



Small-airway disease in asthma: pharmacological considerations

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Purpose of review

To review the pharmacological considerations and rationale for treating small-airway disease in asthma via the inhaled and systemic route, and to also directly address the comparison between small vs. large aerosol particles in the management of asthmatic patients.

Recent findings

Airway inflammation in patients with asthma is predominantly present within the small airways and this region is the main contributor to airflow limitation. Assessing small-airway dysfunction has advanced in the last decade, allowing us to compare this region in disease to health and also in response to treatment. Recent pharmaceutical developments have led to inhaler devices with smaller aerosols and systemic biologic treatments, enabling therapeutic drug delivery to the distal lung regions. The question therefore is does targeting the small airways directly translate into health benefits for asthmatic patients with respect to an improvement in their disease control and quality of life?

Summary

Studies now show that treating the peripheral airways with smaller drug particle aerosols certainly achieve comparable efficacy (and some studies show superiority) compared with large particles, a reduction in the daily inhaled corticosteroid dose, and greater asthma control and quality of life in real-life studies. Hence, the small airways should not be neglected when choosing the optimal asthma therapy.

Keywords

asthma, corticosteroids, inhalation, long-acting beta-agonists, pharmacology, small airways, small particles, systemic therapies

INTRODUCTION

Several studies have highlighted the importance of the small airways in asthmatic patients of different disease severities and different phenotypes, and also in other obstructive lung diseases [1–3,4]. Pathophysiological studies clearly document that airway inflammation in patients with asthma is present within the small airways and that this region is the main contributor to airflow limitation. Physiological techniques of this region using measurements such as impulse oscillometry, multiple breath nitrogen wash-out and nitric oxide, together with high-resolution computed tomography (HRCT) and MRI of the lung have advanced in the last decade, allowing us to assess this region in disease and also in response to drug therapy. Pharmaceutical developments have led to both systemic treatments and inhaler devices with smaller aerosols that enable therapeutic delivery into the distal lung regions. This article will review the rationale and pharmacological considerations for treating the small airways, and will also directly

address the comparison between small vs. large inhaled aerosol particles on the therapeutic ratio (clinical benefit vs. adverse effects) in the management of patients with asthma.

CURRENT ASTHMA CONTROL REMAINS POOR

Despite the improvements in asthma diagnosis and pharmacological advances in more targeted treatment, asthma control remains suboptimal. A recent

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KEY POINTS

Treating the peripheral airways with small-drug particle aerosols

- achieves comparable (and in some studies superiority) in efficacy compared with large particles;
- enables greater asthma control in real-life studies;
- allows a reduction in the daily inhaled corticosteroid dose.

European cross-sectional survey of patient-reported asthma control revealed that a significant proportion (53.5%) of over 3000 treated patients were still not well controlled [5]. Demoly *et al.* [5] additionally confirmed that the levels of asthma control had not improved over a 5-year period. Certainly, the treatment of asthma has greatly improved with the combination of inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) therapy, leading to better disease control than ICS monotherapy [6], and biological mechanisms have been elucidated that may explain their complementary interaction [7]. However, despite the combination therapy, asthma control still remains poor.

In the Gaining Optimal Asthma Control (GOAL) study, Bateman *et al.* [8] observed that regular treatment with the ICS/LABA combination of fluticasone propionate and salmeterol for 1 year led to only 41% of asthmatic patients becoming 'totally' controlled and just 71% being 'well controlled', even though 89% of patients were compliant with inhaled therapy, suggesting patient compliance with medication was not a significant confounding factor influencing the endpoint of asthma control [9]. In a post hoc analysis of the Formoterol and Corticosteroid Establishing Therapy (FACET) study [10,11], only 62% of patients with asthma treated with high-dose combination ICS/LABA of budesonide (BUD) 800 µg/formoterol 24 µg daily for 1 year were characterized as being well controlled in the last 2 months of the study. Indeed, lower levels of asthma control were observed in patients with milder disease on low-dose ICS/LABA and in those receiving ICS monotherapy.

These data suggest that with our current pharmacological approach, asthma control continues to remain poor across all severities of the disease, and this is an unmet problem that must be addressed. Indeed, the term 'asthma' describes a clinical syndrome that collectively encompasses a diverse group of phenotypes and endotypes each having different disease characteristics or mechanisms responding differently to different treatments,

and as such, treatment may therefore need to be customized to the individual patient [12¹¹,13]. Several factors contribute to poor levels of asthma control, including comorbid disease (e.g., rhinosinusitis and gastro-oesophageal reflux disease), environmental exposures (e.g., fungi, house-dust mite, pollen, cigarette smoke and fumes), obesity, asthma and chronic obstructive pulmonary disease overlap syndrome (ACOS), psychological disturbances and lack of adherence to prescribed treatment. Importantly, within this umbrella syndrome is the increasingly recognized entity of the 'small-airways phenotype', that is, persistent pathological airway inflammation and physiological dysfunction within the distal lung compartment that may be contributing to poor levels of asthma control.

SMALL AIRWAYS: DEFINITION, DISEASE AND DYSFUNCTION

The lungs are a branching structure, segmentally dividing from the trachea (airway generation 1) to the alveoli (generation 23), and the small airways are defined as airways with an internal diameter less than 2 mm (comprising generations 8–23), whereas the large airways have an internal diameter greater than 2 mm (generations 1–7). The lungs are also divided into a conducting airway zone (generations 1–16) that transport the inhaled air, with a transition zone at the level of the terminal bronchioles leading to the respiratory acinar zone (generations 17–23) involved in gas exchange [14].

Pathologists have long established that asthma is a disease not only of the large, but also of the small airways [15,16], and it is now generally acknowledged that the small airways are the major site of physiological airflow limitation in asthma [17]. Small-airway dysfunction is clearly evident in patients with severe asthma [18,19], but there is growing evidence supporting its presence in patients with milder disease [20,21]. Distal airway inflammation and physiological dysfunction involving the small airways have also been shown to be present in distinct asthmatic patient phenotypes such as nocturnal asthma [22,23], exercise-induced asthma [24,25] and allergic asthma [26,27].

