REVIEW ARTICLE

Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma

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Abstract

Asthma is a chronic respiratory disease, characterized by airway obstruction and inflammation. Increasing evidence shows that the small airways contribute significantly to the clinical expression and severity of asthma. Traditionally, high levels of disease activity are thought to be necessary before symptoms occur in the small airways because of their large reserve capacity. However, this concept is being challenged and increasing evidence shows small airway disease to be associated with symptoms, disease severity, and bronchial hyper-responsiveness. Particle size and distribution are of key importance when developing inhaled treatments for small airway disease. The availability of small-particle aerosols such as HFA-ciclesonide and HFA-beclomethasone dipropionate (HFA-BDP) enables a higher drug deposition into the peripheral lung and potentially provides additional clinical benefits compared with large-particle treatment. However, improved methods are needed to monitor and assess small airway disease and its response to treatment because conventional spirometry mainly reflects large airway function. This remains a challenging area requiring further research. The aim of the current manuscript is to review the clinical relevance of small airway disease and the implications for the treatment of asthma.

Asthma is a common, chronic respiratory disease with a high personal, social, and economic impact. It is characterized by airway obstruction and an inflammatory process that affects the whole respiratory tract, from the central to peripheral airways (1). In recent years, there has been an emerging interest in the role of the small airways, and there is increasing evidence that they contribute significantly to the clinical expression of asthma. Furthermore, new inhaler devices have become available that enable a higher drug deposition in the small airways. The aim of this manuscript is to review the clinical relevance of small airway disease and the implications for the treatment of asthma.

Small airways are not a quiet zone

The small airways are defined by an internal airway diameter of <2 mm. They have a generation number that is generally higher than 8, and they account for 98.8% (approximately 4500 ml) of the total lung volume (compared to a lung volume of 50 ml in the large airways) (2). Because the small airways contain little or no cartilage, they are easily collapsible,

for example, during forced expiration and/or smooth muscle contraction. With a higher generation number, the airway diameter gradually decreases. This might suggest that obstruction increases with a higher generation. However, the opposite is true: The cumulative cross-sectional area of the airways increases exponentially, and therefore, the overall resistance of nondiseased small airways is very low (2).

Historically, the small airways have been called 'the quiet zone', because of their large reserve capacity and the notion that a high level of disease activity would be necessary before they cause a drop in lung function or an increase in symptoms (3). This concept was challenged for the first time by the landmark study of Wagner et al. (4). Using a wedged bronchoscope with a diameter of 5.5 mm, they demonstrated a striking difference in peripheral airway resistance between asthmatics and healthy individuals, which was sevenfold higher in patients with mild asthma, despite the fact that forced expiratory volume in 1-s (FEV_1) was similar between the two groups. Moreover, a higher peripheral airway resistance was associated with a more severe bronchial hyper-responsiveness to methacholine (4).

Such observations have been confirmed in later studies. Using the same wedged bronchoscope technique, Kraft et al. (5) demonstrated that patients with nocturnal asthma have a higher peripheral airway resistance at night than during daytime, a phenomenon not observed in patients without nocturnal asthma. In another study, Kaminsky et al. showed that after a challenge with cool, dry air, baseline peripheral airway resistance increases to a significantly higher extent in patients with asthma when compared with healthy controls. In addition, they showed that a higher baseline peripheral airway resistance is associated with a more severe exercise-induced bronchoconstriction (6).

The importance of small airway disease to the clinical expression of asthma has also been demonstrated in several other studies (Table 1). Zeidler et al. (7) showed that natural exposure to cat allergen results in worsening of small airway disease as reflected by increased methacholine-induced air trapping on high-resolution computed tomography (HRCT) and a higher closing capacity measured with the single-breath nitrogen washout test. In 't Veen et al. (8) observed that asthma patients who have frequent exacerbations have a higher degree of small airway disease as reflected by increased air trapping and uneven ventilation when compared to asthma patients without frequent exacerbations. Two further studies investigating the drop in forced vital capacity (FVC) during methacholine provocation, which indirectly reflects small airway closure, found that a higher drop in FVC was associated with more severe asthma (9, 10). Moreover, this technique was able to discriminate asthma patients with previous intubation from those without (9, 11).

Taken together, there is now a considerable amount of evidence supporting the concept that a higher level of small airway disease is associated with increased asthma symptoms, more severe bronchial hyper-responsiveness, and an increased number of exacerbations. Currently, a limited number of studies have investigated the underlying pathology of the small airways in asthma.

