Tiotropium for severe asthma: a step forward or more of the same?

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Severe asthma remains a frustrating disease both for the patients and the clinicians who treat them. By recent definitions, the diagnosis of severe asthma implies that a patient is poorly responsive to any of the current medications used to treat asthma. This refractoriness to therapy likely partly explains a disproportionate contribution to total asthma costs associated with this small subset of the general asthma population. Thus, there is an urgent need to identify additional effective therapies for severe asthma.

Considerable attention has focused on biologically-targeted therapies, including the currently approved anti-immunoglobulin E as well as novel targets such as interleukin (IL) 5 and IL-13. However, these therapies come at great financial expense. Less expensive therapies would be highly desirable.

Severe asthma is frequently associated with incomplete reversibility of airway obstruction both to traditional β-agonists and to corticosteroids. Furthermore, there is an association of baseline forced expiratory volume in 1 second percent predicted (FEV₁%; as a measure of airway obstruction) and severity, including risk for asthma exacerbations, suggesting that medications which improve FEV₁ could also improve long-term asthma risk. Tiotropium, a long-acting muscarinic agent, has become one of the most widely used bronchodilators in chronic obstructive pulmonary disease and has been shown to affect both exacerbations and lung function. It has also been shown to improve lung function and symptoms in mild asthmatic patients, comparing well with the long-acting β-agonist (LABA) – salmeterol. Therefore, it is not surprising that there is an interest in a trial of tiotropium in more severe asthma.

The study of Kerstjens et al. combined the 2 largest trials to date of tiotropium in severe asthma, evaluating over 800 subjects in total. The patient population was limited to those who developed the disease before the age of 40 and who admitted to less than 10 pack-year smoking history. They met the American Thoracic Society and European Respiratory Society criteria for severe asthma on the basis of medication use and poor asthma control. Thus, the population studied appears to be appropriate. However, by excluding those with an age of over 40 years at onset, the study also likely failed to include those severe asthmatics with the greatest airway inflammation, which could have enhanced the improvements to a pure bronchodilator. Unfortunately, no phenotyping was reported on the study population to know the level of inflammation present or whether it affected response to therapy.

The authors selected 3-hour post-treatment FEV₁, change and trough FEV₁, at 24 weeks as their coprimary endpoints, with a third primary looking at time to first severe exacerbation if the first 2 primaries had been achieved. Coprimary endpoints require some statistical adjustment regarding the significance level of the P values. The methodology for the third coprimary endpoint reported here could be considered somewhat atypical, perhaps based on the hierarchical approach to the endpoint, but which allowed a P value of 0.03 to be significant as the third coprimary. In any case, the first 2 primary endpoints were achieved with the P values of <0.01 and <0.001 in the 2 individual trials and medians in the range of 72 to 154 ml absolute volume. Given tiotropium’s mechanism of action, these results are not surprising. While the authors argue that the small volume improvements in FEV₁ are due to the high level of background therapy, including LABAs, in fact, the small improvements in FEV₁ do not begin to return the markedly obstructed FEV₁ (% (54%–55%) close to the normal range, suggesting that many other factors are more important in controlling the FEV₁.
omalizumab. These treatments generally target an inflammatory component to asthma, so direct comparisons of efficacy are difficult. Additionally, although exploratory, no consistent or clinically significant effects were seen in asthma control or quality of life. In contrast perhaps to exacerbations, improvements in these areas are not observed with biological therapies either, suggesting that none of the treatments proposed to date for severe asthma consistently make these patients feel better, a critical outcome for most patients.

In conclusion, although the results from the Kerstjens study achieved significance and, at least for the effect on exacerbations, have modest clinical importance, it is unlikely that the addition of tiotropium to LABAs and inhaled corticosteroids is going to dramatically affect the care of severe asthmatics. Like LABAs, tiotropium is unlikely to have any effect on inflammation, an important pathologic feature of the majority of severe asthmatics. Whether a subgroup could be identified where inhibition of the muscarinic pathway had a greater impact awaits further studies.

REFERENCES