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## Original Article

## Dupilumab improves eosinophilic otitis media associated with eosinophilic chronic rhinosinusitis

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## ABSTRACT

**Background:** Eosinophilic otitis media (EOM) is a refractory condition associated with eosinophilic chronic rhinosinusitis and bronchial asthma. EOM is characterized by type-2 inflammation and is refractory to various treatments. We investigated the efficacy of dupilumab, interleukin-4 receptor alpha antagonist, for patients with EOM complicated by eosinophilic chronic rhinosinusitis (ECRS).

**Methods:** Between April 2017 and April 2022, we treated 124 patients with dupilumab for refractory CRS or bronchial asthma. Of these, 14 had EOM concurrently, and 10 of them who had been treated for >6 months were included in our study. We retrospectively evaluated the efficacy of dupilumab by the amount of systemic corticosteroid used, the frequency of exacerbations, severity score of EOM, computed tomography (CT) score of temporal bones, and pure tone audiometry. We also enrolled 8 EOM patients without dupilumab treatment as a control group.

**Results:** Dupilumab significantly improved the amount of systemic corticosteroid used and the frequency of exacerbation and compared with before dupilumab was used ( $p = 0.01$  and  $<0.01$ , respectively). All patients could be weaned from systemic-corticosteroid therapy by 54 weeks of dupilumab use. The severity score of EOM and CT score for temporal bones were significantly lower than before the treatment ( $p = 0.01$  and  $0.01$ , respectively). Compared to the control group, the systemic corticosteroid used and severity scores were improved in the dupilumab group ( $p = 0.02$  and  $<0.01$ , respectively).

**Conclusions:** Dupilumab could be used to wean patients from systemic corticosteroids with the improvement of severity score in EOM associated with ECRS and bronchial asthma.

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## Introduction

Eosinophilic otitis media (EOM) is a disease that was proposed relatively recently. EOM is characterized by a marked viscous effusion in the middle ear. Additionally, accumulation of numerous

eosinophils in the effusion and mucosa of the middle ear has been documented in EOM.<sup>1</sup> Often, EOM is associated with eosinophilic chronic rhinosinusitis (ECRS) and bronchial asthma, including non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NERD). In 2011, recommendations stated that EOM was present if two of four minor criteria were met, in addition to the major criterion of otitis media with effusion or chronic otitis media with eosinophil-dominant effusion.<sup>2</sup>

EOM is a type-2 inflammatory disease induced by interleukin (IL)-4, IL-5, and IL-13 and characterized by an eosinophilic infiltration (similar to ECRS).<sup>3</sup> First-line treatment of EOM is systemic or local administration of corticosteroids. Considering the side-effects of corticosteroids, intratympanic administration of triamcinolone acetate has been shown to be highly efficacious.<sup>4</sup> Chen and

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colleagues carried out a systematic review of EOM studies.<sup>5</sup> They showed that, in terms of improvement of otologic symptoms, hearing, and corticosteroid dependence, success rate was noted for 45% of patients who had an intratympanic corticosteroid injection and for 26% of cases who had a systemic administration of corticosteroids.

Biologic agents have been gaining attention as treatment for patients who are resistant to existing therapies. Recently, various molecular-targeted drugs have been available for the treatment of allergic and autoimmune diseases. Chen and colleagues<sup>5</sup> showed that the biologic agents benralizumab, mepolizumab, omalizumab were more successful than corticosteroids delivered *via* intratympanic or systemic routes. However, treatment success was achieved in only 58% of patients, so this treatment option does not appear to be satisfactory.

Dupilumab is a human monoclonal antibody that blocks the shared IL-4/IL-13 receptor, IL-4R $\alpha$ , which is a key factor in type-2 inflammation. Numerous reports of the efficacy of dupilumab against ECRS and bronchial asthma have been documented,<sup>6,7</sup> but few reports on its effects against EOM have been published.

We evaluated the efficacy of dupilumab in patients who received dupilumab as treatment for ECRS and bronchial asthma complicated by EOM.

## Methods

### Patient recruitment

Between April 2017 and April 2022, we retrospectively enrolled 124 patients treated with dupilumab for recurrent chronic rhinosinusitis with nasal polyps (CRSwNP) or bronchial asthma. Of these patients, 14 had concomitant EOM, and 10 of them who had been receiving dupilumab for >6 months were included in our study. EOM was diagnosed in accordance with criteria set by Iino and coworkers,<sup>2</sup> which comprise one major criterion and four minor criteria. The major criterion is otitis media with an effusion or chronic otitis media with an eosinophil-dominant effusion. The minor criteria are: (i) highly viscous middle ear effusion; (ii) resistance to conventional treatment for otitis media; (iii) association with bronchial asthma; (iv) association with nasal polyposis. Patients who meet more than two criteria in addition to the major criterion are said to be suffering from EOM. The study protocol was approved (33-335 (10,968)) by the ethics review board of The Jikei University School of Medicine.

