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REVIEW

Use of ICS/LABA (extra-fine and non-extra-fine) in elderly asthmatics

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Alida Benfante
Marco Basile
Salvatore Battaglia
Mario Spatafora
Nicola Scichilone

Biomedical Department of Internal and Specialist Medicine, University of Palermo, Palermo, Italy

Abstract: Age represents an exclusion criterion in randomized clinical trials designed to test the efficacy and safety of inhaled drugs in asthma. As a consequence, data on efficacy and safety of inhaled corticosteroid (ICS) and long-acting β2 agonist (LABA) combinations in elderly asthmatics are scanty. Older age is associated with an increased proportion of comorbid conditions; in addition, all organ functions undergo a process of senescence, thus reducing their ability to metabolize the agents. Overall, these age-associated conditions may variably, and often unpredictably, affect the metabolism and excretion of respiratory drugs. However, pharmacological treatment of asthma does not follow specific recommendations in the elderly. In the elderly, the ICS/LABA combinations may carry an increased risk of local indesiderable effects, primarily due to the lack of coordination between activation of the device and inhalation, and systemic adverse events, mainly due to the greater amount of active drug that is available because of the age-associated changes in organ functions as well as drug-to-drug and drug-to-concomitant disease interactions. The extra-fine formulations of ICSs/LABAs, which allow for a more favorable drug deposition in the lungs at a reduced dose, may contribute to overcome this issue. This review revises the efficacy and safety of treatment with ICSs/LABAs, focusing on the main pharmacodynamic and pharmacokinetic properties of the drugs and highlighting the potential risks in the elderly asthmatic population.

Keywords: aging, comorbidity, lung function, inhaled corticosteroids, long-acting β2 agonists, asthma treatment

Introduction

Asthma in the elderly poses enormous challenges to the physicians, mainly because of the lack of clear knowledge on its pathogenetic mechanisms and pathophysiological characteristics, which lead to the erroneous assumption that asthma in older ages replicates the structural and functional changes that occur in younger ages. The age-associated abnormalities of the lungs, which have been largely demonstrated in the past,[1] are responsible for functional changes, such as the reduction in lung elastic recoil and the occurrence of lung hyperinflation that, in turn, may affect the cardinal features of asthma. Indeed, asthma in older ages tends to lose the "reversible" component of airway obstruction, which has diagnostic and therapeutic implications. Another important aspect of the disease in the elderly is the impact of senescence of the immune system on the pattern of airway inflammation. A phenomenon of immunosenescence has been largely described,[2,3] leading to the concept that the inflammatory factors of asthma in the most advanced ages may not be the same as in younger ages, or may not be as active as in the younger ones. Again, not taking these changes into consideration when approaching asthma in older ages may cause erroneous decisions in the choice of proper treatment.

Correspondence: Nicola Scichilone
Dipartimento Biomedico di Medicina Interna e Specialistica, University of Palermo, Via Trabucco 180, 90146 Palermo, Italy
Tel +39 91 680 2655
Fax +39 91 688 2842
Email nicola.scichilone@unipa.it

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The approach to the pharmacological management of asthma in the elderly follows guidelines developed for younger patients with asthma.[4] Published data on effectiveness of current inhaled medications in the elderly are scarce, mainly because age represents an exclusion criterion for eligibility to clinical trials. In addition, studies have shown that T-helper-2 immune deviation may not be generalizable to all patients with asthma, and this is particularly true for the elderly in whom other endotypes of asthma have been described.[5–7] The pharmacological treatment of asthma in elderly population is strongly influenced by the peculiar conditions of this age-group. Older age is associated with an increased proportion of comorbid conditions that can, to a variable and often unpredictable extent, influence the metabolism and excretion of respiratory drugs and may therefore negatively impact on the efficacy and safety of inhaled drugs. For these reasons, the management of asthma in the elderly requires a multidisciplinary approach to obtain the optimal control of symptoms.

