

Leukotriene Receptor Antagonists for the Treatment of Asthma in Elderly Patients

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Abstract Elderly asthma (EA) is regarded as a distinct phenotype of asthma and is associated with age-related changes in airway structure and alterations in lung function and immune responses. EA is difficult to diagnose because of aging and co-morbidities, and overlaps with fixed airway obstructive disease. Novel modalities to differentiate between EA and chronic obstructive pulmonary disease (COPD) are necessary. A multifaceted approach, including clinical history, smoking habits, atopy, and measurement of lung function, is mandatory to differentiate asthma from COPD. There are a variety of co-morbidities with EA, of which COPD, upper airway diseases, depression, obesity, and hypertension are the most common, and these co-morbidities can affect the control status of EA. However, leukotriene receptor antagonists (LTRAs) can facilitate the management of EA, and thus addition of an LTRA to inhaled corticosteroid (ICS) monotherapy or ICS plus long-acting β_2 -agonist therapy improves symptoms in EA patients. LTRA treatment is safe and beneficial in patients who are unable to use inhalation devices properly or who have co-morbid diseases. Therefore, clinical studies targeting a specific population of EA patients are warranted to help achieve a better therapeutic strategy in EA patients.

Key Points

Aging is associated with physiological modifications to airway structure, a decline in lung function, and impaired immune responses. Integrated approaches to the diagnosis of elderly asthma (EA) and differentiation of EA from chronic obstructive pulmonary disease are mandatory.

EA patients have more co-morbid conditions than their younger counterparts, and these may affect asthma control. Co-morbidities should be assessed in EA patients, especially if EA is not well-controlled.

Using leukotriene receptor antagonists in EA patients is safe and effective, especially for those with co-morbid conditions.

1 Introduction

The number of elderly people worldwide is steadily increasing and will double by 2030, imposing an economic burden on public healthcare programs due to increasing medical expenses [1]. The vast majority of elderly people have at least one chronic condition, and asthma is becoming more prevalent in this subpopulation [2, 3]. Patients with elderly asthma (EA) show distinct phenotype and pathogenetic characteristics in comparison to younger patients. Patients with EA usually experience higher rates of mortality and near-fatal asthma-related events, more frequent hospitalization, and longer hospital stays than younger adults [4, 5]. Co-morbidities and polypharmacy are frequently noted in patients with EA, which may serve

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as predictors of poor asthma control [6–8]. Nevertheless, numerous randomized clinical trials of asthma have excluded elderly subjects due to the age criteria and comorbidities [9, 10].

Multifactorial assessment should be taken into account when diagnosing and treating patients with EA [11]. Proper recognition of EA and avoidance of misdiagnosis with obstructive airway diseases are crucial for physicians. Conventional methods that have been used to differentiate between EA and chronic obstructive pulmonary disease (COPD) have several disadvantages, thereby highlighting the need for novel biomarkers and approaches [12]. Adherence to treatment in patients with EA is challenging due to the elderly's impaired ability to handle inhalers, especially metered-dose ones, as well as contraindications to corticosteroids [13, 14]. Leukotriene receptor antagonists (LTRAs) show a high therapeutic efficacy in managing patients with EA. Cysteinyl leukotrienes (CysLTs) produced by diverse inflammatory cells (e.g., eosinophils, macrophages, basophils, and mast cells) are important in asthma pathogenesis and mediate inflammatory cell infiltration, mucus secretion, vascular leak, and smooth muscle proliferation by interacting with CysLT receptors [15]. LTRAs bind to CysLT receptors and then suppress CysLT-induced airway inflammation in asthma. LTRAs can be administered orally in a daily regimen and cause adverse reactions less frequently than glucocorticoids [16]. This review summarizes recent findings on the clinical characteristics of EA, co-morbidities, and the role of LTRAs in the management of EA.

2 Phenotypes of Elderly Asthma (EA)

Asthma can develop at an early age or *de novo* at any age [12, 17]. In terms of the onset of symptoms, EA can be classified as (1) 'early-onset' or (2) 'late-onset' asthma (LOA). Patients with early-onset asthma, also known as long-standing asthma, develop asthma symptoms during childhood or in early adulthood, which may persist or disappear and relapse at older ages [17]. Asthma is commonly associated with atopy and obesity in such cases [1].