A recent review from our research group identified 19 studies, involving a total of 244 asthmatics and 144 controls (1). The majority of these studies involved the collection of lung tissue from autopsied patients with fatal asthma or from patients with asthma needing lung resection because of malignancy, whereas some other studies used transbronchial biopsies. The results from these studies suggest that inflammation is present in the small airways with higher numbers of eosinophils, lymphocytes, and neutrophils (12–18). In addition, an increased area of smooth muscle, mucosal glands, as well as a more occluded lumen, has been observed postmortem in the small airways of fatal asthma cases. The outer small airway wall and peribronchiolar regions are also involved in the inflammatory process (18–21). The latter may increase the collapsibility of the small airways due to their uncoupling of the surrounding lung parenchyma. Thus, all layers of the small airway wall are inflamed with a Th2 type of inflammation similar to that found in the larger airways. This is in agreement with the findings of Van Vyve and Vignola et al. (22, 23) who observed an increased number of eosinophils in the bronchoalveolar lavage fluid, reflecting the alveolar space, of asthma patients compared to nonasthmatic controls.

It can be concluded that the small airways contribute significantly to disease activity and therefore should not be labeled a 'quiet zone' due to their clinical significance in asthma.

Beyond FEV_1 and Peak flow

It is difficult to measure the degree of small airway disease with conventional spirometry as FEV_1 and peak flow mainly reflect large airway function. Several studies have observed a dissociation between FEV_1 and peak flow *vs* respiratory symptoms, quality of life (QoL), and central or peripheral airway inflammation. This raises the question whether conventional spirometry alone is the most reliable method to assess asthma severity and monitor its control.

Several methods are available that do reflect small airway disease more accurately than spirometry.

Lehtimaki et al. (24) found that patients with nocturnal asthma have a higher concentration of alveolar nitric oxide (NO) than patients without nocturnal asthma, whereas the level of FEV_1 was similar between the two groups, suggesting that FEV_1 alone may not sufficiently reflect disease activity. This is in agreement with the findings of Brindicci et al. (25)

Table 1 Examples of studies showing an association between small airway disease and the presence and activity of asthma

Reference	Main findings
Wagner et al. (4)	Sevenfold increased peripheral airway resistance measured with the wedged bronchoscope technique in asthma *vs* healthy controls
	Baseline peripheral airway resistance correlates with bronchial hyper-responsiveness to methacholine
Kraft et al. (5)	Higher peripheral airway resistance at night than during daytime in nocturnal asthma
Kaminsky et al. (6)	Higher peripheral airway resistance correlates with exercise-induced bronchoconstriction
Zeidler et al. (7)	Natural cat allergen exposure increases both methacholine-induced air trapping on HRCT and closing volume measured with the single-breath nitrogen test 6 and 23 h later
In 't Veen et al. (8)	Asthma patients who have frequent exacerbations (≥ 2 per year) have a higher degree of small airway disease measured with the single-breath nitrogen washout test than patients with infrequent exacerbations (<2 per year), whereas their FEV_1 and FEV_1/FVC are similar
Lee et al. (9)	A higher drop in FVC during PD_{20} methacholine is associated with more severe asthma

FVC, forced vital capacity; HRCT, high-resolution computed tomography.

who observed that higher alveolar NO concentrations are associated with an increased level of both daytime and nighttime symptoms in patients with severe asthma. In addition, it has been shown that small airway dysfunction, as reflected by a higher R5–R20 measured using impulse oscillometry (IOS), is associated with symptoms of wheezing, dyspnea, and chest tightness (26).

The degree of ventilation heterogeneity can be measured using the single-breath nitrogen washout (SBNW) test (explained in Fig. 1) or the multiple-breath washout (MBNW) test (27, 28). Farah et al. (28) have shown that a reduction in ventilation heterogeneity after the treatment with inhaled corticosteroids (ICS) was the most important independent predictor of improvement in asthma control. Further to this discovery, the presence of hyperinflation, as reflected by an increased residual volume (RV) and RV/total lung capacity (TLC), predicts the occurrence of exercise-induced bronchoconstriction and correlates with more severe asthma (29, 30).

