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Original Article

Therapeutic Effectiveness of SNOT 22-Based Interdose Interval Adjustment of Dupilumab for Chronic Rhinosinusitis With Nasal Polyps

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Objectives. This study evaluates the enduring efficacy and patient satisfaction of dupilumab with interdose interval adjustments based on the Sino-Nasal Outcome Test (SNOT-22) in chronic rhinosinusitis with nasal polyps (CRSwNP).

Methods. A retrospective analysis was conducted on 44 patients who had been treated with dupilumab for over 6 months. This study targeted individuals diagnosed with CRSwNP according to the 2020 edition of the European Position Paper on Rhinosinusitis and Nasal Polyps Criteria. The treatment involved an add-on dupilumab regimen, where the interdose interval was adjusted based on the SNOT-22 scores. Dosage adjustments were made such that patients with initial SNOT-22 scores greater than 40 were tapered to a target level of 20 or less. Similarly, for patients with initial scores of 40 or less, the treatment aimed for an improvement of 50% or more. At each visit, the effectiveness of the treatment was evaluated using SNOT-22, nasal polyp scores (NPS), and a subjective satisfaction questionnaire adapted from the Treatment Satisfaction Questionnaire for Medication (TSQM v.1.4).

Results. The adjustment of the interdose interval for dupilumab based on SNOT-22 scores demonstrated sustained improvements in patients' subjective symptoms, satisfaction, and NPS. The mean (standard deviation) SNOT-22 scores significantly decreased from 46.04 (22.30) to 14.72 (13.66) over 6 months ($P<0.001$). Similarly, NPS scores improved from 3.20 (2.24) to 1.72 (1.46) within the same period ($P<0.001$). Satisfaction scores, ranging from 0 to 5, consistently remained above 3.5 for up to 6 months ($P=0.166$). Additionally, there was a significant correlation between the improvement in the nasal symptom domain of the SNOT-22 scores and higher satisfaction scores.

Conclusion. Adjusting dupilumab dosing intervals based on SNOT-22 scores from the outset resulted in sustained efficacy and patient satisfaction in Korean patients with CRSwNP. This approach will meaningfully assist clinicians in determining the optimal dupilumab dosing interval.

Keywords. *Biological Therapy; Rhinosinusitis; Nasal Polyps; Dupilumab; Symptom Assessment; Surveys and Questionnaires*

INTRODUCTION

Chronic rhinosinusitis (CRS) is a prevalent medical condition globally, associated with significant healthcare costs, affecting an estimated 5%–12% of the population [1-5]. Initially, CRS was categorized into two types: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps. However, with growing recognition of CRS's complex pathophysiology, the 2020 edition of the

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European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) shifted to a classification based on endotypes rather than phenotypes [6].

The treatment of CRSwNP primarily involves nasal irrigation with saline and the application of topical corticosteroids, supplemented by oral corticosteroids and antibiotics when necessary [7]. However, some refractory CRSwNP cases, particularly those with a dominant type 2 (T2) inflammatory profile, do not respond adequately to standard therapies. These cases often require multiple surgeries or prolonged use of oral corticosteroids [8-10]. This challenge has spurred the development of biologics that target the T2 inflammatory pathway [11]. Following the approval of dupilumab by the U.S. Food and Drug Administration and the European Medicines Agency in 2019, new treatment avenues for T2 CRSwNP have opened up, and the introduction of additional monoclonal antibodies is expected [12].

Dupilumab is a human monoclonal antibody that specifically targets the interleukin (IL)-4Rα receptor subunit, inhibiting IL-4 and IL-13 signaling. It is now approved for use in treating patients with refractory CRSwNP [13]. Dupilumab is recommended for CRS patients with bilateral polyps who have undergone endoscopic sinus surgery (ESS) and meet at least three of the following five criteria: evidence of T2 inflammation, the need for systemic corticosteroids, significantly impaired quality of life, substantial loss of smell, and comorbid asthma [6]. The recommended dosage is 300 mg administered subcutaneously every 2 weeks. In the phase 3 trials (SINUS 24, 52) involving patients with CRSwNP, a 300 mg subcutaneous injection of dupilumab every 2 weeks reduced the nasal polyp score (NPS) by approximately 2 points at week 24 [14].

