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Small Airways Dysfunction in Asthma: Evaluation and Management to Improve Asthma Control

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The small airways have been neglected for many years, but interest in the topic has been rekindled with recent advances in measurement techniques to assess this region and also the ability to deliver therapeutics to the distal airways. Current levels of disease control in asthmatic patients remain poor and there are several contributory factors including; poor treatment compliance, heterogeneity of asthma phenotypes and associated comorbidities. However, the proposition that we may not be targeting all the inflammation that is present throughout the whole respiratory tree may also be an important factor. Indeed decades ago, pathologists and physiologists clearly identified the importance of small airways dysfunction in asthmatic patients. With improved inhaler technology to deliver drug to target the whole respiratory tree and more sensitive measures to assess the distal airways, we should certainly give greater consideration to treating the small airway region when seeing our asthmatic patients in clinic. The aim of this review is to address the relevance of small airways dysfunction in the daily clinical management of patients with asthma. In particular the role of small particle aerosols in the management of patients with asthma will be explored.

Key Words: Small airways; asthma; physiology; pharmacology; inhalation; aerosols; corticosteroids; long-acting beta agonists

INTRODUCTION

There have been many reviews published recently in the last few years on small airways dysfunction and its importance in respiratory disease, particularly in asthma, as interest in this topic has be rekindled by advances in measurement techniques of, and therapeutic delivery to, the peripheral lung regions.[1-4] This review attempts to approach the topic in a different manner. It will address the significance of small airways dysfunction in the daily clinical management of patients with asthma and in particular, the literature will be reviewed to help answer the following pragmatic questions to inform the busy practicing respiratory healthcare professional in clinic.

1. Is small airways dysfunction relevant in the asthmatic patient?
2. If so, how can we target drug to treat small airways dysfunction?
3. Does treatment of the small airways make a difference to the patient and specifically, to asthma control?
4. If so, do doctors need to treat small airways dysfunction?

In particular the role of small particle aerosols in the management of patients with asthma will be explored, and as there have been many terms used to describe these aerosols, for the purposes of this review small particle aerosols are defined as those ≤2 microns in diameter. The manuscript was a review of the literature using keywords of small airways; asthma; physiology; pharmacology; inhalation; aerosols; corticosteroids; long-acting beta agonists; medication.

Asthma control is still not optimal

The last three decades have seen important advances in the management of patients with asthma and these include; greater awareness and timely diagnosis of the disease, pharmacological interventions principally targeted at controlling the underlying airways inflammation, the realisation of and appropriate management of the significant comorbidities associated with the condition, and a multidisciplinary approach to care for

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this chronic disease in the community. However, despite these significant advances, the present day control of disease in patients with asthma remains rather unsatisfactory.

In an European cross-sectional survey, Demoly and colleagues assessed the levels of patient-reported asthma control on the health status of patients and their use of healthcare resources (visits to their doctor, emergency room attendance, and admission to hospital) over a five year period from 2006 to 2010.[5] The authors observed that despite ongoing treatment, more than 50% of all asthmatic patients were still characterized as being not well controlled (54% in 2010, 57% in 2008, and 55% in 2006). The authors also noted that worsening asthma control was associated with significantly greater healthcare resource utilisation in the preceding six months of assessment. Similar findings have also been reported in the Asia Pacific region by Lai and colleagues, where daytime asthma symptoms were reported by 51% of asthmatic patients and only 34% of patients with severe persistent asthma felt their disease was well or completely controlled.[6] Certainly, the compliance of patients with their prescribed medication and also the correct use of inhaled respiratory medicines are important concerns and represent significant factors contributing to reported studies on poor asthma control.[7] The management of patients with asthma has been improved with the advent of combination treatment of inhaled corticosteroids (ICS) with long-acting beta-agonist (LABA), where combination therapy has clearly been shown clinically to improve disease control through mechanisms that modulate the underlying airways inflammation.[8,9] Yet studies have shown that asthmatic patients are still not optimally controlled with such management.

In a *post hoc* analysis of data from the Formoterol and Corticosteroid Establishing Therapy (FACET) study,[10] O'Byrne and colleagues reported that the addition of the LABA, formoterol, to the ICS, budesonide, led to a greater probability of well-controlled asthma compared to an increased dose of budesonide, where treatments were given for one year.[11] However, their data showed that nearly 40% of patients on the combination of formoterol 24 μg/budesonide 800 μg daily, did not achieve sustained well-controlled asthma in the last two months of treatment; that is, the patients were characterised as being poorly controlled or with intermediate controlled asthma. Indeed, of those patients on daily budesonide 200 μg alone, or daily budesonide 800 μg alone, nearly 70% and 60% respectively, did not achieve sustained well-controlled asthma. Bateman and colleagues investigated the ICS/LABA combination of salmeterol/fluticasone over one year of treatment and interestingly, reported very high levels of patient compliance with treatment: nearly 90% of patients. Yet, despite such a high level of compliance, the authors observed only 71% of asthmatic patients were well controlled, whereas just 41% of patients were 'totally' controlled.[12] Indeed, this high level of compliance clearly does not reflect real-life clinical practice, where studies have shown that less than 15% of patients persist with inhaled therapy in the course of a year.[13] These data highlight that despite current therapeutic strategies, there remains a great unmet need in the management of asthmatic patients with mild, moderate and severe disease.

