Treating the Small Airways

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Key Words

Inhaled drug delivery · Small particle aerosols · Asthma · Chronic obstructive pulmonary disease

Abstract

The final article in this series evaluates the approaches undertaken to treating the small-airway region of the lungs and the clinical implications of inhaled therapy targeting the periphery in patients with asthma and chronic obstructive pulmonary disease.

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Introduction

From the previous articles in this current Thematic Review Series in *Respiration*, the authors have described that pathological, immunological and structural abnormalities occur in the small airways of patients with asthma and chronic obstructive pulmonary disease (COPD); that these abnormalities contribute to the physiological observations of the small airways being the major site of airflow limitation, and that small airways are involved in the clinical expression of these diseases [1–3]. Involvement of the small airways has been observed not only in patients with severe asthma [4], but

also in those with mild disease [5, 6] and in patients with nocturnal and exercise-induced asthma [7–9]. There is therefore a rationale to treat the small airways and, importantly, to understand whether treating this airway region impacts on patient symptoms and better control of the disease state.

Certainly, oral and parenterally administered drugs absorbed through the systemic circulation reach the lungs and eventually the small airways, where some studies have shown they can influence markers of small-airway inflammation [10, 11]. However, there are distinct therapeutic advantages to direct a drug to the lungs via the inhaled route: a smaller drug dose can be used; the onset of action is more rapid, and, particularly for corticosteroids, the incidence of side effects is reduced. Recent advances in formulation science and aerosol technology have improved the efficiency of inhaled drug deposition

Previous articles in this series: 1. Usmani OS: Unravelling the small airways: structure-function-treatment relationships in asthma and COPD. *Respiration* 2012;84:1–3. 2. Hamid Q: Pathogenesis of small airways in asthma. *Respiration* 2012;84:4–11. 3. Baraldo S, Turato G, Saetta M: Pathophysiology of the small airways in chronic obstructive pulmonary disease. *Respiration* 2012;84:89–97. 4. Verbanck S: Physiological measurement of the small airways. *Respiration* 2012;84:177–188. 5. King GG: Tomographic imaging of small airways. *Respiration* 2012;84:265–274.

within the lungs and allowed the delivery of aerosolised medicines into the small airways via the inhaled route. This final article in this series evaluates the approaches undertaken to treating the small-airway region of the lungs and the clinical implications of inhaled therapy targeting the periphery in patients with asthma and COPD.

Inhalation Medicine

Inhalation therapy has its roots as far back as 2000 BC in Indian ayurvedic medicine, where the leaves of the plant *Datura stramonium*, which had anticholinergic properties, were made into a paste and smoked from a pipe to help alleviate respiratory symptoms [12]. History shows that all the great ancient civilisations embraced inhaled aerosolised therapy to treat ailments of the chest: the ancient Egyptians inhaled vapours of another anticholinergic, *Hyoscyamus muticus*, placed on hot bricks; Hippocrates advocated the inhalation of sea mists and hot vapours to ease airway obstruction, and, in the Arabian dynasty, the acclaimed physician Ibn Sina (Avicenna) advocated the inhalation of essential oils of pine and eucalyptus, medicaments that are still in use today in proprietary over-the-counter inhalation medicines. During the 1800s, the Industrial Revolution spread throughout the Western hemisphere, and rather extraordinarily it was during this time that cigarettes containing *Datura*-tobacco mixtures became available to be smoked by patients suffering from asthma [13].

Modern-day inhalation therapy began with the infamous words of a 13-year-old asthmatic girl to her father: ‘daddy, why can’t they put my asthma medicine in a spray can like they do hair spray?’ [14]. Susie’s father happened to be George Mason, the president of Riker Laboratories (now 3M), and the following day he instructed his chief chemist, Irving Porusch, to address the problem that had been presented to him by his daughter. Within 1 year, in 1956, Riker Laboratories had invented the Medihaler, the world’s first pressurised metered-dose inhaler (pMDI). However, over 50 years later, there is confusion in aerosol medicine! In any formulary in any part of the world, there will be more than 250 inhaler device, drug and spacer combinations available to health care practitioners to treat their respiratory patients. To compound matters, studies show most health care workers are uncertain about the correct use of inhalers: in particular physicians themselves show the least knowledge with respect to aerosol therapy [15, 16].

The inhaler devices used in current clinical practice include dry-powder inhalers (DPIs), nebulisers and pMDIs with or without valve-holding chambers or spacers. Surprisingly though, most of these devices are quite inefficient where, at best, only 10–20% of the emitted drug dose actually reaches the lungs [17]. The majority of the wasted dose impacts on the oropharynx giving rise to the potential for local and systemic adverse effects. As consumers, we would probably all be complaining if our washing machine required five times as much powder to efficiently give one wash, or our petrol engines required five times as much fuel for one journey; so why, as a respiratory community, have we been complacent about the inefficiency of aerosolised medicine that forms the cornerstone of our therapeutic armoury in the treatment of diseases of the chest?

