

Effect of Dupilumab on Depression in Asthma with Eosinophilic Chronic Rhinosinusitis in the Japanese Population

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Keywords

Dupilumab · Asthma · Eosinophilic chronic rhinosinusitis · Depression · Patient Health Questionnaire-9

Abstract

Introduction: Psychological disorders, such as depression, are markedly prevalent in patients with airway diseases. In this study, we assessed the effect of treatment with dupilumab, an IL-4 receptor α chain antibody, on depressive symptoms in a cohort of patients with asthma with eosinophilic chronic rhinosinusitis (ECRS). **Methods:** The study participants, diagnosed with asthma and ECRS, were assessed for symptoms and quality of life (QOL) scores for asthma and ECRS and medications. The Patient Health Questionnaire-9 (PHQ-9) scores were used to evaluate the depressive state. The depressive symptoms were compared with asthma and ECRS symptoms both at the time of initiation and after 4 months of dupilumab treatment. **Results:** Ultimately, 31 patients were included in the study. Most patients demonstrated a depressive state that was correlated with the nasal

symptom score. In the evaluation 4 months after dupilumab treatment, the PHQ-9 score was significantly reduced, and the decrease was remarkable in patients whose nasal symptom score was reduced by 50% or more. Additionally, the PHQ-9 scores in patients with improved nasal and asthma symptoms were significantly reduced. **Discussion/Conclusion:** Dupilumab may improve QOL in patients with bronchial asthma with ECRS by reducing depressive symptoms through the improvement of clinical symptoms.

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Introduction

Eosinophilic chronic rhinosinusitis (ECRS) is a subgroup of chronic rhinosinusitis (CRS) with nasal polyps, which is associated with severe eosinophilic infiltration and intractable. ECRS is an important comorbidity of asthma and is associated with an intractable pathophysi-

Edited by: D.Y. Wang, Singapore.

ology [1]. Bresciani et al. [2] reported that asthma severity was correlated with the rate of CRS complications; additionally, the number of peripheral blood eosinophils was positively correlated with the CT scan scores of the sinus lesions. Moreover, it is characterized by its association with upper respiratory tract disease, and often treatment of CRS, such as endoscopic surgery (ESS), has a positive effect on asthma [3, 4].

Dupilumab is a monoclonal antibody against the α chain of the anti-interleukin-4 (IL-4) receptor that blocks the binding of IL-4 and IL-13 to the receptor and inhibits their biological actions. In Japan, it is indicated for atopic dermatitis, bronchial asthma, and CRS with nasal polyps, including ECRS. Reduction of exacerbation, increase in forced expiratory volume of 1 second, improvement of clinical symptoms, and a dose-sparing effect for oral steroids have been reported in bronchial asthma [5, 6]. Moreover, improvement of clinical symptoms, decrease in nasal polyp score, and improvement of imaging findings have been reported for CRS with nasal polyps [7].

Comorbid depression and anxiety symptoms have been reported in bronchial asthma [8–10] and have also been related to the severity of asthma, with approximately 10% of steroid-dependent patients reported to experience high depressive symptoms [11]. Moreover, depressive symptoms constitute a major comorbidity of CRS [12]. Additionally, some studies have reported that the presence of depressive symptoms may hinder treatment of CRS [13, 14]. Currently, treatment options for intractable asthma and chronic rhinosinusitis have increased, and the therapeutic effects have improved; however, reports on improvement in clinical symptoms and psychological status are few. In this study, we administered dupilumab to patients with asthma and ECRS and analyzed both changes in clinical symptoms and parameters and in depression symptoms using the Patient Health Questionnaire-9 (PHQ-9) before and 4 months after treatment.

Materials and Methods

Study Participants

The subjects of this study were patients with bronchial asthma and ECRS who had received dupilumab for >4 months. Thirty-three patients (20 women and 13 men) diagnosed with asthma and ECRS by pulmonologists and otolaryngologists participated in this study. These patients were treated with a combination of dupilumab, medium- to high-dose inhaled corticosteroid (ICS), long-acting β -agonists, and nasal corticosteroids at the Niigata University Medical and Dental Hospital from March 2019 to September 2020. The criteria for ECRS have been previously reported [15]. The criteria for dupilumab administration in this study were the