Patients with LOA, also known as adult-onset asthma, present the first exacerbation in late adulthood [1, 12, 17]. The age threshold for LOA is still under debate. Most studies have reported that LOA develops at ages 40–45 years; however, a few studies have reported that LOA develops at ages ≥ 60 years [17–19]. Most LOA patients have a poorer prognosis, a rapid decline in lung function, and more severe airflow obstruction than patients with early-onset asthma, although one study showed no difference in asthma severity, asthma control status, body mass index (BMI), or fractional exhaled nitric oxide

(FeNO) between LOA and early-onset asthma [20, 21]. A long-term follow-up of LOA showed a low remission rate, with 95 % of patients still having active asthma after 5 years. In a previous study, it was found that overall asthma severity changes to a milder state, resulting from the efficacy of treatment [22]. Thus, epidemiological studies are necessary to specify the age threshold for LOA, which can help facilitate the diagnosis and management of LOA.

3 Epidemiology of EA

The prevalence of EA ranges from 3.6 to 17 % worldwide, and is reported to be 7.1 % in a Korean cohort [9, 23–25]. Females are more frequently affected by EA [26]. The significant difference in the results may be attributed to different selection criteria, such as age and methods for the diagnosis of EA. Generally, 'older adults' include persons aged ≥ 64 years, including the early old aged 64–75 years and the older elderly aged 75 years or over [26]. However, many studies have recruited EA patients aged ≥ 60 years, while some studies have also included middle-aged subjects as older adults. Due to the inconsistent cutoff age of EA, current studies have inaccurately estimated the prevalence and incidence of EA.

4 Impacts of Aging on the Pathogenesis of EA

The aging process leads to structural/physiological changes in the airways, loss of lung functions, immunosenescence, and modification of the inflammatory profile [1, 27]. The senile lung is characterized by homogeneous enlargement of airspace without destruction of the lung parenchyma, resulting in hyperinflation [28]. The static elastic recoil pressure diminishes along with alterations in respiratory muscle drive, contributing to the fall in lung capacity, which is a fundamental element in determining bronchoconstrictive responses to spasmogens [28, 29]. In addition, thickening and stiffness of the airway wall are likely to cause resistance to bronchodilators [28]. Given that anatomical changes in the respiratory system cause a gradual decline in forced expiratory volume in 1 second (FEV₁) with aging, FEV₁ declines by 25–30 mL per year starting from the fourth decade of life and the rate of decline doubles to 60 mL per year after the age of 70 years [30]. As a result, interpretation of spirometric results in elderly patients should be cautiously interpreted.

Immunosenescence refers to the dysregulation of both cellular and adaptive immunity with aging [31]. The absolute numbers of T and B cells are reduced with aging together with an impairment of pulmonary functions,

contributing to a high risk of infections and low allergen sensitization in elderly subjects [1, 9, 31, 32]. Therefore, patients with EA are less likely to have allergies than adult asthmatic patients.

EA shows distinct characteristics in inflammatory profiles compared with adult asthmatic patients, including (1) elevated proinflammatory cytokines; (2) changes in cellular components of innate immunity; and (3) a modification of the airway microbiome. Firstly, a long-term state of low-grade inflammation in EA is implicated in enhanced levels of proinflammatory cytokines, such as tumor necrosis factor- α , interleukin (IL)-6, and IL-10 [9, 33]. Secondly, neutrophilia and a reduced number of macrophages have been demonstrated in EA, independent of asthma severity [34–36]. This is hypothesized to be attributed to lifelong exposure to antigens, aging, and the corticosteroids used [17, 37]. Thirdly, the association of the airway microbiome with asthma has been established based on various epidemiological, animal, and in vitro studies. The microbiome status of adult asthmatic patients is characterized by a decreased diversity but a higher proportion of Proteobacteria; however, the microbiome status of EA patients is underexplored [38]. Nevertheless, patients with EA are characterized by long-term antibacterial use, alterations in immune response, airway neutrophilia, and diet-induced changes in gut microbiota, which can modify the airway microbiome in asthma [37].

Aging accompanies multiple changes in the body, thereby complicating the pathogenesis of asthma. From a clinical perspective, aging can make it difficult to establish a diagnosis of asthma in elderly patients, which is discussed later. In addition, novel studies exploring the underlying mechanisms of EA are imperative.