Middle-ear effusions were collected from all patients. Cytology was used to confirm an eosinophil-dominant effusion. The minor criteria stated above had to be met for a diagnosis of EOM. ECRS was diagnosed in patients with a Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis score  $\geq 11$  and an eosinophil count in nasal polyps  $\geq 70$ .<sup>8</sup> Patients with asthma including NERD were diagnosed by respiratory physicians. All data were collected after review of medical records.

The primary treatment for ECRS, EOM, and bronchial asthma is as follows. Those with a long-term and low-dose administration of clarithromycin and L-carbocysteine for three months and nasal corticosteroid spray were inadequately effective for CRS patients all had endoscopic sinus surgery (ESS). Postoperatively, patients are treated the same way as before surgery plus nasal saline irrigation, and those diagnosed with ECRS are treated with systemic corticosteroids and anti-leukotrienes as needed. If patients had complicated EOM with a perforation of the tympanic membrane and eosinophilic mucin accumulation in the tympanic cavity, we performed intratympanic administration of corticosteroids. In patients with bronchial asthma, we adjusted the dose of inhaled corticosteroids according to the results of ACT (Asthma Control Test) and spirometry.

### Dupilumab indications and clinical parameters

Moreover, we considered whether dupilumab was indicated for patients who had undergone surgery for CRSwNP and who were refractory to various treatments, including corticosteroids administered *via* systemic or intranasal routes. Of these, we administered dupilumab to patients with a Nasal Polyp (NP) score  $\geq 5$ , a Nasal Congestion Severity score  $\geq 2$ , and subjective symptoms of olfactory disorder and rhinorrhea lasting  $\geq 8$  weeks. One of 10 patients was prescribed dupilumab for bronchial asthma in a respiratory medicine clinic in another institution after she had been prescribed other biologic agents (omalizumab, mepolizumab, and benralizumab). She switched to dupilumab due to worsening CRS and was transferred to our institution. We wished to ascertain the efficacy of dupilumab against EOM. Hence, we documented the amount of systematic corticosteroid used, the frequency of exacerbations, severity score of EOM, computed tomography (CT) score of temporal bones, and pure tone audiometry, and undertook comparisons for each of these parameters before and after treatment.

We evaluated EOM and overlapping type-2 inflammation (i.e., ECRS, bronchial asthma) in outpatient clinics approximately every 3 months. If patients improved in terms of ear/nasal endoscopic findings and subjective symptoms of EOM or ECRS, we reduced the prednisolone dose by 1 mg, however, if symptoms were aggravated, we increased the prednisolone dose by 1 mg. After patients had been weaned off prednisolone, the dupilumab dose was reduced gradually with the same protocol every 2 weeks, 3 weeks and, finally, every 4 weeks.

“Exacerbation” was defined as an increase in prednisolone dose or myringotomy based on endoscopic ear findings and symptoms. In addition, to ascertain the effect of ECRS, we also compared the CT (Lund–Mackey) score,<sup>9</sup> the cognitive threshold of the T&T olfactometry,<sup>10</sup> NP score,<sup>11</sup> and Open Essence score.<sup>12</sup>

The severity score of EOM was proposed by Iino and colleagues,<sup>13</sup> and graded on five items with scores of 0–2 points (Supplementary Table 1). The CT score for temporal bones was evaluated based on aeration in the middle ear as proposed by Iino and coworkers<sup>14</sup> with reference to the staging system of rhinosinusitis proposed by Lund and Mackey.<sup>9</sup> The scoring system is from 0 (well aerated) to 2 (complete opacification) in the mesotympanum, attic, antrum, and mastoid air cells of the temporal bones, and results in a total score of 0–16.

Pure-tone audiometry was performed using AA-M1B audiometer (RION Co., Ltd, Japan) and we measured the air and bone conduction hearing levels and air-bone gaps of patients before treatment and the time patients were weaned from systemic corticosteroids after starting dupilumab therapy.

### Patient recruitment without dupilumab treatment

We also enrolled 8 EOM patients without dupilumab treatment as a control group and compared them with the dupilumab treatment group in terms of the amount of systemic corticosteroid used, the frequency of exacerbations, severity score of EOM, and pure tone audiometry. Pre- and post-treatment changes were compared between the control and dupilumab groups.