presence of multiple exacerbations and uncontrolled symptoms in asthma or severe symptoms including olfactory loss and reduced quality of life caused by ECRS. Asthma exacerbation was defined as worsening of asthma such that the treating physician elected to administer or increase the dose of systemic corticosteroids for at least 3 days or the patient visited an emergency department or was hospitalized [16]. In addition to asthma exacerbation, events which required systemic corticosteroids for >3 days due to worsening nasal symptoms were also counted. Finally, 31 patients who used dupilumab for >4 months were analyzed. Of the 2 patients who dropped out, one wished to discontinue dupilumab due to inadequate response and the other discontinued due to general malaise. Five patients had been using benralizumab prior to their enrollment in this study; however, in all cases, 4 months or more had passed since their last dose of benralizumab. This study was conducted in accordance with the ethical principles for medical research involving human subjects and the Declaration of Helsinki and was approved by the Ethics Committee of the Niigata University (Approval No. 2019-0022). All participants provided written informed consent prior to enrollment.

Clinical Assessments

All participants underwent physical examination prior to dupilumab treatment, and we also administered the Asthma Control Test (ACT; Japanese version), Asthma Quality of Life Questionnaire (AQLQ; Japanese version), Sino-Nasal Outcome Test-22 (SNOT-22; Japanese version), and PHQ-9 (Japanese version). The SNOT-22 is well validated as a patient-reported outcome measure of disease severity in rhinology patients [17]. The validity of the Japanese version of the SNOT-22 was confirmed by Ogino-Nishimura et al. [18]. Furthermore, Feng et al. [19] analyzed the SNOT-22 and found 4 distinct constructs that the questionnaire measures, that is, 4 subdomains based on the symptoms (nasal, sleep, otologic/facial, and emotional) (online suppl. Table 1; see www.karger.com/doi/10.1159/000519296 for all online suppl. material). The PHQ-9, consisting of 9 items for depression alone, was developed to evaluate depressive states in actual clinical care. Its sensitivity and specificity have been shown to be higher than those of the other depression questionnaires [20]. The validity of the Japanese version of the PHQ-9 was confirmed by Muramatsu et al. [21, 22]. The dupilumab dose and interval were prescribed according to the indication for asthma in Japan; 300 mg of dupilumab was subcutaneously administered every 2 weeks. After 4 months of treatment, the participants were examined using the same questionnaire to evaluate dupilumab efficacy.

Statistical Analysis

Mann-Whitney *U* tests were used to determine differences between the groups. The correlation between parameters was determined using Spearman's rank analysis. Within-group (e.g., before and after treatment) comparisons were conducted using Wilcoxon's signed-rank test. A χ^2 test was also used to assess the significance of the difference in proportions among groups. Multivariate analysis was used to identify the variables that influenced PHQ-9 improvement. Variables associated with the changes in depressive symptoms were assessed in the multivariable logistic regression analysis. All statistical analyses were performed using the JMP software, version 11 (SAS Institute, Inc., Tokyo, Japan). For all statistical analyses, statistical significance was set at $p < 0.05$.

Table 1. Baseline characteristics

Sex (M/F), <i>n</i>	12/19
Age, years	50.0 (23–69)
Duration (asthma), years	17.0 (1–42)
Duration (ECRS), years	6.0 (1–38)
Smoking (never/past), <i>n</i>	21/10
BMI, kg/m ²	21.8 (16.1–33.1)
ACT score (point)	21.0 (7–25)
AQLQ score (point)	5.8 (2.5–7)
SNOT-22 score (point)	42.0 (7–76)
PHQ-9 score (point)	5.0 (0–14)
PHQ-9 < 5, <i>n</i>	14
PHQ-9 ≥ 5, <i>n</i>	17
PHQ-9 ≥ 10, <i>n</i>	3
JESREC score (point)	17.0 (11–17)
ICS, µg/day (equivalent to fluticasone)	1,000 (200–1,125)
LABA usage, <i>n</i>	31
Daily OCS usage, <i>n</i>	9
Exacerbation of asthma in previous year, <i>n</i> /yr	0 (0–11)
Events with transient systemic corticosteroids, <i>n</i> /yr	3 (0–14)
Previous ESS, <i>n</i>	23
Comorbidity	
Atopic dermatitis, <i>n</i>	0
Eosinophilic otitis media, <i>n</i>	10
Diabetes mellitus, <i>n</i>	4
Hypertension, <i>n</i>	3
Gastroesophageal reflux disease	2
Prescription for anxiety and depression, <i>n</i>	0

Data are number or median (range). ECRS, eosinophilic chronic rhinosinusitis; BMI, body mass index; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; SNOT-22, Sino-Nasal Outcome Test-22; PHQ-9, Patient Health Questionnaire; JESREC, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis; ICS, inhaled corticosteroid; ESS, endoscopic surgery.