5 Approaches to the Diagnosis of EA

5.1 Traditional Approaches to EA

Making an accurate diagnosis of asthma in elderly patients remains a challenge for physicians due to difficulties in the evaluation of airway obstruction, consequences of age-related changes, and the overlap with fixed airway obstruction diseases. Traditionally, a diagnosis of asthma is made based on clinical evaluation and variable airflow obstruction assessed by spirometry [39]. In terms of clinical symptoms, most studies have shown a more severe and uncontrolled status in asthmatic patients aged >65 years than in those who are younger [1, 17, 26, 40]. In contrast, a study of very old (>80 years) patients with asthma showed no differences regarding clinical features compared with younger patients [41]. However, that subgroup could bias the results because they belong to a “rare population” [41].

Use of spirometry in elderly subjects may encounter technical difficulties, including improper performance of spirometry and incorrect interpretation of spirometric curves [1, 5, 9, 17, 42]. It is noteworthy that if technicians are adequately trained, most patients with EA are able to correctly perform spirometry [43, 44]. However, EA patients with cognitive impairment may have difficulty in conducting spirometry adequately [45]. Additionally, a fixed cutoff FEV₁ value of 80 % and a Tiffeneau-Pinelli index of 70 % due to a decline in lung function lead to the over-diagnosis of airway obstruction [1]. Therefore, the lower limits of normal for the Tiffeneau-Pinelli index in subjects aged 65–85 years are suggested to be 56–64 %, respectively [46]. In addition, forced expiratory volume in the first 6 s and relaxed vital capacity have been reported to be alternative measurements of lung function [42, 47]. Patients with EA show enhanced airway hyperactivity, but are less likely to recognize bronchoconstriction during a methacholine challenge [48]. Thus, non-stress pulmonary function tests can be more appropriate in patients with EA.

The role of atopy in EA is unclear because of dysfunction in immune responses. Several cross-sectional studies have shown that after peaking by 20 years of age, total IgE subsequently decreases with age, reaching the lowest level after 70 years of age [1, 49]. The Global Allergy and Asthma European Network (GA²LEN) showed that patients >45 years old had a reduced rate of positive skin prick tests for the following allergens: grass, cat, dog, house dust mite, birch, *Artemisia*, olive, and *Alternaria* [1]. In contrast, several studies have demonstrated the association of allergen sensitization and the occurrence of asthma symptoms in older subjects [50, 51]. Therefore, atopy status needs to be assessed in patients with suspected EA.

5.2 Differential Diagnosis of EA

The differential diagnosis of EA is varied, including congestive heart failure, emphysema, gastroesophageal reflux disease (GERD), tracheobronchial tumors, and, most importantly, COPD. Emphysema can be distinguished from EA by measuring lung density using computed tomography [28]. Discrimination of EA from COPD remains a challenge and requires assessment of multiple factors. EA can be misdiagnosed as COPD or co-exist with COPD in elderly subjects [12]. Indeed, in a multicenter clinical trial, elderly patients were recruited and evaluated for asthma or COPD using questionnaires and spirometry. COPD was misdiagnosed in 19.5 % of EA patients, whereas 27.3 % of patients had not displayed any asthma symptoms previously [52]. Commonly used determinants to differentiate between asthma and COPD in younger subjects can be compounded by aging as outlined in Table 1 [1, 12, 17, 18, 28, 49, 53–58]. For example, in a cohort of Turkish patients with EA, male patients, heavy

smokers, and ex-smokers showed a longer duration of EA [53]. About one-third of adult asthmatic patients are current smokers [59]. These results render smoking less convincing in differentiating between the two diseases. In addition, atopy has little value for discriminating between COPD and EA [53]. Fixed airway obstruction was also observed in a group of patients with EA [57]. A few studies have used FeNO, a biomarker for airway inflammation, and the diffusing capacity of the lung for carbon monoxide to differentiate asthma from COPD [54, 55]. However, these results have not been replicated and require more advanced studies.

Given that there is currently no ‘gold standard’ for the discrimination between asthma and COPD, a multifaceted evaluation is imperative for patients with suspected EA and/or COPD. Recently, alternative approaches have been proposed, focusing on the measurement of airway inflammation [12]. There is increasing evidence showing the heterogeneity of sputum cellularity in both diseases, including airway eosinophilia status in COPD patients and airway neutrophilia in asthma [12, 60, 61]. This is of interest as the patterns of inflammatory cells can tailor the response to treatment [12]. However, these findings are restricted only to patients with COPD and remain undiscovered in patients with EA.

