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REVIEW

Extrafine inhaled corticosteroid therapy in the control of asthma

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Abstract: Small airways disease plays an important role in the pathogenesis of asthma, but assessment of small airways impairment is not easy in everyday clinical practice. The small airways can be examined by several invasive and noninvasive methods, most of which can at present be used only in the experimental setting. Inhalers providing extrafine inhaled corticosteroid particle sizes may achieve sufficient deposition in the peripheral airways. Many studies have reported the beneficial effects of extrafine inhaled corticosteroids on inflammation, ie, on dysfunction in both the central and distal airways in asthmatics, and there are some data on asthma phenotypes in which the small airways seem to be affected more than in other phenotypes, including nocturnal asthma, severe steroid-dependent or difficult-to-treat asthma, asthma complicated by smoking, elderly asthmatic patients and/or patients with fixed airflow obstruction, and asthmatic children. The relevant randomized controlled clinical trials indicate that the efficacy of extrafine and nonextrafine inhaled corticosteroid formulations is similar in terms of primary endpoints, but there are certain clinically important endpoints for which the extrafine formulations show additional benefits.

Keywords: small airways, inflammation, dysfunction, noninvasive evaluation methods, peripheral deposition

Introduction

Asthma has several phenotypes and endotypes with different underlying mechanisms,[1,2] and chronic airways inflammation plays a principal role in airways narrowing, hyperreactivity, and remodeling in all of these conditions. Inhaled corticosteroids (ICS) aim to treat this inflammation locally, to improve asthma control, and to decrease mortality from the disease. Hence, ICS constitute the primary maintenance therapy for patients with persistent asthma.[3] Even so, there are some patients who remain uncontrolled despite therapy,[4–6] and progressive asthma-related worsening of lung function can occur, regardless of the treatment used.[4,7,8] The most recent asthma guidelines recommend treatment according to control, but real-life studies show that optimal control is not reached at all in many patients.[9–11] It has been suggested that one reason for therapeutic failure may be impairment of the small airways.[12,13]

Small airways are ≤2 mm in diameter, and are also called peripheral or distal airways according to their location. Inflammation and structural changes are observed in the distal airways in patients with asthma. These changes may be more marked than those in the central airways,[12] and the lung parenchyma may also be affected beyond the airway wall.[14,15] Given that the total volume and combined surface area of the peripheral airways are much greater than those of the large airways,[16] it has been suggested that

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abnormalities occurring in the small airways may be more important in the pathophysiology of asthma than was once believed.[17–19] Recently developed ICS formulations provide extrafine particle sizes for inhalation, which can penetrate more effectively into the distal lung. The aim of this review is to assess the possible role of extrafine ICS preparations in anti-inflammatory maintenance therapy for asthma.

Inflammation and remodeling in the small airways

Autopsy studies have yielded surprising data regarding the role of the peripheral airways in the pathogenesis of asthma, ie, many researchers have found that the entire length of the airways is affected by pathological processes.[15,18,20–28] In acute fatal asthma, there is marked goblet cell hyperplasia and intraluminal accumulation of mucus throughout the whole bronchial tree, which is particularly pronounced in the peripheral airways.[20,21] Mucoinflammatory exudates occluding the lumen contain more cells in the small airways than those in the larger airways.[21] Tissue taken at autopsy from asthmatic patients who died within one hour of onset of symptoms has been reported to contain infiltrates of T cells, macrophages, and eosinophils in both the large and small airways.[22] In fact, several autopsy studies have shown remodeling in the small airways, which might be caused by persistent inflammation.[18,23–27] Moreover, it is likely that mast cells play an important role in distal lung remodeling in patients who succumb to fatal asthma;[15] at the same time, it must also be mentioned that this type of cell is also claimed to protect lung function in those with severe asthma.[29]

Further, inflammation and remodeling are thought to play a crucial role in bronchial hyperresponsiveness.[23,24,30] Chronic inflammation disrupting the parenchyma can cause loss of alveolar attachment in the small airways, resulting in decreased elastic recoil and increased collapsibility of the small airways in fatal asthma.[18,27,28] Analysis in a model of airways narrowing revealed that thickening of the airway wall, especially in the peripheral airways, is the main cause of narrowing of the airways and is attributable to smooth muscle shortening. Apart from that, wall thickening and loss of recoil are more than additive in their effects on airway responsiveness.[24]

