Respiratory epithelial adenomatoid hamartoma with nasal polyps affects dupilumab efficacy*

Teppei Takeda[1], Norihiro Yanagi[1], Nei Fukasawa[2], Eri Mori[1], Mayuka Maeda[1], Ryoko Sakaguchi[2], Masayoshi Tei[1], Kazuhiro Omura[1], Nobuyoshi Otori[1]

[1] Department of Otorhinolaryngology, Jikei University School of Medicine, Japan

[2] Department of Pathology, Jikei University School of Medicine, Japan

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Dear Editor:

Dupilumab inhibits IL-4 and IL-13 signaling, which are hallmark cytokines for type 2 inflammation[(1)]. Dupilumab is effective and safe for treating recurrent chronic rhinosinusitis with nasal polyposis (CRSwNP)[(2)]. However, the efficacy of dupilumab varies due to differences in the duration of time between the last surgery and dupilumab introduction[(3)]. Currently, dupilumab is expensive and not generally prescribed due to the high financial burden[(4)]. Therefore, development of an index that can predict the efficacy of dupilumab in patients with recurrent CRSwNP is pivotal to avoid unnecessary prescriptions.

This study aimed to evaluate changes in the olfactory cleft polyps under dupilumab treatment in difficult-to-treat CRS patients at 16 weeks of treatment with endoscopic outcomes. The aim was to compare the clinical characteristics of patients with resolution and persistence of olfactory cleft polyps and to investigate the pathological characteristics of patients with residual olfactory cleft polyps. Difficult-to-treat CRS was defined as noncontrollable rhinosinusitis despite successful sinus surgery and appropriate conservative management for at least 1 year[(5)].

This retrospective cohort study was approved by the Ethics Committee of the Jikei University School of Medicine (Protocol No. 33-019). From August 2020 to May 2021, 39 consecutive patients with recurrent CRSwNP who received 300 mg of dupilumab subcutaneously every 2 weeks for 16 weeks at the Jikei University School of Medicine Hospital were examined.

The inclusion criteria were histopathologically diagnosed eosinophilic chronic rhinosinusitis (ECRS); difficult-to-treat polyps in both nasal cavities before the introduction of dupilumab; bilateral endoscopic nasal polyp score (NPS) of at least 5 (maximum 8)[(2)], with a minimum score of 2 for each nostril; and patients with T&T olfactometer (Takasago Industry, Tokyo, Japan) recognition threshold score of ≥1.1, defined as olfactory dysfunction by the Japanese Rhinological Association[(6)]. Patients with no NPS evaluation or olfactory function assessment before and after dupilumab introduction and patients with normal olfactory function (recognition threshold score of ≤1.0) before dupilumab introduction were excluded. Written informed consent was obtained from all participants.

Data on patients' age; sex; presence of comorbidities, such as bronchial asthma and aspirin intolerance; years elapsed between the last surgery and dupilumab introduction; NPS before and 16 weeks after dupilumab introduction; T&T recognition threshold; and total IgE level, and Sinonasal Outcome Test (SNOT-22)[(7)] scores were collected. The primary endpoint was to evaluate the morphology of the olfactory cleft on endoscopy at 16 weeks of dupilumab treatment. The secondary endpoints were NPS, T&T recognition threshold, total IgE level, and SNOT-22 scores at baseline and 16 weeks of dupilumab treatment. For each parameter, the change from baseline to week 16 was evaluated (baseline-week 16). If residual olfactory cleft polyps were noted at 16 weeks, histopathological images of the same area were collected and evaluated to differentiate neoplastic diseases. Pathological evaluation was conducted by two head and neck pathologists (N. F., R. S.). The diagnosis of respiratory epithelial adenomatoid hamartoma (REAH) and inflammatory polyps was determined based on the pathological diagnosis reported by Fitzhugh et al.[(8)].

The Mann–Whitney test was used to analyze each parameter before and after dupilumab introduction. Statistical significance was set at $p<0.05$. The statistical analysis software used was StataCorp. 2017 (Stata statistical software: Release 15.1. College Station, TX, StataCorp LLC).

The number of patients who met the inclusion criteria was 16 (Figure 1), of which 63% (10 patients) reported resolution of olfactory cleft polyps at 16 weeks following dupilumab treatment and 37% (6 patients) had residual polyps. Table 1 shows the patient background at baseline and week 16 of dupilumab

Table 1. Patient background at baseline and week 16 of dupilumab treatment.

