Real-world treatment of chronic rhinosinusitis with dupilumab and omalizumab: results from the Korean National Health Insurance Service database

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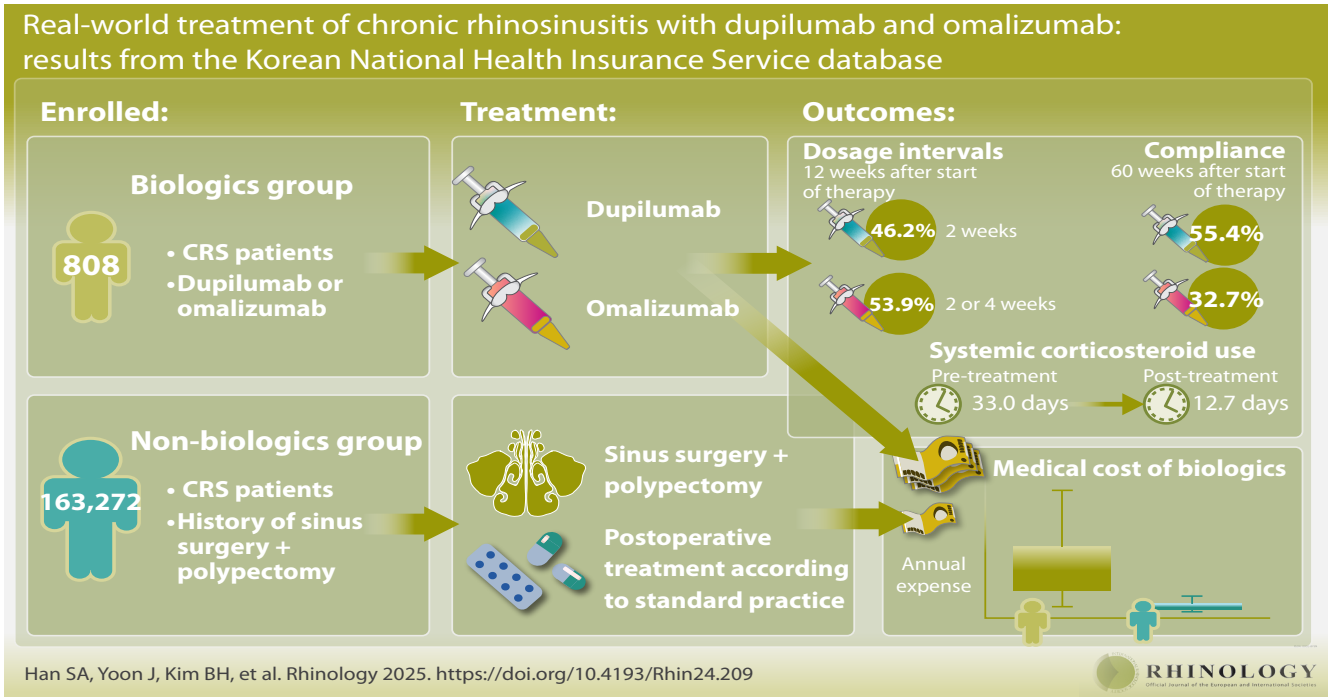

Abstract

Background: Biological treatment has proven effective for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) and is increasingly prescribed. However, in the real-world, strict adherence to the recommended dose may not be feasible and studies on the actual administration patterns of biologics are limited. This study aimed to evaluate the patterns of real-world use of biologics for CRS in Korea, through the National Health Insurance Service (NHIS).

Methods: We analysed data from the NHIS database from January 2010 to March 2024. Patients with CRS or nasal polyp defined by the ICD-10 codes, who had undergone computed tomography, and had a history of being prescribed dupilumab or omalizumab were identified. A total of 808 patients were analysed for their administration patterns and systemic corticosteroid use.

