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CASE REPORT

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Efficacy of tezepelumab against uncontrolled severe non-type 2 asthma refractory to bronchial thermoplasty, benralizumab, dupilumab and mepolizumab

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Abstract

Severe asthma affects approximately 5%–10% of patients with asthma. Herein, we describe a case of non-type 2 asthma that progressively worsened over the years. An 80-year-old woman was diagnosed with asthma 11 years back. She experienced repeated exacerbations requiring treatment with systemic corticosteroid despite therapy with medications including high-dose inhaled corticosteroids/long-acting beta-agonists plus long-acting muscarinic antagonist. The patient presented with non-eosinophilic asthma. Therefore, the patient was initially treated with bronchial thermoplasty, which was effective for 1 year only. Treatment with bronchial thermoplasty, benralizumab, dupilumab, and mepolizumab was ineffective. The fourth treatment, which included tezepelumab, was initiated. The patient's symptoms and quality of life improved significantly. This is the first case of a patient who did not respond to sequential bronchial thermoplasty, benralizumab, dupilumab, and mepolizumab but who presented with good clinical response to tezepelumab. Therefore, tezepelumab may be useful for patients with non-type 2 asthma.

KEYWORDS
benralizumab, bronchial thermoplasty, dupilumab, mepolizumab, tezepelumab

INTRODUCTION

Severe asthma is defined as asthma that remains uncontrolled despite treatment with high-dose inhaled corticosteroids (ICS) and long-acting β2-agonists.[1] Bronchial thermoplasty (BT) can control severe asthma by reducing the amount of smooth muscle in the bronchial wall.[2,3] Furthermore, several clinical studies have shown that biological treatments, such as humanized monoclonal antibody against IL-5 receptor α (benralizumab), humanized antibody against IL-4Rα (dupilumab), and humanized monoclonal antibody against interleukin-5 (IL-5) (mepolizumab) are effective in severe asthma.[1] Tezepelumab is a human IgG2 monoclonal antibody that inhibits thymic stromal lymphopoietin (TSLP).[4] Tezepelumab can be effective in patients with poorly controlled moderate to severe asthma regardless of phenotype (type 2 or non-type 2). Herein, we present a case of non-type 2 severe asthma, which developed during tezepelumab treatment, after failed treatment with BT, benralizumab, dupilumab and mepolizumab.

CASE REPORT

An 80-year-old female patient who is a never-smoker was diagnosed with bronchial asthma at 69 years old. She did not present with comorbid eosinophilic chronic rhinosinusitis. She was sensitivity to aspirin. She presented with persistent cough and shortness of breath. Further, she was on high-dose ICS/long-acting β2-agonists (200 μg/25 μg fluticasone furoate/vilanterol), tiotropium bromide hydrate 2.5 μg and leukotriene receptor antagonists. However, she was at risk for asthma exacerbations requiring treatment with

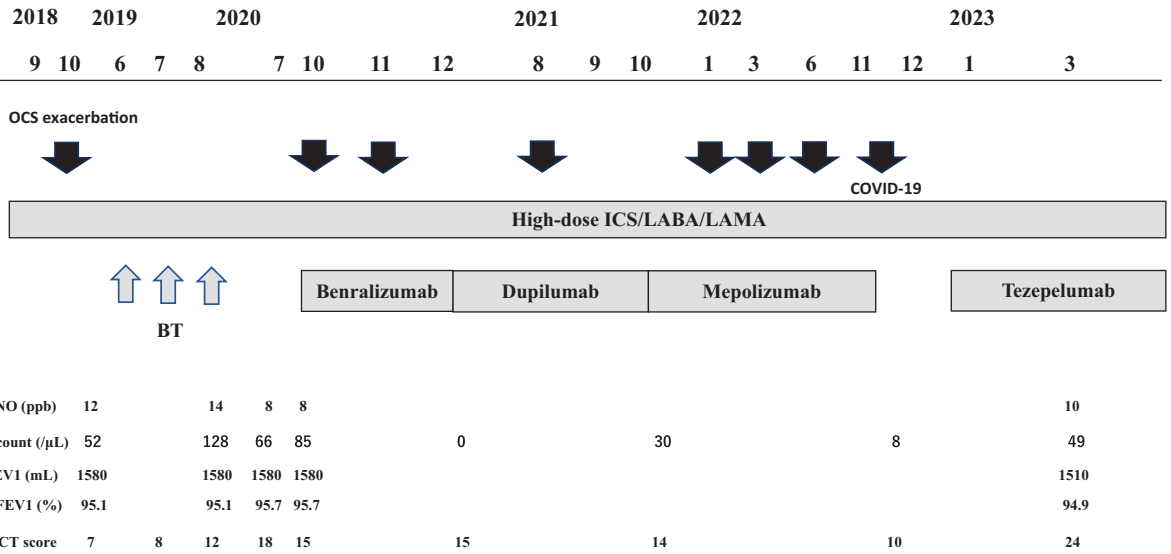

FIGURE 1 Clinical course of the case study. During the clinical course, the patient had low FeNO and peripheral eosinophil count, indicating non-Th2 asthma. With bronchial thermoplasty (BT), benralizumab, dupilumab and mepolizumab treatment, exacerbations were occurred, and symptom improvement was poor. The ACT score improved with treatment with tezepelumab.