DRUGS TARGETING THE SMALL AIRWAYS

Hence, pathophysiological evidence supports the treatment of the small airways; however, most inhaled therapies used in the clinic do not sufficiently reach the distal lung regions [28,29]. The need to treat persistent small-airway inflammation in asthmatic patients was reported in a well designed study by Berry *et al.* [30], who observed elevated

levels of both alveolar nitric oxide and eosinophilia in bronchoalveolar lavage (BAL) from asthmatic patients despite maximal inhaled therapy on step 4 of asthma treatment guidelines. The investigators doubled the ICS dose for 1 month, but there was no attenuation of alveolar nitric oxide levels and they postulated that conventional inhaler devices were unable to effectively deliver medication to treat the persistent small-airway inflammation. However, when patients were treated for 2 weeks with oral corticosteroid therapy, alveolar nitric oxide levels were significantly reduced, supporting their hypothesis for anti-inflammatory treatment to target the small airways.

Different inhalers emit different drug particle sizes, but most conventional devices emit large drug particles (Table 1). Generally, dry powder inhaler (DPI) devices release larger drug particle sizes than pressurized metered-dose inhalers (pMDI), and within the pMDI category, hydrofluoroalkane (HFA)-solution aerosols yield smaller particle sizes than HFA-suspension devices. For the purpose of this review, small-particle aerosols are defined as those with a mass median aerodynamic diameter (particle size) of $2\mu\text{m}$ or less. Most conventional inhaler devices routinely used in the clinic achieve relatively poor levels of total lung deposition (TLD); at best, 10–20% of the inhaled drug deposits in the lungs [39,40], leading to four-fifths of the dose being wasted, and through gastrointestinal absorption this wasted dose potentially contributes to systemic bioavailability and adverse effects. Certainly, studies have shown marked variances in TLD between devices [29,37,38,41–43].

The most important inhaler characteristic that influences the pulmonary deposition and regional (central and distal) airway distribution of inhaled therapy is drug particle size [44]. Technological advances in the last decade by formulation

scientists, device engineers and aerosol physicists have given rise to a new generation of inhalation devices that can emit smaller drug particles at slower velocities (Table 1), thus achieving better TLD ($\sim 30\text{--}50\%$) and importantly, allowing effective aerosol penetration into the lung periphery. Usmani *et al.* [45,46] have shown that small ($1.5\mu\text{m}$) particles of a short-acting beta-2 agonist, salbutamol formulation, achieved better TLD compared with larger 3 and $6\mu\text{m}$ particles (56, 50, and 46%, respectively, as a percentage of delivered dose) in mild asthmatic patients. They also observed significantly greater penetration into the peripheral airways with the smaller salbutamol particles [penetration indices of 0.79 ($1.5\mu\text{m}$), 0.60 ($3\mu\text{m}$) and 0.36 ($6\mu\text{m}$)], and although slow inhalation was better than fast inhalation for effective lung deposition with the large 3 and $6\mu\text{m}$ particles, lung deposition was less affected by the differences in inhalation flows with smaller particles. Importantly, the $1.5\mu\text{m}$ salbutamol particles achieved much lower throat deposition compared with the larger 3 and $6\mu\text{m}$ particles (15, 31 and 43%, respectively).

Lung deposition studies in asthmatic patients using small-particle ICS monotherapy with pMDI HFA-solution ciclesonide (CIC) [$\sim 1.1\mu\text{m}$; mean forced expiratory volume in one second (FEV₁) 94.5% predicted] [43] and beclomethasone dipropionate (BDP; $\sim 0.9\mu\text{m}$; all patients FEV₁ >90% predicted) [29] have, respectively, shown 56 and 42% peripheral lung deposition as a proportion of total lung dose, although in the latter study the deposition analysis was not corrected for lung ventilation/volume [47]. A propellant-free soft-mist inhaler generating small particles ($\sim 2\mu\text{m}$) of BUD emitted with a slow exit velocity showed improved TLD (51.6%), lower oropharyngeal deposition (19.3%) and greater peripheral lung penetration [peripheral/central (P/C) ratio 1.34] compared with

Table 1. Drug particle sizes of common inhaler devices and corticosteroid formulations

Inhaler device	Drug formulation	MMAD (μm)
DPI	Fluticasone propionate [31]	5.4
DPI	Budesonide [31]	4.0
DPI	Mometasone furoate [32]	3.7
pMDI HFA-suspension	Fluticasone propionate and salmeterol [29]	2.7
pMDI HFA-suspension	Fluticasone propionate [33]	2.4
DPI	Beclomethasone dipropionate and formoterol [34]	1.5
pMDI HFA-solution	Beclomethasone dipropionate and formoterol [35]	1.5
pMDI HFA-solution	Flunisolide [36]	1.2
pMDI HFA-solution	Beclomethasone dipropionate [37]	1.1
pMDI HFA-solution	CIC [38]	1.1

CIC, ciclesonide; DPI, dry powder inhaler; HFA, hydrofluoroalkane; MMAD, mass median aerodynamic diameter; pMDI, pressurized metered-dose inhaler.