Small airways phenotype

Asthma is now being recognized as a complex clinical syndrome, rather than a specific disease entity, and as an 'umbrella' term encompassing a heterogeneous group of phenotypes and endotypes that may have different treatment responses.[14,15] In light of this understanding, the approach of 'one treatment to fit all' may not be appropriate, and there is a move towards personalising asthma therapy based on specific phenotypes.[16] So, could it be that asthmatic patients who continue to experience poor disease control and frequent exacerbations exhibit persistent airways inflammation that is not being addressed by existing anti-inflammatory treatments? More specifically, a key contributory factor to poor disease control might be that such patients express a 'small airways phenotype', where there is ongoing and unopposed small airways inflammation and dysfunction that is not being targeted or controlled by current therapies; that is, the inability of the inhaler devices that are routinely being used in clinical practice to effectively deliver and deposit their aerosolised medicine to treat the small airway region of the lung.[17]

Historically, the small airways are defined as airways with an internal diameter of less than 2 mm.[18,19] Weibel's seminal work on the quantitative study of lung anatomy helps us to acknowledge there are three main lung regions to appreciate when considering airway disease and targeted treatment; the large (>2 mm) conducting airway zone which comprises airway generations 1-7; the small (<2 mm) conducting airway zone, which comprises airway generations 8-16; and the small (<2 mm) respiratory acinar zone, which comprises airway generations 17-23.[20] It is well established that inflammation in asthma involves the large airways, but histopathological evidence from several studies have clearly shown that the inflammation in asthmatic subjects also involves the small airways; that is, the complete airway tree.[21,22] It is also now recognised that the small airways are the major site of airflow limitation in both asthma and chronic obstructive pulmonary disease,[23,24] yet they are known as the 'quiet zone' as conventional physiological measurements are unable to sensitively evaluate this airway region.[25,26]

Evaluating small airways dysfunction and asthmatic patient phenotypes

Evidence is accumulating to support the concept that airways dysfunction and inflammation in the small airway region of the lung may be contributing to distinct asthmatic patient phenotypes. Kraft and colleagues have reported that patients with nocturnal asthma demonstrate greater inflammatory involvement of the small airways.[27] In this key study, the authors un-

dertook endobronchial biopsies to sample the proximal airways and transbronchial biopsies to sample the distal airways in patients categorized with nocturnal and non-nocturnal asthma on two occasions; during the day (mid-afternoon) and during the night (early hours of the morning). They observed that patients with nocturnal asthma had increased eosinophil and macrophage counts in biopsies of their distal airways undertaken during the night compared to biopsies taken mid-afternoon. In addition, patients with nocturnal asthma exhibited significantly greater numbers of eosinophils in the distal airways compared to the proximal airway tree in biopsies undertaken during the night. Kraft followed up on these results with a functional physiological study to assess the importance of distal airways inflammation.[28] In this study, the authors showed that patients with nocturnal asthma exhibited significantly increased peripheral airways resistance, both during the night and also during mid-afternoon, in contrast to those with non-nocturnal asthma. In particular, peripheral airways resistance was highest in patients with nocturnal asthma during the night. Collectively, these studies support the concept that small airways dysfunction may contribute to the increased night-time symptoms in patients with nocturnal asthma.

Small airways involvement has also been implicated in the phenotype of patients with exercise-induced asthma and in the severity of exercise-induced bronchoconstriction.[29] Kaminsky and colleagues challenged asthmatic patients with dry cool air, which replicates the changes in airflow and temperature that occur during exercise, using a wedged bronchoscope that was also simultaneously utilized to assess peripheral airways resistance.[30] The authors observed that post-challenge, there was a significant increase in peripheral airways resistance in mild asthmatic patients compared to healthy subjects, which correlated with methacholine-induced airway hyper-responsiveness. These findings suggested that altered small airways physiology is present in asthmatic patients who exercise and that this change in physiology may contribute to the symptoms experienced by patients with exercise-induced bronchoconstriction.

The presence of small airways dysfunction is characteristically associated with patients who have more severe, difficult-to-treat, unstable asthma. The single-breath nitrogen washout test has been utilized to derive the index of closing volume (CV), which reflects air-trapping due to early small airways closure and CV has been shown to have greater sensitivity to small airways inflammation than traditional spirometric measures of forced expiratory flow between 25 to 75 percent of the forced vital capacity (FEF_{25-75}).[31] In a study by in 't Veen and colleagues, the authors observed that difficult-to-treat asthmatics with frequent disease exacerbations exhibited enhanced airway closure (assessed as closing volume) compared to equally severe asthmatics without recurrent exacerbations, and concluded enhanced airway closure was a phenotypic characteristic of difficult-to-treat patients with asthma.[32]

The multiple-breath nitrogen washout test has been advanced by Verbanck and colleagues to derive indices based on Wiebel's partitioning of the lungs, where the test determines indices that distinguish changes in ventilation heterogeneity in the conducting region (Scond) from changes arising in the distal acinar compartment (Sacin).[20,33,34] Thompson and colleagues have recently shown that patients with poorly controlled unstable asthma have abnormal ventilation heterogeneity in both the conducting (Scond) and acinar (Sacin) lung regions.[35] Specifically, the authors observed that the abnormalities in the acinar lung region (Sacin) correlated directly with worsening forced expiratory volume at 1 second percentage predicted (FEV1 % pred), and also with the patient's treatment requirement as determined by the medication step in the asthma GINA (Global Initiative for Asthma) guidelines.[36]