Factors Influencing the Deposition of Medical Aerosols in the Lung: Particle Size

It is well recognised that there are several factors that affect the deposition of medical aerosols in the lung and that, ultimately, these impact upon the efficiency of inhaled drug delivery [18] (table 1). Patient factors are often difficult to control or overcome, and they clearly modify the amount of drug emitted from the inhaler device that eventually reaches the lungs. So should not the scientific direction be to optimise the amount of drug emitted by the inhaler device such that during the device-patient interface, a greater proportion of the drug is available to be deposited in the lungs and lesser amounts are wasted?

Of the aerosol characteristics (table 1), the most important determinant that can improve the efficiency of inhaled drug delivery is particle size. In vitro experimental modelling coupled with mathematical calculations has determined that aerosol particle size influences the total lung and regional airway site of inhaled drug deposition [19, 20]. Particles $>6\ \mu\text{m}$ preferentially deposit in the oropharynx, those between 2 and $6\ \mu\text{m}$ target the lungs and those that are $<2\ \mu\text{m}$ reach the alveoli or are exhaled [21]. However, these models do not account for features of inhaled drug delivery in vivo that can affect aerosol deposition in the lungs, such as a breath-hold pause after inhalation, or the effect of the diseased lung environment or different inhalation manoeuvres from pMDIs and DPIs (single breath) compared to nebulisers (tidal breathing). Usmani et al. [22] undertook a hypothesis-driven study to explore the effect of different drug particle sizes and inhalation flows on aerosol lung depo-

sition in vivo in patients with asthma. The authors radio-labelled monodisperse therapeutic aerosols of salbutamol at particle sizes of 1.5, 3 and 6 μm and undertook two-dimensional γ -scintigraphic imaging to assess drug distribution in the total lung and regional airways. They observed the smaller 1.5- μm aerosols achieved better total lung and greater peripheral-airway deposition than the larger particles (table 2). It was also noted that the smaller aerosols deposited far less in the oropharynx compared to the larger particles, and, interestingly, the smaller 1.5- μm aerosols were exhaled far less than was previously predicted by in vitro models. The authors also found that the smaller aerosols were less affected by rapid changes in inhalation flow and that, overall, slower inhalation flows achieved better lung deposition. These findings have supported the formulation chemistry and aerosol technology developments the pharmaceutical industry and device companies have taken over the last decade with respect to the new generation of inhaler devices for more efficient drug delivery to the lungs.

Particle Size and Formulation Chemistry

The Montreal protocol was the wake-up call to the industry and a driver to respiratory medicine marking a key milestone in inhaled aerosol delivery in modern times since the introduction of the pMDI [14, 23]. This critical turning point in the phasing out of ozone-depleting chlorofluorocarbons (CFCs) from pMDIs propelled the industry and device companies to accelerate the development of alternative formulations, different propellants and newer inhaler devices. The hydrofluoroalkanes (HFA) became promising alternative propellant compounds (HFA-134a and HFA-227) with physicochemical properties similar to the CFCs used in pMDIs, and these propellants allowed the transition of most of the CFC-pMDI devices to the present-day non-CFC pMDIs [24]. Through this advancement in formulation science, it became recognised that the particle size of aerosolised drugs was very much dependent upon the chemical characteristics of the formulation; in particular, the reformulation of existing corticosteroid compounds into HFA propellants resulted in two distinct classes of aerosols: HFA suspensions and HFA solutions. HFA suspension formulations tended to retain the same particle size as the CFC formulations [25]; however it was noted that HFA-solution-based pMDI aerosols had much smaller particle sizes than HFA suspension pMDIs or, indeed, dry-powder formulations in DPIs

Table 1. Factors influencing the deposition of medical aerosols in the lung

Aerosol characteristics	Patient factors
Drug particle	Inhalation manoeuvre
Size	Inspiratory flow
Density	Inhaled volume
Charge	Breath-hold pause
Formulation	Airway
Lipophilicity	Disease
Hygroscopicity	Severity
Plume	Device
Speed	Acceptance
Duration	Compliance
	Adherence

Table 2. Monodisperse salbutamol aerosol deposition in asthmatic subjects

Deposition	Aerosol particle size		
	1.5 μm	3 μm	6 μm
Total lung deposition, %	56	50	46
Oropharyngeal deposition, %	15	31	43
Exhaled fraction, %	22	8	2
Penetration index	0.79	0.60	0.36

Table 3. ICS particle size depends upon the formulation

Drug	Formulation/device	MMAD μm
FP [27]	dry powder/DPI	5.4
BUD [27]	dry powder/DPI	4.0
Mometasone furoate [28]	dry powder/DPI	3.7
FP [29]	HFA suspension/pMDI	2.4
BDP/formoterol [30]	HFA solution/pMDI	1.5
BDP [31]	HFA solution/pMDI	1.1
CIC [32]	HFA solution/pMDI	1.1

MMAD = Mass median aerodynamic diameter.

[26–32] (table 3). The HFA solution pMDI formulations currently available are the long-acting β_2 -agonist formoterol; the corticosteroids ciclesonide (CIC), beclomethasone dipropionate (BDP) and flunisolide, and the drug combination of BDP/formoterol in a single inhaler.

