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Inhaled Corticosteroids and Adult Asthma

To the Editor:

We read with interest the concise review by Beasley and colleagues on inhaled corticosteroids (ICS) in adult asthma (1). We agree that the definition of low, moderate, and high doses of ICS is arbitrary, as stated in the Global Initiative for Asthma report, although the Global Initiative for Asthma makes clear that it is simply an assessment of estimated clinical comparability based on available studies and product information, and that a large number of patients with asthma need only a low dose of ICS (www.ginasthma.org).

However, with regard to the statement that the maximum obtainable patient benefit is with low-dose ICS, we would like to emphasize that the evidence provided to support this statement is from studies on nonphenotyped asthma, a significant proportion of which probably have no or low levels of airway eosinophilia. The main therapeutic target of ICS is the eosinophil, and the degree of airway eosinophilia varies significantly from one patient to another, so that the dose of ICS needed to reduce such eosinophilia significantly varies greatly. It is likely that the "classical" benefit/systemic effects curve differs significantly in eosinophilic asthma, and that the observed plateau is shifted to the right in this population. The reason for the reported lack of efficacy of doubling and quadrupling of doses of ICS is likely that the nature of airway inflammation was not considered in those clinical trials. Furthermore, studies that have looked at sputum eosinophils have demonstrated that high doses of corticosteroids are as effective as prednisone in moderate to severe exacerbations (2, 3). Another study showed that high-dose ICS is also effective in treating exacerbations of asthma (4).

The best way to show an ICS dose response and compare ICS products is therefore not to use unselected patients but, rather, to choose patients with either high sputum eosinophils or high F_{ENO} and then perform dose escalation studies (5). Furthermore, ICS dose response also depends on the outcome measured, with airway hyperresponsiveness showing the best dose-dependent improvement over time (6).

As stated in all guidelines, we should always consider using the lowest possible dose of ICS (or oral corticosteroids [OCS], and ideally no OCS) to control asthma while avoiding the risks for

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adverse effects. Doses of ICS may be minimized by various measures, including environmental control, use of adjunct therapies such as long-acting inhaled bronchodilators, and in the more severe patient, by the early introduction of biologics. However, prevention of OCS use and related exacerbations should be a priority, which could be avoided in some patients by using high doses of ICS. In this regard, in a study over a median period of 10 years (maximum, 30 yr), we showed that when the dose of ICS/prednisone was adjusted to keep sputum eosinophils under control, exacerbations and the rate of decline of lung function were significantly reduced, although at a price of adverse effects, mainly when OCS was needed (7). Adverse effects of high doses of ICS have been confounded by methodologic issues and intercurrent OCS use, and there is probably also a variation in susceptibility to those effects from one patient to another.

We therefore agree with Beasley and colleagues that we should prevent overdosing with ICS when not necessary, and that in this regard, there is a significant care gap in asthma management with an underutilization of noninvasive measurements of airway inflammation, particularly in moderate to severe asthma. We endorse the need for rigorous dose–response studies of ICS to be conducted in patients who are well characterized on the basis of their inflammatory endotypes. ■

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Reply to Boulet and Nair

From the Authors:

We read with interest the comments of Louis-Philippe Boulet and Parameswaran Nair regarding our review on inhaled corticosteroids (ICS) in adult asthma (1). We appreciate their agreement with our view that titration of maintenance ICS doses in accordance with changes in biomarkers of responsiveness may represent the optimal approach to ICS dosing in individual patients, particularly with biomarkers of type 2 inflammation. We also concur regarding priorities for research. As we recommend in our conclusion, a research priority is to determine the dose–response relationship of ICS in phenotypes defined by clinical characteristics such as type 2 biomarker status, and to better define how to titrate the ICS dose in accordance with changes in type 2 biomarkers in asthma. Two important goals would be to determine which patients require relatively higher doses and to establish whether any benefit of higher-dose ICS is a result of the systemically available fraction. ■

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