Management of Inflammation in Chronic Obstructive Pulmonary Disease-Update

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Abstract:
Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory condition, the earliest manifestation of which is airway obstruction which is only partially reversible and the treatment rationales are provided accordingly. 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. Current COPD management focuses predominantly on symptom relief by optimizing bronchodilatation. The role of phosphodiesterase type 4 inhibitors (PDE4), statins, angiotensin converting enzyme inhibitors, theophylline and tumor necrosis factor inhibitors in COPD management will be reviewed. Targeting COPD inflammation with the goal of reducing exacerbations is a major focus of current clinical practice & outcome research.

Key words: COPD, GOLD, Spirometry, Roflumilast, Bronchodilators.

Introduction:
Chronic obstructive pulmonary disease is a major cause of morbidity and mortality throughout the world. An estimated three million deaths worldwide in 2005 were attributed to chronic obstructive pulmonary disease (COPD)¹. Studies have predicted that COPD will jump from the sixth to the third most common cause of death and morbidity worldwide between 1990 and 2020²,³. Cigarette smoking is by far the most common cause of COPD. However, other factors like extended exposure to air pollution and a hereditary deficiency of the anti-protease alpha -1 antitrypsin also contribute to the reduced lung function. COPD can be exacerbated by respiratory infections and is often associated with various comorbid conditions, including heart disease and lung cancer⁴,⁵. Much has been learned about COPD since the Global Initiative for Chronic Obstructive Lung Disease (GOLD) issued its first report, Global Strategy for the Diagnosis, Management and Prevention of COPD in 2001. Optimal management of COPD is crucial, as the costs incurred from this illness by society can be significant⁶. COPD is manifested by the presence of airflow limitation and systemic manifestations. Two different schools of thought relating to association of COPD found in the literature. One group thinks that a systemic spillover of inflammatory events occurring in the lungs is thought to happen in systemic manifestations. Another group believes that the effects represent a systemic inflammatory state as a part of common inflammatory genotype²,³,⁹. The disease impact can be minimized with smoking cessation, regular physical activity and available medications.
Inflammation in Chronic Obstructive Pulmonary Disease

Patients with stable COPD have evidence of systemic inflammation, particularly when the disease is severe or during exacerbation. This is characterized by elevated circulating pro-inflammatory cytokines, acute phase reactants, and increased number of immune cells. These components of inflammation can account for systemic manifestations of COPD and exacerbate comorbid conditions. Moreover systemic inflammation has been associated with a greater decline in lung function. Cytokines are small-signaling protein molecules secreted by immune cells. Interleukin-6 (IL-6) and plasma tumor necrosis factor (TNF) are increased in COPD, particularly during exacerbation. Elevated IL-6 induces the release of acute phase reactants from the liver cell and may account for the increase in C-reactive protein (CRP) found in patients with COPD. Increased CRP levels have been associated with decreased lung function, increase disease severity and increased hospitalization. Fibrinogen, another acute reactant that is synthesized in the liver in response to IL-6 has been found to be elevated in patients with COPD. Increased CRP levels have been associated with decreased lung function, increase disease severity and increased hospitalization. Leucocytes and platelets are also released from bone marrow. A link between persistent pulmonary low-grade inflammation and many comorbidities have been suggested, including deconditioning anaemia, cardiovascular disease and osteoporosis. To manage this inflammation two different therapeutic management schemes may be required, one targeting disease in the lungs while other focuses on the systemic inflammatory state.

Diagnosis and Staging of Chronic Obstructive Pulmonary Disease

An important issue in the treatment of COPD is early diagnosis. COPD has a long subclinical phase leading to underdiagnosis and therefore delayed treatment. Considering that various studies have demonstrated the potential long term benefit of early intervention. A detailed assessment of smoking history and symptoms including dyspnoea, limitation of physical activity due to breathlessness, and chronic cough or sputum production, should lead to the suspicion of COPD. Once the disease is suspected, spirometry is essential for confirmation by demonstrating airflow limitation i.e. a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) that is not fully.

Chronic Obstructive Pulmonary Disease Remains Underdiagnosed

Underdiagnosis of COPD may be the result of a number of problems. Factors contributing to the underdiagnosis of chronic obstructive pulmonary disease are.

* Many patients with chronic obstructive pulmonary disease do not present to their primary care physician until their symptoms are severe and they have moderately advanced airflow obstruction

* Patients adopt their lifestyle and physical activity to minimize their symptoms

* Spirometry remains underutilized in the primary care setting.