Small-Particle Aerosols

In vitro Analysis

In an *in vitro* analysis study, the performance of four inhaled corticosteroid (ICS) HFA-pMDIs of different particle size (median volume diameter) were compared: budesonide (BUD, 3.5 μm), fluticasone propionate (FP, 2.8 μm), BDP (1.9 μm) and CIC (1.9 μm) [33]. The authors observed the HFA solution aerosols of CIC and BDP had a greater proportion of their drug dose as 'finer particles' (defined as particles $<3.1 \mu\text{m}$) than the HFA suspension aerosols of BUD and FP. Indeed, CIC had the largest proportion of its drug mass in the 'fine-particle fraction' (defined as particles $<5 \mu\text{m}$). In addition, differences in inspiratory flow (range studied: 10–30 l/min) and air humidity had no significant influence on the particle size distribution for either aerosol. In an *in vitro* study incorporating the Andersen cascade impactor, the aerodynamic characteristics of the HFA solution pMDI drug combination of BDP/formoterol was investigated [34]. Both drugs had an $\sim 40\%$ fine-particle dose (defined as particles $<4.7 \mu\text{m}$) and both drugs exhibited a similar particle size distribution at each stage of the cascade impactor. These technological advances in achieving a smaller aerosol particle size and a greater fraction of the drug mass as finer particles have, consequently, been utilised to investigate drug delivery to the pulmonary tree.

Lung and Oropharyngeal Deposition

In previous studies, the size of the ICS particle strongly affected the aerodynamic properties of the drug and its delivery to the pulmonary tree, in particular, to the distal airways. In a two-dimensional γ -scintigraphy study in healthy volunteers ($n = 6$), 55–60% of an HFA solution BDP aerosol (1.1 μm , ex-actuator dose) was deposited in the lungs in contrast to only 4–7% with a CFC-BDP aerosol of larger-particle size (3.5 μm) [31]. Interestingly, oropharyngeal deposition was markedly reduced with the small-particle aerosols such that $\sim 30\%$ of the HFA solution BDP aerosol deposited in the oropharynx, whereas this was 90–94% with the CFC-BDP aerosol. It was also noted that the HFA-BDP aerosol distribution in the lung images was seen throughout the airways, whereas the larger-particle size CFC-BDP aerosol predominantly deposited in the proximal airways. Similar results were observed in another study involving healthy subjects ($n = 9$) where the airway deposition of HFA-BDP (0.9 μm), CFC-FP (2.0 μm) and CFC-BDP (3.5 μm) were examined [35]. The smaller-particle aerosols achieved greater lung depo-

sition (53% ex-actuator dose vs. ~ 13 vs. 4%) and lower oropharyngeal deposition (29 vs. ~ 78 vs. 82%) for HFA-BDP, CFC-FP and CFC-BDP, respectively. In a separate study, the total lung deposition of the HFA solution small-particle corticosteroid aerosol CIC (1.1 μm) was studied in healthy volunteers ($n = 6$) using both two- and three-dimensional γ -scintigraphic techniques [32]. HFA-CIC achieved a high lung deposition at 52% (ex-actuator dose) and a low oropharyngeal deposition of 38%, and, in addition, HFA-CIC was found to be distributed throughout the lung regions. Aerosol deposition patterns in healthy subjects may not always translate into drug distribution within the diseased lungs, and it is important to ascertain the behaviour of aerosolised medication within the airways of the patients themselves.

In the above study involving healthy subjects with HFA solution BDP aerosol [31], the authors also investigated deposition effects in patients with asthma ($n = 16$): 56% of the HFA aerosol was deposited in the lungs and 33% in the oropharynx. In a recent two-dimensional γ -scintigraphy lung deposition study in asthmatic patients, the deposition effects of the HFA suspension drug combination aerosol of FP/salmeterol (2.7 μm) was compared to the HFA solution corticosteroid aerosol of BDP (0.7 μm) [36]. Consistent with other studies investigating small-particle aerosol deposition, the authors observed smaller aerosol particles achieved greater total lung deposition (58 vs. 16%) and lower oropharyngeal deposition (35 vs. 77%) compared to larger-particle aerosols. The small-particle corticosteroid aerosol of HFA-CIC (1.1 μm) has also been studied in mild asthmatics ($n = 12$) using two-dimensional γ -scintigraphy, and high lung deposition (52%) and low oropharyngeal deposition ($\sim 33\%$) was reported [37].

An often overlooked characteristic is the ability to achieve lower oropharyngeal deposition by using smaller-particle aerosols, as has been described above, which not only decreases the potential for local side effects and systemic absorption from the swallowed dose, but in parallel improves the amount of drug able to reach the lungs as a result of bypassing the barrier of the oropharyngeal structures. Another important consideration is the exhaled dose from these aerosols. *In vitro* modelling data have often suggested that a large proportion of inhaled small aerosolised particles eventually become exhaled, suggesting as much as 80% of the aerosol [20]. However, *in silico* and *in vivo* patient data show this not to be the case [22, 38] where $\sim 20\%$ of a monodisperse salbutamol aerosol of 1.5 μm delivered to asthmatics was exhaled (table 2). Using HFA solution clinical aerosols of small

particles in both healthy subjects and asthmatics, it can also be noted from an assessment of the studies presented above that the exhaled fraction ranged between <4 and 24% [31, 32, 35–37].