6 Co-Morbidities in Patients with EA

The frequency of co-morbid conditions is higher in patients with EA than in younger adult asthmatic patients, with more than 80 % of elderly asthmatic patients having accompanying co-morbidities [8, 62]. The patterns of co-morbidities

differ among different countries. For example, in a survey conducted in the USA in patients with poorly controlled asthma, including elderly patients, EA patients frequently have co-morbidities that lead to activity limitations, such as hives, chronic sinusitis, arthritis, GERD, hypercholesterolemia, and depression [63]. A retrospective, observational study conducted in Korean elderly asthmatic patients revealed a pattern of co-morbid diseases as follows: allergic rhinitis (AR) and/or nasal polyp (76.9 %), cardiovascular disease (65.7 %), chronic pulmonary disease (29.6 %), diabetes mellitus (22.2 %), GERD (15.7 %), malignancies (10.2 %), arthritis (8.3 %), IgG subclass deficiency (8.3 %), and depression (5.6 %) [8]. Co-morbidities impact negatively on quality of life (QoL) and worsen respiratory symptoms and sleep disturbance [64–66]. They are also associated with increased mortality, more emergency department visits, and low adherence to medication use [8, 62, 66]. Identification of co-morbidities should be considered in patients with EA in order to achieve better asthma control. In Sects. 6.1–6.5, we have reviewed the associations and impacts of five major co-morbid diseases on patients with EA: COPD, chronic rhinosinusitis, obesity, depression, and hypertension.

6.1 Chronic Obstructive Pulmonary Disease

Asthma and COPD are considered distinct disease entities, but recent guidelines have defined the asthma–COPD overlap syndrome (ACOS) as an independent disease entity [39, 56]. The prevalence of ACOS is estimated to be approximately 20 % [67]; in elderly patients, the

Table 1 Common determinants for differentiating between asthma and chronic obstructive pulmonary disorder and their limitations in older adult asthmatic patients

Determinant	COPD	Older adult asthmatic patients
Age of onset	COPD usually occurs after the age of 40 years [56]	Adult-onset asthma can occur in EA [1, 12, 17]
Variability of symptoms	Symptoms progress over time [12]	In EA, fixed airflow obstruction can exist [57]
Response to bronchodilators	COPD patients respond partially to bronchodilator [12, 39]	Response to bronchodilators can be reduced in EA [28]
Smoking	History of smoking [12]	In one study, 25 % of patients with EA had a history of smoking [53]
Atopy	Usually non-atopic [12]	Atopy rate reduces with advancing age [1, 49]
FeNO	Cutoff value of 35 ppb can identify patients with asthma–COPD overlap [54]	In stable EA, FeNO is not elevated and not associated with the subject’s symptoms [55]
DLCO	DLCO is often reduced [120]	DLCO should be normal in elderly asthma [18] A subgroup of adult, non-smoking patients with asthma presents unsuspected mild emphysema [58]
Treatment trials of a short course of systemic corticosteroids and 3 month-course of ICS	COPD with eosinophilic asthma is prone to respond to corticosteroids [12]	Patients with non-eosinophilic asthma may be less responsive to corticosteroids [12]

COPD chronic obstructive pulmonary disorder, *DLCO* diffusing capacity of the lung for carbon monoxide, *EA* elderly asthma, *FeNO* fractional exhaled nitric oxide, *ICS* inhaled corticosteroids

prevalence increased to 29–78.2 % [68–70]. Co-existence of COPD with EA contributes to worse clinical outcomes that result in higher medical costs than asthma alone [68, 71]. The Italian observational study ELSA (ELderly Subjects with Asthma) revealed that patients with ACOS are associated with lower Modified Medical Research Council dyspnea scores, lower mean of Asthma Control Test scores, higher rate of asthma exacerbation, and lower predicted values of percentage FEV₁ (FEV₁%) and percentage forced vital capacity (FVC%) [69]. Similarly, a multicenter population-based survey undertaken in five Latin countries indicated that patients with ACOS are associated with worse general health status, higher exacerbation risk, and more frequent hospitalization than COPD patients [72]. In a Korean population, we found a similar result, showing that patients with ACOS have worse self-related health [73]. However, ACOS remains debatable due to inconsistent definitions and a paucity of studies on phenotyping and underlying mechanisms [74]. Treatment modalities for ACOS include a combination of inhaled corticosteroids (ICS) plus long-acting β_2 -agonists (LABA) and/or long-acting muscarinic receptor antagonists [74–76]; LTRAs can be beneficial in ACOS patients with atopy [77]. Given that our understanding of ACOS is still limited, especially in the elderly population, further studies are required to establish the definition and sub-phenotypes of ACOS, with which physicians would be able to perform long-term interventional studies for elderly patients with ACOS.