Autopsy studies have been carried out primarily in subjects with acute fatal exacerbations, but data on small airways pathology can also be obtained from living asthmatics. In one study investigating surgical specimens from patients with asthma who underwent thoracic surgery, there was an increase in the numbers of T cells and total and activated eosinophils both in the large and small airways when compared with the airways of healthy controls. However, the number of activated eosinophils was greater in the small airways than in the large ones, indicating similar but more severe inflammation in the peripheral airways as compared with the central airways.[12] In another study investigating the same lung specimens, the investigators found increased interleukin (IL)-5 and IL-4 mRNA-positive cells in the large and small airways and lung parenchyma of asthmatics, but expression of IL-5 mRNA was greater in the small airways than in the large airways.[31] The authors observed increased eosinophil-associated chemokines, including eotaxin and monocyte chemotactic protein-4 mRNA expression, in both the large and small airways of asthmatics compared with nonasthmatics, and showed that expression of eotaxin mRNA correlated with the number of eosinophils present in the airways of asthmatic subjects.[32] Given that traditional ICS reach mainly the larger airways, more severe inflammation observed in the small airways may be caused by suppressed inflammation in the large but not small airways due to regular ICS therapy.[33,34]

Investigation of transbronchial biopsy specimens provides further evidence about the role of small airways pathology in asthma. An interesting study was carried out by Kraft et al, who performed endobronchial and transbronchial biopsies in patients with nocturnal asthma and in those with non-nocturnal asthma at 4 pm and 4 am. Patients with nocturnal asthma had increased numbers of eosinophils in their distal lung parenchyma at night compared with patients with non-nocturnal asthma, but there was no difference in numbers of eosinophils in the proximal airways between the two groups.[14] Other researchers analyzed bronchoalveolar lavage specimens from severely symptomatic, high-dose, oral glucocorticoid-dependent asthmatics as well as endobronchial and transbronchial biopsy specimens, and despite high-dose steroid treatment, they found higher numbers of neutrophils and elevated levels of eicosanoid mediators in specimens from these patients compared with those from mild-to-moderate asthmatics or healthy controls,[35] suggesting persistent proximal and distal airways inflammation in severe asthmatics regardless of use of systemic corticosteroids. Furthermore, other studies investigating bronchial and transbronchial biopsies from severe asthmatics found that severe patients have increased parenchymal infiltration also of mast cells as compared with their large airways.[29,36] The smaller number of mast cells in the large airways may be due to treatment with corticosteroids.[33]

In a recent review, Contoli et al evaluated data on small airway abnormalities in severe asthma, asthma in smokers,

and asthma in the elderly.[37] With ageing and/or a long duration of disease, the elastic fibers in the small airways degenerate, resulting in increased collapsibility and air trapping, with additional development of fixed airflow obstruction over time.[38] Smoking asthmatics are characterized by a faster decline in lung function, frequent exacerbations, worse asthma control, enhanced remodeling,[39] and impaired sensitivity to both inhaled and oral corticosteroids.[40,41] Contoli et al concluded that small airways involvement plays a major role in the pathogenesis of these phenotypes.[37] It follows from this that clinical trials of pharmaceuticals which are able to penetrate the distal segment are needed in these subgroups. Given that it is still an open question as to whether small airways are affected in all asthmatics or only in some phenotypes, further studies seem necessary to phenotype patients according to small airway abnormalities.[37] The abovementioned histological evidence regarding small airway pathology is summarized in Table 1.

Evaluation of small airways function in obstructive lung disease

Measurements of lung function

Using retrograde catheter examination in animal models, low resistance values have been found in the lower airways, which have been demonstrated to contribute less than 10% to total lung resistance.[42] This can be explained by the fact that the total volume of the airways increases with the number of generations of the bronchial tree.[16] Therefore, the small airways normally contribute very little to parameters obtained by standard lung function measurements, which are more reflective of conditions in the large airways; hence asthmatic patients with normal or near normal forced expiratory volume in one second (FEV_1) values can still have small airways dysfunction, as confirmed by a study using invasive measurements with wedged bronchoscopy.[19] Moreover, in another invasive study using endobronchial catheterization, researchers demonstrated an increased contribution of the small airways to total lung resistance in moderate to severe asthmatics with airflow obstruction and in patients with chronic bronchitis or emphysema as compared with mild asthmatics without airflow obstruction and healthy controls. This suggests that the peripheral airways are the predominant site of chronic airflow obstruction.[17] Because traditional spirometric parameters mostly fail to detect small airways impairment, there is a need for other noninvasive methods by which to investigate lung function. The lung function parameter most commonly considered to reflect small airways obstruction is forced expiratory flow at 25%–75% of forced vital capacity (FVC), ie, $FEF_{25\%–75\%}$. Nonetheless, this parameter is highly variable in serial measurements and is influenced by both central airway obstruction and alterations in lung volume due to air trapping or bronchodilation. Further, this parameter fails to correlate with other parameters of air trapping, such as FVC or residual volume (RV)/total lung capacity (TLC)[43] or with inflammation of the small airways, as the research on transbronchial biopsy specimens in patients with severe asthma has demonstrated.[44]

Air trapping frequently results from small airways inflammation, reflects hyperinflation, and causes elevated RV. The RV/TLC ratio is a more valid parameter of small airways impairment because TLC is often increased in patients with asthma,[45] and is more elevated in severe than in nonsevere asthma, so air trapping is considered a characteristic feature of the population with severe asthma.[43] Decreased FVC is also related to air trapping,[46,47] and FVC shows an inverse correlation with RV/TLC.[43] However, this parameter alone is not sensitive enough to air trapping and assumes normal TLC, which can be elevated in obstructive diseases as a means of compensation, hence reduction in FVC should only be used as an air trapping marker in the absence of lung volume measurements.