Pharmacologic Therapies for Chronic Obstructive Pulmonary Disease

Pharmacologic therapy is used to reduce symptoms, reduce the frequency and severity of exacerbation, improve health status and exercise tolerance, and also reduce the lung function decline. Each treatment regimen needs to be patient-specific as the relationship between the severity of symptoms and the severity of airflow limitation is influenced by other factors, such as the frequency and severity of exacerbations, the presence of respiratory failure, co-morbidities and general health status. Very few agents in the COPD therapy focus on decreasing the systemic inflammation seen in the chronic lung condition. This may explain why some patients with COPD continue to progression of disease and recurrent exacerbation despite optimal treatment with standard therapy. Therefore new therapeutic approaches are of increasing interest. Potential therapies targeting the inflammatory component of COPD will be discussed.
Corticosteroids

Oral corticosteroids are potent, relatively non-specific anti-inflammatory agents that are commonly used to treat acute exacerbation of COPD. Calverly et al have shown that treatment with oral corticosteroids decrease the time to resolution of exacerbation & relapse rate\textsuperscript{24}. However, oral corticosteroids are associated with many side effects, and maintenance oral steroid therapy has been associated with increased mortality rates in patients with COPD\textsuperscript{24}.

Inhaled corticosteroids (ICS) have been shown to be beneficial in the treatment of COPD owing to the weaker corticosteroid-sensitive pattern of inflammation\textsuperscript{25}. ICS reduce CRP & IL-6, inhibit the expression of certain inflammatory genes, leading to reduction of cytokine levels\textsuperscript{26}. Several placebo-controls have shown that it reduces the rate of COPD exacerbation by approximately 25%\textsuperscript{27}.

ICS when combined with long-beta agonists (LABA) have greater effect\textsuperscript{28,29,30}. In the TORCH trial, combination therapy reduced the rate of lung function decline, and delayed and reduced the numbers of exacerbations in patients, particularly those with moderate to severe COPD. However, there is no difference in mortality\textsuperscript{31}. Therefore ICS immunotherapy is generally not recommended as a part of COPD management, but rather used in combination with LABAs in symptomatic patients with moderate to severe COPD and frequent exacerbations\textsuperscript{32,33}. Despite recommendations from various authorities, studies have failed to demonstrate that ICS suppress inflammation, particularly in patients with COPD\textsuperscript{34}. A randomized placebo-controlled, multicenter clinical trial that involving 11 centers in Canada failed to demonstrate any significant effect of ICS or combination therapy on systemic levels of CRP or IL-6 in patients with COPD. However, it showed a significant reduction in surfactant protein D levels and improved health status and lung function in patients with moderate to severe COPD over a four week period\textsuperscript{35}. Studies have also failed to demonstrate that a ICS-LABA combination has any significant effect on neutrophilic inflammation of COPD patients\textsuperscript{36,37}.

Selective Phosphodiesterase-4 Inhibitors

GOLD recently added roflumilast, a selective PDE4 inhibitor, to its latest international treatment guidelines for COPD\textsuperscript{38}. This once daily active therapy is recommended for patients with severe COPD or very severe COPD and history of exacerbations and chronic bronchitis\textsuperscript{38}. Selective PDE4 inhibitors act as anti-inflammatory agents and have the ability to suppress the release of inflammatory mediators implicated in COPD\textsuperscript{39,40}. Roflumilast also significantly reduces sputum neutrophil and eosinophil counts by 35.5 % and 50.0 % respectively compared with placebo\textsuperscript{40}. Therefore, PDE4 inhibitors may present significant advantage over other drugs that primarily target single mediators or singe biochemical pathways.

PDE4 acts to degrade c-AMP, a secondary messenger involved in pro-inflammatory mediators. One of the principal effects of PDE4 inhibitors is their ability to increase c-AMP levels, subsequently activating protein kinase A. This in turn phosphorylates proteins, thereby inhibiting many inflammatory cells\textsuperscript{41}. PDE4 inhibitors have been shown to target three important components of COPD: airway obstruction, inflammation & structural changes\textsuperscript{34}.

Millis et al conducted a multiple treatment meta-analysis to determine the relative effectiveness of LABAS, long acting anti-cholinergics (LAACs), PDE4 inhibitors, and ICS in various combinations in reducing the rate of COPD exacerbations. Adding roflumilast to LAACs had the most significant effects and the highest probability of being the best first-line treatment\textsuperscript{42}. Roflumilast may cause gastrointestinal symptoms, weight loss and to a lesser extent headache and increased patient withdrawal\textsuperscript{43}. In an attempt to administer relatively high doses of PDE4 inhibitors to the lungs while reducing the potential for systemic side effects, inhaled PDE4 inhibitors are currently being developed\textsuperscript{44}. Overall, roflumilast is considered safe and relatively well tolerated.