Results

Table 1 shows the clinical background of the patients. The total number of patients was 31, with a slightly higher proportion of women. The median of disease history was 17 years and 6 years for patients with asthma and ECRS, respectively. The median ACT and AQLQ scores were 21 and 5.8 points, respectively, indicating that the symptoms and QOL for asthma were sustained to some extent. However, the SNOT-22 score showed a median of 42 points, indicating worse control of symptoms and QOL for ECRS. The median PHQ-9 score was 5; 17 patients had PHQ-9 ≥ 5, and 3 patients had PHQ-9 ≥ 10, which are considered as mild depressive and moderate depressive states, respectively [23]. High doses of ICSs and long-acting β agonists were used for treatment prior

to the introduction of dupilumab, and 9 (29%) patients also used daily oral corticosteroids. The median number of asthma exacerbations in the year before dupilumab administration was zero, and about half of the patients had no exacerbations. On the other hand, the number of times the patients received temporary systemic corticosteroids, for conditions including nasal symptoms, was high, which may reflect symptoms other than asthma exacerbations. Twenty-three patients underwent ESS prior to the use of dupilumab. In terms of comorbidity, eosinophilic otitis media was the most common, while atopic dermatitis was not. No patient was administered medications as well as psychological counseling (cognitive behavior therapy) for anxiety or depressive symptoms prior to the introduction of dupilumab.

We analyzed the correlation between ACT, AQLQ, SNOT-22, and PHQ-9 scores before the use of dupilumab. As shown in Figure 1, the ACT and AQLQ scores were not significantly correlated with the PHQ-9 score (Fig. 1a, b), whereas the SNOT-22 score was positively correlated with the PHQ-9 scores (Fig. 1c). In addition, a comparison of patients in a depressive state (PHQ-9 ≥ 5) with those in a minimally depressive state (PHQ-9 < 5) revealed a significantly higher SNOT-22 score and stronger olfactory dysfunction in patients with depression (Table 2).

Regarding the 4 subdomains of SNOT-22, more patients in the group with depressive state complained of symptoms associated with sleep and otologic/facial pain than in the group with minimally depressive state (Fig. 2). In each question, more patients complained of “reduced productivity,” “reduced concentration,” and “sad” in the group with depressive state than in the group with minimally depressive state (online suppl. Fig. 1).

In the evaluation 4 months after dupilumab treatment, the total PHQ-9 score significantly decreased (Fig. 3a). Decrease in the PHQ-9 score was associated with changes in nasal symptoms and QOL, and the total PHQ-9 score was clearly decreased in cases where the improvement in the SNOT-22 score reached 50% (Fig. 3b), whereas decrease in the PHQ-9 was not significant in cases where the improvement in the SNOT-22 score did not reach 50% (Fig. 3c).

Decrease in the PHQ-9 was also related to the improvement of asthma symptoms, and the total PHQ-9 score was significantly decreased in cases in which the ACT score became a full score or increased by 3 or more points (Fig. 4a), whereas decrease in the PHQ-9 was not significant in cases where the improvement in the ACT score did not reach the meaningful change (Fig. 4b). Fur-

thermore, univariate analysis was performed to compare cases with decreased PHQ-9 score and those with unchanged or increased scores. A $\geq 50\%$ improvement in the SNOT-22 score following dupilumab use was considered a statistically significant improvement of the PHQ-9 score (online suppl. Table 2). A logistic analysis was performed using items that were related to the changes in depressive symptoms. As a result, a $\geq 50\%$ improvement in SNOT-22 score working status was shown to be independently related to PHQ-9 improvement (Table 3).

Finally, initiation of dupilumab treatment improved the symptoms of all subdomains (Fig. 5a). With regard to each question, various symptoms, mainly in the nasal and sleep domains, such as “need to blow nose,” “nasal blockage,” “runny nose,” “cough,” “postnasal discharge,” “thick nasal discharge,” and “fatigue,” were obviously improved (online suppl. Fig. 2A). A comparison of the depressive state cases with the minimal depressive state cases showed a significant improvement in symptoms of all subdomains in the depressive state cases, whereas a significant improvement only of symptoms in the nasal domain was

