

Predicting response to triamcinolone in severe asthma by machine learning: solving the Enigma

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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 either 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 recognised 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 a quarter of patients with poorly-controlled asthma had relative corticosteroid insensitivity as judged by an improvement in peak expiratory flow rates of <15% of baseline after a course of oral prednisolone of 30 mg per day 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 FEV₁ after an injection of 40 mg of triamcinolone (5). The predictors of corticosteroid response were found to be a greater bronchodilator response, a high level of exhaled nitric oxide (FeNO) of >20ppb and a sputum eosinophilia of >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 compared to the traditional management approach that only assesses the level of control of asthma (8).

In the study by Wu and colleagues, 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 more effectively complementary information from multiple views 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 following 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, gender, race and body mass index) were chosen as carrying greater weight than other parameters.

Of the 4 clusters defined, the most highly responsive to triamcinolone in terms of FEV₁ and inflammatory markers (Cluster 3) grouped those with the highest baseline blood and sputum eosinophilia, airflow obstruction and with highest prevalence of nasal polyps, high frequency of exacerbations and oral CS use and late onset of severe asthma, a phenotype that has been recognised as a late onset severe eosinophilic asthma (10). On the other hand, 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 also had the highest percentage of Black/African Americans. The two other clusters (Clusters 1 and 2) were the intermediate responders to triamcinolone with the best lung function, better control of asthma and with less number of severe asthma patients. The main differentiation was a lower baseline sputum neutrophil with a greatest increase in neutrophil count in sputum following triamcinolone reported in Cluster 2 compared to Cluster 1.

One of the strengths of this analysis is that these 4 clusters were replicated and validated in a separate independent cohort by using machine learning. Support-vector machines are supervised modelling algorithms used in machine learning that analyse data used for classification and regression analysis. By using 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 4 clusters, with a 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.

While further validation is likely to be needed, this information could be useful to the clinician to decide 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 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 finding new treatments? Differential analysis of the omics data characterising each of these 4 clusters may provide clues to the pathways that may be underlying corticosteroid responsiveness. The other approach would be to first cluster on available transcriptomic or proteomic data. Taking this approach in the U-BIOPRED 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). Using an inference scheme, these molecular clusters could be predicted by using the inflammatory biomarkers of sputum eosinophilia and FeNO levels, along with oral corticosteroid use, with a good sensitivity and specificity.

The work of Wu and colleagues emphasises the need for the unsupervised approach and the application of machine learning techniques that can provide useful tools for the clinician while at the same time improving our understanding of corticosteroid insensitivity in severe asthma.

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