In contrast, clinicians may under-appreciate the presence and contribution of small airways dysfunction to patients at the other end of the disease spectrum; that is, with mild-to-moderate asthma. Data show that persistent small airways dysfunction occurs despite treatment at steps 2 through 4 of current asthma guidelines and that small airways dysfunction contributes to poor asthma control even in the mild group of patients. Exhaled nitric oxide is a biomarker of the underlying airways inflammation, which can be partitioned to assess inflammation arising from the central large airways to that arising from the peripheral alveolar airways. This anatomical partitioning can be undertaken using different exhalation flows of nitric oxide[37] and more recently, assessing differential airway responses to a bronchoconstrictor challenge.[38,39] Schichilone and colleagues have utilised the index of alveolar nitric oxide as a marker of small airways inflammation in patients with mild asthma and established that their level of disease control, assessed using the asthma control test (ACT), was directly associated with peripheral airways inflammation; that is, alveolar nitric oxide concentrations were significantly higher in uncontrolled asthmatic patients compared to controlled patients and that worsening alveolar nitric oxide concentrations correlated with worsening ACT scores.[40] Interestingly, the authors also observed that alveolar nitric oxide concentrations appeared to predict the response to treatment with small particle aerosols of inhaled corticosteroid in terms of asthma control, where the degree of improvement in asthma control in patients receiving small particle aerosols of corticosteroid therapy correlated highly with their baseline alveolar nitric oxide.

Impulse oscillometry utilises the indices of reactance (X), resistance (R) and impedance (Z) that are based on a theoretical model where oscillating pressure/flow signals of moving air within the lungs, when generated at different frequencies, are used to determine airway mechanics from different lung regions.[41] There is ongoing applied research to understand the anatomical region that the IOS indices at different frequencies reflect in the disease expression of patients with asthma and

other respiratory disease.[42,43] Generally lower frequencies, in particular frequency dependent changes in resistance between 5 and 20 Hz (R5-R20 Hz) and capacitive reactance at 5 Hz (X5 Hz) are reported to reflect changes arising from more distal airways, whereas higher frequencies are considered to reflect changes from more central larger airways. Anderson and colleagues have employed IOS measurements in persistent asthmatic patients treated in primary care and observed that R5-R20 Hz was abnormal in approximately two-thirds of patients at each step of the asthma treatment guidelines.[44] The authors noted that in those patients with mild asthma (step 2), small particle corticosteroid treatment significantly lowered total airway resistance (R5 Hz) compared to those on standard corticosteroid therapy, yet no difference between the treatment groups was observed in the spirometry index of FEV1. Similarly, Perez and colleagues have demonstrated the presence of small airways impairment (defined primarily by body plethysmography measures of lung hyperinflation such as functional residual capacity (FRC), residual volume (RV) and the ratio of RV/total lung capacity) in nearly 40% of clinically stable moderate-to-severe asthmatics treated with ICS/LABA who had a normal FEV1, supporting the observation that conventional physiological measurements are unable to sensitively evaluate this airway region.[45] The forced vital capacity (FVC) is gaining support as an indirect marker of air trapping, where in the severe asthma research programme, the FVC as a percentage of predicted was shown to be highly inversely correlated to the ratio of residual volume to total lung capacity (RV/TLC) as a percentage of predicted[46] Indeed, Papi and colleagues have shown that improvements in FVC may reflect reduction in air trapping and small airways obstruction.[47] The authors investigated the effects of 3 months of treatment with small particle (~1.5 microns) combination ICS/LABA aerosols (beclomethasone dipropionate [BDP] with formoterol [Form], 400/24 μg daily) delivered via an hydrofluoroalkane (HFA)-solution pressurised metered dose inhaler (pMDI) and compared this to large particle (~2.7 microns) combination ICS/LABA aerosols (fluticasone propionate (FP) with salmeterol (Salm), 500/100 μg daily) administered as an HFA-suspension pMDI, and observed a significant improvement in FVC with the small particle aerosols. This study supported the notion that the FVC is able to reflect changes from more distal airways that are targeted by small particle aerosols. Table 1 summarises noninvasive methods of assessing small airways disease.

Table 1. Noninvasive assessment of small airways disease

Assessment Method [ref]	Small Airway Measure
Spirometry[46,47]	FVC/SVC, FEV_3, FEV_6, FEF_{25-75}
Body Plethysmography[45]	RV/TLC, DLCO, Raw
Single Breath Nitrogen Washout [31,32]	CV, CC
Multiple Breath Nitrogen Washout[20,33,34]	Sacin, Scond
Forced Oscillation Technique[41-44]	R5-R20, X5, AX, Fres
Exhaled Nitric Oxide[37,40]	FVC/SVC
Bronchoconstrictor Airway Challenge[38]	AMP
Prolonged Sputum Induction[68,95]	Late-phase sputum
High Resolution Computed Tomography[73-75]	Air trapping

FEF_{25-75}, forced expiratory flow through 25-75% of the forced vital capacity; FEV_3, forced expiratory volume in 3 seconds; FEV_6, forced expiratory volume in 6 seconds; FVC, forced vital capacity; SVC, slow vital capacity.