Another important observation with small-particle aerosols has been the finding of consistent lung deposition in differing disease severities. De Backer et al. [39] assessed the aerodynamic behaviour of the small-particle HFA solution drug combination aerosol of BDP/formoterol (1.37 μm) in the airways of healthy subjects ($n = 8$, forced expiratory volume in 1 s, FEV_1 , 112% of predicted), asthmatic patients ($n = 8$, FEV_1 75% of predicted) and patients with COPD ($n = 8$, FEV_1 44% of predicted). The authors observed high total lung deposition (34%) in healthy subjects, but also, total lung deposition was similar between the different patient populations who had markedly varying airway disease severity: asthmatics (31%) and COPD patients (33%; percentages are of the nominal dose). Haussermann et al. [40] investigated the lung deposition of the HFA solution pMDI long-acting β -agonist (LABA) formoterol (0.8 μm) in healthy subjects ($n = 6$, FEV_1 107% of predicted), asthmatics ($n = 6$, FEV_1 72% of predicted) and COPD patients ($n = 6$, FEV_1 40% of predicted). Total lung deposition was comparable between healthy subjects (31%), asthmatics (34%) and COPD patients (35%). In both these studies with HFA-BDP/formoterol [39] and HFA formoterol [40], no correlation was observed between baseline pulmonary function and the lung deposition in the healthy subjects, asthmatics or COPD patients. These findings are of significance as it has been thought that with increasing lung disease severity, the structural changes causing the airways to narrow lead to an overall decrease in lung deposition [41, 42]. The data above would suggest that smaller-particle aerosols may be able to overcome one of the key patient factors influencing the lung deposition of medical aerosols and, as such, allow aerosolised medicine to reach the lungs even when they become progressively obstructed as disease severity worsens.

Distal-Airway Deposition

Probably the most significant feature of the small-particle HFA solution formulation aerosols has been the observation of a change in the pattern of drug deposition and regional-airway distribution within the lungs compared to existing larger-particle aerosols, such that smaller particles are able to penetrate more deeply into the peripheral lung. In the study reported above comparing the HFA suspension combination aerosol of FP/salmeterol (2.7 μm) to the HFA solution corticosteroid aerosol of

BDP (0.7 μm) in patients with asthma, two-dimensional γ -scintigraphy was used to assess regional-airway drug deposition in the central (C) and peripheral (P) lung [36]. It was observed that the smaller aerosol particles were able to penetrate deeper into the peripheral lung region (C/P ratio: 1.6) in contrast to the larger particle aerosols (C/P ratio: 4.9), which showed a more proximal central region deposition pattern. The regional-airway deposition of the HFA solution combination aerosol of BDP/formoterol (1.5 μm) has also been studied in asthmatic patients using two-dimensional γ -scintigraphy where $\sim 1/3$ of the drug was deposited in the peripheral lung region and $\sim 2/3$ in the central airways [43]. In the study by De Backer et al. [39], C/P ratios of the HFA solution BDP/formoterol (1.37 μm) were assessed in healthy subjects (1.42), asthmatics (1.96) and COPD (1.94) patients. Although the C/P ratio was higher with greater airway obstruction (C/P ratios of asthma and COPD patients exceeded that of healthy controls) and statistically significant differences were noted between asthmatics and healthy subjects (suggesting a more central lung region shift of drug in asthmatics), by contrast it was observed that the C/P ratio was lower in the more obstructed COPD patients (FEV_1 44% of predicted) compared to the asthmatics (FEV_1 75% of predicted) and was not statistically significant between COPD patients and healthy subjects. An explanation for this latter finding was the observation in their study of greater heterogeneity of drug deposition in the COPD patients compared with the healthy subjects. These data support that the often held belief of severe airway obstruction leading to a significant redistribution of the regional aerosol deposition of inhaled drug within the lungs with a substantially more proximal airway deposition pattern may not be that important with the use of smaller-particle aerosols, which allow the inhaled drug to reach the peripheral lung region in such conditions.

The disadvantage with the imaging technique of two-dimensional γ -scintigraphy is that the three-dimensional lung structure has to be 'collapsed' onto two-dimensional planar images and, thereby, overlying small peripheral airways may be included in the analysis of the central lung region. To circumvent this difficulty, three-dimensional imaging in the form of single-photon emission computed tomography (SPECT) has been utilised, which gives better spatial resolution to assess the regional airways. SPECT imaging was utilised in the above-described study involving healthy volunteers ($n = 6$) and small-particle corticosteroid aerosols of HFA-CIC (1.1 μm), which were observed to be sufficiently distributed to both the central, intermediate and peripheral lung regions in equal

proportions (30, 36 and, 34%, respectively) [32]. Newman et al. [37] also analysed the regional-airway distribution of HFA-CIC (1.1 μm) in patients with asthma ($n = 12$) using SPECT imaging and a 'shell contour', dividing the lungs into six regions of interest. The authors observed good drug distribution throughout the airways with 44% central lung deposition (first four lung 'shell' regions) and 56% peripheral-airway deposition. Although the role of small-airway inflammation and remodelling in the pathophysiology of asthma is not yet fully understood, the data above show the technological advances that have been achieved within aerosolised medicine to allow inhaled therapy to potentially target the pathophysiology and inflammation in both the central and peripheral lung regions. Certainly, there is evidence to support asthmatic inflammation is not just confined to the large airways, but also present in the small airways [1], and it would seem intuitive that there is a need to treat both the large and small airways; that is, inhaled therapy should be distributed throughout the airway tree.