Nitric oxide

Fractional exhaled nitric oxide has been proposed as a marker of eosinophil inflammation in asthma. The threshold level of ≥3% eosinophils in sputum is usually considered clinically relevant, and a threshold of 42 ppb fractional exhaled nitric oxide value has been confirmed to distinguish between eosinophilic (≥3%) versus noneosinophilic (<3%) asthma with reasonable accuracy. A high dose of ICS and cigarette smoking can decrease this threshold while atopy can increase it.[48] In a 5-year, prospective follow-up study of difficult-to-treat patients, it was observed that asthmatics with high total fractional exhaled nitric oxide (≥20 ppb) had an excessive decline in lung function as compared with patients having low fractional exhaled nitric oxide, and this relationship was even stronger in the subgroup of patients with normal baseline FEV_1, suggesting that this difference was not reflecting large airways impairment but rather small airways impairment.[8]

However, exhaled nitric oxide without further refinement is not selective for small versus large airways, but there are methods which can discriminate between the bronchial and alveolar contribution to production of nitric oxide.[49–52] A higher alveolar nitric oxide level was shown to correlate with small airways dysfunction in a subgroup

Table 1 Histological evidence of small airways pathology in asthma

Authors	Type of specimen	Subjects	Findings in small airways
Hamid et al[12]	Surgically resected lungs	6 asthma, 10 controls	Increased T cells and eosinophils in all asthmatic airways. Greater numbers of activated eosinophils in the small airways.
Kraft et al[14]	Transbronchial biopsy (proximal airway endobronchial and distal alveolar tissue)	11 nocturnal asthma, 10 non-nocturnal asthma	Greater number of eosinophils in nocturnal asthma alveolar tissue at 4 am as compared with non-nocturnal asthma. Greater number of eosinophils and macrophages in the nocturnal asthma alveolar tissue at 4 am as compared with 4 pm. Only alveolar tissue eosinophils correlated with the nocturnal decrement in lung function.
de Magalhães Simões et al[15]	Nasal mucosa, trachea, intrapulmonary airways and peribronchiolar and distal parenchyma	20 fatal asthma, 10 controls	Higher eosinophil content in all studied areas in fatal asthma. The outer wall of small membranous bronchioles is the main site of inflammatory changes in fatal asthma. There is a localized distribution of alveolar inflammation at the peribronchiolar region for mast cells and neutrophils.
Kuwano et al[18]	Autopsied lungs Surgically resected lungs	8 fatal asthma, 7 nonfatal asthma, 15 mild COPD, 15 controls	The membranous airways showed a gradation in wall thickening in fatal asthma > nonfatal asthma > COPD > control.
Aikawa et al[20]	Autopsied lungs	3 died of severe acute asthma attack, 5 died of nonstatus asthmaticus, 4 died of nonrespiratory causes (controls)	Increased goblet percent and mucus in patients who died of a severe acute asthma attack; more dominant in the peripheral airways. Mucus correlated with goblet percent in the peripheral airways.
Kuyper et al[21]	Autopsied lungs	93 fatal asthma, including 19 children	Cells made up a higher proportion of exudate in the small airways.
Faul et al[22]	Autopsied lungs	5 sudden asphyxic asthma deaths	Both proximal and distal tissues showed infiltrates of T cells, macrophages, and eosinophils, with a CD8+ T cell predominance; a high proportion of eosinophils were activated.
James et al[23]	Autopsied lungs	18 asthma, 23 controls	Greater wall area (epithelium, muscle, and submucosa) both in the membranous and cartilaginous airways in asthma.
Carroll et al[26]	Autopsied lungs	11 fatal asthma, 13 nonfatal asthma, 11 controls	Greater total and outer wall areas in the small membranous bronchioles (perimeter <2 mm) in fatal and nonfatal asthma. Structural changes occur in the large and small airways in fatal asthma, but predominantly in the small airways in nonfatal asthma.
Dolhnikoff et al[27]	Autopsied lungs	24 fatal asthma, 11 controls	Increased collagen I and decreased collagen III content in the small airways, increased fibronectin and MMP-1, MMP-2, and MMP-9 content at the outer area of the small airways, increased MMP content in the peribronchiolar parenchyma in asthmatics.
Mauad et al[28]	Autopsied lungs	15 fatal asthma, 9 controls	Increased proportion of abnormal alveolar attachments and decreased elastic fiber content in the small airways adventitial layer and in the peribronchial alveoli (but not in the distal alveoli) in fatal asthma.
Balzar et al[29]	Endobronchial and transbronchial/surgical biopsy tissue	20 severe asthma	The number of inflammatory cells increased toward the periphery, but the percentage of T lymphocytes, eosinophils, monocytes/macrophages, and neutrophils remained at a similar value or decreased from the large to the small airways. In contrast, mast cell number and percentage, as well as the chymase-positive phenotype increased in the small airway regions. Chymase-positive mast cells in the small airway/alveolar attachments lung region correlated positively with lung function.
Minshall et al[31]	Surgically resected lungs	6 asthma, 10 controls	Increased IL-5 and IL-4 mRNA-positive cells both in the large and small airways in asthmatics, but increased expression of IL-5 mRNA in the small airways as compared with the large airways.
Taha et al[32]	Surgically resected lungs	6 asthma, 10 controls	Increased expression of eotaxin and monocyte chemotactic protein-4 mRNA in the large and small airways of asthmatics.