Inhaled corticosteroids (ICSs) are the cornerstone of asthma treatment, reducing hospital admissions and mortality in the asthmatic population.[8] The long-term use of ICSs has raised safety concerns, although benefits have been proven to largely overcome the risks. When full control of the disease is not achieved, the addition of long-acting β2 agonist (LABA) is recommended.[4] If, on the one hand, inhaled treatment with ICSs/LABAs represents the first-line treatment for asthma, concerns are raised on the efficacy and safety of these drugs in the advanced ages. This review revises the available evidence on the efficacy and safety of ICSs and LABAs in elderly asthmatics and speculates on the potential remedies to implement the beneficial effects and reduce the risks of ICSs/LABAs. Although this is intended as a narrative review, we used a structured approach for PubMed search of articles of interest to identify articles specifically focused on elderly populations. First, a predefined search was performed by using the entry terms "elderly", "aging", "ageing", or "older" in the field "title" for articles published in English in the past 10 years. Second, the reference lists from relevant eligible studies were also hand-searched for articles of interest. Finally, additional articles were identified in a broader (ie, less specific) search using the MeSH terms "aged" and "aged, 80 and over". The latter was however less effective, because it mainly selected studies in which elderly patients were recruited as part of the larger sample size, and very often these articles did not include (sub) analysis for the elderly.

Inhaled corticosteroids

Is airway inflammation responsive to treatment?

Airway inflammation in asthma is usually characterized by the presence of eosinophils, which are the main targets of treatment with ICSs. The neutrophilic inflammatory phenotype is less likely to respond to ICSs. In elderly asthmatics, neutrophilic airway inflammation has been shown to be more common than in younger ages:[9] does this imply that, in clinical practice, direct (sputum) or indirect (markers of inflammation in the exhaled air) assessments of the predominant type of inflammation should be pursued? Currently, there is no evidence that this is the case. We suggest that the use of ICSs in the elderly should primarily take into consideration safety issues. In this respect, asthma treatment in the elderly is usually complicated by impaired coordination when using the inhaled device, increased number of comorbidities, and multiple concomitant treatments.[10] These factors may influence the inhaled treatment and potentially lead to serious side effects. As a result, optimal pharmacological management strategies may be more difficult to be established in this population.

Do ICSs carry the risk of local and systemic side effects?

Although the occurrence of side effects of ICSs is lower compared with that of systemic corticosteroids, the long-term use of high doses of ICSs seems to be associated with an increased risk of local and systemic side effects, particularly in the geriatric populations. The most frequent local side effects are dysphonia, oral candidiasis, and hoarseness, which can be reduced using a spacer and rinsing the mouth.[11] The most frequent systemic side effects are cataract, glaucoma, skin thinning, diabetes, osteoporosis, and pneumonia, which are associated with the suppression of hypothalamic–pituitary–adrenal (HPA) axis function.[12] The HPA axis suppression is a pharmacodynamic (PD) effect, and its magnitude is related to the dose, the duration of treatment, and the timing of corticosteroid administration.[13] As a general rule, the lowest possible ICS dose is recommended to minimize complications. In particular, the monitoring of ocular pressure may be mandatory in patients on long-term ICS therapy,[14] and bone-protective drugs may be indicated. In this respect, the characteristics of extra-fine ICS/LABA formulations provide significant advantages in lowering the occurrence of side effects. First, the slower velocity and the longer

duration of the plume facilitate hand-breath coordination, thus reducing the amount of drug deposited in the mouth. Second, similar clinical benefit can be attained with a lower dose of the drug,[15] minimizing the risks of drug-related systemic adverse events.