	Olfactory Cleft Polyps		Resolution Group median difference vs
	Resolution Group	Residual Group	Residual Group (95% CI; p value)
Age	54.5 (46-57)	66.5 (52-70)	P= 0.16
Sex (male, female)	5:5	3:3	
Presence of comorbidities such as bronchial asthma and aspirin intolerance (%)	100	83	P= 0.38
Time from last surgery to dupilumab introduction (years)	3.0 (2.0-7.0)	6.5 (3.0-10.0)	P= 0.15
Evaluation Items at Baseline			
Bilateral endoscopic nasal polyp score (scale 0–8)	6 (6-6)	6 (6-6)	P= 0.44
Olfactory Recognition Thresholds (T&T Olfactometer) (scale -2.0–5.8)	5.8 (5.6-5.8)	5.8 (5.8-5.8)	P= 0.62
SNOT-22 total score (scale 0-110)	54.3 (29.2-79.4)	56.5 (28.0-85.0)	P= 0.88
Total IgE (IU/mL)	94 (75-135)	474 (210-675)	P= 0.02*
Blood eosinophils (%)	5.9 (4.1-9.6)	4.1 (1.8-8.2)	P= 0.38
Evaluation Item Change from Baseline at 16 Weeks (Baseline - Week 16)			
Bilateral endoscopic nasal polyp score	4 (4-4)	0.5 (0-1)	P< 0.01*
Olfactory Recognition Thresholds (T&T Olfactometer)	2.8 (0.6-4.2)	0.6 (0-2.0)	P= 0.04*
SNOT-22 total score	33.1 (11.2-55.1)	31.0 (3.3-58.7)	P= 0.88
Total IgE (IU/mL)	40 (21-54)	149 (67-328)	P= 0.05*
Blood eosinophils (%)	-3.5 (-10.2--0.9)	-10.4 (-17.4--6.1)	P= 0.15

At 16 weeks after dupilumab administration, patients were divided into two groups: those with resolution of olfactory cleft polyps (Resolution Group) and those with residual polyps (Residual Group). The data were expressed in median (IQR). SNOT-22: Sinonasal Outcome Test.

treatment, divided into two groups: no olfactory cleft polyps (resolution group) and residual polyps (residual group) at week 16 after dupilumab treatment. In terms of patient background, the total IgE level at baseline was predominantly higher in the group with residual polyps, but no significant difference was observed in other parameters. In terms of changes from baseline at 16 weeks after initiation of dupilumab treatment, the resolution group showed improvement in all parameters except blood eosinophils. In contrast, only SNOT-22 improved in the residual group, whereas the other parameters showed little improvement (Figure S1). Furthermore, the improvement factor in NPS and T&T recognition thresholds was not significantly better in the residual group than in the resolution group.

Table 2 shows the histopathological diagnosis of olfactory cleft polyps in the residual polyp group at 16 weeks following dupilumab treatment. The degree of inflammatory cell infiltration, including eosinophils, differed in each case, but all cases showed REAH with inflammatory polyps (Figure 2 and Figure S2).

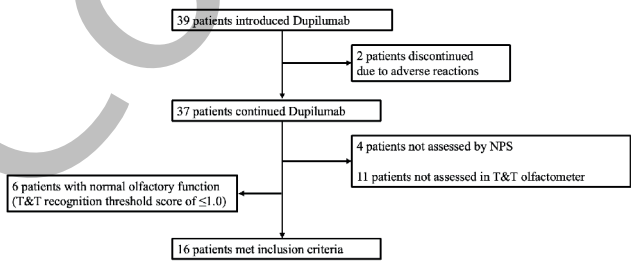

Figure 1. Patient disposition. During this period, 39 patients were introduced to dupilumab, and 16 patients met the inclusion criteria for this study.

All cases with residual polyps in the olfactory cleft showed histopathological findings of REAH with inflammatory polyps. In the group with residual olfactory cleft polyps, the degree of improvement in olfaction with dupilumab was lower. REAH is a reactive disease causing marked glandular proliferation with multilineage ciliated respiratory epithelium lining arising from the epithelial surface[9]. As REAH is a reactive rather than inflammatory lesion, unlike ECRS, which causes type 2 inflammation, it is difficult to predict the efficacy of dupilumab, and the presence of REAH in the olfactory cleft may result in lesser improvement in olfaction.