6.2 Upper Airway Disease

Asthma, AR, and chronic rhinosinusitis (CRS) commonly occur in all age groups. CRS is common in all EA patients, although younger EA patients more commonly have AR [1, 78]. The GA²LEN study of European patients has demonstrated that CRS without AR is positively associated with adult-onset asthma [79]. In a Swedish cohort of asthmatic patients (age 17–76 years), CRS was associated with reduced QoL [80]. This trend is even more prominent in elderly patients, which could be explained by underestimation of breathlessness or misinterpretation of co-morbidities [80]. In patients with EA, CRS is an independent risk factor for frequent asthma exacerbations and disease severity [81]. Specifically, IgE sensitization to staphylococcal enterotoxins is associated with severe eosinophilic asthma and co-morbid CRS [81]. AR frequently occurs in younger patients with EA and its estimated prevalence is 13–15, 47.6, and 80 % in Switzerland, Italy, and Portugal, respectively [78, 82, 83]. EA is associated with persistent and severe AR [83].

Nevertheless, upper airway diseases are frequently underdiagnosed and undertreated in EA, with 40–60 % of

EA patients with rhinitis being undertreated [82, 83]. This finding highlights the need for a routine evaluation of AR and CRS in patients with EA to improve QoL.

6.3 Obesity

Integrated data from the World Health Organization's SAGE (Study on Global AGEing and Adult Health) survey and the COURAGE (Collaborative Research on Ageing in Europe) survey revealed that 17 % of patients with EA were obese [68]. Elderly patients with abdominal obesity and a high BMI are significantly associated with a high prevalence of asthma compared with normal weight subjects [84–86]. Impacts of obesity on adult asthmatic patients have been fully established, but not so on EA patients. Asthma in obese subjects is regarded as a distinct phenotype [87]. Obese asthmatic patients are susceptible to severe symptoms, and show reduced asthma control and poor responses to ICS [88]. This can be explained by impaired pulmonary function due to anatomical changes in the airway, modifications of immune responses, and systemic inflammatory cytokines such as leptin and adipokines [89, 90]. In addition, obesity is a risk factor for obstructive sleep apnea and GERD, which also affects asthma control [91]. In a Korean study that aimed to phenotype patients with EA, one cluster with high BMI and borderline lung function was identified and showed a relatively high frequency of exacerbations [92]. However, it is still unclear to what extent obesity can influence EA, and thus further studies are warranted.

6.4 Depression

In the data from the SAGE and COURAGE surveys, depression developed in 23 % of patients with EA [68]. A survey of a Korean cohort reported the prevalence of depression to be higher in EA patients than in middle-aged asthmatic (26.7 vs. 24.4 %) and non-asthmatic patients (17.8 % in the elderly, 15.3 % in the middle aged) [23]. There is still controversy as to whether asthma can increase the risk of depression; however, patients with depressive symptoms may have an increased risk of developing adult-onset asthma [93, 94]. The impacts of depression on asthma outcomes are well-known in adult asthma: adult asthmatic patients with depression show significantly increased asthma-related hospitalization, emergency department visits, and general practitioner visits compared with those without depression [95]. In patients with EA, depression leads to poorer asthma control and lower QoL as well as lower treatment compliance [93, 96]. A cross-sectional study of asthmatics aged 20–79 years showed a linear relationship of asthma with the severity of depression (mild depression: odds ratio [OR] 1.68, 95 %

confidence interval [CI] 1.31–2.16; severe depression: OR 3.95, 95 % CI 2.38–6.56). In addition, major depression (moderately severe and severe depression) may reduce bronchodilator responses [97]. However, clinical trials on better outcomes after treatment of depression in patients with EA are limited, and only a few reports have advocated that improvement in depression is correlated with better asthma control [98]. Thus, routine assessment of psychological disorders should be taken into account when treating patients with EA.

