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Managing Small Airways Dysfunction in Asthma

About the Reviewer

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Jeff was President of the New Zealand Branch of the Thoracic Society of Australia and New Zealand for 5 years from 2002. He has chaired or been a member of a number of national respiratory committees including the National Respiratory Standards Committee, National COPD, Lung Cancer and Oxygen Service Committees and National Asthma Standards Committee. He sat on the European Respiratory Society Committee as an overseas delegate for 5 years, the Asian Pacific Asthma Advisory Committee, the International Advisory Committee on inhaler therapy and the Australian Lung cancer Guidelines committee. He has published 70 papers in peer reviewed journals and written 5 book chapters.

This article is a review of the contribution of small airways dysfunction in the pathogenesis of asthma and the role of targeted treatment of the small airways with small-particle aerosols. Expert commentary by Associate Professor Jeff Garrett (CMDHB) discusses the clinical practice realities of small airways dysfunction faced by general practitioners and respiratory healthcare professionals in the management of patients with asthma. This review is sponsored by an educational grant from Radiant Health.

Background

Despite many advances in the management of asthma over the past several decades, including improved accuracy of diagnosis and better pharmacological control of underlying airways inflammation, clinical outcomes for many patients with asthma remain unsatisfactory.[1,2] Whilst a number of studies have shown that standardised analysis of induced sputum samples contributes substantially to accuracy of diagnosis and to better targeting of therapy,[3] with better control than achieved with any other intervention, no ideal surrogate exists in routine clinical practice. Considerable effort has therefore been spent on developing expired nitric oxide as an alternative,[4,5] but it is relatively expensive and, in the end, no more accurate at predicting the inflammatory cell present in the airway than a straightforward eosinophil blood count.[6-10] We can now reasonably confidently predict that if a patient presents with symptoms of bronchitis or asthma, and has an eosinophil level of >0.35, that inhaled or oral corticosteroids will contribute to a better outcome.

Multiple factors may, nevertheless, contribute to a suboptimal outcome, including poor patient adherence and inhaler technique, heterogeneity in asthma, the presence of neutrophilic inflammation, and the presence of co-morbidities.[2] Other factors include either a suboptimal dose of inhaled corticosteroid or the inability of most inhaled therapies to reach inflammation that is present in the outer branches of the respiratory tree, i.e. the distal or small airways.[1,2]

Pathophysiology

Inflammation and remodelling of the airways are fundamental pathophysiological features of asthma, resulting in airflow obstruction and the manifestation of the classical asthma symptoms of wheeze, chest tightness, cough, and dyspnoea.[1,2] Historically, it was believed that airways inflammation, remodelling, and surrounding-tissue changes involved only the medium sized and central airways but it has since been established that this also occurs in the small airways and there is recent evidence that it may first start in the small airways.[1,2] A systematic review undertaken by van der Wiel et al. demonstrated that small airways dysfunction is associated with worse asthma control, a higher number of exacerbations, more nocturnal symptoms, more severe bronchial hyper-responsiveness, and more troublesome exercise-induced asthma.[11] Moreover, it also revealed that small airways dysfunction can already be present in cases of mild asthma.[11]

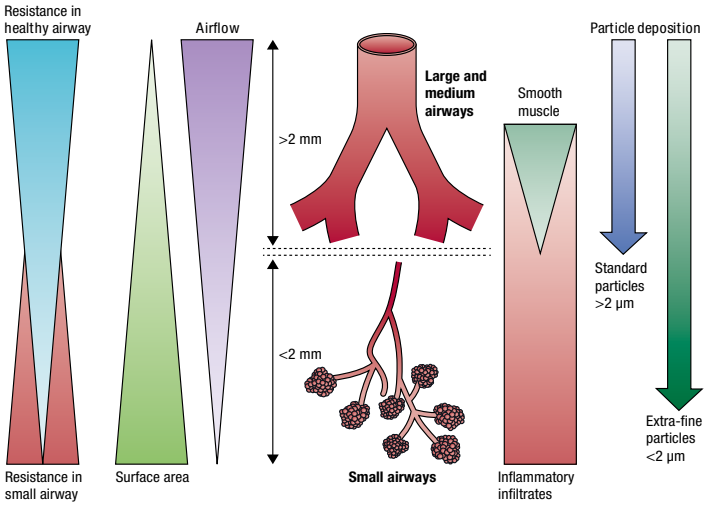

Figure 1. Comparison of pathophysiological characteristics of the large and small airways in asthma.[12]