In Korea, dupilumab received approval from the Korean Food and Drug Administration and has been available for prescription since September 2018 [15]. Currently, the National Healthcare Insurance of Korea covers dupilumab for severe atopic dermatitis or asthma when specific criteria are met, but it does not extend coverage to patients with CRSwNP. Consequently, due to the burden of continuous biweekly injections of dupilumab, ESS, which is more cost-effective, is often prioritized as the treatment of choice over dupilumab in clinical practice [16].

HIGHLIGHTS

- The interval adjustment of dupilumab based on Sino-Nasal Outcome Test (SNOT-22) scores demonstrated sustained improvement in both patient symptoms and nasal polyp scores.
- Patient satisfaction scores with dupilumab remained consistent at 1 month, 3 months, and 6 months in relation to symptomatic improvement.
- Improvement in the nasal domain of SNOT-22 scores was significantly correlated with symptomatic satisfaction, treatment preference, willingness to continue treatment, willingness to recommend the treatment to others, and global satisfaction.

Korean patients with T2 CRSwNP have a lower burden of T2 inflammation and fewer CRS comorbidities than patients from Western regions [17-19]. Since dupilumab, a monoclonal antibody, is cleared through a target-mediated mechanism, it is possible that fewer target molecules are present in Korean patients with a lower disease burden than in Western patients with a higher disease burden, such as asthma comorbidity. This suggests the possibility of extending the dosing interval in South Korea [18]. Notably, a randomized, double-blind phase 3 trial of dupilumab showed no statistically significant difference in efficacy between patients who received dupilumab every 2 weeks for 52 weeks and those who received it every 2 weeks for 24 weeks followed by every 4 weeks for the remaining 28 weeks [14]. This finding suggests the potential for extending dosing intervals in CRSwNP patients once the disease burden has been sufficiently reduced.

Despite the ongoing debate regarding the optimal frequency and duration of dupilumab prescriptions for Korean patients, particularly in light of cost-effectiveness concerns, a recent study has shown promising results. It reported that extending the interval between doses to 2 weeks was effective for those who had a moderate to excellent response after 24 weeks of biological treatment. This method of adjusting dupilumab dosage based on the biological response and control of CRS could potentially be applied to most patients, thereby improving cost-effectiveness over time [20]. Additionally, for Korean patients with a low disease burden, it is anticipated that increasing the dosing interval with minimal interim periods could be feasible. In our research, we adjusted the dosing intervals based on patient symptoms, utilizing the Sino-nasal Outcome Test (SNOT-22), and evaluated the outcomes. The goal of this study is to determine if adjusting the interdose intervals of dupilumab based on SNOT-22 results can maintain long-term efficacy and patient satisfaction in cases of CRSwNP.

MATERIALS AND METHODS

Ethics statement

The study protocol was approved by the Institutional Review Board of the Clinical Research Institute at Boramae Medical Center (No. 10-2022-63), and in this retrospective study, informed consent was waived for the patients involved. All methods were performed in accordance with the approved guidelines and the Declaration of Helsinki. All personal information was kept confidential, as required.

Subjects

A retrospective review of medical records was conducted for patients who met the biologics indication criteria according to EPOS 2020 and were prescribed dupilumab 300 mg from March 2021 to February 2023 at a single tertiary referral center. Patients without a history of prior surgery were excluded.

SNOT-22 based interdose interval adjustment

The time frame for adjusting the interval (tapering) was as follows: when subjects with >40 SNOT-22 at pretreatment evaluation were controlled at the level of ≤20 SNOT-22; when subjects with ≤40 SNOT-22 at pretreatment evaluation were controlled at the level of ≥50% improvement [21,22].

