Editorial

The Vexed Problem of Corticosteroid Toxicity in Asthma: Time for Standardized Assessment

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The systemic toxicity from inhaled corticosteroids (ICS) in adult asthma has long been considered an inevitable and justifiable consequence of attempting to obtain optimal asthma control and reduce the risk of severe exacerbations, including mortality. Although the widespread use of ICS has contributed to the marked global reduction in asthma mortality since the 1990s,[1] there is increasing awareness that "high" doses of ICS, either alone or as combination ICS/long-acting β-agonist (LABA) therapy, are likely to be excessive for most patients in whom they are prescribed.[2] This inappropriate use may lead to unnecessary and avoidable risk of systemic adverse side effects such as adrenal suppression, osteoporosis, cataracts, and diabetes. Specifically, there is evidence that 80% to 90% of the maximum achievable efficacy, including reduction in the risk of mortality, can be achieved with "low" doses of ICS, around 200 to 400 μg per day of beclomethasone dipropionate or equivalent, with higher doses leading to modest further benefit, yet being associated with significant risk of systemic adverse effects.[2]

There is also substantive risk of systemic side effects from the long-term use of oral corticosteroids in those with the most severe forms of chronic asthma, and from short-term use of oral corticosteroids for severe exacerbations of asthma, which are also associated with an acute risk due to sepsis, venous thromboembolism, and fracture.[3] Such risk has rightly been considered an inevitable and justifiable consequence of the requirement to reduce the risk of morbidity and mortality with both therapeutic approaches. However, with advances in asthma treatments, including the ICS/formoterol maintenance and reliever therapy regimen, add-on tiotropium, and monoclonal antibody therapies, there is real potential to reduce the requirement for such acute and long-term use of oral corticosteroids, and additionally for the use of high-dose ICS. This has led to the recognition that identification and quantification of corticosteroid-related systemic adverse effects, and their targeted treatment, represent an important component of the individualized "treatable traits" approach to asthma management.[4]

These issues have been investigated in the study of McDowell et al[5] published in this issue of *JACI: In Practice*. The authors report the devastating impact of systemic adverse effects of corticosteroid treatment in a cohort of patients with severe asthma attending a regional severe asthma specialist clinic in the United Kingdom. This population had a major burden from asthma in terms of poor quality of life, low lung function, frequent severe exacerbations, substantive treatment requirements, and extensive corticosteroid-related toxicity. Despite a mean age of 54 years, two-thirds were either hypertensive or receiving medications for hypertension, 4 of 5 had neuropsychiatric morbidity, about half had a body mass index >30, one-quarter had candidiasis or herpes zoster in the last year, 1 in 5 had a grade 3 infection in the previous year, and 1 in 8 had serious ocular complications. There was wide individual variability in the occurrence of these different systemic adverse effects, indicating that a comprehensive enquiry is required in clinical practice. Indeed, the case for systematically assessing and treating these complications, as part of standard asthma management, is evident from these data.

The authors investigated the utility of the Glucocorticoid Toxicity Index (GTI) in this population. The GTI is a measure that assigns relative weights to each toxicity item, thereby representing a composite measure of "total" corticosteroid toxicity. The GTI provides the opportunity to assess both the association between total corticosteroid toxicity and treatment exposure, and changes over periods of time in response to treatments.

The main finding was that the GTI score showed only modest associations with maintenance prednisolone dose (on average 10 mg per day) or the cumulative prednisolone dosage in the previous 12 months (on average 2480 mg). This suggests that measuring recent corticosteroid exposure is a poor predictor of toxicity at the individual patient level. This is perhaps not surprising when one considers the importance of lifetime exposure in toxicity risk, differences in adherence to prescribed treatments, individual variation in susceptibility to the different systemic adverse effects of corticosteroids, and the likely contribution of ICS doses to the toxicity. The importance of lifetime exposure is suggested by the observation that age was a predictor of greater corticosteroid toxicity. The importance of ICS load is suggested by the evidence that the mean daily dose of 1000 μg fluticasone propionate equivalent in this study has a similar effect on adrenal function as 5 mg daily of prednisolone, thereby representing one-third of the daily systemic corticosteroid exposure in this population.[6]

