Effectiveness of dupilumab treatment against refractory eosinophilic chronic rhinosinusitis

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Background: Eosinophilic chronic rhinosinusitis (ECRS) is a subgroup of chronic rhinosinusitis with nasal polyps (CRSwNP), which is a disease characterized by eosinophilic infiltration of the sinonasal mucosa. Few studies that reported the effect of dupilumab on CRSwNP focused on a single phenotype of CRSwNP, such as ECRS.

Objectives: This study aimed to determine the effectiveness of dupilumab in ECRS with postoperative recurrence.

Methods: We retrospectively enrolled 107 patients and assessed the effectiveness of dupilumab by various clinical outcomes. We performed multivariable analysis on nasal polyp score (NPS) and computed tomography score and a meta-analysis of the effect of dupilumab on chronic rhinosinusitis regarding improvement in the NPS.

Results: At 12 months of dupilumab treatment, there were 65 patients (60.7%) in the excellent response group and 42 (39.3%) in the moderate response group. Nasal polyps had disappeared in 91 patients (85.9%) at 12 months, and there was improvement in all end points; 104 patients (97.2%) were able to eliminate systemic corticosteroid therapy. In the multivariate analysis, male sex was significantly associated with patients who did not show an improvement to 0 in the NPS and computed tomography score (odds ratios: 7.58 and 2.45; $P = .01$ and $P = .04$, respectively). The meta-analysis showed that dupilumab treatment resulted in a trend toward better improvement in the NPS (mean difference = −5.41) than previously reported results.

Conclusions: Dupilumab shows effectiveness in treating ECRS and could serve as an alternative therapeutic option to systemic corticosteroids. This effectiveness may be further enhanced by limiting the target population to recurrent ECRS. (J Allergy Clin Immunol Global 2025;4:100412.)

Key words: *Eosinophilic chronic rhinosinusitis, dupilumab, corticosteroid, meta-analysis*

Chronic rhinosinusitis (CRS) is a multifactorial and heterogeneous disease characterized by the presence of symptoms, such as nasal blockage, obstruction, congestion, nasal discharge, facial pain/pressure, and a reduction or loss of sense of smell for longer than 12 weeks.[1,2] Eosinophilic CRS (ECRS) is a subgroup of CRS and is a disease characterized by eosinophilic infiltration of the sinonasal mucosa.[3] Independent clinical features of ECRS, such as bilateral nasal polyps, ethmoid sinus dominant opacification on computed tomography (CT), peripheral blood eosinophilia, and concomitant bronchial asthma, have led to ECRS being treated as 1 phenotype of CRS in the guideline.[1] The pathogenesis of ECRS is also different from that of non-ECRS, and ECRS may form 1 endotype.[4]

CRS can recur postoperatively even when endoscopic sinus surgery (ESS) is performed properly without residual lamellae of the sinuses. Postoperative treatments, such as intranasal corticosteroid sprays and saline lavage of the sinuses, are not sufficient to control the recurrent condition, and systemic corticosteroids are required in some cases. However, the long-term use of systemic corticosteroids leads to several side effects including osteoporosis, hyperglycemia, and ease of infection,[5] and alternative treatment is desired. In Japan, dupilumab is approved for treating recurrent CRS with nasal polyps (CRSwNP), following the approval for bronchial asthma and atopic dermatitis since March 2020. The indication for dupilumab is restricted to recurrent CRSwNP, and the medical insurance system largely limits this indication to moderate and severe ECRS as defined by the JESREC (Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis) study.[6] Therefore, dupilumab is only used for recurrent moderate or severe ECRS in Japan. However, there have been limited reports on the effectiveness of dupilumab in the single phenotype.

Therefore, we evaluated the effectiveness of dupilumab in patients treated with dupilumab for moderate and severe ECRS that recurred after surgery. We also analyzed the risk factors for incomplete therapeutic response to dupilumab based on nasal polyp score (NPS) and CT score not improving to 0 and compared our results with other studies using a meta-analysis.

METHODS

Study design and participants

This was a retrospective, single-center study and the study protocol was approved (33-407[11032]) by the Ethics Review Board of The Jikei University School of Medicine.