Results: Twelve weeks after initiation of therapy, 46.2% of patients received dupilumab at 2-weekly intervals and 53.9% of patients on omalizumab patients were receiving treatment at 2- or 4-week intervals. The annual expense of CRS patients treated with biologics was greater than for those receiving other treatments. The average annual usage of systemic steroids was decreased from 33.0 days to 12.7 days after using biologics.

Conclusions: The results of this study which analysed real-world data in a large population, suggest a discrepancy between the recommended dose and real-world administration of biologics. Further studies are warranted on feasible administration schedules that reflect various patient factors and healthcare costs.

Key words: biologics, chronic rhinosinusitis, nasal polyps, dupilumab, omalizumab

Introduction

Chronic rhinosinusitis (CRS) affects 4-12% of patients globally [1-5], and symptoms of CRS can greatly affect patients' quality of life [6]. Classically, CRS has been categorized depending on the presence of nasal polyps. However, advances in drugs that target specific inflammatory pathways show the importance of identifying endotypes [7, 8]. Generally, CRS in the non-western regions was considered to have a non-type 2 dominant endotype. However, a shift towards type 2 inflammation is being observed in Asian countries [9]; similarly, eosinophilic polyps are increasing in the Korean population [10]. Currently, two drugs that target type 2 inflammation have been approved for use in chronic rhinosinusitis with nasal polyps (CRSwNP) in Korea – omalizumab and dupilumab. Omalizumab (Xolair®), an anti-IgE antibody, was approved in April 2021, while dupilumab (Dupixent®), an anti-IL-4Rα antibody was approved in March 2021, by the Korean Ministry of Food and Drug Safety (MFDS), for use in CRSwNP. The directions for the use of dupilumab are 300 mg subcutaneous injections every two weeks, while omalizumab is injected every 2 weeks or 4 weeks depending on the weight and baseline IgE levels. These recommended directions for use are based on the phase 3 clinical trials [11, 12]. However, in the real world, strict adherence to the instructions may not be possible due to costs and the clinical environment. The medical costs related to receiving endoscopic sinus surgery (ESS) in Korea are relatively less compared with surgical costs in the US [13]. Meanwhile, both drugs are not reimbursed by the National Health Insurance in Korea for use in CRSwNP, meaning that the patients need to pay for the full cost of the medication. Recently several real-world studies on the efficacy of biologics have been published, including a study on the efficacy of dupilumab used at a tapering dose [14-21]. As the relative cost of biologics compared with surgery is different among the various countries, the administration patterns may be different as well. Recent studies that evaluate the usage patterns of biologics were performed in Western countries [15-21]; however, those in Asian countries are limited. The primary outcome of this study was to investigate the real-world pattern of biologics use for CRS in Korea. The secondary outcome was to assess the costs related to prescribing biologics and the effectiveness of biologics in reducing systemic steroid use.

Materials and methods

This study analysed data from the Korean National Health Insurance Service (NHIS) database from January 2010 to March 2024. We estimated medical costs for surgery, medication, other procedures such as endoscopic examination, based on the ICD-10 code for CRS and/or nasal polyps (ICD-10: J32, J32.0-4, J32.8-9, J33, J33.0-1, J33.8 or J33.9). We converted the direct medical costs into US$, based on the following exchange rate: US$1 = ₩1,300. The requirement to obtain informed consent was waived by the Institutional Review Board of Dongguk University Ilsan Hospital (IRB No. 2023-04-001).