Clinical Relevance of Small-Airway-Targeted Therapy

So what does this all mean for the patient? Patients do not report an improvement or worsening in their physiological indices when they see their physician but rather what matters to them is how the disease – or indeed the therapy – impacts on their symptoms, exercise capacity and quality of life. What is the link between physiology (function) and pharmacology (treatment), and how does small-airway drug targeting relate to patient-centred clinical outcomes? Although few in number, some studies are now addressing these questions to help us understand the clinical implications of inhaled therapy targeting the periphery in patients with asthma and COPD.

Asthma Control

The effect of small- versus large-particle aerosols of ICS on small-airway function and asthma control were recently studied [44]. Hoshino et al. [44] recruited mild persistent asthmatics ($n = 30$) who were treated for 2 months during a run-in phase with DPI-FP 100 μg twice daily (5.4 μm) and then randomised for a further 2 months to either continue to receive DPI-FP 100 μg twice daily or receive HFA solution pMDI aerosol of CIC 200 μg once daily (1.1 μm). No significant changes in the spirometry indices of FEV₁, forced expiratory flow (FEF) and maximum expiratory flow were observed with either

treatment arm during the study. However, in contrast to the large-particle aerosols of FP, the small-particle aerosols of CIC significantly improved impulse oscillometry markers of small-airway resistance (R5-R20 Hz) and distal reactance (X5 Hz), and small-particle aerosols significantly reduced the percentage of eosinophils in late-phase induced sputum. Of further interest, HFA-CIC was also able to significantly improve symptoms and asthma control in patients compared to DPI-FP.

This study highlights some interesting observations. Firstly, it supports the notion that traditional spirometric markers of asthma are insensitive to assess the effects of peripherally targeted aerosols [45]. Usmani et al. [45] have observed that FEF_{25–75}, FEV₁ and peak expiratory flow were unable to assess the deposition effects of mono-disperse aerosols of the small-particle (1.5 μm), short-acting β -agonist salbutamol that preferentially targeted the small airways, whereas FEV₁ was better able to detect bronchodilator changes with the larger (6- μm) aerosols that targeted the proximal larger airways [45]. Secondly, Hoshino [44] demonstrated the effect of small particles on physiological markers of small-airway disease. Indices obtained from impulse oscillometry have been utilised to assess small-airway dysfunction, including frequency-dependent changes in resistance between R5 and R20 Hz (R5-R20) and capacitive reactance at 5 Hz (X5) [46, 47]. Fahy et al. [48] have demonstrated that induced sputum obtained in the early phase after inhalation of hypertonic saline samples the proximal airways, whereas, in contrast, late-phase sputum reflects sampling of the peripheral airways. The beneficial effects of CIC on these small-airway markers may be related to the fact that the small-particle corticosteroid aerosols are able to preferentially reach the distal airways [37], unlike the larger-particle aerosols of FP. Finally, and of great interest, Hoshino [44] observed that the effects of CIC on small airway pulmonary function and lung inflammation were translated into an effect on patient-centred outcomes; in that, asthma control test scores were significantly improved after patients were switched to the CIC treatment arm after the FP run-in phase, but not in those that continued FP treatment.

Stepping Down Inhaled Corticosteroids and Asthma Control

Most asthma guidelines advocate stepping down ICSs once patients are controlled and stable on their current therapy [49, 50]. However, it is recognised that although stepping down therapy is recommended, it is often not implemented, leading some patients to be over-treated

with corticosteroids. Physicians acknowledge patients should be maintained on the lowest dose of ICS that achieves maximal clinical benefit and minimises adverse effects, a principle that applies to any medication used in clinical practice. The British Thoracic Society guidelines advocate health care practitioners consider reductions in the ICS dose in stable asthma patients every 3 months, and specify the dose of ICS should be reduced by 25–50% [50].

This latter recommendation is based on a prospective 1-year, double-blind, randomized, controlled trial of stepping down ICS in stable asthmatic patients in primary care [51]. In this step-down study by Hawkins et al. [51], family practitioners in Scotland recruited 259 stable, well-controlled adult asthmatic patients receiving regular medium- to high-dose ICS treatment (mean daily dose of 1,430 µg beclomethasone) and allocated them to two parallel groups: no alteration in treatment (control group) or active reduction of their ICS (step-down group). The authors achieved a reduction in the ICS in the step-down patients of 348 µg per day without clinically significant differences in asthma exacerbations, visits to the family practitioner or oral corticosteroid use in contrast to the control group (no treatment alteration). The authors concluded that by adopting a step-down approach to the use of high-dose ICS in asthma, a reduction in the drug dose could be achieved without compromising asthma control. In a step-down ICS study undertaken in secondary care, Lee et al. [52] observed that stepping down ICS therapy in stable asthmatics was not being routinely adopted and in those patients in whom step-down therapy was implemented, no deterioration in asthma control occurred.