Imaging is another way to assess the presence of small airway disease. Although HRCT scanning does not allow direct assessment of airways >2 mm in diameter, the amount of air trapping can be measured indirectly by analysis of the density distribution in Hounsfield units, resulting in lung attenuation curves during inspiration and expiration. Using
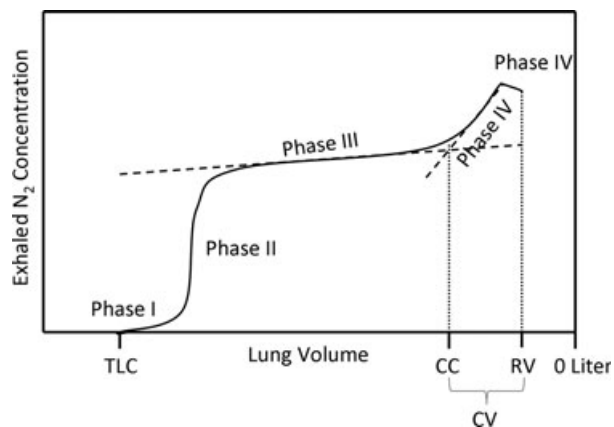
this technique, it has been shown that inhalation of methacholine induces air trapping in patients with asthma, but not in healthy controls. In addition, a higher degree of air trapping on HRCT was found to be associated with an increase in RV and RV/TLC and decrease in FEF$_{25-75}$ (31–33). A major disadvantage of HRCT is the use of ionizing radiation which limits its use for research practices. For this reason, there is now increasing interest in the role of magnetic imaging after inhalation of hyperpolarized helium or xenon to enhance resolution. Hyperpolarized helium MRI has been shown to be sensitive tool to assess regional ventilation defects both in asthma and in COPD. However, at present, this technique is technically demanding and only available in a few highly specialized centers (34).

Taken together, these studies strongly suggest that measurement of small airway inflammation and function provides additional information beyond conventional spirometry in asthma. Unfortunately, there is no *golden standard* test with accepted cutoff values, and therefore, assessment and monitoring small airway involvement continues to be challenging. Table 2 gives an overview of currently available measurements and discusses the advantages and disadvantages of each test (1).

How to reach the small airways: particle size matters

Regional oropharyngeal and lung deposition of inhaled particles depends on many factors including the type and output velocity of the inhaler device, inhalation technique and airway geometry of the patient, and aerodynamic behavior of the particles; this has been extensively reviewed elsewhere (35). One factor of key importance is particle size. The Montreal Protocol of 1987 required the worldwide phase-out of ozone-depleting chlorofluorocarbons (CFCs). Reformulation of CFC-based metered dose inhaler (MDI) technology to the alternative propellant hydrofluoroalkane-134a (HFA) gave the opportunity to produce a solution instead of a suspension formulation.

In a solution formulation, nanoparticles of the drug are dissolved in the propellant/co-solvent allowing the generation of smaller particles when the propellant/co-solvent evaporates during dosing. Table 3 gives the particle sizes, shown as mass median aerodynamic diameters (MMADs) of the most commonly prescribed ICS with or without a long-acting beta-agonist. Compared with larger particles, small particles (MMAD 1–2 μm) are expected to have a lower oropharyngeal deposition (20–30% *vs* >80%) and a higher lung deposition (50–60% *vs* 10–20%; Fig. 2 and Table 3) (36,37). In addition, once the smaller particles have passed the oropharynx, they are more likely to reach the small airways.

Studies with small particles have shown that half of the lung dose is deposited in the large and intermediate airways and half is distributed to the small airways (38,39). In this context, it is important to consider that β$_2$-receptors and corticosteroid receptors are abundantly present in both the small and large airways (40,41). The study of monodisperse aerosols has increased our knowledge of the effects of particle size on regional drug deposition in the

Figure 1 At the start of the single-breath nitrogen washout (SBNW) test, subjects inhale pure oxygen from residual volume (RV) to total lung capacity (TLC). Then, they exhale at a constant flow rate of approximately 0.5 l/s to RV. Throughout exhalation, the nitrogen concentration in exhaled breath is measured. During phase I, the concentration of exhaled nitrogen is nearby 0% when oxygen from the central airways comes out first. After that, the nitrogen concentration rises rapidly during phase II due to a mixture of gas from the anatomical dead space and alveoli. The next part, phase III, is the called the nitrogen alveolar sloping plateau. A higher slope, which can be calculated by drawing the best-fit straight line through the curve, indicates a higher level of ventilation heterogeneity. The start of phase IV is defined as the first departure of this line. The absolute lung volume at this point is called closing capacity (CC). The closing volume (CV) is defined as residual volume – CC.

