiencing an exacerbation or with concomitant asthma.[15] Furthermore, COPD or asthma severity is associated with different predominant types of inflammatory cells and levels of inflammatory mediators (**Table 1**) and therefore, different treatments may be needed.[27,28]

The differing inflammatory patterns between COPD and asthma result in dissimilar consequences and disease characteristics. In COPD, chronic inflammation results in lung parenchymal destruction and contributes to small/peripheral airway narrowing, causing progressive airflow obstruction that is not fully reversible.[29] In asthma, chronic inflammation is associated with basement membrane thickening and increased smooth muscle mass predominantly in the central/large airways, causing intermittent and reversible airflow obstruction.[29,30] Asthma may, however, lead to fixed airflow limitation, which may be due to small airway disease, and the basement membrane thickening may not reverse when remission is induced with anti-inflammatory therapy.[31] The role of inflammation in fixed airflow limitation in asthma is less well understood than in COPD.

In some cases, differences in inflammatory patterns between asthma and COPD are less distinct. While airway remodeling processes in asthma and COPD may be mechanistically different, some asthma patients also may have remodeling in the small airways, like in COPD.[29] Further, in cases of severe asthma (~5%-10% of asthmatics[32]) and asthmatic patients who smoke (>20% of asthmatics[33]), relative and absolute neutrophil counts are elevated compared with control subjects and mild asthmatics, and cell counts begin to resemble those seen in stable COPD.[10,27,34,35] In contrast, some COPD patients without an asthma history have sputum eosinophilia, suggesting that some eosinophilic bronchitis patients may develop the fixed airflow obstruction that is characteristic of COPD.[36]

Exacerbations

In both COPD and asthma, patients experience exacerbations in which elevated levels of inflammatory cells and mediators are often present in the airways.[5] Asthma exacerbations are usually triggered by viral respiratory tract infections, inhaled allergens, or air pollutants, while COPD exacerbations are usually triggered by bacterial or viral

infections. As previously stated, COPD inflammatory processes are mostly neutrophilic, while those in asthma are eosinophilic. However, during virally induced exacerbations, inflammation patterns can be similar between diseases, with increased eosinophil or neutrophil counts in either COPD or asthma.[5,25,37]

CLINICAL MANIFESTATIONS OF COPD AND INFLAMMATION

Stable COPD

Clinical and systemic consequences are believed to result from chronic inflammation in the lungs of COPD patients. Although conclusive longitudinal studies have not been performed, cross-sectional studies have correlated inflammation and COPD severity. For instance, lung function decline has been linked to increased inflammatory markers such as sputum neutrophils, myeloperoxidase levels, fibrinogen, and CRP.[38] Airway inflammatory cells (eg, neutrophils, macrophages, lymphocytes) and also inflammatory markers (eg, IL-8 and serum tumor necrosis factor alpha [TNF-α] and CRP levels) increase with increasing COPD severity. These results and other studies indicate that persistent systemic inflammation is present in COPD patients and suggest links between persistent systemic inflammation seen in COPD and comorbidities commonly seen with COPD, such as cardiovascular (atherosclerotic) disease, diabetes, cachexia, and osteoporosis. The fact that systemic inflammation also is observed in these comorbidities suggests clinical overlap among COPD and its comorbidities.

Exacerbations of COPD

Cross-sectional studies also correlate airway inflammation markers and exacerbation severity and risk. Exacerbation-related changes in airway inflammation markers such as sputum IL-8 and IL-6 are inversely correlated with pre-exacerbation lung function, indicating that acute inflammatory response intensity during an exacerbation is related to the lung function level found in stable disease.[39] Furthermore, baseline IL-8 and IL-6 levels were greater in frequent exacerbators compared with infrequent exacerbators.[20,39,40] Changes in airway inflammatory markers (eg, sputum IL-8, TNF-α, sputum neutrophil elastase, serum CRP) also were related to exacerbation severity as determined by clinical signs and symptoms.[26] Additionally, a relationship between systemic inflammation and exacerbation risk is evident.[41,42] Patients with concurrent COPD and metabolic syndrome exhibit greater systemic inflammation (increased CRP), more exacerbations, and longer exacerbation-related hospitalizations compared with COPD patients without metabolic syndrome.[43]