Outcome assessments

We assessed the demographic profile of patients, including age, sex, asthma comorbidity, symptom score, subjective satisfaction regarding medication, endoscopic physical examination, and laboratory and computed tomography (CT) findings. Laboratory findings included absolute eosinophil count, total immunoglobulin E (IgE), perennial allergy-specific IgE, and *Staphylococcus aureus* enterotoxins-specific IgE. The absolute eosinophil count was based on the maximum value measured before the use of dupilumab. Patients received add-on dupilumab with adjustments to the injection interval based on SNOT-22. For each patient, the SNOT-22 (0–110), NPS (0–8), and a subjective satisfaction questionnaire modified from Treatment Satisfaction Questionnaire for Medication (TSQM v.1.4) were assessed. The loss of smell scores was extracted separately from the SNOT-22 scores for further analysis. The subjective satisfaction questionnaire included symptomatic satisfaction, convenience, adverse events, preference, willingness to continue treatment, willingness to recommend treatment to other patients, and global satisfaction (Supplementary Table 1). The improvement of each symptom was calculated by subtracting the post-treatment questionnaire symptom score (0–5) from the pre-treatment questionnaire symptom score (0–5). Asthma severity was classified into mild and severe categories, with patients receiving ongoing asthma treatment at an allergy clinic classified as severe, and other patients classified as mild.

Statistical analyses

All statistical analyses were conducted using commercially available software applications, specifically IBM SPSS version 25 (IBM Corp.) and GraphPad Prism software 9.0 (GraphPad Software Inc.). Sociodemographic and clinical characteristics were presented with mean±standard deviation (SD) for continuous variables. Two-tailed independent *t*-tests for normally distributed data and Mann-Whitney *U*-tests for not normally distributed data were employed to compare all continuous scale data, while chi-square tests were utilized to assess categorical variables. Data after revision sinonasal surgery were set to missing, and multiple imputation (MI) was applied to address the missing values. Outliers were defined as observations with Z-scores exceeding ±3 and were excluded from the analysis. Results were presented as odds ratios with 95% CI and *P*-values. $P<0.05$ was considered statistically significant. Confounders were identified based on prior research and expert opinions and were controlled for using multiple regression analysis. These confounders included age and gender. Prior to the analysis, we noted missing values on multiple prognostic factors. As a complete case analysis may introduce bias and loss of statistical power, we applied MI for logistic regression. MI was performed with predictive mean matching for continuous variables and logistic regression for categorical variables. All the pre-specified prognostic factors and outcomes were included in the imputation.

RESULTS

Clinical characteristics of patients

A total of 44 CRSwNP patients were enrolled in the study. The mean age of the participants was 51.0 years, with a SD of 13.7 and an age range of 28–86 years. Of these, 61.4% were male and 38.6% were female. The baseline NPS was 3.28 (SD, 2.0; range, 0–8). Laboratory data showed average absolute blood eosinophil counts of 773.5/mm^3 (SD, 501.9; range, 56–1,768) and total IgE levels of 468.2/μL (SD, 814.4; range, 23–5,000), suggesting T2 inflammation characteristics in the patients. Additionally, 68.2% of the patients had comorbid asthma, and allergic CRS was identified in 56.1% of the cases (Supplementary Table 2).

Ongoing therapeutic efficacy of SNOT-22-based interdose interval adjustment

The injection interval was adjusted according to patients' SNOT-22 scores (Fig. 1) and was subsequently extended. It was found that gradually increasing the dosing interval to ≥4 weeks, while maintaining symptom control as per SNOT-22 scores and patient

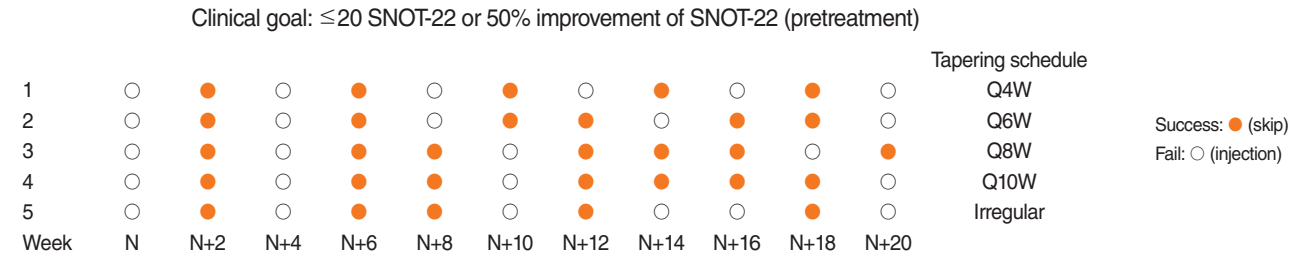

Fig. 1. Examples of interdose interval adjustment. SNOT-22, Sino-Nasal Outcome Test.

