



Targeting the small airways asthma phenotype: if we can reach it, should we treat it?

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ABSTRACT

Objective: To review the available methods of evaluating the small airways disease in asthma and the therapeutic strategies to achieve better control using emerging extrafine particle inhaler technologies.

Data Sources: The PubMed, MEDLINE (Ebsco), Scirus, Scopus, and Google Scholar databases were all scanned with Cross-search using the following keywords: *asthma, small airways, hydrofluoroalkane 134a, extrafine particle, inhaled corticosteroid, long-acting β -agonist, spirometry, impulse oscillometry, nitrogen washout, exhaled nitric oxide, airway hyperresponsiveness, and adrenal suppression.*

Study Selection: Key clinical studies considered to being relevant to the topic under review were evaluated.

Results: There is an unmet need in current asthma guidelines for those individuals who exhibit the small airways asthma phenotype with a preserved forced expiratory volume in 1 second but abnormal forced midexpiratory flow and peripheral airway resistance, which tends to be associated with poorer control. Extrafine hydrofluoroalkane solution formulations of inhaled corticosteroid either alone or in combination with long-acting β -agonist may improve small airways outcomes and associated control.

Conclusion: From a pragmatic perspective, it makes sense to try to deliver asthma treatment to more of the lung to improve clinical outcomes, especially in patients who exhibit the small airways asthma phenotype.

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Introduction

Current asthma management guidelines advocate the use of inhaled corticosteroids (ICSs) for persistent asthma as the mainstay of anti-inflammatory therapy.¹ For those patients whose asthma is not controlled with an ICS alone, addition of a long-acting β -agonist (LABA) is the preferred option as a second-line controller agent for use as steroid-sparing therapy. Although ICS-LABA combination inhalers are extensively used, there is increasing evidence that this may not be the complete answer for achieving optimal control. For example in a study of 3421 patients who were titrated with ICS-LABA combination therapy, only 41% achieved total asthma control, whereas 71% had well-controlled asthma.¹ In another observational study of 64,348 asthmatic patients, adding a LABA to an ICS was not as effective compared with increasing the dose of ICS alone in reducing exacerbations and hospitalizations.²

These observations suggest an unmet need for patients taking an ICS alone at step 2 and those taking ICS-LABA combination at step 3 or 4 of current guidelines. One possible strategy is to identify individuals with the small airways asthma phenotype to target

peripheral airways dysfunction that is not being controlled with conventional coarse particle ICS or ICS-LABA formulations. The principal aims of this article are to review the available methods of evaluating small airways disease in asthmatic patients and the therapeutic strategies to achieve better control using the emerging extrafine particle inhaler technologies, which may achieve improved penetration into the small airways with both the ICS and LABA moieties. The PubMed, MEDLINE (Ebsco), Scirus, Scopus, and Google Scholar databases were all scanned with Cross-search using the following keywords: *asthma, small airways, hydrofluoroalkane 134a, extrafine particle, inhaled corticosteroid, long-acting β -agonist, spirometry, impulse oscillometry, nitrogen washout, exhaled nitric oxide, airway hyperresponsiveness, and adrenal suppression.* Key clinical studies considered to being relevant to the topic under review were evaluated.

Clinical Assessment of Small Airways Dysfunction

Other review articles have detailed the supporting evidence for inflammation in the small airways of asthmatic patients and will therefore not be discussed in this review.³ Small airways are conventionally defined as those less than 2 mm in caliber.⁴ In relative terms, the available mucosal cross-sectional area is much greater in the distal than the proximal airways, which is also reflected by overall airway resistance. Before reviewing the key therapeutic intervention trials, it is important to appraise the

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different noninvasive methods of assessment of *in vivo* small airways function, using imaging and pulmonary function testing.

Conventional chest radiography or high-resolution computed tomography (HRCT) does not detect small airways abnormalities in asthmatic patients. However, HRCT can discriminate evidence of regional air trapping distal to small airways obstruction, which may be accentuated by performing the scan at residual volume after methacholine-induced bronchoconstriction.⁵

The main methods of pulmonary function testing are summarized in Table 1. Measurement of dynamic lung volumes, such as forced expiratory volume in 1 second (FEV₁) using spirometry, is considered to be the criterion standard for assessing treatment response in asthma. In this regard, the measurement of FEV₁ is more reflective of large and medium airways. The maneuver results in progressive volume-dependent airway closure as the patient breathes with forced expiration from total lung capacity to residual volume, which can be seen as the typical scalloping of the expiratory phase of the flow-volume loop. The forced mid-expiratory flow between 25% and 75% of forced vital capacity (FEF_{25%-75%}) is considered to be more reflective of small airways than the FEV₁.