BUD optimally administered from a DPI in asthmatic patients (TLD 28.5%, oropharyngeal deposition 49.3%, P/C ratio 0.95, respectively) [48,49]. Although this particular drug–device combination has not proceeded to development, other small-particle therapies (tiotropium and olodaterol) are available in this device for patients with chronic obstructive pulmonary disease and there is recent interest in the use of tiotropium in asthma [50,51]. Deposition studies in asthmatic patients using a small-particle ($\sim 1.5\ \mu\text{m}$) combination aerosol of BDP and formoterol in an HFA solution pMDI showed approximately one-third peripheral lung deposition and two-thirds central lung deposition as a proportion of the total lung dose [34], and more recently a similar ratio of peripheral/central lung deposition for BDP/formoterol delivered as small particles ($\sim 1.5\ \mu\text{m}$) from a novel DPI device has also been reported [52]. In contrast, several studies show that large-particle aerosols have poor peripheral airway penetration [29,45]. Taken together, lung deposition data in asthmatic patients show that small-particle aerosols not only achieve better pulmonary deposition, but also effective penetration into the peripheral lung, thereby reaching not only the large but also the small airways.

SMALL VS. LARGE PARTICLE AEROSOLS

Several studies have shown that small-particle aerosols improve markers of small-airway dysfunction and inflammation in asthmatic patients [1–3,53–55]. However, the critical question is does this innovation in small-particle inhalation technology directly translate into benefits for asthmatic patients with respect to an improvement in their disease control and quality of life? Specifically, is there an added advantage of using small-particle aerosols in patients with asthma when directly compared to large-particle aerosols?

Tables 2 and 3 detail the clinical trials, and Table 4 the real-life studies using ICS monotherapy and ICS/LABA combination treatment in asthmatic patients directly comparing small-particle aerosols to large-particle aerosols on patient-centred outcomes, including asthma control, symptom scores and quality of life. Review of the data suggests that the key messages are:

- (1) smaller particles achieve comparable efficacy (and some studies show superiority) compared with large particles;
- (2) small-particle aerosols achieve a reduction in the daily ICS dose;
- (3) smaller particles achieve greater asthma control and quality of life in real-life studies;

- (4) some studies show an improved therapeutic ratio with smaller particles.

These points will be discussed below in more detail.

Asthma control and clinical trials

Several controlled clinical trials have shown small-particle aerosols of ICS monotherapy achieve better asthma control than large-particle aerosols (Table 2). Hoshino [62] studied the effects of 2 months of treatment with small-particle ($\sim 1.1\ \mu\text{m}$) aerosolized pMDI CIC (200 μg once daily) on levels of asthma control compared with large particle ($\sim 5.4\ \mu\text{m}$) DPI-fluticasone propionate (FP) (100 μg twice daily) in patients with mild asthma, in which patients underwent a prior run-in phase receiving DPI-FP 200 μg daily for 2 months to stabilize their disease. It was observed that the smaller particle CIC aerosols significantly improved the physiological measures of small-airway dysfunction (IOS assessments of distal airway function and the percentage of eosinophils in late-phase-induced sputum) compared with large-particle FP aerosols; yet, there was no change in spirometric measures between treatments, suggesting that these measures are rather insensitive and do not adequately reflect the effects of small-particle aerosols preferentially targeting the peripheral airways. However, small-particle CIC aerosols led to significant improvements in asthma control and asthma symptoms when compared with the large particle FP aerosols. Improvements in the measures of asthma control and quality of life have also been observed using small particles of pMDI-BDP when compared with larger ICS particle aerosols [68–70].

Studies investigating small-particle combination ICS/LABA aerosols on asthma control compared with large-particle combination aerosols have shown overall comparable levels of control between treatments, although some studies show significant improvements with small-particle aerosols (Table 3). Huchon *et al.* [73] studied 645 moderate-to-severe asthmatic patients treated for 6 months with small-particle ($\sim 1.5\ \mu\text{m}$) HFA-BDP/formoterol (200 μg /12 μg twice daily) aerosols delivered from a single pMDI-HFA inhaler, and noted significant improvements in the levels of asthma control compared with large-particle aerosols of the same drugs delivered using two separate inhalers: CFC-BDP (500 μg twice daily) and CFC-formoterol (12 μg twice daily). Vos *et al.* [77] observed significant improvements in asthma control compared with the baseline levels in 24 stable asthmatic patients switched from their large-particle asthma therapy to small-particle pMDI-BDP/formoterol

Table 2. Clinical trials in adult asthmatic patients comparing small-particle aerosols to large particles of ICS monotherapy on patient-centred outcomes