Study population

Participants who were prescribed biologics for the treatment of CRS were defined as those who had been diagnosed more than two times with CRS or nasal polyps based on ICD-10 codes; had undergone computed tomography (CT) of the head-and-neck region; and had a history of being prescribed dupilumab or omalizumab between March 1st 2021 and February 15th 2023, ensuring a follow-up period of at least 60 weeks after the initial administration. To compare the direct medical costs of using biologics with those related to surgery, we also selected CRSwNP patients who underwent surgery but were not prescribed biologics, defining them as non-biologics group. The non-biologics group was defined as patients diagnosed more than twice with CRS or nasal polyps, who had undergone CT of the head-and-neck region, and who had a history of having polypectomy with sinus surgery between January 1st 2010 and February 15th 2023; a history of having undergone nasal polypectomy was included to make certain that patients in the non-biologics group had CRSwNP due to possibility of missing nasal polyp codes (when only a CRS code was included). Figure S1 illustrates the enrolment and analysis periods for the participants included in this study. The prevalence of asthma was also evaluated as a comorbidity, and participants were defined as having asthma when they were diagnosed with asthma (J45) or status asthmaticus (J46) more than two times, by a physician, and were treated with asthma-related medications. These included ICSs or ICSs combined with LABAs oral leukotriene antagonists, short-acting b2-agonists (SABAs), systemic LABAs, xanthine derivatives, or systemic corticosteroids. The claim codes, pharmaceutical substance codes and surgery codes used to define the patient population can be found in the supplementary material.

Outcome measures

Administration patterns of the biologics were evaluated at 12, 24, 36, 48, and 60 weeks from the first use of biologics. The intervals between doses were calculated as weeks from previous dosage, and classified into less than 2-, 4, 6, 8, and more than 12-week intervals. Weeks from previous dosage that did not exactly fit into these categories were classified into the closest interval. To assess the effectiveness of biologics in the treatment of CRS, systemic steroid use was compared in the period before and after the administration of biologics.

Statistical analyses

Compliance rates between dupilumab and omalizumab were compared by using chi-squared test. The direct medical costs are demonstrated as the median with interquartile range (IQR) and analysed using the Mann-Whitney U-test. In the multiple com-

Table 1. Demographics of patients treated with biologics for CRS.

	Biologics (n = 808)
Age at initiating treatment (years) †	49 (36-61)
Sex (M:F)	449: 359
Diagnosis of asthma	376 (46.53%)
Number of ESS and/or polypectomy in previous 10 years (0,1, ≥2)	559: 201: 48
Biologics prescription duration (days)*	381 (70-728)

All values are presented as median (IQR); † Age when biologics was first prescribed; *Prescription duration during the investigational period (January 2021 to April 2023).

parison analyses for the medical cost, P-values were calculated using the Kruskal-Wallis test with the Dunn multiple comparison test. The duration of using the systemic steroids is presented as a mean with 95% confidence interval, and the reduction in the duration of using systemic steroids was analysed using paired t-test. A P-value of <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) statistical software.

Results

Demographics of study population

A total of 808 patients who were prescribed biologics for the treatment of CRS were identified (Table 1). The median age at which biologics were initiated was 49 (IQR, 36-61) years. Of these patients, 46.5% (n = 376) had asthma as a comorbidity. Five-hundred and fifty-nine patients had not received ESS or polypectomy in the 10 years preceding the usage of biologics, while 201 patients had history of surgery once, and 48 had had surgery twice or more. The biologics prescription was maintained for a median of 381 days (IQR, 70-728) during the investigational period.

Biologics administration pattern

The administration patterns of the two biologics, omalizumab and dupilumab, were analysed. Dupilumab was prescribed in 442 patients, while 385 patients were prescribed omalizumab. Both drugs were prescribed in 19 patients. Of these 19 patients, 16 had switched from omalizumab to dupilumab, and 2 patients had switched to omalizumab from dupilumab, and 1 patient initially received dupilumab, transitioned to omalizumab, and later returned to dupilumab.

