Dupilumab remarkably improved eustachian tube obstruction: a case of mepolizumab-resistant eosinophilic otitis media

Takeshita Y[1], Tada Y[1], Okano M[2], To M[3], To Y[4]

[1]Department of Pulmonary Medicine, International University of Health and Welfare Narita Hospital, Chiba, Japan.

[2]Department of Otorhinolaryngology, International University of Health and Welfare, Chiba, Japan.

[3]Department of Laboratory Medicine, Dokkyo Medical University, Saitama Medical Center, Koshigaya City, Saitama, Japan.

[4]Department of Pulmonary Medicine, International University of Health and Welfare Atami Hospital, Shizuoka, Japan.

Corresponding Author:

Yasuo To, MD, PhD

Department of Pulmonary Medicine, International University of Health and Welfare Atami Hospital, 13-1 Higashi-Kaigancho, Atami City, Shizuoka 413-0012, Japan; E-mail address: y.to@iuhw.ac.jp

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Eosinophilic otitis media (EOM) is a refractory disease characterized by an eosinophil-dominated middle ear viscous effusion, often associated with sinusitis and bronchial asthma. [1] Dupilumab, an anti-interleukin (IL)-4Rα antibody, is a targeted drug originally indicated for the treatment of atopic dermatitis, moderate to severe asthma, and sinusitis with nasal polyps. However, there are limited reports showing the effect of dupilumab on EOM. Herein, we present a case of EOM with tympanic membrane perforation, in which eustachian tube obstruction was significantly relieved by administration of dupilumab.

A 56-year-old woman first visited our hospital because of wheezing despite continuous treatment for severe asthma, which included oral corticosteroids. She was subsequently hospitalized for asthma exacerbation. She had a medical history of childhood asthma and NSAID-exacerbated respiratory disease (N-ERD); she had exacerbation of asthma with loxoprofen sodium. She also had chronic otitis media with effusion, for which myringotomy was needed for the therapy since the age of 47. Eosinophilia (eosinophil ratio 10%) were detected in otorrhea, and EOM was diagnosed at the age of 54.

Her asthma symptoms improved within a few days of systemic corticosteroid administration, and she was discharged from the hospital with prescription for mepolizumab (Supplementary Figure 1). Since the patient exhibited nasal obstruction and olfaction disorder, sinus computed tomography (CT) was performed, and the patient was referred to the otolaryngology department. Mucosal thickening was noted in the right maxillary sinus, in both the frontal and sphenoid sinuses, which are typical of chronic sinusitis. Aeration of the tympanic cavity and mastoid cells were normal. Nasal polyps were identified using nasal endoscopy, and a biopsy was performed, which showed 50 eosinophil infiltrations/ high power field (HPF) or more (many other destroyed eosinophils). The possibility of eosinophilic chronic rhinosinusitis as the diagnosis was likely based on the criteria for the diagnosis of eosinophilic chronic rhinosinusitis score (JESREC score, 15 points) [2]; however, a definitive diagnosis of eosinophilic sinusitis was not obtained because the number of eosinophil infiltrations was less than 70/ HPF. Her hearing test results were 11.3 dB and 22.5 dB in the right and left ears, respectively. On inspection, tympanic membrane perforation in the left ear was detected, while the right tympanic membrane was normal. CT scan revealed closure of the left eustachian tube and a normal right eustachian tube. Therefore, she was diagnosed with chronic otitis media with perforation in the left ear and otitis media with effusion in the right ear.

After initiation of mepolizumab treatment, asthma symptoms remarkably improved; systemic corticosteroid treatment was terminated. We expected mepolizumab to be effective for

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EOM and chronic rhinosinusitis with nasal polyps (CRSwNP) because it has the potential to improve eosinophilic diseases other than asthma. [3,4] However, nasal and ear symptoms did not improve even with betamethasone topical treatment used concomitantly with nasal drops and ear drops (Supplementary Figure 1). Four months after the administration of mepolizumab, her left ear obstruction, runny nose, and nasal obstruction worsened. CT showed that the ethmoid sinus, bilateral maxillary sinus, and sphenoid sinus were filled with shadows (Supplementary Figure 2) and that the eustachian tube was obstructed (Figure 1A). Mepolizumab was discontinued based on the assessment that both sinusitis and otitis media were exacerbated.

Immediately after the discontinuation of mepolizumab, dupilumab was introduced for CRSwNP, EOM, and severe asthma. Six weeks after dupilumab initiation, the patient's nasal symptoms dramatically improved (Supplementary Figure 1). The feeling of obstruction in her left ear significantly improved, and the need to use betamethasone ear drops was also reduced, although improvements were not detected by a hearing test (conductive hearing loss). Tympanic membrane perforation in the left ear was still observed upon inspection. However, CT confirmed improved control of CRSwNP and EOM, showing that the eustachian tube opened (Figure 1B and C), and opacification of the mastoid cell, bilateral maxillary sinuses, ethmoid sinus, and sphenoid sinus diminished (Supplementary Figure 2). No asthma exacerbations occurred during the period in which the biological agents were switched. Invasive treatment for

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sinusitis, such as endoscopic surgery or myringotomy for otitis media, was also not needed.

In this case, the administration of dupilumab significantly improved left eustachian tube obstruction despite its resistance to mepolizumab. Three cases of EOM successfully treated with dupilumab have been reported, [5] wherein all the cases were chronic otitis media with perforation and of the granulomatous type. Furthermore, other biologics (mepolizumab, benralizumab, or omalizumab) were initially administered, but were not effective for EOM, and a subsequent introduction of dupilumab therapy improved the clinical condition of these patients. Thus, our case is consistent with the three cases of EOM.

Based on the findings of our case and recent literature, dupilumab may be more effective than other biologics for EOM. The following hypothesis may be considered the mechanism how dupilumab resolved EOM. Periostin reported to be involved in the pathophysiology of EOM. [6] The expression of periostin is induced by type 2 cytokines such as IL-4 and IL-13. Its localization has also been confirmed in granulation tissue in nasal polyps and the middle ear. [6,7] In addition, periostin is present in the thickened mucosa and is thought to be involved in the prolongation of inflammation. [8] Thus, decreasing IL-4 and/or IL-13 induced by dupilumab may suppress the induction of periostin, resulting in a reduction of inflammation and a subsequent improvement of the eustachian tube obstruction.

In our case, the CRSwNP also improved with dupilumab. Bachert et al. reported that in adult patients with severe CRSwNP, dupilumab reduced the severity of symptoms. These results

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support the benefits of adding dupilumab for patients with severe CRSwNP who have few therapeutic options. [9] Our case was consistent with the findings. According to Fokkens' report, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 steering group advises to use dupilumab in patients with CRSwNP fulfilling the criteria for treatment with monoclonal antibodies. [10] Our case met the criteria.

In conclusion, eustachian tube obstruction in EOM may be treatable with dupilumab. Dupilumab therapy may be a good treatment option for EOM when it relapses or is resistant to corticosteroid therapy.

Conflict of Interest

Y. To received lecture fees from GlaxoSmithKline, AstraZeneca, and Novartis Pharma. All other authors state that they have no significant conflicts of interest with any companies/organizations whose products or services may be discussed in this article.

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Figure Legends

Figure 1. CT imaging of eustachian tubes before and after dupilumab treatment A: CT imaging before dupilumab administration. **B:** CT imaging 1 month after dupilumab administration (left). **C:** CT imaging 2 months after dupilumab administration (left). Open circles indicate eustachian tubes.