Rationale to treat the lung periphery

The data above give support to the rationale for treating the lung periphery and this reasoning was clearly established in a proof-of-concept study by Berry and colleagues who showed the ongoing presence of persistent distal airways inflammation in asthmatic subjects treated with conventional inhalers, which was subsequently attenuated with targeted small airways therapy.[48] In this study, the authors observed that patients on maximal inhaled therapy on step 4 of the asthma guidelines had significantly elevated levels of distal airways inflammation, as determined by alveolar nitric oxide, and this was highly correlated with broncholalveolar lavage eosinophil counts. In response to this ongoing inflammation, the investigators doubled the dose of inhaled corticosteroid that the patients were receiving and observed no reduction in the increased levels of alveolar nitric oxide, concluding that conventional inhaler devices delivering large particles of inhaled corticosteroid were unable to target the persistent distal airways inflammation. Consequently the authors undertook to administer an anti-inflammatory treatment that would effectively reach the small airways -oral corticosteroid-and after 2 weeks of treatment, the levels of alveolar nitric oxide were dramatically reduced.

This study supports the fact that the majority of conventional inhaler devices used in current clinical practice predominantly utilise large drug particles that are not effective in delivering and depositing aerosolised medicine to treat the small airway region of the lung. Indeed, such devices overall are generally inefficient at achieving adequate lung deposition, where at best, approximately 20% of the inhaled drug reaches the lungs and 80% of the dose is wasted; with the latter, much of the dose impacts in the oropharynx with the potential to give rise to adverse local and systemic effects.[49] Surely this inefficiency can be improved? When engineers from the aeronautical and automobile industries have made significant advances in the last few decades improving the efficiency of the aerodynamic exterior and engine interiors of their machines, surely the respiratory community and aerosol scientists can adopt similar principles to achieve an improved medical product for patients?

The interaction of an inhaler device with a patient is complex, and the factors determining the lung deposition of inhaled

medical aerosols can be broadly categorized into aerosol/device characteristics and patient-related features.[50] We have little control over the patient-related features in this interaction in order to influence and improve lung deposition, but we can develop our inhaler devices to become more efficient in the delivery of drug to the lungs and, of all the aerosol characteristics, drug particle size is the most important factor determining the amount of drug depositing in the lungs. Usmani and colleagues have definitively shown that aerosol particle size influences the total and regional site of airway drug deposition *in vivo* in asthmatic patients.[51] The investigators observed that smaller drug particles (1.5 microns) of salbutamol achieved better total lung deposition and peripheral airways distribution compared to larger particles (3.0 and 6.0 microns) and that the smaller particles gave less oropharngeal deposition and were less affected by rapid changes in inhalation flow compared to the larger particles. This data has informed and advanced aerosol science, with the development of new inhalers, devices and drug formulations to achieve more efficient total lung delivery and to accomplish peripheral airways deposition from inhaled therapeutics.

Drug delivery to the peripheral airways

In recent years, formulation scientists have led the innovation in the development of more efficient inhaler devices and have ascertained that the chemistry of the drug formulation determines the resulting aerosol particle size in that; dry powder inhalers (DPIs) generate larger particles than HFA-pMDI inhalers, and HFA-solution pMDI inhalers achieve the smallest aerosol particle sizes compared to HFA-suspension aerosols. Differences in the particle size of the drug formulations, and hence in the inhaler devices, have been observed to lead to marked differences in the lung deposition of inhaled aerosolised medicines.[52-57] The capability to generate small particle aerosols of ICS and LABA has been utilised to improve the total lung dose of delivered drug to levels between 30 to 50%, which is a significant improvement compared to conventional devices.[56-60] Of greater significance is that these small aerosol particles are able to effectively deliver inhaled drug to the periphery of the lungs.

Newman and colleagues have shown that small particles (~1.1 microns) of the HFA-solution pMDI corticosteroid ciclesonide achieved 44% deposition in the central airways and 56% deposition in the peripheral airways.[57] Nicolini and colleagues have shown that the small particle (~1.5 microns) combination therapy of ICS/LABA (BDP/Form) delivered from an HFA-solution pMDI achieved 2/3rd central airways deposition and 1/3rd peripheral airways deposition.[58] Recently, Scichilone and colleagues have replicated this distribution in the regional airways distribution of 2/3rd central and 1/3rd peripheral, for the same combination therapy of ICS/LABA (BDP/Form) delivered from a novel DPI, where the inhaler device also generates small particle (~1.5 microns) sized aerosols.[59] Hence, the development of inhalers delivering small particle aerosols now allows us to achieve deposition to treat the whole airway tree; that is, simultaneously targeting drug to the large and also the small airways. De Backer and colleagues have also shown a rather important finding with small particle sized aerosols: that of consistency in deposition of drug in the lungs in patients with differing severities of airfow obstruction. The authors observed that the small particle (~1.5 microns) combination ICS/LABA therapy of HFA-solution pMDI BDP/Form achieved 34% total lung deposition in healthy subjects (FEV1 112% of predicted), 31% in asthmatic patients (FEV1 75% of predicted) and 33% in patients with chronic obstructive pulmonary disease (FEV1 44% of predicted).[60] So do these technological advances in achieving peripheral lung deposition to treat small airways dysfunction translate into benefits for patients with asthma? Specifically, can small particle aerosol therapy improve asthma control?

