Response to Parenteral Triamcinolone in Severe Asthma: A Useful Induced Phenotype for Clinicians?

Irrespective of the specific disease entity, clinicians and patients desire information on which to build reliable prognosis. Ideally, these data will be readily available clinically, be relatively inexpensive, provide robust predictions, and have actionable implications for treatment. In this issue of the *Journal*, Denlinger and his SARP3 (Severe Asthma Research Program 3) colleagues (pp. 841–852) address the question of predicting lung function in patients with severe asthma (1). Severe asthma has been a focus of several cohort studies (2–5), which have predominantly provided characterizations (5, 6), molecular and clinical phenotypes (7, 8), and informative clustering data (4, 8–11). These studies suggest that patients with severe asthma have greater use of health care, more frequent exacerbations, and loss of lung function (5, 12, 13). However, the ultimate goal of robust, accurate, predictive phenotyping largely remains elusive. This work begins to fill that gap.

The study was based on the well-established, well-characterized SARP3 cohort (2) and was designed and executed by an outstanding group of investigators with superb expertise, experience, and insights in this field. The study was hypothesis driven rather than observational. The methodologies employed represent the standard of care and practice. Outcomes were chosen that plausibly could reflect therapeutic effects of parenteral corticosteroids and were readily available to clinicians to maximize the practical impact of the work. Subjects with lung function measurements over at least 2 years were included. On the basis of the calculated FEV_1 trajectories, four categories were developed: severe decline, mild decline, no change, or improvement.

The analyses are statistically dense, with which most clinicians are unfamiliar. These analyses were well designed and performed. Descriptive statistics were presented in a meaningful form. Statistical models were selected to match model assumptions and are examples of good statistical practices that increase the inferential value of results and conclusions.

The key finding of this study that will likely influence care of patients with severe asthma is that improvement in FEV_1 about 3 weeks after intramuscular injection of 40 mg triamcinolone appears to predict the likelihood of improvement in lung function over the ensuing 2 years, and, conversely, lack of FEV_1 improvement appears to predict a more rapid decline in lung function over that same period of time. In this regard, careful study of Figure 4A by Denlinger and colleagues, particularly the curves depicting those with severe decline versus those with improvement, will be instructive (1).

It is notable that only triamcinolone-induced change in FEV_1, and no other putative metric of steroid response (eosinophils, fractional exhaled nitric oxide, Asthma Control Questionnaire [ACQ], and others), differed among the four categorical trajectories, which argues that although those other metrics might change with systemic steroid therapy, those changes are not helpful in predicting lung function changes in the ensuing 2 years. Those subjects with severe decline used more controllers than the other groups, but the variability in use of controllers in clinical practice is such that the number of controllers is not a useful predictor of loss of lung function. The authors' observations are largely consistent with the existing literature suggesting that lung function decline in asthma is associated with greater symptom burden (ACQ) and exacerbations (14, 15). In the present study, no association of sex, baseline asthma severity, or lung function was seen with categorical lung function trajectory, but the association seen in other studies (13), and not seen in this work, is likely a consequence of the specifics of the population studied, as some of those with more severe, or more difficult to control disease were excluded (Figure E1 in the online supplement of Denlinger and colleagues) (1).

For example, 130 subjects were excluded from analysis because of initiation of biologic therapy for asthma or dropped out for other reasons. These subjects collectively had worse symptom scores, lower compliance, lower FEV_1, and more exacerbations and were at least quantitatively different from the 396 included in the analysis. These exclusions do not diminish the validity of their report but could limit generalizability of the findings.

Within the study population, 57% either improved or did not change over the 2 years of observation; only 20% of the cohort lost lung function at the rate of 2%/year or greater. This observation is a silver lining in the dark cloud of severe asthma: more than half the subjects enrolled did not suffer lung function decline or showed improvement, presumably resulting from the effective standard combination small molecule therapy provided. Although this study is the largest of its kind to address this specific question, the modeling of severe decline in FEV_1 is based on about 80 patients, and therefore there may be some uncertainty around specific quantitative details.

The physiologic details reported in this study are worthy of consideration. Changes in FEV_1, both in positive and negative directions, were twice as likely to be related to changes in FVC than to changes in FEV_1/FVC ratio. Vital capacity changes, absent changes in TLC, must relate to reciprocal changes in residual volume—air trapped in the lungs following complete exhalation. Air trapping suggests, but does not prove, an important component of small airways dysfunction. This mechanism contrasts sharply with FEV_1 variation due to changes in large airway caliber, measured by FEV_1/FVC ratio.

The observation that air trapping, rather than large airway obstruction, is related to FEV_1 changes has important diagnostic and therapeutic implications. Given the relative insensitivity of FEV_1/FVC ratio to isolated small airways dysfunction, broader use of impedance oscillometry to quantify small airway function may

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be of diagnostic utility in these patients. Alternatively, formal lung volume testing, including residual volume (RV) and RV/TLC, to measure air trapping could be informative. Therapeutically, if large airways are involved, then inhaled therapies, even with relatively large particle size distributions, should effectively target the site of disease. In contrast, targeting of small airways disease requires ultrafine inhaled particles or therapy delivered systemically.

What are the clinical implications of this authoritative work, and how might it affect practice? How might the FEV_1 response to parenteral steroids be useful in managing individual patients? Should every patient with severe asthma receive a diagnostic trial of triamcinolone parenterally? Are patients with blunted triamcinolone responses better served by biologic agents rather than standard small molecule inhaled therapy? Is there any intervention that prevents accelerated decline in lung function? Answers to those questions are less clear. However, Denlinger and colleagues (1) have described a clinically accessible method to begin to address those questions using hypothesis-driven, prospective trials that ultimately can provide data to inform advances in the management of severe asthma. ■

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