Table 2 Overview of tests for small airway obstruction

	Ability to detect small airway abnormalities	Reproducibility	Advantages	Disadvantages
ΔFVC at PC_{20}	Closely related to: • Disease severity (10) • MCh-induced air trapping (CT) • Maximal airway response to MCh (11)	Good	• Noninvasive • Easy to perform • Widely available	• Bronchial challenge test, time-consuming • High costs • Performing complete FVC maneuver twice at each dose is strenuous
FVC/SVC	• Detects and monitors small airway disease in BOS after lung transplantation (72)	Poor	• Noninvasive • Easy to perform • Low costs • Not time-consuming	• Not a very specific test for the measurement of small airway disease
FEF_{25-75}	Closely related to: • Air trapping (CT) (73) • FEF_{25-75} is often normal when FEV_1/FVC ≥ 75% (74)	Poor	• Noninvasive • Easy to perform • Low costs • Not time-consuming	• Not a very specific test for the measurement of small airway disease • Wide range of normal • Dependence on FVC
IOS or FOT	Closely related to: • FEF_{25-75} (75) • Methacholine (MCh)-induced changes in ventilation Heterogeneity (76)	Fair	• Noninvasive • Easy to perform • Low costs • Not time-consuming	• Not a very specific test for the measurement of small airway disease
SBNW: closing volume	Closely related to:Alveolar NO in severe asthma (27)	Fair	• Noninvasive • Relatively low costs • Not time-consuming	• Difficult measurement to perform without flow restrictor • High variability • Lack of certainty about interpretation
MBNW	Closely related to: • Alveolar NO (77)	Good	• Noninvasive • Easy to perform	• Not widely available • High costs • Lack of certainty about interpretation
(MCh-induced) air trapping with CT	Closely related to: • ΔFVC at PC_{20} • High costs • RV/TLC (33)	Good	• Noninvasive • Direct visualization of air trapping, which may reflect small airway disease	• Radiation load is unfavorable • High costs • Time-consuming (approximately 70 min including MCh challenge)
RV/TLC	Closely related to: • N Alveolar NO in severe asthma (27) • Air trapping (CT) (33, 73)	Fair	• Noninvasive	Relatively time-consuming (30 min)

(continued)

Table 2 (continued)

	Ability to detect small airway abnormalities	Reproducibility	Advantages	Disadvantages
Alveolar and bronchial NO	Alveolar NO related to: • RV/TLC and closing volume in severe asthma (27) • Ventilation heterogeneity in stable asthma (77) Bronchial NO related to: • Air trapping (CT)	Fair	• Noninvasive	• Relatively time-consuming (20 min) • Influenced by smoking, caffeine, diet
Small-particle AMP provocation	Closely related to: • Treatment response to small-particle aerosol (ciclesonide) (56)	Unknown	• Noninvasive • Promising new tool to investigate small airway inflammation	• Bronchial challenge test, relatively time-consuming • Little evidence
Late-phase sputum induction	• The concentration of surfactant protein A was significantly higher in a late-vs early-phase sputum, suggesting sampling of the more distal airways (78) • Small-particle HFA-beclomethasone, but not large-particle DPI-budesonide, significantly reduced the percentage of eosinophils and expression of IL-4 and IL-5 mRNA in late-phase sputum	Unknown	• Noninvasive	• High costs • Little evidence
Transbronchial biopsies	• The number of transbronchial biopsy eosinophils was found to be associated with TLC and FRC, but not with FEF$_{25-75}$ or FVC Unfortunately, no data on RV/TLC were presented (79)	Unknown	• Direct measurement of small airway inflammation and remodeling	• Invasive • Few studies available on the association between markers of inflammation and/or remodeling in transbronchial biopsies and other parameters of small airway inflammation and/or dysfunction

Adapted with permission from reference (1). FVC, forced vital capacity; CT, computed tomography; MCh, methacholine; FEV$_1$, forced expiratory volume in 1-s; PC$_{20}$, provocative concentration causing the FEV$_1$ to drop with 20%; FEF$_{25-75}$, forced expiratory flow between 25% and 75% of the FVC; NO, nitric oxide; RV, residual volume; TLC, total lung capacity; SBNW, single-breath nitrogen washout test; MBNW, multiple-breath nitrogen washout test; AMP, adenosine 5′-monophosphate; IL, interleukin; FRC, functional residual capacity; DPI, dry powder inhaler; FOT, forced oscillometry.