Finally, markers of systemic inflammation (eg, plasma IL-6 and IL-8 and serum IL-5 receptor, CRP, TNF-α, and neutrophil elastase) also correlate with improvements in clinical status, symptoms, and lung function after exacerbations.[26,44-46] Although recovery time is not different between individuals with frequent exacerbations and those with infrequent exacerbations, persistently elevated systemic inflammation markers (sputum IL-8, serum TNF-α, neutrophil elastase, serum CRP) are characteristic of those with frequent exacerbations, and correlate with shorter time-to-onset for subsequent exacerbations.[26,44] Likewise, greater airway inflammation in the form of sputum IL-6 and IL-8 correlates with longer recovery times.[44] These data suggest that inflammation intensity is a key factor in COPD and exacerbation severity.

TREATMENT OF INFLAMMATION IN COPD

Currently Available Drugs for Stable COPD

Goals for successful COPD management include immediately relieving and reducing symptom burden and the risk of adverse health events (eg, exacerbations) that may affect patients in the future.[4] Drugs approved by the US Food and Drug Administration (FDA) for use in COPD include theophylline; the long-acting muscarinic antagonist (LAMA) tiotropium; long-acting beta-2 agonists (LABAs) formoterol, arformoterol, salmeterol, and indacaterol; LABA/inhaled corticosteroid (ICS) combinations salmeterol/fluticasone and formoterol/budesonide; and the phosphodiesterase-4 (PDE4) inhibitor roflumilast. Several of these medications, including others that have not been approved by the FDA for this purpose, have been demonstrated to reduce exacerbations (**Table 2**).[4,47]

Bronchodilators are first-line therapy in COPD. LAMAs and LABAs are central to symptomatic COPD management[4] by improving lung function and quality of life and reducing exacerbations.[48,49] In vitro and animal research has shown that both LAMAs[50-55] and LABAs[52,56-62] may have anti-inflammatory properties, but the clinical significance of these observations has not been established.

While ICSs are highly effective and central to asthma management, their efficacy is limited in most COPD patients[63] and their use in COPD is as add-on therapy to long-acting bronchodilators.[4] Clinical studies have shown that ICS use may be associated with increased risk of adverse effects such as hoarseness, candidiasis, or pneumonia.[64-67] The TORCH (Towards a Revolution in COPD Health) trial demonstrated that ICS treatment slowed lung function decline over 3 years compared with placebo, an effect that was comparable with that of salmeterol in COPD patients.[68] A number of other studies, but not all, have demonstrated similar effects which are supported by meta-analyses;[69,70] however, the clinical importance of these effects remains uncertain. In one study, ICS therapy decreased inflammation and attenuated lung function decline in steroid-naïve patients with moderate-to-severe COPD;[71] in another study, ICS therapy reduced some inflammatory markers (eg, CD8:CD4 cell ratio) but did not alter levels of key COPD-related inflammatory cells (eg, CD8+ cells, neutrophils).[72]

Anti-inflammatory ICS effects in COPD are not as robust as observed in asthma.[73] The poorer ICS efficacy in COPD

Table 2 Treatments to Reduce Exacerbations in COPD

Class of Agent	Evidence[4,47]	FDA Approval	Anti-inflammatory Actions in COPD
LABA/ICS	Multiple PCTs	Yes	Possible
LAMA	Multiple PCTs	Yes	Possible
PDE4 inhibitor	Multiple PCTs	Yes	Possible
Macrolide antibiotic (low-dose continuous regimen)	Multiple PCTs	No	Possible
Fluoroquinolone antibiotic (intermittent regimen)	One PCT	No	Unknown
Statin	One retrospective cohort study	No	Possible
Mucolytic	Multiple PCTs	No	Possible

COPD = chronic obstructive pulmonary disease; FDA = Food and Drug Administration; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic antagonist; PCT = placebo-controlled trial; PDE4 = phosphodiesterase-4.