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Abbreviations used
CRS: Chronic rhinosinusitis
CRSwNP: Chronic rhinosinusitis with nasal polyps
CT: Computed tomography
ECRS: Eosinophilic chronic rhinosinusitis
ESS: Endoscopic sinus surgery
EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps
FENO: Fractional exhaled nitric oxide
ILC2: Group 2 innate lymphoid cells
NPS: Nasal polyp score
T&T: Toyoda and Takagi

Patients with CRS initially received long-term and low-dose clarithromycin treatment for ≥3 months and intranasal corticosteroid spray at our hospital. When these therapies were inadequately effective, they all had ESS. The exclusion criteria were known hypersensitivity to dupilumab, cystic fibrosis, and pregnancy. ECRS was diagnosed when the patient met the criteria of a JESREC score ≥11 and mucosal eosinophil count in nasal polyps ≥70/hpf.[7] Details about ECRS are available in this article's Online Repository at www.jaci-global.org. We considered initiating dupilumab treatment for patients who were refractory to various treatments, including systemic or intranasal corticosteroids after ESS. No residual lamellae were confirmed in all patients after ESS on CT. The CT scan was performed using the 3D Accuitomo 170 XYZ Slice View Tomograph (Morita Co, Ltd, Kyoto, Japan). Of these patients, those with an NPS ≥5 (0-8), nasal congestion severity grade ≥2 (0-3), and subjective symptoms of anosmia and rhinorrhea lasting ≥8 weeks, and who agreed to use dupilumab were administered dupilumab 300 mg and enrolled in this study. Whether patients used corticosteroids prior to dupilumab administration was not included as enrollment or exclusion criteria. The enrolled flowchart is shown in Fig E1, *A* in this article's Online Repository at www.jaci-global.org. Patients with bronchial asthma and nonsteroidal anti-inflammatory drug–exacerbated respiratory disease were diagnosed by respiratory physicians. Eosinophilic otitis media was diagnosed by confirming eosinophil infiltration in the middle ear effusion.[8] All data were collected after review of medical records.

Assessment of effectiveness of dupilumab

We performed the following outcome measures before dupilumab treatment and at 3 and 12 months after starting to use dupilumab to evaluate its effectiveness. The outcome measures were the NPS,[8] the CT score,[9] Toyoda and Takagi (T&T) olfactometry,[10] Open Essence,[11] the Self-Administered Odor Questionnaire,[12] rhinomanometry, fractional exhaled nitric oxide (FENO) test, the blood eosinophil count, and total IgE. Once patients were sufficiently accustomed to self-administering dupilumab, they were assessed approximately every 3 months to monitor its effectiveness. If dupilumab was effective, we reduced the prednisolone dose by 1 mg/day. After the patients were weaned off from prednisolone, the dupilumab dose was tapered every 2, 3, and 4 weeks using the same protocol. The patients also self-reported their symptoms every 2 weeks by using a symptom diary made by Sanofi (Paris, France) to analyze subjective symptoms. The symptom diary includes the score of nasal obstruction, olfactory disturbance, and rhinorrhea. This scoring system is from 0 (no symptoms) to 3 (severe). Additionally, the total rhinosinusitis visual analog scale score (0-10) was used. We evaluated the effectiveness of dupilumab using the guidelines presented in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 (in this article's Online Repository at www.jaci-global.org).[1]

Univariate and multivariate logistic regression analysis

The NPS and CT score were also used as objective variables to examine risk factors for failure to achieve complete healing after 12 months of dupilumab administration. A univariate logistic regression analysis was performed using sex, age, history of multiple surgeries, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease, the T&T recognitive score, FENO, and the percentage of the blood eosinophil count, mucosal eosinophils count, and total IgE as explanatory factors. The multivariate analysis was conducted using a forward stepwise selection method.

Meta-analysis

A systematic review and meta-analysis of the effectiveness of dupilumab treatment for CRS using the NPS were performed. Two authors (D.N. and T. Nakayama) were responsible for screening all titles and abstracts and evaluating the complete text of the articles. Retrospective studies using dupilumab for uncontrolled CRS not responding to existing therapy were included. Studies in which the NPS was not evaluated or dupilumab was not administered for 12 months, and the participants who had cystic fibrosis or immunodeficiency were excluded. Data extraction was performed through PubMed (2015 to October 2023) and the Cochrane Library (2019 to October 2023) using the following string: "chronic rhinosinusitis" AND "dupilumab." After duplicate records of 34 articles were excluded and the initial screening process of the titles and abstracts excluded 362 articles, 338 articles not targeted for CRS or without original data such as review and meta-analysis. Two articles that lacked NPS data were excluded, and we read 22 full-text articles to assess for eligibility. Five retrospective studies on dupilumab administration for 12 months were selected, and the NPS at predupilumab treatment and postdupilumab treatment at 12 months were extracted by 2 reviewers. Finally, we performed a meta-analysis of the NPS including our results. A PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) diagram of the study selection progress is shown in Fig E1, *B*.