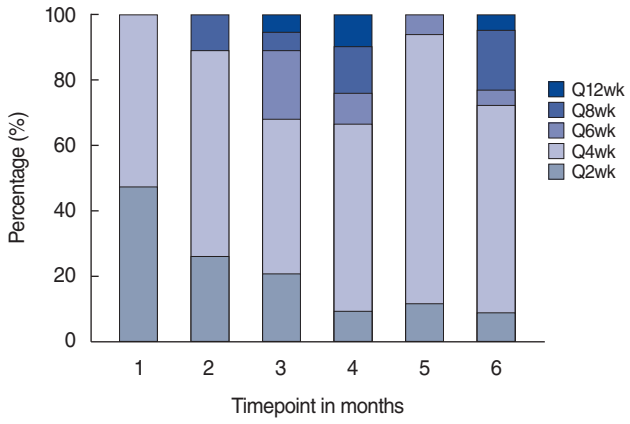

Fig. 2. Progression of tapering dupilumab.

satisfaction, was feasible for 52%, 79%, and 91% of patients at 1 month, 3 months, and 6 months, respectively. Additionally, some patients were able to extend the dosing interval to ≥8 weeks, which was applicable to 23% of the patients at 6 months (Fig. 2). The SNOT-22-based interval adjustment of dupilumab demonstrated sustained improvement in symptoms according to SNOT-22 and NPS scores. The mean SNOT-22 scores improved from 46.04 (22.30) at baseline to 21.86 (19.99) at 3 months, and further to 14.72 (13.66) at 6 months ($P<0.001$). Similarly, mean olfaction scores improved from 4.2 (1.15) at baseline to 2.43 (1.86) at 3 months, and to 1.72 (1.81) at 6 months ($P<0.001$). Mean NPS scores also showed improvement, moving from 3.20 (2.24) at baseline to 1.88 (1.64) at 3 months, and to 1.72 (1.46) at 6 months ($P<0.001$) (Fig. 3). Out of the total 44 patients in

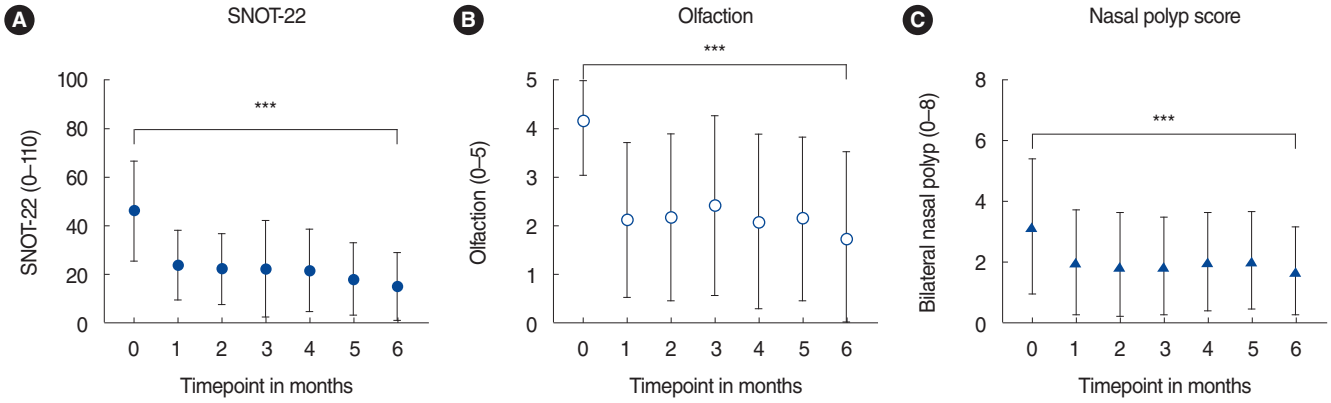

Fig. 3. Sustained improvement during tapering periods: (A) Sino-Nasal Outcome Test (SNOT-22), (B) olfaction (visual analog scale), and (C) nasal polyp score. ***$P<0.001$.