may be due to active steroid resistance caused by reduced levels of histone deacetylase-2 (HDAC2),[74] a nuclear enzyme involved in corticosteroid deactivation of pro-inflammatory genes. Reduced HDAC2 levels are thought to result from *HDAC2* gene inactivation by oxidants in cigarette smoke. This corticosteroid resistance can persist in COPD patients, because HDAC2 levels are as low in ex-smokers as in current smokers.[74] The steroid resistance theory in COPD is supported by studies showing that steroid treatment alone does not substantially reduce inflammation in COPD patients.[75-78] Furthermore, the addition of low-dose theophylline (an activator of HDAC2) to ICS may improve the anti-inflammatory properties of ICS in COPD, although the clinical relevance of this effect is still unknown.[79,80] While the hallmark of asthma treatment is ICS use to reduce eosinophilic inflammation,[81] ICSs appear to be largely ineffective in reducing neutrophilic and peripheral lung inflammation associated with stable COPD.[65,82] Instead, COPD treatment algorithms recommend ICS treatment combined with long-acting bronchodilators, and only in patients with severe COPD or frequent exacerbations.[7,83] Such combination therapy is more effective than the individual components in reducing exacerbations and improving lung function and health status in COPD patients,[84] and the combination of salmeterol/fluticasone propionate also can reduce inflammatory cell numbers (eg, CD8+ cells, neutrophils, CD4+ cells, eosinophils) in current and former smokers with COPD.[85]

Many cells involved in COPD pathogenesis express PDE4, and its inhibition can have anti-inflammatory effects in these cells. Additionally, studies of smoke-exposed mice show that PDE4 inhibitors such as roflumilast limit smoke-induced lung inflammation and destruction.[86] Roflumilast, when added to bronchodilator therapy, reduces the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[87]

Emerging Therapies

Several drugs with anti-inflammatory actions in stable COPD are emerging, such as anticytokine and antichemokine agents. A pilot study in COPD patients of ABX-IL8, a monoclonal antibody against IL-8, demonstrated reduced dyspnea, suggesting anti-inflammatory effects.[88] As the cytokine TNF-α is integral to the inflammatory process, a therapy targeting TNF-α was assessed as an attractive option in COPD.[89] Etanercept, a soluble TNF-α receptor that blocks soluble and cell-bound TNF-α, reduced hospitalization rates in COPD patients.[90] However, the anti-TNF-α antibody infliximab did not improve quality of life, exercise tolerance, or exacerbations in COPD patients, and showed a trend towards more cases of cancer and pneumonia.[47] Thus, more research is needed to develop therapeutic agents targeted towards specific inflammatory targets.

PERCEPTION OF INFLAMMATION IN COPD AND IMPACT ON PRACTICE PATTERNS

In addition to making recommendations for COPD diagnosis and management, the GOLD guidelines define COPD as a disease that is associated with an enhanced inflammatory response.[4] However, many physicians are not aware of these guidelines,[91,92] and thus may not be familiar with the COPD-specific characteristics of this inflammatory response. It is important for primary care physicians to understand that the inflammatory processes and components differ in COPD and asthma in order to optimize COPD patient treatment.

One problem faced by physicians is differentiating COPD from asthma, with under-recognition of the different inflammatory cells and mediators involved in both diseases. This can lead to treatment with drugs that are approved for use in both asthma and COPD, but that may not provide the maximal benefit achievable for the COPD patient. Research has shown that, when treatment was chosen, 32% of primary care physicians preferred to use ICS for patients with subtle symptoms and spirometry-confirmed mild COPD.[93] This is in direct opposition to GOLD guidelines, which recommend ICS treatment only in combination with long-acting bronchodilators and only in COPD patients with severe disease or frequent exacerbations.[83] The development of anti-inflammatory drugs specific to the COPD inflammatory processes will make it increasingly important

to distinguish between asthma and COPD inflammatory processes.

CONCLUSIONS

In COPD patients with severe airflow obstruction, significant symptoms, or frequent exacerbations, anti-inflammatory therapy is often indicated and recommended in current guidelines.[4] Although some inflammatory characteristics in COPD overlap with those seen in asthma, their underlying inflammatory patterns differ, and each disease responds differently to anti-inflammatory therapy. A clearer understanding of these differences will allow practitioners to choose the optimal therapy for each condition. Because frequent exacerbations can adversely affect health-related quality of life in COPD, it is essential for clinicians to also understand the importance of successful therapies that reduce exacerbation risk and slow disease progression. There are currently a number of effective treatment options for stable COPD that provide meaningful improvements, and new drugs are on the horizon.[94] Research into inflammatory pathophysiology will likely lead to the development of new and more targeted therapies for treating COPD.

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