Statistical analyses

Statistical analyses were carried out using R 4.1.3 (R Institute for Statistical Computing, Vienna, Austria). The distribution of data was examined with the Shapiro-Wilk test. Differences in data before and after treatment were analyzed by the Wilcoxon signed-rank test. Friedman test with the Nemenyi post hoc test was used for comparison of data at 3 time points. The univariate and multivariate analyses were performed using IBM SPSS

version 29 (IBM Inc, Armonk, NY). The meta-analysis was performed with EZR[13] (Saitama Medical Center, Jichi Medical University, Saitama, Japan) software package, which is a graphical user interface for R.

RESULTS

We retrospectively enrolled 167 patients treated with dupilumab for recurrent ECRS between April 2017 and May 2023. Four patients were excluded owing to insufficient data. Of these 163 patients, 56 were excluded because they were not administered dupilumab for >12 months. Finally, 107 patients were enrolled in the study. Table I shows the demographics of the patients. Of the 107 patients selected, 54 were women and 53 were men. The patients' age ranged from 21 to 75 years, with a mean age of 48 years. A total of 101 patients had bronchial asthma, 37 had nonsteroidal anti-inflammatory drug–exacerbated respiratory disease, and 10 had eosinophilic otitis media, of whom the effectiveness of dupilumab was previously reported.[14] A total of 90 patients underwent surgery at our hospital and 17 at other institutions. All patients were diagnosed with ECRS according to the definition of the JESREC study.[7] The severity of the disease was classified as severe in 51 patients, moderate in 53 patients, and mild in 3 patients.

The NPS, CT score, T&T recognitive threshold score, Open Essence score, and Self-Administered Odor Questionnaire score were significantly improved at 3 months compared with predupilumab administration (baseline), and showed further improvement at 12 months (all $P < .05$) (Fig 1). Similarly, FENO showed significant improvement at 3 and 12 months compared with baseline (both $P < .01$). However, rhinomanometry did not significantly improve after 3 months of dupilumab use, but it showed improvement after 12 months of continuous use compared with baseline ($P = .17$ and $P = .02$, respectively). Moreover, the blood eosinophil count was significantly increased at 12 months compared with baseline ($P < .01$). However, no adverse events, such as eosinophilic pneumonia and eosinophilic granulomatosis with polyangiitis, were observed. Total IgE concentrations were significantly lower at 3 and 12 months than at baseline (both $P < .01$). Additionally, the NPS, CT score, and total IgE were significantly improved at 12 months compared with 3 months ($P < .01$, $P < .01$, and $P < .01$, respectively) (Fig 1).

To visualize the course of treatment with dupilumab, alluvial plots were created to show changes in flow over time. Among the 107 patients, at 3 months, 47 patients (43.9%) in the excellent response group met 5 EPOS 2020 criteria[1] related to nasal polyp size, systemic corticosteroids, quality of life, sense of smell, and comorbidities; 56 (52.3%) in the moderate response group met 3 to 4 criteria; and 4 (3.7%) in the poor response group met 1 to 2 criteria. At 12 months of treatment, there were 65 patients (60.7%) in the excellent response group and 42 (39.3%) in the moderate response group (Fig 2).

Subjective symptoms scores using the symptom diary are shown in Fig E2 in this article's Online Repository at www.jaci-global.org. The total rhinosinusitis visual analog scale score, which is the sum of nasal obstruction, olfactory disturbance, rhinorrhea, and their 3 symptom scores, were significantly improved at 2 weeks after dupilumab treatment (all $P < .01$) compared to baseline and remained improved after 12 months. A total of 104 patients (97.2%) were weaned from systemic corticosteroid therapy and were able to extend the dupilumab dosing interval (Fig 3). At 12 months, 30 (28.0%) and 31 patients (29.0%) were able to extend the dosing interval up to 4 weeks and up to 3 weeks, respectively. Of the 107 patients, 91 showed improvement in the NPS (= 0) and 36 patients showed improvement in the CT score (= 0). In the multivariate analysis, male sex was significantly associated with patients who did not show an improvement to 0 in the NPS and CT score (odds ratios: 5.67 and 2.44; $P = .01$ and $P = .04$, respectively). High FENO was significantly associated with patients who did not show an improvement to 0 in the CT score (odds ratio: 1.01; $P = .04$) (Table II).