Table 1. Comparison of demographics and baseline characteristics between two groups divided based on a 2-month injection interval

Variable	Interval <8 wk (n=19)	Interval ≥8 wk (n=6)	*P*-value
Sex (male:female)	13:6	3:3	0.608
Age (yr)	51.05±15.37	48.50±13.90	0.828
Injection interval (mo)	1.12±0.35	2.00±0.00	<0.001
Eosinophil (%)	10.41±5.27	11.72±8.11	1.000
Blood eosinophil count (/mm^3)	772.29±496.34	828.47±685.36	0.923
Total IgE (/μL)	463.18±473.71	322.17±299.73	0.658
Instances of iCAP or MAST positivity	12 (67)[a]	2 (33)	0.242
Patients with comorbid asthma	12 (63)	4 (67)	0.926
Asthma severity (mild:moderate-severe)	3:9	4:0	0.030
Baseline NPS	3.58±2.22	2.00±0.63	0.090
Baseline total SNOT-22 score	49.00±20.78	36.67±19.62	0.246
Baseline olfactory SNOT-22 score	4.37±1.01	3.67±1.51	0.246
SNOT-22 change	27.74±16.57	23.67±17.56	0.733
Olfactory SNOT-22 change	2.58±1.61	2.33±1.63	0.780
Symptomatic satisfaction (0–5)	3.58±0.69	3.52±0.55	0.826
Global satisfaction (0–5)	3.26±0.45	3.33±0.52	0.828
Cost effectiveness (0–4)	1.47±0.51	1.00±0.63	0.156

Values are presented as mean±standard deviation or number (%).
Ig, immunoglobulin; iCAP, immunoCAP; MAST, Multiple Allergen Simultaneous Test; NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test.
[a]One case with missing data was not included.

the study, 25 patients with a complete data set, including pretreatment symptom assessments and baseline satisfaction surveys, were analyzed based on a 2-month injection interval. Significant differences in asthma severity were observed between groups with <8 weeks and ≥8 weeks injection intervals (P=0.030) (Table 1). This suggests that a shorter injection interval may be necessary for patients with concomitant severe asthma.

Ongoing patient satisfaction with SNOT-22-based interdose injection interval adjustment

The mean (SD) satisfaction scores for symptomatic improvement were 3.53 (0.60) at 1 month, 3.3 (0.95) at 3 months, and 3.76 (0.90) at 6 months (P=0.166). Overall satisfaction scores were 3.27 (0.46) at 1 month, 3.2 (0.63) at 3 months, and 3.41 (0.71) at 6 months (P=0.380). Convenience scores (0–4) averaged 3.8 (0.41) at 1 month, 3.96 (0.20) at 3 months, and 3.76 (0.44) at 6 months (P=0.317). Adverse events scores (0–5) were 4.64 (0.49) at 1 month, 4.8 (0.41) at 3 months, and 4.6 (0.5) at 6 months (P=0.739). Preference scores (0-4) were 3.8 (0.41) at 1 month, 3.60 (0.50) at 3 months, and 3.92 (0.27) at 6 months (P=0.257). Willingness to continue scores were 3.2 (0.76) at 1 month, 3.4 (0.50) at 3 months, and 3.44 (0.51) at 6 months (P=0.157). Willingness to recommend scores were 3.4 (0.50) at 1 month, 3.56 (0.51) at 3 months, and 3.6 (0.50) at 6 months (P=0.197) (Fig. 4). This indicates that the scores in all categories of the patient satisfaction survey remained consistently high from 1 month to 6 months.