### Statistical analyses

Statistical analyses were carried out using R 4.1.3 (R Institute for Statistical Computing, Vienna, Austria). All data are noted as mean  $\pm$  SD. Differences in data were analyzed by the Wilcoxon

signed-rank test and Mann–Whitney U test. One-way ANOVA with the Holm multiple-comparisons test was employed for comparisons of data from more than two groups. A P value of <0.05 was considered to indicate a statistically significant difference.

## Results

### Patients' demographic characteristics

The clinical characteristics of the patients are shown in Table 1. All patients with EOM were diagnosed with both ECRS and bronchial asthma including two with NERD. They also had ESS for ECRS. Perforation of the tympanic membrane in either ear was observed in six patients (right ear in five patients and left ear in four patients). Four patients did not have a perforation of the tympanic membrane in either ear. No patients had granulation formation. Systemic steroids were used in nine patients, and all were used for ECRS. No serious adverse events associated with dupilumab administration, including anaphylaxis symptoms and eosinophilic pneumonia were observed.

### Efficacy of dupilumab on eosinophilic otitis media

Dupilumab reduced the amount of prednisolone used significantly compared with that used before treatment ( $3.4 \pm 1.9$  to  $0.0 \pm 0.0$ ;  $p = 0.01$ ) (Fig. 1A). The changes over time in prednisolone dose after dupilumab administration are shown in Figure 2. All patients using systemic corticosteroids were able to withdraw from corticosteroid use by week-54, and the mean prednisolone dose was half that administered during the first 16 weeks. All patients who were observed for <54 weeks were able to be weaned off corticosteroids within that time. Despite the reduction in the prednisolone dose, the frequency of exacerbations decreased from  $1.70 \pm 1.71$  to  $0.41 \pm 0.52$  per year ( $p = 0.01$ ) (Fig. 1B). Next, the efficacy of dupilumab was evaluated using the severity score and the CT score for temporal bones (Fig. 3). There were significant reductions from before to after treatment for the severity score of EOM ( $4.9 \pm 1.6$  to  $0.8 \pm 1.4$ ) and CT score for temporal bones ( $6.3 \pm 2.3$  to  $2.7 \pm 1.7$ ) ( $p = 0.01$  and  $0.01$ , respectively) (Fig. 1C, D). In the severity score, middle ear effusion (MEE)/otorrhea was improved from  $1.2 \pm 0.6$  to  $0.4 \pm 0.7$  ( $p = 0.02$ ) and condition of the middle ear mucosa was also improved from  $1.0 \pm 0.7$  to  $0.2 \pm 0.4$  ( $p < 0.01$ ). One patient with slight improvement (severity score 5 to 4 and temporal CT score 5 to 4) had severe ECRS with blood eosinophil percentage increasing to a maximum of 34% during follow-up. However, NP score improved from 5 to 0 at 3 months and bronchial asthma was well controlled with an ACT score of 23/25 at 3 months and 24/25 at 1 year after dupilumab administration; no correlation in response to dupilumab was observed in these diseases.

Table 2 shows the air and bone conduction hearing levels and air-bone gaps before and after treatment. Speech range was set as mean at 0.5, 1 and 2 kHz. None of the patients showed significant change in speech range and 4 kHz after the withdrawal from systemic corticosteroids.

### Efficacy of dupilumab on eosinophilic chronic rhinosinusitis

Supplementary Fig. 1 shows the efficacy of dupilumab against CRSwNP. The mean mucosal eosinophil count in nasal polyps was  $111 \pm 65$ /high power field, and all of these patients were diagnosed as having ECRS. The CT (Lund–Mackey) score and NP score were significantly different before treatment and 3 months after treatment ( $p = 0.03$  and  $0.04$ , respectively) as well as before treatment and 12 months after treatment ( $p = 0.04$  and  $0.04$ , respectively)

