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Oral Corticosteroid Use in Asthma: A Wolf in Sheep's Clothing

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Recognition of the significant adverse effects and comorbidities associated with long-term systemic oral corticosteroid (OCS) exposure led to the development of inhaled corticosteroids (ICS) for maintenance therapy in asthma. More recently, the cumulative dose of OCS has been shown in multiple previous reports to be positively associated with certain adverse events.[1] Yet, the effectiveness of OCS in the treatment of acute asthma exacerbations is well accepted, and recent reports using large national and insurance databases document the continued high prevalence of OCS use across the United States and globally.[2,3]

Growing evidence suggests that even very brief courses of OCS cause significant negative outcomes for patients, including increased rates of sepsis, heart attack, stroke, venous thromboembolism, and fracture among patients receiving OCS for fewer than 30 days.[4] Yao et al[5] reported on the potential harms of 14 or fewer days of OCS exposure. A longitudinal study of data from the United Kingdom collected between 1984 and 2017 found that adverse outcomes of systemic corticosteroid use increased with dose, starting with a cumulative exposure of 1.0 g (equivalent to just 4 bursts of OCS per year) to <2.5 g for some outcomes and as low as 0.5 g to <1 g for others.[6] Ekstrom et al[7] observed that regular OCS use, defined as ≥5 mg/day/year, was associated with greater all-cause mortality, adjusted hazard ratio 1.34 (95% confidence interval [CI], 1.24–1.45).[7] In a recent review, Price et al[8] highlighted that "inappropriate short-term use of OCS for treatment of mild exacerbations or symptoms of asthma should be recognized as a significant healthcare problem, and more attention needs to be directed to limiting the annual cumulative dose to 1 g."

The study by Tran et al[3] published in this month's issue of the journal is a retrospective cohort study, using data from 2012 to 2017 from the IBM MarketScan Commercial, Medicare Supplemental and Coordination of Benefits, and Medicaid Multi-state Claims Data databases (Truven Health Analytics, Ann Arbor, MI), to assess the frequency and treatment patterns of OCS in patients with persistent asthma. The authors observed that nearly two-thirds of patients with persistent asthma (65.0%) received OCS during the follow-up period with nearly one-fifth (19% [n = 83,890]) classified as high OCS users

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at some point during the follow-up period. High OCS use was primarily defined as a cumulative dosage of ≥450 mg within 90 days, corresponding to ≥5 mg/day. High OCS users were more likely to be older, female, experienced exacerbations, and had severe asthma. Patients with severe asthma or a history of exacerbations during the baseline period were not only more likely to become high OCS users during the follow-up, but also filled more OCS prescriptions and consumed greater average daily dosages of OCS than patients with mild or moderate asthma. High OCS users also had a higher level of comorbidity at baseline (assessed by Charlson comorbidity index), and the prevalence of each comorbidity increased over the duration of the follow-up period; the increases were greater for patients who used OCS compared with those who did not.

The variability in prescribing patterns for OCS bursts is documented,[9] with bursts varying in length, intensity, and whether they have a taper. By categorizing exposure as a cumulative measure, Tran et al highlight that the risk of OCS-related adverse effects is independent of whether it is achieved via chronic low-dose OCS or recurrent brief OCS bursts. Importantly, Tran et al observed that most of high OCS users were based on prescription of multiple bursts of OCS to treat exacerbations. Combined with the growing understanding of the risks associated with even brief courses of OCS, this analysis supports the need to shift our focus from the number of OCS bursts to cumulative systemic steroid exposure. It should be noted that another recent report suggests that high doses of ICS should potentially be considered as harmful as low doses of ICS[10] and should be considered cumulative on top of OCS. However, Bourdin et al's[10] results do not detract from the importance of better understanding the impact of OCS bursts and minimizing their use.

Tran et al also noted that a substantial percentage of patients with mild-to-moderate asthma at baseline used OCS during the follow-up and that many of these patients eventually became high OCS users. Notably, a greater proportion of high OCS use patients were treated solely with short-acting β-agonist (SABA) inhalers during the baseline period compared with those who never used OCS.[3] Excess use of SABA inhalers has been associated with chronic OCS use in prior studies and adds to the recent epidemiological data from England and Wales, demonstrating an increasing trend of deaths from asthma. The number of deaths due to asthma has increased 25% over the last decade.[11] Based on these safety concerns and the results of the SYGMA1/2 (Symbicort Given as Needed in Mild Asthma 1 and 2) trials, the Global Initiative for Asthma (GINA) guidelines no longer recommend treatment with SABA monotherapy in any step, but now recommend either symptom-driven or daily low-dose ICS in all adults and adolescents with mild asthma.[12] The SYGMA 2 trial observed that budesonide-formoterol used as needed was noninferior to twice-daily budesonide with respect to the rate of severe asthma exacerbations, despite having approximately one-quarter of the ICS exposure.[13] Although symptom control favored twice-daily budesonide, the difference in asthma control questionnaire score between the groups was less than the minimal clinically important difference for the asthma control questionnaire (0.11) 95% CI, 0.07–0.15. Although low-dose maintenance ICS remains the most effective treatment option for patients with mild asthma, in view of our current understanding of the risks of even short courses of OCS, symptom-driven ICS combined with rapid onset long-acting β-agonist should be considered an option, particularly if there are concerns about adherence to the daily maintenance dosing. Although the impact of the recent changes in the GINA

guidelines on the use of OCS in patients with mild disease could not be assessed in the current analysis, the follow-up investigation of this issue would be beneficial to our understanding of the ongoing use of OCS in this patient population.

The limitations to using claims data are well understood, but the advantage of access to large, geographically diverse populations continues to make such databases attractive for this type of analysis. The authors acknowledge the issue that 60% of patients were excluded because they were not continuously enrolled in their insurance plan during the study period for the minimum time required. Despite this limitation, the authors identified 17,661,913 patients with evidence of asthma and 2,207,921 with persistent asthma using the Healthcare Effectiveness Data and Information Set criteria.

In a recent editorial on the use of OCS, Wallace and Waljee[14] outlined the parallels between use of corticosteroid bursts and other short-term medications, such as antibiotics and opiates, stating: “All of these treatments have well-defined indications but can cause net harm when used—as they frequently are—when evidence of benefit is low.” It takes time, effort, and resources to optimize the many facets of asthma care needed to achieve well-controlled asthma including objective confirmation of the diagnosis, identification and management of alternative/additional conditions, verifying inhaler technique and adherence, and addressing asthma triggers and modifiable risk factors including psychosocial status and the home environment. Further, when patients who may benefit from novel targeted therapies are identified, the costs of these medications may be prohibitive and/or the time/effort needed to get them approved challenging. In contrast, the prescription of a brief burst of OCS is easy and relatively inexpensive. Yet, although the direct cost of a single OCS burst may be low, oral/systemic corticosteroid exposure is associated with increased costs and health care resource use.[15] The report by Tran et al and several other recent publications call for a renewed focus on OCS use in which the cumulative exposure to corticosteroids, whether as burst or maintenance therapy, should be minimized.

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