Predicting Response to Triamcinolone in Severe Asthma by Machine Learning

Solving the Enigma

A large dose of corticosteroids such as a 14-day course of oral prednisolone or an intramuscular dose of triamcinolone is often administered for the treatment of uncontrolled asthma, including that of exacerbations (1). Triamcinolone injections are sometimes used for patients with uncontrolled asthma who are not adherent to maintenance treatment with inhaled and/or oral corticosteroid therapy. Another reason for such an administration is to assess the degree of corticosteroid insensitivity in patients with asthma. Knowledge of the steroid responsiveness would be helpful in the assessment of the benefit/side effects ratio of corticosteroid therapy in managing these patients. Corticosteroid insensitivity has been recognized for a long time, particularly in patients with severe asthma, who continue to experience poorly controlled asthma despite taking high-dose corticosteroid therapy (2, 3). Up to one-fourth of patients with poorly controlled asthma had relative corticosteroid insensitivity as judged by an improvement in peak expiratory flow rates less than 15% of baseline after a course of oral prednisolone of 30 mg/d for 7–12 days (4). In the Severe Asthma Research Project (SARP) cohort, up to 80% of patients with severe asthma showed less than a 15% improvement in FEV_1 after an injection of 40 mg of triamcinolone (5). The predictors of corticosteroid response were found to be a greater bronchodilator response, a high $F_{E_{NO}}$ level greater than 20 ppb, and sputum eosinophilia greater than 2%, which is in accord with previous work (6, 7). Sputum eosinophilia has been used as a marker of steroid responsiveness in the management of patients with uncontrolled asthma, an approach that has been reported to lead to better treatment outcomes than the traditional management approach that assesses only the level of control of asthma (8).

In this issue of the *Journal* (pp. 1358–1367), further analysis of the SARP triamcinolone study using an unsupervised learning approach to identify clusters of corticosteroid responsiveness has provided more precision to asthma phenotyping that may be helpful to the clinician (9). Wu and colleagues used a multiple-kernel *k*-means clustering method that they have pioneered, with the aim of using complementary information from multiple views more effectively to identify clusters. They optimized the unsupervised clustering by assigning more weight to views that have weak but informative signals for cluster identification while allowing the use of biological prior knowledge to inform the clustering. This allowed them to overcome the challenge of integrating up to 100 different types of baseline data together with the parameters that were altered after triamcinolone intervention in only one analysis, while providing different levels of clinical importance or significance to the various parameters. Thus, 15 variables that changed after triamcinolone and 5 demographic variables (age of onset, age at baseline, sex, race, and body mass index) were chosen as carrying greater weight than other parameters.

Of the four clusters defined, the most highly responsive to triamcinolone in terms of FEV_1 and inflammatory markers (cluster 3) grouped those with the highest baseline blood and sputum eosinophilia, airflow obstruction, highest prevalence of nasal polyps, high frequency of exacerbations and oral CS use, and late onset of severe asthma, a phenotype that has been recognized as a late-onset severe eosinophilic asthma (10). However, the least responsive cluster to triamcinolone (cluster 4) consisted predominantly of young obese women with the most symptoms and highest frequency of severe exacerbations, and it also had the highest percentage of black individuals. The two other clusters (clusters 1 and 2) were the intermediate responders to triamcinolone with the best lung function, better control of asthma, and fewer patients with severe asthma. The main differentiation was a lower baseline sputum neutrophil count with greatest increase in neutrophil count in sputum after triamcinolone reported in cluster 2 compared with cluster 1.

One of the strengths of this analysis is that these four clusters were replicated and validated in a separate independent cohort by using machine learning. Support-vector machines are supervised modeling algorithms used in machine learning that analyze data used for classification and regression analysis. With this approach, this model led to the identification of the top 12 baseline variables for prediction of cluster label. Using an independent cohort distinct from the SARP cohort but whose patients were similar in many clinical characteristics, but without the use of sputum variables, this support-vector machine approach led to the identification of the same four clusters, with very good specificity but less good sensitivity. This is very encouraging because this approach could become a tool to predict responsiveness to an injection of triamcinolone based on 12 baseline variables that should be available to the clinician.

Although further validation is likely to be needed, this information could be useful to the clinician when deciding on the future management of particular patients with severe asthma in relation to whether corticosteroid therapy, particularly via the systemic route, should be altered. For example, cluster 3, being the late-onset severe eosinophilic asthma, might respond well to systemic corticosteroid therapy, although an alternative consideration would be the currently available T2-targeted biologic therapies. However, cluster 4 patients are less likely to benefit from

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maintenance oral corticosteroid therapy, and alternative therapeutic approaches might be best, although these are limited for those with no evidence of eosinophilic inflammation.

How can this precision medicine approach be further improved, particularly for those with no evidence of eosinophilic inflammation, to find new treatments? Differential analysis of the omics data characterizing each of these four clusters may provide clues to the pathways that may underlie corticosteroid responsiveness. The other approach would be to first cluster on available transcriptomic or proteomic data. Taking this approach in the U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes project) cohort, Kuo and colleagues clustered transcriptomic pathways associated with inflammatory and immune mechanisms in bronchial biopsies and epithelial cells using machine learning to obtain T2-high molecular phenotypes associated with corticosteroid insensitivity (11). With use of an inference scheme, these molecular clusters could be predicted by using the inflammatory biomarkers of sputum eosinophilia and F_{ENO} levels, together with oral corticosteroid use, with good sensitivity and specificity. The work of Wu and colleagues emphasizes the need for the unsupervised approach and the application of machine learning techniques that can provide useful tools for the clinician while improving understanding of corticosteroid insensitivity in severe asthma. ■

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Kian Fan Chung, M.D., D.Sc.
National Heart & Lung Institute
Imperial College London
London, United Kingdom

ORCID ID: 0000-0001-7101-1426 (K.F.C.).

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Predicting Outcomes of High-Flow Nasal Cannula for Acute Respiratory Distress Syndrome

An Index that ROX

Noninvasive forms of ventilatory assistance, including noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC), have emerged as important modalities to treat acute respiratory failure during the last 2 decades. NIV use grew rapidly during the decade from 2000 through 2010 (1), when NIV as a proportion of initial ventilator starts in the United States rose as high as 40% (2), and HFNC use has risen during the present decade. According to current guidelines (3), NIV is considered the ventilatory modality of first choice to treat acute hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease, as well as cardiogenic pulmonary edema. NIV has not been so successful in patients with *de novo* hypoxemic respiratory failure resulting from pneumonia/acute respiratory distress syndrome (ARDS), with intubation rates as high as 50–66% (2, 4) and with particularly high mortality rates in these NIV failures (5). The European Respiratory Society/American Thoracic Society guideline on NIV made no recommendation on whether NIV should be used or not in *de novo* hypoxemic respiratory failure because of the high failure rates and the conflicting evidence.

In contrast, HFNC has been gaining traction as a therapy for *de novo* hypoxemic respiratory failure. This is partly because HFNC is an effective oxygenator related to its ability to keep up with the high inspiratory flows of dyspneic, hypoxemic

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