Table 2. Histopathological diagnosis of olfactory cleft polyps in the residual polyp group.

				Features of REAH			Features of Inflammatory Polyps				
Case No.	Age	Sex	Histopathology	Glandular Proliferation	Surface Epithelial Invagination	Periglandular Hyalinization	Stromal edema	Eosinophils Infiltration	Lymphocyte/ Plasmacytoid Infiltration	Vascular Proliferation	time from last surgery to dupilumab introduction (years)
1	70	M	REAH	+++	o	o	-	-	+	o	8
2	70	F	REAH with Polyps	+++	o	o	+	++	++	o	19
3	72	F	REAH with Polyps	++	o	o	++	+++	+	-	3
4	52	F	REAH with Polyps	++	o	o	-	++	++	-	2
5	51	M	REAH with Polyps	++	o	o	+	+	+	o	10
6	63	M	REAH with Polyps	+	o	o	++	++	+	o	5

o: Existence. -: Absence. +: Mild existence. ++: Moderate existence. +++: Severe existence. REAH, respiratory epithelial adenomatoid hamartoma

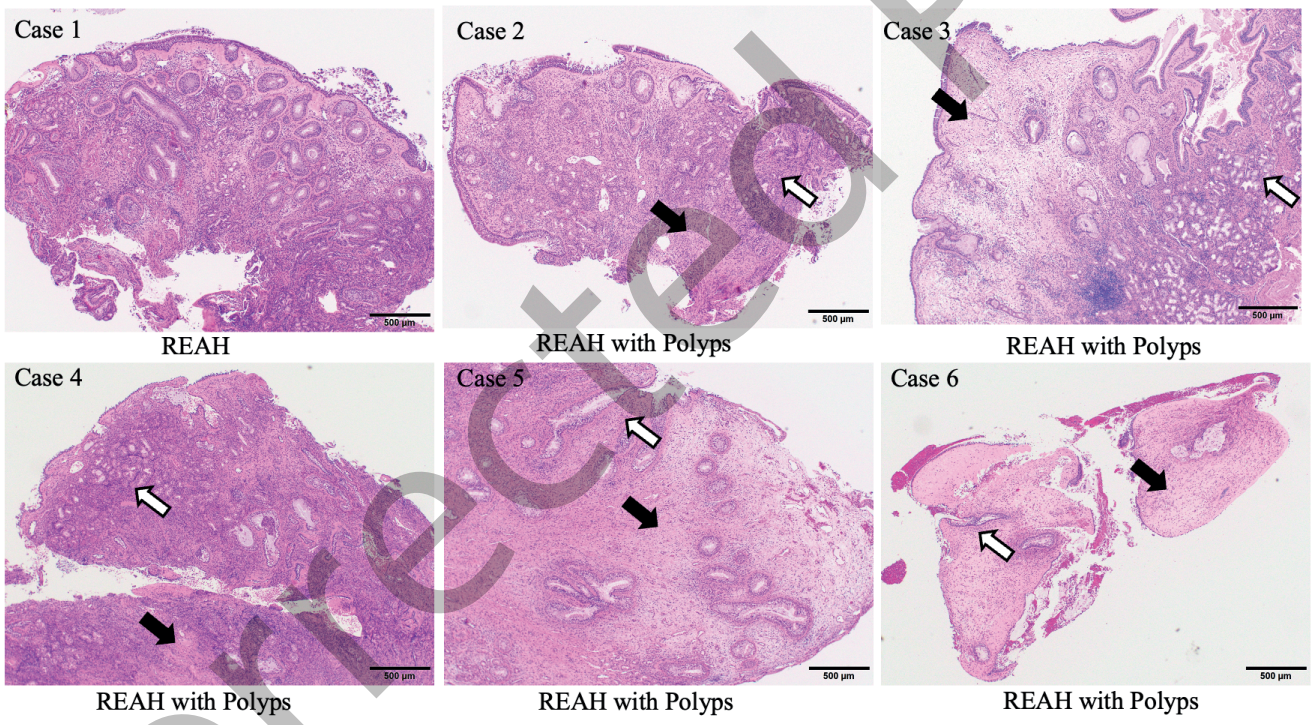

Figure 2. Olfactory cleft polyps in the residual polyp group at 16 weeks following dupilumab treatment. REAH: respiratory epithelial adenomatoid hamartoma. White arrow: pathological image showing REAH. Black arrow: pathological image showing inflammatory polyps.