One reason for the distal airways having been largely ignored in the treatment of asthma is that they were originally thought to contribute minimally to total lung resistance.[1,13] However, with the advent of more sophisticated measurement techniques of lung function, the distal airways were subsequently shown to contribute substantially to total lung resistance in asthmatics.[1] Another reason that the small airways are important in asthma treatment is that the total volume and collective surface area of the distal airways greatly exceed those of the central airways (**Figure 1**);[12,13] and possibly as a consequence, there are also more steroid receptors located in the small airways. Hence, pathogenic changes in the small airways are likely to have a major effect on both the pathophysiology and treatment of patients with asthma.[13] Indeed, the peripheral portions of the respiratory tree have been demonstrated to be a primary site of airflow obstruction, with higher numbers of activated eosinophils and mast cells present in the small airways than in the large airways of asthmatics, and suggests that there is possibly a more severe inflammatory process taking place within the distal airways (**Figure 1**).[1,12,13]

Although more is known about the nature of airway remodelling in the larger airways than in the distal airways, evidence of remodelling beginning first in the peripheral airways is giving greater support to the fact that the small airways are important.[13] Furthermore, high-resolution computed tomography using expiratory films, which allows for the evaluation of morphological changes associated with small airways dysfunction, is identifying a larger number of patients with functional small airway disease than is identified by lung function testing alone.[1] Airways remodelling in asthma is also associated with increased thickness of the airways smooth muscle layer throughout the respiratory tree.[14]

Assessment

The presence of small airways dysfunction in patients with asthma is common and is always present in severe, difficult-to-treat, unstable asthma.[2,15] For this reason, assessing functional and biological parameters indicative of small airways involvement has value in assessing whether good control has been achieved and in informing treatment decisions.

Although there is no definitive assessment method for peripheral airways dysfunction, standard spirometric and body plethysmography tests, including forced vital capacity (FVC), forced expiratory flow rates at 50% or 25-75% of FVC, residual volume, and total lung capacity, have some correlation with distal airways function.[2,15] The single-breath nitrogen wash-out test, impulse oscillometry, and high resolution computed tomography utilising expiratory scans are other potentially useful non-invasive methods of assessment.[2,15,16]

Additionally, the forced oscillation technique and multiple breath washout are non-invasive assessments that can reveal ventilation heterogeneity in the peripheral lung (a marker of asthma disease activity) even without abnormalities in standard spirometric measurements.[2,16] Recent advances in imaging technology, particularly with xenon ventilation computed tomography and hyperpolarised xenon magnetic resonance imaging can also reveal ventilation heterogeneity in the peripheral lung.[16]

Early recognition of small airways dysfunction is important because it indicates the need to consider treatment targeting the small airways.[11] Hence, there is a requirement for a more straightforward and reliable tool to be used in daily clinical practice to assess the presence of small airways dysfunction.[11] The first step in the development of a simple small airways dysfunction questionnaire has been undertaken by a group of Dutch researchers.[17] Through a series of in-depth interviews they revealed that patients with and without small airways disease perceive differences in signs, symptoms, and health-related issues. The testing and validation of these items in a large asthmatic population will hopefully identify the most relevant items for inclusion in a short and simple questionnaire to screen for the possible presence of small airways disease in asthmatics in clinical practice.[17]

Treatment

Given that inflammation in the small airways appears to contribute significantly to the pathophysiology of asthma, including patients with mild asthma, targeting airways inflammation in both the proximal and distal parts of the airway may result in better clinical outcomes.

The proof-of-concept study by Berry et al. validated the rationale for treating the lung periphery by demonstrating that persistent distal airways inflammation in patients with asthma treated with conventional inhalers could be attenuated by targeted small airways therapy.[18] Their results raised concerns regarding the fact that the majority of conventional inhaler devices used in clinical practice currently utilise large aerosolised drug particles, which do not reach the small airways of the lung.[2]

Relevance of particle size

Lung deposition of inhaled drugs depends on many factors including the characteristics of the inhaler device, patient inhalation technique and airway geometry, the amount of mucous present in the airways, and the aerodynamic behaviour of the particles.[19] However, a particularly important consideration is drug particle size,[19] with the internal diameter of the large airways being >2mm compared with that of the small airways being <2mm (**Figure 1**).[2,12] It is only when drug particle size is <2µm that it has the realistic potential of reaching the small airways.