**Table 1**  
Characteristics of patients with EOM.

| Case | Age | Gender | ECRS | Asthma | NERD | Blood eosinophils (/μl) | EOS + | Right side      |                 |                  | Left side       |                 |                  | PSL Initial dose (mg/day) | Total F/U Period (months) | Dupilumab usage (months) |
|------|-----|--------|------|--------|------|-------------------------|-------|-----------------|-----------------|------------------|-----------------|-----------------|------------------|---------------------------|---------------------------|--------------------------|
|      |     |        |      |        |      |                         |       | Ear Perforation | MEE or otorrhea | Mucosa condition | Ear Perforation | MEE or otorrhea | Mucosa condition |                           |                           |                          |
| 1    | 33  | f      | Yes  | Yes    | Yes  | 208                     | Yes   | Yes             | 1               | 1                | No              | 0               | 0                | 2.5                       | 49                        | 34                       |
| 2    | 44  | f      | Yes  | Yes    | No   | 148                     | Yes   | Yes             | 1               | 1                | Yes             | 0               | 0                | 5                         | 46                        | 20                       |
| 3    | 47  | m      | Yes  | Yes    | No   | 444                     | Yes   | No              | 0               | 0                | No              | 1               | 1                | 5                         | 61                        | 19                       |
| 4    | 53  | f      | Yes  | Yes    | No   | 112                     | Yes   | No              | 0               | 0                | Yes             | 2               | 2                | 0                         | 75                        | 19                       |
| 5    | 42  | f      | Yes  | Yes    | No   | 210                     | Yes   | No              | 0               | 0                | No              | 1               | 1                | 5                         | 45                        | 18                       |
| 6    | 67  | m      | Yes  | Yes    | No   | 222                     | Yes   | No              | 0               | 0                | No              | 1               | 1                | 5                         | 57                        | 17                       |
| 7    | 49  | f      | Yes  | Yes    | No   | 356                     | Yes   | Yes             | 0               | 0                | Yes             | 1               | 0                | 5                         | 72                        | 16                       |
| 8    | 75  | f      | Yes  | Yes    | No   | 434                     | Yes   | Yes             | 0               | 0                | Yes             | 2               | 2                | 5                         | 68                        | 10                       |
| 9    | 62  | f      | Yes  | Yes    | No   | 76                      | Yes   | Yes             | 1               | 1                | No              | 1               | 0                | 2.5                       | 50                        | 9                        |
| 10   | 62  | m      | Yes  | Yes    | Yes  | 372                     | Yes   | No              | 0               | 0                | No              | 0               | 0                | 4                         | 49                        | 6                        |

ECRS, Eosinophilic chronic rhinosinusitis; NERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; EOS+, eosinophil-dominant middle ear effusion. "MEE or otorrhea" and "mucosa condition" were scored with reference to the Severity score of eosinophilic otitis media.

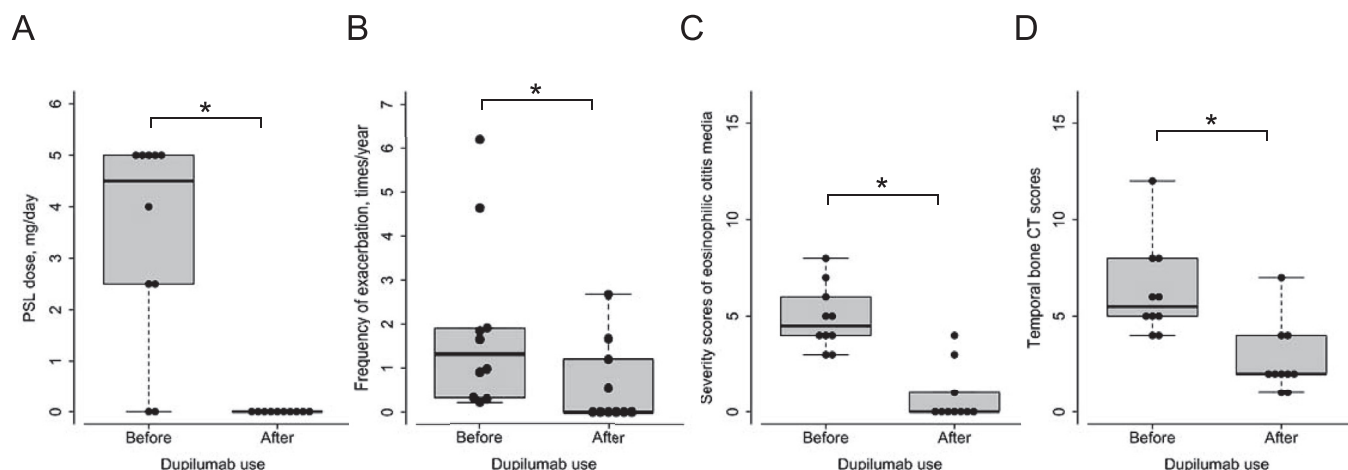


**Fig. 1.** Comparison of the therapeutic effects of dupilumab against EOM. **(A)** Change in the prednisolone (PSL) dose (mg/day). **(B)** Frequency of EOM exacerbations (times/year). **(C)** Severity score of EOM. **(D)** CT score of temporal bones. \* $P < 0.05$ ; Wilcoxon signed-rank test.