Administration patterns of dupilumab and omalizumab are shown in Figure 1. The figure shows the interval of dosage calculated as weeks from previous dosage. All initial dosing intervals (at 0 week) are depicted as less than or equal to 2 weeks since there is no "previous dose". At 12 weeks, from the initiation of dupilumab therapy (Figure 1A), 353 patients (79.9%) maintained their treatment with dupilumab. It is recommended that dupilumab is used at two-week intervals [11]. However, among the 353 patients the most common dosage, accounting for 46.2% of patients, the two-week interval applied, while 53.8% of the patients were prescribed treatment at four-week or longer intervals. At 12 weeks from the initiation of omalizumab therapy, 256 patients (66.5%) maintained their treatment, showing a lower

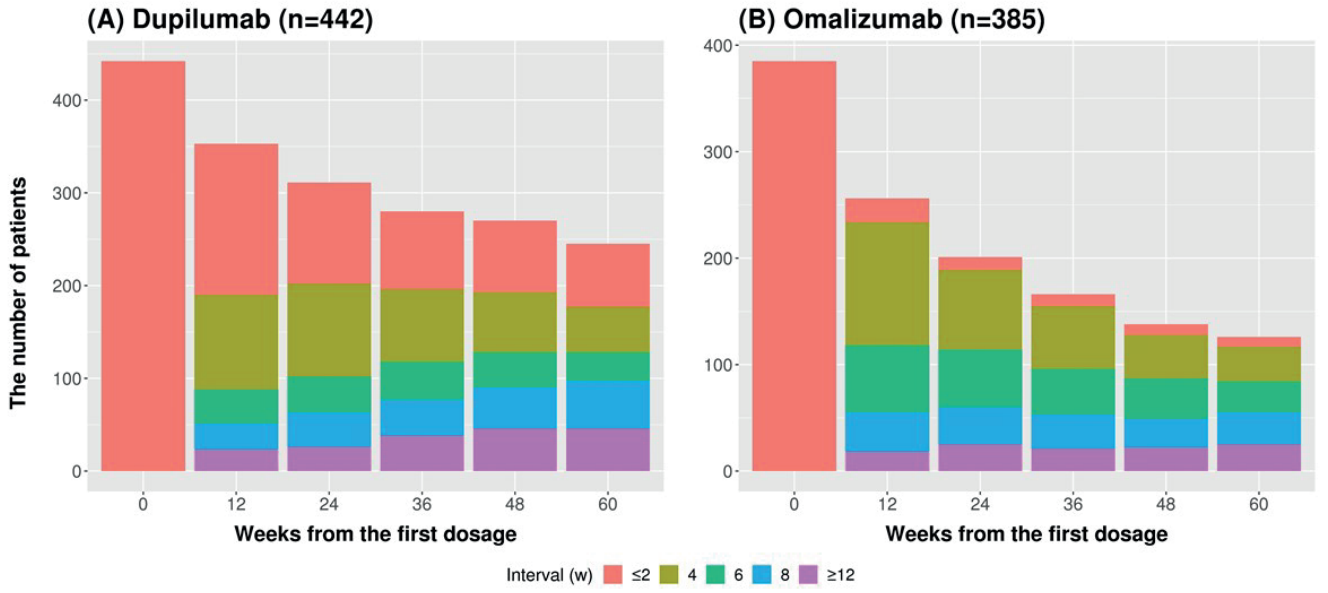

Figure 1. Dosing intervals calculated as weeks from previous dosage. (A) Dupilumab (B) Omalizumab. All initial dosing intervals (at 0 week) is depicted as less than or equal to 2 weeks since there is no "previous dose".

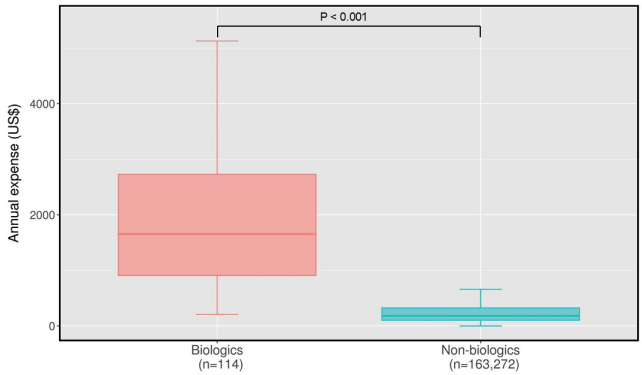

Figure 2. Annual CRS-related expenses in patients treated with biologics and those not treated with biologics.