Relationship between improvement in each SNOT-22 domain and patient satisfaction

The improvement in the nasal domain of SNOT-22 scores was significantly correlated with several factors: symptomatic satis-

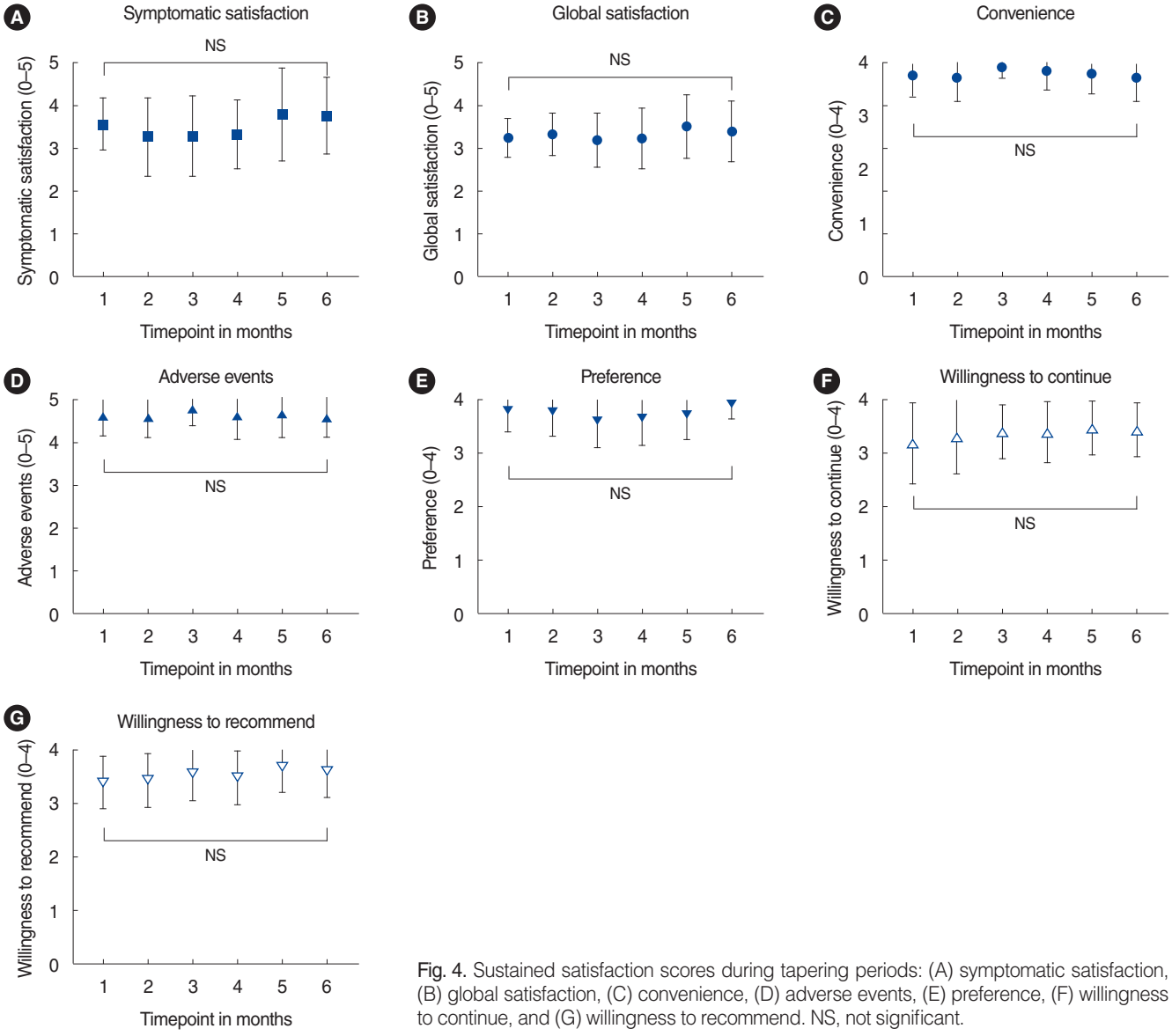

Fig. 4. Sustained satisfaction scores during tapering periods: (A) symptomatic satisfaction, (B) global satisfaction, (C) convenience, (D) adverse events, (E) preference, (F) willingness to continue, and (G) willingness to recommend. NS, not significant.

Table 2. Regression analysis between improvement in each SNOT-22 domain and satisfaction scores

Dependent variable	Independent variable	B	SE	b	*t*	*P*-value
Symptomatic satisfaction	SNOT_nasal	0.103	0.016	0.854	6.574	<0.001
	SNOT_ear/facial	–0.093	0.040	–0.367	–2.326	0.045
Treatment preference	SNOT_nasal	0.068	0.023	0.687	2.989	0.014
Willingness to continue treatment	SNOT_nasal	0.053	0.021	0.620	2.499	0.032
Willingness to recommend treatment	SNOT_nasal	0.043	0.019	0.579	2.246	0.048
Global satisfaction	SNOT_nasal	0.061	0.019	0.710	3.192	0.010

SNOT-22, Sino-Nasal Outcome Test; SE, standard error.