(*Continued*)

Table 1 (*Continued*)

Authors	Type of specimen	Subjects	Findings in small airways
Wenzel et al[35]	Bronchoalveolar lavage fluid Endobronchial and transbronchial biopsies	14 severe, high-dose oral glucocorticoid-dependent asthma, 12 moderate asthma, 6 controls	Higher numbers of neutrophils and elevated levels of eicosanoid mediators in severe asthma.
Andersson et al[36]	Bronchial and transbronchial biopsies	14 uncontrolled asthma, 8 allergic rhinitis, 8 controls	Increased alveolar mast cell density, FcεRI expression and surface-bound immunoglobulin E in asthma.

Abbreviations: COPD, chronic obstructive pulmonary disease; CD, cluster of differentiation; IL, interleukin; MMP, matrix metalloproteinase; FcεRI, low-affinity immunoglobulin E (IgE) receptor.

with stable asthma.[49] Further, in patients with severe asthma, strong correlations were found between alveolar nitric oxide levels and RV/TLC, functional residual capacity (FRC), the slope of the single-breath nitrogen washout curve (dN2), and closing capacity/TLC (see below). Hence, the authors concluded that alveolar nitric oxide is closely related to parameters of peripheral airway dysfunction in patients with severe asthma.[50] Another study showed that patients with refractory asthma had elevated alveolar nitric oxide levels as compared with mild-to-moderate asthmatics or healthy controls and, more importantly, it was claimed that oral prednisolone caused a fall in the alveolar nitric oxide level but doubling the dose of already received nonextrafine ICS therapy did not.[51] However, the limitations of these data must also be pointed out because elevated alveolar nitric oxide in these studies may reflect at least partial back-diffusion of nitric oxide from the conducting airways, so these values must be corrected. Indeed, in a more recent study, corrected alveolar nitric oxide was not elevated in treated severe asthmatics as compared with mild-to-moderate asthmatics or healthy volunteers.[52]

High-resolution CT scanning

High-resolution computed tomography (CT) scanning is a sensitive imaging technique which objectively shows indirect signs of small airways obstruction, such as heterogeneity in ventilation (areas of mosaic lung attenuation on inspiratory CT) and air trapping (on expiratory CT).[53–57] Studies showed a higher degree of air trapping on high-resolution CT scan even in mild asthma,[53,54] and more severe asthma is associated with more severe air trapping.[55] Air trapping scores were also higher in mild asthmatics after metacholine challenge, but air trapping only partially disappeared after inhalation of salbutamol. Further, lung attenuation was higher in patients with asthma in this study.[53] In contrast, unstable asthmatics with exacerbations had lower mean lung density and a higher relative lung area with low attenuation than controls or stable asthmatics, which was at least partially reversible using systemic glucocorticoid therapy and in parallel with improvements in FEV_1 and RV.[56] Moreover, in stable patients, the percentage of lung field occupied by low attenuation areas on expiratory scan correlated negatively with FEV_1/FVC and with indices of peripheral airflow obstruction, such as $FEF_{25\%–75\%}$.[57] Systemically administered drugs reach the small airways via the circulation; 4 weeks of treatment with oral montelukast in fact resulted in less metacholine-induced air-trapping on high-resolution CT as well as in improved quality of life in mild-to-moderate asthmatics.[58]

Single-breath and multiple-breath washout tests

Dysfunction of the small airways can be evaluated by single-breath washout tests and more accurately by multiple-breath washout tests.[45,59–65] Both techniques use endogenous or exogenous inert gases and can provide several parameters reflecting distribution of inhomogeneity in ventilation and/or air trapping.[60,61]

