Asthma: From Diagnosis to Endotype to Treatment

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Aaron SD, *et al.*; Canadian Respiratory Research Network. Reevaluation of Diagnosis in Adults with Physician-diagnosed Asthma. *JAMA* (1)

Reviewed by Akhilesh Jha

Asthma diagnosis is based on classical symptoms together with variable airflow limitation (2). Accuracy is essential to ensure appropriate long-term medication; misdiagnosis can lead to unnecessary drug-related adverse effects and medical expenditure.

Aaron and colleagues (1) assessed whether a diagnosis of current asthma could be ruled out in a randomly selected population of "asthmatic" adults and evaluated the safety of weaning medication. A prospective 4-year multicenter study across Canada using random digit dialing was performed, identifying adults with an asthma diagnosis within 5 years. Exclusion criteria included use of long-term oral corticosteroids, inability to perform spirometry, contraindication to bronchial challenge, and a smoking history greater than 10 pack-years. The primary outcome assessed the proportion of participants in whom current asthma could be ruled out, using post-bronchodilator reversibility and methacholine challenge. Repeat testing was performed after stopping all asthma medications. Secondary outcomes assessed the proportion of participants without asthma after 12 months and the appropriateness of initial diagnostic evaluation.

Of 16,931 participants, 1,026 were eligible, 701 were enrolled, and 613 completed the study. Current asthma was ruled out in 33.1% of participants (95% confidence interval [CI], 29.4–36.8%) and continued to be ruled out in 29.5% (95% CI, 25.9–33.1%) at 1 year. Those with asthma ruled out were less likely to have had objective assessment of airflow limitation compared with those with asthma (absolute difference, 11.8%; 95% CI, 2.1–21.5%; $P = 0.02$).

The authors postulate that a failure to validate a finding of current asthma was due to incorrect initial diagnosis or spontaneous regression. The latter represented approximately 11.8% of participants, similar to other studies (3, 4). This, coupled with recurrence of airway hyperresponsiveness in 22 participants, highlights the variability of asthma pathophysiology. The findings have significant implications for medication use and economic impact. The study design suggests similarly economically developed countries might see comparable results, and the follow-up period permitted adequate study of a full seasonal cycle.

Caveats to consider include the following: 18.2% of screened individuals declined to answer eligibility questions and one-third of eligible individuals did not enroll, which may have led to selection bias; more than one-quarter of excluded individuals were diagnosed with asthma more than 5 years earlier, with the potential for different endophenotypes; and those receiving long-term oral corticosteroids were excluded, which may have resulted in recruitment of participants with less severe asthma. Methacholine challenge has high sensitivity and negative predictive value but reduced specificity for asthma diagnosis (5), which may have led to overrecruitment of other individuals, such as those with allergic rhinitis.

Future research might explore the reasons behind an incorrect diagnosis of asthma—is there reluctance to reevaluate once empirical treatment has commenced? The study emphasizes the importance of an objective assessment of airflow limitation in diagnosing asthma. ■

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Lefaudeux D, *et al.*; U-BIOPRED Study Group. U-BIOPRED Clinical Adult Asthma Clusters Linked to a Subset of Sputum Omics. *J Allergy Clin Immunol* (6)

Reviewed by Martin D. Knolle

Advances in asthma phenotyping (7–9) have enabled more effective and targeted asthma treatments. However, a mechanistic understanding of these inflammatory endotypes remains limited. To this end, the U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) consortium has applied "multiomics" approaches to well-characterized asthma patient cohorts (10).

Lefaudeux and colleagues (6) identified patient clusters from a subset of U-BIOPRED subjects and examined inflammatory pathways using sputum proteomics and transcriptomics. Cluster analysis based on eight clinical characteristics identified four clusters. Cluster 1 consisted of patients with well-controlled asthma, whereas the others contained patients with less well-controlled asthma. Cluster 2 patients had increased body mass index, poor lung function, positive smoking status, and high eosinophils. Cluster 3 patients tended to have worse lung function, were nonsmokers and less obese, and received higher levels of oral corticosteroids. Cluster 4 was characterized by obese females with frequent exacerbations. Of note, these clusters mirrored those identified in the SARP (Severe Asthma Research Program) (9) and Leicester (7) cohorts.

Sputum proteins were analyzed, allowing detection of up to 1,129 separate analytes ($n = 86$). However, only 10 appeared differentially expressed, preventing detailed pathway analysis. Among these, IL-16 (a lymphocyte chemokine) was elevated in clusters 2 and 3 compared with cluster 1, and cluster 2 had higher levels of granulocyte–macrophage colony–stimulating factor and the chemokine CXCL7 compared with cluster 1. Compared with cluster 3, cluster 2 patients had more LYN kinase, which has been implicated in the regulation of T-helper cell type 2 (Th2) responses.