6.5 Hypertension

The prevalence of cardiovascular disease increases with aging, with approximately 56 % of patients with EA having hypertension, as shown in the SAGE and COURAGE surveys [68]. From clinical and pathological perspectives, antihypertensive drugs, such as β -blockers (β -adrenoceptor antagonists) and ACE inhibitors, can produce adverse effects, including bronchoconstriction and cough, and thus aggravate asthma symptoms [99]. Systemic high-dose corticosteroid use can induce hypertension and mineralocorticoid-like actions, such as sodium and water retention [100]. Unfortunately, current evidence for hypertension in asthmatic patients is provided only for adult asthmatic patients, and not specifically for elderly asthmatic patients. Adult asthmatic patients are more likely to have hypertension than healthy subjects [101, 102]. Co-morbid hypertension in adult asthmatic patients is related to severe lower airway obstruction, frequent use of medications such as short-acting β -agonists and oral corticosteroids, and frequent emergency department visits or hospitalization [99, 103]. Further studies of patients with EA and hypertension are required to elucidate the association between the two diseases and the management of hypertension in EA patients.

7 Role of Leukotriene Receptor Antagonists (LTRAs) in EA

LTRAs have been developed for asthma treatment, and their efficacy in improving asthma control has been demonstrated in mild to moderate asthma in both adult and pediatric patients [104–112]. Most clinical studies of LTRAs have included a small proportion of elderly subjects, and only a few studies focused on the efficacy of LTRAs in EA patients [104–112]. We reviewed recent studies on the efficacy and safety of LTRAs, especially in EA populations. It is known that no dosage adjustment is necessary for the elderly, for patients with renal insufficiency, or those with mild to moderate hepatic impairment [113]. The effectiveness of LTRA in patients with EA is

discussed here from a clinical and pathogenetic perspective.

7.1 Studies on the Efficacy of LTRAs in EA patients

Table 2 outlines clinical trials conducted in EA patients using LTRAs during the past few years. A randomized, open-label, parallel-designed study conducted for 12 weeks demonstrated the efficacy of montelukast in asthmatic patients older than 60 years [112]. The study subjects had mild asthma and were randomized to take either inhaled budesonide 800 μ g (800BUD) or budesonide 400 μ g plus montelukast 10 mg (MON-400BUD) daily during the 12-week study period. The efficacy of the addition of montelukast to a low-dose ICS was similar to that of a medium-dose ICS. Furthermore, the MON-400BUD group had less frequent asthma exacerbations and adverse events, especially sore throat. This study suggests that the addition of an LTRA to a low-dose ICS can be a better treatment option than doubling the ICS dose for patients with mild EA that is not well-controlled by low-dose ICS monotherapy. Another report studied the efficacy of addition of montelukast to anti-asthmatic therapy in a total of 512 patients with severe EA (patients >60 years of age) who were enrolled and observed over 24 months of therapy [109]. After the first 12 months with a combination of an ICS and LABA (ICS/LABA), two-thirds of the total study subjects were randomly assigned to receive montelukast add-on treatment (active group) and the remaining subjects were assigned to the ICS/LABA treatment (control group). After 24 months, the active group, but not the control group, showed an increased number of asthma symptom-free days, reduced β -agonist use, increased asthma control test scores, and improved asthma control status as defined by the GINA (Global Initiative for Asthma) guideline. A comparative study was performed in patients with mild EA (>65 years of age) to determine the clinical usefulness of pranlukast compared with ICS [111]. A total of 41 elderly patients with mild asthma who were taking step 1 or 2 anti-asthmatic medication were randomly assigned to either the pranlukast or the ICS treatment group for 8 weeks. Both treatment groups showed similar improvement in the use of rescue medication, serum or sputum eosinophil cationic protein levels, and FEV₁, which implies the equivalent clinical efficacy of pranlukast and ICS treatments in patients with mild EA. Taken together, these results showed a non-inferiority efficacy of LTRAs rather than ICS, as well as that the addition of an LTRA to low-dose ICS was not superior to doubling ICS in mild EA. In a study of severe EA, addition of an LTRA to an ICS/LABA showed high therapeutic efficacy in symptoms and asthma control status [109].