The association between the occurrence of pneumonia and the long-term use of ICSs in asthma is a matter of debate. The incidence of pneumonia is highest at the extremes of age[16,17] and represents one of the major causes of mortality and morbidity in elderly individuals.[18] Important risk factors for the development of pneumonia in the elderly includes age >70 years, asthma, immunosuppression, alcoholism,[19] suspected aspiration, low serum albumin level, swallowing disorders, and poor quality of life,[20] and in particular, the relative risk (RR) of asthma is estimated to be 4.2.[17] The available literature on the association between community-acquired pneumonia and the use of ICSs in elderly asthmatic patients is scanty, and the data are extrapolated by the findings of studies conducted in the general population. A recent meta-analysis performed by Bansal et al[21] investigated the role of ICSs on the incidence of pneumonia in asthmatics with controversial findings: on the one hand, the analyses of randomized clinical trials (RCTs) show a decreased risk of pneumonia in patients treated with ICSs (RR, 0.74; 95% confidence interval [CI], 0.57–0.95; *P*-value, 0.02) suggesting a protective role of ICSs; on the other side, an increased risk of pneumonia is registered in some observational studies.[18,19] These differences are probably explained by a greater risk of bias carried out by the observational studies. In particular, the case–control study by McKeever et al[22] underlines an increased risk of pneumonia in patients under high doses of ICSs, especially of fluticasone propionate (FP; odds ratio [OR], 1.87; 95% CI, 1.63–2.15), budesonide (BUD; OR, 1.26; 95% CI, 0.96–1.65), and beclomethasone dipropionate (BDP; OR, 1.24; 95% CI, 0.99–1.54), compared with low doses of ICSs, suggesting a dose-dependent relationship. In contrast, in the study by O'Byrne et al,[23] the high dose of ICSs (BUD or FP) does not appear to show an increased risk of pneumonia. This retrospective analysis on ~15,000 individuals demonstrates an increased incidence of pneumonia with age in patients who did not assume ICSs, especially in the elderly (>60 years). Conversely, the RR of pneumonia appears to decrease in elderly subjects who take ICSs.

In this scenario, the role of ICSs in the development of pneumonia in elderly asthmatics is unclear, and more studies are required to clarify the potential association. It is important to underline that asthma per se is an independent risk factor for pneumonia in the elderly.[24] Overall, the best therapeutic strategy could be the use of ICSs at the lowest effective dose which are able to control asthma. Obviously, it should be recommended to prevent or minimize other risk factors for pneumonia, such as the functional and nutritional status, avoiding when possible the impairment of renal and hepatic functions. It is known that respiratory diseases, diabetes mellitus, chronic heart diseases, and smoking habitus not only are important risk factors for the development of pneumococcal pneumonia but also can increase the mortality rates for all ages.[25] In this regard, the role of pneumococcal vaccination remains controversial. *Streptococcus pneumoniae* is the major infectious agent in bacterial pneumonia. Although several studies have demonstrated its efficacy in preventing pneumococcal diseases such as otitis media, asthma exacerbations, bronchitis, and other pneumococcal-related diseases also in the elderly people, there is no definite evidence on its specific protective role in avoiding pneumonia in the elderly.[26,27]

Pharmacokinetic (PK) and PD properties of ICSs

Safety and efficacy profiles of ICSs are influenced by the PK and PD properties of the drugs.[28] The PK and PD characteristics of the currently available ICSs may differ, and they should be taken into account in clinical practice. The PK characteristics are crucial for the anti-inflammatory activity of the ICSs, as well as for their safety[28,29] An ideal ICS should be characterized by PK parameters that minimize the side effects and maximize the efficacy; ie, it should be characterized by high pulmonary deposition and residency time, low systemic bioavailability, and rapid systemic clearance. Several properties describe the PK and PD properties of an ICS:[30–32] receptor affinity, bioavailability, particle size and formulation, half-life, protein binding, bioactivation, lipophilicity, lipid conjugation, and metabolism. With regard to the formulation, the development of small particles has allowed to obtain extra-fine formulations that lead to a greater proportion of particles to be deposited in the lungs and minimize the local and systemic side effects associated with the deposition in the mouth and in the stomach, respectively. This was addressed by Nicolini et al,[33] who reported that the 24-h systemic exposure of the active ICS was 35% lower with the BDP/formoterol fixed combination as compared to non-extra-fine BDP and formoterol given with separate inhalers. The 1:2.5 clinical equivalence ratio between extra-fine BDP and non-extra-fine BDP is clearly described in the review article by Vanden Burgt et al.[34]