Study	Treatment comparisons	Outcomes
ICS monotherapy		
Small particles of CIC		
Bateman <i>et al.</i> [56] Moderate-to-severe asthma (<i>n</i> = 528), 24 weeks	HFA-CIC (320 µg twice daily) vs. HFA-FP (330 µg twice daily)	Comparable efficacy (FEV ₁ , PEF) between treatments. Comparable improvement in asthma symptom scores, AQLQ and need for rescue medication use. Similar asthma exacerbation rates but significantly more adverse effects (candidiasis and dysphonia) with FP.
Boulet <i>et al.</i> [57] Moderate asthma (<i>n</i> = 474), 12 weeks	HFA-CIC (320 µg once daily) vs. DPI- FP (200 µg twice daily)	Comparable efficacy (FEV ₁ , FVC, PEF and SVC) and similar improvements in asthma symptom scores and need for rescue medication between treatments. Significantly greater improvement in HRQoL and significantly less oral candidiasis with CIC compared with FP.
Boulet <i>et al.</i> [58] Stable asthma (<i>n</i> = 359), 12 weeks	HFA-CIC (320 µg once daily) vs. DPI- BUD (320 µg once daily)	Comparable efficacy (FEV ₁) between treatments. Comparable improvement in asthma symptoms, but significantly greater decrease in the need for rescue medication with CIC.
Buhl <i>et al.</i> [59] Mild-to-moderate asthma (<i>n</i> = 529), 12 weeks	HFA-CIC (80 or 160 µg once daily) vs. HFA-FP (88 µg twice daily)	Comparable efficacy (FEV ₁ , FVC and PEF) and improvement in asthma symptoms and the need for rescue medication between CIC once daily and FP twice daily.
Dahl <i>et al.</i> [60] Mild-to-moderate asthma (<i>n</i> = 480), 24 weeks	HFA-CIC (80 µg once daily) vs. HFA- FP (100 µg twice daily)	Comparable efficacy (FEV ₁) between low-dose CIC and high-dose FP. Comparable improvement in asthma control (ACT; no asthma symptoms and no rescue medication use) and asthma-specific quality of life.
Hansel <i>et al.</i> [61] Mild-to-moderate asthma (<i>n</i> = 554), 12 weeks	HFA-CIC (80 or 320 µg once daily) vs. DPI-BUD (400 µg twice daily)	Similar efficacy (FEV ₁ and PEF), asthma symptom scores and rescue medication use of both doses of CIC compared to BUD in improving the pulmonary function. Significant urinary cortisol suppression with BUD.
Hoshino [62] Mild asthma (<i>n</i> = 30), 8 weeks	HFA-CIC (200 µg once daily) vs. DPI- FP (100 µg twice daily)	Significant improvement in small-airway inflammation (late-phase sputum eosinophil counts) and small-airway function (IOS R5–R20) with CIC. Significant improvement in ACT with CIC vs. fluticasone propionate.
Knox <i>et al.</i> [63] Moderate asthma (<i>n</i> = 106), 12 weeks	Run-in 2 weeks on HFA-FP 250 µg twice daily then stepped down to HFA-CIC (160 µg once daily) or continued on HFA-FP (250 µg twice daily)	Similar levels of asthma control (days without asthma symptoms and without rescue medication use) between treatments.
Magnussen <i>et al.</i> [64] Persistent asthma (<i>n</i> = 808), 12 weeks	HFA-CIC (80 µg or 160 µg once daily) vs. HFA-FP (88 µg twice daily)	Comparable efficacy (FEV ₁) between low-dose and high-dose CIC once daily vs. FP twice daily. Comparable improvement in the asthma symptom scores.
Nipadkar <i>et al.</i> [65] Stable asthmatic patients (<i>n</i> = 405), 12 weeks	HFA-CIC (160 µg once daily given either AM or PM) vs. pMDI-BUD (200 µg twice daily)	Comparable efficacy (FEV ₁) between CIC (given at different times of the day) and BUD. Comparable improvement in the asthma symptoms and the need for rescue medication.
Zietkowski <i>et al.</i> [66] Mild allergic asthma (<i>n</i> = 35), 12 weeks	HFA-CIC (80 or 160 µg once daily) vs. HFA-FP (100 µg twice daily)	Comparable efficacy (spirometry) and decrease in the exhaled nitric oxide levels between treatments. Comparable improvement in the asthma symptoms and need for rescue medication.
Small particles of BDP		
Boulet <i>et al.</i> [67] Moderate-to-severe asthma (<i>n</i> = 141), 24 weeks	HFA-BDP (800 µg daily) vs. CFC-BDP (1500 µg daily)	No significant difference between treatments in efficacy (spirometry), systemic tolerability (24-h urine cortisol, ACTH stimulation, morning plasma cortisol), asthma symptoms or in onset of first asthma exacerbation.
Juniper <i>et al.</i> [68] Stable asthma (<i>n</i> = 395), 12 months	HFA-BDP (200–800 µg daily) vs. CFC-BDP (400–1500 µg daily)	Significant difference between treatment groups in change from baseline in overall AQLQ in favour of HFA-BDP after 12 months of therapy. No significant difference in spirometry, SABA use or asthma symptoms.

Table 2 (Continued)

Study	Treatment comparisons	Outcomes
Ohbayashi and Adachi [69] Stable mild-to-moderate persistent asthma (<i>n</i> = 50), 3 months	HFA-BDP vs. DPI-FP (equivalent doses used but actual doses not specified)	Significant difference between treatment groups in AQLQ domains of symptom and activity limitation in favour of HFA-BDP associated with a significant decrease in late-phase sputum eosinophil counts.
Worth <i>et al.</i> [70] Moderate-to-severe asthma (<i>n</i> = 209), 2 months	HFA-BDP (800 µg daily) vs. DPI-BUD (1600 µg daily)	Patients receiving HFA-BDP had significant improvement in percentage days free from dyspnoea, chest tightness, nocturnal awakenings, wheeze and daily asthma symptoms. No significant difference between treatments in spirometry or SABA use.

ACT, asthma control test; ACTH, adrenocorticotrophic hormone; AQLQ, asthma quality of life questionnaire; BDP, beclomethasone dipropionate; BUD, budesonide; CFC, chlorofluorocarbon; CIC, ciclesonide; DPI, dry powder inhaler; FEV₁, forced expiratory volume in one second; FP, fluticasone propionate; FVC, forced vital capacity; HFA, hydrofluoroalkane; HRQoL, health related quality of life; ICS, inhaled corticosteroid; PEF, peak expiratory flow; pMDI, pressurised metered-dose inhaler; SABA, short-acting beta-agonist; SVC, slow vital capacity.

aerosols, and this was also associated with significant changes in small-airway imaging parameters, although the inhaled treatments the patients were using prior to switching were rather heterogeneous.

Lowering the inhaled corticosteroid dose

A goal of asthma management is to regularly reassess stabilized patients and step-down therapy in order to avoid overtreatment, especially with high-dose ICS [87]. Studies show the ICS dose can be effectively decreased without worsening asthma control using large-particle ICS aerosols [88–92], and this has also recently been shown with small-particle ICS aerosols, either as monotherapy (Table 2) or in combination with LABA (Table 3).