The most widely used method is the N_2 single-breath washout test.[60] In this test, increased closing volume (expired volume from the start of phase IV to the end of the breath) implies airway closure at relatively high lung volumes. Indeed, closing volume has been shown to correlate with RV/TLC.[62] Closing volume and closing capacity (CC = CV + RV) were increased in patients with difficult-to-control asthma as compared with a group with equally severe but stable asthma even during a clinically stable period and after bronchodilation. This suggests that collapsibility of the small airways might be a risk factor for exacerbations in asthmatics.[63] Similarly, another cross-sectional study of patients with variable severity of asthma but normal FEV_1 showed that the closing capacity/TLC and phase III slope of the washout curve (ie, alveolar phase; S_{III} or dN2) was increased in asthma. Moreover, dN2 increased significantly in patients with frequent exacerbations as compared with those with rare exacerbations at steady-state after bronchodilation. Further, dN2 correlated negatively with asthma control (assessed by the Asthma Control Questionnaire) and positively with the number of exacerbations and RV/TLC. The results of this study indicate

that an abnormal dN2 value can be associated with the need for a high daily dose of ICS.[45]

The multiple-breath washout test can locate the affected small airways in acinar (Sacin, index of acinar ventilation heterogeneity) and conductive (Scond, index of conductive ventilation heterogeneity) lung zones.[59] Both parameters have been found to be abnormal in asthma.[64] Moreover, Scond was shown to be a strong predictor of airways hyperresponsiveness in asthma, irrespective of airways inflammation.[65] Single-breath and multiple-breath washout tests are suitable for assessment of small airways impairment in experimental models but not in clinical settings at present.

Impulse oscillometry

Impulse oscillometry is another noninvasive technique developed to measure airway mechanics expressed by the parameters of resistance (R) and reactance (X) at different frequencies. An important advantage of this method is that, unlike spirometry, it does not require any respiratory maneuvers but simply normal breathing while small-amplitude pressure oscillations at multiple frequencies are sent into the respiratory system and parameters are derived from the reflected signals. Therefore, it may be concluded that this method is both effort-dependent and cooperation-independent.[52,66] Using this technique, it is possible to discriminate between functions of the large and small airways; small airways obstruction is sensitively detectable with increased resistance predominantly at low frequencies.[13,66] Peripheral resistance (R5–R20) was observed to correlate with $FEF_{25\%–75\%}$ and alveolar nitric oxide levels.[52] Impulse oscillometry parameters are more sensitive than spirometric parameters in recognizing subtle dysfunction, as was shown in a study involving subjects with normal spirometry following the World Trade Center dust exposure[67] and in other studies where asthmatic children receiving oral montelukast[68] or patients with asthma or chronic obstructive pulmonary disease receiving bronchodilator pharmaceuticals were examined,[69] and in yet other studies where healthy individuals were tested after exercise in the cold and at room temperature.[70] Moreover, impulse oscillometry was shown to correlate better than spirometry with clinical symptoms and asthma control.[13] Noninvasive investigation methods that can be used in assessment of the small airways are summarized in Table 2.

Extrafine ICS therapy for airways inflammation in asthmatics

As seen above, there is evidence in support of inflammatory processes also occurring in the distal lung in asthma. From this, it follows that targeting inflammation in both the central and peripheral airways may be beneficial in pharmacotherapy for asthma. Lung deposition studies show that there is an inverse correlation between the particle size of inhaled drug formulations and extent of deposition in the lung.[71–73] Traditional dry powder inhalers or chlorofluorocarbon-metered dose inhaler devices generate particles with a median mass aerodynamic diameter of 2–4 μm.[73] However, newer pressurized metered dose inhalers have recently been developed using hydrofluoroalkane solution, and generate an aerosol of smaller particles with a median mass aerodynamic diameter of approximately 1 μm[30] (eg, hydrofluoroalkane-beclomethasone dipropionate, hydrofluoroalkane-beclomethasone dipropionate/formoterol, hydrofluoroalkane-flunisolide, and hydrofluoroalkane-ciclesonide). Extrafine formulations have a lung deposition rate of 50%–60% and penetrate more deeply into the peripheral airways than drugs delivered via traditional inhalers. In a study comparing healthy subjects and patients with chronic obstructive pulmonary disease or asthma, deposition of hydrofluoroalkane-formoterol in the lung was shown to be independent of lung function,[74] and it was also demonstrated that deposition of hydrofluoroalkane-beclomethasone dipropionate in the lung was not affected in the event of transient deterioration in $FEV_{1.}$[75]

Hauber et al investigated the effect of hydrofluoroalkane-flunisolide on airway inflammation using transbronchial and endobronchial biopsies. They found reductions in eosinophil numbers and IL-5 and eotaxin levels both in the peripheral and central airways accompanied by an improvement in lung function after 6 weeks of treatment. However, neutrophils increased and lymphocytes remained unchanged.[34] A similar study demonstrated the effect of hydrofluoroalkane-flunisolide, which caused a decrease in α-smooth muscle actin area (a sign of airways remodeling) in the peripheral airways. This change correlated with improvement in $FEF_{25\%–75\%}$.[76] The effect of hydrofluoroalkane- beclomethasone dipropionate on eosinophil inflammation was assessed in a long-term study, where patients receiving traditional ICS therapy (budesonide or fluticasone administered by dry powder inhaler) were switched to extrafine ICS treatment.[77] On the basis of induced sputum investigations, there was a decrease in the number of patients with eosinophilic inflammation. Further, reductions in sputum eosinophil cationic protein and eotaxin were observed after 8 weeks, and their concentrations continued to decrease for one year.[77] In another study, late-phase sputum eosinophil levels decreased after the introduction of treatment with extrafine ciclesonide as opposed to treatment with nonextrafine fluticasone.[78]