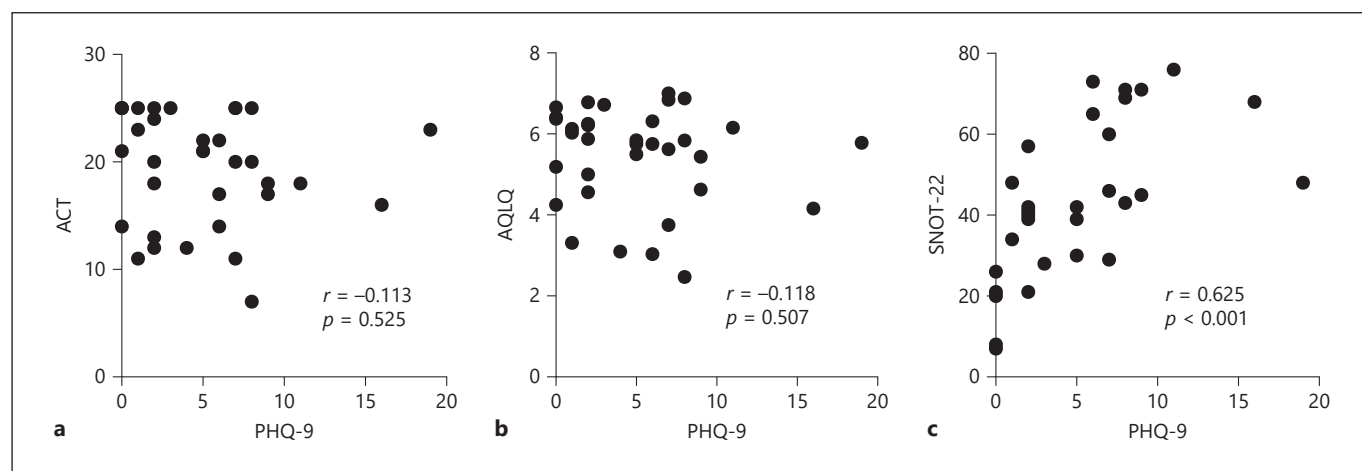


Fig. 1. Correlation between the PHQ-9 score and asthma or ECRS symptoms in patients with asthma and ECRS. ACT (a), AQLQ (b), and SNOT-22 (c). ECRS, eosinophilic chronic rhinosinusitis; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; SNOT-22, Sino-Nasal Outcome Test; PHQ-9, Patient Health Questionnaire.

Table 2. Comparison of baseline characteristics between patients in a depressive state and in a minimally depressive state

	Depressive state (PHQ-9 ≥ 5)	Minimally depressive state (PHQ-9 < 5)	<i>p</i> value
Sample, <i>n</i>	17	14	
Male, %	41.2	35.7	1.000
Age, years	47.0 (23–67)	50.0 (36–69)	0.361
Duration (asthma), years	15.0 (1–43)	18.0 (6–46)	0.189
Duration (ECRS), years	6.0 (2–38)	5.5 (1–31)	0.961
BMI, kg/m ²	22.6 (19.1–33.1)	20.9 (16.1–31.5)	0.128
ACT score (point)	21.0 (7–25)	22.5 (11–25)	0.727
AQLQ score (point)	5.75 (2.47–7.00)	6.13 (3.31–6.78)	0.415
SNOT-22 score (point)	53.0 (29–76)	31.0 (7–57)	<0.001*
Daily OCS usage, %	17.6	42.9	0.233

Data are median (range). Asterisks indicate a significant difference between the groups (* $p < 0.05$). ECRS, eosinophilic chronic rhinosinusitis; BMI, body mass index; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; SNOT-22, Sino-Nasal Outcome Test; PHQ-9, Patient Health Questionnaire; OCS, oral corticosteroid.

observed in minimal depressive state cases (Fig. 5b, c). Especially, nasal symptoms such as “need to blow nose,” “nasal blockage,” “runny nose,” and “thick nasal discharge” were greatly improved in the depressive state cases (online suppl. Fig. 2B, C).

Discussion/Conclusion

In this study, we administered dupilumab to patients with asthma and ECRS and evaluated changes in depressive symptoms along with changes in asthma and nasal symptom control and QOL after 4 months of treatment. The highlight of this study is that the induction of dupilumab improved depressive symptoms. To the best of our knowledge, we firstly reported that the use of biologics reduces the PHQ-9 score in patients with asthma or CRS. In CRS cases, including ECRS, the effects of ESS on depression symptom improvement are controversial.