Table 3 Mass median aerodynamic diameter (MMAD) of most frequently prescribed inhaled corticosteroids (ICS) and ICS/long-acting beta-agonist (LABA) formulations (36, 80, 81)

	MMAD
Inhaled corticosteroids	
DPI-Fluticasone	4.0–5.4 μm
DPI-Budesonide	~4.0 μm
HFA-Fluticasone	2.4–2.6 μm
HFA-Ciclesonide	~1.0 μm
HFA-Beclomethasone	~1.1 μm
Combination treatment	
DPI-fluticasone/salmeterol	~3.5 μm
HFA-fluticasone/salmeterol	Not known
DPI-budesonide/formoterol	~3 μm
HFA-beclomethasone/formoterol	1.4–1.5 μm

DPI, dry powder inhaler.

human lung. Monodisperse means that all particles have the same size and is defined as a geometric standard deviation of the aerosol MMAD of <1.2 μm. Usmani et al. (39) performed gamma-scintigraphy to investigate the radio-aerosol lung distribution of monodisperse albuterol with particle sizes of 1.5, 3, and 6 μm and demonstrated that smaller particles have a better deposition in the small airways. Nevertheless, treatment with the 'larger-particle' albuterol (MMAD 3 and 6 μm) improved FEV_1 more effectively. The latter is in agreement with the findings of Zanen et al. who showed that inhalation of monodisperse salbutamol (MMAD of 2.8 μm) improved FEV_1 more effectively than that of monodisperse salbutamol (MMAD of 1.5 μm) (42).

Although the landmark studies of Usmani and Zanen have improved our insights into the effects of particle size on lung deposition and function, there are several limitations regarding the interpretation of their results. They assessed the effects of treatment on FEV_1, which mainly reflects the large airway patency. It could be speculated that their results would have been different if they had measured the effects of treatment with a small airway parameter such as peripheral airway resistance measured with IOS or forced oscillometry (FOT), air trapping in the small airways measured with body plethysmography, or ventilation heterogeneity measured with the single- or multiple-breath nitrogen washout test. It should be noted that the effects of monodisperse albuterol and salbutamol were investigated, whereas commercially available aerosols are, without exception, heterodisperse, which means that they consist of a mix of differently sized particles (Fig. 3). In this case, not only MMAD but also particle size distribution will be of importance to the overall clinical effectiveness of the aerosol, especially because patients may benefit the most if *both* the large *and* the small airways are properly treated. The optimal particle size and size distribution of an ICS and β_2-agonist remains the subject of debate. Further research using large and well-designed clinical
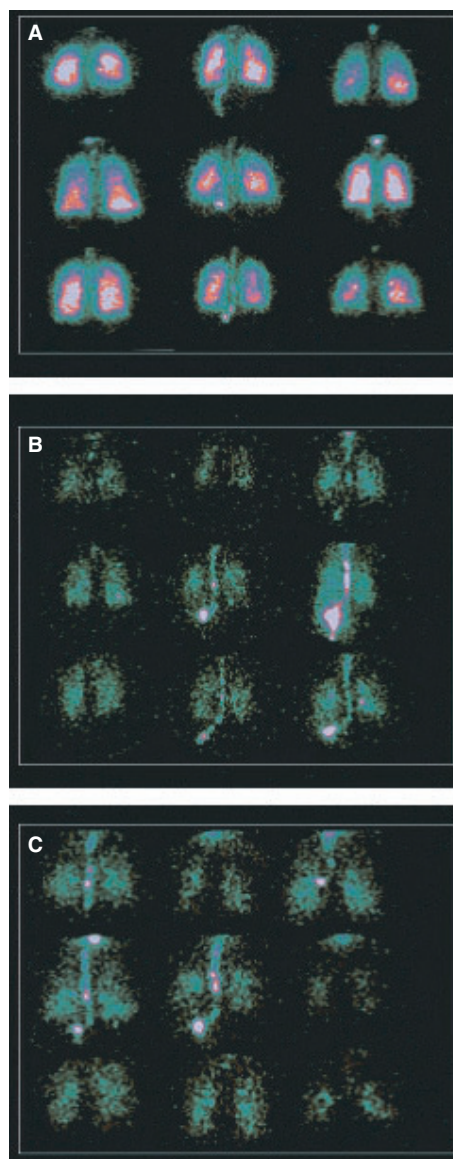

