Editorial
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Size of Inhaled Corticosteroid and Small Airway Inflammation in Asthma

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On the basis of knowledge that asthma is a chronic inflammatory disorder of the airways, evidence-based practice guidelines have recommended anti-inflammatory controller therapy to improve asthma outcomes during the past 3 decades. Recently published guidelines have emphasized the role of anti-inflammatory maintenance therapy to prevent chronic persistence and troublesome exacerbations of asthma by controlling asthma risk factors.[1-3] Regular use of inhaled corticosteroids (ICS) can reduce asthma exacerbation rates,[4] decrease bronchial hyperresponsiveness.[5] and prevent loss of lung function.[6] In addition, a large retrospective case-control study demonstrated a reduced rate of asthma mortality by regular use of ICS.[7]

Several decades ago, the importance of small airway dysfunction was clearly identified in asthmatics. There are 3 main lung regions: the large (>2 mm) conducting airway zone, the small (<2 mm) conducting airway zone, and the respiratory acinar zone.[8] Inflammation in asthma definitely involves large airways, but histopathological evidence has clearly shown that the inflammation involves small airways as well.[9] Small airway dysfunction may be more implicated in unstable asthma.[10] Asthmatic patients who continue to experience poor disease control and frequent exacerbations exhibit persistent airways inflammation that is not well controlled by existing anti-inflammatory drugs. More specifically, a key contributory factor for poor disease control may be ongoing and unopposed inflammation as well as dysfunction of small airways.[11] Smokers and patients with unstable asthma may have more prominent small airway disease. Therefore, clinicians should not underestimate the presence of small airway dysfunction.

Inhaler devices that have been routinely used in clinical practice may not effectively deliver ICS into small airways. With advances in inhaler technologies for delivering drug to the whole respiratory tree, greater consideration has been focused on the treatment of the small airway region. In particular, the role of fine and ultrafine particles has been explored in the management of patients with asthma. ICS is available in pressurized metered dose inhalers (pMDI) using a hydrofluoroalkane (HFA) propellant for both fine-particle formulations with a particle mass median aerodynamic diameter (MMAD) of 2-4 μm and aerosols of extrafine particles with an MMAD of 1 μm.[12] Recently, patients with poor inhaler techniques have benefited from extrafine-particle ICS.[13]

In this issue, Postma *et al.*[14] compared asthma-related outcomes after patients initiated extrafine-particle ciclesonide or fine-particle ICS (fluticasone propionate or non-extrafine beclomethasone) in a matched cohort study that prescribed the first ICS as ciclesonide or fine particle ICS. Ciclesonide is one of the extrafine-particle ICS (MMAD 1.0 μm) that shows both high lung deposition and peripheral lung distribution in healthy volunteers and patients with asthma.[15,16] compared to the bigger sizes of fluticasone and budesonide (MMAD 2.4-3 μm). They also found that ciclesonide-prescribed patients experienced a lower severe exacerbation rate and a higher overall asthma control than fine-particle ICS-prescribed patients. This data support the concept that initiation of ultrafine ICS leads to better outcomes in asthma management. Indeed, Papi *et al.*[17] have shown that ciclesonide-induced improvements in FVC may reflect reductions in air trapping and small airway obstruction. They also demonstrated the effects of 3 months of treatment with a small particle (-1.5 microns) combination of ICS/LABA aerosols (beclomethasone dipropionate with formoterol) delivered via an HFA-suspension pMDI and compared this to a large particle (-2.7 microns) combination of ICS/LABA aerosols administered as an HFA-suspension pMDI, and observed a signif-

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icant improvement in FVC with the small particle aerosols.

In addition, bioavailability is another important consideration in use of ICS. Corticosteroids, either systemic or inhaled, are exquisitely active and effective in asthma, but their mechanism of action is broad, and concern for toxicity has limited their wider use. A variety of approaches are being attempted to maximize local activity within the airways and at the same time to minimize systemic absorption and toxicity.[18] One approach is development of on-site-activated steroids, such as ciclesonide, which is one of the non-halogenated ICS prodrug that require endogenous cleavage by esterases to become active form. All these data support the superiority of ultrafine ICS over fine ICS in the management of asthma, especially the small airway disease phenotype.

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