The measurement of airway resistance during normal tidal breathing is more physiologic than performing an artificial forced expiratory maneuver and in turn is more sensitive to alterations in small airways geometry. Total airway resistance can be assessed using either whole-body plethysmography in a constant volume body box or more easily using impulse oscillometry (IOS). The latter involves a loudspeaker, which imparts an oscillatory wave signal onto the respiratory tract, and offers the possibility of measuring frequency dependence of resistance, typically at 5 Hz (R5) and 20 Hz (R20), reflecting total and central resistance, respectively, and hence deriving the total peripheral airway resistance as the difference between R5 and R20 (R5–R20).⁶ In addition, IOS can derive the reactance that reflects the capacitive and inertial properties of the airways, with the reactance at 5 Hz (X5) reflecting the small airways component along with the area under the reactance curve (AX) between 5 Hz and the resonant frequency. For detecting either acute bronchoconstriction or acute bronchodilatation in asthma, IOS has been reported to be superior to spirometry with regard to the signal to noise ratio for different response outcomes.^{6,7} However, studies have not been performed with extrafine LABA or ICS-LABA in patients who *a priori* exhibit impaired small airways dysfunction.

In a study of 378 asthmatic adults,⁸ a comparison was made across British Thoracic Society (BTS) treatment steps for abnormalities of spirometry vs IOS outcomes, which reflected persistent small airway dysfunction. There was a high proportion of abnormal

values for peripheral airway resistance as R5–R20 (>0.03 kPa/L/s) at BTS treatment steps 2, 3, and 4 (64.6%, 63.5%, and 69.9%, respectively), with a significant difference in mean values for R5–R20 but not FEF_{25%-75%} between step 3 and step 2 patients. From a pragmatic point of view in everyday clinical practice, it is clearly possible to identify patients who have a small airway asthma phenotype (ie, individuals who have a relatively well-preserved FEV₁ with an impaired FEF_{25%-75%} and/or impaired R5–R20).

A key question to therefore consider is how do small airway measurements relate to asthma control in patients who exhibit the small airways asthma phenotype (Table 2). In a study of 107 children by Shi and coworkers,⁹ a comparison was made between controlled and noncontrolled asthma, with 83% and 85% of cases being correctly classified on the basis of R5–R20 and AX, respectively. In the same study there were 5% in each group with abnormal FEV₁ values (<80% predicted) compared with 64% with abnormal FEF_{25%-75%} values (<65% predicted) in the uncontrolled group and 4% abnormal in the controlled group. In a further analysis of the same cohort, a comparison was made of 2 groups of children with controlled asthma at baseline, who either remained controlled at follow-up 2 to 3 months later or subsequently lost control. Significant differences between these groups were seen at baseline for R5, R5–R20, and AX but not FEV₁ nor FEF_{25%-75%}, with 83% and 91% of cases being correctly classified in predicting subsequent loss of control on the basis of R5–R20 and AX, respectively.¹⁰ In another database study of asthmatic children who were followed up for a year, those who had a normal FEV₁ with an abnormal FEF_{25%-75%} were associated with higher controller use, increased oral corticosteroid use, and more exacerbations compared with those with normal FEV₁ and normal FEF_{25%-75%}.¹¹

Another way of assessing small airways involves the use of the multiple breath nitrogen washout method using phase 3 slope analysis to assess ventilation heterogeneity of diffusion- and convection-dependent airways, showing worse ventilation heterogeneity in patients with poorly controlled asthma.¹² Both of these outcomes were also highly predictive of symptom response to ICS dose titration, during both step-up and step-down.¹³ Using single-breath washout to measure static lung volumes, evidence of significantly increased air trapping was seen when comparing controlled vs poorly controlled asthma patients in terms of recurrent exacerbations for the ratio of closing volume to vital capacity and closing capacity to total lung capacity but not for FEV₁.¹⁴

Taken together these physiologic studies provide strong evidence to support a group of patients who have a distinct small airway phenotype with preserved FEV₁ but abnormal peripheral airway function in terms of airway resistance, compliance,

