Successful Treatment of Eosinophilic Chronic Rhinosinusitis and Secretary Otitis Media Associated with Refractory Asthma by TSLP Receptor Monoclonal Antibody

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Abstract

Eosinophilic chronic rhinosinusitis (ECRS) is a type 2 inflammatory disease that frequently co-occurs with bronchial asthma. The current treatment options for ECRS include endoscopic sinus surgery and oral corticosteroid therapy (OCS). However, recurrence after surgery is common and OCS therapy may cause side effects. We present the case of a 74-year-old woman with severe asthma, ECRS, and secretary otitis media with possible eosinophilic otitis media who experienced significant improvement in both conditions after treatment with tezepelumab, an anti-thymic stromal lymphopoietin antibody. Tezepelumab treatment led to a reduction in blood and tissue eosinophil counts and improved the nasal polyp and computed tomography scores, tympanic and hearing test results, and asthma symptoms, without the use of OCSs. Our findings suggest that tezepelumab may be a promising option for those patients with asthma, ECRS, and secretary otitis media, who do not respond well to conventional treatment because upstream of the type 2 inflammation pathway is suppressed. Further to this case report, future studies are required to confirm the long-term efficacy and safety of tezepelumab in the treatment of ECRS and secretary otitis media due to type 2 inflammation.

Categories: Internal Medicine, Otolaryngology, Allergy/Immunology
Keywords: type 2 inflammation, tezepelumab, anti-thymic stromal lymphopoietin, chronic rhinosinusitis without nasal polyp, eosinophilic chronic rhinosinusitis

Introduction

Eosinophilic chronic rhinosinusitis (ECRS) is a type 2 inflammatory disease characterized by chronic inflammation of the upper airways, intractable nasal polyps with eosinophilic infiltration, and olfactory disturbances [1]. Endoscopic sinus surgery (ESS) and oral corticosteroid (OCS) therapy are the primary treatment modalities for ECRS; however, recurrence after ESS is common, and oral steroid therapy can cause multiple side effects. Eosinophilic otitis media (EOM) is a type 2 inflammatory disease that presents as a refractory condition characterized by yellow colloidal middle ear effusions and numerous eosinophils [2]. These diseases frequently co-occur with bronchial asthma.

Recently, several biological agents, including anti-interleukin (IL)-4 receptor-alpha, anti-immunoglobulin E (IgE), anti-IL-5, anti-IL-5 receptor-alpha, and anti-thymic stromal lymphopoietin (TSLP) antibodies, have been approved for the treatment of severe type 2 asthma. Among these, anti-TSLP antibodies (tezepelumab) are effective in suppressing the upstream factors that cause type 2 inflammation, with potentially beneficial effects in cases that respond poorly to conventional antibody drugs [3]. However, only anti-IL-4 receptor-alpha antibodies are currently approved for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in Japan.

Herein, we present a case of a patient with severe asthma who showed improvement in concomitant ECRS and secretary otitis media after treatment with tezepelumab.

Case Presentation

Informed consent was obtained from the patient for the publication of this report.

A 74-year-old woman with a history of adult-onset asthma, rhinitis, and hearing loss, and no history of smoking, was diagnosed with asthma at 32 years of age and prescribed a fixed-dose combination of inhaled corticosteroids (ICS)/long-acting β2-agonist (LABA). However, she experienced repeated exacerbations during winter and was hospitalized several times for asthma attacks. At the age of 53 years, she developed nasal obstruction and rhinorrhea, and at the age of 60 years, she underwent ESS at another hospital. She experienced hearing loss at 72 years of age and was diagnosed with ECRS and secretary otitis media.
patient was treated for asthma by a respiratory physician at another hospital and frequently used OCSs. She had a history of a compression fracture. The patient’s Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) score for ECRS diagnosis was 17. The eosinophil count in a sample of an ethmoid sinus polyp obtained during surgery at another hospital was 397/HPF (Fig. 1A).

FIGURE 1: Pathological findings
(A) initial surgery (B) 3 months after treatment. Compared to the histological findings at the time of the initial surgery, the histological findings at 4 months after tezepelumab treatment show a marked decrease in eosinophils in the tissues.

Eight months after the initial visit to our Ear, Nose, and Throat Department, the patient complained of breathlessness, and treatment for asthma was initiated at the Department of Allergy and Rheumatology of our hospital. Her medication was changed to ICS/long-acting muscarinic antagonist (LAMA)/LABA, and then to high-dose ICS/LAMA/LABA; however, no improvement was observed.

Nasal endoscopy revealed bilateral nasal polyps extending from the middle nasal meatus to the inferior margin of the middle nasal concha, with a total polyp score (TPS) of 6 (Fig. 2A and 2B). Computed tomography (CT) imaging of the sinuses revealed soft tissue density lesions in all bilateral sinuses, with a Lund-Mackay CT score (LMS) of 24 (Fig. 2C).

