Dupilumab eliminated airway hyperresponsiveness in a 12-year-old boy with severe atopic asthma.

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To the Editor

Asthma is characterized by recurrent airflow limitation with airway hyperresponsiveness (AHR) due to chronic inflammation.[1] Various types of cells, cytokines, chemokines and mediators are involved in the pathogenesis of asthma.[2] The mechanisms underlying AHR have attracted considerable attention in recent decades. AHR reportedly did not develop in several asthma models, e.g., mice lacking certain cell types—such as mast cells or eosinophils—or not expressing certain genes, such as for type 2 cytokines or FcεRI. However, T2 inflammation itself is also impaired in some of these genetically-engineered mice. In addition, these models do not completely recapitulate human asthma. Therefore, the specific molecular pathway(s) regulating human AHR remains unknown.[3]

In humans, mechanisms of AHR have been partially identified in *ex vivo* models using lung, trachea, or bronchi,[4,5] but the *in vivo* mechanisms remain unclear. Recently, biologics have been approved for steroid-refractory asthma and provide strong evidence of roles for certain molecular pathways in the pathogenesis of asthma.[6,7] For example, an anti-IgE monoclonal antibody (omalizumab) did not alleviate AHR even after the symptoms were significantly reduced.[8] However, no studies have investigated AHR after treatment with anti-IL-5, anti-IL-5R, or anti-IL-4Rα antibodies.

Here, we describe our experience using dupilumab, an anti-IL-4Rα antibody, to treat a 12-year-old boy with refractory atopic asthma.

An 8-year-old boy who had suffered from bronchial asthma since he was 3 years old was admitted to a tertiary-care hospital, Yawatahama City General Hospital, due to a severe asthma exacerbation in May 2016. Following discharge, he visited the allergy unit of the hospital. He was treated with an oral leukotriene receptor antagonist, a β2 agonist and slow-release theophylline (SRT), as well as with inhaled high-dose corticosteroid and a long-acting β2 agonist. However, his asthma symptoms did not fully resolve. In Spring of 2019, he developed pertussis, with repeated chronic coughing and wheezing episodes, and his respiratory function subsequently worsened. He became unable to exercise normally at school due to exercise-induced bronchoconstriction. In September 2019, he was subcutaneously injected with 600 mg of dupilumab, followed by 300 mg every 2 weeks.

AHR, respiratory function, serum total and specific IgE levels, and peripheral eosinophil counts were evaluated before and at 4 and 6 months after starting dupilumab. AHR was assessed by the standard acetylcholine inhalation test (AcIT) in accordance with the guideline of the Japanese Society of Allergology. That is, he inhaled acetylcholine chloride solutions diluted with saline from low to high concentrations (0, 39, 78, 156, 313, 625, 1250, 2500, 5000, 10000, 20000 μg/mL) for two minutes, followed by a pulmonary function test; this was repeated until there was a 20% decline in his forced expiratory volume in one second (FEV_1). The

last concentration of inhaled solution was defined as the threshold of the AcIT, and the cut-off concentration between asthma patients and normal subjects was 10000 μg/ml. All medications except SRT were stopped 48 hours before the AcIT, and SRT was stopped 18 hours before the AcIT.

His subjective symptoms gradually improved during the first 4 months of dupilumab treatment. Surprisingly, his AHR induced by acetylcholine inhalation completely disappeared at that point, and that status continued for two months. SRT and other oral and inhaled bronchodilators were discontinued 7 months after dupilumab was started. Since then, he has experienced no asthma symptoms, such as cough, wheeze or dyspnea, even after daily exercise, although his respiratory function has not yet fully recovered.

Table 1 shows the following data that were determined before and at 4 and 6 months after starting dupilumab: respiratory function data, serum theophylline level, AcIT threshold concentration, serum total IgE level,*Dermatophagoides pteronyssinus* -specific IgE level, and peripheral eosinophil count. After starting dupilumab, the AcIT threshold concentration increased dramatically, from 313 to over 20000 μg/mL, and the total and specific IgE levels decreased, but the peripheral eosinophil count decreased only by half.

We administered dupilumab, an anti-IL-4Rα antibody, to a 12-year-old boy with severe atopic asthma, and his asthmatic symptoms disappeared, with drastic improvement of AHR. His total and specific IgE levels decreased markedly, but his peripheral eosinophil count decreased only by half. On the other hand, an earlier study found that omalizumab, an anti-IgE biologic, improved the clinical symptoms and decreased the peripheral eosinophil count, but AHR remained unchanged.[8] Taken together, those findings imply that blockade of IL-4 and IL-13 is involved in the causation of AHR.

IL-4 and IL-13, but not IL-5 or IL-17A, were reported to induce hyperresponsiveness to histamine by enhancing expression of histamine H_1 receptor and cysteinyl leukotriene receptor 1 in isolated human small airway tissue.[5] On the other hand, dupilumab treatment abrogated those effects of IL-4 and IL-13.[5] The clinical course of our case is in good agreement with those earlier findings.

This report has a limitation, since it reports a single case. Nevertheless, we believe that this is the first study showing that dupilumab therapy directly improved AHR in an atopic asthma patient. In the present patient, the peripheral eosinophil count after dupilumab treatment decreased only by half. That is presumably because IL-5, the critical cytokine for eosinophil development, activation and survival, was not inhibited by dupilumab. The dupilumab treatment also reduced his asthma symptoms and improved his quality of life, although his respiratory function, especially the maximal mid-expiratory flow, was not normalized, presumably due to the presence of airway remodeling. We expect that his respiratory function will improve later, and further observation and assessment are thus needed.

In conclusion, IL-4R signaling is likely involved in development of AHR in atopic asthma patients.

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CONFLICT OF INTEREST

The authors declare that they have no relevant conflicts of interest.

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