Table 1
Noninvasive small airway assessment

Assessment	Measure
Spirometry	FEF _{25%-75%} , FVC/RVC
Impulse oscillometry	R5–R20, AX, X5, RF
Body plethysmography	Raw, RV/TLC
Nitrogen washout	CV/VC, CC/TLC, S(acin), S(cond)
HRCT with or without challenge	Air trapping in Hounsfield units
Exhaled nitric oxide	Alveolar fraction of nitric oxide

Abbreviations: AX, area under reactance curve between 5 Hz and resonant frequency; CC/TLC, ratio of closing capacity to total lung capacity; CV/VC, ratio of closing volume to vital capacity; FEF_{25%-75%}, forced midexpiratory flow between 25% and 75% of forced vital capacity; RF, resonant frequency; FVC/RVC, ratio of forced to relaxed vital capacity; HRCT, high-resolution computed tomography; R5–R20, peripheral airway resistance as difference [total – central] between resistance at 5 Hz minus 20 Hz; X5, reactance at 5 Hz; Raw, total airway resistance; RV/TLC, ratio of residual volume to total lung capacity; S(acin), phase 3 slope index of ventilation heterogeneity in diffusion-dependent airway; S(cond), slope index of ventilation heterogeneity in convection-dependent airway.

Table 2
Key studies evaluating relationships between small airways dysfunction and asthma control

Reference	Outcomes	Results
Farah et al ^{12,13}	N2 washout	S(cond) and S(acin) associated with poor control and ICS response
Shi et al ^{9,10}	IOS	R5–R20 and AX but not FEV ₁ predicts poor control
in 't Veen et al ¹⁴	N2 washout	CV/VC and CC/TLC but not FEV ₁ associated with exacerbations
Rao et al ¹¹	Spirometry	FEF _{25%-75%} but not FEV ₁ associated with exacerbations

Abbreviations: AX, area under reactance curve between 5 Hz and resonant frequency; CC/TLC, ratio of closing capacity to total lung capacity; CV/VC, ratio of closing volume to vital capacity; FEF_{25%-75%}, forced midexpiratory flow between 25% and 75% of forced vital capacity; ICS, inhaled corticosteroid; IOS, impulse oscillometry; R5–R20, peripheral airway resistance as difference [total – central] between resistance at 5 Hz minus 20 Hz; S(acin), slope index of ventilation heterogeneity in diffusion-dependent airway; S(cond), slope index of ventilation heterogeneity in convection-dependent airway.

ventilation heterogeneity, or air trapping, which seems to be associated with poorer control.

Fractionating of exhaled breath nitric oxide to evaluate the bronchial and alveolar moieties may be assessed by performing measurements at different flow rate.¹⁵ By plotting nitric oxide levels vs flow rates, the alveolar fraction may be calculated from the slope gradient, whereas the intercept is the bronchial flux. Mathematical corrections have been advocated to correct for axial back diffusion from the conducting to the alveolar compartments, especially when the bronchial component is elevated.¹⁵ The usual measurement of tidal exhaled breath nitric oxide is performed at a single flow rate of 50 mL/s. Levels of uncorrected exhaled nitric oxide are elevated in patients with severe asthma, despite taking high doses of conventional coarse particle ICS, along with elevated levels of R5-R20.¹⁶

Targeting Inhaled Therapy to the Small Airways

The advent of solution-based, hydrofluoroalkane (HFA)–propelled, pressurized metered-dose inhalers has enabled delivering formulations with extrafine particles of ICSs, namely, HFA-beclomethasone, HFA-ciclesonide, HFA-flunisolide (not in Europe); LABAs, namely, HFA formoterol (not in the United States); and ICS-LABA combination, namely, HFA-beclomethasone and HFA-formoterol (not in the United States). The situation is somewhat confused because not all HFA formulations are solution based. For example, HFA formulations of fluticasone, fluticasone-salmeterol, fluticasone-formoterol, budesonide-formoterol, and mometasone-formoterol are all coarse particle suspension–based formulations. HFA solution–based formulations that emit extrafine particles with a mass median aerodynamic diameter less than 2 μm will effectively reach the peripheral airways. However, because there is a normal distribution of particle size around the mass median aerodynamic diameter, there will be a small proportion of extrafine particles even with the coarse particle HFA suspension formulations. In this regard, there appears to be a reasonable relationship between in vitro particle impactor distribution and in vivo radionuclide lung delivery.¹⁷ The key studies evaluating effects of ICS on small airways are summarized in Table 3.