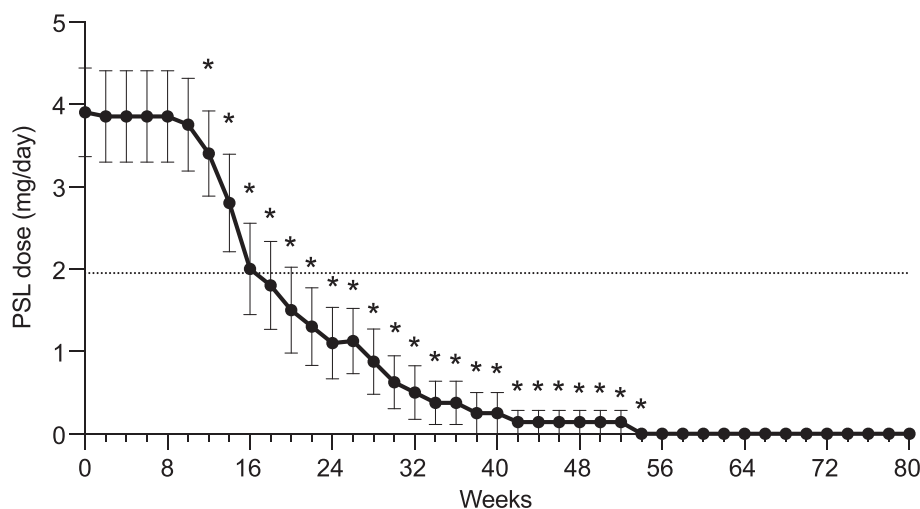


**Fig. 2.** Line graph showing changes in the mean prednisolone (PSL) dose of 10 patients after dupilumab therapy. The horizontal axis represents the weeks from starting dupilumab therapy. The vertical axis represents the PSL dose (mg/day). The dotted line shows the half dose to the average amount of the PSL dose prior to dupilumab administration and the prednisolone dose was reduced to half during the first 16 weeks. Error bars represent SEM. Each week was compared with pretreatment (0 week). \* $P < 0.05$ ; Wilcoxon signed-rank test.

(Supplementary Fig. 1A, B). The T&T cognitive threshold tended to improve, but not significantly so, from before to after treatment (Supplementary Fig. 1C). The Open Essence score was improved at 12 months compared with that before treatment ( $p < 0.01$ ) (Supplementary Fig. 1D).

#### Comparison of the clinical outcomes of patients treated with and without dupilumab

The patients' characteristics of the dupilumab and control groups are summarized in Table 3, and there are no significant background differences between the two groups. We compared them in terms of the amount of systemic corticosteroid used, the frequency of exacerbations, and the severity score of EOM. The change in prednisolone dose and severity score were significantly higher in the dupilumab group (Fig. 4A, C,  $p = 0.02$  and  $< 0.01$ , respectively). In contrast, the frequency of exacerbations was not different (Fig. 4B,  $p = 0.20$ ).

Supplementary Table 2 shows the air and bone conduction hearing levels and air-bone gaps before and after the control group.

Table 4 also compares the degree of improvement in hearing levels between the dupilumab and control groups. There was no significant difference between the two groups.

#### Discussion

Dupilumab is a humanized immunoglobulin-G4 monoclonal antibody. It inhibits IL-4R $\alpha$  and suppresses the type-2 inflammation involved in the pathogenesis of ECRS, bronchial asthma, and atopic dermatitis. Since March 2020, dupilumab has been approved for use in Japan for the treatment of recurrent CRSwNP, following the approval of bronchial asthma and atopic dermatitis. EOM is considered to be a type-2 inflammatory disease similar to the diseases for which dupilumab is indicated. Previously, we showed that expression of eosinophil-derived neurotoxin (EDN), IL-4, and IL-5 was significantly high in middle-ear effusions.<sup>15</sup> Esu and colleagues revealed that periostin expression was significantly high in severe cases of EOM who had little response to corticosteroid treatment.<sup>16</sup>

The patients suffering from EOM were administered dupilumab for ECRS and bronchial asthma, both of which are commonly

