Case report

Three-dimensional bronchial tree visualization in exercise-induced severe asthma following tezepelumab treatment

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Airway hyperresponsiveness, a key feature of asthma, is associated with exercise-induced asthma. Tezepelumab was reported to reduce airway hyperresponsiveness. Tezepelumab was confirmed through 3-dimensional bronchial tree visualization to be effective for exercise-induced asthma, reducing the need for a short-acting β2 agonist. (J Allergy Clin Immunol Global 2025;4:100398.)

Key words: *Airway hyperresponsiveness, asthma, exercise-induced asthma, thymic stromal lymphopoietin, tezepelumab*

Abbreviations used
ACT: Asthma Control Test
AHR: Airway hyperresponsiveness
CT: Computed tomography
EIB: Exercise-induced bronchoconstriction
FENO: Fractional exhaled nitric oxide
ICS: Inhaled corticosteroid
LABA: Long-acting β_2-agonist
LAMA: Long-acting muscarinic antagonist
SABA: Short-acting β2-agonist
TSLP: Thymic stromal lymphopoietin

Airway hyperresponsiveness (AHR) is a key clinical feature of asthma; it is defined as increased sensitivity and reactivity of the airways in response to various stimuli and contributing to airflow obstruction and symptoms such as breathlessness and wheezing.[1] Bronchial asthma is often induced by exercise and associated with AHR.[2] Acute airway narrowing occurring as a result of exercise is known as exercise-induced bronchoconstriction (EIB).[3] Tezepelumab, a human mAb that inhibits thymic stromal lymphopoietin (TSLP), is approved for severe asthma treatment. However, its effects on exercise-induced severe asthma remain unclear. Patients with exercise-induced asthma frequently require a short-acting β2-agonist (SABA). Although SABAs are the usual treatment for EIB, their effect is short-lived.

We report the case of a patient with severe exercise-induced asthma who responded well to tezepelumab, resulting in reduced need for a SABA. The effectiveness of tezepelumab was confirmed through 3-dimensional bronchial tree visualization following treatment. The patient, a 16-year-old male nonsmoker who engaged in rigorous basketball training daily in high school, was diagnosed with asthma 10 years ago. He frequently (8-10 times per day) relied on rescue therapy with budesonide (1280-1600 μg per day) and formoterol (36-45 μg per day)—a combination equivalent to a high-dose inhaled corticosteroid (ICS) and long-acting β_2-agonist (LABA). He used this treatment while playing basketball but did not follow a regular inhalation regimen. He experienced nocturnal coughing due to uncontrolled asthma and exertional dyspnea during physical activity, likely related to exercise-induced asthma. He did not experience any exacerbation of asthma after taking aspirin. He had multiple exacerbations of asthma requiring systemic corticosteroid treatment twice a year. Because of his poorly controlled severe asthma, he was referred to our hospital for further evaluation.

Chest computed tomography (CT) revealed mucus plugs and pulmonary infiltration in the patient's right upper lobe, suggesting potential eosinophilic inflammation (Fig 1). His mucus score was 4, based on the involvement of right B1 × 2, right B3, and left B1 + 2 (Fig 1).[4] His paranasal sinus CT findings were normal, and his Asthma Control Test (ACT) score was 9. His total serum IgE level was 1130 IU/mL (normal range 0-148 IU/mL). His Multiple Allergen Simultaneous Test results, classified into 7 levels (0-6) based on specific IgE concentration, indicated *Dermatophagoides farina*, house dust, cat, dog, timothy grass, orchard grass, mugwort, cedar, hinoki cypress, Japanese white birch, latex, sesame, wheat, peanuts, and peaches as classes 2, 4, 5, 5, 2, 2, 1, 6, 3, 3, 1, 1, 1, 2, and 1, respectively. His inflammatory markers included an elevated peripheral blood eosinophil level (537 cells/μL) and elevated fractional exhaled nitric oxide (FENO) level (118 ppb). Pulmonary function (% predicted) testing revealed an FEV_1 value of 2980 mL (80.1%) and a ratio of FEV_1 value to forced vital capacity of 0.729 (Table I). On referral, his treatment was revised to a high-dose inhaled ICS, LABA, and long-acting muscarinic antagonist (LAMA) (fluticasone, 200 μg; umeclidinium, 62.5 μg; and vilanterol, 25 μg) and leukotriene receptor antagonist (montelukast, 10 mg). After 3 months of high-dose ICS, LABA, and LAMA administration, his peripheral blood eosinophil count decreased to 162 cells/μL, his ACT score improved from 9 to 13, and his FEV_1 ($\%FEV_1$) value increased

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Received for publication August 2, 2024; revised October 4, 2024; accepted for publication October 6, 2024.

Available online December 24, 2024.