The step-down approach of inhaled therapy and its effect on asthma control have been investigated in a small number of studies using conventional large-particle inhalers. Collectively, the studies have supported the notion that stable asthmatic patients on high-dose ICS may be over-treated and that reductions in the inhaled dose can be achieved without worsening disease control [53–57].

Small-Particle Aerosols and Stepping Down ICS

The role of new HFA solution small-particle aerosols in the step-down management approach of asthma has recently been studied using the corticosteroids BDP, CIC and, also, the BDP/formoterol drug combination. Fowler et al. [58] stabilised moderate-to-severe uncontrolled asthmatic patients ($n = 39$) with high-dose ICS (BDP 1,000 µg twice daily via a DPI) for 4 weeks and then randomised their patients to either step down to a fixed-dose

combination DPI inhaler (FP/salmeterol 100/50 µg twice daily; $n = 19$) or to step down to a small particle HFA solution pMDI aerosol of corticosteroid alone (BDP 200 µg twice daily; $n = 20$) for 8 weeks. The authors observed that in the step-down combination treatment arm, there were improvements in methacholine bronchoprotection, lung function (determined by FEV₁ and peak expiratory flow) and the asthma quality-of-life questionnaire (symptoms and emotions) compared to stepping down to the small-particle aerosol corticosteroid. This observation could be explained by the fact that the study endpoints of bronchial provocation and lung function were more selective to assess changes in the proximal large airways where the fixed-dose large-particle combination therapy would have predominantly deposited [59], rather than assess changes in the distal small airways where the small-particle aerosol with a greater fine-particle fraction would have preferentially deposited [60].

In the study by Bateman et al. [61], the effectiveness of the small-particle aerosol of HFA-pMDI corticosteroid CIC to reduce the use of oral corticosteroids in steroid-dependent patients with severe persistent asthma was investigated. The lowest effective dose of oral prednisone was established for each patient before randomisation at which their current ICSs were discontinued, and patients were treated in three parallel groups to receive either CIC 320 or 640 µg twice daily, or placebo for 3 months. Both doses of CIC significantly reduced prednisone use (47 and 63% for CIC 640 and 1,280 µg daily, respectively) whilst maintaining asthma control in patients (determined using a 24-hour asthma symptom rating score). In contrast, probably unsurprisingly, the use of oral corticosteroids increased in the placebo group (4% increase). Interestingly, 30% of all patients treated with CIC were able to completely stop prednisone. As commented above, oral corticosteroids, through their systemic delivery to the lungs, are able to treat asthmatic inflammation in both the large and also the small airways, which has clearly been shown to be present in patients with severe asthma [1, 62]. However, oral corticosteroids are associated with significant adverse effects. The study by Bateman et al. [61] demonstrated that by using the inhaled route to deliver a small-particle aerosol of corticosteroid to target small (and large)-airway inflammation allowed patients to reduce or discontinue their oral prednisolone without worsening asthma control [61]. This study shows that small-particle aerosols of corticosteroids can achieve reductions in oral corticosteroid usage and allow discontinuation of oral corticosteroid in patients with severe asthma in a similar approach to studies reported using

the ICSs of DPI-FP and DPI-BUD that have larger aerosol particle size [63, 64].

Papi et al. [65] recently reported the first study to assess asthma control after step-down of treatment based on the GINA guidelines comparing the small-particle HFA solution combination aerosol of BDP/formoterol to the DPI combination of FP/salmeterol. In a prospective, 6-month, parallel trial, asthmatic patients ($n = 378$) controlled for 2 months on fixed high-dose DPI-FP/salmeterol (1,000/100 μg daily) during run-in were randomised to step down to either the DPI FP/salmeterol (500/100 μg daily) that was half the corticosteroid dose compared to run-in or to a small-particle HFA-BDP/formoterol (400/24 μg daily), where the ICS dose of BDP (400 μg) was kept equivalent to the ICS dose in the arm of the parallel step-down treatment with FP (500 μg). Compared to the ICS dose at the end of the run-in phase, a significant reduction in the weekly mean ICS dose was noted in both the DPI-FP/salmeterol group (51% ICS dose reduction) and the HFA-BDP/formoterol group (62% ICS dose reduction). The cumulative mean ICS dose during the 6-month study period was significantly lower in the HFA-BDP/formoterol group compared to the DPI-FP/salmeterol group. The authors observed that in the primary outcome of morning peak expiratory flow, the small-particle aerosol HFA-pMDI combination showed equivalent efficacy to the larger-particle DPI combination. It was also noted that the small-particle combination aerosols achieved asthma control to similar levels compared to the large-particle combination inhaler and that the small particles achieved reductions in the ICS dose without worsening disease control; in that, over 90% of patients stepped down to either treatment arm continued to remain controlled or partially controlled according to GINA criteria.