Pulmonary Function Outcomes

The use of extrafine particle solution–based inhalers results in not only more of the drug reaching the lung in terms of the overall fine particle dose but also the drug reaching more of the lung in terms of overall lung distribution (Fig 1). This will in turn result in a leftward shift in the dose response curve for antiasthmatic efficacy but perhaps also a greater achievable maximal response. For example, in a dose-ranging study with extrafine particle HFA

solution vs coarse particle chlorofluorocarbon (CFC) suspension beclomethasone dipropionate (BDP) formulations, the dose ratio for relative potency was 2.6-fold for FEV₁, indicating a commensurate leftward shift on the dose response curve (ie, 400 μg of CFC-BDP would produce the same improvement in FEV₁ as 150 μg of HFA-BDP).¹⁸ Furthermore, at a dose of 800 $\mu\text{g}/\text{d}$ the maximum FEF_{25%–75%} response was 98.9% with HFA-BDP vs 76.7% with CFC-BDP, perhaps indicating a greater response in the peripheral airways due to the smaller particle size reaching more of the lung. This finding was supported by another comparison of 400 μg of CFC-BDP twice daily vs 200 μg of HFA-BDP twice daily using IOS as the primary outcome measure.¹⁹ After 12 weeks there was a significant decrease in R5-R20 with HFA-BDP but not CFC-BDP, while the decrease in AX was also significantly greater with HFA-BDP than CFC-BDP (Fig 2).

Inflammatory Markers

Berry et al²⁰ reported that treatment with oral corticosteroid but not an increased dose of conventional coarse particle ICS produced a significant decrease in uncorrected alveolar nitric oxide fraction in patients with refractory asthma, pointing to its suppression by a systemic anti-inflammatory effect in the distal lung compartment.²⁰ In a comparison of HFA-BDP, 100 μg twice daily, vs CFC-BDP, 250 μg twice daily, both formulations significantly reduced exhaled bronchial nitric oxide, whereas for alveolar nitric oxide there was only a significant reduction with HFA-BDP, with the decrease in both bronchial and alveolar nitric oxide being greater with HFA than CFC.²¹ In asthmatic children already receiving ICS (mean daily fluticasone dose, 312 μg), no difference was seen after 3 months for the primary outcome of uncorrected alveolar nitric oxide when comparing HFA-BDP, 100 μg twice daily, vs fluticasone dry powder, 100 μg twice daily, although neither drug produced a significant decrease from baseline.²²

A potentially interesting but nonlicensed therapeutic use for HFA-BDP is to use it as add-on therapy in patients whose asthma is not controlled despite taking conventional coarse particle ICS-LABA combination. Such a proof-of-concept study was performed in 15 adults with severe asthma (FEV₁, 58%) with elevated levels of alveolar nitric oxide, who received an initial run-in period with fluticasone-salmeterol, 250 and 50 μg , respectively, twice daily, followed by 500 and 50 μg twice daily via dry powder inhaler for 6 weeks, after which they were randomized to receive additional therapy with either fluticasone dry powder, 250 μg twice daily, or HFA-BDP, 200 μg twice daily, for a further 3 weeks of each, with a non-randomized, 1-week run-out while taking oral prednisolone, 25 mg daily.²³ For the primary outcome of corrected alveolar nitric oxide, there was no significant further suppression with either randomized treatment arm or with prednisolone as add on to

Table 3

Key studies comparing small airway outcomes and asthma control outcomes with extrafine vs coarse particle inhaled corticosteroids

Reference	Comparison ^a	Outcome	Result
Busse et al ¹⁸	100–800 HFA vs CFC-BDP	FEF _{25%–75%}	HFA > CFC-BDP
Yamaguchi et al ¹⁹	HFA 400 vs CFC 800	R5-R20	HFA > CFC-BDP
Nicolini et al ²¹	HFA 200 vs CFC 500	Alv NO	HFA-BDP > HFA-BDP
Robroeks ²²	HFA-BDP 200 vs FP DPI 200	Alv NO	HFA-BDP = FP-DPI
Williamson et al ²³	HFA-BDP 400 vs FP DPI 500 (+FP/SM1000/100)	Alv NO	HFA-BDP = FP-DPI
Cohen et al ²⁷	HFA-CIC 160 vs HFA-FP200	AMP challenge	HFA-CIC > HFA-FP
Goldin et al ⁵	HFA-BDP 400 vs CFC-BDP 400	HRCT and challenge	HFA-BDP > CFC-BDP
Price et al ³⁰	HFA-BDP vs HFA/CFC-FP	Asthma control	HFA-BDP > HFA (HFA-BDP at lower dose)
Juniper et al ³²	HFA-BDP vs CFC-BDP	Quality of life	HFA-BDP > CFC-BDP (HFA-BDP at half dose)
Barnes et al ³¹	HFA-BDP vs CFC-BDP	Asthma control	HFA-BDP = CFC-BDP (HFA-BDP at lower dose)