The vast majority of ICSs are inhaled in their pharmacologically active form, whereas ciclesonide (CIC) and BDP are inhaled as inactive drugs. The latter undergo a process of bioactivation and are converted into their active metabolites by esterases located in the lung epithelium.[29,35] The protein-binding activity contributes to the ICS safety profile, since only the free drug is pharmacologically active. It widely differs among currently available ICSs: 71% for triamcinolone acetonide (TAA), 87% for BDP, 88% for BUD, 98% for mometasone furoate (MF), and 99% for CIC.[36] The receptor-binding affinity is the potency by which corticosteroid binds to its cytoplasmatic receptor.[37–39] It is expressed in terms of relative receptor affinity (RRA) with reference to the known standard dexamethasone. RRA widely differs between ICSs and has implications for the clinical safety profile. The pulmonary bioavailability corresponds to the rate of deposition of the ICS in the lungs, accounting for the efficacy of the drug. The blood concentration of an ICS is the sum of the pulmonary and orally absorbed fractions.[28] Oral bioavailability corresponds to the dose that is swallowed and is available for systemic absorption from the gastrointestinal tract, thus increasing the risk of systemic side effects.[24,40–42] The oral bioavailability of ICSs differs widely from <1% for CIC, MF, and FP to 15% for BDP.[43–46] The bioavailability may be also affected by the process of bioactivation by first-pass metabolism of the liver that can be altered in the most advanced ages. A faster metabolism usually is associated with lower concentrations, reducing the risk of systemic side effects. ICSs are rapidly cleared by multiple organs, primarily the liver, after systemic absorption. The half-lives of available ICSs range from 1.6 to 14.4 h.[28,31] The lipophilicity of ICSs facilitates the passage of the drug through the phospholipid bilayer of cell membranes, positively correlating with the pulmonary retention time and volume of distribution of the drug. However, it may also alter the ICS distribution after systemic absorption, facilitating the drug accumulation in other body tissues. The lipophilicity varies widely among the available ICSs; lipid conjugation is characterized by a reversible chemical bond between fatty acids and ICSs.[47] Lipid conjugation makes the drug available for binding to glucocorticoid receptors; it follows that the lung residence time is prolonged resembling a slow-release reservoir in the tissue. Lipid conjugation has been reported for BUD,[48] TAA,[49] and desisobutyryl–CIC.[35] The mechanism of lung retention allows for the once-daily administration of the drug, minimizing the concentration of the free drug in the circulation and, therefore, the risk of systemic effects. The efficacy of once-daily dosing with CIC has been shown in clinical trials in comparison with placebo, BUD, and FP.[50] Furthermore, Szefler et al[51] demonstrated no appreciable adverse effects on endogenous cortisol secretion after short- and long-term treatment of asthma with CIC.

Do PD and PK characteristics of ICSs change in the elderly?

Elderly subjects experience more adverse side effects because of PD and PK changes and particularly drug–drug and drug–disease interactions. Toogood[52] reported that the long-term administration of doses as high as 2,000 μg of BDP does not affect calcium and phosphate metabolism in the elderly. However, this risk may increase in the presence of predisposing metabolic disorders, which are common among geriatric subjects.[53] From a clinical perspective, attention should be paid to the main determinants of drug interactions, such as first-pass metabolism and bioavailability. The hepatic metabolism of ICSs is influenced by changes in the activity of cytochrome P450 (CYP3A4).[54] Obviously, the use of lower efficacy dose of ICSs is recommended in the elderly, whereas the withdrawal of the ICS becomes mandatory if prolonged coadministration of enzymatic inhibitors is required. An alternative approach is the use of an ICS metabolized through a process of hydrolysis such as BDP. The PK profile of inhaled BDP/formoterol extra-fine fixed formulation was assessed in healthy volunteers as well as in patients with asthma. In their review article,[33] Nicolini et al reported findings from a study on 12 volunteers who were exposed to receive, in single dose, either four inhalations of BDP/formoterol 100/6 μg (400/24 μg), or an equipotent non-extra-fine regimen of BDP and formoterol given via separate inhalers (1,000 μg BDP non-extra-fine and 24 μg formoterol) or placebo, in an open, three-way crossover design. The plasma levels in the first 30 minutes, which are considered as an index of pulmonary deposition, were 86% greater with BDP/formoterol than with the concurrent administration.