TABLE I. Clinical characteristics of the patients

	N = 107
Age (y)	47.7 ± 10.1
Male	53 (49.5)
Asthma	101 (94.4)
N-ERD	37 (34.6)
EOM	10 (9.3)
No. of previous surgeries	
1	67 (62.6)
2	22 (20.6)
>3	16 (15.0)
Blood eosinophils, %	
Mean	5.6 ± 5.0
Median	4 (2-7)
Serum total IgE (IU/mL)	
Mean	346.0 ± 460.0
Median	187 (87-362)
Mucosal eosinophil count (/hpf)	
Mean	146.4 ±142.5
Median	120 (77-167)
NPS (0-8)	
Mean	5.9 ± 0.4
Median	6 (6-6)
CT score (Lund-Mackey)	
Mean	13.3 ± 4.7
Median	13 (10-17)
T&T recognitive score	
Mean	4.4 ± 1.7
Median	5.6 (3.0-5.8)
Open Essence	
Mean	3.6 ± 3.4
Median	3 (0-6)
Severity of ECRS	
Mild	3 (2.8)
Moderate	53 (49.5)
Severe	51 (47.7)
Baseline medications	
PSL usage	102 (95.3)
PSL dosage (mg/d)	
Mean	4.1 ± 0.2
Median	5 (4-5)
Short-term escalation of PSL in the previous 12 mo	59 (55.1)
INS	107 (100.0)
LTRAs	105 (98.1)
Antihistamines	99 (92.5)
ICS	75 (70.1)

Values are mean ± SD, n (%), or median (IQR).
EOM, Eosinophilic otitis media; *ICS*, inhaled corticosteroids; *INS*, intranasal corticosteroids; *LTRAs*, leukotriene receptor antagonists; *N-ERD*, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease; *PSL*, prednisolone.