Abbreviations: Alv NO, alveolar nitric oxide fraction; AMP, adenosine monophosphate; BDP, beclomethasone dipropionate; CFC, chlorofluorocarbon; CIC, ciclesonide; DPI, dry powder inhaler; FEF_{25%–75%}, forced midexpiratory flow; FP, fluticasone propionate; FP/SM, fluticasone-salmeterol combination; HFA, hydrofluoroalkane; HRCT, high-resolution computed tomography; R5-R20, peripheral airway resistance.

^aDoses are in micrograms per day.

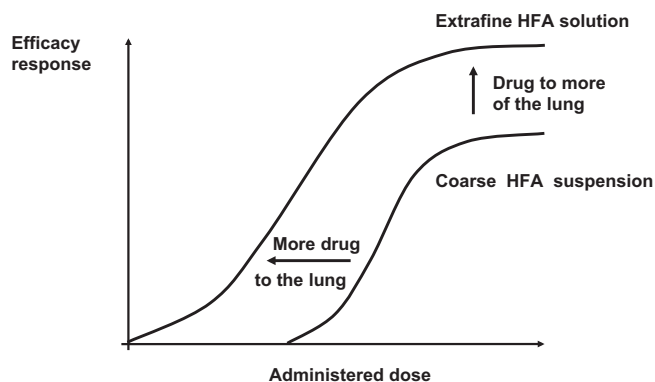


Figure 1. Schematic of lung dose vs efficacy response. Schematic dose-response relationships are depicted for extrafine solution vs coarse particle suspension hydrofluoroalkane (HFA) formulations. With the extrafine particle formulation delivering more drug to the lung results in a leftward shift in the dose-response curve while at the same time delivering the drug to more of the lung results in a higher plateau response.

fluticasone-salmeterol. However, for exhaled breath nitric oxide (at 50 mL/s) and bronchial nitric oxide flux, there was significant additional suppression with both HFA-BDP and prednisolone, whereas only the latter suppressed systemic markers, including plasma eosinophilic cationic protein, E-selectin, intracellular adhesion molecule 1, and cortisol. These observations show that HFA-BDP may confer additional anti-inflammatory activity in patients with severe asthma already taking a maximal dose of ICS combination therapy but without causing systemic adverse effects.

In a study with extrafine HFA-flunisolide, transbronchial and endobronchial biopsy specimens were taken before and after 6 weeks of treatment in 12 patients with mild to moderate asthma, showing significant reductions in interleukin 5, eotaxin, and eosinophils in both central and peripheral airways.²⁴ Further analysis from the same biopsy study looking at remodeling revealed a significant reduction in small airway expression of smooth muscle α -actin, which correlated to improved FEF_{25%-75%} but no effect on collagen deposition or expression of transforming growth factor β .²⁵

Imaging Studies

In asthmatic patients with technetium Tc 99m-labeled HFA-ciclesonide using 2-dimensional γ -scintigraphy, whole lung deposition was 52% with the actuator alone.²⁶ Moreover, 3-dimensional, single-photon emission computed tomography was used to assess regional distribution, with the highest deposition in the peripheral regions of the lung. A similar technetium Tc 99m-labeled study in asthmatic patients showed 2-dimensional total lung deposition of 58% with HFA-beclomethasone solution and 16% for HFA-fluticasone-salmeterol combination suspension, both given via actuator alone, in turn reflecting the respective in vitro cascade impactor particle sizes at 0.7 and 2.7 μ m.¹⁷ The data with 3-dimensional, single-photon emission computed tomography revealed that the mean ratio for regional deposition in central vs peripheral zones was 4.9 for HFA-fluticasone-salmeterol and 1.6 for HFA-beclomethasone, with greater variability of deposition with the former.