compliance rate than dupilumab patients (p<0.001). The recommended use of omalizumab is at two or four-week intervals, depending on patient's weight and baseline IgE levels [12], however, only 8.6% of the patients were prescribed at two-week intervals, while 45.3% were treated at four-week intervals at 12 weeks.
At 60 weeks after the initiation of treatment with biologics, 245 patients (55.4%) were still on dupilumab therapy, which was higher than those on omalizumab therapy (126 patients, 32.7%) (p<0.001). The most common schedule at 60 weeks after starting dupilumab treatment was the 2-weekly interval, constituting 27.8% of the patients, followed by the 4-week interval (20.0%) schedule. In the group on omalizumab, the 4-week and 8-week interval schedule were common (26.2% and 23.8%, respectively). The treatment intervals for the biologics in both groups tended to increase as treatment proceeded.
In these 808 patients, the times from the last sinus surgery to initiation of treatment with biologics were heterogeneous. This influenced the total direct medical cost for CRS management. Therefore, we further selected patients with a history of sinus surgery in the 3 years preceding initiation of treatment with biologics. This criterion was met by 114 patients. In these patients 76 were prescribed dupilumab, 41 were prescribed omalizumab, and 3 patients were prescribed both (Figure S1). Dupilumab therapy was maintained in 45 patients (59.2%) and 25 patients (61.0%) were maintained on omalizumab therapy at 12 weeks, showing no statistically significant difference in the compliance rates between therapy (p=1.000). At 60 weeks, the compliance rates were 18.4% and 22.0% for dupilumab and omalizumab, respectively, which also did not show a statistically significant difference (p=0.830).

Medical cost of biologics

We identified the costs of hospital visits due to CRS, including those that were outpatient and inpatient, based on the ICD codes. In the 808 patients using biologics, the median of annual CRS-related expenses was calculated to be $3,328 (IQR, 1,225-9,674). In addition, we compared the annual CRS-related expenses in the patients in biologics and non-biologics groups. The annual direct medical cost for the postoperative treatment for the non-biologics patients were estimated, to compare with those of the patients treated with biologics (Figure 2). Patients not treated with biologics were assumed to be receiving postoperative treatment according to standard practice, such as nasal steroid spray, saline irrigation, and intermittent oral steroids if needed. The non-biologics group included 163,272 patients who had a history of polypectomy and sinus surgery, and the demographics of these patients are demonstrated in Table S1. Furthermore, to estimate the direct medical cost of patients treated with biologics during postoperative status, the subgroup of patients who started biologics within 3 years after surgery was compared with the non-biologics group.
In the 114 patients who were prescribed biologics within 3 years after the surgery, the annual expense of CRS patients on treatment with biologics was estimated to be $1,733 (IQR, 1034-2,756). This amount showed an increased cost burden compared with average annual expense of $182 (IQR, 102-324) in patients in non-biologics group (p<0.001) (Figure 2). This indicates that the cost of postoperative treatment with biologics is higher than that of conventional postoperative treatment. The CRS-related expense calculated in the selected patients with history of surgery, within 3 years was significantly less than that of the 808 patients cohort: $1,733 and $3,328, respectively (p<0.001). The median direct medical cost of sinus surgery with polypectomy per case was estimated to be $1,121 (IQR, 753-1740) in Korea.

