



Inflammation of the Bronchial Tree and Respiratory Syncytial Virus

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Abstract

Bronchodilators have been described as the pharmacological equivalent of lung volume reduction surgery. The National Emphysema Treatment Trial showed that LVRS achieved significant improvements in exacerbation frequency and time to first exacerbation. The effect on exacerbations could be attributed to a quite modest bronchodilator effect and those patients with the largest post-operative improvement in FEV1 had a significantly longer time to first exacerbation. Indeed, the same mechanical principle in LVRS, i.e. stabilisation of the airways and reduction of air trapping, may explain the reduction of exacerbations observed with tiotropium.

Keywords: COPD; Bronchodilator; Tiotropium; Exacerbations; Disparity; Macrophages

Introduction

Significant correlations between changes in FEV1 and exacerbation frequency have been demonstrated for tiotropium. However, in contrast to bronchodilator therapy, increased elastic lung recoil pressure and decreases in dead space-to-alveolar ventilation ratio are important mechanisms of lung deflation in LVRS. Recent studies have demonstrated that combining LAMA and LABA bronchodilators have additive effects on airway function in patients with moderate-to-severe COPD [1]. Therefore, if the beneficial effect of bronchodilators on exacerbations is due to reduced airway resistance, improved IC and reduced hyperinflation, which is likely, then the improved lung function that can be achieved using combined LABA and LAMA bronchodilators should also confer further benefits in terms of exacerbations. However, this remains to be confirmed in appropriately designed clinical studies. Evidence indicates that once-daily LAMAs and LABAs have superior bronchodilation and clinical efficacy over twice-daily agents, as demonstrated by the superior effect of tiotropium compared with salmeterol on exacerbation outcomes in the POET-COPD study. This may simply reflect the action of a more potent bronchodilator. The sustained bronchodilator effect of a once-daily bronchodilator compared with the more variable effect of a twice-daily agent may also be relevant. The range of long-acting bronchodilators available to treat COPD has expanded with the availability of the once-daily LABA, indacaterol, for which there is some clinical evidence that outcomes are at least as good as those with tiotropium. Further research into the effect of bronchodilator treatment on exacerbations could usefully compare these two once-daily bronchodilators [2]. Exacerbations are a critical outcome measure in COPD that are associated with poor HRQoL, place a greater burden on the healthcare service and, ultimately, shorten survival. There is a large body of clinical evidence showing that long-acting bronchodilators are effective in preventing both moderate and severe exacerbations. Although various mechanisms are likely to be involved in the effect of bronchodilators on exacerbations, the most important probably involves reduction of hyperinflation and a re-setting of lung function dynamics. It is possible that future developments in bronchodilator treatments will further improve the efficacy of these agents on this critically important feature of COPD.

Discussion

Muscarinic receptor activation appears to have pro-inflammatory effects in a variety of cells, and in vitro studies have demonstrated that tiotropium exhibits an anti-inflammatory effect, including inhibition

of acetylcholine-induced release of leukotriene (LT)B4 from human isolated lung alveolar macrophages and A549 cells, regulation of CD4+ and CD8+ apoptosis of peripheral blood T-cells from patients with COPD, and inhibition of the pro-inflammatory effects of acetylcholine in neutrophils isolated from patients with COPD [3]. Such findings do suggest that LAMAs are capable of exerting anti-inflammatory effects, as well as bronchodilator effects; however, this is currently not supported by in vivo studies in COPD. In a study directly evaluating the effect of tiotropium on exacerbations in COPD and associated inflammatory markers in sputum and in serum, a reduction in exacerbation frequency was observed, but there was no corresponding significant change in IL-6 or myeloperoxidase, although it is possible that measurement of sputum cytokines is not the optimal means of assessing airway inflammation. In this study, change in LTB4 or transforming growth factor- β , which may be more relevant to cholinergic effects, were not measured. Representative pressure volume plots during stable COPD and COPD exacerbation. During exacerbation, worsening airflow limitation results in dynamic hyperinflation with increased end expiratory lung volume and residual volume. Corresponding reductions occur in inspiratory capacity and inspiratory reserve volume [4]. Total lung capacity is unchanged. As a result, tidal breathing is shifted right on the pressure volume curve, closer to TLC. Mechanically, increased pressures must be generated to maintain tidal volume. At EELV during exacerbation, intrapulmonary pressures do not return to zero, representing the development of intrinsic positive and expiratory pressure which imposes increased inspiratory threshold loading on the inspiratory muscles. During the subsequent respiratory cycle, PEEP_i must first be overcome in order to generate inspiratory flow. The measurements of inflammatory markers were made on sputum and airway secretions and, therefore, might not reflect changes in bronchial mucosa. The LABAs salmeterol and formoterol also elicit an anti-inflammatory effect on cells. Both LABAs have been shown to decrease neutrophil recruitment, activation and function in vitro, however, the relevance of these findings to COPD