An imaging study was performed comparing 200 μ g twice daily of HFA-BDP vs CFC-BDP given for 4 weeks with functional HRCT performed at residual volume before and after methacholine challenge to assess regional hyperinflation.⁵ The results revealed that after 4 weeks HFA-BDP conferred significantly better protection against air trapping after acute bronchoconstriction. This finding may assume physiologic relevance in the setting of an acute

asthma exacerbation, where the HFA formulation affords greater anti-inflammatory protection against acute bronchoconstriction due to distribution of extrafine particles to more of the lung.

Challenge Studies

In a comparison of extrafine HFA-ciclesonide, 160 μ g once daily, vs coarse HFA-fluticasone, 100 μ g twice daily, their relative effects were evaluated on airway hyperresponsiveness (AHR) to adenosine monophosphate challenge delivered via small or large particles. Ciclesonide improved AHR to small particle challenge, whereas fluticasone improved AHR to large particle challenge, in turn suggesting effects on inflammation in respective airways.²⁷ Another challenge study found dose-related improvements in methacholine AHR between 50 μ g twice daily and 200 μ g twice daily of HFA-BDP, whereas adding in zafirlukast but not theophylline achieved the same effect as increasing the dose of ICS, with a similar picture being seen on exhaled breath nitric oxide.²⁸ In a 12-month prospective dose titration study, patients had the dose of HFA-ciclesonide titrated upward against either BTS outcomes or purely against mannitol AHR, with the latter strategy resulting in fewer exacerbations and significant reductions in exhaled nitric oxide and salivary eosinophilic cationic protein, symptoms, and reliever use.²⁹

Asthma Control

To further investigate the putative link between improved physiologic and imaging outcomes and real-life clinical control with regard to ICS particle size, a study was performed using the UK database of asthmatic patients aged 5 to 60 years, which was able to link prescribing to composite clinical control outcomes.³⁰ An assessment was made during a 1-year period before and after an index prescription for ICS formulations comprising either extrafine HFA-BDP solution vs coarse particle CFC- or HFA-fluticasone suspension, with 1319 patients being allocated to each group who initiated treatment. For the primary outcome of asthma control in patients who had an initial prescription of either formulation, the adjusted odds ratio for achieving control was 1.30 (95% CI, 1.02–1.65) significantly in favor of HFA-BDP relative to fluticasone, with no differences in exacerbation rates. The mean daily dose requirement was significantly lower with HFA-BDP vs fluticasone at 198 μ g vs 376 μ g. Aside from the enhanced lung deposition characteristics with the extrafine HFA-BDP formulation, other possible reasons for the improved control might be the ease of use with the softer warmer spray, even in patients who are poor coordinators. However, in another US database study comparing HFA-BDP vs CFC-BDP in 2,882 and 8,646 patients, respectively, during 12 months, no differences in control outcomes were observed with HFA-BDP at half the dose.³¹ In a database evaluation of patients with persistent asthma at step 2 of guidelines, those receiving extrafine HFA-BDP ($n = 67$) had a lower airway resistance at R5 (124% vs 138%) compared with those taking conventional coarse particle ICS ($n = 125$), with no difference in FEV₁ (88.9% vs 90.3%).⁸ Moreover, those taking HFA-BDP received a significantly lower nominal dose of ICS (279 vs 406 μ g/d). In a prospective, 12-month evaluation, patients who were taking coarse particle CFC-BDP were randomized to either continue taking the same dose of the CFC-BDP or switched to extrafine HFA-BDP at half the dose. The group taking half the dose of HFA-BDP achieved superior control in terms of asthma quality of life and reduced symptoms during a 12-month period without any difference in FEV₁.³²

Systemic Adverse Effects

BDP is a prodrug that is converted to both an active and inactive metabolite, beclomethasone-17 monpropionate (17-BMP) and beclomethasone-21 monpropionate (17-BMP), respectively, which