Treating the small airways in asthma

Several studies have investigated the ability of both inhaled small particle aerosols and oral treatments to target drug to the distal airways and their consequent effects on physiological indices and levels of asthma control. Huchon and colleagues have shown that six months treatment with the inhaled small particle combination ICS/LABA therapy of HFA-solution pMDI BDP/Form in one inhaler significantly improved asthma control in 645 patients with moderate-to-severe asthma compared to large particle therapy using two separate inhalers of chlorofluorocarbon (CFC)-pMDI BDP and CFC-formoterol.[61] Studies using large particle aerosols confirm that the ICS dose can be successfully decreased in asthmatic patients without worsening levels of disease control,[62-66] and this important observation has recently been reinforced also using small particle aerosol therapy. Papi and colleagues have shown that inhaled small particle combination therapy of ICS/LABA maintains asthma control after step-down of treatment from high-dose large particle combination therapy.[67] The authors studied asthmatic patients (n=378) who in the preceding 2 months prior to step-down, had been well controlled on high-dose large particle aerosols of DPI-FP/Salm (1,000/100 μg daily). Patients were stepped down to six months therapy with half the dose of corticosteroid in 2 parallel treatment groups of either (i) large particle aerosols of DPI-FP/Salm (500/100 μg daily) or (ii) small particle aerosols of HFA-solution pMDI BDP/Form (400/24 μg daily). The authors observed that the small particle aerosols were as efficacious as the parallel treatment group of large particle aerosols in peak expiratory flow measures from spirometry. More importantly, the levels of asthma control in patients treated with small particle aerosols were not significantly different compared to those patients treated with large particles, where over 90% of patients in both treatment groups remained well controlled or partially controlled. It was also noted that the weekly mean ICS dose was significantly reduced in both paral-

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lel treatment groups; DPI-FP/Salm (51% reduction) and HFA-pMDI BDP/Form (62% reduction), and that over the period of six months treatment the reduction in the mean ICS dose was significantly greater with the small particle HFA-pMDI BDP/Form group compared to the large particle DPI-FP/Salm group. The study reinforces the practice that healthcare professionals should consider to step down patients with well controlled asthma. Although we are attentive and confident in stepping-up therapy in poorly controlled patients, practitioners tend to be less assertive and do not routinely consider stepping down therapy in well controlled patients, even though asthma guidelines emphasize this practice with clear concerns that well controlled patients with asthma may be unnecessarily over-treated with high-dose ICS.[36]

The efficacy of small particle aerosolised ICS monotherapy on levels of asthma control has also been studied.[68] Hoshino and colleagues treated patients with mild asthma for two months with large particle (~5.4 μm) DPI-FP (100 μg twice daily) to achieve disease control and then randomised patients to two parallel group treatments with either (i) small particle aerosols (~1.1 μm) of HFA-solution pMDI ciclesonide (200 μg once daily) or (ii) to continue to receive DPI-FP large aerosols, for a further two months. The authors observed that small particles of ciclesonide compared to large particles of fluticasone propionate significantly improved distal airway inflammatory and physiological measures; that is, there was a significant reduction in the percentage of eosinophils in late-phase induced sputum and an improvement in distal airway IOS measures (reactance X5 Hz and resistance R5-R20 Hz). However, there was no effect on spirometry indices, supporting again previous observations that spirometry is rather poor at assessing the effects of small particle aerosols that are able to target the distal airways.[69] Of particular note in the study, the investigators found that the effects of small aerosol particles on distal airways function were translated into improvements in levels of asthma control and patient reported symptoms, where HFA-pMDI ciclesonide significantly improved the asthma control test (ACT) compared to treatment with DPI-FP.

Bateman and colleagues have shown the ability of small particle monotherapy of ICS corticosteroid to achieve step down of asthmatic patients from the burden of high dose oral corticosteroid therapy without worsening their overall asthma control.[70] In this study, the investigators treated severe asthmatic steroid-dependent patients for three months in three parallel groups; small particle aerosols (~1.1 microns) of HFA-solution pMDI ciclesonide 640 μg daily, or HFA-pMDI ciclesonide 1,280 μg daily, or placebo. The authors observed that the use of oral prednisolone was significantly reduced in both active treatment groups with a 47% dose reduction for ciclesonide 640 μg daily and 63% reduction for ciclesonide 1,280 μg daily and that this was accompanied without worsening levels of asthma control. Indeed of note, 30% of all patients actively treated with ciclesonide were able to completely stop prednisone and this study shows that stepping down can be undertaken using small particle monotherapy corticosteroid aerosols even in severe asthma patients who are stable on their therapy and that, in some cases, patients can discontinue their oral corticosteroid usage, which is similar to findings observed using the same approach with large particle sized monotherapy corticosteroid aerosols such as DPI-budesonide and DPI-FP.[71,72] Table 2 summarises the interventional efficacy studies in asthmatic patients comparing small versus large particle inhaled aerosols of ICS monotherapy and ICS/LABA combination therapy.