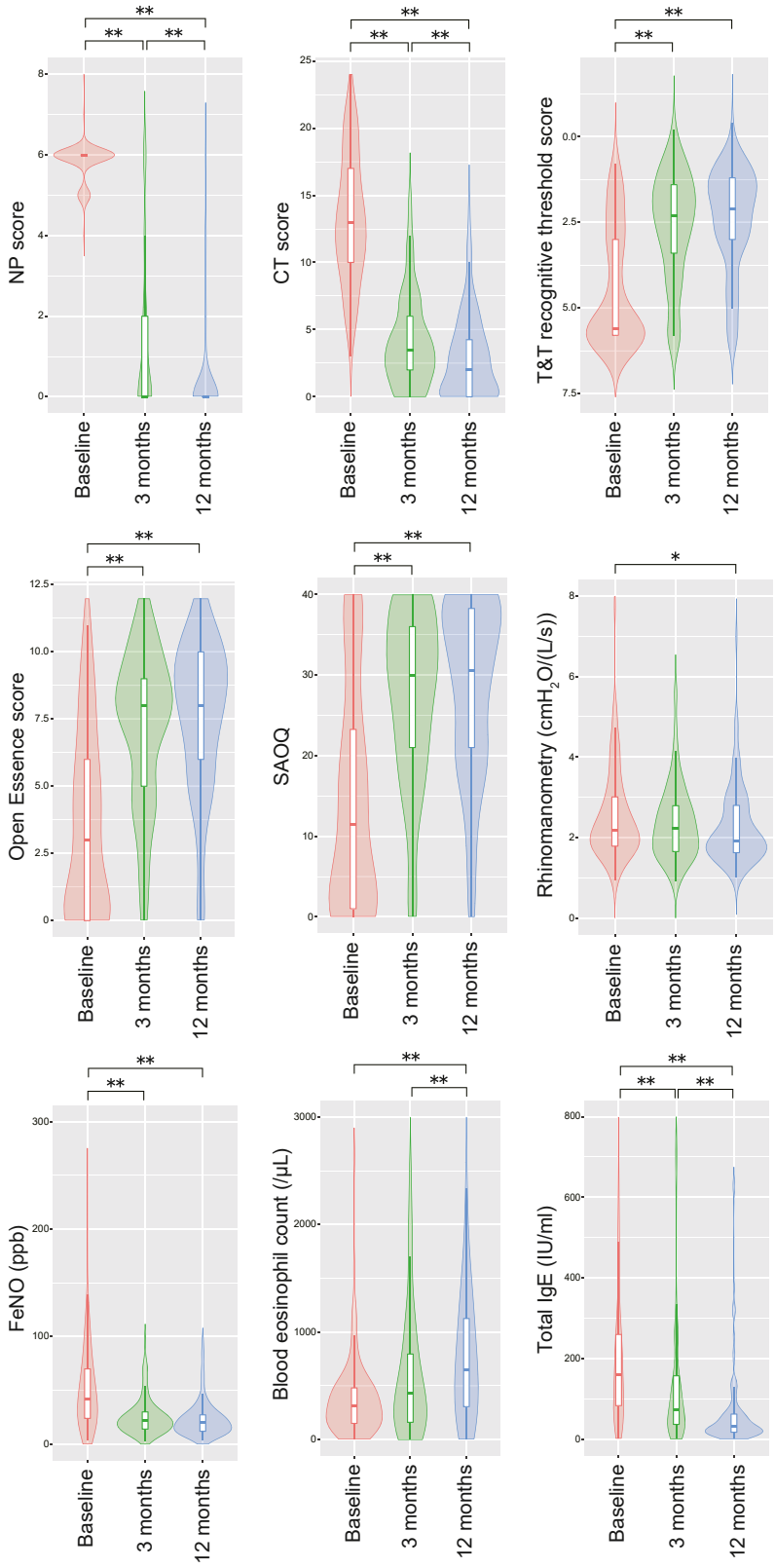

FIG 1. Comparison of the therapeutic effects of dupilumab treatment for ECRS between before treatment (baseline) and at 3 and 12 months after treatment. Data were analyzed by the Wilcoxon signed-rank test; $*P < .05$, $**P < .01$. *SAOQ*, Self-Administered Odor Questionnaire.

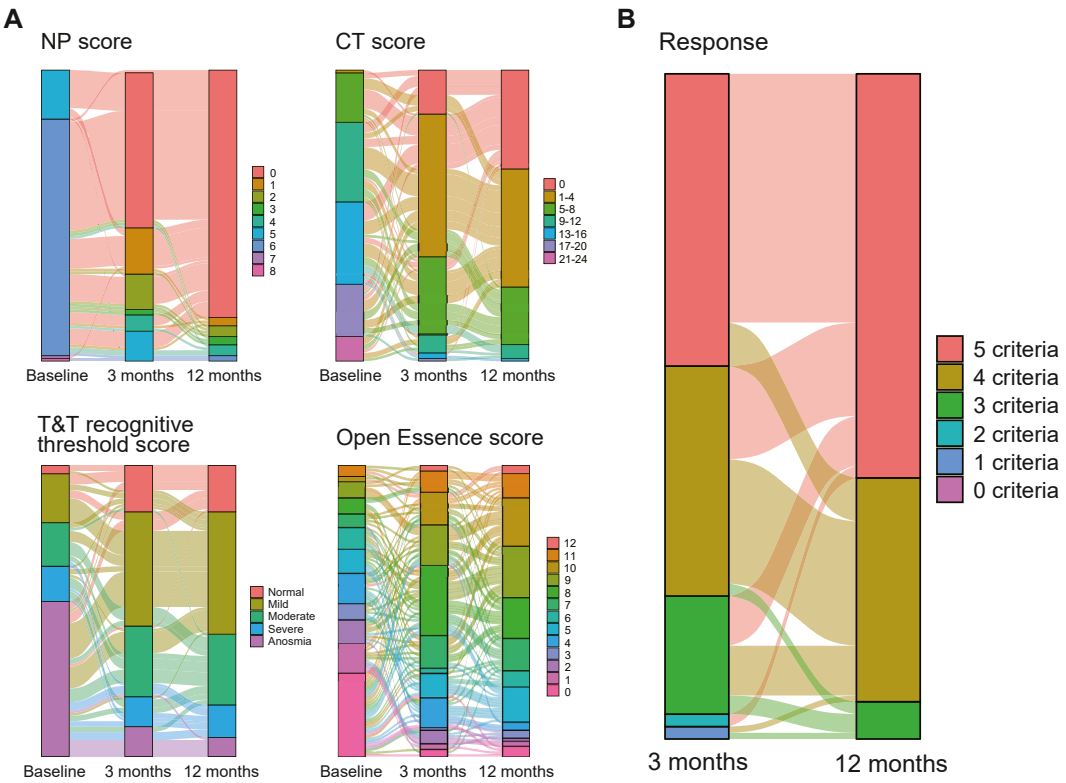

FIG 2. Alluvial plots of the nasal polyp score, computed tomography score, T&T recognitive threshold score, and Open Essence score **(A)** and the therapeutic response based on EPOS 2020 **(B)**.

We performed a meta-analysis of NPS at 12 months after dupilumab administration. Six studies including our study reported changes in the NPS with dupilumab administration and adopted in the analysis (Table E1 in this article's Online Repository at www.jaci-global.org). These findings showed a significant reduction in the NPS at 12 months after dupilumab treatment compared with baseline, although there was considerable heterogeneity between studies ($I^2 = 95\%, \tau^2 = 0.64, P < .01$). The effect of dupilumab on the NPS in our study was greater than that in other studies (mean difference = −5.41; 95% CI: −5.66 to −5.16) (Fig 4).