Knox *et al.* [63] investigated step-down with small-particle ICS monotherapy, in which patients well controlled on pMDI-FP 500 µg daily were randomized to 12 weeks treatment of either step-down to small-particle aerosols of pMDI-CIC 160 µg daily or continue with the same dose (500 µg daily) of large-particle pMDI-FP aerosols. The investigators observed similar levels of asthma control between treatments, although step-down to a lower ICS dose of FP as another limb may also have effectively maintained asthma control. Bateman *et al.* [93] investigated step-down with small-particle CIC aerosols in severe persistent asthmatic patients requiring maintenance oral corticosteroid treatment. Patients were randomized to three parallel treatments: pMDI-CIC 640 µg daily, pMDI-CIC 1280 µg daily or placebo for 3 months, and it was observed that the prednisolone dose was significantly reduced, 47 and 63% dose reduction, respectively, for CIC 640 and 1280 µg daily, without worsening levels of asthma control. Similar findings in achieving oral corticosteroid dose reduction have been observed using large-particle ICS aerosols such as DPI-FP and DPI-BUD [94,95].

The small-particle combination ICS/LABA aerosol therapy of BDP/formoterol has been shown to maintain asthma control in patients following step-down from high-dose large-particle combination treatment. Papi *et al.* [76] stepped-down patients well controlled on high-dose large-particle FP and salmeterol (1000/100 µg daily) for 2 months to two parallel groups of either half the ICS dose with the large particle DPI-FP/salmeterol (500/100 µg daily) or half the ICS dose with the small-particle pMDI-BDP/formoterol (400/24 µg daily) for 6 months. Comparable efficacy between both treatments in the morning peak expiratory flow was observed and, notably, there was no worsening of asthma control when patients stepped-down to small-particle pMDI BDP/formoterol (96.0% of patients controlled) compared with those stepped-down to large particle DPI-FP/salmeterol (94.4% of patients controlled). It was also observed that over the 6-month treatment the cumulative mean ICS dose was significantly lower with small aerosols of pMDI-BDP/formoterol (57.7 mg) compared with large aerosols of DPI-FP/salmeterol (75.4 mg).

Asthma control and real-life studies

Most of the studies reported in Tables 2 and 3 are controlled clinical trials involving highly selected asthmatic patients fulfilling precise inclusion and exclusion criteria, which may not represent the heterogeneity of disease seen in 'real-life' daily clinical practice [96,97^{***}]. Indeed, it has been observed that as little as 6% of real-life asthmatic patients fit the criteria of controlled clinical trials, questioning the application of results to patients seen in daily clinical practice [98]. Several real-life studies have shown small-particle ICS monotherapy aerosols of pMDI-BDP achieve better levels of asthma control and similar levels of disease exacerbation rates in comparison with larger particle ICS

Table 3. Clinical trials in adult asthmatic patients comparing small-particle aerosols to large particles of ICS and LABA combination treatment on patient-centred outcomes

Study	Treatment comparisons	Outcomes
ICS/LABA combination therapy		
Small particles of BDP/formoterol		
Barnes <i>et al.</i> [71] n = 416 Stable asthma (n = 416), 12 weeks	Step across from FP/salmeterol (500/100 daily, in any device) to (i) HFA-BDP/formoterol (200/12 µg twice daily) vs. (ii) DPI-FP/salmeterol (250/50 µg twice daily)	Comparable efficacy (morning predose FEV ₁) between treatments. Patients stepped across from FP/salmeterol (500/100 daily, in any device) to HFA-BDP/formoterol maintain asthma control (ACQ-7).
Corda <i>et al.</i> [72] Moderate asthma (n = 8), 24 weeks	HFA-BDP/formoterol (200/12 µg twice daily) vs. DPI-FP/salmeterol (250/50 µg twice daily)	Significant improvement from baseline measures in small-airway dysfunction (closing volume) with BDP/formoterol vs. FP/salmeterol. Comparable improvement in asthma control (ACT) between treatments.
Huchon <i>et al.</i> [73] Moderate-to-severe asthma (n = 645), 24 weeks	HFA-BDP/formoterol (200/12 µg twice daily) vs. separate inhalers of CFC-BDP (500 µg twice daily) plus DPI-F (12 µg twice daily) vs. CFC-BDP alone (500 µg twice daily)	BDP/formoterol comparable efficacy (PEF, spirometry) to separate CFC-BDP+F inhalers and more effective to CFC-BDP alone. Significantly greater improvement in asthma control with HFA-BDP/formoterol vs. separate CFC-BDP+F inhalers and CFC-BDP alone.
Papi <i>et al.</i> [74] Moderate-to-severe asthma (n = 228), 12 weeks	HFA-BDP/formoterol (100/6 µg twice daily) vs. HFA-FP/salmeterol (125/25 µg twice daily)	Comparable efficacy (PEF) between treatments. Significant increase in FVC and faster bronchodilation (FEV ₁) with BDP/formoterol vs. FP/salmeterol. Comparable improvement in symptom scores, symptom-free days and rescue medication between treatments. No significant difference between treatments in time to the first exacerbation.
Papi <i>et al.</i> [75] Moderate-to-severe asthma (n = 219), 12 weeks	HFA-BDP/formoterol (200/12 µg twice daily) vs. DPI-BUD/formoterol (400/12 µg twice daily)	Comparable efficacy (PEF) between treatments. Comparable improvement in symptom scores, symptom-free days and rescue medication between treatments. No significant difference between treatments in time to the first exacerbation.
Papi <i>et al.</i> [76] Stable asthma (n = 422), 24 weeks	Step down from FP/salmeterol (1000/100 daily, in any device) to (i) HFA-BDP/formoterol (200/12 µg twice daily) vs. (ii) DPI-FP/salmeterol (250/50 µg twice daily)	Comparable efficacy (morning PEF) between treatments. No worsening of asthma control (asthma symptom scores) when patients stepped down to BDP/formoterol (96.0% patients controlled) compared to when patients stepped down to FP/salmeterol (94.4% patients controlled). Mean ICS dose significantly lower with BDP/formoterol (57.7 mg) vs. DPI-FP/salmeterol (75.4 mg).
Vos <i>et al.</i> [77] Stable asthma (n = 24), 6 months	Switched from current asthma therapy (heterogenous group including SABA, LABA, SABA and SAMA, or ICS and LABA) to HFA-BDP/formoterol (200/12 µg twice daily)	Significant improvement in the level of ACT after 6 months compared with the baseline levels. Significant changes in the imaging parameters with smaller airway indices more pronounced than larger airways.