The role of oral anti-inflammatory anti-leukotriene agents, where drug is delivered to the lungs via the systemic circulation, has also been investigated in their ability to control airways inflammation in the distal airways. Zeidler and colleagues used high-resolution computed tomography (HRCT), executed at residual volume, before and after airway challenge with methacholine, to assess the effects of montelukast therapy on distal airways function in 16 mild-to-moderate steroid-naïve asthmatics.[73] Compared to placebo, the authors observed that after 1 month treatment with montelukast there was decreased regional air-trapping on HRCT in the pre-methacholine images which correlated with an improvement in symptoms and also, montelukast showed less increase in air trapping post-methacholine compared to placebo. The responses that were seen in the lung images occurred without any significant change in measures of spirometry, supporting the fact that conventional spirometry is rather insensitive to detect distal airway dysfunction. The same functional imaging CT technique to assess the small airways has also shown that regional air-trapping decreased after treatment with small particle HFA-solution BDP compared to large particle aerosols of CFC-BDP in corticosteroid-naive asthmatic patients.[74,75] In a study exploring the effects of add-on treatment with anti-leukotriene therapy to ICS treatment, Fritscher and colleagues investigated the utility of central/bronchial and distal/alveolar exhaled nitric oxide concentrations in 18 mild adult asthmatic patients.[76] The authors observed that the addition of oral montelukast (10 mg daily) to inhaled fluticasone propionate (500 μg daily) for three weeks led to a reduction in alveolar nitric oxide levels, although this was not statistically significant compared to baseline measurements. It was also noted that there was no translation of this reduction to an improvement in asthma symptom scores. However, in a subgroup of patients where the inhaled fluticasone propionate treatment was stopped and oral montelukast monotherapy continued, it was observed that the improvement in alveolar nitric oxide levels observed with the combination dual therapy was lost. This study would suggest that, overall, oral montelukast was not efficacious with respect to modulation of small airways inflammatory responses as determined by alveolar nitric oxide.

In contrast, Gelb and colleagues evaluated four weeks of add-

Table 2. Interventional efficacy studies comparing small versus large particle inhaled aerosols of ICS monotherapy and ICS/LABA combination therapy

Ref	Treatments	Study Design	Efficacy Outcomes
ICS/LABA combination therapy			
47	HFA-BDP/F (100/6 μg bd) HFA-FP/Salm (125/25 μg bd)	N=228 moderate to severe asthma, 3 months	BDP/F as efficacious as FP/Salm for PEF and symptom-free days. BDP/F showed significantly faster bronchodilation than FP/S. BDP/F showed a significant increase in FVC compared to FP/Salm
96	HFA-BDP/F (200/12 μg bd) DPI-BUD/F (400/12 μg bd)		BDP/F as efficacious to BUD/F for morning PEF and symptom free days
61	HFA-BDP/F (200/12 μg bd) separate inhalers of CFC-BDP (500 μg bd) plus DPI-F (12 μg bd) CFC-BDP alone (500 μg bd)	N=645 moderate to severe asthma, 6 months	BDP/F as efficacious to separate BDP+F inhalers and superior to CFC-BDP alone. Asthma control significantly higher with HFA-BDP/F vs. separate BDP+F inhalers and CFC-BDP alone
97	HFA-BDP/F (200/12 μg bd) DPI-FP/Salm (250/50 μg bd)	N=416 asthma, 3 months	BDP/F as efficacious to FP/Salm for morning pre-dose FEV1. Stepping controlled patients across from FP/S (500/100 daily, in any device) to HFA-BDP/F maintains asthma control
67	HFA-BDP/F (200/12 μg bd) DPI-FP/Salm (250/50 μg bd)	N=422 asthma, 6 months	BDP/F as efficacious as FP/Salm on morning PEF. Over 96% patients remain controlled on BDP/F (400/24 μg daily) after being stepped down from FP/Salm (1,000/100 μg daily)
99	HFA-BDP/F (200/12 μg bd) DPI-FP/Salm (250/50 μg bd)	N=10 moderate asthma, 6 months	BDP/F led to a significant decrease in closing volume whereas no significant changes from baseline were detected with FP/Salm.
ICS monotherapy			
68	HFA-CIC (200 μg od) DPI-FP (100 μg bd)	N=30 mild asthma, 2 months	CIC significantly improves small airway function (IOS R5-R20) and inflammation (late-phase sputum) and asthma control (ACT) compared with FP
100	HFA-CIC (80 μg od) HFA-FP (100 μg bd)	N=480 mild to moderate asthma, 6 months	Low-dose CIC as efficacious as high-dose FP in FEV1 improvement
101	HFA-CIC (80 μg od or 160 μg od) HFA-FP (88 μg bd)	Children (6-11 y) N=744 moderate to severe asthma, 3 months	Once-daily CIC (160 μg) as efficacious as FP in lung function and quality of life. Urine cortisol decreased significantly with FP but not with CIC
102	HFA-CIC (320 μg bd) HFA-FP (330 μg bd)	N=528 moderate to severe asthma, 6 months	Similar efficacy between CIC and FP in lung function, asthma symptoms and asthma exacerbations. CIC associated with fewer local side effects than FP
103	HFA-CIC (160 μg od) HFA-FP (250 μg bd)	N=106 moderate asthma, 3 months	Patients well controlled on FP250 μg bd (or equivalent) stepped down to CIC maintained similar asthma control to those continued on same dose FP
104	HFA-CIC (80 μg od or 160 μg od) HFA-FP (88 μg bd)	N=808 persistent asthma, 3 months	Both low- and high-dose once daily CIC showed comparable efficacy in FEV1 and asthma symptom scores to twice daily FP
105	HFA-CIC (200 μg od) DPI-BUD (400 μg od)	Children (6-11 y) N=621 asthma, 3 months	Once-daily CIC as efficacious as BUD on FEV1, PEF and asthma symptom scores. CIC had significantly less reduction in body height and suppression of urinary cortisol excretion vs. BUD
106	HFA-CIC (400 μg od or 800 μg od no Spacer) CFC-BDP (800 μg od plus Spacer)	N=319 moderate to severe asthma, 2 months	CIC (800 μg od) significantly more effective in PEF than BDP
107	HFA-CIC (320 μg od) DPI-FP (200 μg bd)	N=474 moderate asthma, 3 months	CIC as efficacious as FP in FEV1 improvement. CIC showed significantly more improvement in HRQoL and significantly less oral candidiasis than FP
108	HFA-CIC (400 μg od) DPI-BUD (400 μg od)	N=399 asthma, 3 months	Once-daily CIC significantly more effective than once daily BUD in improving FEV1, FVC and PEF
109	HFA-CIC (80 μg bd) HFA-FP (88 μg bd)	Children (6-15 y) N=556 asthma, 3 months	CIC as efficacious as FP on FEV1, PEF and asthma symptoms
110	HFA-CIC (80 μg od or 320 μg od) DPI-BUD (400 μg bd)	N=554 mild to moderate asthma, 3 months	Both CIC doses as efficacious as BUD in improving pulmonary function FEV1, PEF and asthma symptom control. CIC was not associated with significant urinary cortisol suppression, unlike BUD
111	HFA-CIC (80 μg od or 160 μg od) HFA-FP (88 μg bd)	N=529 mild to moderate asthma, 3 months	Once daily CIC as efficacious as twice daily FP in improving lung function FEV1, FVC, PEF and asthma symptoms
112	HFA-CIC (160 μg od) HFA-FP (100 μg bd)	N=35 mild allergic asthma, 3 months	Clinical (non-significant) trend where CIC compared to FP produced a higher decrease in exhaled nitric oxide levels

