Oral corticosteroids in asthma and beyond – moving forward

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As some of the earliest-known and most effective anti-inflammatory agents, corticosteroids have long been a part of physicians' armamentarium against asthma and other chronic inflammatory conditions. While inhaled corticosteroids (ICS) are the cornerstone of asthma therapy, both the Global Initiative for Asthma (GINA) and British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN guidelines recommended the use of oral corticosteroids (OCS) as intermittent therapy in severe acute asthmatic attacks and as maintenance therapy in selected patient with severe asthma refractory to inhaled therapies. [1, 2] More recently, OCS have also been recommended as an adjunct to biologic therapies [1, 2]. However, it has become abundantly clear that OCS use is associated with a wide range of short- and long-term adverse effects. For example, their use is associated with a 2-fold increase in the risk of pneumonia and opportunistic infections and up to a 2.5-fold increase in the risk of other chronic physical and psychiatric conditions such as diabetes, osteoporosis, adrenal insufficiency, heart failure, depression, and anxiety [3–8]. Despite such, supposedly, limited indications of OCS use in asthma, a recent systematic review by Bleecker and colleagues found that approximately a quarter of patients with asthma required short-term OCS use during a one-year period, with up to 12% of patients having long-term OCS use [3]. A recent analysis from the International Severe Asthma Registry also found that almost half of patients with severe asthma treated at GINA step 5 were receiving regular OCS therapy [9].

In this issue of the *European Respiratory Journal*, Skov and colleagues further consolidated our understanding of OCS-related adverse outcomes[10]. Incorporating a new-user design, they performed propensity score-matched analyses of a prospective population-based Danish cohort of patients with asthma. Analyzing the comprehensive OCS prescription records of 151,760 patients in the matched cohort, they found that OCS use was associated with increased risk of morbidity, mortality, and hospital attendances, with a strong dose-response relationship noted. Importantly, even patients who received ≤500 mg of OCS were at

increased risk of adverse events [10]. Although some studies have reported dose-response relationships in the past, with higher cumulative exposures shown to be associated with elevated risk of numerous adverse effects that translated into higher healthcare costs, the adverse effects associated with such low-dose OCS use, as reported by Skov *et al*, have been relatively under-explored [6, 8, 11, 12]. The findings by Skov and colleagues, thus, confirmed prior observations, and bettered our understanding of the adverse effects associated with the full spectrum of OCS doses, particularly at the lower end of the dose spectrum. Notably, in this study, whilst OCS users had significantly higher risk of all-cause and respiratory mortality, no difference was observed for cardiovascular mortality [10].

Whilst we appreciate this study's high data quality and good representation of real-world practice, it is important to note its limitations [10]. For example, only patients aged 18-45 years old were studied, which limits the applicability of findings to older patients with asthma. Also, the follow-up duration of OCS non-users was significantly shorter than that of OCS users, an issue which the authors themselves addressed by a sensitivity analysis which restricted follow-up durations to five years [10]. Although the results demonstrated robustness and validity of the findings, the study's overall implications about the long-term detriments of OCS use were nonetheless impacted by the short follow-up duration for OCS non-users.

Furthermore, Skov and colleagues did not report, nor analyze, prescription patterns; no distinction was made between intermittent or maintenance OCS use [10]. Indeed, this issue is a common one among other studies, most of which did not distinguish between intermittent or long-term OCS use, or focused solely on OCS use as maintenance therapy [11, 13–15]. As over half of the patients in the study by Skov and colleagues received low dose OCS, it seems likely that these patients mostly received intermittent OCS prescriptions, especially given the relatively low intensity of maintenance asthma therapy reported at baseline (14.6% of OCS users did not receive any ICS, and 55.9% received only low dose ICS) [10]. This propensity

for intermittent OCS prescription has been reported by others [3], which begs the question 'why do many clinicians continue to prescribe OCS for their patients with asthma?' One obvious answer is that OCS are lifesaving in severe cases. Physicians may also view OCS as an inexpensive, effective, and low-risk therapy [16]. More studies focusing on the effects of intermittent OCS therapy are urgently needed. One such study, presented as an abstract at the 2021 European Respiratory Society (ERS) International Congress, systematically classified intermittent OCS therapy [17]. It found that even infrequent intermittent OCS use was associated with increased risk of adverse outcomes, with more frequent use patterns associated with further increase in risk [17]. The final results of that study will likely be important for bridging this gap in evidence. Similarly, little is known about the longitudinal trajectory of OCS prescription patterns, such as prescription frequencies or dosages, or risk factors that predict progression and intensification of OCS regimens. Understanding the trajectories of OCS use is critical, not only for our overall understanding of OCS use in asthma, but also for identifying patients at risk of intensive OCS use and potential OCS-related morbidities. A recent abstract at the BTS 2021 Winter Meeting presented initial work on the longitudinal patterns of OCS prescriptions in patients with asthma and other diseases [18]. It showed that since 2013, despite a gradual decrease in the use of high-dose systemic corticosteroids among patients with asthma, low-dose prescriptions have driven an overall increase in the prevalence of systemic corticosteroid prescriptions [18]. The final results of that study will be an important addition to the asthma and OCS therapy literature.