Reduction in the required dose of systemic steroid

Systemic steroids were prescribed in 688 patients within 1 year before treatment with biologics. The mean number of days steroids prescribed in the one-year period before using biologics was compared with those in the period after the initiation of biologics, until 2 months after cessation. Before using biologics, the average annual usage of systemic steroids was 33.0 days (IQR, 14.0–67.0), which decreased significantly, to 12.7 days (IQR, 1.3–41.9) days after using biologics (p < 0.001). The mean number of days systemic steroids were prescribed before using dupilumab were 35.0 days (IQR, 14.0–70.0) which decreased to 9.4 days (IQR, 1.1–29.4) (p<0.001). For patients treated with omalizumab, systemic steroid use decreased from 31.0 days (IQR, 12.0–62.0) to 19.6 days (IQR, 3.5–53.9) (p<0.001) (Figure 3). The reduction in steroid use was significantly greater in patients treated with dupilumab than omalizumab (p<0.001).

Discussion

Many recognize the importance of classifying CRS according to inflammatory endotypes, as suggested by the EPOS 2020 guidelines [22]. Advancements in monoclonal antibodies targeted at inflammatory pathways have added a new armamentarium

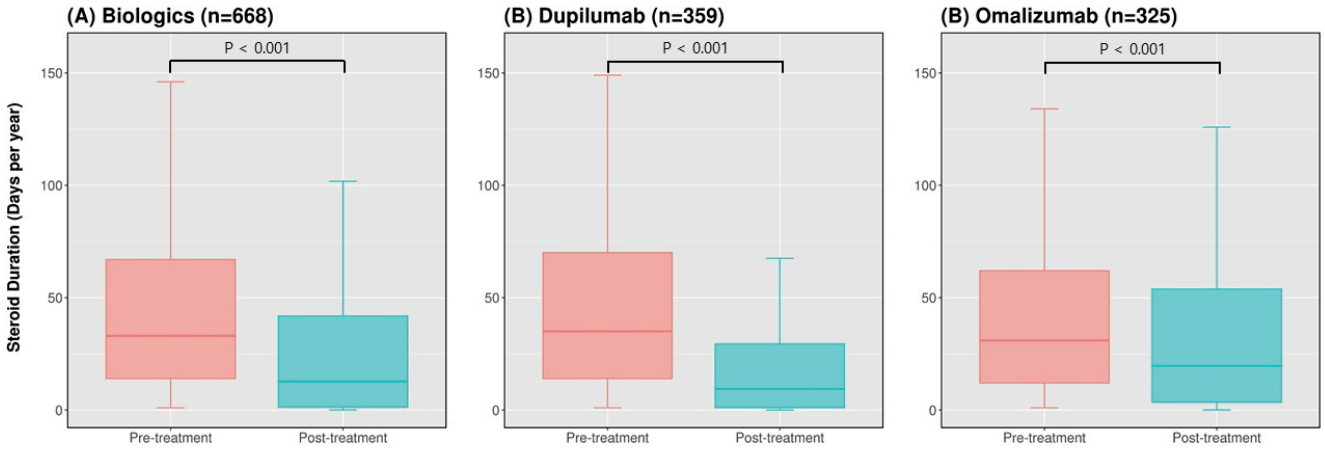

Figure 3. Change in systemic steroid prescription duration before and after biologics. (A) Biologics (n=668), (B) Dupilumab (n=359), (C) Omalizumab (n=325). Sixteen patients were treated with both dupilumab and omalizumab.

in the treatment of CRS. Biologics have been prescribed for CRS in recent years, after approval for use in the US and Europe [23]. Korea has followed, and as Asian countries are experiencing a type 2 shift [9], biologics such as dupilumab and omalizumab are expected to play greater roles in the future. Recently, the real-world effectiveness of biologics and tapered dose of dupilumab in western countries have been published [16-19, 21]. To our knowledge, this is the largest study yet, and the first in Asia to analyse real-world data on biologics including administration patterns, expenses, and effect on systemic corticosteroid reduction.

