

Editorial



Staphylococcus aureus Enterotoxin-Specific IgE Sensitization in Severe Eosinophilic Asthma Phenotype

Kian Fan Chung

Experimental Studies Unit, National Heart & Lung Institute, Imperial College London, London, United Kingdom

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Correspondence to

Kian Fan Chung, MD, DSc, FRCP

Experimental Studies Unit, National Heart & Lung Institute, Imperial College London, Dovehouse Street, London SW3 6LY, United Kingdom.

Tel: +44-207-5947954

Email: f.chung@imperial.ac.uk

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ORCID iDs

Kian Fan Chung

<https://orcid.org/0000-0001-7101-1426>

Disclosure

KFC has received honoraria for participating in Advisory Board meetings of GSK, AZ, Roche, Novartis, Merck, BI and Shionogi regarding treatments for asthma, chronic obstructive pulmonary disease and chronic cough and has also been remunerated for speaking engagements.

► See the article “Staphylococcal Enterotoxin-Specific IgE Sensitization: A Potential Predictor of Fixed Airflow Obstruction in Elderly Asthma” in volume 15 on page 160.

Staphylococcus aureus enterotoxin-specific immunoglobulin E (SE-sIgE) sensitization, defined by a high level of SE-sIgE in serum, has been associated with chronic rhinosinusitis and asthma. In addition, patients with SE-sIgE sensitization have been found to have an increased risk of developing asthma and, in particular, more severe asthma.^{1,2} The link with severe asthma had been reinforced by the association of SE-sIgE sensitization with the subsequent risk of severe asthma and of experiencing severe exacerbations.^{1,3} One of the first reports of SE-sIgE sensitization from Korea described elderly patients with more severe eosinophilic asthma and chronic rhinosinusitis compared to those who were not sensitized, indicating an association that was independent of other co-variables.⁴

In this issue of *Allergy, Asthma & Immunology Research*, Won et al.⁵ from a 2-year follow-up prospective study of a Korean cohort links the severe eosinophilic asthma phenotype associated with SE-sIgE sensitization to fixed airflow obstruction, raising the possibility that the SE-sIgE sensitization might lead directly to airway wall remodelling that could underlie the fixed airflow obstruction. The authors report that airflow obstruction was associated with current smoking and SE-sIgE sensitization at baseline, but after a 2-year follow-up, baseline SE-sIgE sensitization was related to fixed airflow obstruction.⁵ This is the first study that directly links the occurrence of airflow obstruction to SE-sIgE sensitization, thus providing further characterization of the SE-sIgE-sensitized severe eosinophilic asthma as a distinct phenotype of asthma.

It is now time to determine the molecular pathways underlying this new phenotype of SE-sIgE-sensitized severe eosinophilic asthma, particularly as to whether there is any distinction from the SE-sIgE-nonsensitized phenotype(s). There is already some understanding of how *S. aureus* can orchestrate the inflammation of SE-sIgE-sensitized eosinophilic asthma.⁶ *S. aureus* enterotoxin can act as a T cell superantigen by cross-linking T cell receptors with major histocompatibility complex class II molecules, leading to polyclonal activation of T cells, including T helper type 2 (Th2) cells. *S. aureus* can also secrete staphylococcal protein A that can act as B cell superantigen to degranulate mast cells by binding to immunoglobulin E on mast cells. In addition, *S. aureus* itself can induce the release of the alarmins, thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33,⁷ to recruit innate lymphoid cell (ILC)-2 and Th2 cells to release IL-4, IL-5, and IL-13, which form the backbone of type 2 inflammation.

IL-5 released by ILC2 and Th2 cells activate eosinophils, which interact with epithelial cells to release major basic protein, DNA, and galectin 10 to form Charcot-Leyden crystals.^{8,9}

Airway wall remodelling that would account for the chronic airflow obstruction described by Won et al.⁵ could occur through the effects of TSLP and IL-33, which can induce the epithelial-mesenchymal transition in airway epithelial cells¹⁰ and activate human lung fibroblasts to release collagen and fibronectin, and promote the proliferation of airway smooth muscle cells.^{11,14} Furthermore, eosinophils recruited and activated by IL-5 are the major source of transforming growth factor (TGF)- β , which promotes subepithelial and peribronchial fibrosis and epithelial-mesenchymal transition.^{5,17}

That type 2 inflammation may be involved in the airway wall remodelling is supported by the effect of the anti-IL-5 antibody, mepolizumab, that reduced eosinophil numbers together with TGF- β 1+ eosinophils on the biopsied samples, and sub-basement membrane thickening and tenascin immunoreactivity of the airways in severe eosinophilic asthma.¹⁸ Benralizumab, an anti-IL5R α antibody, reduced airway smooth muscle mass,¹⁹ while omalizumab, an anti-IgE antibody, reduced the thickness of the basement membrane and fibronectin in the airways.^{20,21}

It remains to be seen whether the patients with severe eosinophilic asthma and SE-sIgE sensitization have worse airway wall remodelling than those without sensitization to common inhalant allergens. In a similar vein, it would be interesting to note whether the various anti-T2 biologics will be more effective in these patients with SE-sIgE sensitization. Thus, in future studies of the effectiveness of anti-T2 biologics, sIgE level might be useful as a measure of SE-sIgE sensitization. The next step would be to carry out studies that will confirm the molecular pathways that drive this particular phenotype of SE-sIgE-sensitized severe eosinophilic asthma and determine the best available therapeutic approaches for this more clearly defined phenotype of eosinophilic asthma.

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