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Case Report

Dramatic Response to Tezepelumab as an Initial Biologic Agent for Refractory Asthma Associated with Type 2 and Non-type 2 Traits

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A 74-year-old Japanese woman presented with a 45-year history of refractory asthma. She had been treated with inhaled corticosteroids, a long-acting β2-agonist, and a long-acting muscarinic antagonist for 6 months. She also had a repeated viral infection. Her condition had been characterized as a refractory asthma associated with type 2 and non-type 2 traits. We began treatment with tezepelumab. The control of the patient's asthma symptoms and quality of life improved greatly within 1 month (changes in eosinophil count from 748 to 96 /μL, in FeNO from 32 to 17 ppb, in the Asthma Quality of Life Questionnaire score from 3.59 to 6.68, and in the Asthma Control Test score from 13 to 23). Tezepelumab was effective as an initial biologic agent for a patient with refractory asthma associated with type 2 and non-type 2 traits.

Key words: tezepelumab, biologic agent, eosinophilic, non-type 2, severe asthma

The human monoclonal antibody tezepelumab is useful for treating individuals with type 2 asthma and the non-eosinophilic/non-type 2 asthma phenotypes [1]. A study of tezepelumab versus placebo described significant improvements in the tezepelumab-treated patients' forced expiratory volume in 1 second (FEV1), Asthma Control Questionnaire-6 score, Asthma Quality of Life Questionnaire score, and asthma symptom diary as well as substantial decreases in the frequency of exacerbations [2]. The greatest improvements in the tezepelumab treatment group were observed in the patients with a baseline count of ≥ 300 cells/μL and FeNO > 25 bbp [2]. Here, we present the case of an adult patient who achieved a dramatic response to initial treatment with tezepelumab for refractory asthma associated with type 2 and non-type 2 traits.

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Case Report

A 74-year-old Japanese woman with refractory asthma had been treated with inhaled corticosteroids, a long-acting β2-agonist, a long-acting muscarinic antagonist (indacaterol acetate 150 μg, glycopyrronium bromide 50 μg, mometasone furoate 160 μg), and antiallergic drug therapy (montelukast sodium 10 mg/day and bilastine 20 mg/day) for 6 months. She had a 45-year history of refractory asthma, allergic rhinitis, and repeated viral infection. She did not have a history of smoking. Although she had been treated with oral corticosteroids (prednisolone 7.5 mg/day) for 2 weeks, the treatment was ineffective. She was indicated for treatment with a biological agent because of prolonged stable and exertional dyspnea.

In physical examinations, the patient's peripheral arterial blood oxygen saturation was 97% on room air,