The recommended dose for dupilumab is subcutaneous injections of 300 mg every 2 weeks, while the dose and interval of omalizumab administration may depend on the patient's weight and baseline IgE levels [11, 12]. In the real-world setting, however, strictly adhering to the recommended dose may not be possible. This may be due to the clinical environment, costs, and patient preference. Results from our study show that at 12 weeks, the recommended 2-weekly administration schedule for dupilumab therapy was maintained in about a half of the patients (46.2%). In the other half of the patients (53.8%), a 4-week or longer interval was maintained at 12 weeks, which indicates a discrepancy between the recommended administration schedule and the real-world administration schedule. Furthermore, as treatment progressed, an increased proportion of patients were prescribed 4-week or longer intervals. Similarly, in patients treated with omalizumab, about a half of the patients (53.9%) were receiving treatment at 2 and 4-week intervals, at 12 weeks after the initiation, while the other half (46.1%) were receiving treatment at six-week or longer intervals. This suggests that the recommended schedule for biologics was not completed in the real-world, which may be due to the economic burden, and that patients preferred to receive treatment after the most prolonged interval possible. In a recent study, a tapered dose of up to every 8 weeks for dupilumab was proven feasible [21]. Therefore, based on this real-world data, further studies are warranted to develop a consensus on tapering protocols that are acceptable for patients with CRS who do not tolerate with the recommended administration schedule, by considering both clinical and socioeconomic factors.

In analysing the administration patterns and annual expense, we selected patients with history of surgery within the 3 years preceding initiation of biologics, to evaluate the patients who were administered biologics after the surgery. A 3-year period was used to define this cohort, as only 56 patients had started biologics within one year after sinus surgery. The overall compliance rates at 12 weeks and at 60 weeks were significantly lower in the cohort of 114 patients compared to the group of 808 patients (the biologics group). We suspected that some of the 114 patients may have been stable, after the cessation of biologics due to the effect of surgery. At both 12 weeks and 60 weeks after initiating biologic therapy, compliance rates were significantly higher in the dupilumab group. Also, more patients switched from omalizumab to dupilumab compared to vice versa, as was observed in a previous study [24]. A possible explanation for this is that dupilumab is considered more effective than other biologics in the treatment of CRSwNP [25, 26]. However, in the group of 114 patients with history of surgery within 3 years, no significant difference was found in the compliance rates between dupilumab and omalizumab.

To evaluate the direct medical costs of biologics, CRSwNP patients who were not treated with biologics were compared with the participants treated with biologics. For the biologics group, the annual direct medical cost of postoperative treatment within 3 years after surgery was calculated based on the most recent surgery performed before initiating biologics, as this criterion was deemed the most appropriate for evaluating the impact of biologics. In the non-biologics group, the annual direct medical cost within 3 years after surgery was calculated