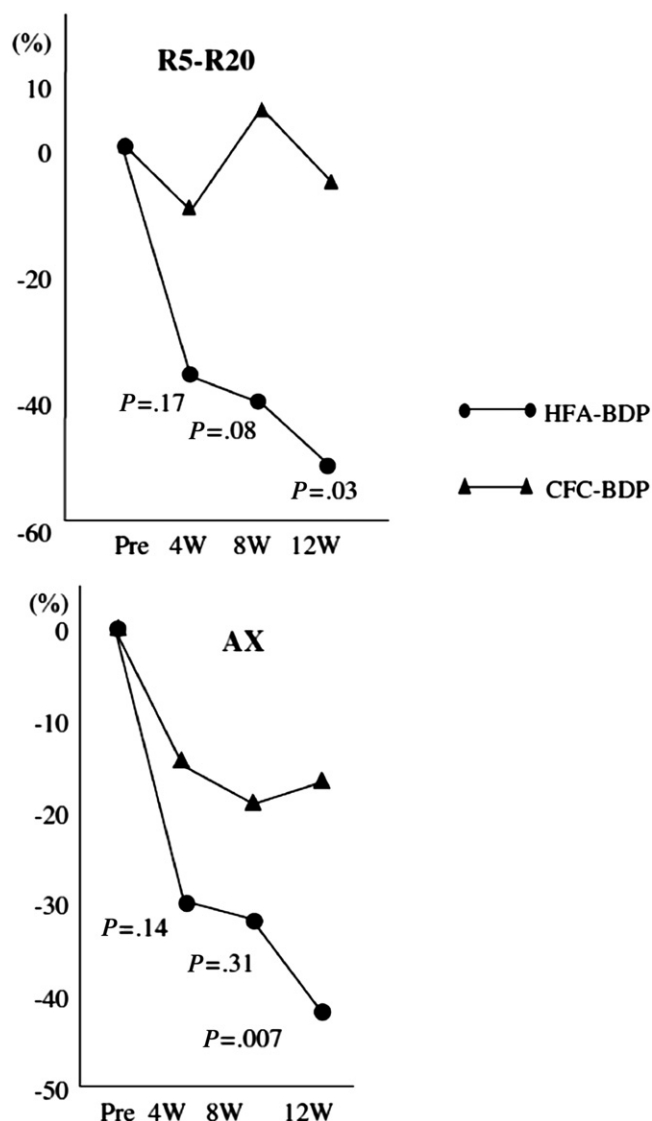


Figure 2. Comparative effect of 200 μ g bid of hydrofluoroalkane (HFA)–beclomethasone dipropionate (BDP) or 400 μ g bid chlorofluorocarbon (CFC)–BDP on peripheral airway resistance (R5–R20) and peripheral reactance (AX) in steroid-naïve patients with asthma.¹⁹ Figure reprinted with permission of Yamaguchi et al. *Pulm Pharmacol Ther.* 2009;22:326–332.

are both in turn converted to beclomethasone alcohol (BOH). These agents have the relative glucocorticoid receptor affinities of 53, 1,345, 0.9, and 76, respectively.³³ Delivering a higher fine particle dose to the lungs may not only improve efficacy but also increase systemic bioavailability.³⁴ However, although more fine particles of HFA-BDP are delivered to the lung, the converse applies to deposition of larger particles in the oropharynx. Subsequently, for the swallowed fraction there is 60% first pass hepatic inactivation of BDP, whereas there is almost complete and rapid conversion to 17-BMP in the lung. Thus, a comparison of the HFA and the CFC formulation will reveal relatively less systemic availability from the gut but increased availability from the lung. Using a spacer device with HFA-BDP will further reduce the gut bioavailability component by eliminating oropharyngeal deposition, but because the spacer does not appreciably increase the fine particle dose to the lungs, it will not increase lung bioavailability, with the net effect being lower systemic exposure of 17-BMP. For coarse particle HFA formulations such as fluticasone, use of a spacer will increase the fine particle dose to the lungs and associated systemic exposure³⁵

because there is almost complete first pass inactivation of fluticasone in the liver but not in the lung. A further consideration is that the elimination half-life of 17-BMP is short at 2 to 3 hours³³ such that by the end of the usual 12-hour dosing interval there will be relatively little drug accumulation at steady state, in contrast to fluticasone, which has a longer half-life of 14 hours. This finding reflects the lower lipophilicity of 17-BMP, which results in higher plasma levels but much reduced systemic retention in fat tissue at steady state after chronic dosing.³⁶ Conversely, drugs with higher lipophilicity, such as fluticasone, have lower plasma levels but greater retention in systemic fat tissue at steady state (ie, a higher volume of distribution). This in turn explains why HFA-BDP exhibits a relatively safe systemic adverse effect profile, with little evidence of significant adrenal suppression up to a dose of 200 μ g twice daily in adults and 100 μ g twice daily in children.^{28,37} In asthmatic children older than 12 months, there was no evidence of suppression of growth or biochemical bone markers comparing 100 μ g twice daily of HFA-BDP vs 200 μ g twice daily of CFC-BDP via spacer.³⁷ In another study with 50 μ g twice daily of HFA-BDP, there was a 1.1-cm reduction in growth velocity in the first year of exposure, which is a class effect seen with other ICS.³⁸