The phasing out of ozone-depleting chlorofluorocarbons (CFCs) as a propellant in asthma metered-dose inhalers (MDIs), as required by the 1987 Montreal Protocol,[20] created the opportunity for the development of small-particle formulations in asthma inhalers.

Drug formulations used in MDIs are developed as either a solution or a suspension. The alternative 'ozone-friendly' propellant, hydrofluoroalkane-134a (HFA), allows for the use of solution formulations in which nanoparticles of the drug are dissolved in the propellant, enabling generation of smaller particles when the propellant evaporates during dosing.[19,21]

Thus, drug formulation chemistry determines the resulting aerosol particle size such that dry powder inhalers (DPIs) generate larger particles than HFA-suspension metered-dose inhalers (MDIs) [**Table 1**] and HFA-solution

Large-particle aerosol formulations	Particle size (MMAD)	Small-particle aerosol formulations	Particle size (MMAD)
DPI-fluticasone	4.0-5.4µm	HFA-MDI-fluticasone	2.4-2.6µm
DPI-budesonide	4.0µm	Extrafine HFA-MDI-BDP/formoterol	1.4-1.5µm
DPI-fluticasone/salmeterol	3.5µm	Extrafine HFA-MDI-BDP	1.1µm
DPI-budesonide/formoterol	3.0µm		

Table 1. Comparison of particle sizes, shown as mass median aerodynamic diameter (MMAD), produced by dry-powder inhaler (DPI) and hydrofluoroalkane-134a (HFA)-metered dose inhalers (MDI).[19] BDP = beclomethasone dipropionate

MDIs generate smaller aerosol particle sizes than HFA-suspension MDIs.[2,19] Compared with MDIs delivering large-particle aerosol corticosteroids (MMAD 3-4 µm), MDIs delivering small-particle aerosol corticosteroids (MMAD 1-2µm) achieve much higher lung deposition (50-60% vs 10-20%).[19]

Systemic effects

The deposition of inhaled corticosteroids (ICS) in the lung is the main source for systemic absorption.[22] Given that the primary site of absorption of ICS is from the alveoli, it is possible that smaller corticosteroid particles, which tend to penetrate better into the alveoli than their larger counterparts, may be more likely to be absorbed and cause systemic effects.[22]

In two randomised, open-label, multicentre studies, asthma control was maintained with no differences in systemic effects over a period of 12 months in adolescents/adults[23] and children (aged 5-11 years) with asthma[24,25] who were switched from stable doses of CFC-beclomethasone dipropionate (BDP) to the small-particle aerosol formulation extrafine HFA-BDP at approximately half of the CFC-BDP dose. In addition, there were no differences between the treatments with regard to 24-hour urinary free cortisol levels, growth velocity, and bone markers in the paediatric study.[24,25] As yet, however, the lowest dose of extrafine HFA-BDP that causes suppression of the hypothalamic-pituitary axis, bone mineral density effects, or growth retardation has not been established.[26] This is because the active metabolite of BDP, beclomethasone-17 monpropionate (17-BMP) has a short half-life of only 2 to 3 hours. This means that at the end of a 12-hour dosing interval there is very little drug accumulation at steady state of 17-BMP. In contrast, fluticasone has a longer half-life of 14 hours. This difference reflects the fact that 17-BMP has low lipophilicity and thus can be seen in higher levels in the plasma but not in systemic fat tissue compared with fluticasone where the opposite occurs. Fluticasone at a dose of >375 µg/day is estimated as a result to cause 30% adrenal suppression.[27]

Clinical studies

Clinical research supports the fact that smaller particle inhaled formulations (either ICS alone or ICS/LABA combination therapy) reach the small airways and are 2- to 5-times superior to conventional formulations with larger particle size.[2,28]

