

# Medications tailored to the elderly asthma

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Asthma is a common disease in the older population that is frequently under- or mis-diagnosed and undertreated. Compared with asthma in younger population, asthma in older people was more severe and was highly associated with hospitalization and a poor quality of life. However, the underlying pathophysiology and optimal management of asthma among older patients has still been overlooked. Because ageing affects airway physiology and inflammation, asthma in older patients is less likely to respond to inhaled corticosteroids. Recently adds-on of antileukotrienes or anticholinergics to older asthmatics whose asthma was not controlled with inhaled steroids and/or long-acting beta2-agonist have been tried. Elderly asthmatics have an increased risk of polypharmacy and comorbidities leading to a decreased treatment adherence and frequently unaccomplished asthma control. Asthma management in elderly patients is also directed at controlling current symptoms and preventing exacerbation. Multidimensional intervention are needed to provide a best solution to integrate various challenges including drug delivery, treatment adherence, and adverse reactions, comorbidities, in elderly asthma.

## 1. Introduction

It has been reported that the prevalence of current asthma was 2.0% in subjects younger than 40 and 12.7% in those 65 years and older in Korea.<sup>1)</sup> The goal of asthma treatment is achievement and maintenance of disease control. Uncontrolled asthma is more common in older adults than in younger ones with a substantial clinical burden, a greater proportion of asthma medication use, hospitalizations, and death.<sup>2-4)</sup> Guidelines recommend a stepwise approach for management according to the individualized assessment of asthma control as is the same for all ages.<sup>5)</sup> Asthma is a heterogeneous disease with significant variability in phenotypes, severity, and response to therapeutic measures.<sup>5)</sup> The aim of this review is to assess the current modalities of asthma management in the elderly.

## 2. Asthma control and comorbidities in elderly asthma

Asthma control is the most important clinical outcomes for adjusting treatment steps also in elderly asthmatics, even though they have difficulties in recognition of asthmatic symptoms. A higher rate of comorbidities in elderly asthmatics is commonly associated with polypharmacy and drug-drug interactions, confused recognition of asthmatic symptoms, and incorrect or inadequate use of medications, especially inhalers.<sup>6,7)</sup> Moreover, comorbidities lead to frequent asthma exacerbations and may increase the rate of hospitalization, emergency department visit, and mortality.<sup>8,9)</sup> To reduce the severity and mortality of asthma in elderly asthmatic patients, we need to manage the predictors of their asthma control. A previous prospective observational study proved that the number of medications for comorbidities and performance status are important parameters for assessing asthma control in elderly asthmatic patients.<sup>10)</sup> Frequently associated comorbid conditions of elderly asthmatics in the study were hypertension, rhinosinusitis, diabetes, COPD and hyperlipidemia in order.<sup>10)</sup> Obesity has been reported to increase asthma development and the proportion of uncontrolled asthma, and corticosteroid insensitivity in other studies.<sup>11,12)</sup> Smoking was found to cause more severe symptoms, accelerated decline in lung function, and impaired response to corticosteroids in asthma patients.<sup>13)</sup> Particularly in elderly patients, smoking has been found to be a risk factor of asthma development and bronchial hyperresponsiveness.<sup>1)</sup> Depression, anxiety and cognitive impairments are common and also associated with higher exacerbation rates and mortalities among older patients with asthma.<sup>14-16)</sup> To achieve optimal asthma control in elderly patients, a multidisciplinary intervention for evaluating multiple comorbidities and integrative treatment is important.

## 3. Therapeutics: Effectiveness and safety proven in elderly asthmatics

Although effective asthma management in the elderly relies on the same guidelines applicable to all age, undertreatment of asthma remains an issue for older people. The evidence for supporting therapeutic decisions in elderly asthmatics is still insufficient because clinical trials usually exclude older patients, or subjects with comorbidities, or a smoking history.<sup>17)</sup>

