Editorial
Allergy Asthma Immunol Res. 2015 September;7(5):419-420.
http://dx.doi.org/10.4168/aair.2015.7.5.419
pISSN 2092-7355 • eISSN 2092-7363

More Effective Strategies are Needed for Elderly Asthmatics in Real-World Practice

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The elderly are not merely 'more aged' people just as children are not 'little' adults. This may hold true particularly when we discuss asthma. Along with the rapid aging of global populations, the burden of elderly asthma is expected to rise dramatically in the near future.[1] Recent research highlights of elderly asthmatics reflect emerging significance. However, one thing that comes to us more clearly is that asthma in the elderly is more heterogeneous and complex than previously thought. A considerable proportion of elderly asthmatics are considered to have late-onset disease with distinct pathophysiology, being less associated with genetic factors but more related to comorbidities, occupations, or environment. Moreover, in the context of real-world practice, poor adherence resulting from the lack of socio-familial support or multiple comorbidity poses significant challenges in managing elderly asthmatics.[2]

Recently, several major guidelines for asthma have been updated. However, only a few or no descriptions have still been made for elderly patients, which may reflect the lack of available evidence obtained from them.[2] Indeed, being elderly has been one of the major exclusion criteria for many asthma clinical trials. Thus, we may not be sure whether the recommendations from current guidelines can be translated directly to elderly patients.

In this issue of the AAIR journal, Ye *et al.*[3] have provided a very good news on the treatment strategy to be applied in elderly patients with asthma. In their 12-week randomized, open-labelled, parallel-designed, non-inferiority trial involving 140 elderly patients (60-75 years), the addition of montelukast to low-dose inhaled corticosteroid (ICS) (MON-400BUD group) had comparable efficacy to that of medium-dose ICS (800BUD group) in elderly patients with mild asthma. In addition, the MON-400BUD group had less frequent asthma exacerbation (9 vs 20, $P=0.036$) and showed a reduced frequency of sore throat compared to the 800BUD group (11 vs 22, $P=0.045$).

The novelty of their study is that this is the first randomized trial to extend earlier findings[4-6] from adult patients into elderly ones, showing that a leukotriene receptor antagonist (LTRA) as add-on to ICS is superior to constant-dose ICS monotherapy in improving clinical outcomes of asthma. In that trial,[3] LTRA add-on therapy (MON-400BUD) increased the rate of well-controlled asthma from 2.9% at baseline to 36.9% at 12 weeks. Moreover, the efficacy of LTRA add-on therapy was not inferior, or better in a few outcomes, compared to doubling ICS strategy (800BUD). Thus, that paper would serve as reference to validate the role of LTRA add-on therapy in elderly patients with mild asthma who remain inadequately controlled by ICS monotherapy.

Another reason this work of Ye *et al.*[3] is intriguing is that there have previously been rather negative data on LTRA in elderly patients. In the Accolate Clinical Evidence and Pharmacoepidemiology Trial (ACCEPT), which was the large-scale open-labelled trial for 4 weeks involving more than 3,700 asthmatics across various age groups, the addition of zafirlukast 20 mg twice daily improved several outcomes of asthma across the age groups; however, the clinical effect was less remarkable in the elderly compared to younger counterparts.[7] This finding was not conclusive because the trial had limitations such as short duration, lack of control arm, insufficient number of elderly patients (8.5%), and more severe asthma in the elderly

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Received: June 5, 2015; Accepted: June 6, 2015
• There are no financial or other issues that might lead to conflict of interest.

group.[7] In a retrospective analysis of 5 randomized double-blind trials comparing fluticasone to zafirlukast as monotherapy, zafirlukast resulted in small improvement in asthma symptoms but minimal improvement in lung functions, and moreover more exacerbations in asthma patients older than 50 years.[8] In a pilot study on sputum leukotriene (LT) levels, older asthmatics (n=6; mean age, 64 years) showed comparable eosinophils but much less LTB4 and cys-LT levels in induced sputum, compared to young asthmatics (n=12; mean age, 27 years).[9] In this regard, the randomized trial of Ye *et al.*[3] tackles the previous concept that LTRA may be less effective in elderly patients. This conclusion is supported by a recent 24-month long-term clinical observation study that LTRA as add-on to ICS improved clinical outcomes in elderly patients with severe asthma.[10]

Particular implication of their trial[3] may be that LTRA may be potentially a preferred option in the real-world practice of elderly asthmatics. LTRA has generally shown a good safety profile[11] and better adherence rates in recent pragmatic trials (65% vs 41% compared to ICS as the first-line controller; and 74% vs 46% compared to long-acting beta2-agonist [LABA] as the add-on therapy).[12] Adherence is a part of treatment effect, and would be more important in elderly patients.

Elderly patients have usually multiple comorbid conditions, affecting more than 3 organs/systems.[13] They are also prone to have poor inhaler technique and adherence combined with lack of caregivers, cognitive impairment, and low health literacy,[2] which lead to asthma exacerbation and poor control. For these reasons, it is difficult to conduct perfect clinical trials on elderly patients, and clinical values from conventional efficacy trials are limited in terms of external validity in the elderly. This is why we need pragmatic trials for elderly patients.

Finally, further important questions may include: will the effectiveness of LTRA be similar to that of ICS as initial monotherapy in elderly patients?; will LTRA be equivalent to LABA as add-on therapy in elderly patients receiving ICS?; which subgroups of elderly patients will get more clinical benefit from LTRA? We look forward to forthcoming clinical trials to provide us better therapeutic strategies for elderly asthmatics.

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