In an early clinical study to test the hypothesis that small particle ICS therapy would provide improved asthma control compared with large-particle ICS, extrafine HFA-BDP was compared with CFC-BDP in a double-blind, randomised study in patients with moderately severe asthma.[29] Extrafine HFA-BDP was found to provide asthma control equivalent to CFC-BDP in at least half the daily dose.[29] This potency advantage was also demonstrated in a blinded, randomised, dose-escalation study in which extrafine HFA-BDP produced effective asthma control at doses 2.5-fold less than that with CFC-BDP.[30] Two subsequent longer-term randomised studies also confirmed the equivalent efficacy of extrafine HFA-BDP in at least half the dose of CFC-BDP over a treatment period of 12 months.[23-25]

These findings were not just noted with monotherapy. Huchon et al. also found enhanced benefit from using small particle ICS/LABA combination therapy.[31] Their double-blind randomised study targeted patients with moderate to severe asthma and demonstrated that after six months' treatment with the small-particle ICS/LABA therapy extrafine BDP/formoterol (400µg/24µg) patients had significantly improved asthma control compared with the same large-particle therapy delivered via two separate inhalers of BDP (1000µg) and DPI-formoterol (24µg) [**Figure 2**].[31] Again, the equivalent efficacy of small-particle versus large-particle aerosol BDP at a dose ratio of 1:2.5 was demonstrated.[31]

Step-down studies

Once asthma is controlled, and as recommended in international asthma guidelines,[32] ICS monotherapy should be attempted rather than leaving patients on ICS/LABA combination therapy long term. If attempting ICS monotherapy, then a switch to small-particle formulations could be considered as studies have revealed that you can maintain asthma control after step-down of treatment from high-dose large-particle inhaled therapy to small-particle formulations at lower dose.[2,28] One of the early studies to investigate stepping-down with a small-particle formulation was the randomised non-blinded study by Juniper et al.[33] They demonstrated similar levels of asthma control and improved quality of life in asthma patients at 12 months after switching from ICS monotherapy with large-particle CFC-MDI-BDP to equipotent doses of extrafine HFA-BDP (at 50% of the dose of the CFC-BDP) compared with patients who continued to receive CFC-BDP.[33] A further example of stepping-down with small-particle formulations in ICS/LABA combination therapy is the 6-month, randomised, non-blinded study by Papi et al.[34] In this study, switching to low-dose extrafine BDP/formoterol (400/24µg daily) maintained asthma control in patients who were previously controlled using high-dose large-particle aerosols of fluticasone/salmeterol (1000/100µg daily).[34]

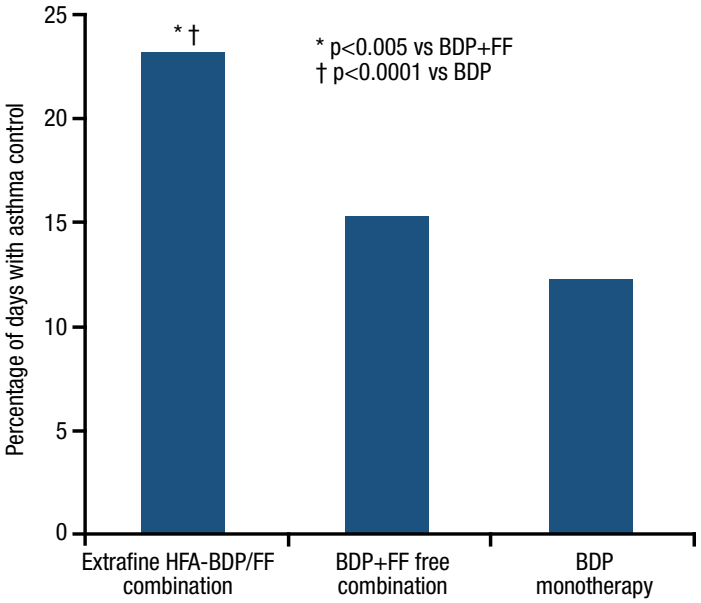

Figure 2. Percentage of days with asthma control achieved with extrafine BDP/FF in a single inhaler using an HFA propellant compared with BPD and FF delivered separately via a CFC-MDI and DPI, respectively, and BDP monotherapy via a CFC-MDI.[31]

Abbreviations: BDP = beclomethasone dipropionate; CFC = chlorofluorocarbon; DPI = dry powder inhaler; FF = formoterol fumarate; MDI = metered-dose inhaler.