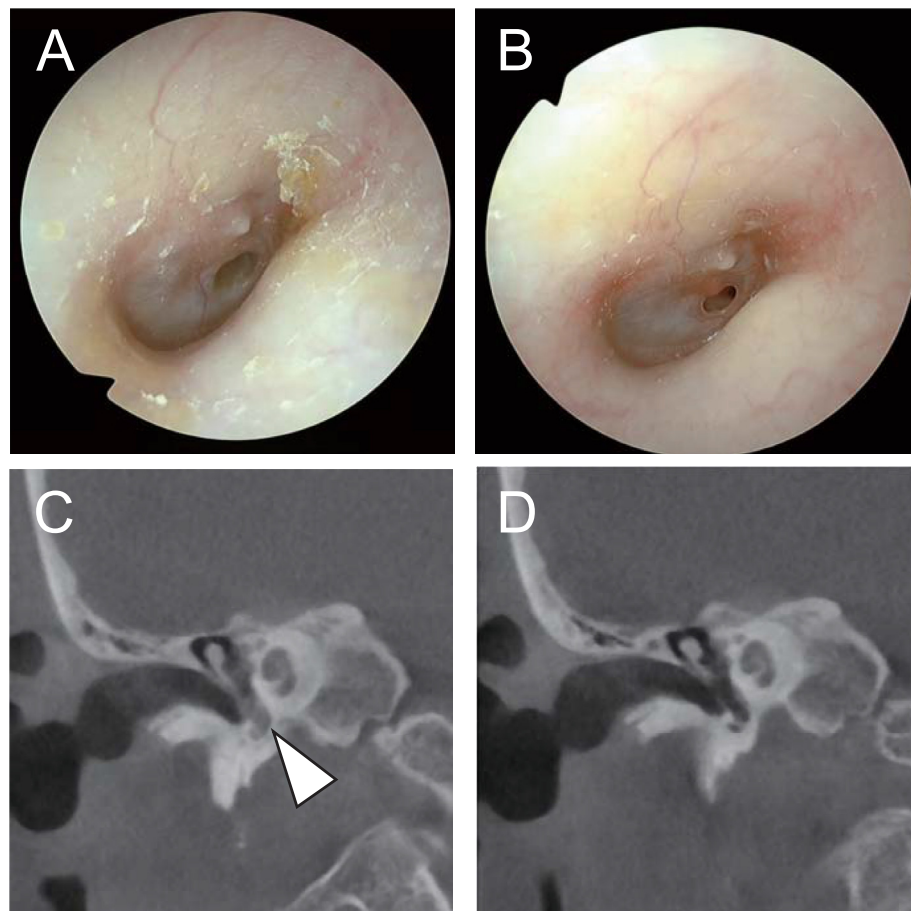


**Fig. 3.** Otoloscopic findings and temporal CT findings. (A) Before dupilumab treatment, the middle ear cavity cannot be seen through the perforation due to the viscous effusion. (B) The middle ear mucosa can be seen after the treatment. (C) Coronal CT scan shows a soft density shadow in the tympanic cavity before the treatment (arrowhead) (Temporal bone CT score is 5). (D) The aeration can be seen after the treatment (Temporal bone CT score is 2).

**Table 2**

Air and bone conduction hearing levels and air-bone gaps with EOM before and after dupilumab treatment (n = 10 patients, 20 ears).

|         | Air conduction    |             | Bone conduction   |             | Air-Bone gaps     |            |
|---------|-------------------|-------------|-------------------|-------------|-------------------|------------|
|         | Speech range (dB) | 4 kHz (dB)  | Speech range (dB) | 4 kHz (dB)  | Speech range (dB) | 4 kHz (dB) |
| Before  | 18.9 ± 10.0       | 25.3 ± 20.2 | 12.5 ± 5.8        | 17.3 ± 16.1 | 6.4 ± 9.7         | 8.0 ± 6.8  |
| After   | 21.2 ± 14.3       | 24.8 ± 23.4 | 14.3 ± 7.7        | 17.0 ± 15.9 | 6.8 ± 11.6        | 7.8 ± 8.6  |
| P value | 0.554             | 0.837       | 0.265             | 0.888       | 0.763             | 0.940      |

Speech range: mean at 0.5, 1, and 2 kHz.

**Table 3**

Patients' baseline characteristics.

|                               | Dupilumab (n = 10) | Control (n = 8) | P value |
|-------------------------------|--------------------|-----------------|---------|
| Age(y), mean (SD)             | 53 (12)            | 56 (7)          | 0.487   |
| Sex, no female (%)            | 7 (70)             | 8 (100)         | 0.114   |
| ESS operation, yes, n (%)     | 10 (100)           | 8 (100)         | —       |
| History of asthma, n (%)      | 10 (100)           | 8 (100)         | —       |
| History of N-ERD, n (%)       | 2 (20)             | 3 (38)          | 0.457   |
| Severity score                | 4.9 (1.6)          | 4.0 (1.0)       | 0.184   |
| Follow up period, months (SD) | 57 (11)            | 50 (15)         | 0.321   |

associated with EOM,<sup>1</sup> because there is no indication for dupilumab for EOM. For bronchial asthma, biologics are generally used with reference to serum total IgE, blood eosinophil count, and

