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Oral Corticosteroids Tapering in Severe Asthma

First marketed 70 years ago, corticosteroids transformed the life of patients suffering from asthma and quickly became the mainstay of treatment for this condition. Despite major developments in therapeutic options since, particularly with the use of inhaled corticosteroids more than 40 years ago, the powerful antiinflammatory effects of oral corticosteroids (OCS) are as of yet impossible to replace completely, explaining their persistent use in asthma management. Most of the time, they are prescribed intermittently to treat severe exacerbations, although some patients require them chronically to achieve asthma control (1). However, OCS are associated with well-recognized long-term side effects and an increase in mortality (2, 3). Recent evidence suggests that this risk is related to the cumulative lifetime exposure to OCS (4, 5), implying that even repeated short courses may have a significant impact on their associated morbidity.

More recently, monoclonal antibodies brought the first real long-term alternative to OCS in severe asthma since the 1950s. They are powerful antiinflammatory agents targeting T-helper cell type 2 (Th2) inflammation with minimal side effects and with corticosteroid-sparing properties (6–9). Their availability provoked a change in OCS perception in severe asthma, from a necessary evil to an increasingly avoidable one. With the increasing use of biologics, tapering and cessation of maintenance OCS has become much more common and feasible, but specific guidance on how to proceed is lacking.

Numerous studies exploring steroid-sparing drugs have reported their OCS weaning protocols. The OCS tapering regimens used were quite variable, as were the assessments of asthma control, biomarker use, and screening for adrenal insufficiency, thus making generalization difficult. Many of them also lacked the details needed to be efficiently implemented in clinical practice. An exception would be the ongoing PONENTE trial, investigating the safety and efficacy of OCS tapering after initiation of benralizumab. Although not evidenced-based, it provides a detailed OCS reduction algorithm with systematic assessment of adrenal insufficiency that could be used by clinicians.

Research and guidelines have recognized the need to reach the minimal effective dose when OCS are needed for long-term treatment of severe asthma. To achieve this, their focus and advice has been to optimize asthma control strategies and use of OCS-sparing drugs without clear guidance on how to actually proceed with weaning. Hence, there are currently no standardized guidelines on how and when to safely perform OCS tapering. A recent review identified this lack of clear recommendations as a clinical barrier to reduce OCS exposure in severe asthma (10).

In this issue of the *Journal*, Suehs and colleagues (pp. 871–881) provide an expert consensus report on the important topic of OCS use and tapering in patients with asthma, including statements on less frequent conditions such as eosinophilic granulomatosis with polyangiitis and allergic bronchopulmonary aspergillosis (11). A modified Delphi method was used to develop a consensus (>70% agreement) among 131 experts from different specialties, mostly pulmonologists (73%) and allergists (18%), in addition to patient advocacy organization representatives. Although opinions sometimes differed, some general principles for use and reduction of OCS were agreed on.

This study is a first major attempt to provide clinicians with guidelines based on expert opinion specifically on OCS use for

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asthma. In the absence of evidenced-based clinical data to support such recommendations, using a Delphi approach to reach consensus statements is a sensible and pragmatic approach. The study included a considerable number of experts, more than expected in a usual Delphi method. However, the criteria used for expert selection were sound and the resulting panel, although large, had the required expertise in severe asthma needed to provide valuable opinions.

The project undertaken by the panel of experts is substantial, with 296 final statements to agree on, from an initial 1,447 raw statements produced from brainstorming. Nevertheless, the participating experts were dedicated, with 96 of the 131 answering the three ranking rounds.

In line with current recommendations, almost all experts on the panel (95%) agreed that our goal should be not to use OCS, but they also acknowledged that maintenance OCS, although a last resort, are still required in some situations. On this matter, the optimal daily OCS dose-reaching consensus was equivalent to 5 mg of prednisone. Up until now, only the Global Initative for Asthma group committed to an "acceptable" OCS dose for maintenance therapy and they settled on the dose corresponding to the physiological steroid production, 7.5 mg daily (1). However, the lower threshold agreed on by the experts may only reflect the submitted statements as it seems that 7.5 mg was not an option to choose from.

The OCS consensus report in this issue of the *Journal* puts forward the important concept of cumulative OCS exposure. Physicians tend to underestimate repeated OCS bursts' long-term side effects. However, research has revealed that there is no benign OCS prescription, as the risk of adverse events is cumulative and escalates with each treatment. An increase in morbidity is seen after only four short courses of OCS (5). In terms of lifetime cumulative dose, most side effects begin after 1–2.5 g, but the diabetes incidence starts to increase after only 0.5 g (4). This may be reflected in the 0.5–1 g yearly threshold chosen by the expert panel to indicate poor asthma control (11). Hopefully, this statement will raise awareness on the consequences of using OCS and reinforce the recommendation that all options must be considered before considering OCS.

Experts agreed that OCS tapering should be attempted in every patient and the Delphi method achieved a consensus on several statements concerning OCS decrease, which are summarized in the graphical abstract available in the publication (11). Although it does not constitute a specific algorithm, for the first time, it provides clinicians with management strategies on how to proceed with OCS tapering. Many aspects to consider when undertaking OCS weaning were covered, but no agreement could be reached regarding biomarkers. Yet, evidence exists linking OCS responsiveness to Th2 inflammation and small studies suggested that sputum eosinophils, blood eosinophils, and fractional exhaled nitric oxide could be useful in OCS dose adjustments (12–14). A large, randomized trial exploring the value of composite biomarkers to titrate OCS therapy should bring more evidence to support biomarker use for OCS tapering (15).

Major advances have been made in asthma care in the last two decades. OCS, once a frequently unavoidable treatment for severe asthma, are progressively being replaced by safer options. We can dream of a day when OCS will not be needed anymore in asthma management, but until then, we should learn to use them cautiously. Suehs and colleagues provide expert advice establishing groundwork to regulate OCS use. Research will be needed to substantiate future recommendations with evidence-based data. ■

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Louis-Philippe Boulet, M.D., F.R.C.P.C.
Krystelle Godbout, M.D., F.R.C.P.C.
Québec Heart and Lung Institute
Laval University
Quebec City, Quebec, Canada

ORCID ID: 0000-0003-3485-9393 (L.-P.B.).

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