Naturalistic studies

The therapeutic effects of both small-particle aerosol ICS monotherapy and small-particle aerosol ICS/LABA combination therapy on levels of asthma control have been studied in the real-world setting using pharmacoepidemiological studies.[2,28] The findings suggested that ICS formulation, aerosol particle size, and airways drug deposition characteristics play important roles in the effectiveness of asthma therapy.[2]

Two retrospective observational studies analysed asthma-related outcomes data from large primary care databases and compared ICS monotherapy with extrafine BDP with large-particle aerosol BDP and large-particle aerosol fluticasone over a period of one year.[22,35] Whether initiating or stepping up ICS therapy by MDI, patients who received extrafine HFA-BDP were more likely to achieve asthma control than those receiving CFC-BDP. Moreover, extrafine BDP could be used at half the dose of the large-particle formulation with at least as good clinical outcomes.[22] Similarly, in the comparison with fluticasone (HFA or CFC formulation), extrafine HFA-BDP had a better chance of achieving asthma control at significantly lower prescribed doses than with fluticasone (**Figure 3**).[35]

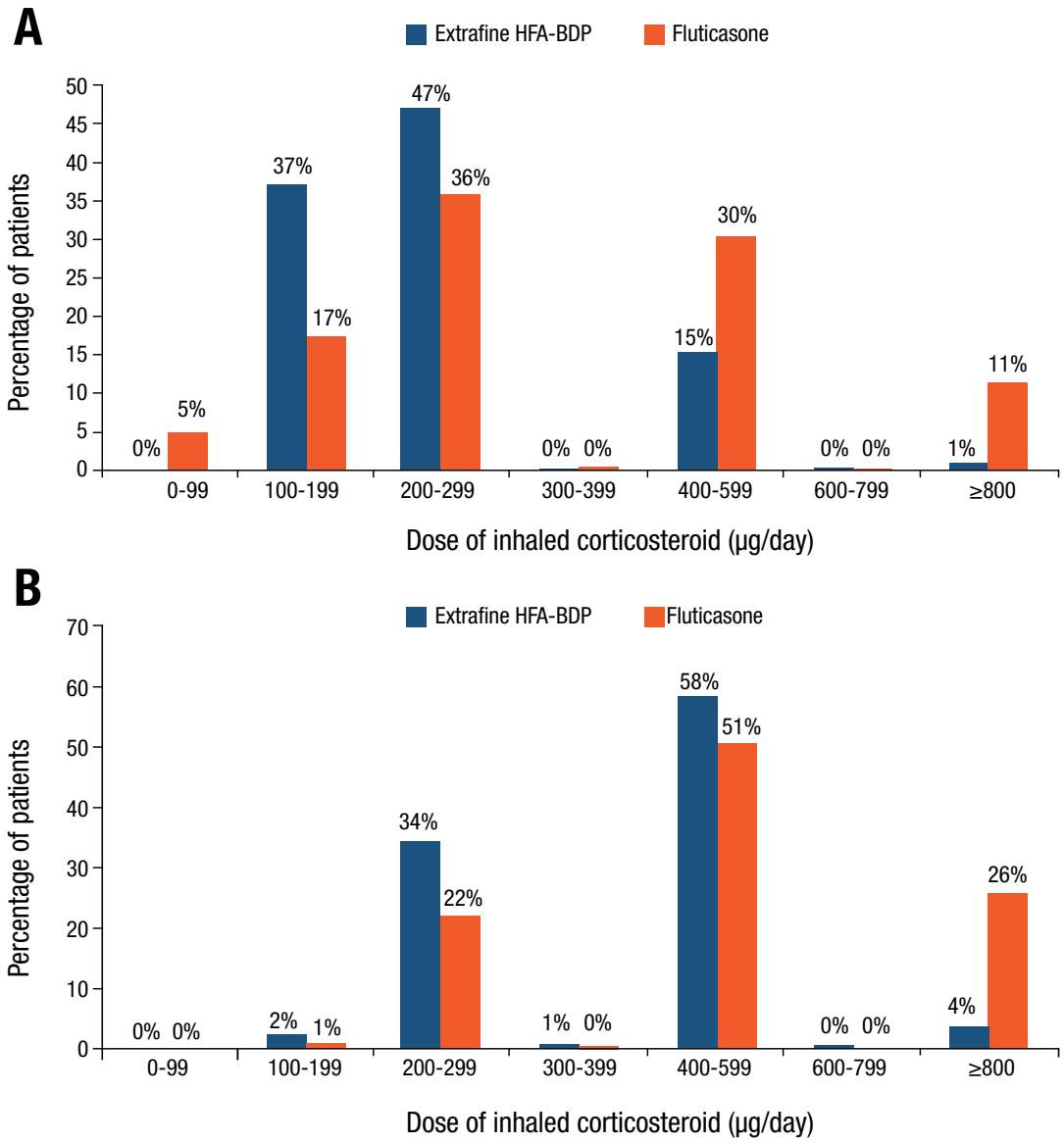

Figure 3. Distribution of prescribed doses for patients initiating an ICS (**A**) and for patients receiving their first increase in ICS dose (**B**) administered by means of an MDI, showing that patients in the extrafine HFA-beclomethasone (BDP) cohort were prescribed significantly ($p<0.001$) lower doses than patients in the fluticasone (HFA or CFC) cohort.[35]

Another small-particle aerosol ICS/LABA combination therapy observational study, which included a cross-sectional phase followed by a 12-month prospective phase, demonstrated patients receiving small-particle aerosol treatment with extrafine BDP/formoterol had better asthma control and health-related quality of life than patients receiving large-particle aerosol treatment with either budesonide/formoterol or fluticasone/salmeterol.[36]

Cost-of-therapy analyses

A health-economic benefit of treatment with small-particle aerosol ICS monotherapy and small-particle aerosol ICS/LABA combination therapy is suggested by cost analyses in retrospective observational studies.[2,15]