It is necessary to exclude REAH with inflammatory polyps to increase the effectiveness of dupilumab in improving olfactory function. However, since REAH often occurs secondary to the progression of the disease[10], it is also short-sighted to conclude that the absence of REAH in the histopathological results at the time of the final surgery excludes REAH. The definitive diagnosis of REAH is through pathological diagnosis by biopsy, but biopsy of the olfactory cleft is not recommended because of the potential risk of skull base injury. An olfactory cleft extension of ≥10 mm on sinus computed tomography (CT) scan is highly likely to indicate REAH[11]. Therefore, evaluating the opening of the olfactory fissure by sinus CT before dupilumab administration is also recommended. Future studies are needed to find a better method to diagnose the disease.

A limitation of this study is the small sample size, which limited statistical generalizability. Moreover, we could not determine whether the predominantly higher baseline total IgE level in

the group with residual polyps contributed to the outcomes because of the small number of patients.

Regarding total IgE levels as a predictor of the effect of dupilumab treatment, a report on asthma showed that dupilumab improves asthma symptoms without affecting the level of total IgE before the introduction of dupilumab[12]. However, since the correlation between CRSwNP and IgE levels has not been investigated, further studies with a larger number of patients are needed to address this issue, and multivariate analysis should be performed.

In conclusion, we investigated the efficacy of dupilumab based on the morphology of the olfactory clefts at 16 weeks of treatment. Patients with residual olfactory cleft polyps had REAH with inflammatory polyps and showed fewer olfaction improvements. Elucidation of the clinical and biological profiles of REAH with inflammatory polyps may lead to more selective treatment strategies for difficult-to-treat CRS.

Abbreviations

CRSwNP, chronic rhinosinusitis with nasal polyposis; CT, computed tomography, ECRS, eosinophilic chronic rhinosinusitis; NPS, nasal polyp score; SNOT-22, Sinonasal Outcome Test; REAH, respiratory epithelial adenomatoid hamartoma.

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Authorship contribution

TT was responsible for data collection and management, data analysis, and manuscript writing. NY, EM, MM, MT, KO collected the data. NF, RS analyzed data. EM, KO, NO edited the manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

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Ethics approval and consent to participate

All procedures were performed in accordance with the ethical standards of the Ethics Committee of the Jikei University School of Medicine (Protocol No. 33-019) and adhered to the tenets of the 1964 Declaration of Helsinki and its later amendments.

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon request. The data are not publicly available due to privacy and ethical restrictions.

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Teppei Takeda, MD
Department of Otorhinolaryngology
The Jikei University School of Medicine
3-19-18 Nishi-shinbashi
Minato-ku
Tokyo, 105-8471
Japan

Tel: +81-3-3433-1111
Fax: +81-3-3578-9208
E-mail address:
t-takeda.1020@jikei.ac.jp
ORCiD ID: https://orcid.org/0000-0002-7549-4856