Table 2 Summary of clinical trials of leukotriene receptor antagonists in elderly asthma patients

LTRA	Subjects	Comparison group	Study period	Efficacy and safety	References
Montelukast	Patients with mild elderly asthma	Montelukast plus low-dose ICS (MON-400BUD) ($n = 70$) vs. medium-dose ICS (800BUD) ($n = 70$)	12 weeks	At week 12, mean ACT scores were not different between two groups (19.4 ± 4.7 vs. 18.9 ± 4.6 ; $P = 0.525$) The proportion of subjects with an ACT <20 was lower in the montelukast group (35.4 vs. 56.3 %; $P = 0.022$) Total number of asthma exacerbations was lower in the montelukast group (14 vs. 28; $P = 0.016$) Total number of sore throat events was lower in the montelukast group (11 vs. 22; $P = 0.045$)	[112]
	Patients with severe elderly asthma	Montelukast plus ICS/LABA ($n = 341$) vs. ICS/LABA ($n = 171$)	24 months	Mean asthma-free days and mean ACT were higher in montelukast group (78.4 vs. 66.2 % and 18.98 vs. 15.98, respectively; $P < 0.05$ for all) Mean days with β -agonist use were lower in the montelukast group (39.5 vs. 44.1 %; $P < 0.05$)	[109]
Pranlukast	Patients with mild elderly asthma	Pranlukast ($n = 21$) vs. ICS ($n = 20$)	8 weeks	Frequencies of SABA inhalation per week were significantly reduced after treatment in both groups (pranlukast group: 2.80 ± 1.22 to 1.50 ± 1.06 , $P < 0.05$; ICS group: 2.34 ± 0.74 to 1.42 ± 0.64 , $P < 0.01$) Changes in the serum and sputum ECP were significantly reduced after treatment in both groups (pranlukast group: from 14.2 ± 8.89 to 9.08 ± 4.92 $\mu\text{g/L}$, $P < 0.05$, and from 132 ± 203 to 93.5 ± 48.5 $\mu\text{g/L}$, $P < 0.05$, for serum and sputum ECP, respectively; ICS group: from 13.0 ± 17.2 to 9.13 ± 4.31 $\mu\text{g/L}$, $P < 0.05$, and from 220 ± 114 to 134 ± 86.5 $\mu\text{g/L}$, $P < 0.01$, for serum and sputum ECP, respectively) FEV ₁ was significantly increased after treatment in both groups (pranlukast group: from 1446 ± 695 to 1586 ± 729 mL, $P < 0.05$; ICS group: from 1320 ± 348 to 1714 ± 372 mL, $P < 0.05$)	[111]

800BUD budesonide 800 μg , ACT asthma control test, ECP eosinophil cationic protein, FEV₁ forced expiratory volume in 1 second, ICS inhaled corticosteroid, LABA long-acting β_2 -agonist, LTRA leukotriene receptor antagonist, MON-400BUD budesonide 400 μg plus montelukast 10 mg, SABA short-acting β_2 -agonist

7.2 Factors that Contribute Towards the Efficacy of LTRAs in EA

Multiple factors can contribute to the efficacy of LTRAs, including (1) inadequate inhalation techniques; (2) adherence to medication; (3) prevention of adverse effects of ICS; and (4) co-morbidities. Elderly asthmatic patients are prone to poor inhalation techniques due to impaired vision, musculoskeletal problems, or cognitive dysfunction. An observational cohort study involving 433 elderly subjects (>60 years of age) with moderate to severe persistent asthma was conducted to examine the inhalation technique, medication adherence, and their association with health literacy [114]. It found that the inhaler technique was poor:

only 38 and 54 % had good metered-dose inhaler (MDI) and dry powder inhaler (DPI) techniques, respectively. For both devices, exhalation to residual volume and holding the breath for 5–10 seconds were the most frequent errors. Medication adherence was low (38 %) in the total study population. Poor inhaler techniques and low medication adherence were observed in patients with low healthy literacy. Another study on the accuracy of skills in handling inhalers in the general asthmatic population noted that 12.8 % of study subjects using Turbuhaler®, 6.2 % using Diskus®, and 23.4 % using an MDI had a poor inhalation technique [14]. Furthermore, older age was an independent risk factor of a poor inhalation technique in multivariate analysis. A prospective, observational, multicenter cohort