DISCUSSION

Dupilumab inhibits signaling of IL-4 and IL-13 through binding to IL-4α and suppresses type 2 inflammation in ECRS. We previously reported that dupilumab showed effectiveness for mild-to-moderate asthma complicated by ECRS and in 10 eosinophilic otitis media cases associated with ECRS.[14,15] The effectiveness of dupilumab in uncontrolled CRSwNP has been reported in real-world data from many countries, following phase III randomized, controlled trials by Bachert et al.[16] Torretta et al[17] and De Corso et al[18] showed excellent-moderate responses in 92.5% and 97.5%, respectively, of patients at 12 months based on EPOS 2020 criteria[1] in Italy. In another study by van der Lans et al[19] in The Netherlands, the excellent response rate was 94.2% at 12 months according to the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) 2023 biological response.[20] In these studies, dupilumab was indicated for CRSwNP cases that did not improve with existing therapy clinically, and the tissue eosinophil count in the sinonasal mucosa was not measured. In contrast to these studies, dupilumab was administered to patients with a mucosal eosinophil count >70/hpf and a JESREC score >11 who relapsed after surgery in our study. The surgical procedure was also performed with the maxillary, sphenoid, and frontal sinus opened as much as possible, and total ethmoidectomy. Residual lamellae in the ethmoid sinuses, which can cause recurrence[21,22] was not confirmed on CT (Fig E3 in this article's Online Repository at www.jaci-global.org). Therefore, we administered dupilumab only to patients with ECRS who had recurrence, despite appropriate surgery.

In our study, an excellent-moderate response was observed in 100% of patients (107 of 107 patients) at 12 months based on EPOS 2020 criteria.[1] The meta-analysis, which included our data with previous studies,[17-19,23,24] also strengthened the evidence supporting the benefit of 1 year of dupilumab administration for NPS. However, our study observed a greater reduction in NPS, with a mean difference of 5.41, compared to a decrease of approximately 2 in prior studies after 12 months of treatment. A potential explanation for this substantial difference in meta-analysis may be the distinct characteristics of our study population. Specifically, our cohort consisted of patients with recurrent ECRS who had undergone prior surgical intervention and exhibited a mean tissue eosinophil count of 146.4 ± 142.5/hpf, with no residual lamellae observed on postoperative CT. In contrast, earlier studies included in the meta-analysis did not uniformly apply surgical treatment nor did they consistently assess tissue eosinophil levels. This variation suggests that our study population represents a more specific type 2 endotype, which is more responsive to biologic therapy targeting IL-4 and IL-13 pathways.

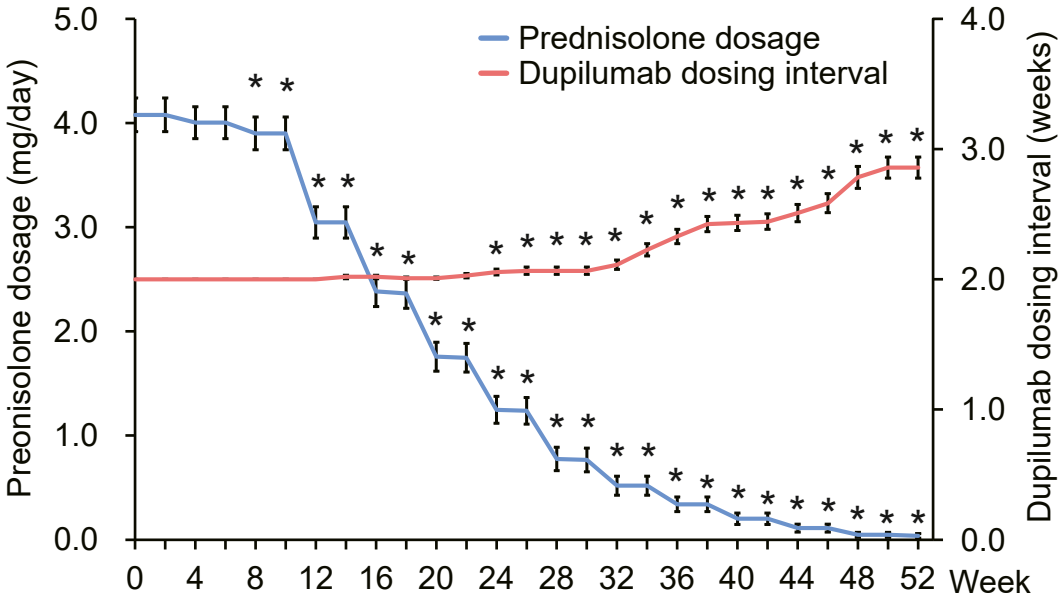

FIG 3. Line graphs show changes in the mean ± SE of the prednisolone dose and mean ± SE of the dupilumab dosing interval after dupilumab therapy. The horizontal axis represents the weeks from starting dupilumab therapy. The left vertical axis represents the prednisolone dose (mg/day), and the right vertical axis represents dupilumab dosing therapy (weeks).