Table 3. Regression analysis between improvement in each nasal symptom and satisfaction scores

Dependent variable	Independent variable	B	SE	b	*t*	*P*-value
Symptomatic satisfaction	Nasal congestion	0.426	0.122	0.741	3.491	0.006
Treatment preference	Nasal congestion	0.426	0.122	0.741	3.491	0.006
	Cough	0.425	0.176	0.608	2.419	0.036
	PND	0.319	0.114	0.664	2.810	0.018
Willingness to continue treatment	Cough	0.425	0.094	0.818	4.500	0.001
	Nasal congestion	0.278	0.102	0.651	2.712	0.022
Willingness to recommend treatment	Nasal congestion	0.370	0.105	0.745	3.536	0.005
	Rhinorrhea	0.248	0.108	0.589	2.305	0.044
Global satisfaction	Cough	0.384	0.148	0.635	2.597	0.027
	Nasal congestion	0.296	0.126	0.596	2.349	0.041

SE, standard error; PND, post-nasal drip.

faction (R=0.854, P<0.001), treatment preference (R=0.687, P=0.014), willingness to continue treatment (R=0.620, P=0.032), willingness to recommend the treatment to others (R=0.579, P=0.048), and global satisfaction (R=0.710, P=0.010). Specifically, symptomatic satisfaction was correlated with improvements in nasal congestion (R=0.741, P=0.006), cough (R=0.725, P=0.008), post-nasal drip (PND; R=0.682, P=0.015), and watery rhinorrhea (R=0.646, P=0.023). Treatment preference was associated with improvements in nasal congestion (R=0.741, P=0.006), PND (R=0.664, P=0.018), and cough (R=0.608, P=0.036). Willingness to continue treatment was linked to improvements in cough (R=0.818, P=0.001) and nasal congestion (R=0.651, P=0.022). Willingness to recommend the treatment was related to improvements in nasal congestion (R=0.745, P=0.005) and watery rhinorrhea (R=0.589, P=0.044). Global satisfaction was associated with improvements in cough (R=0.635, P=0.027) and nasal congestion (R=0.596, P=0.041). We frequently observed improvements in nasal congestion and cough in patients who scored higher on the satisfaction questionnaire (Tables 2 and 3).

Adverse events

Among the 44 individuals, adverse events occurred in 9 (20.5%), including pruritus (n=5), hyper-eosinophilia (n=2), myalgia (n=1), and fatigue (n=1).

DISCUSSION

CRS is classified into type 2 and non-type 2 based on the primary pathophysiological inflammation mechanism [13]. The prognosis varies depending on the type. T2 CRS is associated with a higher incidence of anosmia, asthma comorbidity, and a higher recurrence rate following ESS [23,24]. The primary treatments for CRS are intranasal corticosteroids and nasal irrigation [6,25]. If these are ineffective, treatment may include systemic montelukast and/or short-term systemic corticosteroids [6]. Conventional surgical treatment is considered for patients who do not respond to these medications [6]. While ESS can significantly reduce the disease burden in a short period, it is associated with a high recurrence rate and does not markedly improve olfaction [26]. After ESS, patients may occasionally need systemic oral steroids, a strategy that is not sustainable due to the potential for iatrogenic harm [27].

The emergence of biologics signifies a fundamental change in the treatment paradigm for CRSwNP. Conditions previously considered refractory to medical and surgical treatments for CRSwNP are now often effectively managed with biologic therapies [11,12]. A post hoc analysis of phase 3 studies on dupilumab revealed substantial improvements in nasal congestion symptom scores, NPS, and Lund-Mackay CT scores following biweekly administration of dupilumab for a minimum of 24 weeks in patients with CRSwNP [14].