Table 2 Noninvasive tools suitable for assessment of small airways

Method	Scope	Strengths	Weaknesses
$FEF_{25\%–75\%}$[43,44]	Small airways obstruction Correlates with IOS and HRCT indices	Easy to perform	Too variable Influenced by central airways obstruction or lung volume alterations Fails to correlate with other parameters of air trapping or with small airway inflammation
RV/TLC[43,45]	Air trapping Elevated in asthma, particularly in severe disease	Easy to perform	Relatively time-consuming
FVC[43,46,47]	Decreased FVC was related to air trapping; FVC correlates inversely with RV/TLC	Easy to perform	Not sensitive Assumes normal TLC
CA(NO)[49–52]	Ventilation heterogeneity (particularly in severe and refractory asthma) Correlates with RV/TLC, FRC, dN2, CC/TLC, R5–R20	Good reproducibility	Back-diffusion of NO from the conducting airways Corrected CA(NO) is not elevated in treated severe asthmatics
HRCT[53–58,81]	Ventilation heterogeneity (inspiratory CT), air trapping (expiratory CT) Negatively correlates with FEV_1/FVC and $FEF_{25\%–75\%}$ and positively with RV/TLC	Sensitive Good reproducibility and objective if computerized and spirometrically controlled	Radiation Expensive
SBW, MBW tests[45,59–65]	Ventilation heterogeneity, air trapping, collapsibility of small airways CV and dN2 correlate with RV/TLC dN2 correlates with recurrent exacerbations and asthma control Scond predicts airway hyperresponsiveness	Sensitive, able to detect early changes in small airways Good reproducibility (if computerized)	Difficult to perform
IOS[13,52,66–70]	Airway mechanics, small airway obstruction R5–R20 correlates with $FEF_{25\%–75\%}$ and CA(NO) Correlates with symptoms and control better than spirometry	Sensitive Able to distinguish reliably between peripheral and proximal airway effects Does not require any respiratory maneuvers	Relatively time-consuming

Abbreviations: $FEF_{25\%–75\%}$, forced expiratory flow at 25%–75% of forced vital capacity; IOS, impulse oscillometry; HRCT, high-resolution computed tomography; RV, residual volume; TLC, total lung capacity; FVC, forced vital capacity; CA(NO), alveolar concentration of nitric oxide; dN2, slope of Phase III of the washout curve; CC, closing capacity; R5–R20, resistance from 5 to 20 Hz; FEV_1, forced expiratory volume in one second; SBW, single-breath washout; MBW, multiple-breath washout; CV, closing volume; Scond, index of conductive airways ventilation heterogeneity; FRC, functional residual capacity.

In a study by Cohen et al, who tested the effect of ciclesonide in mild-to-moderate asthmatics from a functional point of view, improvements were observed in methacholine-induced air trapping on high-resolution CT scan compared with placebo.[79] Goldin et al directly assessed the difference in efficacy of large versus small particle size ICS, comparing the same drug, ie, beclomethasone, at the same dose but in two different formulations.[80] After 4 weeks of treatment, they could not detect any difference between the treatment groups based on conventional physiological tests, such as FEV_1, or symptoms. Nevertheless, they found greater reduction in air trapping in the hydrofluoroalkane-beclomethasone dipropionate group than in the chlorofluorocarbon-beclomethasone dipropionate group, suggesting an improvement in small airways function. Moreover, after provocation with metacholine, patients treated with hydrofluoroalkane-beclomethasone dipropionate showed a less marked increase in air trapping.[80] In another study of patients with mild-to-moderate uncontrolled asthma, 3 months of treatment with traditional or extrafine ICSs resulted in similar improvements in air trapping.[81] Hydrofluoroalkane-beclomethasone dipropionate has been shown to improve bronchial hyperresponsiveness,[30,82] impulse oscillometry-measured resistance of the small airways (R5–R20), and reactance area[82] to a greater extent than chlorofluorocarbon-beclomethasone dipropionate. Similarly, ciclesonide (but not fluticasone) improved R5–R20, reactance area, and distal reactance (X5),[78] and decreased alveolar nitric oxide levels in mild-to-moderate asthmatics.[79] In uncontrolled asthmatic patients who received hydrofluoroalkane-beclomethasone dipropionate, improvements in single-breath washout values, ie, closing volume and closing volume/vital capacity, were more noticeable, along with improvement in postbronchodilator $FEF_{25\%–75\%}$ as compared with patients treated with chlorofluorocarbon-fluticasone propionate.[83] Moreover, multiple-breath washout tests in patients with stable asthma and abnormal acinar airways function showed improvements in acinar heterogeneity (Sacin) after switching to hydrofluoroalkane-beclomethasone dipropionate therapy. This improvement correlated with baseline acinar heterogeneity, indicating that patients with more severe inhomogeneity of ventilation benefited most from treatment with the extrafine formulation.[84] Histological