FIGURE 2: Nasal findings prior to tezepelumab treatment
(A, B) Intranasal findings. Nasal endoscopy at the time of initiation shows right side (A) and left side (B) nasal polyps extending from the middle nasal meatus to the inferior margin of the middle nasal concha (yellow arrow). (C) Computed tomography images prior to tezepelumab treatment. CT scan of the sinuses at initiation showed soft tissue density lesions in all bilateral sinuses.

The proportion of blood eosinophils was 15.8%, blood eosinophil count was 1220, and total IgE levels were 179 IU/mL. The total subjective nasal and Sino-Nasal Outcome Test (SNOT)-22 score was 59. The T&T olfactometer threshold test indicated a threshold of 5.8. Swelling of the bilateral posterior superior quadrant of the tympanic membrane and middle ear effusions were observed (Fig. 3A). In addition, pure tone audiometry revealed a conductive hearing loss of 48.8 dB in the right ear and 41.3 dB in the left ear (Fig. 3B). CT imaging demonstrated soft tissue shadows in the bilateral tympanic cavities and mastoid air cells (Fig. 3C).
FIGURE 3: Ear findings prior to tezepelumab treatment
(A) Otoscopic finding prior to tezepelumab treatment. Swelling of the bilateral posterior superior quadrant of the tympanic membrane and middle ear effusions were observed. (B) Pure tone audiometry prior to tezepelumab treatment. Pure tone audiometry revealed a conductive hearing loss. (C) Temporal bone CT scan shows soft tissue shadows in the tympanic cavity before treatment (yellow arrow).

Asthma examination results showed a fractional exhaled nitric oxide (FeNO) level of 33 ppb, forced expiratory volume in 1 second (FEV1) of 0.92, %FEV1 of 57.5%, Asthma Control Test (ACT) score of 17, and Asthma Control Questionnaire 5 (ACQ5) score of 1.4.

Therefore, 3 months after the patient’s first visit to the Internal Medicine Department, subcutaneous monthly doses of tezepelumab (210 mg) were initiated.

Four months after tezepelumab initiation, the patient showed significant improvement. The total SNOT-22 score decreased to 39, TPS reduced to 3 (Fig. 4A, B), and sinus CT findings improved, with an LMS of 11 (Fig. 4C).

FIGURE 4: Nasal findings after 4 months of treatment
(A, B) Intranasal findings. (A) Right side polyps remain in the olfactory fissure on the right (white arrow). (B) On the left the polyps have disappeared. (C) Paranasal sinus computed tomography images. All sinus shadows improved by 4 months after treatment.

The tympanic effusion resolved (Fig. 5A). The proportion of blood eosinophils was 3.8%, the blood eosinophil count was 230, and total IgE levels were 141 IU/mL. The olfactory T&T test threshold improved to 3, and the pure tone audiometric airway threshold improved to 30.0 dB on the right and 12.5 dB on the left (Fig. 5B), and soft tissue shadows in the bilateral tympanic cavities were lightened on temporal bone CT (Fig. 5C).
There was mild improvement of bronchial asthma, with an FEV1 of 1.04, %FEV1 of 65%, and FeNO level of 13 ppb. Subjective improvement was noted as the ACT score increased to 20 and the ACQ5 score decreased to 1.2. The patient’s condition was managed without OCSs. A biopsy of the remaining polyp in the right olfactory cleft, conducted 3 months after starting tezepelumab, revealed an eosinophil count of 17/HPF, which was a significant decrease compared to the preoperative count (Fig. 10).

**Discussion**

ECRS is characterized by predominant ethmoid sinus involvement, intractable nasal polyps with eosinophilic infiltration, and comorbid bronchial asthma. According to the classification system proposed by the latest European Rhinologic Society Guidelines, ECRS is a bilateral type 2 inflammatory disease [1]. In Japan, ECRS was first defined by Haruna et al. [4] in 2001. The multicenter JESREC study conducted in 2015 established ECRS diagnostic criteria based on the JESREC score [5].

The pathogenesis of ECRS involves type 2 inflammation and release of cytokines such as IL-4, IL-13, and IL-5, which cause eosinophilic inflammation and mucin formation [6,7]. External stimuli, such as coagulolytic molds, antigens, and viruses, induce the release of epithelial cytokines (e.g., IL-33 and TSLP) from the nasal mucosal epithelium. These cytokines subsequently activate the receptors on T cells, type 2 innate lymphoid cells (ILC2s), and mast cells, leading to the production of large amounts of type 2 cytokines (IL-4, IL-5, and IL-13) [6].

