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Inflammation of an Upper Respiratory Tract Infection by Viral Agents

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Abstract

It is well established that severe exacerbations of COPD requiring hospitalisation are associated with high in-hospital mortality, with one meta-analysis citing an average in-hospital mortality rate. However, it has been shown that the critical period for mortality exceeds the duration of hospitalisation, increasing the estimated overall average case fatality rate for severe exacerbation resulting in hospitalisation.

Keywords: COPD; Lung function; Resource; Glucocorticoids; Cross-study interpretation; Reported outcomes

Introduction

Exacerbations are also associated with profound long-term effects in terms of worse HRQoL, peripheral muscle weakness, reduced physical activity and exercise endurance, and poor disease prognosis. This may not be surprising considering that several studies have demonstrated that the frequency of exacerbations contributes to long-term decline in lung function of patients with COPD. However, some predominantly older studies have reported little impact of exacerbations on lung function, but these studies did not define exacerbations as currently accepted and the landmark study, only studied mild patients with relatively few events [1]. The impact of COPD exacerbations on decline in lung function is, therefore, still uncertain and the heterogeneity of COPD has been proposed as the most likely explanation for the variable susceptibility of lung function to exacerbations. It has been proposed that COPD can be divided into subtypes that are dominated by either parenechymal pathology or small airways disease and that have COPD phenotypes, including exacerbation frequency and level of functional impairment, which may differ within subtypes. Definitions of an exacerbation The definition of an exacerbation by GOLD is an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. Although definitions of exacerbations often vary between clinical studies, they are usually based upon clinical presentation and healthcare resource utilisation. Recent pivotal studies, e.g. the Understanding Potential Long-Term Impacts on Function with Tiotropium study in 2008, define exacerbations as an increase or new onset of at least one respiratory symptom for few days. It is generally considered that moderate exacerbations are those requiring treatment with systemic glucocorticoids and antibiotics, while severe exacerbations are those that require hospitalisation [2]. In the clinical studies evaluated in this review, most definitions are based on a worsening of symptoms that required additional treatment with systemic glucocorticoids and/or antibiotics, or that required hospitalisation. Although there are many reasons why results cannot be directly compared across clinical studies, the absence of a consistent definition for exacerbations has been a major limitation to cross-study interpretation. This has led to the development and validation of the Chronic Pulmonary Disease-Patient Reported Outcomes (EXACT-PRO) tool, a 14-item questionnaire that aims to provide a standardised method of defining and reporting exacerbations based on symptoms, which is currently undergoing validation.

Discussion

Early clinical studies of the once-daily LAMA tiotropium demonstrated increased efficacy compared with placebo and salmeterol in preventing moderate and severe COPD exacerbations and exacerbation-related hospitalisations, and lengthening the time to first COPD exacerbation. However, in these studies, exacerbation data were collected as adverse events. In response to these preliminary findings, two placebo-controlled clinical studies were specifically designed to prospectively test the hypothesis that tiotropium reduces exacerbations in patients with COPD [3]. In these studies, both of which involved patients, tiotropium significantly reduced the proportion of patients with at least one COPD exacerbations. Time to first exacerbation was significantly extended. While the 1-yr study was not powered to detect a reduction in exacerbation-related hospitalisations, exacerbation-related hospitalisation was a primary end-point, during which the proportion of patients with at least one exacerbation-related hospitalisation tended to decrease with tiotropium, and time to first exacerbation-related hospitalisation tended to increase. More recently, the UPLIFT trial evaluated the effect of tiotropium on the rate of decline in mean forced expiratory volume, as well as exacerbations. In this large study, patients with moderate-to-severe COPD received tiotropium or placebo in addition to their usual treatment. Although tiotropium did not significantly reduce the rate of decline in lung function, time to first exacerbation, time to first hospitalisation for exacerbations and mean number of exacerbations were all significantly improved compared with placebo. In a pre-specified sub-set analysis of patients from the UPLIFT study with GOLD stage II COPD, tiotropium improved exacerbation rate, time to first exacerbation and hospitalisation for exacerbation [4]. Clinical studies of the once-daily LABA indacaterol also show that it has increased efficacy versus placebo in preventing exacerbations. In the recent Indacaterol versus Tiotropium to Help Achieve New COPD Treatment Excellence study, indacaterol significantly reduced the time to first COPD exacerbation and the rate of COPD exacerbations versus placebo. Furthermore, the twice-daily LAMA aclidinium and once-daily LAMA NVA237, which are in development for COPD, have demonstrated increased efficacy versus placebo in preventing moderate and severe exacerbations. In the phase III Aclidinium to Treat Airway obstruction In COPD Patients