Litvack et al. [24] examined changes in depressive symptoms with the PHQ-9 in patients with CRS who underwent ESS; disease-specific QOL questionnaires, such as the Rhinosinusitis Disability Index (RSDI) score, as well as the PHQ-9 score, were improved with ESS. In contrast, Adams et al. [25] reported that changes in the average score of the Hospital Anxiety and Depression Scale (HADS) after ESS were nonsignificant despite a remarkable improvement in the RSDI score. According to the

pretreatment PHQ-9 score in this study, the degree of depressive symptoms was relatively mild [22], and cases in which treatment intervention could easily recover may have been many. In other words, few patients in this study would be considered to require psychiatric intervention for depression treatment. Although the PHQ-9 has simi-

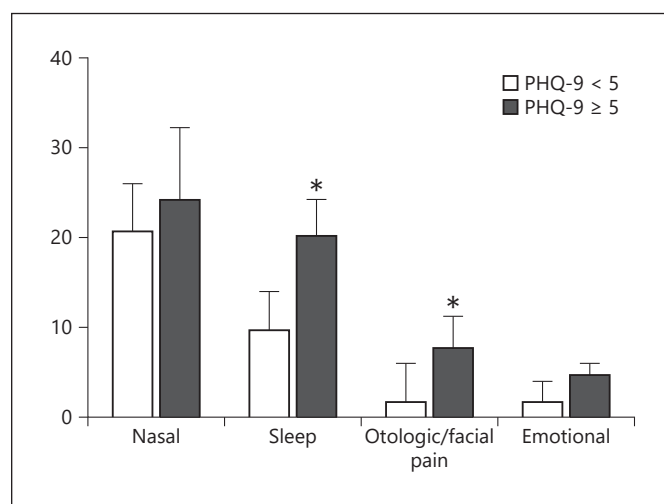


Fig. 2. Differences in the subdomains of ECRS symptoms between patients in a depressive state (PHQ-9 ≥ 5) and those in a minimally depressive state (PHQ-9 < 5). Asterisks indicate a significant difference between the groups (** $p < 0.001$, * $p < 0.05$). ECRS, eosinophilic chronic rhinosinusitis; PHQ-9, Patient Health Questionnaire.

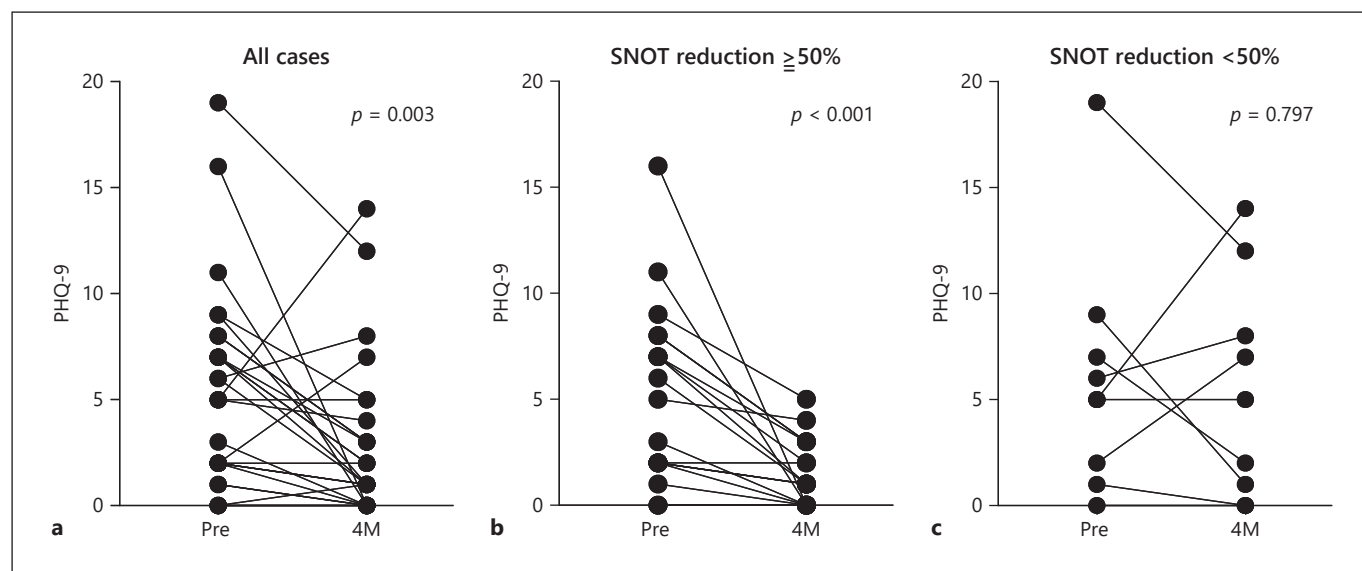


Fig. 3. Changes in the PHQ-9 score after using dupilumab treatment. All patients (a), patients whose SNOT-22 score was reduced by >50% (b), and patients whose SNOT-22 score was reduced by <50% (c). PHQ-9, Patient Health Questionnaire; SNOT-22, Sino-Nasal Outcome Test.