Figure 2 Scintigraphic images showing the deposition of a large-particle aerosol *vs* a small-particle aerosol. A brighter image represents a better deposition. Small-particle HFA-beclomethasone (A) has a better lung deposition than chlorofluorocarbons (CFC)-fluticasone (B) or CFC-beclomethasone (C). Reprinted with permission from reference (37).

trials is needed to investigate the treatment for both the large and small airways in asthma.

Treatment for small airway inflammation – clinical implications

Below, we will review the clinical studies that have been performed with the most commonly prescribed small-particle ICS that are currently available for the treatment of asthma: HFA- beclomethasone dipropionate (BDP) and HFA-ciclesonide.
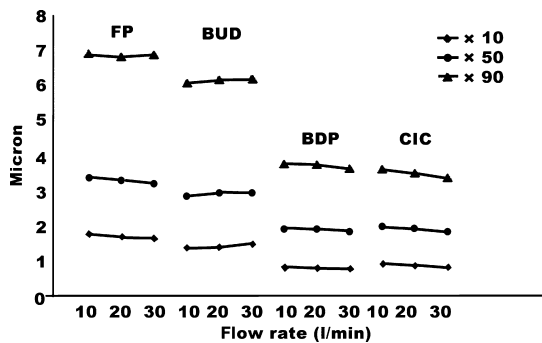
Figure 3 Particle size distribution in the aerosol as a function of the flow rate. Fluticasone propionate (FP) = HFA-fluticasone 125 μg/dose; BUD = chlorofluorocarbons (CFC)-budesonide 200 μg/dose; beclomethasone dipropionate (BDP) = small-particle HFA-beclomethasone 100 μg/dose; CIC = HFA-ciclesonide 160 μg/dose. Reproduced with permission of reference (80).

Small-particle HFA-beclomethasone dipropionate

Small-particle HFA-BDP is as effective as 2–3 times the dose of CFC-beclomethasone (CFC-BDP) for improving FEV_1 (43). So far, a limited number of studies have investigated whether small-particle HFA-BDP treatment has additional clinical benefits with respect to specific measures of small airway function in asthma. For instance, small-particle HFA-BDP is superior to large-particle ICS in improving airway resistance (R5-R20 measured with IOS), methacholine-induced air trapping on HRCT, and ventilation heterogeneity measured with the multiple-breath nitrogen washout test (44–46).

Unfortunately, studies comparing small- and large-particle ICS often used different types of ICS and different inhalers, making it difficult to draw a definitive conclusion based on their results. In addition, some studies compared HFA-BDP with the same dose of CFC-BDP; this may not be correct because HFA-BDP provides a higher lung deposition and is therefore approximately 2–3 times more potent than CFC-BDP with respect to improvement in FEV_1, at least at doses up to 640 μg daily. In this context, the studies of Yamaguchi and Hauber are of special interest (44, 47). Yamaguchi et al. (44) showed that 12 weeks of treatment 400 μg HFA-BDP was superior to an equipotent dose of 800 μg CFC-BDP with respect to improvement in peripheral airway resistance measured with IOS, whereas FEV_1 improved to a similar extent with both treatments. Hauber et al. investigated the effects of 4 weeks of treatment with HFA-BDP (200 μg twice-daily) *vs* dry powder inhaler (DPI)-budesonide (400 μg twice-daily) on early- and late-phase sputum samples in 17 patients with mild asthma. Both treatments significantly reduced the percentage of sputum eosinophils and levels of IL-4 and IL-5 mRNA expression in the early-phase sputum samples, compared to placebo. However, in the late-phase sputum samples (which more closely reflect peripheral airway inflammation), only treatment with small-particle HFA-BDP significantly reduced the percentage of sputum eosinophils and IL-4 and IL-5

mRNA expression compared to placebo. Importantly, HFA-BDP demonstrated a significantly higher reduction in late-phase IL-4 mRNA expression compared to DPI-budesonide, despite the relatively low power of the study which had a small sample size of 17 patients (47).