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2772-8293

https://doi.org/10.1016/j.jacig.2024.100398

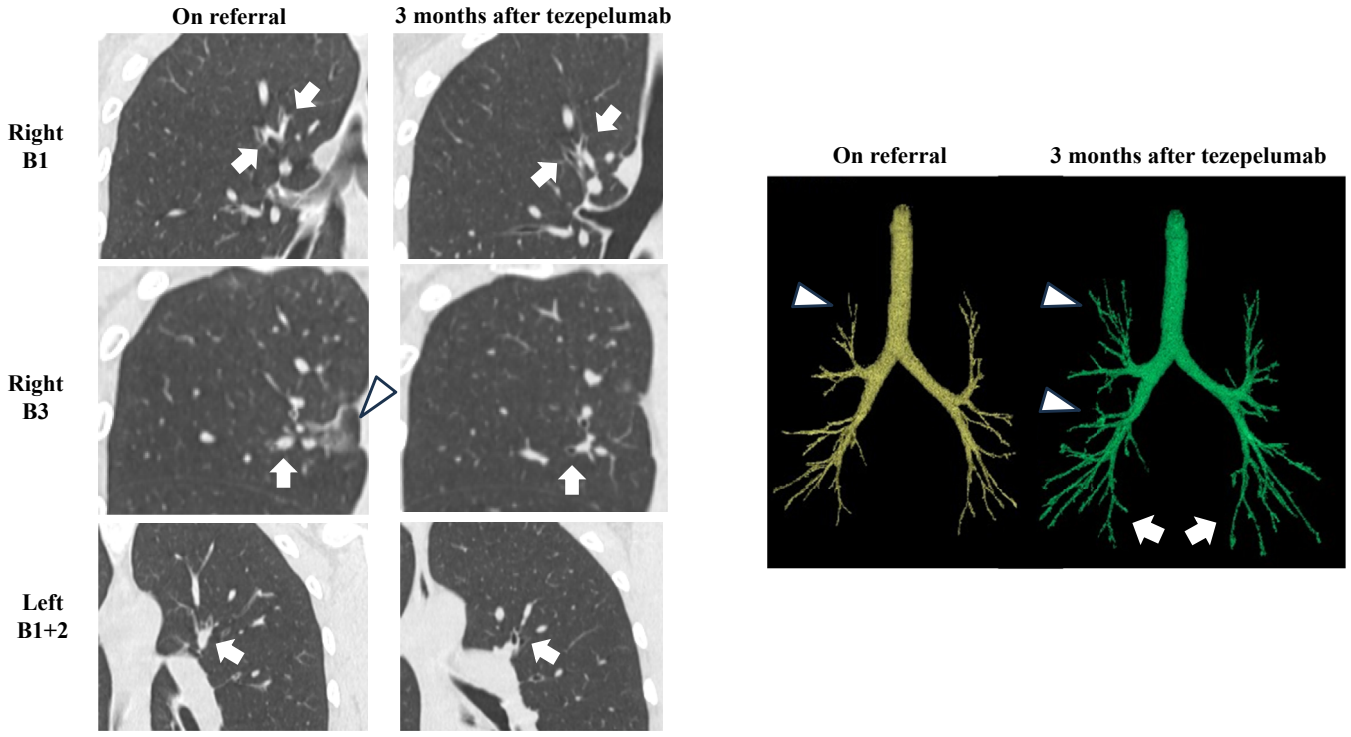

FIG 1. Chest CT images on referral and 3 months after tezepelumab treatment. Arrows indicate mucus plugs, and the arrowhead indicates areas of infiltration. Three-dimensional bronchial tree visualizations on referral and 3 months after tezepelumab treatment are also shown. The arrowhead indicates a bronchial tree defect, and arrows further indicate dilatation of the peripheral bronchial trees.

TABLE I. Time course of treatment with tezepelumab

Indicator	December 2023 (on referral)	March 2024 (after a high-dose ICS/LABA/LAMA for 3 mo before tezepelumab)	May 2024 (after tezepelumab for 2 mo)
VC (mL)	4090	4140	4030
%VC (% predicted)	98.5	99.2	96.4
FEV_1 (mL)	2980	3620	3770
$\%FEV_1$ (% predicted)	80.1	96.7	100.0
FEV_1/FVC (%)	.729	.874	.935
FEF_{25-75} (L/s)	2.28	3.79	4.57
FEF_{25-75} (% predicted)	49.3	81.3	97.2
FENO level (ppb)	118	10	13
Peripheral eosinophil count (/μL)	537	162	63
IgE (U/L)	1130	983	840
ACT	9	13	22

FEF_{25-75}, Forced mid-expiratory flow at 25% to 75% of forced vital capacity; *FVC*, forced vital capacity; *VC*, vital capacity.

from 2980 (80.1%) to 3620 mL (96.7%). After high-dose ICS, LABA, and LAMA administration, his nocturnal coughing related to uncontrolled asthma was slightly improved; however, his exercise-induced dyspnea persisted. A SABA was still required 4 to 6 times per day. Therefore, subcutaneous tezepelumab (210 mg every 4 weeks) was administered after 3 months of referral. After 2 months of tezepelumab administration, his peripheral blood eosinophil count decreased to 63/μL, his ACT score improved to 22, and his FEV_1 ($\%FEV_1$) value increased to 3770 mL (100.0%) (Table I). The patient was able to play basketball without requiring a SABA. Three months after tezepelumab treatment, his mucus plugs and pulmonary infiltration had resolved (Fig 1). His mucus score improved from 4 to 0 (Fig 1).