ACT, asthma control test; BDP, beclomethasone dipropionate; BUD, budesonide; CFC, chlorofluorocarbon; DPI, dry powder inhaler; FEV₁, forced expiratory volume in one second; FP, fluticasone propionate; FVC, forced vital capacity; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; PEF, peak expiratory flow; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic agonist.

aerosols [78–80]. Important considerations with respect to the real-life studies is that some have required adjustment for confounding factors, some have studied particle size comparisons in first/initiation prescription cohorts vs. step-up/dose-increase cohorts and some studies have defined

asthma control in different ways, usually as a composite measure incorporating a number of outcomes. Real-life studies utilizing small-particle pMDI-BDP/formoterol aerosols have shown significantly higher levels of asthma control, better quality-of-life indices and lower daily ICS dose when

compared with larger particle ICS/LABA aerosols [82–86] (Table 4).

Allegra *et al.* [82] undertook a cross-sectional survey in asthmatic patients in Italy and observed that those ($n=454$) receiving small-particle pMDI-BDP/formoterol aerosols achieved significantly higher levels of asthma control (76%) compared with those ($n=453$) receiving large-particle DPI-BUD/formoterol aerosols (69%), and similar levels of control compared to those ($n=473$) receiving large-particle FP/salmeterol aerosols of either pMDI or DPI (71%). Health-related quality-of-life status was significantly better with small-particle BDP/formoterol aerosols compared with large-particle FP/salmeterol aerosols, and of comparable levels to large-particle DPI-BUD/formoterol aerosols, with a much lower mean daily ICS dose for the small-particle combination aerosols (pMDI-BDP/formoterol, FP/salmeterol, DPI-BUD/formoterol; 311, 675 and 590 μg , respectively). Studies have also investigated the effects of switching treatments from large- to small-particle combination aerosols on levels of asthma control (Table 3). Popov *et al.* [84] showed that patients switched from large-particle DPI-BUD/formoterol or DPI-FP/salmeterol aerosols to 2 months of treatment with small-particle pMDI-BDP/formoterol experienced significant improvements in asthma quality-of-life measures compared with baseline values. A subgroup analysis of the 'top responders' (using forced vital capacity, an indirect small-airway marker) demonstrated significant improvements in inflammatory indices (exhaled breath temperature, blood eosinophils and C-reactive protein) with small-particle pMDI-BDP/formoterol treatment. Price *et al.* [85] showed no loss of asthma control in patients switched from large-particle FP/salmeterol combination (either pMDI or DPI) treatment to small-particle pMDI-BDP/formoterol aerosols, and noted the switch to smaller aerosols was achieved with an equivalent or lower ICS dose and this was associated with a significant reduction in asthma-related healthcare costs. Reductions in the ICS dose have also been observed in studies utilizing small-particle ICS monotherapy [80,99].

Safety and efficacy

The amount of inhaled drug depositing in the lungs (total lung dose) determines the clinical efficacy, and for corticosteroids there is a dose–response relationship that reaches a plateau around 800–1000 μg BDP equivalent, beyond which increasing the ICS dose will not lead to significant improvements in clinical efficacy [100]. However, upon reaching the lungs a drug may be absorbed into

the systemic circulation and give rise to the potential for systemic adverse effects (pulmonary bioavailability). Additionally, the inhaled dose that deposits in the oropharynx can contribute to local oropharyngeal side-effects, and this can be swallowed into the gastrointestinal tract and also give rise to systemic adverse effects (oral bioavailability). So, a considered judgement by the clinician needs to be undertaken in order to maximize the efficacy and minimize the adverse events, depending upon the pharmacological properties of the ICS, the dose of the ICS, and the inhaler device and its aerosol characteristics.

With respect to the aerosol characteristics, smaller particles compared with the larger particles lead to less oral deposition and a shift to greater TLD [45,101], that is, there is less potential for oral bioavailability and greater potential for clinical efficacy as this may improve the therapeutic ratio; but there is also the possibility for greater pulmonary bioavailability. In this context, we should recognize that not all corticosteroids are the same with respect to their pharmacological and pharmacokinetic behaviour, and these aspects need to be taken into account when understanding the deposition effects on the therapeutic ratio of inhaled aerosols [102]. For example, the corticosteroids CIC and FP have high first-pass metabolism with relatively negligible oral bioavailability and decreasing oral deposition with these drugs may not be that important in contrast to corticosteroids with higher oral bioavailability such as BUD and BDP. However, decreasing actual oropharyngeal deposition may decrease local side-effects. Additionally, some ICS such as BDP and CIC are inhaled as prodrugs and require local lung esterases to become activated.

Studies show an improved safety profile in local and systemic exposure with small particles when equivalent ICS doses of small vs. large aerosols are compared. Newman *et al.* [43] observed low oropharyngeal deposition (~33%) with small-particle pMDI-CIC aerosols in mild asthmatic patients, and in a separate study, Bateman *et al.* [103] noted significantly less oral adverse events with small-particle pMDI-CIC aerosols (640 μg daily) compared with large-particle FP aerosols (750 μg daily). Newman [43] also noted high levels of lung deposition (~52%) with pMDI-CIC aerosols and proportionally, approximately 50% of this targeted the distal lung region, but this did not translate into greater pulmonary bioavailable adverse effects as noted by Derom *et al.* [104], in which small-particle CIC aerosols (640 μg daily) did not cause significant suppression of 24-h urinary cortisol levels in contrast to large-particle FP aerosols (880 μg daily). Indeed, both treatments decreased