FeNO,<sup>17</sup> and dupilumab is efficacious against severe asthma, but also in patients with mild-to-moderate asthma complicated by CRSwNP.<sup>18</sup> There are case reports of a patient with bronchial asthma complicated by ECRS and EOM who had ECRS and EOM worsened with benralizumab and/or mepolizumab, whereas ECRS and EOM including bronchial asthma improved with dupilumab.<sup>19,20</sup> The present study also showed that dupilumab was effective against both EOM and refractory ECRS in all the patients. This suggests that EOM, along with refractory ECRS, would be a purer single endotype with IL-4 and IL-13 involved in the pathogenesis than bronchial asthma. It is also possible that dupilumab improves EOM via improvement of eustachian tube function, as cases of eustachian tube opening after treatment with dupilumab have been reported.<sup>20,21</sup>

The effect of dupilumab against EOM has been shown by Iino and collaborators.<sup>14</sup> It was efficacious for three patients with severe EOM and bronchial asthma after they had been administered omalizumab and mepolizumab; they had improved severity scores and air-conduction hearing levels. De Corso and colleagues<sup>22</sup> retrospectively evaluated the efficacy of biologic agents (omalizumab, mepolizumab, and benralizumab in one-patient each) in addition to dupilumab (five patients) for the control of EOM by calculating the Chronic Otitis Media Outcome Test (COMOT)-15 score, Otitis Severity score, and air-conduction hearing level. COMOT-15 is a questionnaire employed to assess the subjective symptoms for quality of life of patients suffering from chronic suppurative otitis media.<sup>23</sup> De Corso and colleagues showed that the

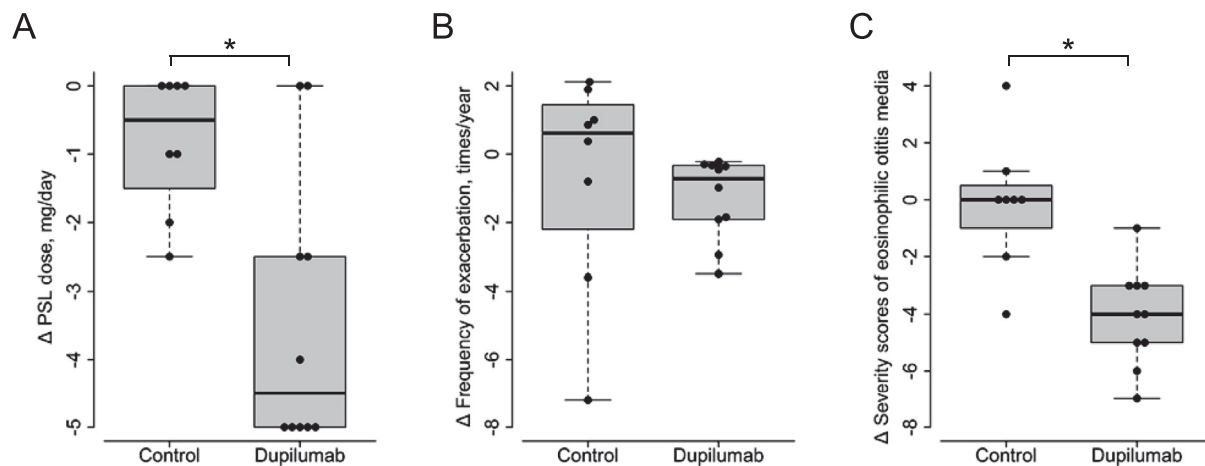


**Fig. 4.** Comparison of the therapeutic effect against EOM between the dupilumab and control group. (A) Change ( $\Delta$ ) in the prednisolone (PSL) dose (mg/day). (B)  $\Delta$  in frequency of exacerbations (times/year). (C)  $\Delta$  in severity score. \* $P < 0.05$ ; Mann–Whitney U test.

**Table 4**  
Comparison of hearing improvement in the dupilumab and control group.

|           | Air conduction    |                 | Bone conduction   |                | Air–Bone gaps     |                |
|-----------|-------------------|-----------------|-------------------|----------------|-------------------|----------------|
|           | Speech range (dB) | 4 kHz (dB)      | Speech range (dB) | 4 kHz (dB)     | Speech range (dB) | 4 kHz (dB)     |
| dupilumab | 2.2 $\pm$ 5.8     | −0.5 $\pm$ 10.3 | 1.8 $\pm$ 4.6     | −0.3 $\pm$ 5.3 | −0.4 $\pm$ 4.0    | −0.3 $\pm$ 9.6 |
| control   | −1.8 $\pm$ 4.9    | 0.9 $\pm$ 7.8   | −0.7 $\pm$ 5.8    | 3.4 $\pm$ 8.0  | −1.1 $\pm$ 5.2    | −2.5 $\pm$ 7.2 |
| P value   | 0.155             | 0.756           | 0.363             | 0.313          | 0.545             | 0.599          |

Speech range: mean at 0.5, 1 and, 2 kHz.