Long-acting β2 agonists

Is airway smooth muscle responsive to treatment?

β2 adrenergic receptors (β-ARs) are present in high concentrations in the lungs.[55] They are divided into three types: β1, β2, and β3, with ~70% of pulmonary β-ARs belonging to the β2-AR subtype. These receptors are localized in the airway smooth muscle, epithelium, vascular smooth muscle, and submucosal glands,[56,57] whereas β1-ARs in the lungs are confined to glands and well represented in the alveoli.[58] The density of β2-ARs tends to increase with increasing airway

generations, including the alveoli.[59] The β2-AR stimulation induces airway relaxation; however, persistent and prolonged activation of β2-AR leads to a decrease in receptor responsiveness.[60] This phenomenon should be taken into account in the context of chronic treatments.

Do LABAs carry the risk of local and systemic side effects?

Because of the widespread distribution of β2-ARs, the risk of undesired responses is common when LABAs are absorbed into the systemic circulation.[61,62] It is commonly accepted that selective β2-AR agonists are safer than nonselective β-agonists. β2-ARs are present in the atria and ventricles.[61,62] It follows that LABAs should be used with caution in asthmatic patients with hyperthyroidism or cardiovascular diseases (arrhythmias, hypertension, QT interval prolongation), the latter being almost the norm in the elderly.[61,62] Hypokalemia is a potential side effect that can occur as a consequence of skeletal muscle stimulation by LABAs, which facilitate intracellular accumulation of K^+, thereby lowering plasma levels. This is augmented by the LABA-mediated vasodilation at the level of the skeletal muscles, which contributes to the increase in skeletal muscle K^+ levels.[63] Several studies have shown a dose-related reduction in serum K^+ levels with increasing doses of β2-agonists,[64] although there is some evidence that tolerance develops after regular treatment.[65] By inducing hypokalemia, β2-agonists may precipitate arrhythmias,[66] and hypokalemia can be aggravated by concomitant treatments promoting potassium loss, such as diuretics, ICSs, and theophylline. Combining thiazide and loop diuretics with LABAs may enhance hypokalemia and, therefore, the risk of electrocardiogram modifications, especially with doses that are above the recommended range.[67] Prior treatment with diuretics has been shown to increase the hypokalemic and electrocardiographic effects of inhaled albuterol.[68]

An interesting and largely unknown phenomenon is the transient and mild decrease in partial pressure of oxygen in arterial blood (PaO_2) following the administration of LABAs to obstructive patients, despite concomitant bronchodilation. This has been attributed to the pulmonary vasodilating action of these agents[69] as a result of the activation of β2-ARs that are present in pulmonary blood vessels,[70] increasing blood flow to poorly ventilated lung regions and thus increasing ventilation–perfusion inequality, as shown in asthmatics.[71] This effect does not seem to be relevant in clinical practice. LABAs should also be used with caution in patients with diabetes because of the risk of ketoacidosis. β2-AR stimulation in the liver induces glycogenolysis and therefore raises blood sugar levels.[72]

The other side of the coin is the use of β-blockers in asthma. Although cardioselective β-blockers have been developed to selectively target β1-ARs, they tend to be only relatively selective and exert significant β2-AR antagonism at therapeutic doses, although to a lesser extent than nonselective β-AR blockers such as propranolol.[73] In fact, there is considerable risk of bronchospasm in asthmatic patients. Nonetheless, an observational study showed that the β-AR blocker did not worsen health conditions when added to a LABA.[74]

How relevant are LABA-associated side effects in subjects with preexisting cardiac diseases?