HMG-CoA Reductase Inhibitors

Statins, 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-Coa) reductase inhibitors, are commonly used as cholesterol-lowering drugs and have been shown to decrease cardiovascular mortality\textsuperscript{45}. Statins having anti-inflammatory and antioxidant properties have been found to be effective in management of COPD. Statins act by inhibiting mevalonic acid in alveolar
It also reduces neutrophil migration, cytokine production, adverse matrix remodeling, small airways inflammation, and apoptosis. As such in neutrophil mediated COPD, statins attenuate persistent neutrophilic inflammation by reducing recruitment &/or activation of inflammatory cells in the lungs. Statins reduced both cardiovascular and respiratory mortality seen in retrospective study. Patients of COPD with high CRP levels may benefit from statin treatment seen in studies. It is remarkable that the mortality benefit seen in patients with COPD on statins appears to be greater than that seen with ICS or ICS-LABA combinations.

Angiotensin-converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB)

It is widely accepted that ACEI have a significant therapeutic effect on major cardiovascular diseases. Inhibition of the renin-angiotensin system produces anti-inflammatory effect in patients with COPD. Anti-inflammatory effect causes reduction in pro-inflammatory genes and other pro-inflammatory substances in patients with COPD. This effect leads to significant immune-modulatory effects, resulting in reduction of systemic cytokine levels. This lower ACE activity has been shown to improve pulmonary haemodynamic variables, reduce hypoxic pulmonary hypertension and pulmonary vascular remodeling. Moreover ARB has been shown to significantly reduce hyperinflation in patients with COPD by an unknown mechanism.

Theophylline

Although theophylline has been used in the management of patients with COPD, its exact mechanism of action in the airway is still unclear. Theophylline is a weak bronchodilator with some anti-inflammatory properties. It is unclear whether this anti-inflammatory effects influence the systemic inflammation in COPD. Theophylline has been shown to non-selectively inhibit several PDE isoforms in the airways. Randomized controlled studies have shown that theophylline alone or in addition to bronchodilators and corticosteroids improves respiratory function, dyspnoea and exercise tolerance in patients with severe COPD.

Tumor Necrosis Factor-alpha Inhibitors

Studies have shown that patients with COPD have increased levels of TNF-alpha in their sputum, especially during acute exacerbations. The levels are also elevated in the plasma, possibly due to an overspill from the inflamed lung. The increase in systemic TNF-alpha has also been implicated in cachexia and skeletal muscle wasting in patients with severe COPD. It has been postulated that inhibiting TNF-alpha may be beneficial in reducing inflammation. Hence studies have evaluated the effectiveness of specific TNF-alpha inhibitor in patients with COPD. Surprisingly, TNF-alpha inhibitors have not been shown to significantly benefit patients with moderate to severe COPD in the short term. Again, there were no improvements in symptom score, lung function, exercise capacity, dyspnoea and acute exacerbations over two years. However, an observational study suggests that etanercept, systemic monoclonal antibody, may reduce COPD hospital admissions. Lack of significant benefit from TNF agents may be explained by the fact that COPD is a highly complex inflammatory disease with many other cytokines and mediators. So more long-term trials are required to clearly identify or dismiss the effect of TNF-alpha inhibitors on COPD.

Conclusion

COPD is a disease resulting from abnormal inflammatory response of the lungs to irritant particles and gases. The disease is marked by airflow limitation as well as systemic inflammation. Once COPD has been diagnosed, current effective management should be based on an individualized assessment of current symptoms and future risks with a goal to relieve symptoms, improve exercise tolerance, improve health status, prevent disease exacerbation, prevent and treat exacerbations and reduce mortality. Despite evidence that there may be an exaggerated decline in patients with higher inflammatory markers, current treatment approach may not target the inflammation in COPD. Although patients on ICS & LABAs have shown clinical improvement and reduction of exacerbation rates, this treatment has failed to show any mortality benefit. Further studies demonstrate there is little reduction in inflammatory markers with this treatment. Selective PDE4 inhibitors decrease inflammation by inhibiting many inflammatory cells. These agents show promising results in patients with moderate to severe COPD. However, gastrointestinal tolerability & weight loss are not infrequently reported. Adding roflumilast to LAACs had the most significant treatment effects & the highest probability of being the best first line treatment. Overall, roflumilast is considered safe and relatively well tolerated. Theophylline has mild non-specific anti-inflammatory properties and patients receiving this treatment have shown clinical improvement. However,
side effects and potential drug interactions outweigh its everyday use. Other agents, including statins, ACE inhibitors/ARBs, and TNF-alpha inhibitors have been studied to reduce inflammation levels. However, further research is needed to elucidate their role in patients with COPD to have better treatment and thereby goal of therapy will be achieved.

References:


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