In one such study, which compared real-life asthma outcomes and costs for extrafine BDP and large-particle aerosol fluticasone ICS monotherapy in the US, treatment outcomes were similar or better with extrafine BDP prescribed at significantly lower doses and with lower healthcare costs than large-particle aerosol fluticasone.[37] Total mean respiratory-related healthcare costs for the extrafine BDP cohort were significantly lower than for the large-particle fluticasone cohort (**Table 2**); mean annual savings were $US390 (95%CI, $165-$620) per patient prescribed extrafine BDP versus fluticasone. Similarly, total mean respiratory-related healthcare costs excluding ICS costs were significantly lower for the extrafine BDP cohort (**Table 2**); mean annual savings were $US306 (95%CI, $80-$535) per patient prescribed extrafine BDP.[37]

In another retrospective cohort study, switching from large-particle aerosol fluticasone/salmeterol to extrafine BDP/formoterol ICS/LABA combination therapy resulted in no loss of asthma control at the same or lower corticosteroid dose compared with the large-particle aerosol formulation and with a significant reduction in mean asthma-related healthcare costs.[38]

Respiratory-related resource	Costs for the initiation population		
	Extrafine HFA-BDP (n=2578)	Fluticasone (n=7734)	P value
Respiratory-related medication	800 (709)	840 (666)	.13
Respiratory-related primary care consultation	387 (1244)	328 (915)	.14
Total respiratory-related hospitalisations	765 (3816)	1201 (4191)	.15
Respiratory inpatient	428 (3152)	842 (8052)	.15
Respiratory outpatient	323 (1763)	328 (1935)	.95
Respiratory ED	15 (155)	31 (332)	.17
Lower respiratory, other medical	20 (188)	26 (335)	.66
Total asthma/respiratory primary and secondary care, including ICS costs	1952 (4191)	2369 (8491)	.17
Total asthma/respiratory primary and secondary care, excluding ICS costs	1717 (4161)	2057 (8470)	.26
Total adjusted costs per patient (95% CI)	1869 (1727-2032)	2259 (2111-2404)	—
Total adjusted costs per patient, excluding ICS costs (95% CI)	1659 (1516-1823)	1965 (1817-2109)	—

Table 2. Mean respiratory-related medical costs (in $US adjusted to 2010 prices) for asthma patients treated with HFA-beclomethasone (BDP) versus fluticasone.[37] Values are means (standard deviations), unless otherwise noted.

Expert commentary by Jeff Garrett

Two conceptually different discoveries over the past 10-20 years have emerged which need to be incorporated into routine management of asthmatics. One relates to the need to consider biomarkers in both diagnosis and management and the other to the realisation that small airways disease is both underdiagnosed and undermanaged. These discoveries may be complementary because suboptimal control of inflammation within the airways (including the small airways) is likely to lead to remodelling and to the subsequent development of fixed airways obstruction.