Obviously, the side effects commonly associated with the LABAs are mostly referred to the heart, especially in the context of preexisting cardiac diseases. In patients with heart failure, bronchodilators have been demonstrated to worsen the cardiac condition and to affect mortality.[75] Higher mortality rates were observed in LABA users (mean age: 70.6 years) compared with controls.[76] However, this higher risk disappeared after adjustment of the survival curves for confounders, including the severity of concomitant diseases and B-type natriuretic peptide levels.[76] A population-based nested case–control study,[77] carried out in Taiwan, compared >7,000 cases with atrial fibrillation with ~10,000 controls of mean age of 71 years and showed that asthma was a risk factor for atrial fibrillation, with an OR of 1.2. The risk was independent of asthma medications and comorbidities and was higher in steroid and bronchodilator users, especially in new users (OR =2.85).[77]

In patients with heart failure in the absence of chronic obstructive pulmonary disease (COPD), inhaled β2-agonists are associated with worse outcomes.[78] Interestingly, however, the acute administration of β2-agonists improves the cardiac performance in patients with heart failure in a dose-dependent manner,[73] and they are often used for the short-term enhancement of heart contractility. Although useful acutely, the long-term use of β2-agonists leads to increases in mortality[79] The Washington DC Dilated Cardiomyopathy Study compared 129 subjects with newly diagnosed idiopathic dilated cardiomyopathy with 258 control subjects[80] and found a strong association between idiopathic dilated cardiomyopathy and β2-agonist use (OR =3.2). In particular, one out of five subjects had a reported history of LABA use compared with <10% of the control subjects. These findings were not confirmed in another study.[81]

The underlying physiological mechanism by which β2-agonists may exacerbate heart failure is based on the fact that β1-ARs are downregulated and desensitized in patients with systolic dysfunction, with a relative increase in β2-ARs.[73] β2-agonists augment the cardiac function, but the long-term exposure induces downregulation and desensitization of myocardial β2-ARs. In this context, the long-term inhaled salmeterol therapy (100 μg bid) was shown to improve pulmonary function without the augmentation of neurohormonal systems or ventricular ectopy in subjects with symptomatic heart failure.[82] The safe profile of salmeterol was also confirmed by another study,[83] at least at the recommended doses. A further side effect of selective β2-agonists is a fine tremor of skeletal muscle, particularly of the hands.[63] The tremor has been closely correlated with the hypokalemia, as a result of the raised intracellular K^+ levels in skeletal muscle.[63] However, tolerance to the tremorogenic effects of β2-agonists occurs with their long-term use.[84,85] Albuterol, terbutaline, and fenoterol can induce suppression of appetite, headache, nausea, and sleep disturbances,[86,87] due to their ability to cross the blood–brain barrier, with a consequent effect on central nervous system.[88] The use of indacaterol can seldom elicit cough, although it is mild and transient and declines with the duration of treatment.[89]

Anticholinergic drugs may represent an alternative to LABAs; however, their use in the elderly should take into consideration the potential risk of side effects. The anticholinergic response is different in elderly asthmatics due to the decrease in parasympathetic activity and reduction in receptor numbers with aging.[90] The most frequent side effects are dry mouth and unpleasant taste, which in the elderly may alter the ability to speak, mucosal damage, and respiratory infection due to the reduction in antimicrobial activity of saliva.[91] Theophylline use is limited by its narrow therapeutic range and by the risk of interaction with several drugs. Since the most frequent side effect is the occurrence of arrhythmias, it should be avoided in elderly patients with cardiac diseases.