The recent interest in 'real-life' research reflects the importance of understanding how data from selected patients enrolled in clinical trials are representative to that of a real-life population of 'unselected' patients [66, 67]. In a real-life observational study involving 2,853 adult asthmatic patients from hospital respiratory units in Italy, the prevalence of asthma control and its relationship to health care resource consumption was investigated [68]. The authors observed 19.8% of the patients were uncontrolled, 15.8% were partially controlled and 64.4% had controlled asthma based on the asthma control test. Of the patients ($n = 1,380$) treated with an ICS/LABA combination inhaler for a minimum of 4 weeks, 14.2% were uncontrolled, 13.7% were partially controlled and 72.1% had controlled asthma. Of the 1,380 patients as-

sessed for asthma control, 454 patients were treated with BDP/formoterol, 453 with BUD/formoterol and 473 with FP/salmeterol. The proportion of controlled asthma was significantly higher in those patients given the small-particle aerosol of BDP/formoterol (76% controlled) than in those treated with BUD/formoterol (69% controlled), and at similar levels compared to FP/salmeterol (71% controlled). The mean daily ICS dose was lower for the small-particle aerosol of BDP/formoterol compared to BUD/formoterol and to FP/salmeterol (311.7 vs. 590.1 vs. 675.3 μg , respectively), with a significantly better health-related quality-of-life status achieved with small-particle BDP/formoterol compared to FP/salmeterol, and similar levels compared to BUD/formoterol.

Small-Particle Aerosols and COPD

Recently, the role of small-particle aerosols on patient-centred outcomes has also been investigated in patients with COPD. In a randomised, double-blind, double-dummy, parallel, 3-month study, Tzani et al. [69] evaluated the effects of the small-particle HFA solution pMDI combination aerosol BDP/formoterol (400/24 μg daily) and the DPI-FP/salmeterol combination (500/100 μg daily) on air trapping, lung hyperinflation and dyspnoea in 18 patients with severe stable COPD. Compared to baseline values, the small particles of HFA-BDP/formoterol achieved a significant reduction in the air-trapping physiological indices of residual volume (RV), total lung capacity (TLC) and functional residual capacity, which was not achieved with the DPI-FP/salmeterol combination. Comparing HFA-BDP/formoterol treatment to DPI-FP/salmeterol, a significantly greater reduction in RV was observed with the small-particle HFA aerosols. Interestingly, not only did this study explore the relationship between the effect of two different formulations of combination therapy on physiological variables, but also their association with patient-centred outcomes. HFA-BDP/formoterol significantly improved the transition dyspnoea index total score compared to DPI-FP/salmeterol and, importantly, the improvement in dyspnoea reported by the patients was above the clinically relevant threshold only with the small-particle aerosols of HFA-BDP/formoterol [70]. The authors reasoned that the small particles and greater fine-particle fraction with the HFA-BDP/formoterol aerosol would allow the drug to preferentially reach the small airways compared to a large-sized aerosol allowing an effect on distal air trapping, which was observed to translate into patient benefit. Indeed, this would seem plausible as the small airways are recognised as the major site of airflow limitation in COPD [71, 72], and

peripheral-airway obstruction is known to cause progressive air trapping during expiration with limitation of exercise capacity in COPD patients [73]. The data by Tzani et al. [69] are consistent with the observation that parameters of hyperinflation show better correlation with patient-centred health outcomes than the FEV₁ [74].

The recent study by Calverley et al. [75] in patients with COPD, although not significant in its co-primary endpoints of FEV₁ and disease exacerbation, provides insight into the role of small-particle HFA combination aerosol therapy in (i) molecular drug interactions, (ii) small-airway physiological assessment and (iii) translation of small-airway-directed therapy into patient-centred outcomes. In a large, randomized, controlled study, Calverley et al. [75] investigated the effect of combination ICS/LABA treatment delivered as small-particle HFA-pMDI aerosol versus larger-particle DPI delivery on pulmonary function, respiratory symptoms and disease exacerbation in severe stable COPD patients (n = 703) [75]. After a run-in phase of 4 weeks with the ipratropium bromide/salbutamol combination (40/200 µg, three times a day), patients were randomised to three parallel groups of treatment with HFA-pMDI BDP/formoterol (200/12 µg, twice daily), DPI BUD/formoterol (400/12 µg, twice daily) or DPI formoterol alone (12 µg, twice daily) for 48 weeks. Both the small-particle HFA-pMDI combination aerosol and the DPI combination treatment showed comparable efficacy in the change (at 48 weeks vs. baseline) of the pre-dose morning FEV₁, which was achieved with the small-particle aerosols despite the lower daily ICS in the HFA-pMDI aerosol. The study also indicated that the small-particle HFA combination aerosol showed a significantly greater improvement in FEV₁ compared to the DPI-LABA treatment alone, an effect which was also observed with the DPI combination inhaler. This probably reflected the additional contribution of the anti-inflammatory effect of the corticosteroid in the combination formulations over and above single-agent LABA treatment [76]. Indeed, there is growing evidence for the molecular rationale of the complementary interactions and effects between corticosteroids and LABA both in vitro [77–80] and in vivo [81–84], where studies have shown that corticosteroids up-regulate β-receptors and LABAs increase glucocorticoid receptor translocation and uptake into the nucleus. This molecular basis may explain the improvement in lung function and symptoms, and effects on disease exacerbation in both asthma and COPD achieved with the combination treatment compared with either drug alone in large clinical trials [85–91]. These data on a complementary clinical effect between cortico-

steroid and LABA using small-particle aerosols is also consistent with a previous observation using small-particle aerosols in asthma, where the HFA-pMDI BDP/formoterol combination achieved significantly greater asthma control than either BDP or formoterol alone [92].