Volume rendering images (Ziostation, Ziosoft Inc, Japan) of the bronchial tree revealed a peripheral bronchial tree defect in the right upper lobe and total swallowing of the peripheral bronchial tree. After 3 months, the defect improved and the peripheral bronchial tree was completely dilated (Fig 1).

Here we have reported the successful treatment of severe exercise-induced asthma with tezepelumab. TSLP, produced by airway epithelial cells after tissue injury, is induced by mechanical stimuli and inflammatory agents. TSLP is crucial in the activation of mast cells, eosinophils, and group 2 innate lymphoid cells, inducing the production of type 2 cytokines, including IL-4, IL-5, and IL-13. In the NAVIGATOR study, tezepelumab treatment resulted in fewer exacerbations and better lung function, asthma control, and health-related quality of life.[5] In the CASCADE study, tezepelumab reduced airway eosinophil counts in bronchoscopic biopsy samples.[6] Therefore, tezepelumab blocks type 2 inflammation upstream. In this report, the patient's peripheral eosinophil count, FENO level, and IgE level were elevated, indicating severe type 2–high inflammation.

Before referral, the patient was frequently treated with rescue budesonide and formoterol (8-10 times per day), equivalent to a high-dose ICS and LABA. Because of poor asthma control, the patient was switched to high-dose ICS, LABA, and LAMA

therapy. Although the patient's nocturnal cough improved and exertional dyspnea, (including exercise-induced dyspnea) improved slightly, he still required a SABA 4 to 6 times per day. Therefore, tezepelumab was introduced, which improved his exercise-induced dyspnea. The patient's SABA use promptly decreased, and within 2 months, he was able to engage in rigorous basketball training without the need for a SABA.

Tezepelumab reduces AHR in response to methacholine or mannitol.[7] Exercise-induced asthma is often associated with AHR,[2] as exercise induces respiratory water loss and mucosal dehydration, leading to increased airway surface liquid osmolarity. This mechanism is similar to that of mannitol.[2] EIB occurs when the airways narrow during physical activity. EIB is characterized by postexercise airway obstruction that results in symptoms such as coughing, dyspnea, and wheezing. Diagnostic tools such as eucapnic voluntary hyperventilation or inhaled mannitol are commonly used as indirect bronchoprovocation tests to diagnose EIB. However, in this case, a challenge test was not performed because of the risk of exacerbation of asthma. Small airway involvement is associated with airflow obstruction, airway hypersensitivity, and more severe diseases.[8] Furthermore, FENO levels are associated with the severity of EIB.[3] The patient's forced mid-expiratory flow at 25% to 75% of forced vital capacity, a pulmonary function test used to assess small airway disease, was also improved in this case. Treatment with tezepelumab reduced the patient's FENO levels and improved his forced mid-expiratory flow at 25% to 75% of forced vital capacity, suggesting that the drug reduced AHR associated with exercise-induced asthma.

Airway eosinophils and mucus largely contribute to airway obstruction associated with IL-4/IL-13 pathway upregulation.[9] In a randomized controlled trial in patients with moderate-to-severe uncontrolled asthma, tezepelumab reduced mucus score, with the reduction in mucus score correlating with improvements in lung function and reductions in blood eosinophil count.[10]

In mucus plug pathogenesis, IL-5–induced airway eosinophilia and IL-13–induced mucus hypersecretion play pivotal roles in mucoid impaction development.[6] Notably, after treatment with tezepelumab, the patient's levels of these 3 biomarkers decreased. Therefore, tezepelumab inhibits TSLP, blocking epithelial cell–derived proinflammatory cytokines implicated in multiple downstream processes, including the IL-5, IL-13, and group 2 innate lymphoid cell pathways.

Although the patient's mucus plugs and infiltrations were initially detected on chest CT, they resolved following treatment with tezepelumab. Three-dimensional bronchial tree visualization initially revealed a bronchial tree defect in the right upper lobe and total swallowing of the bronchial tree. After 3 months of treatment with tezepelumab, the patient's defect improved and his peripheral bronchial tree was fully dilated. The improved 3-dimensional bronchial tree visualization correlated with both enhanced pulmonary function test results and improved mucus plugging. These results suggest the potential role of 3-dimensional bronchial tree visualization in assessing functional response after biologic treatments in patients with severe asthma. However, further studies are needed to investigate the general and specific roles of tezepelumab in severe exercise-induced asthma treatment.

Informed consent: Appropriate written informed consent was obtained for the publication of this case report and accompanying images.

Data sharing statement: Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

We thank Mayu Isota, Kentaro Suzuki, and Ryosuke Kataoka for their assistance with preparation of this article. We would like to thank Editage (www.editage.jp) for the English language editing.

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