Integrating high dose inhaled corticosteroids into oral corticosteroids stewardship

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If high doses of ICS are equivalent to low dose OCS, they should be considered as such
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Uncertainties still surround high dose inhaled corticosteroids (ICS) use in asthma. In hindsight, certain aspects of the ICS development story can help elucidate why. In 1973, Cameron *et al.* [1] signed a brilliant paper reporting the results of a double blind, randomised controlled trial demonstrating the oral corticosteroid (OCS)-sparing effect of ICS as the primary outcome. A few years later, the assessment of this benefit was mitigated when a complete weaning of OCS remained unachievable [2]. The benefit of ICS was therefore understood to be mostly based on an improved safety profile purportedly due to reduced systemic diffusion. Thus, the understanding of how ICS was of any benefit to asthma patients when compared to OCS was mostly based on a greater safety profile supposedly due to a reduced systemic diffusion. Similarly, topically administered corticosteroids were also developed in the same time period for diseases affecting the skin, the eyes, the nose or the joints. As for ICS, whether or not these formulations reduce corticosteroid-associated adverse events remains largely debated [3].

Outside rare conditions such as eosinophilic granulomatosis with polyangiitis, the systemic components of asthma are not obvious and the reasons driving requirements for systemic corticosteroids quite unknown [4]. Interestingly, multiple studies have raised safety concerns related to the use of ICS, especially at high doses [5]. Specific adverse-effect studies have focussed mainly on skin bruising or osteoporosis [6, 7]. However, hypothalamo-pituitary axis (HPA) suppression has been described for high-dose ICS since at least the 1990s [8, 9]. In a slightly provocative way, Maijers *et al.* [10] suggest in the present issue of the *European Respiratory Journal* that around two thirds of high-dose ICS effects are due to their systemic diffusion. To reach this point, they compiled studies where OCS-sparing effects attributed to ICS were studied, and then computed the meta-regression between the change in prednisone dose and the dose of ICS. Based on HPA suppression data, their findings suggest that at least 60% of the OCS dose reduction can be attributed to systemic absorption.

Although the conclusion put forward by Maijers *et al.* [10] is limited by a paucity of studies and patients, it provides evidence that the systemic diffusion of ICS is far from minimised. Moreover, even though HPA suppression is not necessarily related to efficacy, the result is more consistent when considering the

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relatively homogeneous results observed with either budesonide or fluticasone. Thanks to these data, the distinction between Global Initiative for Asthma step 4 and step 3 is better justified, and a debate is justified on whether high doses of ICS should be placed just next to low OCS doses within step 5. Why "very high" doses of ICS are not providing clear advantages beyond "high" doses is a relevant mechanistic question [11]. Corticosteroid resistance is a paradox within the T2 pathway eventually overwhelmed by IL-4, -5 and -13 targeting drugs, even though their mechanisms of action largely overlap [12].

Beyond these observations and questions, the main practical conclusion from the paper by Maijers *et al.* [10] might be that high doses of ICS should be considered as potentially as harmful as low doses of OCS. In this context, the development of equivalencies between ICS and OCS dosing regimens will be necessary for describing the systemic distribution of ICS. It follows that methods for quantifying cumulative doses of corticosteroid treatment that appropriately take into account different modes of administration will take on increased importance as markers of disease severity and/or the success of corticosteroid-sparing strategies. A recent worldwide initiative aimed at reaching consensus around OCS tapering has recently finished data collection and is currently undergoing analysis [13]. Consensus statements related to high doses of ICS and cumulating doses of corticosteroids in general are particularly poised for discussion, and will likely affect the view of corticosteroid stewardship the asthma world stakeholders are currently promoting. Finally, like a little brother to OCS-sparing, ICS-sparing is attaining position as a relevant outcome in future trials, especially among asthma patients who are biological super-responders.

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