(Continued to the next page)

Table 2. Continued

Ref	Treatments	Study Design	Efficacy Outcomes
113	HFA-CIC (320 μg od) DPI-BUD (320 μg od)	N=359 asthma, 3 months	CIC as efficacious as BUD in FEV1
114	HFA-CIC (160 μg given either AM or PM) MDI-BUD (200 μg bd)	N=405 asthma, 3 months	CIC (given at different times of the day) as efficacious as BUD in FEV1
115	HFA-CIC (400 μg bd) HFA-FP (1,000 μg bd)	N=14 moderate asthma, 1 month	Both CIC and FP significantly improved airway hyper-responsiveness and nitric oxide levels. Unlike CIC, FP but not CIC significantly suppressed overnight urinary cortisol levels

BDP, beclomethasone dipropionate; BUD, budesonide; CFC, chlorofluorocarbon; CIC, ciclesonide; DPI, dry-powder inhaler; F, formoterol; FP, fluticasone propionate; HFA, hydrofluoroalkane; Salm, salmeterol

on anti-leukotriene therapy (zileuton 2,400 mg daily) in 19 stable moderate-severe patients with asthma who had been receiving inhaled combination ICS/LABA treatment (FP/Salm 500/100 μg daily) for at least 1 year.[77] The authors observed there was no significant effect on either distal/alveolar or central/bronchial airway nitric oxide concentrations with the addition of oral anti-leukotriene therapy, compared to when patients were only receiving inhaled ICS/LABA. In paediatric mild asthmatic patients, Nieto and colleagues have observed that montelukast treatment administered for one month in an open study led to significant improvements in impulse oscillometry indices of both central airway resistance (R20 Hz) and distal airway capacitive reactance (X5 Hz) compared to an untreated control group.[78] It was also noted that conventional expiratory flows assessed by forced spirometry did not change following treatment.

Systemic parenteral treatment with omalizumab (an anti-immunoglobulin (Ig)-E monoclonal antibody) is used in selected patients with severe allergic asthma on treatment step 5 of asthma guidelines.[36] Berger and colleagues studied the effects of different concentrations of omalizumab *in vitro* on human bronchi specimens incubated in asthmatic medium and the authors observed that both specific and nonspecific bronchial hyper-responsiveness were significantly blocked by omalizumab in both proximal and distal airways.[79] Although the clinical potential of several biomarkers have been investigated to assess the effects of treatment with anti-IgE therapy, these biomarkers assess whole airway function, and there is little data specifically exploring effects of anti-IgE treatment on the distal airway lung region.[80,81]

Although the above studies highlight the role of the systemic bioavailability of oral and parenterally administered drugs to treat inflammation throughout the airway tree targeting both proximal and distal lung regions, systemic therapy, and in particular oral corticosteroids, are associated with notable side effects and hence, there remain distinct therapeutic advantages to deliver drug to the airways using the inhalation route. Indeed, inhaled medicines achieve a more rapid onset of action by delivering the drug directly to the site of action, and allow a much smaller dose of drug to be administered leading to a lower incidence of adverse effects.