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patients is unclear. Further investigations into inflammatory mechanisms of LABAs and LAMAs are warranted and, in particular, appropriate inflammatory markers should be measured in lung biopsies [5]. In COPD, mucus hyper-secretion may contribute to airflow obstruction and increase the risk of pulmonary infection. It has been speculated that extended bronchodilator from tiotropium might reduce infection rates by improving clearance of respiratory secretions, such as sputum production during exacerbations, which in turn improves lung defence mechanisms. As with the putative anti-inflammatory effect of long-acting bronchodilators, clinical trials have yet to convincingly demonstrate a reduction in mucus output with these agents in patients with COPD. Given that viral infection is an important trigger of COPD exacerbation, preliminary evidence suggesting that tiotropium can inhibit viral activity in the lung may be relevant in relation to tiotropium-induced reductions in COPD exacerbation rates. Viral inflammation-induced changes in neuronal M2 receptors have been shown to be associated with enhanced acetylcholine release in animal models of asthma and, although the neuronal M2 receptor appears normal in patients with stable COPD, this has not been investigated in patients with viral-induced exacerbations. Although the mechanisms involved in exacerbations of COPD are still not fully established, they involve an amplified inflammatory response [6]. These increases in airway inflammation during an exacerbation result in increased ventilation/perfusion imbalance, leading to worsening hyper-inflation, dyspnoea, hypoxemia and hypercapnia in more severe COPD. It has also been hypothesised that increased local expression of pro-inflammatory cytokines observed in the external intercostal muscles of patients with COPD may contribute to respiratory muscle dysfunction, potentially having a progressively detrimental impact as ventilator demands increase, such as during a COPD exacerbation. The progression of stable COPD is characterised by increased numbers of CD8+ lymphocytes, macrophages and neutrophils in the bronchial mucosa [7]. This pattern of inflammation changes during an exacerbation to predominantly neutrophil inflammation. Furthermore, the clinical severity and inflammatory responses in COPD exacerbations are modulated by the nature of the infecting organism, with bacterial and viral pathogens interacting to cause additional rises in inflammatory markers and greater exacerbation severity. Sputum and peripheral blood neutrophils have been shown to be significantly increased in all exacerbations, regardless of aetiology, compared with levels during stable convalescence. The increase in sputum neutrophils was also directly related to exacerbation severity. Although traditionally viewed as a neutrophil-predominant inflammatory response, eosinophilia airway inflammation also plays a role in exacerbations of COPD. In a study of patients with COPD, treatment to reduce eosinophilia airway inflammation was associated with a significant reduction in the frequency of COPD exacerbations requiring hospital admission. In particular, an increase in sputum eosinophil's has been detected in exacerbations associated with viral infections, but their role as biomarkers for viral exacerbations either in the presence or absence of a bacterial co-infection has yet to be confirmed. However, patients with sudden onset exacerbations experienced a significantly shorter recovery time than patients with gradual onset exacerbations, which the investigators considered clinically important [8]. This study also showed that in most cases, worsening of respiratory symptoms resolved spontaneously and did not result in an exacerbation. Despite the worsening of symptoms and significant reduction in quality of life associated with exacerbations, as many as exacerbations go unreported. This may reflect patients with COPD just accepting their condition and/or being accustomed to symptom fluctuation as the disease

progresses. Identification and education of patients who delay or fail to seek treatment for exacerbations might increase and improve the rate of exacerbation reporting, and reduce patient morbidity and the substantial burden of in-patient treatment of exacerbations on healthcare services. COPD exacerbations are heterogeneous events caused by complex interactions between the host, respiratory viruses, airway bacteria and environmental pollution, which lead to an increase in the inflammatory burden. In general, viral and bacterial infections are the most important triggers of exacerbations. Respiratory bacteria and viruses often act in combination, and have a synergistic inflammatory effect in COPD exacerbations [9]. Co-infection with viruses and bacteria has been detected in exacerbations and is associated with more severe functional impairment and longer hospitalisations. However, in approximately one-third of severe exacerbations a specific aetiology cannot be identified. Although exacerbations generally become more frequent and more severe as COPD progresses, a specific phenotype of patients experience a high frequency of exacerbations independent of disease severity. Indeed, a history of frequent exacerbations is often the best predictor of future exacerbations, with patients having consistent exacerbation frequencies when studied from year to year. There is evidence that an initial exacerbation increases susceptibility to a subsequent one; hence exacerbations tend to occur in temporal clusters [10].

Conclusion

The high-risk period for recurrence was shown to be within few weeks after the initial exacerbation. Until recently, few studies had investigated the pattern of onset of COPD exacerbations. Using data from daily symptom diaries of few patients with COPD, it has now been shown that COPD exacerbations exhibit two distinct patterns, sudden onset and gradual onset and that these two types were found to be predictive of subsequent clinical outcomes.

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Conflict of Interest

None

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