Table 4. Real-life studies in adult asthmatic patients comparing small-particle aerosols to large particles of ICS monotherapy and ICS/LABA combination treatment on patient-centred outcomes

Study	Treatment comparisons	Outcomes
ICS monotherapy		
Small particles of BDP		
Barnes <i>et al.</i> [78] Retrospective observational matched cohort in UK primary care database, 1 year	Two groups of asthmatic patients: (i) First/initiation prescription of HFA-BDP ($n=2882$) vs. CFC-BDP ($n=8646$) or (ii) Step-up/dose-increase treatment with HFA-BDP ($n=258$) vs. CFC-BDP ($n=516$)	No significant difference in patients achieving asthma control (ACT; composite measure of no hospital attendance, oral corticosteroid prescription, or antibiotics for LRTI) between treatments in both groups (i) HFA-BDP (83.5%) vs. CFC-BDP (81.6%) and (ii) HFA-BDP (82.6%) vs. CFC-BDP (75.8%). Only after adjustment for confounding factors was statistical significance achieved for asthma control with HFA-BDP, but disease exacerbation rates between treatments in both groups remained the same even with adjustment.
Colice <i>et al.</i> [79] Retrospective matched cohort in the USA healthcare claims database, 1 year	Two groups of asthmatic patients: (i) first/initiation prescription of HFA-BDP ($n=2578$) vs. HFA-FP ($n=7734$) or (ii) Step-up/dose-increase treatment (limited analysis as total sample size $n=579$)	No significant difference in patients achieving 'risk domain' asthma control (composite measure of no hospital attendance, oral corticosteroid prescription, antibiotics for LRTI, or hospital attendance for LRTI), or in having a severe exacerbation between treatments in group (i). HFA-BDP was significantly more likely to achieve 'overall' asthma control (risk domain plus limited SABA use) in group (i) when data was adjusted for confounding factors. No significant differences in asthma control measure between treatments in group (ii). Median daily ICS dose higher for HFA-FP (440 µg) vs. HFA-BDP (320 µg).
Price <i>et al.</i> [80] Retrospective matched cohort in UK primary care database, 1 year	Two groups of asthmatic patients: (i) First/initiation prescription of HFA-BDP ($n=1319$) vs. HFA-FP ($n=1319$) or (ii) Step-up/dose-increase treatment with HFA-BDP ($n=250$) vs. HFA-FP ($n=250$)	In group (i), asthma control (composite measure of no hospital attendance, oral corticosteroid prescription, or antibiotics for LRTI) was achieved in 86.0% (HFA-BDP) and 82.9% (HFA-FP) and the unadjusted and adjusted odds ratios for achieving asthma control were significantly higher with HFA-BDP, but disease exacerbation rates were not significantly different between treatments during the outcome year In group (ii), adjusted odds ratios for the primary measure of asthma control and disease exacerbation rates were not significantly different between treatments. HFA-FP prescribed at significantly higher doses than HFA-BDP for both groups.
Price <i>et al.</i> [81] Retrospective matched cohort in UK primary care database, 1 year	Two groups of asthmatic patients: (i) First/initiation prescription of HFA-BDP ($n=7526$) vs. CFC-BDP ($n=3763$) or (ii) switch ICS treatment with no dose change to HFA-BDP ($n=6355$) vs. CFC-BDP ($n=12710$)	Adjusted odds ratio of no loss of asthma control (composite measure of no hospital attendance, oral corticosteroid prescription, or consultation for LRTI) significantly higher in patients on HFA-BDP in both groups (i) first/initiation and (ii) switch population. No significant differences between treatments in the rate of severe exacerbations after adjustment for residual baseline confounders in either group (i) or (ii).
ICS/LABA combination therapy		
Small particles of BDP/formoterol		
Allegra <i>et al.</i> [82] Cross-sectional survey in adult asthmatic patients in Italy ($n=2853$)	HFA-BDP/formoterol ($n=454$) vs. DPI-BUD/formoterol ($n=453$) vs. DPI-FP/salmeterol or HFA-FP/salmeterol ($n=473$)	Significantly higher levels of asthma control (ACT) with HFA-BDP/formoterol vs. DPI-BUD/formoterol (76 vs. 69% of patients) and comparable vs. DPI-FP/Salm (71% of patients), in which treatments given for more than 1 month. HRQoL (EQ-5D) significantly better with HFA-BDP/formoterol vs. DPI-FP/Salm, and comparable levels vs. DPI-BUD/formoterol. Mean daily ICS dose higher for large-particle drug aerosols of DPI-BUD/formoterol and DPI-FP/salmeterol compared with small-particle aerosols HFA-BDP/formoterol (590, 675, and 311 µg, respectively).

Table 4 (Continued)

Study	Treatment comparisons	Outcomes
Müller <i>et al.</i> [83] Cross-sectional survey in adult asthmatic patients in Hungary (n = 111)	HFA-BDP/formoterol (n = 53) vs. DPI-BUD/formoterol (n = 33) vs. DPI-FP/salmeterol (n = 25)	Significant improvements in asthma control score, daytime symptom score and rescue medication use with HFA-BDP/formoterol vs. DPI-BUD/formoterol and vs. DPI-FP/salmeterol in which treatments given for more than 4 weeks.
Popov <i>et al.</i> [84] Observational study in asthmatic patients in Bulgaria (n = 59), 2 months	Patients stepped-across from other ICS and LABA to HFA-BDP/formoterol	Significant improvements in the quality-of-life measures (AQLQ) after 2 months of treatment compared with the baseline values. No improvement in inflammatory indices (exhaled breath temperature, blood eosinophils and C-reactive protein). Subgroup analysis of the 'top responders' (using FVC, a small-airway marker) demonstrated significant improvements in the inflammatory indices.
Price <i>et al.</i> [85] Retrospective matched observational cohort in UK primary care database, 1 year	Patients switched from FP/salmeterol to (i) remain on FP/salmeterol (n = 1146) or to new treatment (ii) HFA-BDP/formoterol (n = 382) at an equivalent or lower ICS dose	Significantly better odds with HFA-BDP/formoterol in achieving asthma control (composite measure of no hospital attendance, oral corticosteroid prescription, LRTI and limited SABA use). Comparable levels of disease exacerbations between switch to group (i) vs. (ii).
Terzano <i>et al.</i> [86] Prospective observational survey in adult asthmatic patients in Italy (n = 1017), 12 months	HFA-BDP/formoterol (n = 301) vs. DPI-BUD/formoterol (n = 145) vs. DPI-FP/salmeterol or HFA-FP/salmeterol (n = 123)	Proportion of asthmatic patients fully controlled (ACT) with HFA-BDP/formoterol significantly greater than DPI-BUD/formoterol. HRQoL (EQ-5D) significantly better with HFA-BDP/formoterol vs. DPI-BUD/formoterol.