Fig. 4. Relationship between changes in asthma symptoms and PHQ-9 score in patients with asthma and ECRS. Patients whose ACT score was increased to 3 or more or to the total score (**a**); patients whose ACT score was increased by <3 (**b**). PHQ-9, Patient Health Questionnaire; ECRS, eosinophilic chronic rhinosinusitis; ACT, Asthma Control Test.

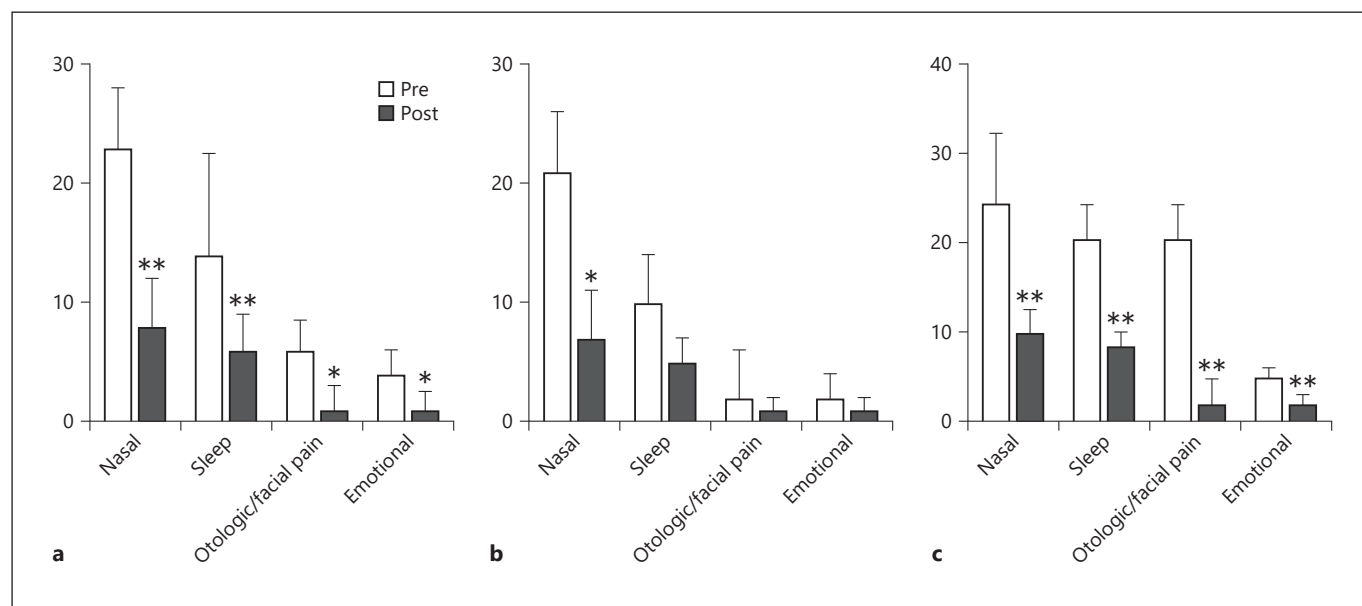
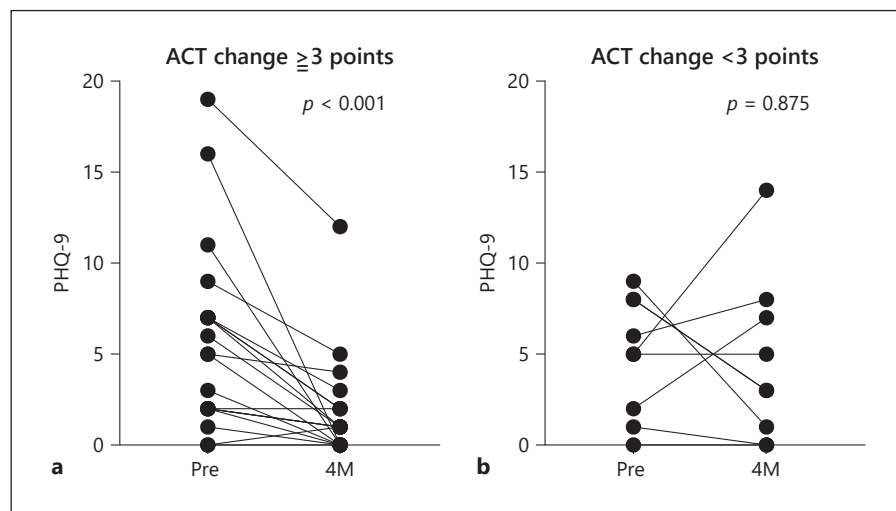