HFA-ciclesonide

So far, most clinical studies with HFA-ciclesonide have focused on standard lung function parameters such as FEV_1 or peak flow. In these studies, HFA-ciclesonide showed similar efficacy to fluticasone propionate (FP) or budesonide (48–51). Interestingly, when looking at other parameters such as exhaled NO or QoL, HFA-ciclesonide showed better results than FP. Zietkowski et al. (52) observed a faster and stronger decrease in exhaled NO after the treatment with HFA-ciclesonide (80 μg or 160 μg once-daily) compared to HFA-FP (100 μg twice-daily). Boulet et al. (53) compared the effects of 12 weeks' treatment with HFA-ciclesonide (320 μg once-daily) or DPI-FP (200 μg twice-daily) in 474 asthma patients. In this second study, HFA-ciclesonide proved to be noninferior to FP with respect to improvement in FEV_1, which was the primary outcome measure. However, a significantly higher improvement in asthma-related QoL was observed after the treatment with HFA-ciclesonide, especially for the domains 'activities' and 'symptoms'.

The effects of HFA-ciclesonide on small airway parameters have been investigated in three studies. In the first study, 16 patients with mild-to-moderate asthma were randomized to treatment with HFA-ciclesonide, 320 μg once-daily ($n = 9$) or placebo ($n = 7$), and the effects on several small airway parameters were investigated (54). In this pilot study, treatment with HFA-ciclesonide reduced the levels of bronchial and alveolar NO and the degree of methacholine-induced air trapping on HRCT to a higher extent than placebo (54).

In the second study, 30 asthma patients were pretreated with 100 μg DPI-FP during a run-in of 8 weeks (55). Thereafter, patients were randomized to receive 8 weeks' treatment with HFA-ciclesonide (200 μg once-daily) or DPI-FP (100 μg twice-daily), and the effects on small airway resistance (R5–R20) were measured using IOS. Small airway resistance remained unchanged in the FP group, but decreased significantly with HFA-ciclesonide. At the same time, a significant improvement in asthma control was observed with HFA-ciclesonide.

Finally, Cohen et al. (56) investigated the protective effects of small-particle HFA-ciclesonide and large-particle DPI-FP during the inhalation of adenosine 5′-monophosphate (AMP) which consisted of small particles (MMAD approximately 1.1 μm). Interestingly, treatment with HFA-ciclesonide, but not FP, had a significant protective effect against small-particle AMP (56).

These data provide some evidence that small-particle ICS, such as HFA-BDP and HFA-ciclesonide, treat the small airways more effectively than large-particle ICS. However, large and well-designed, controlled clinical trials are now needed to confirm that this is indeed the case and to investigate whether small-particle ICS are associated with better long-term

asthma control, that is, a lower level of symptoms and fewer exacerbations.

Safety profile of small-particle ICS

HFA-beclomethasone

With the introduction of small-particle aerosols, there has been some concern that their use may be accompanied by an increase in systemic side-effects. However, this does not appear to be the case with small-particle treatment. Beclomethasone dipropionate is a pro-drug with weak corticosteroid receptor–binding affinity that is converted by airway esterase activity to its active metabolite beclomethasone 17-monopropionate (57). Although it is well known that inhaled BDP has an effect on the hypothalamic-pituitary-adrenal (HPA) axis, a larger decrease in either 24-h urinary free cortisol or serum cortisol was not observed after 12 weeks of treatment with 800 μg HFA-BDP in comparison with the same dose of CFC-BDP (43, 58, 59). In addition, there was no difference in local side-effects such as dysphonia or oral candidiasis between the two treatments.

HFA-ciclesonide

HFA-ciclesonide is a topically active ICS that is converted *in situ* by airway esterase activity in the lung to form its active metabolite, desisobutyryl-ciclesonide (60). Because <20% of HFA-ciclesonide deposited in the oropharyngeal region is converted into des-HFA-ciclesonide, the local concentration of active drug in the throat is very low (61, 62). For this reason, a low incidence of local side-effects can be anticipated with HFA-ciclesonide. Indeed, several studies have shown that the incidence of oropharyngeal side-effects, such as dysphonia or oral candidiasis, was lower or similar with HFA-ciclesonide compared to FP, budesonide, or CFC-BDP (48–51, 53).