Of interest with respect to small-airway therapy was the finding by Calverley et al. [75] that though all treatments improved forced vital capacity (FVC), this improvement was only significant with the small-particle HFA-pMDI aerosol treatment. FVC has been used as an indirect indicator of small-airway function, where an improvement in FVC may indicate a reduction in airway closure and air trapping [3]. In the Severe Asthma Research Program, Sorkness et al. [93] observed marked physiological air trapping in the cohort with severe asthma (n = 287) compared to the non-severe asthmatics (n = 383), with a significant increase in RV, TLC, functional residual capacity and the RV/TLC ratio as a percentage of predicted values in the severe asthmatics. The investigators noted a strongly significant inverse correlation of FVC percentage predicted with the RV/TLC ratio percentage predicted, giving support to FVC as an indirect spirometric surrogate of air trapping. Interestingly, in the same study cohort, the authors found that the FEF_{25–75} showed a poor correlation with the RV/TLC ratio percentage predicted. These observations again highlight the fact previously discussed that traditional spirometry is insensitive to detect effects on the peripheral airways [45]. The effect on FVC using the small-particle aerosols of HFA-BDP/formoterol has also been observed in moderate-to-severe asthmatic patients. In a study by Papi et al. [94], FVC significantly improved with HFA solution pMDI BDP/formoterol (400/24 µg daily) compared to HFA suspension pMDI FP/salmeterol (500/100 µg daily) after 3 months of treatment leading to the conclusion that the improvement in FVC reflected a reduction in air trapping and small-airway obstruction. Both the consistent observations in FVC improvement in the study by Calverley et al. [75] in COPD patients and the study by Papi et al. [94] in asthmatic patients may be explained by the greater peripheral-airway deposition of the smaller-particle (1.5 µm) HFA solution BDP/formoterol aerosol [43] in contrast to the relatively more central-airway deposition of the larger-particle (2.7 µm) HFA suspension FP/salmeterol aerosol and (4.0 µm) DPI BUD/formoterol [27, 36]. The findings related to FVC are interesting and require further investigation and validation, as with other physiological markers [95], particularly as this spirometric marker is easily accessible and measurable in primary care and could help in the day-to-day control and management of patients

with asthma and COPD, tantalisingly identifying those patients with small-airway involvement [1, 2].

The study by Calverley et al. [75] of small-particle aerosols in COPD also highlights the translation of small-airway-directed therapy into the clinical scenario with respect to patient-centred outcomes. A co-primary endpoint in the study was the mean rate of disease exacerbations per patient per year. It is recognised that the frequency of disease exacerbations contributes to long-term lung function decline in patients with COPD [96]. It was surprising that there was no difference between the three treatment groups regarding this endpoint, and the authors attributed this to potential bias in the inclusion criteria of their study, where closer disease monitoring leading to better symptom management as part of a clinical trial may have resulted in an overall lower disease exacerbation in the studied cohort. However, in contrast, at 48 weeks of assessment, in all three treatment groups the 6-min walking distance was significantly improved compared to baseline measurements, and the greatest improvement occurred in the group with the small-particle aerosols of HFA-BDP/formoterol. Of further note, only the small-particle aerosol achieved an improvement in the 6-min walking distance that was above the clinically relevant threshold of 37 m [97]. This improvement in daily activity could be attributable to the peripheral deposition of the small-particle aerosol and its physiological effects on dynamic hyperinflation and distal-airway air trapping [3, 98]. This finding encourages us to acknowledge the important notion of the 'minimal clinically important difference' with respect to outcome measures or physiological endpoints in clinical trials and to understand what the relationship is between a given change in the magnitude in any one of these outcomes with respect to the clinical importance to health care professionals or to the perceptible meaningfulness by the patient [99–102]. This is equally important for measures of small airways as it is for the established physiological measures of large-airway bronchodilation.

Concluding Remarks

The last decade has seen greater confidence in our ability to utilise physiological techniques and imaging modalities to assess small-airway structure and function [3, 103], which have been coupled with technological advances in inhaled drug delivery that now allow us to deliver aerosolised medicine to the small airways. Thus, we can now use these tools and treatments, and take up the challenge to prove (or disprove!) the hypothesis that inhaled drug delivery to the small airways is clinically beneficial and translates into improved patient outcome in asthma and COPD. Recent times have also heralded clinical trials of bronchoscopic surgical techniques where interventions undertaken within the large airways may indirectly treat the pathophysiological consequences of small-airway disease in COPD [104]; larger patient trials and prospective long-term follow-up are needed here. Finally, our allergy, rhinology and ENT colleagues remind us not to forget the 'one-airway hypothesis' and to treat inflammation in the 'top part' of the respiratory tract; where treating allergic rhinitis has been shown to translate into improved overall asthma control [105]. Maybe we should not forget to treat the 'bottom part' of the respiratory tract either: the overlooked 'silent' small airways, so that we wholly manage the mucosal carpet of inflammation in the 'unified-airway' paradigm [106]. These truly are exciting times for all researchers involved in unravelling the mysteries of the small airways [107].

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