Ciclesonide is also a prodrug that is converted on site in the lung to its active metabolite des-ciclesonide but has almost complete first-pass inactivation in the liver for the swallowed fraction. Moreover, des-ciclesonide has 99% plasma protein binding such that the amount of free drug is low despite a high degree of pulmonary bioavailability. This finding may explain why clinical studies have reported minimal or no suppression of adrenocortical activity or biochemical bone markers.^{39,40} With any ICS the propensity for developing long-term systemic adverse effects will be minimized by always trying to ensure that patients step down to their lowest effective maintenance dose once control has been achieved, in keeping with asthma management guidelines.

Inhaled Long-Acting β -Agonists

Although the density of glucocorticoid receptors is similar in the large and small airways,⁴¹ the density of β_2 -adrenoceptor is higher in the latter,⁴² suggesting that delivery of extrafine β -agonist particles might confer some therapeutic advantage given either alone or combination with ICS. Usmani et al evaluated a radio-labeled monodisperse salbutamol formulation with particles sizes of 1.5, 3, and 6 μ m using γ -scintigraphy, which showed that although smaller particles produced better overall lung deposition and small airways penetration, the converse applied to bronchodilatation as FEV₁ response.⁴³ Pointedly, no measurement of small airways function was assessed, with FEV₁ reflecting effects in larger airways.

The only currently licensed extrafine LABA formulations comprise HFA-formoterol and HFA-beclomethasone-formoterol combination, which has a mass median aerodynamic diameter of 1.5 μ m, with 66% and 34% deposited, respectively, in large and small airways.⁴⁴ In a single dosing study comparing 12 μ g of extrafine HFA vs coarse particle dry powder formulations of formoterol, no significant differences were found in R5, resonant frequency, X5, or FEF_{25%–75%} in patients with mild to moderate asthma.⁴⁵ However, these patients were not selected a priori on the basis of having persistent small airway dysfunction. In a comparison of extrafine HFA-beclomethasone-formoterol, 200 and 12 μ g twice daily, and fluticasone propionate, 250 and 50 μ g twice daily, for 12 months, there were significant improvements in methacholine AHR with the former and a nonsignificant trend toward reduced single-breath nitrogen closing capacity.⁴⁶ In a 24-week comparison of the same formulations, both significantly improved FEV₁ and FEF_{25%–75%} and asthma control score, but only beclomethasone-formoterol significantly reduced closing volume,

with a similar nonsignificant trend toward a lower single-breath phase 3 slope.⁴⁷ In patients with moderate to severe asthma, using the extrafine HFA-beclomethasone-formoterol combination, 200 and 12 µg twice daily, resulted in better asthma control during 6 months than equipotent doses of the same moieties in coarse particle formulations.⁴⁸ In a real-life setting the proportion of patients achieving optimal control was better with extrafine beclomethasone-formoterol compared with coarse particle combination therapy with dry powder formulations of either budesonide-formoterol or fluticasone-salmeterol but at a significantly lower ICS dose. Another real-life study also found significantly better control and quality of life in patients taking extrafine beclomethasone-formoterol vs dry powder budesonide-formoterol or fluticasone-salmeterol for 1 year but at a lower ICS dose exposure.^{49,50}

Conclusions

The advent of extrafine solution-based ICS and ICS-LABA formulations is an important therapeutic advance for the treatment of asthma, especially given the evidence of persistent small airways dysfunction in a large proportion of patients despite conventional coarse particle inhaled therapy across all treatment steps of current guidelines. There are also data to support the presence of persistent small airway dysfunction being associated with impaired asthma control. From a pragmatic point of view, it therefore makes sense to try to deliver ICS and LABA to more of the lung to improve clinical outcomes, especially in patients who exhibit the small airway asthma phenotype. Further prospective randomized clinical trials are required to provide the missing link as to whether targeted inhaled therapy for this particular phenotype results in commensurate long-term improvements in clinical outcomes, such as asthma control, exacerbations, AHR, and inflammatory markers.

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