TABLE II. Univariate and multivariate logistic regression analysis of risk factors for not improving to a score of 0 at 12 months for the NPS and CT score

	Univariate			Multivariate		
Risk factor	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Risk factor for not improving to 0 of NPS						
Male	5.52	1.65-25.30	.01	5.67	1.51-21.27	.01
Age (y)	1.00	0.95-1.06	.98	—	—	—
Multiple surgeries	1.47	0.95-2.22	.07	—	—	—
N-ERD	1.58	0.52-4.66	.41	—	—	—
T&T recognitive score	1.34	0.94-2.08	.14	—	—	—
FENO (ppb)	1.01	0.99-1.02	.28	—	—	—
Serum eosinophils (%)	1.03	0.93-1.13	.51	—	—	—
Mucosal eosinophils count (/hpf)	0.99	0.98-1.00	.25	—	—	—
Total IgE (IU/mL)	1.00	0.99-1.00	.82	—	—	—
Risk factor for not improving to 0 of CT score						
Male	2.36	1.04-5.52	.04	2.44	1.05-5.71	.04
Age (y)	0.98	0.95-1.02	.46	—	—	—
Multiple surgery	0.95	0.66-1.40	.80	—	—	—
N-ERD	0.92	0.40-2.17	.85	—	—	—
T&T recognitive score	0.99	0.78-1.25	.96	—	—	—
FENO (ppb)	1.01	1.00-1.03	.04	1.01	1.00-1.03	.04
Serum eosinophils (%)	1.00	0.92-1.09	.97	—	—	—
Mucosal eosinophils count (/hpf)	1.00	0.99-1.00	.15	—	—	—
Total IgE (IU/mL)	1.00	0.99-1.00	.16	—	—	—

OR, Odds ratio.

This may explain the superior outcomes observed in our study. However, it is important to note that we did not measure cytokine and chemokine levels in the nasal polyps, limiting our ability to definitively confirm whether this population represents a true type 2 endotype. Future studies investigating the molecular profile of these patients will be essential to validate our findings and further refine the identification of subgroups most likely to benefit from dupilumab treatment.

Almost all patients (97.2%) in this study could be weaned off systemic corticosteroids by 52 weeks. Although systemic corticosteroids are effective in patients with ECRS, long-term corticosteroid use should be avoided because of a wide variety of adverse events, including osteoporosis, hyperglycemia, and ease of infection.[5] The clinical effectiveness at 12 months after patients were able to wean off from systemic corticosteroids was similar to or better for clinical items than at 3 months when

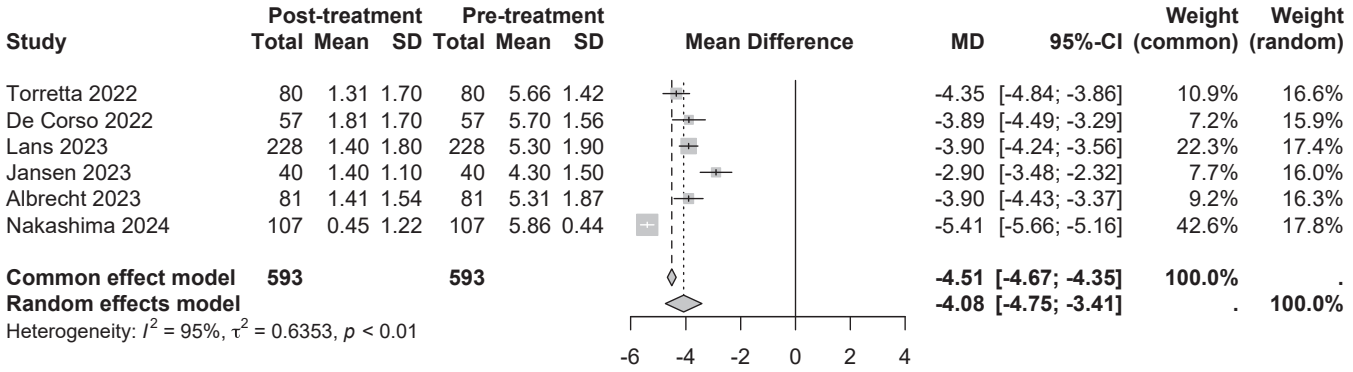

FIG 4. Meta-analysis of the effectiveness of dupilumab as assessed by the nasal polyp score. *MD,* Mean difference.

many patients were still using corticosteroids. This finding suggests that dupilumab has a potential benefit over oral corticosteroids with fewer adverse events.