Fig. 5. Changes before and after dupilumab treatment for the subdomains of the SNOT-22. All patients (**a**), patients in a minimally depressive state (PHQ-9 < 5) (**b**), and patients in a depressive state (PHQ-9 ≥ 5) (**c**). Asterisks indicate a significant difference between the groups (** $p < 0.001$, * $p < 0.05$). SNOT-22, Sino-Nasal Outcome Test; PHQ-9, Patient Health Questionnaire.

lar responsiveness and internal reliability as the HADS [26, 27], different results may be obtained because of differences in the types of questions and data acquisition timing. In this study, PHQ-9 was considered improved if the score improved by at least 1 point. Although a candidate study has been reported [28], the meaningful change threshold for PHQ-9 has not been defined at this time. Furthermore, since most of the PHQ-9 scores in this

study were <10 points, corresponding to minimal to mild depression, an improvement of 1 point or more was defined as a threshold.

The SNOT-22 includes questions about sleep and emotional symptoms as well as nasal and otologic symptoms. In this study, depressive state cases strongly complained of sleep-related symptoms compared to minimal depressive state cases. Moreover, the usage of

Table 3. Multiple regression analysis of variables that influenced PHQ-9 improvement

	Odds ratio (95% confidence interval)	<i>p</i> value
Age (>50)	0.22 (0.03–1.99)	0.180
ACT improvement ^{#1}	5.72 (0.58–56.6)	0.136
SNOT improvement ^{#2}	17.2 (1.37–216.0)	0.028*
OCS daily usage	0.07 (0.004–1.2)	0.069

ACT, Asthma Control Test; SNOT-22, Sino-Nasal Outcome Test; PHQ-9, Patient Health Questionnaire; OCS, oral corticosteroid. ^{#1} ACT score increased by ≥ 3 or became 25. ^{#2} $\geq 50\%$ reduction in the SNOT-22 score.

dupilumab dramatically improved their symptoms. A previous study investigating the relationship between CRS and depression also reported a correlation between depression and sleep symptoms [29]. It is speculated that sleep disorders associated with worsening CRS symptoms cause depression, and the cases with strong sleep-related symptoms may be associated with depressive symptoms.

Although the patients in this study were diagnosed with asthma, there was no correlation between asthma symptoms or asthma-related QOL and PHQ-9 scores. In our previous report, patients with asthma in a depressive state (PHQ-9 ≥ 5) had significantly higher symptom rates, exacerbation experience rates, and treatment steps than those with minimal depression (PHQ-9 < 5) [30]. In uncontrolled asthma, asthma-specific questionnaire scores, such as those on the Asthma Control Questionnaire and mini-AQLQ, have been reported to correlate with anxiety and depressive symptoms [31]. The asthma control status of the participants in this study was relatively good. In this study, 67% of patients demonstrated favorable asthma control (ACT ≥ 20) and 32% total control (ACT = 25), suggesting that asthma symptoms were not associated with anxiety and depressive symptoms in this study.

Biologics are used in a variety of diseases and contribute to the improvement of symptoms, prognosis, and QOL. A study of Japanese patients with rheumatoid arthritis (RA) reported that the biotreated group had clearly less-frequent depressive symptoms than the non-biotreated group [32]. An improvement in depressive symptoms has been reported with several antibodies in RA [33, 34], possibly because inflammatory cytokines such as IL-6 and TNF- α are associated with depression as

well as the psychological burden associated with the medical condition [35, 36]. Type 2 cytokines affecting depressive symptoms have not yet been reported; however, IL-6 involvement in exacerbations in severe allergic diseases has been reported [37, 38]. Moreover, a previous report demonstrated that dupilumab treatment suppressed local IL-6 production in atopic dermatitis cases [39]. These findings suggest that these inflammatory cytokines may partially affect depressive symptoms in allergic diseases, and dupilumab may have a potential to improve depressive symptoms in allergic diseases by reducing the levels of IL-6.