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SUPPLEMENTARY MATERIAL

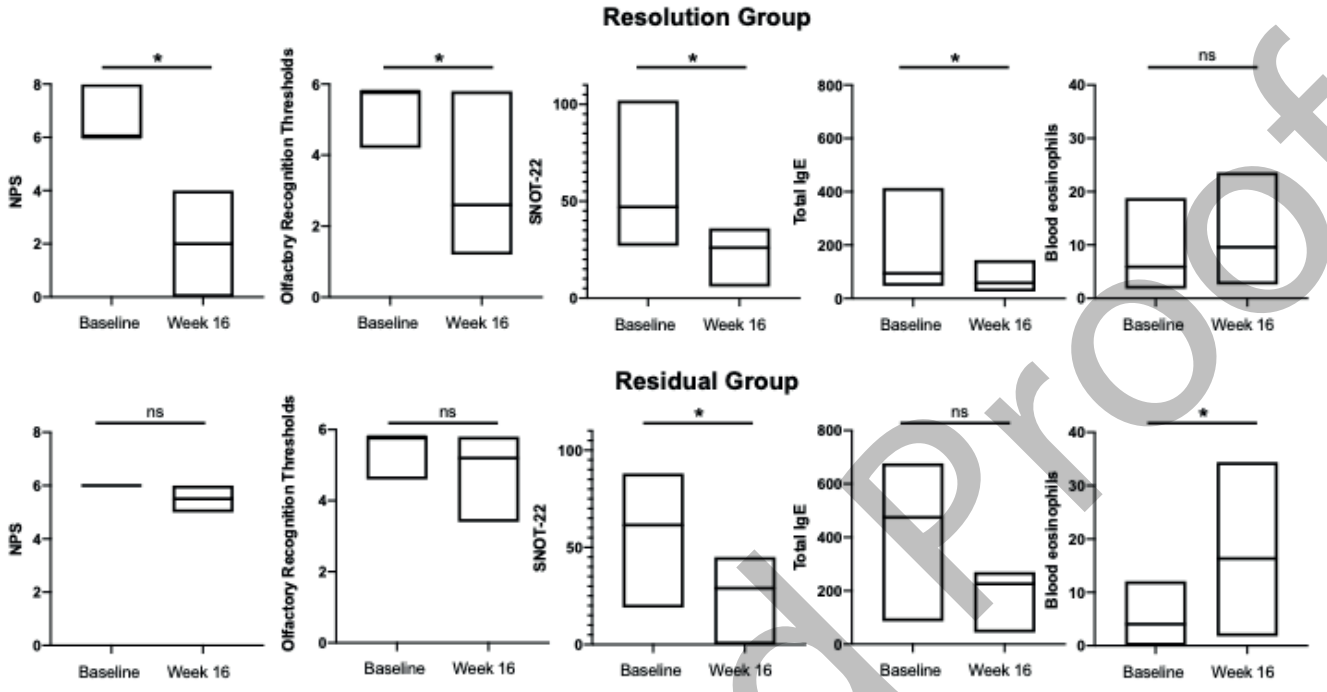

Figure S1. Comparison between baseline and week 16 of introduction for each parameter. No olfactory cleft polyps (Resolution group) and residual polyps (Residual group) at week 16 after dupilumab treatment. *; statistically significant difference ($p<0.05$). ns; No statistically significant difference. NPS; nasal polyp score. SNOT-22; Sinonasal Outcome Test.

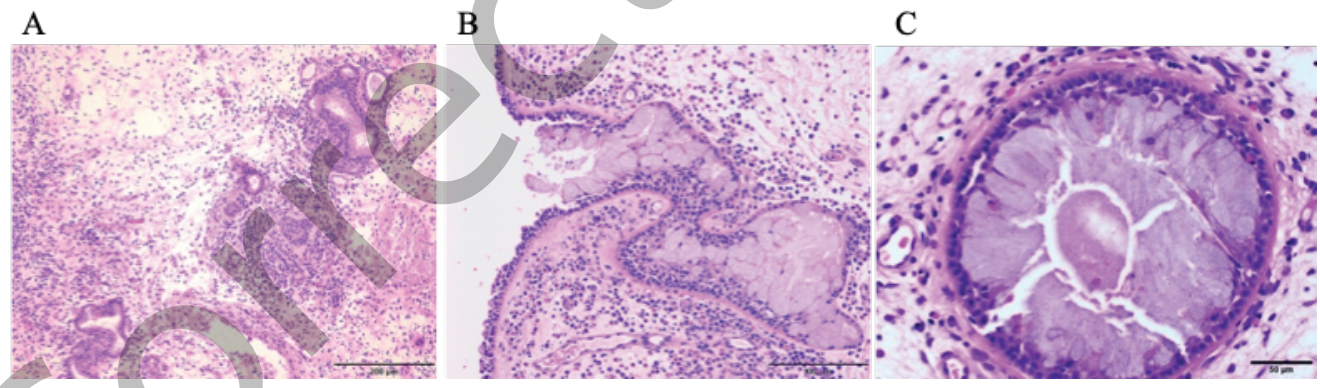

Figure S2. Histologic features of Respiratory Epithelial Adenomatoid Hamartoma (REAH). A; Glandular proliferation. The presence of a glandular proliferation with a polypoid appearance. The proliferation tends to be submucosal. B; Surface epithelial invagination. Figure shows epithelial invagination. C; Periglandular hyalinization. Stromal hyalinization may be seen but is not present in all cases.