

Asthma at the 2016 American Thoracic Society International Conference

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Year in Review

The Year in Review in asthma was presented by Dr. Akshay Sood from the University of New Mexico, featuring several high profile articles published over the last year. Of particular interest, favorable phase 3 data were presented supporting the use of reslizumab, a humanized monoclonal antibody against IL5, in the treatment of moderate-to-severe asthma in patients with blood eosinophil counts greater than 400 cells per microliter (1). Patients receiving reslizumab had fewer asthma exacerbations over 1 year than patients receiving placebo in two duplicate studies published as a single manuscript. Reslizumab was approved earlier this year in the United States for the treatment of severe asthma.

A phase 2a trial demonstrating the potential benefit of a novel inhaled GATA3-specific DNzyme, SB010, was initially unveiled during the 2015 ATS International Conference and discussed during the 2016 Year in Review (2). GATA3 is a key transcription factor in promoting the Th2 inflammation seen in allergic endotypes of asthma. SB010 attenuated the late asthmatic response, as measured by FEV₁ after allergen challenge (2).

With increasing recognition of the heterogeneity of both asthma and COPD, the concept of the asthma-COPD overlap syndrome (ACOS) has emerged and was prominently discussed at the international conference (3). Along this vein, treatments for asthma and COPD are converging. The Year in Review covered a manuscript in *Lancet Respiratory Medicine* that added to previous data that suggest that tiotropium is as effective as salmeterol as step-up therapy in asthma (4).

The close connection between asthma and obesity was also discussed. A translational study by Ahangari *et al.*

used murine experiments and a case-control human study to show a connection between asthma and obesity through the Chitinase 3-like-1 (Chi3l1) pathway (5). Chi3l1 was upregulated by both a high-fat diet and Th2 inflammation using an aeroallergen challenge. Serum Chi3l1 levels correlated with ongoing asthma symptoms and lower lung function in obese asthma patients as well as with the prevalence of truncal obesity. Therapeutic targeting of this Chi3l1 pathway may lead to improvements in both asthma and obesity. Another study published in the *Annals of the American Thoracic Society* showed that weight loss of at least 10% was needed to make a clinically significant improvement in obese, uncontrolled asthma patients (6).

New Concepts in Asthma Biology

“New Concepts in Asthma Biology” were presented as a scientific symposium to highlight recent mechanistic insights in asthma. Dr. John Fahy from University of California San Francisco spoke about immune mechanisms in asthma. He pointed out that type 2 inflammation has long been considered the dominant paradigm in asthma, with epithelial responses to allergens producing IL-25, IL-33, and TSLP, activating effector cells such as CD4⁺ T cells. Eotaxin-3 generation by epithelium leads to eosinophil recruitment. Elucidation of these pathways has led to the development of multiple biologic medications against type 2 inflammation targets. While current guidelines reflect the view that worsening asthma is due to increased type 2 inflammation; it has become clear in recent years that type 2 inflammation is absent in some patients. Certain individuals have a poor steroid response, and there is heterogeneity

in asthma traits (7). Endotyping, such as that done by the Severe Asthma Research Program (SARP) has resulted in the identification of asthma clusters and recognition of asthma as a heterogeneous disease (8).

Dr. Bart Lambrecht (Ghent University) spoke about the potential of farm dust and endotoxin to protect against asthma, discussing animal models that support this hypothesis. House dust mite allergen is complex and largely composed of mite droppings, exposing patients to the entire house dust mite microbiome. Dendritic cells are necessary for Th2 responses to HDM (9,10). Chronic low dose LPS exposure or farm dust exposure in mice prevents house dust mite-induced asthma by reducing dendritic cell-activating cytokine exposure by epithelial cells (11).

Dr. Jin-Ah Park of the Harvard School of Public Health delineated her work focusing on “unjammed” and cell shape of epithelial cells in the asthmatic airways. Cells that are unjammed have more fluid-like flow collectively; asthmatic epithelial cells are more unjammed than non-asthmatic cells, which may have implications in understanding the mechanics of asthma (12,13).

Dr. Max Seibold from National Jewish Health described methods for using epithelial cell culture models for translational genetic studies in asthma. Progenitor cells from the airway can be cultured on air-liquid interface, followed by exposure. Investigators may then perform RNAseq, methylation, and cellular readouts.

Dr. Julian Solway of the University of Chicago discussed a newly-discovered class of small molecules that may prevent airway remodeling. These molecules inhibit *in vitro* human airway smooth muscle myosin and actin accumulation, myofibroblast transformation and *in vitro* bronchoconstriction.

Other asthma updates

Asthma is always a highly discussed topic at the annual international conference. This year, we heard from investigators looking at childhood factors that may predict lung function in adulthood. A new study published in the *New England Journal of Medicine (NEJM)* was discussed by Dr. Jeffrey Drazen, Editor-in-Chief of *NEJM*, looking at the use of lung-function growth curves in children with asthma (14). Individuals with impairment of lung function in childhood and males were more likely to develop abnormal lung growth curves. In addition, children with reduced lung function and those with persistent asthma symptoms were at higher risk of developing a fixed airflow obstruction.

Brehm *et al.* published a study in *AJRCCM* evaluating the impact of stress on children with asthma (15). It was found that high levels of stress resulted in a reduction of bronchodilator response in children with asthma. A genetic association was discovered between reductions in bronchodilator response and the ADCYAP1R1 single-nucleotide polymorphism, which in turn is associated with reduced gene expression of the beta2-adrenergic receptor (ADRB2) in CD4⁺ lymphocytes.

Evaluation of people with asthma in the Copenhagen General Population Study showed that only asthma patients who are current and former smokers carried an increased risk of lung cancer, ischemic heart disease, ischemic stroke, and all-cause mortality (16).

Conclusions

While not a comprehensive accounting of the depth and breadth of advances in asthma presented at ATS 2016, we present here highlights of interest in asthma therapeutics, epidemiology, and mechanism.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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