Table 3 Changes in small airway inflammation and function as described in studies on extrafine particle sizes of ICS

Authors	Subjects	Treatment	Period	Assessment methods	Outcomes
Micheletto et al[30]	15 mild asthma (steroid-naïve)	CFC-BDP 1000 μg (n = 8) versus HFA-BDP 400 μg (n = 7)	12 weeks	MCh challenge	Greater increase in PD_{20} FEV_1 to MCh while treated with HFA-BDP.
Hauber et al[34]	12 mild-to-moderate asthma	HFA-flunisolide 340 μg bid	6 weeks	Transbronchial and endobronchial biopsies	Reduction in eosinophils, IL-5, and eotaxin, increase in neutrophils, no change in lymphocytes either in peripheral or central airways. Improvement in lung function.
Bergeron et al[76]	12 mild-to-moderate asthma	HFA-flunisolide 340 μg bid	6 weeks	Transbronchial and endobronchial biopsies	Decrease in α-smooth muscle actin area in peripheral airways, which correlates with the percentage increase in $FEF_{25\%–75\%}$. No changes in collagen deposition and TGF-β expression.
Ohbayashi[77]	74 moderate stable asthma	FP (n = 37) or BUD (n = 37), then switch to HFA-BDP	One year	Induced sputum	Fewer eosinophil-positive patients in both groups and reduction in sputum ECP and eotaxin.
Hoshino[78]	30 mild asthma	Ciclesonide 200 μg versus FP 200 μg	8 weeks	IOS Induced sputum	Ciclesonide improved resistance of small airways (R5–R20), distal reactance, reactance area, decreased late-phase sputum eosinophils, increased ACT scores and decreased rescue β_2 inhalation compared with FP. No changes in spirometry indices in either group.
Cohen et al[79]	16 mild-to-moderate asthma	Ciclesonide 320 μg (n = 9) versus placebo (n = 7)	5 weeks	HRCT SBNW test CA(NO)	Improvements in CA(NO) and MCh-induced air trapping on HRCT as compared with placebo. No changes in other small airways parameters.
Goldin et al[80]	31 mild-to-moderate asthma (steroid-naïve)	CFC-BDP 100 μg bid versus HFA-BDP 100 μg bid	4 weeks	HRCT	Greater improvement in air trapping, and less marked increase in MCh-induced air trapping in the HFA-BDP group. Similar improvements in symptoms, spirometry, and PC_{20} MCh.
Tunon-de-Lara et al[81]	25 mild-to-moderate uncontrolled asthma	FP 250 μg bid versus HFA-BDP 200 μg bid	3 months	HRCT	Similar improvements in air trapping.
Yamaguchi et al[82]	38 mild-to-moderate asthma (steroid-naïve)	HFA-BDP 200 μg bid (n = 26) versus CFC-BDP 400 μg bid (n = 12)	12 weeks	IOS MCh challenge	Greater improvements in the resistance of small airways (R5–R20) and reactance area (AX) while treated with HFA-BDP. HFA-BDP attenuated MCh sensitivity.
Thongngarm et al[83]	30 uncontrolled asthma	HFA-BDP 160 μg bid (n = 20) versus CFC-FP 330 μg (n = 10) in addition to the previous treatment (moderate to high doses of ICS and other controller medications)	3 months	SBNW test	Greater improvements in CV, CV/VC and postbronchodilator $FEF_{25\%–75\%}$ while treated with HFA-BDP.
Verbanck et al[84]	30 stable asthma (wide range of severity)	BUD, then switch to HFA-BDP (the same dose for 6 weeks, then half dose for another 6 weeks)	12 weeks	MBNW test	With the switch to HFA-BDP, improvements in Sacin and RV in the subgroup of patients with abnormal baseline Sacin (n = 16) occurred. Although all patients presented abnormal baseline Scond, no changes were observed in this lung zone.

Abbreviations: CFC, chlorofluorocarbon; BDP, beclomethasone dipropionate; HFA, hydrofluoroalkane; MCh, methacholine; PD_{20} FEV_1, dose of methacholine required to produce a 20% fall in the forced expiratory volume in one second; bid, twice a day; IL-5, interleukin-5; FP, fluticasone propionate; HRCT, high-resolution computed tomography scan; $FEF_{25\%–75\%}$, forced expiratory flow at 25%–75% of forced vital capacity; TGF-β, transforming growth factor beta; BUD, budesonide; ECP, eosinophil cationic protein; IOS, impulse oscillometry; R5–R20, resistance from 5 to 20 Hz; X5, reactance at 5 Hz; AX, reactance area; ACT, Asthma Control Test; SBNW, single-breath nitrogen washout; CA(NO), alveolar concentration of nitric oxide; PC_{20} MCh, the provocation concentration of methacholine causing a 20% reduction in FEV_1; ICS, inhaled corticosteroids; CV, closing volume; VC, vital capacity; MBNW, multiple-breath nitrogen washout; Sacin, index of acinar airways ventilation heterogeneity; RV, residual volume; Scond, index of conductive airways ventilation heterogeneity.