RNA extracted from induced sputum ($n = 94$) was more revealing and showed 345 differentially expressed transcripts. Compared with cluster 1, cluster 2 exhibited increased hematopoietic cell lineage gene expression, and cluster 3 showed increased expression of genes linked to antigen processing. Comparing cluster 3 with cluster 2 revealed differential expression of genes involved in the actin pathway. Comparing cluster 4 with cluster 3 showed differential expression of cell cycle and growth factor pathways as well as immune responses, especially the interferon pathway.

The authors address limitations including overrepresentation of one recruiting center in cluster 2 and clustering around omics instead of clinical variables. A further limitation relates to bulk RNA sequencing, which prevents identification of which cell types are responsible for the differential RNA signatures.

These data highlight potential new treatment targets and biomarkers. Further articles from U-BIOPRED, published in this and other journals (11, 12), include data sets from epithelial brushing and biopsies (13) and blood (14). An integrated analysis across different tissue compartments may highlight consistent signals and potentially identify lung-specific treatment targets. ■

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Nair P, *et al.*; ZONDA Trial Investigators. Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma. *N Engl J Med* (15)

Reviewed by Katharine M. Lodge

Patients with treatment-refractory asthma account for a large proportion of asthma health care costs and suffer substantial

glucocorticoid-induced comorbidities (16, 17). Type 2 immune response–driven eosinophilia is associated with severe and uncontrolled asthma (18). IL-5, a proinflammatory cytokine produced by Th2 cells, promotes eosinophil recruitment and survival, and represents an important therapeutic target (19). Monoclonal antibodies against IL-5 (mepolizumab and reslizumab) or the IL-5 receptor (benralizumab) reduce exacerbation frequency in severe eosinophilic asthma, with potential for lung function and quality-of-life improvement (20–22).

In this trial, designed and analyzed by AstraZeneca, Nair and colleagues assess the effect of subcutaneous benralizumab versus placebo on oral glucocorticoid use (15). Three hundred and sixty-nine patients with severe asthma and peripheral blood eosinophilia, treated with daily oral glucocorticoids, were enrolled. After 4 weeks of oral glucocorticoid dose reduction, 220 patients were randomized to 30 mg of benralizumab every 4 or 8 weeks, or placebo. During the intervention, the glucocorticoid dose was reduced every 4 weeks, provided asthma control was maintained. At Week 24, the achieved glucocorticoid dose was maintained, with no further benralizumab doses.

Nair and colleagues demonstrated that, comparing median oral glucocorticoid dose at baseline with Week 28, both benralizumab treatment groups achieved 75% dose reductions, whereas the placebo group achieved 25% reduction ($P < 0.001$). The odds of ceasing oral glucocorticoids were 5.23 (95% CI, 1.92–14.21; $P < 0.001$) and 4.19 (95% CI, 1.58–11.12; $P = 0.002$) in the 4- and 8-week benralizumab groups, respectively, compared with placebo. Both benralizumab regimens resulted in a reduction in blood eosinophil count, a longer time to first exacerbation, and a lower overall exacerbation rate, but only the 8-week benralizumab group showed improvement in ACQ-6/AQLQ(S)+12 (Asthma Control Questionnaire-6/standardized Asthma Quality of Life Questionnaire valid for patients 12 yr of age and older) scores, compared with placebo. Neither prebronchodilation FEV_1 nor total asthma symptom score was significantly different between groups.

Limitations include extrapolation of annual exacerbation rates, which may yield inaccurate estimates. Future studies should take into account identification of different clinical endotypes (6), given a predominantly white middle-aged overweight/obese female population and exclusion of patients with life-threatening asthma in this trial.

There were two deaths in the benralizumab 8-week group and none in the placebo group. Previous trials have shown a good safety profile, but longer-term studies are warranted to ensure safety in these patients.

Benralizumab has the potential to enable oral glucocorticoid reduction in patients with severe eosinophilic asthma, which should produce patient benefit, although cost–benefit analysis would be informative given a median glucocorticoid dose of only 10 mg at baseline in all groups. Although mepolizumab has shown similar results (23), benralizumab, with its more rapid, marked, and prolonged induction of eosinopenia (24), may have a role as an adjunctive treatment in acute exacerbations (25). The effectiveness of anti–IL-5 therapy will rely on patient selection, and accessible and reliable phenotyping. ■

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