ACT, asthma control test; ACQ-7, asthma control questionnaire - 7 questions; AQLQ, asthma quality of life questionnaire; BDP, beclomethasone dipropionate; BUD, budesonide; CFC, chlorofluorocarbon; DPI, dry powder inhaler; EQ-5D, EuroQol - 5 domains; FEV₁, forced expiratory volume in one second; FP, fluticasone propionate; FVC, forced vital capacity; HFA, hydrofluoroalkane; HRQoL, health related quality of life; ICS, inhaled corticosteroid; LRTI, lower respiratory tract infection; PEF, peak expiratory flow; SABA, short-acting beta-agonist.

airway hyper-responsiveness to adenosine monophosphate and so in this scenario, the therapeutic ratio (clinical benefit vs. adverse effects) may actually be improved with smaller particle size aerosols of CIC. With respect to the small-particle aerosols of ICS/LABA treatment and their effect on the therapeutic ratio, in the Huchon study described above [73], inhaled small particles of HFA-BDP/formoterol (200 µg/12 µg twice daily) resulted in significantly lower levels in the morning urinary cortisol compared with larger particles of CFC-BDP (500 µg twice daily) and CFC-formoterol (12 µg twice daily), and small-particle treatment also achieved significantly better levels of asthma control; hence, supporting an improved therapeutic ratio. Studies described above [76,82] also show that lower ICS doses can be used with small-particle combination ICS/LABA therapy, whilst achieving the same levels of efficacy as large-particle combinations.

TREATING SMALL-AIRWAY DISEASE WITH SYSTEMIC THERAPY

Oral and parenteral anti-inflammatory drugs used in asthma target both proximal and distal lung regions. However, these drugs are usually associated with

higher systemic bioavailability and greater adverse effects compared with the inhaled route and so, only few studies have investigated their potential to attenuate small-airway inflammation and directly relate this to levels of asthma control.

Kraft *et al.* [105] administered the antileukotriene agent montelukast (10 mg daily) for 4 weeks to mild asthmatic patients and noted significant improvements in distal airway physiology (residual volume) compared with placebo, and this correlated with improved asthma symptoms. Zeidler *et al.* [106] assessed 4 weeks of montelukast therapy (10 mg daily) on imaging metrics of the distal airways in mild-to-moderate steroid-naïve asthmatic patients and observed significantly less regional air-trapping on HRCT in pre-methacholine images compared with placebo that correlated with an improvement in asthma symptoms. However, in post-methacholine images, montelukast was unable to prevent increases in regional air-trapping on HRCT induced by methacholine challenge. In contrast, Fritscher *et al.* [107] used add-on montelukast (10 mg daily) for 3 weeks in mild asthmatic patients stabilized with inhaled FP (500 µg daily) and showed reduced alveolar/distal nitric oxide levels compared with the pretreatment values, but this was not statistically significant and nor was there an improvement in

asthma symptom scores. Indeed, in those patients in whom montelukast was continued but inhaled FP stopped, the improvement observed in alveolar/distal nitric oxide levels with the combination was lost, suggesting poor efficacy of montelukast in treating small-airway inflammation. Similarly, Gelb *et al.* [108] added zileuton 2400 mg daily for 4 weeks in moderate-to-severe asthmatic patients stabilized on inhaled FP/salmeterol 500/100 µg daily, and observed no significant effect on alveolar/distal airway nitric oxide levels and no significant difference on Juniper asthma symptom scores. In a crossover study, Yasui *et al.* [109] added pranlukast (450 mg daily) for 2 months to patients stable on inhaled combinations of ICS and LABA, followed by a wash-out interval and another treatment period of no-added therapy. They observed that add-on pranlukast treatment led to a significant decrease in alveolar/distal nitric oxide levels, which was associated with an improvement in asthma control.

Omalizumab is a systemic parenteral anti-immunoglobulin (Ig)-E monoclonal antibody used in carefully selected patients with severe allergic asthma on step 5 of the asthma treatment guidelines [110], and although ex-vivo studies utilizing human bronchi specimens incubated in asthmatic medium show that omalizumab can block both specific and nonspecific bronchial hyper-responsiveness in distal airway regions, there is paucity of in-vivo patient data investigating its effects on small-airway dysfunction and asthma symptoms [111,112].

CONCLUSION

With definite pathophysiological evidence for small-airway dysfunction and the clinical emergence of a small-airway phenotype, we should certainly consider treating the small-airway region when reviewing our asthmatic patients in clinic. Further studies are needed to conclusively show that targeting the distal airways with smaller particle aerosols shows superior clinical efficacy and asthma control to larger particle aerosols, but data is certainly beginning to support this notion. With the innovations in pharmaceutical technology allowing us to target inhaled drug to specific lung regions and developments of new systemic biologic therapies, coupled with advances in imaging and physiological assessments of the distal lung region, we are now equipped to directly test whether there is an added advantage of targeting the small airways. These are exciting times. The quiet zone of the lungs is finally being heard!

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