This study has limitations, as it was a single-arm study without a controlled comparison and the sample size was small due to the single-center nature of the study. Moreover, many of the evaluation items were based on questionnaires, and objective parameters such as pulmonary function, fractional exhaled nitric oxide, endoscopic, and CT findings could not be evaluated. Therefore, it was not possible to analyze the relationship between the changes in objective parameters and depressive symptoms. This issue should be clarified in the future.

In summary, we analyzed the changes in depressive symptoms in patients with asthma and ECRS based on dupilumab treatment. More than half of the patients were in a depressive state, which correlated with the SNOT-22 score. In the evaluation 4 months after dupilumab treatment, a significant decrease in the PHQ-9 score was observed, and the decrease was remarkable when the SNOT-22 score was reduced by 50% or more. In addition, the PHQ-9 scores in patients with improved nasal and asthma symptoms were significantly reduced. In patients with bronchial asthma and ECRS, dupilumab may be expected to improve the QOL by reducing depressive symptoms through the improvement of clinical symptoms.

Acknowledgment

The authors are grateful to Ms. Asako Maruyama for helping with data collection.

Statement of Ethics

This study was conducted in accordance with the ethical principles for medical research involving human subjects and the Declaration of Helsinki and was approved by the Ethics Committee of the Niigata University (Approval No. 2019-0022). All participants provided written informed consent prior to enrollment.

Conflict of Interest Statement

The authors have no competing interests to declare.

Funding Sources

This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (No. 20K17212 and 20K18273).

Author Contributions

T.Ko. designed the study and wrote the manuscript. T.Ko., N.S., T.S., K.S., A.N., Y.K., M.T., M.H., A.S., Y.N., and T.H. contributed to data collection. T.Ko., T.H., Y.M., K.M., A.H., and T.Ki. performed the statistical analysis and interpretation of the results. All authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online suppl. material files. Further inquiries can be directed to the corresponding author.

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Supplemental table 1: Correspondence table of each question and subdomain in Sino-Nasal Outcome Test 22

	Question	Subdomain
1	Need to blow nose	Nasal
2	Nasal blockage	Nasal
3	Sneezing	Nasal
4	Runny nose	Nasal
5	Cough	Nasal
6	Post-nasal discharge	Nasal
7	Thick nasal discharge	Nasal
8	Ear fullness	Otologic / facial
9	Dizziness	Otologic / facial
10	Ear pain	Otologic / facial
11	Facial pain / pressure	Otologic / facial
12	Decreased sense of smell / taste	Nasal
13	Difficulty falling asleep	Sleep
14	Wake up at night	Sleep
15	Lack of good night's sleep	Sleep
16	Wake up tired	Sleep
17	Fatigue	Sleep
18	Reduced productivity	Sleep
19	Reduced concentration	Sleep
20	Frustrated / restless / irritable	Sleep
21	Sad	Emotional
22	Embarrassed	Emotional

Supplemental table 2: Patient characteristics

	Patients in whom PHQ-9 decreased	Patients in whom PHQ-9 increased or remained unchanged	p value
Sample (n)	21	10	
Male (%)	42.9	30	p = 0.697
Age > 50 y.o (%)	42.9	80	p = 0.068
Duration (asthma) > 15 y (%)	52.4	60	p = 1.000
Duration (ECRS) > 6 y (%)	57.1	50	p = 1.000
BMI (kg/m ²) > 25 (%)	23.8	20	p = 1.000
ACT score < 20 (%)	42.9	30	p = 0.697
ACT improved ^{#1} (%)	57.1	30	p = 0.252
AQLQ score < 5.5 (%)	28.6	40	p = 0.685
AQLQ improved ^{#2} (%)	42.9	60	p = 0.458
SNOT-22 score > 40 (%)	71.4	50	p = 0.423
SNOT-22 improved ^{#3} (%)	81	30	p = 0.013*
PHQ-9 score > 5 (%)	61.9	40	p = 0.441
Daily OCS usage (%)	23.8	40	p = 0.417

ECRS: eosinophilic chronic rhinosinusitis, BMI: body mass index, ACT: Asthma Control Test, AQLQ: Asthma Quality of Life Questionnaire, SNOT-22: Sino-Nasal Outcome Test, PHQ-9: Patient Health Questionnaire, OCS: oral corticosteroid. Asterisks indicate a significant difference between the groups (*p < 0.05).

#1: ACT score increased by ≥3 or became 25. #2: AQLQ score increased by ≥0.5. #3: The reduction of SNOT-22 score was ≥50%.