The essential traits of an ideal biomarker are that it must indicate a key pathophysiological process, be responsive to changes in disease activity, be easily measured, minimally invasive, reproducible and responsive within a time frame which precedes changes in clinical status. Defining "steroid responsive airways disease' using such biomarkers is essential to best practice as defined by the presence of >2% eosinophils in the sputum. However, this test is relatively costly and time-consuming and thus not readily available to clinicians managing patients within an outpatient or primary care setting. Until a point of care test is developed to evaluate sputum in the clinic room, a surrogate for sputum testing is required. Although many biomarkers have been tested a straightforward full blood count which identifies an eosinophil level above 0.35umol appears to be at least as accurate as the more expensive expired nitric oxide test (FeNO) in identifying the presence of eosinophils within the airway. If the patient is symptomatic or has suboptimal control on an Asthma Control Test or impaired lung function then a more energetic approach to managing the eosinophilic inflammation is required. If a patient has been fully compliant with the current dose of inhaled steroid then elevating the dose is necessary as well as considering the place of a small particle aerosol.

The lack of attention to small airways disease in asthma likely relates to the difficulty in evaluating them. As the accompanying article suggests, physiological measurements of the small airways have improved and whilst measuring FEF25-75 on spirometry remains worthwhile it is not particularly sensitive in identifying small airways narrowing. We therefore also need a more sophisticated bedside test for measuring small airways disease.

Whilst we await the advent of more sophisticated bedside testing and the results of well-designed studies to better understand the role of small airways disease in asthma (i.e. how it contributes to asthma severity, heterogeneity, management, progression and outcome), we need to reflect on the fact that at least 50% of asthmatics are suboptimally controlled on surveys undertaken internationally. Given that the evidence is pointing towards unresolved inflammation in the small airways as being important in contributing to both current symptoms and to remodelling and if eosinophils are present as judged by blood or sputum testing then transferring to small particle corticosteroid aerosol inhalers seems logical. Further, small particle aerosols are cheaper, more cost effective (due to greater clinical efficacy), and overcome many of the problems associated with poor inhaler technique. Further, they have not been associated with any increase in adverse effects from their local administration into the airways. As long as corticosteroids with a short half-life are utilised such as beclomethasone, they are also not associated with any of the systemic effects identified with the use of long-acting inhaled corticosteroids such as fluticasone.

Take-home messages

- Poorly controlled inflammation in the small airways is likely to contribute to airways remodelling and the deterioration of lung function in patients with asthma.
- Small-particle aerosol formulations allow for deposition of the inhaled treatment throughout the respiratory tree, including the peripheral airways.
- Clinical and real-world study evidence is accumulating that small-particle aerosol corticosteroids (as monotherapy and combination therapy) are associated with significant benefit in terms of asthma control, number of exacerbations, and quality of life compared with large-particle aerosol corticosteroids.
- Clinical and real-world studies have shown that extrafine BDP (as monotherapy and combination therapy) requires a lower dose to achieve equivalent asthma control compared with equipotent doses of large-particle aerosol corticosteroids, and hence the potential for a lower risk for adverse effects and lower asthma-related healthcare costs.

Transferring patients from other inhaled corticosteroids to extrafine HFA-MDI-BDP Beclomethasone (QVAR Inhaler)

Because the smaller particle size for extrafine HFA-MDI-BDP results in greater deposition in the airways, care must be taken to ensure that the appropriate dose is administered.[26]

Step 1 - Consider the dose of the inhaled corticosteroid appropriate to the patient's current condition. Symptomatic patients may require an increased dose of their current inhaled corticosteroid and this increased dose should be considered in transferring patients to QVAR.

Step 2 - Convert the appropriate inhaled corticosteroid dose to the QVAR dose according to the table on the right.

	Daily Dose (µg)				
CFC-BDP	200-250	400-500	800-1000	1200-1500	1600-2000
Budesonide DPI*	200	400	800	1200	1600-2000
Fluticasone pMDI*	100	200-250	400-500	600-750	1000
Extrafine HFA-MDI-BDP	100	200	400	600	800

* dry powder inhaler **pressurised metered dose inhaler

Note also that because QVAR and other brands of BDP are not interchangeable it is important to specify 'QVAR' when prescribing extrafine HFA-MDI-BDP to avoid generating a generic beclomethasone script.

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