However, the method of discontinuation of oral corticosteroids requires attention.[25] We did not immediately discontinue oral corticosteroids after initiating dupilumab, but they were reduced after the disappearance of nasal polyps. Subsequently, dupilumab dosing intervals were extended after the patients were able to wean completely from corticosteroids. This extension is another reason why dupilumab was highly effective in this study and may also be a way to prevent treatment-emergent eosinophilia and associated complications observed with dupilumab. In fact, no cases of eosinophilic pneumonia were observed in our study. Although some reports have suggested that the increase in the blood eosinophil count with dupilumab is transient,[26] in our study, there was still a significant increase at 12 months of treatment compared with baseline, and this count was higher than that at 3 months. In patients receiving dupilumab, blood eosinophilia may not be transient, and this should be checked by blood tests and physicians should be aware of possible hypereosinophilic symptoms. We also found a significant decrease in total IgE compared to the baseline. Local IgE in nasal polyp of patients with CRSwNP has been shown to be associated with nasal polyp pathogenesis, including local eosinophil cationic protein levels.[27] In this study, dupilumab reduced total IgE, but future studies are needed to determine whether it also local IgE in nasal polyps.

Unlike asthma, extension of the dosing interval to once every 4 weeks has been approved for CRSwNP in Japan. Van der Lans et al[19] investigated whether extending dosing intervals is associated with clinical effectiveness. They reported that tapering was feasible in 93.7% of patients with CRSwNP at 12 months, and no significant difference was observed when the dosing interval was extended up to 8 weeks. In the present study, tapering was possible in more than one-half of the patients (57.0%), and an exacerbation of asthmatic conditions or elevation of nitric oxide was not observed with the extended administration period. There is still no established consensus on the duration of dupilumab administration. In this study, 12-month treatment outperformed 3-month treatment in multiple measures, including the NPS, the CT score, the T&T cognitive score, and FENO. Tsunemi et al[28] reported an improvement in the CT score and T&T detection/recognition threshold with the long-term use of dupilumab for approximately 1.5 years compared with short-term use. They concluded that dupilumab should be administered for longer than 1 year. Our results are consistent with their study, as we found an improvement in olfactory function, both subjectively and objectively, even after 1 year. Reporting new studies on the duration of administration is required as the number of patients receiving long-term therapy increases.

We examined groups of patients who did not show an improvement to 0 in the NPS and CT score and found that male sex was a risk factor. Men and women have different immunological responses and T_H2 cell biases, including a higher CD4+ T-cell count and CD4/CD8 T-cell ratio in women.[29] Additionally, the mechanism by which androgens suppress type 2 cytokine production in T_H2 cells is through the binding of dual specificity phosphatase (DUSP)-2 to the androgen receptor, which promotes p38 dephosphorylation.[30] Moreover, sex hormones including androgen and estrogen regulate the development and function of group 2 innate lymphoid cells (ILC2), a potent innate immune cell that contributes to type 2 inflammation.[31,32] In the field of lower airway, estrogen increased IL-33 release and ILC2-mediated airway inflammation, while androgen receptor agonists inhibited ILC2-dependent lung inflammation.[33,34] Therefore, dupilumab may be more effective in women because they have T_H2-cell and ILC2 bias immune response and thus have more type 2 endotypic CRS than men do. In fact, women have more severe disease in CRSwNP[35] and more recurrence after surgery than men do.[36] However, there have been no studies of sex differences in CRS endotypes. Therefore, further investigation is required in the future to examine sex differences of treatment effects.

There are several limitations to our study. First, dupilumab was used in combination with systemic steroids part of the time, which may have affected the therapeutic effect of dupilumab. Second, the number of cases with long-term follow-up is small compared with other reports[16,19] from Europe. We hope to increase the number of cases in the future. Third, this study was not randomized because it lacked a placebo control group and randomization and objective measurements such as the NPS and the CT score were not done in a blind fashion, leaving room for bias. Fourth, we have not endotyped patients by measuring cytokines or chemokines, and phenotypic information limited the number of patients who were eligible for dupilumab. The results of treatment effects in patient groups differentiated by endotyping are required.

CONCLUSIONS

Dupilumab seems effective in ECRS based on various clinical parameters, including olfactory function, and could be an

alternative treatment to systemic steroids. The effectiveness of dupilumab may be further enhanced by limiting the target population to recurrent ECRS.

DISCLOSURE STATEMENT

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Key messages

- **Dupilumab has a high effectiveness in ECRS, including improvement in olfactory function.**
- **The effectiveness would be further enhanced by limiting the target population to ECRS who have type 2 inflammation.**
- **Female patients with ECRS are more likely to benefit from dupilumab.**

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