Regarding cost-effectiveness, some ethical challenges have emerged in formulating individual treatment plans [28]. The strat-

egy must benefit patients, avoid harm, respect patient autonomy, and ensure equitable resource distribution—these are the primary concerns. In Korea, for instance, patients are required to pay the full cost of dupilumab, which is 506.13 USD (675,807 KRW) per 300 mg dose. Consequently, biweekly dupilumab therapy incurs a monthly cost of 1,012.26 USD (1,351,625.23 KRW), representing a substantial financial burden for CRSwNP patients lacking national or private health insurance coverage. The application of real-world evidence and practical experience will continue to refine treatment methodologies, improving patient selection, optimizing therapies, and enhancing cost-effectiveness. This iterative process is designed to promote the long-term, sustainable use of this costly treatment option [29,30].

Tapering, also known as gradual dose reduction, is a strategy commonly employed in the clinical use of biological therapies across a wide range of medical conditions [31-35]. This approach is often associated with significant costs; therefore, the primary objective is to improve cost-efficiency while reducing risks, particularly when agents might lead to unpredictable or unintended effects [36]. By extending the intervals between doses of dupilumab, this method aims to lessen the burdens on patients by addressing issues related to the administration of the medication and its impact on daily life. Gradual dose reduction not only decreases the frequency of injections but also has the potential to mitigate common side effects [37]. Similar strategies have been evaluated in other medical conditions, such as rheumatoid arthritis, psoriasis, and closely related conditions like asthma and atopic dermatitis [38-40].

Although a formal evaluation of the cost-effectiveness of dupilumab for CRSwNP is still pending, it is likely that the direct costs associated with this treatment are significantly higher compared to conventional non-biological therapies. The annual cost of dupilumab is estimated at US $31,000, with single costs of US $8,968 for uncomplicated ESS and US $16,877 for an ESS with a major complication. In contrast, the surgical strategy incurs a total cost of US $50,436.99 and yields 9.80 quality-adjusted life years (QALYs), while the total cost of dupilumab treatment reaches US $536,420.22, generating 8.95 QALYs over a 10-year period. Consequently, treatment with dupilumab is more than 10 times as expensive per QALY, according to published improvements in quality of life [41]. It may be possible to extend the interval between treatments once disease control is achieved, as demonstrated in the LIBERTY NP SINUS-52 study. In this study, patients who transitioned to a 4-weekly dupilumab schedule maintained improvements comparable to those on a 2-weekly regimen [14]. This approach has been further validated in a large cohort of CRSwNP patients treated with dupilumab. The practice of gradually increasing dosage intervals, sometimes up to one injection every 8 weeks, is also being emphasized and attempted in Western countries, while still maintaining effective disease control [42]. A recent study suggested that tapering dupilumab by extending dosing intervals to at least every 8 weeks, based on biological response and CRS control assessments every 24 weeks, could be applicable to the majority of patients, potentially enhancing cost-effectiveness [20]. Additionally, the milder histological characteristics of T2 CRSwNP in Korea compared to Western countries may facilitate the feasibility of dupilumab tapering [1].

This study has several limitations due to its retrospective nature. Objective outcome measurements, including molecular biomarkers and smell tests, should be incorporated in future studies. Additionally, prospective studies involving larger patient populations and extended treatment periods with dupilumab are needed to assess the clinical efficacy of tapering the medication.

In conclusion, this study is the first to demonstrate in a real-life setting that gradually tapering dupilumab is highly effective for Korean patients with CRSwNP that is difficult to manage, in line with EPOS 2020 criteria. Adjusting the timing of dupilumab injections based on SNOT-22 scores consistently improves clinical outcomes and patient satisfaction. Further prospective trials and broader studies are necessary and will greatly aid in the development of clinical guidelines for dupilumab use.

CONFLICT OF INTEREST

Dae Woo Kim is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: DWK. Methodology: DWK, MSY. Software: SNH. Validation: DWK. Formal analysis: SNH. Investigation: SYY, HC, MSY. Resources: MSY. Data curation: HC, SNH. Visualization: DWK. Supervision: DWK. Project administration: DWK. Funding acquisition: DWK. Writing–original draft: SYY.

Writing–review & editing: DWK. All authors read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found online at https://doi.org/10.21053/ceo.2024.00233.

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