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study, the rate of exacerbations of any severity was significantly lower with aclidinium versus placebo rate ratio with aclidinium and aclidinium versus placebo. The frequency of moderate or severe exacerbations was also lower for aclidinium versus placebo, although the rate ratios did not reach statistical significance respectively. In the recently completed phase III GLOW1 study, NVA237 significantly decreased the risk of a moderate-to-severe COPD exacerbation. Time to first exacerbation is considered the most robust way to measure exacerbations in clinical studies. This end-point is unlikely to be affected by early discontinuations and associated missing data, which is generally considered a limitation for most studies in COPD, including the TORCH and UPLIFT studies. Furthermore, the data distribution is generally less skewed than for the annual number of exacerbations, and it is less affected by patients who have a disproportionately high number of exacerbations. However, in many studies exacerbations are secondary outcomes, and the studies are not designed in the optimal way to examine effect of treatment on exacerbations. The Prevention of Exacerbations with Tiotropium COPD study was specifically designed to compare the effects of a LAMA and LABA on the risk of exacerbations [5]. The results of this study showed that once daily tiotropium was superior to twice-daily salmeterol in prolonging the time to first exacerbation, and reduced the risk of an exacerbation. However, once-daily LABAs such as indacaterol are now becoming available in Europe, and there is some clinical evidence that outcomes with indacaterol are similar to those with tiotropium, this is being investigated further in an ongoing phase III study comparing the effects of indacaterol and tiotropium on exacerbations. Recommendations for the use of ICS in COPD centre on their effectiveness in patients with frequent exacerbations, severe airflow limitation and significant health status impairment based on modified British Medical Research Council or COPD Assessment Test score. Combinations of LABA plus ICS have been shown to significantly reduce exacerbation frequency in patients with COPD to a greater extent than using a LABA or ICS alone. However, in the INSPIRE study that compared LABA plus ICS with tiotropium, overall exacerbation rates were similar [6]. Comparing the two treatments in this study, exacerbations requiring systemic corticosteroids occurred less frequently in patients receiving salmeterol/fluticasone propionate than in those receiving tiotropium, while those requiring antibiotics were less frequent in the tiotropium-treated patients than in those receiving salmeterol/fluticasone propionate. This suggests that the two treatments exerted their effects on exacerbations via different mechanisms, and raises the possibility that the different drug classes of bronchodilator are affecting exacerbations in different ways; these differences may also reflect the anti-inflammatory effects of the ICS component [7]. For example, sputum eosinophilia is associated with corticosteroid responsiveness, whereas an exacerbation characterised by high bacterial load will have a favourable response to antibiotics. Bacteria-associated and sputum eosinophil-associated exacerbations rarely coexist and, because they are repeatable in patients with multiple exacerbations, they can be predicted from the stable state, thus, it may be possible, and appropriate, to provide targeted tiotropium immunotherapy in patients with bacteria-associated exacerbations, and combined bronchodilator/ICS therapy in patients with sputum eosinophil-dependent exacerbations. Furthermore, COPD exacerbations that begin with bacterial symptoms are more likely to have sudden, rather than gradual, onset, suggesting that sudden onset exacerbations may be preferentially preventable with bronchodilators, whereas gradual onset exacerbations may require the addition of corticosteroid therapy [8]. Since most exacerbations are considered to be of infectious aetiology, leading to increased small airway inflammation, the mechanisms by which long-acting bronchodilators prevent exacerbations are unclear. Bronchodilators may act by re-setting the threshold of lung function/dynamics at which an exacerbation is triggered. Improvements in resting inspiratory capacity have been shown to occur as a result of treatment with all classes of bronchodilators. Increases in IC after bronchodilator therapies, which signify a reduction in EELV, result in a reduced work and oxygen cost of breathing. This lung deflation primarily reflects an improvement in mechanical lung emptying and increased functional strength of the inspiratory muscles, rather than increasing the static elastic recoil of the lung. Increased IC at rest is an important element in the decrease in dynamic EELV during exercise that occurs with bronchodilator treatment, compared with placebo. The reduction in exacerbations during treatment with long-acting bronchodilators may be explained, in part, by sustained bronchodilator and the consequent improvement in airflow and reduction in lung hyperinflation, resulting in a reduction in dyspnoea, reduced lung hyperinflation has been demonstrated with bronchodilators during rest and exercise, leading to increased exercise endurance time. Reduction in lung hyperinflation during exacerbations may lessen the ventilation/perfusion imbalance, so that patients may be less vulnerable to triggers of exacerbations [9]. Indeed, improvement in hyperinflation correlates better with improvements in exacerbation frequency than FEV1.It is possible that, in addition to bronchodilator effects and resultant reductions in lung hyperinflation, long-acting bronchodilators may also have direct or indirect effects on lung inflammation but, to date, there is little clinical evidence that LABAs or LAMAs are directly associated with improvement in airway or systemic inflammation [10]. It has been suggested thatthe INSPIRE study finding that tiotropium resulted in similar reductions in exacerbation rates compared with combination salmeterol/fluticasone propionate, which has been associated with reduced lung inflammation in COPD, indicates that tiotropium may also have an anti-inflammatory effect.

Conclusion

Evidence for an anti-inflammatory effect of combination therapy came from bronchial biopsies, whereas sputum analysis revealed little evidence of an anti-inflammatory effect.

Acknowledgement

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Conflict of Interest

None

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