Small airways therapy and real life asthma

Many of the clinical trials undertaken in asthma involve carefully selected patients fulfilling specific inclusion and exclusion criteria that are often not representative of the heterogeneity of asthma observed in 'real-life' unselected patients seen in daily clinical practice.[82,83] The role of small airways treatment on levels of asthma control has been studied in real-life studies using small particles of ICS monotherapy and also small particles of combination ICS/LABA therapy.[84-91] Collectively, these studies support our understanding that (i) aerosol particle size, (ii) the physicochemical properties of the corticosteroid, (iii) the airway drug deposition characteristics (greater lung deposition and lower oropharyngeal deposition) and, (iv) the need for less reliance on an optimal inhalation flow (particularly compared to conventional DPIs) are all important aspects in the effectiveness of these small particle aerosol asthma treatments in real-life clinical practice.

Several of the studies have utilised monotherapy with small particle aerosols of BDP.[84-86] In a retrospective observational study involving patients identified in a primary care research database, Price and colleagues assessed the effect of the first (initiation) prescription in patients with small particle aerosol treatment of HFA-solution BDP and compared this to treatment with large particle therapy of FP (HFA-suspension or DPI) over one year on levels of asthma control and exacerbation rates.[84] The authors observed that patients in both treatment groups achieved more than 80% asthma control, determined as a composite index of hospitalisation, oral corticosteroid use and antibiotic prescription, and the authors also noted that both treatment groups had similar rates of disease exacerbation. However, those patients receiving small particle BDP aerosols had significantly lower prescribed mean doses of ICS compared to those on FP. Similar conclusions in achieving lower ICS doses and equally effective asthma outcomes have been observed in other studies where long-term therapy with small particle HFA-solution BDP aerosols have been compared to larger particle CFC-BDP aerosol treatment[85] and to larger aerosols of HFA-

suspension FP.[86]

The effect of combination ICS/LABA small particle aerosol therapy of BDP and formoterol on levels of asthma control has also been studied in the real life setting.[87-91] In a large cross-sectional study of adult asthmatic patients from hospital respiratory units in Italy, Allegra and colleagues observed that in a subgroup of patients (n=1,380) receiving small particle aerosol treatment with BDP/Form the proportion of levels of asthma control determined by the Asthma Control Test (ACT) were significantly higher than in those patients receiving Budesonide/Form (76% vs 69%) and at similar levels of control compared to those patients receiving FP/Salm (71% controlled), where treatments has been taken for greater than 1 month.[87] Additionally, the authors observed that the mean daily dose of ICS was much higher for the large particle aerosols of FP/Salm and Budesonide/Form compared to the small particle aerosols of BDP/Form (675 μg, 590 μg, 311 μg respectively), and that health-related quality of life status was significantly better with small particle BDP/Form aerosols compared to FP/Salm, and of similar levels compared to Budesonide/Form. Similar observations on levels of asthma control and quality of life for small particle BDP/Form aerosols compared to larger particle DPIs have also been observed in other real-life prospective (over 12 months)[88] and cross-sectional[89] studies. Investigators have also assessed the effects of changing patients from combination ICS/LABA large particle DPIs to small particle HFA-solution pMDI aerosols in real-life asthmatic populations. Popov and colleagues showed an improvement in quality of life with small particle HFA-solution BDP/Form aerosols compared to when they were on large particle DPI of FP/Salm or Budesonide/Form, and in a subgroup of patients there were significant improvements in FVC and an improvement in inflammatory markers with small particle BDP/Form.[90] Brusselle and colleagues have also shown that the benefits of small particle HFA-solution BDP/Form aerosols on improving levels of disease control in non-smoking patients with asthma are also observed in asthmatic patients who currently smoke, reflecting real-life clinical practice, as often smoking asthmatic patients are excluded from randomized controlled clinical trials.[91] The health-economic benefit of treatment with combination small particle ICS/LABA aerosol therapy has been recently demonstrated. Price and colleagues have shown in a large asthmatic cohort of patients who were switched from large particle FP/Salm aerosols to small particle BDP/Form treatment that there was no loss of asthma control.[92] The authors observed this switch was achieved at an equivalent or lower ICS dose with the small particle aerosols and associated with this there was significant reduction in mean asthma-related healthcare costs.

CONCLUSION

We started the review with the proposition that current levels of disease control in patients with asthma may be poor because of several factors; poor treatment compliance, heterogeneity of asthma phenotypes, comorbidities, but also the proposition that we may not be targeting all the inflammation that is present throughout the whole respiratory tree. Indeed, rhinologists, allergologists and ear nose and throat physicians remind pulmonologists and respiratory physicians that the airways are 'united' [93]; they start at the nares, and we are prompted not to forget treating the 'top' part of the respiratory tree in order to achieve complete asthma control.[94] So using this analogy, maybe we should remember to treat the 'bottom' 'quiet' end where the united airways finish; that is, the small airways, so that we do ultimately treat the whole airway tree. Indeed decades ago, the pathologists and the physiologists clearly highlighted the importance of the small airways in patients with asthma, which till recently remained forgotten, but with renewed awareness we should certainly give greater consideration to treating the small airway region when seeing our asthmatic patients in clinic. And so what about our final question; do doctors need to treat small airways dysfunction? Do medications that target the small airways show clinical efficacy that is superior to that of conventional asthma medications with larger particle size? Certainly, data is accumulating to show this is the case (Table 2), and as we finally now have the technology to deliver drug to target the whole respiratory tree (large and small airways) and we have developed more sensitive physiological techniques to assess the distal airway tree, we should confidently be able to test this hypothesis in the clinic over the next few years.[98] The small airways are no longer silent!

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