RCTs have confirmed the efficacy of leukotriene receptor antagonists (LTRAs) when added to ICSs in improving symptoms, lung function, quality of life, as well as asthma-related hospitalizations and mortality.[92–95] Yasui et al[96] showed that additional administration of oral pranlukast to ICSs in stable asthmatics provided additional clinical benefit. Interestingly, add-on oral pranlukast was found to significantly reduce the levels of alveolar nitric oxide, suggesting that the clinical benefit of oral pranlukast could be mediated by the reduction in peripheral airway inflammation. Available studies specifically addressing the role of montelukast in the elderly are scarce; in a multicenter study, asthmatics aged 18–79 years were randomized to receive montelukast or placebo on top of regular treatment with BUD for 16 weeks.[92] In the LTRA arm, a 35% reduction in exacerbations was recorded compared with placebo, with no additional adverse events. Overall, LTRAs have been demonstrated to be safe in this age range. In elderly patients, the simpler route of administration of LTRA, compared with the inhaled one, could represent a more effective strategy in improving the outcomes of asthma therapy.

Do age-associated changes and real-life conditions influence the responses to LABAs?

Aging-related modifications in lung mechanics, in receptor populations, and in nervous system control might be responsible for a different effectiveness of bronchodilators in elderly patients compared with younger subjects.[97] A modification of bronchodilator responses to β2-AR agonists in elderly people has been suggested.[98] There is considerable evidence relating to the reduction in β2-AR affinity (or a reduced percentage of high-affinity receptors) with increasing age, possibly in association with receptor internalization in membrane-bound vesicles.[99] The bronchodilator effects of albuterol after methacholine-induced bronchoconstriction were tested in a study carried out in healthy elderly individuals.[98] The study showed that the elderly group (age range, 60–76 years) had a lower sensitivity to bronchodilator effects of albuterol and was interpreted by the authors due to an age-related decrease in airway β2-AR responsiveness. However, a retrospective analysis showed that aging does not affect bronchodilator response to β-AR agonists after methacholine-induced bronchoconstriction.[100] Furthermore, a study aimed at exploring the effect of age on bronchodilator responses in acute severe asthma concluded that age is not a predictor of response to β2-agonists.[101] However, in this study, the age groups were arbitrarily established using the cutoff of 35 years of age, which is inadequate to infer on elderly patients' responses to treatment.

The question is whether LABA use in real-life scenario may provide information that is unknown from RCTs. It is widely accepted that the use of LABAs alone is harmful in asthma, as warned by the Food and Drug Administration (FDA)[102] Nevertheless, in clinical practice, this warning may be disregarded in the elderly due to the confusion (ie, misdiagnosis) with COPD. In this context, a recent German study[103] aimed at evaluating the change in prescriptions of LABAs and ICSs in asthma after

the FDA warning. Although an increase in appropriate LABA prescriptions was observed, the results demonstrated that the prevalence of LABA users without ICSs (ie, wrong use) steadily increased with age, with a peak of 19.1% in asthmatics aged 80–90 years, and this proportion was even higher in males.[103] The authors proposed that the concomitant presence of COPD (ie, asthma–COPD overlap syndrome) could explain the observed findings. In the context of real-life settings, Pauwels et al[104] evaluated the safety of formoterol compared with salbutamol as rescue medication. In this study on ~18,000 patients, the elderly (>65 years) were 10% of the entire sample. No differences between the study treatments for safety variables related to age were reported, and a good safety profile for formoterol was demonstrated. However, it is interesting to highlight that adverse events and rates of discontinuation due to an adverse event increased with age, and the incidence was higher with formoterol in all subgroups.[104] On the other hand, the same study showed that the reduction in the risk of an exacerbation increased with age for users of formoterol as rescue medication. It is interesting to evaluate the characteristics of patients with severe asthma attacks. They showed lower use of ICSs and higher use of short-acting β2 agonists in 3 months before the hospitalization for severe acute asthma, compared with outpatient asthmatics.[105] In the same study, the authors proposed five clusters of patients with severe attacks; among them two are of interest for the purposes of the current review: 1) female-predominant elderly asthma and 2) male-predominant COPD-overlapped elderly asthma. The first cluster showed female predominance with the mean age of 65 years, high prevalence of concomitant rhinosinusitis/nasal polyposis, and the longest disease duration. The second cluster consisted of mainly males with the mean age of 68 years and high prevalence of concomitant smoking exposure and COPD.