Desisobutyryl-ciclesonide is 99% plasma-protein-bound, resulting in a low number of free molecules available in peripheral blood to interact with receptors outside the lungs and potentially cause systemic side-effects (63). In addition, desisobutyryl-ciclesonide is effectively eliminated by the liver with a clearance rate of 3 l/h/kg. This is even higher than the hepatic blood flow in humans, suggesting extrahepatic mechanisms of elimination. It is therefore not surprising that several studies have shown that HFA-ciclesonide, up to doses of 640 μg twice-daily, does not suppress HPA axis function, a marker for systemic exposure to ICS, when compared to placebo. In the same studies, significant HPA suppression was found with FP, 440 μg twice-daily (64–66).

In another study, budesonide 800 μg once-daily, but not the equipotent dose of HFA-ciclesonide (320 μg once-daily), suppressed 24-h urinary cortisol secretion in adolescent patients, the difference between budesonide and HFA-ciclesonide being statistically significant (67). These data demonstrate that HFA-ciclesonide has a favorable local and systemic safety profile, which has also been shown in several other studies (48, 53, 68). In this context, the results of Van

der Molen et al. (69) are of special interest. They compared HFA-ciclesonide with FP and showed that HFA-ciclesonide induces less self-reported side-effects, as measured with the newly developed Inhaled Corticosteroid Questionnaire (69).

Discussion and conclusion

In recent years, there has been an increasing amount of evidence that supports the involvement of small airways contributing to asthma symptoms and severity. Importantly, small-particle aerosols have become available enabling a higher deposition of drug into the peripheral lung. Several studies have shown that these small-particle aerosols more effectively treat the small airways and therefore may have additional clinical benefits when compared to large-particle treatment.

However, a number of questions remain unanswered. First, it is unknown whether small airway disease is present in all patients or whether it represents a specific phenotype of asthma. Second, the question remains whether the presence of small airway disease is a risk factor for a poorer outcome, that is, difficult to manage asthma, a higher number of exacerbations, or development of fixed airway obstruction. To investigate this, prospective clinical studies are needed with extensive baseline and longitudinal characterization of large cohorts of asthma patients. In such studies, variables such as the type of allergy and levels of exposure to noxious particles and gases including cigarette smoke, smog, and exhaust fumes should also be incorporated into the study design, because these factors could potentially affect the presence and extent of small airway disease in asthma, or irritate the small airways leading to bronchoconstriction, due to their variation in particle size (70). In addition, it is of critical importance to develop new improved methods to measure small airway involvement in asthmatic inflammation and remodeling. In this context, small-particle AMP provocation is a promising new test as it not only reflects small airway disease, but also predicts a better response to small-particle HFA-ciclesonide treatment (56). Finally, the optimal treatment for asthma patients who have a high level of small airway disease is unknown.

Although these patients are likely to benefit from small-particle inhaled treatment, it should be taken into account that the cross-sectional area of small airways increases exponentially after the eighth generation, resulting in a low concentration of the drug per area in the tissue even when it is administered as a small-particle aerosol. For this reason, a higher inhaled dose of the small-particle aerosol might be necessary to achieve an optimal effect in the small airways. Alternatively, systemic administration of drugs, such as a leukotriene antagonist, will have to be given or added to the treatment regimen (71).

Overall, the emerging evidence from recent years suggests an important role of the small airways in asthma because they contribute to the clinical expression of the disease and responsiveness to treatment with small- or large-particle inhaled drugs. More research is now urgently needed to answer the many remaining questions which currently impact

the treatment for asthma and obstructive airway diseases in general.

Author contributions

Dr. M van den Berge was actively involved in the writing and designing of the manuscript. Professor DS Postma has made substantial contributions to the conception and design of this review paper, including in-depth discussions and important intellectual contributions. Comments have been made on all parts of the paper, including the final version. Professor DS Postma gave her approval for the final version submitted for publication. Drs. E van der Wiel and Dr. NHT ten Hacken were actively involved in writing and critically reviewing the content of this manuscript.

Conflicts of interest

Dr. M van den Berge has received consulting fees/honoraria, paid to The Department of Pulmonary Disease (University Medical Center, Groningen) as payment for lectures (including participation on speaker bureaus) provided on behalf of Nycomed. Professor DS Postma has received financial support for travel to meetings in relation to this manuscript and for other purposes from Astra Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Nycomed. Professor DS Postma has also received grants or has grants pending from Astra Zeneca, Chiesi, GlaxoSmithKline, and Nycomed. Drs. E van der Wiel and Dr. NHT ten Hacken have no potential conflicts of interest to declare.

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