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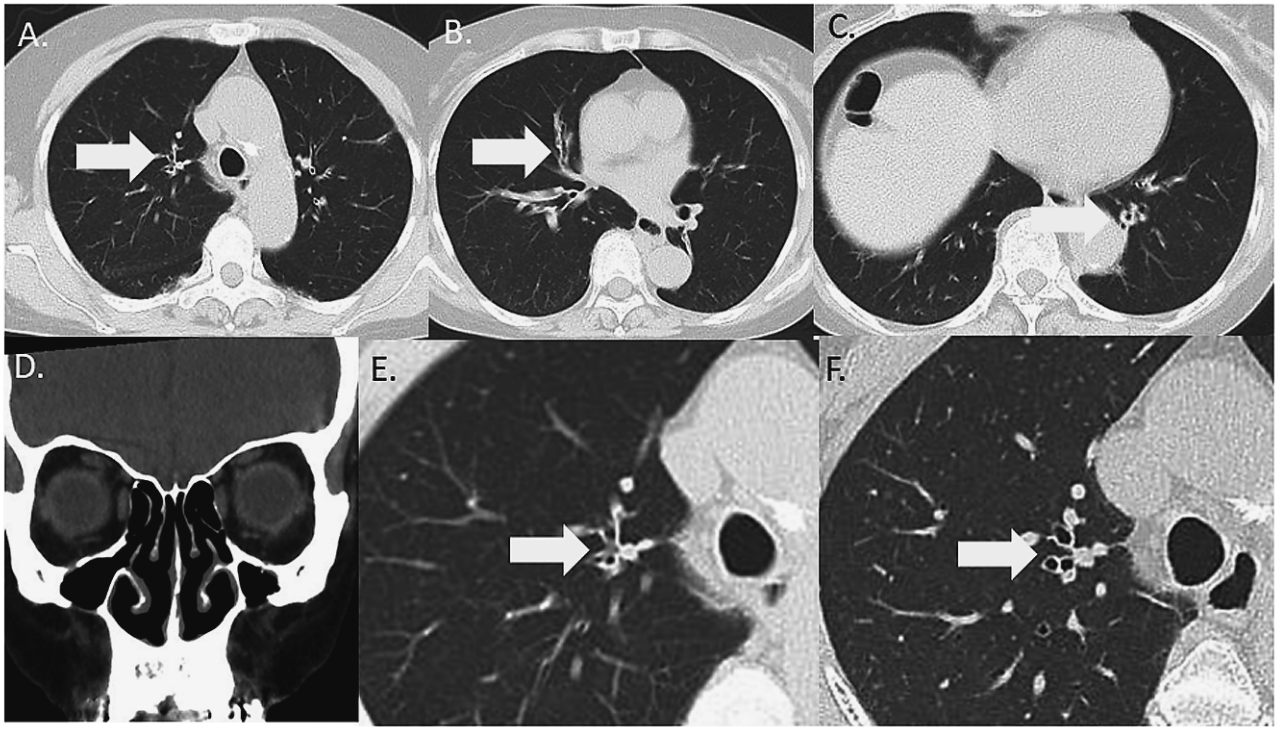

Fig. 1 CT scans showing diffuse bronchial wall thickening, postinflammatory changes, and slight sinusitis. **A–C**: Lung window. **D**: Paranasal sinus window. CT scans of the lung window showing diffuse bronchial wall thickening before the start of the patient's tezepelumab (**E**) and at 1 month after the start of the tezepelumab treatment (**F**).

but chest auscultation revealed diffuse expiratory wheezing. A computed tomography (CT) scan revealed diffuse bronchial wall thickening, post-inflammatory changes, and slight sinusitis (Fig. 1A-D). The CT scan did not show any nasal polyps. Laboratory findings indicated an increase in the eosinophil count. The levels of lymphocytes, monocytes, and neutrophils were relatively normal. The immunoglobulin (Ig)E level was 68 IU/mL. Antigen-specific IgE levels (VIEW39) and all other data were normal (Table 1).

Autoimmune diseases and vasculitis were not indicated based on the following laboratory test results: negative for antinuclear antibody, rheumatoid factor, perinuclear anti-neutrophil cytoplasmic antibody, and cytoplasmic anti-neutrophil cytoplasmic antibody. The FEV1 was 840 mL (%FEV1; 52.8%) and the vital capacity (VC) was 1, 240 mL (%VC; 56.8%) in the pulmonary function test (Table 2). The fractional exhaled nitric oxide (FeNO) level was 32 ppb, and sputum eosinophil levels were < 3%. Before the induction of tezepelumab treatment, we referred the patient to the general hospital for medical cooperation in an emergency. The patient underwent a pulmonary function test, FeNO test, chest CT, and sinus CT in the hospital. We started the tezepelumab treatment as an outpatient therapy and followed up weekly for 1 month.

Table 1 Laboratory findings

Laboratory findings	
WBC ($10^3/\mu$L)	4.4
Nt (%)	49
Eosi (%)	17
Baso (%)	0
Mono (%)	7
Lymph (%)	27
C-reactive protein (mg/dL)	0.16
IgE (IU/mL)	68

WBC, white blood cells; Nt, neutrophilic granulocytes; Eosi, eosinophilic granulocytes; Baso, basophilic granulocytes; Mono, monophilic granulocytes; Lymph, lymphocytes; IgE, Immunoglobulin E.