COMOT-15 score, Otitis Severity score, and air-conduction hearing level were improved at 6-month follow-up compared with those at baseline. They concluded that biologic agents that were efficacious against type-2 inflammation could also be efficacious against EOM. Those reports revealed the efficacy of dupilumab against EOM, but the study cohorts were small and statistical analyses insufficiently robust. Therefore, we examined the efficacy of dupilumab against EOM. We treated 10 patients, a study cohort larger than that in previous studies, and we consider our results to be valuable. In addition, all patients in our study underwent CT before and after treatment, which is a more objective evaluation compared with the evaluations made in the studies stated above. Moreover, we could show the efficacy of dupilumab compared to the control group.

Systemic or topical administration of corticosteroids is efficacious for patients with EOM.<sup>5</sup> However, systemic corticosteroids in particular can lead to osteoporosis, hyperglycemia, and infection. A position paper from the European Society of Allergy and Clinical Immunology concluded that systemic corticosteroids should not be considered as first-line treatment for chronic diseases of the upper airways.<sup>24</sup> Our data showed that gradual reduction of the dose of systemic corticosteroid led to all 10 patients being weaned off the drug by 54 weeks. This observation suggests that introducing dupilumab therapy may lead to a reduction in corticosteroid use. We also examined the frequency of EOM exacerbations, severity score, and CT scores after treatment with dupilumab and showed that the frequency of the exacerbations, severity scores, and CT score were significantly reduced. Compared to the control group, the change in exacerbation frequency did not reach the significance. However, the change in prednisolone usage and severity scores were significantly improved. Therefore, dupilumab could be a useful treatment for EOM by allowing patients to be weaned off corticosteroids and improving middle ear conditions.

Patients with EOM present a high risk of sensorineural hearing loss, which may progress rapidly to deafness,<sup>25</sup> so evaluation by

audiometry is considered very important. In this study, the air and bone condition hearing levels and air–bone gaps did not change significantly after dupilumab treatment. We believe that the reason for the difference between this study and previous research is that systemic corticosteroids prevented the reduction in hearing levels in our study before dupilumab administration. In our study, the mean air conduction hearing level was 18.9 dB, and the bone conduction hearing level was 12.5 dB, which are almost normal hearing levels compared to previous studies by Iino *et al.*<sup>14</sup> and De Corso *et al.*<sup>22</sup> From another perspective, although administration of systemic corticosteroids was gradually reduced, hearing levels were not deteriorated. This was because dupilumab therapy could control the hearing condition of EOM.

However, our study had four main limitations. First, although subjective symptoms were discussed during patient interviews, they were not scored. Iino and colleagues<sup>26</sup> evaluated eight symptoms (echo in the ear, tinnitus, otorrhea, dizziness, breathing sound in the ear, autophony, aural fullness, otalgia) and graded each of them from 0 points to 5 points. Subjective evaluation is as important as objective evaluation in assessing treatment efficacy, so scoring of subjective symptoms should also have been undertaken. Second, the study cohort was small compared with studies focusing on ECRS, bronchial asthma, and atopic dermatitis. The main reason is that EOM is a relatively rare disease. Third, the amount of systemic corticosteroid used was altered by the status of EOM but also by the status of ECRS or bronchial asthma. Often, the symptoms of these diseases complicate each other, thereby hampering evaluation of EOM symptoms. Fourth, in this case series, we had no experience in treating cases with grade 2 or grade 3 granulation of the middle ear mucosa. This may be because we have already controlled the EOM condition by using systemic corticosteroids. Future studies on the efficacy of dupilumab in severe cases with high-grade middle ear mucosal granulation are needed.

In conclusion, dupilumab could be used to wean patients from systemic corticosteroids in EOM associated with ECRS and bronchial asthma. Furthermore, despite weaning from systemic corticosteroids, dupilumab improved the EOM severity score and showed a trend toward a reduction in the frequency of EOM exacerbations and CT score. Multicenter studies with much larger patient cohorts are needed to determine whether dupilumab should be used for EOM treatment.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2023.03.007>.

## Conflict of interest

TNakay reports lecture fees and research grants from Sanofi, Japan. YM received an honorarium from Olympus Corporation. The rest of the authors have no conflict of interest.

## Authors' contributions

YM designed the study. DN, SM, TA, CM, YS, TNakaj, SH, and YM contributed to data collection. DN carried out statistical analyses. DN and TNakay wrote the manuscript. DN, TNakay, and YM contributed to data interpretation and revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

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