Given Skov and colleagues' findings, it is ever more important to research and establish pragmatic strategies for avoiding OCS use, or for limiting OCS use to only when absolutely necessary. In this regard, both the GINA strategy and BTS/SIGN guidelines emphasize the importance of risk factor modifications and inhaler technique improvement [1, 2], both of which have proven efficacious when properly executed [19, 20]. The prevalence of OCS

prescriptions despite these clear recommendations, points to a problem not in the recommendations themselves, but in the adoption of these recommendations. The most important and obvious solution to this problem is to increase the general medical community's awareness of OCS' detrimental effects on morbidities, mortality, and costs. Early intervention, specifically early introduction of ICS, should be emphasized which have been consistently shown to reduce symptoms, improve lung function and slow down its decline, reduce exacerbations, and improve quality of life [21]. Risk stratification tools, that can reliably predict risk of OCS-related adverse events, would also aid the translation of research findings into clinical practice and curtail excessive OCS prescriptions, thus allowing clinicians to easily identify patients at particularly high risks of these adverse events. Recently, an abstract presented at the 2021 ERS International Congress reported a model predicting osteoporosis among patients with asthma who received OCS [22]. Developed from a large British general practice cohort, this model may further facilitate efforts for reducing OCS use and OCS-related morbidities amongst patients with asthma [22].

Clinicians also need to be aware about newer classes of therapeutic agents which can mitigate OCS overuse, particularly biologics, and ensure that patients are referred in a timely manner to specialists when appropriate who can prescribe biologics. Currently six biologic agents are approved by the Food and Drug Administration for treating severe asthma [23]. Evidence for biologic associated reduction of OCS use comes not only from randomized controlled trials but also real-life observational studies [23, 24]. But what is the best way of reducing OCS use in biologic treated patients? Most landmark trials have adopted a uniform OCS tapering approach for all participants, without considering individual patients' response to therapy and clinical status; an approach which may not be entirely relevant and reproducible in real-life clinical practice [25–27]. This issue of OCS tapering was addressed by Menzies-Gow and colleagues in a recent multicentre study [28]. They demonstrated that in selected

patients with severe asthma, the co-initiation of benralizumab and a personalized OCS reduction algorithm (which considered initial OCS dosage, asthma control, and adrenal function) was efficacious in eliminating or minimizing OCS use [28]. Such personalized approaches may be more relevant in clinical practice. Further exploration of similar approaches for substituting OCS use with biologics are needed. Lastly, the significant cost of biologics has also impeded their widespread use leading to debate about their cost-effectiveness [29, 30]. Existing cost-effectiveness evaluations have focused on costs directly related to asthma only and neglected costs related to OCS use and its consequences [29, 30]. Given the significant cost burden incurred by OCS use [12, 31], OCS-related costs should be considered in future cost-effectiveness evaluations of biologics. Currently, biologics remain underutilized, and switching or stopping of biologics is not uncommon [32, 33]. Much remains to be done in order for biologics to be accepted as a cost-effective steroid-sparing agent for widespread clinical use.

Finally, OCS-related morbidities are clearly not specific to asthma, and the burden of OCS beyond asthma should not be overlooked. Chronic obstructive pulmonary disease (COPD) is another prevalent disease that often requires systemic corticosteroid therapy. High dose systemic corticosteroid use in COPD has been associated with an estimated 63% increase in the risk of mortality and more than double the risk of vertebral fracture [34, 35]. Like in asthma, existing literature on systemic corticosteroid-related morbidities in COPD generally lack granularity, such as prescription patterns and dosage. Further investigations in this area are much needed. Beyond asthma and COPD, systemic corticosteroid therapy is indicated for many other diseases, including autoimmune diseases, and organ transplants. While investigations of corticosteroid-related adverse effects for the latter have been relatively thorough [36], only a few common autoimmune diseases, such as systematic lupus erythematosus [37] and rheumatoid arthritis [38, 39], have been investigated. Remarkably, biologics also reduce

corticosteroid usage in these conditions with varying levels success [40–42]. As such, it is not unlikely that OCS use and thus OCS-related morbidities in other steroid-treated respiratory diseases (such as eosinophilic granulomatosis with polyangiitis), can also be minimized by using alternative agents such as biologics. Investigations of OCS-related morbidities in such conditions are thus warranted.

In the end, it will not be easy to thoroughly convince the general medical community of the treacherous nature of OCS. Given the many harms of OCS though, it is a worthwhile effort that deserves wider and deeper investigations irrespective of the underlying condition. The present work by Skov and colleagues[10] should not be the end of the road, but the start of a journey – one which translates research findings into clinical practice and effects changes to improve patient care. It is high time to move forward.

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