The patient's eosinophil count decreased from 748 to 61 μL after 1 week and to 96 /μL after 4 weeks of tezepelumab treatment. Her FeNO level decreased

Table 2 Pulmonary function test and ACT, AQLQ score findings

	Before tezepelumab	After 1 month	After 4 months
FEV1 (mL)	840	1,540	1,490
%FEV1 (%)	52.8	95.0	93.1
VC (mL)	1,240	1,830	1,880
%VC (%)	56.8	76.0	85.0
ACT score	13	23	24
AQLQ score	3.59	6.68	6.37
FeNO (ppb)	32	17	14

FEV1, Forced expiratory volume in 1.0 s; VC, Vital capacity; ACT, Asthma control test; AQLQ, Asthma Quality of Life Questionnaire.
FeNO, Fractional concentration of Nitric Oxide.
Improvement of symptoms or pulmonary function was observed 1 and 4 months after tezepelumab.

from 32 to 17 ppb after 4 weeks of tezepelumab treatment. Moreover, according to a CT scan 1 month after the completion of the 4-week tezepelumab treatment, bronchial wall thickening decreased (Fig. 1E, F). Dramatic improvement in the patient's symptoms and pulmonary function were observed at 1 and 4 months after the start of treatment. Her Asthma Quality of Life Questionnaire improved from 3.59 at baseline to 6.68, and her Asthma Control Test score increased from 13 to 23 after 1 month treatment (Table 2).

Discussion

Tezepelumab treatment has resulted in low exacerbation rates in Japanese patients; in the NOZOMI study, tezepelumab improved lung function and controlled asthma [1]. It has been estimated that 5-10% of individuals with asthma worldwide have severe asthma [3]. An estimated 7-10% of Japanese individuals with asthma have severe asthma, and 2.5% have severe uncontrolled asthma [4]. In our case, tezepelumab immediately improved her asthma symptoms and pulmonary function after initial treatment for eosinophilic-predominant asthma (eosinophil count 748 /μL and FeNO 32 ppb). In patients with eosinophilic asthma, baseline blood levels of eosinophils ($\geq$300 /μL) and FeNO ($\geq$25 ppb) predict the response to tezepelumab [2]. Thus, initial treatment with tezepelumab is recommended for eosinophilic-predominant asthma.

The majority of the aforementioned randomized controlled trials on biologics in refractory asthma patients have demonstrated a significant response to placebo with reductions in exacerbations, improved lung function, and improved patient-reported outcomes [5]. Claims of superiority of one biologic over another have been made based on indirect treatment comparisons using meta-regression and matching-adjusted strategies; this is due to the lack of a head-to-head comparison between these biologics [6-8]. Although anti-interleukin-5 biologics may have been useful as an initial treatment for our patient, we selected a thymic stromal lymphopoietin (TSLP)-targeted agent because of its effects on type 2 and non-eosinophilic/non-type 2 asthma traits and low pulmonary function. Our patient's predominant type was eosinophilic asthma (eosinophil count 748) but her sputum eosinophil levels were $<$3%, with slightly high FeNO (32 ppb) and normal IgE (68 IU/mL) levels. She had also experienced a repeated viral infection.

In the clinical identification of non-type 2 asthma, sputum cytology can be used to categorize airway inflammation as eosinophilic, neutrophilic, mixed granulocytic, or paucigranulocytic [9]. Type 2 asthma with $>$3% sputum eosinophil levels generally encompasses the eosinophilic category. Our patient's sputum eosinophil levels were $<$3%, and her IgE value was almost normal. The predominant characteristics of her case were not only eosinophilic traits but also non-type 2 traits. The role of TSLP in type 2 immune responses in asthma has been studied extensively, and a recent

study revealed additional roles for this cytokine in infectious diseases, cancer, fat metabolism, and inflammatory diseases [10].

The present case report is the first published description of a dramatic response to initial treatment with tezepelumab in a Japanese patient with refractory asthma associated with type 2 and non-type 2 traits. A prospective large-scale study comparing tezepelumab and similar agents in Japanese individuals with asthma would be of interest.

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