Table 4 Clinical outcomes as described by some studies on extrafine particle sizes of ICS

Authors	Subjects	Treatment	Period	Assessment methods	Outcomes
Juniper et al[85]	473 stable asthma	CFC-BDP 400–1600 μg, then switch to half dose HFA-BDP (n = 354)	12 months	AQLQ Pulmonary function tests	Greater improvements in AQLQ scores while treated with HFA-BDP. No difference in lung function parameters, symptoms, or β_2-agonist use.
Worth et al[86]	209 moderate-to-severe asthma	HFA-BDP 800 μg (n = 111) versus BUD 1600 μg (n = 98)	8 weeks	Symptoms Pulmonary function tests	Greater improvements in the percentage of days with no experience of shortness of breath, chest tightness or wheeze, nights without sleep disturbance, and daily asthma symptoms while treated with HFA-BDP. No difference in FEV_1, PEF, or β_2-agonist use.
Tatsis et al[87]	40 moderate asthma or COPD	BUD 400 μg bid or FP 250 μg bid, then switch to HFA-BDP 200 μg (n = 20)	8 weeks	Symptoms Pulmonary function tests	Greater improvements in respiratory symptoms, spirometric values, and β_2-agonist use while treated with HFA-BDP.
Boulet et al[88]	141 moderate-to-severe asthma	HFA-BDP 800 μg (n = 70) versus CFC-BDP 1500 μg (n = 71)	6 months	Symptoms Pulmonary function tests	Onset of the first exacerbation tended to occur later and asthma symptoms tended to decrease while treated with HFA-BDP. Similar pulmonary function. Similar systemic safety.
Barnes et al[89]	Large primary care database for asthma patients	HFA-BDP (n = 3140) versus CFC-BDP (n = 9162)	1 year	Asthma control Exacerbation rate	Patients receiving HFA-BDP are more likely to achieve asthma control.
Huchon et al[90]	645 uncontrolled moderate-to-severe asthma	HFA-BDP 200 μg/formoterol 12 μg bid (fixed combination) versus CFC-BDP 500 μg bid and formoterol 12 μg bid, or CFC-BDP 500 μg bid	24 weeks	Primary outcome: morning PEF Secondary outcomes: pulmonary function test symptoms, control, exacerbations	Similar improvements in PEF while using single inhaler HFA-BDP/formoterol or while using separate traditional inhalers. HFA-BDP/formoterol was superior for asthma control and also with reference to the percentage of symptom-free days.
Müller et al[91]	111 moderate-to-severe asthma	HFA-BDP/formoterol (n = 53) versus FP/salmeterol (n = 25) or BUD/formoterol (n = 33)	Cross-sectional real-life study	Asthma control	Better asthma control total score, daytime symptom score, and rescue medication use score; lower mean daily ICS dose while treated with HFA-BDP/formoterol.

Abbreviations: CFC, chlorofluorocarbon; BDP, beclomethasone dipropionate; HFA, hydrofluoroalkane; AQLQ, Asthma Quality of Life Questionnaire; BUD, budesonide; FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; COPD, chronic obstructive pulmonary disease; bid, twice a day; FP, fluticasone propionate; ICS, inhaled corticosteroids.

and functional studies using extrafine ICS are summarized in Table 3, while the outcomes of clinical studies are reviewed in Table 4.

Conclusion

Small airways disease plays an important role in the pathogenesis of asthma, but the assessment of small airways impairment is not easy in everyday clinical practice. The small airways can be examined by several invasive and noninvasive methods, most of which can at present be used only in experimental settings. Inhalers that provide extrafine particle sizes of ICS may enable sufficient drug deposition in the peripheral airways. Many studies have shown the beneficial effects of extrafine ICS on inflammation in asthma, including dysfunction in both the central and distal airways, and there are data on some asthma phenotypes in which the small airways seem to be affected more than in other phenotypes, including nocturnal asthma, severe steroid-dependent or difficult-to-treat asthma, asthma complicated by smoking, elderly asthmatic patients and those with fixed airflow obstruction, and asthmatic children. The randomized clinical trials reported to date show that the extrafine and nonextrafine ICS formulations have similar efficacy in terms of primary endpoints; however, there are certain clinically important endpoints for which the extrafine formulations show additional benefits.

Disclosure

The authors report no conflicts of interest in this work.

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