To date, little information is available on new LABAs. Olodaterol has been investigated in moderate-to-severe asthma.[106] In this study, adverse events in the placebo and active treatments were similar; however, only seven out of 206 patients were aged >65 years, thus making impossible to draw any conclusion. It is important to point out that data on differential responses of elderly asthmatics to standard therapies are lacking, since most patients enrolled in RCTs are young.[107]

How do ICSs/LABAs work in real-life settings?

Our group demonstrated that RCTs often exclude elderly asthmatic subjects, mainly due to the presence of comorbidities.[107] For this reason, real-life (or pragmatic) studies may be useful in addressing unanswered questions regarding the safety and efficacy of ICSs/LABAs in the elderly. Unfortunately, the vast majority of real-life studies that included a relevant sample of elderly subjects did not perform a specific analysis for this age-group. In this regard, Price et al[108] designed a real-life study to investigate whether switching from FP–salmeterol to extra-fine particle BDP–formoterol is safe and cost-effective in patients with asthma. Although Price et al's study did not carry a specific analysis for elderly individuals, it included a sample (~37% of total) of patients aged 61–80 years. Apparently, the elderly group did not differ from the whole sample, and the study demonstrated that the extra-fine beclometasone–formoterol fixed combination was at least as effective as non-extra-fine fluticasone–salmeterol fixed combination in preventing severe exacerbations, and less costly at the same time.

It is interesting to note that a pragmatic Italian survey[109] pointed out that elderly patients could be less confident with the use of devices for their inhaled therapy, and they may experience more fear compared with younger users. This condition could be, at least in part, responsible for lower efficacy of inhaled therapy in the elderly and should be regularly assessed to enhance coping strategies of elderly patients with their inhalation devices. Indeed, the poor inhaler technique and the low adherence have been identified as factors predicting future exacerbations in elderly adults with asthma.[110]

Conclusion

This review provides an update on the pharmacological management strategies for asthma in elderly populations. In particular, the safety and efficacy profiles of commercially currently available ICSs and LABAs are investigated, including the new molecules such as olodaterol. The most important is the PK and PD properties of the drugs, and their potential relationships with the age-associated changes are explored. Asthma in the elderly can no longer be considered a rare disease, and physicians will have to face it on daily basis. In the context of the pharmacological management of the disease, ICSs/LABAs play a central role; however, it should be emphasized that no formal RCTs have been carried out to establish the efficacy and safety of these inhaled combinations in elderly populations. The internal validity of a trial requires the exclusion of factors (ie, older age and comorbidities) that can affect the outcomes. In the absence of this type of information, the efficacy of ICSs/LABAs in elderly populations must be weighed together with the safety concerns. Studies specifically designed for elderly patients

are largely advocated. Whereas in younger asthmatics this is a trivial issue, the age- and comorbid-associated alterations of the main organ functions interfere with the metabolism and excretion of the drugs, thus potentially reducing their efficacy and/or increasing the risk of adverse events. In addition, the potential for drug-to-drug interactions is high in this age range. Pragmatic studies could contribute to overcome these issues when addressing the efficacy of ICSs/LABAs in elderly populations. Moreover, studies should be designed to compare the conventional pharmacological approach with a comprehensive therapeutic approach that includes a predefined management of the associated pathological conditions, as part of the multidisciplinary treatment. Physicians must be aware that asthma in the elderly is a complex and complicated condition that cannot be properly managed unless a multidimensional assessment and a multidisciplinary approach are in place.

Disclosure

The authors report no conflicts of interest in this work.

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