Several studies have reported the efficacy of biological agents in the treatment of type 2 inflammatory diseases. For example, dupilumab, a biological agent that blocks the shared receptor components of IL-4 and IL-13, is the only antibody product approved for the treatment of CRSwNP in Japan. It decreases polyp size, sinus opening, and symptom severity [7]. Dupilumab, an anti-interleukin (IL)-4 receptor (R)alpha drug, is effective in patients with moderate to severe bronchial asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyps. Iino et al. reported that dupilumab was also effective in patients with severe refractory EOM who did not respond to treatment, including other molecular targeted therapies [2]. Nakashima et al. investigated the efficacy of dupilumab in patients with EOM complicated by ECRS [8]. Further, both mepolizumab (anti-IL5 antibody) and benralizumab (anti-IL5 receptor antibody) have been reported to be effective against EOM [9]. Therefore, tezepelumab, a human monoclonal antibody that inhibits TSLP, has been the focus of considerable attention in recent years [3].

TSLP is a cytokine produced by airway epithelial cells in response to inflammatory agents or mechanical stimuli [10]. TSLP activates dendritic cells and innate lymphocytes (ILC2s), induces type 2 cytokine production by Th2 cells, directly activates mast cells and basophils, and induces Th2 cytokine, IL-5, and IL-13 productions [11]. Furthermore, TSLP stimulates the differentiation of eosinophil precursor cells into mature eosinophils in airway tissues [12] and induces the release of Th17 cells, which are involved in both type 2 and non-type 2 inflammation [13]. In a previous report on bronchial asthma, TSLP expression was increased in the airways of patients with asthma and correlated with asthma severity. The inhibition of TSLP prevents asthma exacerbation and improves asthma control [9]. A multicenter randomized double-blind placebo-controlled trial showed that the rate of asthma exacerbation at 52 weeks was significantly lower in the tezepelumab group than in the placebo group [3]. Additionally, regardless of the baseline eosinophil count, FeNO level, or allergic status, patients with poorly controlled severe asthma treated with tezepelumab had fewer exacerbations and better lung function, asthma control, and health-related quality of life than patients who received placebo. In addition, increased TSLP expression and activity have been observed in nasal polyp tissues compared to healthy sinus tissues and tissues of patients with CRSwNP [14]. This suggests that tezepelumab may also be effective in treating ECRS, a subgroup of CRSwNP. Miura et al. [15] reported that the presence of epithelial-derived TSLP in the Eustachian tube plays a crucial role in the pathogenesis of EOM. In this case, we did not perform a tympanostomy to avoid ear discharge associated with the treatment.
with tympanic membrane perforation. Therefore, secretory otitis media did not meet the diagnostic criteria for EOM [2], thus precluding the diagnosis of EOM.

In this case, the FeNO level was relatively low under inhaled steroid treatment. However, the Global Initiative for Asthma defines type 2 inflammation as an FeNO level of 25 ppb or higher. Chest CT imaging showed no emphysematous changes in this case, and type 2 inflammation was suspected due to concomitant ECRS.

In the present case, the endoscopic findings of ECRS and the otoscopic findings of secretory otitis media significantly improved after 4 months of tezepelumab treatment. Blood and tissue eosinophil counts decreased after treatment with tezepelumab in this patient, whereas blood eosinophil counts are often increased after treatment with dupilumab. This finding suggests that tezepelumab can reduce Th2 biomarker levels upstream. Clinically, tezepelumab improved asthma symptoms, ECRS subjective symptoms, and other results, such as nasal polyp and CT scores. The tympanic and hearing test findings also improved without the use of OCSs.

Tezepelumab is considered effective regardless of biomarkers, although subanalyses have shown that it is more effective in patients with high type 2 inflammatory biomarker levels. Tezepelumab was predicted to be highly effective in this patient with CRSwNP because of high type 2 inflammation.

Tezepelumab treatment may provide significant benefits for patients experiencing side effects of OCSs, including reduced OCS use, albeit at a cost to the patient.

Although the efficacy of anti-TSLP agents for the treatment of ECRS and EOM has not been reported previously, the improvements observed with tezepelumab in this case clearly suggest that TSLP plays an important role in the pathogenesis of ECRS and secretory otitis media associated with asthma. Further studies are required to confirm these findings and determine the long-term efficacy and safety of tezepelumab for the treatment of ECRS and EOM.

Conclusions

Herein, we reported a case in which tezepelumab, administered to a patient with refractory asthma, markedly improved the outcome of ECRS and secretory otitis media, both subjectively and objectively. By suppressing type 2 inflammation upstream, tezepelumab holds great promise for patients with ECRS and secretory otitis media, who do not respond adequately to conventional treatment. This case did not meet the diagnostic criteria for EOM and, therefore, could not be shown to be effective for this. Hence, it is necessary to study tezepelumab efficacy for ECRS cases or to study its efficacy for confirmed EOM cases.

Additional Information

Disclosures

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