systemic corticosteroid (2–3 times per year). The total serum immunoglobulin E (IgE) level was 14.1 (0–148) IU/mL. The inflammatory markers indicated normal peripheral blood eosinophil count (82/μL) and fractional exhaled nitric oxide (FeNO, 14 ppb). In terms of pulmonary function (% predicted), the patient's forced expiratory volume in 1 s (FEV1) was 1580 mL (95.1%), and the FEV1/forced vital capacity was 82.3%. Computed tomography scan revealed bronchial wall thickening. Figure 1 shows the clinical course of the patients. The Asthma Control Test (ACT) score was 7. Due to non-type 2 asthma, BT was selected (Alair™; Boston Scientific, Marborough, MA, the USA). She had three scheduled sessions based on the standard protocol. After treatment with BT, her symptom stabilized without exacerbation, and the ACT score improved from 8 to 18. After 1 year and 2 months, the patient's asthma symptoms exacerbated. In September 2020, treatment with benralizumab was started (30 mg administered subcutaneously every 4 weeks for 3 doses and then once every 8 weeks). However, her symptoms did not improve (ACT score of 15), and systemic corticosteroid was used to treat asthma exacerbation for the treatment of benralizumab (2 times/3 months). In December 2020, treatment with dupilumab was started at 600 mg administered subcutaneously and then at 300 mg every 2 weeks. Her symptoms did not improve (ACT score of 14), and systemic corticosteroid was used to treat the asthma exacerbation for the treatment of dupilumab (1 time/10 months). In October 2021, treatment with mepolizumab (100 mg administered subcutaneously every 4 weeks) was started. Her symptoms did not improve (ACT score of 10), and systemic corticosteroid was used to treat asthma exacerbation for the treatment of dupilumab (3 times/1 year and 1 month). In November, her condition worsened due to COVID-19 infection. She was hospitalized for 12 days, and dexamethasone and remdesivir were administered. In December 2022, she received treatment with tezepelumab (210 mg administered subcutaneously every 4 weeks). After treatment with tezepelumab, persistent cough and shortness of breath improved immediately, and her ACT score improved from 10 to 24 despite the absence of FEV1 improvement. Systemic steroids have not been used since treatment with tezepelumab 9 months ago.

DISCUSSION

Eosinophils play an important role in the pathogenesis of asthma.[1] Type 2 inflammatory cascade inhibitors such as mepolizumab, benralizumab, and dupilumab are often effective in the treatment of Th2-severe asthma.[1] In this study, the eosinophil count and FeNO level of the patient were constantly low during the clinical course. Therefore, these biologics do not suppress IL-5-regulated eosinophilic inflammation and IL-13-regulated FeNO. Recently, macrolide and BT have been used as therapy for uncontrolled severe non-type 2 asthma.[3] According to a previous study, administration of macrolide have reduced exacerbations.[3] However, our patient was allergic to macrolide. Although BT had sometime been shown to improve management of severe non-type 2 asthma, the therapeutic effect did not continue in our patient. TSLP is produced by airway epithelial cells after the inhalation of allergens, virus, and cold air.[4]

In the NAVIGATOR study, tezepelumab was associated with a reduced rate of annual asthma exacerbation in the subgroup with blood eosinophil counts <150 cells/μL and low FeNO <25 ppb.[4] Among specialist-treated patients with severe asthma, the number of asthma trigger was positively and significantly associated with uncontrolled disease.[5] In 1434 (51%) of 2793 patients, the most frequent triggers were

weather or air changes, viral infections, seasonal and perennial allergies, and exercise. The trigger number of this patient was seven (weather changes, cold air, viral infections, exercise, dust, smoke, strong smells and cleaning/housework). Tezepelumab significantly improved the ACT score, regardless of lung function improvement. The lack of lung function improvement influence airway remodelling with a long asthma history. However, the mechanism of efficacy in patients with non-type 2 phenotypes are still unclear, and it should be further evaluated. In our case, tezepelumab was effective in controlling the disease. Tezepelumab treatment might be a novel therapeutic approach in patients with uncontrolled severe non-type 2 asthma despite BT and previous biologic treatments with benralizumab, dupilumab and mepolizumab. Nevertheless, further studies evaluating the efficacy and safety of tezepelumab against uncontrolled severe non-type 2 asthma should be performed.

AUTHOR CONTRIBUTIONS

Y.K. wrote the manuscript. All authors contributed to editing the manuscript and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article.Further enquiries can be directed to the corresponding author.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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