study with a 5-year follow-up of EA patients (>65 years of age) evaluated the factors predicting future asthma exacerbations [6]. This study found that poor inhalation techniques and low adherence to medication can predict future asthma exacerbations in EA patients using logistic regression analysis (relative risk [RR] = 0.57 and 0.62, respectively). In addition, 8 weeks of assistance by caregivers in the inhalation procedure improved the peak expiratory flow and FEV₁ in elderly asthmatic patients (>65 years of age). Collectively, poor inhalation techniques and low adherence to medication predict poor asthma control; therefore, physicians should overcome these factors for better asthma control. Previous studies reported that higher adherence to drug therapy was observed in patients who were taking LTRAs than those who were using ICS. The compliance rates of LTRAs versus ICS were 80.1 versus 69.4 % as estimated by drug packages [109]; 82.1 versus 77.5 % as estimated by a visual analog scale in a Polish cohort of patients with EA [109]; and 93 versus 81 % in a Japanese cohort of EA patients [111]. Additionally, adverse effects of ICS, including voice change, sore throat, and oral thrush, may contribute to low adherence to ICS treatment. The adverse effects of ICS were more frequent in subjects using high-dose ICS than in those using a combination of low-dose ICS and montelukast [112]. Of 28 subjects who had experienced at least one local adverse event during the study period, nine (32.1 %) had asthma exacerbation, whereas five (5.9 %) of 85 subjects without local adverse events had experienced an exacerbation ($P = 0.001$) [112]. This study result implies that adverse events affect adherence, which may eventually influence the asthma outcome. Finally, co-morbidities, such as arthritis, tremor, and cognitive impairment, may result in both poor inhalation techniques and low adherence. Therefore, the clinical features of LTRAs, including better safety and simpler administration, compared with ICS may provide a good strategy for the treatment of EA.

7.3 Pathogenetic Perspective on the Therapeutic Efficacy of LTRAs

CysLTs, which play an important role in asthma pathogenesis, are not completely suppressed by treatment with corticosteroids alone. The effects of LTRAs are suggested to be complementary to ICS, allowing a reduction of the ICS dose in patients with moderate to severe asthma [115]. Despite physiological changes in asthma with fixed airway obstruction, the cytological, histochemical, and inflammatory characteristics of airways in EA have been shown to be unchanged with the development of fixed airflow obstruction [116]. Thus, the inflammatory process of asthmatic airways is not completely affected by age [115]. Collectively, LTRAs may be effective in elderly asthmatic

patients by suppressing inflammatory pathways that are different from those of ICS. Lipoxins, which are derived from the lipoxygenase pathway of arachidonic acid metabolism, have anti-inflammatory effects, in contrast to CysLTs [117]. A study of urinary levels of lipoxin A₄ and CysLT in healthy subjects at different ages has indicated that urinary levels of lipoxin A₄ decrease with age, whereas those of CysLT increase with age. This observation leads us to speculate that LTRAs offer additive efficacy in elderly asthmatic patients.

7.4 New Perspectives of LTRAs

A study on a protective role of LTRAs on the future risk of incident or recurrent myocardial infarction and ischemic stroke was performed in a nationwide population-based Swedish cohort [118]. Montelukast use was associated with a low risk for recurrent myocardial infarction in males (hazard ratio [HR] 0.65; 95 % CI 0.43–0.99) and recurrent stroke in both sexes (HR 0.62; 95 % CI 0.38–0.99). These findings imply the secondary preventive role of montelukast in cardiovascular disease [118]. In addition, considering a higher prevalence of cardiovascular disease in the elderly population than in the younger population, LTRAs may become a first-line drug for elderly asthmatic patients with a history of cardiovascular events.

Given that LABAs are often contraindicated in elderly patients, especially those with co-morbidities, including cardiovascular disease, LTRAs can be used as add-on therapy to ICS. In addition, for the elderly who are concerned about ICS use or who are using high-dose ICS, LTRAs may be a good therapeutic option to reduce the ICS dose.

8 Conclusion

EA should be considered a distinct phenotype with different characteristics to adult asthma. Efforts have been made to establish a universally accepted definition for EA in order to avoid over-diagnosis, under-diagnosis, and even misdiagnosis of EA; however, further studies are warranted. Co-morbidities should be assessed not only in making a proper diagnosis but also in properly managing EA patients. Studies investigating the efficacy of LTRAs in EA patients are limited, and there is insufficient evidence to support LTRAs as a first-line drug therapy [109, 111, 112]. However, previous studies have consistently reported the safety of LTRA in EA patients [112, 119], and there is only one study showing that patients of an older age are less likely to respond to LTRAs using logistic regression analysis [119]. In a specific population, such as elderly asthmatic patients with a history of

cardiovascular/cerebrovascular co-morbidities or those with a poor inhaler technique or low adherence to ICS, LTRAs can be an alternative to ICS or LABAs. In the future, a better understanding of the pathogenesis of EA and the benefits of administration of LTRAs in a specific population of EA patients may help achieve better management and control of EA.

Compliance with Ethical Standards

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