As a cross-sectional survey, it was not possible to determine whether a reduction in oral corticosteroid exposure may lead to a

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reduction in corticosteroid toxicity in this population. This is an important consideration, as recent therapeutic approaches in asthma have led to significant reductions in systemic corticosteroid exposure, and the ability to assess the effect such reductions may have in reducing the severity of systemic adverse effects from corticosteroid would have clinical utility. One such therapeutic approach is the moderate-dose ICS/formoterol maintenance and reliever regimen, which results in a reduction in short courses of oral corticosteroids, compared with high-dose ICS/LABA plus short-acting β-agonist reliever, due to the one-quarter reduction in risk of severe exacerbations, as well as a reduction in ICS load.[7] The biologics targeted against IgE, IL-4, IL-5, IL-13, and thymic stromal lymphopoietin markedly reduce long-term use of oral corticosteroids, and/or their acute use for severe exacerbations, in patients with severe asthma.[8]

From a survey of clinicians using hypothetical cases, the authors were able to estimate that the minimal clinically important difference (MCID) for the GTI may be approximately 10 points. Further work is needed in another cohort of patients and possibly with different study design, to validate this estimate of the MCID for this instrument. If this was the case, then the GTI would have utility for health care funders of expensive monoclonal antibody therapies, in their attempt to define a clinically significant reduction in corticosteroid exposure/requirement that would justify continuation of funding. Because of the wide variation in corticosteroid toxicity among patients with severe asthma and poor association between toxicity and recent corticosteroid exposure, it seems unsatisfactory to define a specific dose reduction as being clinically significant, as it is unlikely to result in a similar reduction in toxicity between individuals. The alternative approach suggested by the authors is to measure the change in GTI score, to determine if there has been a change greater than the MCID, thereby indicating a clinically significant effect.

A case could now be made for the use of the GTI in the management of adolescents and adults with severe asthma in routine clinical practice. At least, it would enable the physician to undertake a structured assessment of the systemic adverse effects of corticosteroids, and thereby facilitate their management, in accordance with the individualized treatable traits approach.[9,10] At best, it will enable an assessment of the clinical significance of the reduction in systemic corticosteroid exposure achieved with optimal asthma management with established and novel therapeutic regimens.

REFERENCES

1. Ebmeier S, Thayabaran D, Braithwaite I, Benamara C, Weatherall M, Beasley R. Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). Lancet 2017;390:935-45.
2. Beasley R, Harper J, Bird G, Maijers I, Weatherall M, Pavord ID. Inhaled corticosteroid therapy in adult asthma: time for a new therapeutic dose terminology. Am J Respir Crit Care Med 2019;199:1471-7.
3. Waljee AK, Rogers MA, Lin P, Singal AG, Stein JD, Marks RM, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ 2017;357:j1415.
4. Pavord I, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet 2018;391:350-400.
5. McDowell J, Stone JH, Zhang Y, Honeyford K, Dunn L, Logan RJ, et al. Quantification of glucocorticoid-associated morbidity in severe asthma using the Glucocorticoid Toxicity Index. J Allergy Clin Immunol Pract 2021;9:365-72.
6. Masoli M, Weatherall H, Holt S, Shirtcliffe P, Beasley R. Inhaled fluticasone propionate and adrenal effects in adult asthma: systematic review and meta-analysis. Eur Respir J 2006;28:960-7.
7. Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, et al. Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma a systematic review and meta-analysis. JAMA 2018;319:1485-96.
8. Peters MC, Wenzel SE. Intersection of biology and therapeutics: type 2 targeted therapeutics for adult asthma. Lancet 2020;395:371-83.
9. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J 2016;47:410-9.
10. Agusti A, Bafadhel M, Beasley R, Bel EH, Faner R, Gibson PG, et al. Precision medicine in airway diseases: moving to clinical practice. Eur Respir J 2017;50:1701655.