Regular use of inhaled corticosteroid (ICS) is strongly recommended for all patients with uncontrolled or partly controlled asthma.<sup>5)</sup> The safety and efficacy profile of an ICS is influenced by the pharmacokinetic and pharmacodynamics properties of the drug.<sup>18)</sup> Fine particle size, high receptor binding affinity, long residence time in the lung and lipid conjugation can enhance the efficacy of ICS. On the contrary, the extent of oral bioavailability, on-site activation in the lung, protein-binding and systemic clearance is associated with the safety of ICS. Potential systemic side-effects including osteoporosis, diabetes, skin thinning, cataracts and glaucoma, are related to hypothalamic-pituitary-adrenal axis (HPA) suppression. Oral bioavailability ranging from <1% for ciclesonide, mometasone and fluticasone propionate (FP), 11% for

budesonide, to 26% for beclomethasone affects HPA suppression. Particle size is an important determinant of the proportion of ICS targeting small airway inflammation which is highly involved in the elderly asthma.<sup>19)</sup> FP delivered by DPI has the largest mass median aerodynamic diameter and BDP delivered by hydrofluoroalkane MDI having the smallest particles.<sup>18)</sup> Pulmonary residence time determined by lipophilicity and lipid conjugation influences anti-inflammatory effects. FP has known to have a longer pulmonary residence time as compared with BUD.<sup>20)</sup> Potential risks of pneumonia have been found to be related to FP but not BUD in patients with COPD and asthma.<sup>21-23)</sup>

To reduce dose-dependent adverse reactions of ICSs while maintaining their clinical efficacy as much as possible, adding long-acting beta2-agonist (LABA), long-acting muscarinic antagonist (LAMA) and leukotriene receptor antagonist (LTRA) have been recommended for patients with uncontrolled asthma under ICS monotherapy.<sup>5)</sup> In general, combined LABA with ICS shows better efficacy than ICS dose-up or adding LTRA in improved lung function and asthma control.<sup>24,25)</sup> There is a little evidence on the efficacy of these steroid-sparing approaches in older patients with asthma. Initiation of ICS plus LABA treatment for elderly asthmatics reduced asthma exacerbations over a 12-month period without increase in healthcare costs as compared with patients under ICS therapy.<sup>26)</sup> However, previously reported age-related decrease in bronchodilator response to beta2-agonist and increased risk of arrhythmia particularly in patients with cardiovascular comorbidities are raised as potential concern of LABA use.<sup>27,28)</sup> Long-acting anticholinergics, tiotropium has been demonstrated to improve lung function as added in ICS plus LABA treatment for older asthmatics with smoking and comorbid COPD.<sup>29)</sup> However, in respect of inhalers, addition of LABA and LAMA has serious restrictions for patients who cannot use inhalers due to inadequate inhaler technique, oropharyngeal side effects, and preference to oral medications. Active inhaler technique education is also important for elderly asthmatics to improve asthma outcomes.<sup>30)</sup> Even though a little effect in improving lung function or reducing exacerbation is reported in patients with LTRA treatment, however, with a better compliance and safety it can be a good alternative of LABA for asthmatics.<sup>24,31)</sup> Previous studies demonstrated LTRA add-on to ICS with or without LABA reduced exacerbation rate in older patients with severe and mild asthma.<sup>32,33)</sup> Theophylline can be used as steroid-sparing agents based on the roles of bronchodilation and anti-inflammation.<sup>5)</sup> However, a relatively higher incidence of adverse events, such as nausea, poor appetite, hyperuricemia and palpitation has been reported by less than 5% in patients using low-dose theophylline.<sup>34)</sup>

The prevalence of atopy in elderly asthmatics varies and house dust mites are also major allergens for older population. In a recent observational study, atopy was found in 62.9% of elderly asthmatics particularly higher in those with early onset asthma.<sup>35)</sup> The diagnosis of allergic asthma in elderly patients makes physicians consider environmental control, allergen specific immunotherapy, and anti-IgE treatment. It has been reported that allergen specific immunotherapy reduced medication and symptom scores in older patients with asthma.<sup>36)</sup> Effectiveness of omalizumab in older patients with severe uncontrolled asthma has

been proven as 68.9% of decrease in exacerbation and improved lung function with no difference in the frequency of adverse events compared with younger group.<sup>37)</sup>

#### 4. Conclusion

As asthma pharmacologic therapies become more individualized, it will be crucial to distinct asthma phenotypes and associated endotypes in elderly asthmatics for further tailored therapy. Ageing impacts airway responses, immune function, pharmacokinetic changes, medication adherence and thus influences both efficacy and safety of asthma drugs when applied to the elderly patient. A multidisciplinary treatment strategy to manage comorbid diseases and appropriate medication use and to monitor potential harms even uncommon events in younger patients should be considered to achieve asthma control in elderly asthmatics.

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