based on the first surgery conducted during the observation period. The annual expense was greater for the biologics patients compared with the non-biologics group. The annual costs for the 808 patients on biologics were higher when compared with those of the 114-patient cohort with a history of surgery in the 3 years preceding the initiation of biologics. As was hypothesized for compliance rates, the possible explanation is that the patients who had surgery more than 3 years ago, or who not had surgery at all, were probably severe refractory cases and thus had a greater dependence on biologics. Patients treated with ESS for CRSwNP had comparable improvement in symptoms to biological treatment [27]. However, when analysing cost-effectiveness, ESS was more cost-effective in the treatment of CRSwNP compared with dupilumab [28, 29]. The cost for ESS with polypectomy was estimated to be $1,121 in this study. This is relatively cheaper than in other countries such as the US, where the outpatient ESS cost is reported to be $8,200 to $10,500 per case 2014 USD [13]. Since the costs of surgery in Korea are not high, this may affect the clinician's decision and patient preference for using biologics. Decreased systemic corticosteroid use is one of the 5 criteria used to evaluate response to biological treatment according to the EPOS 2020 and EPOS/EUFOREA 2023 (22, 30). The results of this study showed that treatment of CRSwNP with either dupilumab or omalizumab is effective in reducing the prescription duration of systemic corticosteroids. The reduction in average corticosteroid use following treatment with dupilumab was greater than that observed with omalizumab in this study. This finding is consistent with the results of a network meta-analysis, which demonstrated a superior effect of dupilumab in reducing the need for rescue oral corticosteroids [26].
The strength of this study is a large study population from which administration patterns and costs were analysed in a real-world context. Since this data is based on the reimbursement of NHIS in which the whole Korean population is included, all patients were followed up to the end of the investigational period. This study design took advantage of analysing administration patterns, as administrations of biologics in all clinics and hospitals were included. Moreover, even if patients changed their hospitals, their treatment history could still be tracked. In addition, a nationwide population was used; therefore, the largest population treated with biologics in Asia was analysed. However, this study has a limitation in that factors such as improvement in sense of smell, reduction in nasal polyp size, improvement quality of life and reduction in the impact of comorbidities, which are also used to define response to biological treatment in CRSwNP could not be assessed, since it was based on the NHIS claims data base. Instead, we analysed reduction in systemic steroid use to evaluate the effectiveness of the biologics. Furthermore, due to the nature of the study, we were not able to identify the presence of nasal polyps in individual endoscopic exams. However, since the prescription of biologics is indicated for patients with CRSwNP, we believe that biologics were prescribed to patients with CRSwNP, and we selected a control group with CRSwNP who had undergone surgery. Out of the 808 patients treated with biologics, we identified 249 who underwent surgery in the 10 years prior to the initiation of biologics. We acknowledge that not all of the remaining 559 patients were without a history of sinus surgery; some of them may have had surgery before the 10 years investigational period. As biologics are approved for CRS recently, some patients who have been refractory for more than 10 years might be included. Additionally, some patients who do not suffer from other CRS symptoms but only have olfactory loss and were prescribed biologics might also be included in this study, since it is most effective in improving olfaction [31].

Conclusion

Through analysing real-world data of biologics' use in a large population, this study was able to evaluate administration patterns, compliance, expenses related to biologics, and its effect on systemic steroid use. The discrepancy between the recommended and the real-world administration schedules in this study suggests that feasible administration schedules for the real-world should be investigated, considering the various economic statuses of patients and healthcare costs.

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Authorship contribution

SAH and JYK conceptualized and designed thestudy. JYK acquired the datasets used in the study. SAH, JHY, and JYK contributed to the analysis and interpretation. BHK, JHP, YSL and CGC reviewed the data. SAH and JYK drafted the article under supervision of YBK and SWP. All authors revised the manuscript and approved the final version.

Conflict of interest

All authors have no conflict of interest.

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Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Dongguk University Ilsan Hospital (IRB No. 2023-04-001). The

requirement to obtain informed consent was waived.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPLEMENTARY MATERIAL

Supplementary methods

Study population

Patients who were prescribed biologics for the treatment of CRS were defined as those who were diagnosed more than two times for CRS or nasal polyps (ICD-10: J32, J32.0-4, J32.8-9, J33, J33.0-1, J33.8 or J33.9). The diagnosis of CRS or nasal polyps was required to be recorded as the primary diagnosis, the first secondary diagnosis, or the second secondary diagnosis. Additionally, participants had undergone computed tomography (CT) of the head-and-neck region (claim codes: HA401-HA416, HA441-HA443, HA451-HA453, HA461-HA463, or HA471-HA473), and had a history of being prescribed dupilumab or omalizumab (pharmaceutical substance code: 670401BIJ, 572903BIJ, 572904BIJ, 572901BIJ) from March 1st 2021 to February 15th 2023. To compare the direct medical costs of using biologics with those related to surgery, we also selected CRSwNP patients who underwent surgery, but were not prescribed biologics, defining them as non-biologics group. The non-biologics group was defined as patients diagnosed more than two times with CRS, had undergone CT of the head-and-neck region, and had a history of having polypectomy (surgery codes: O0952, O0954, O1954, O00950, O00951, O00953) with or without sinus surgery (surgery codes: O1050, O1070, O1100, O1120, O1130, O1140, O1150, O1160, O1170, O1175, O1180, O1051, O1101, O1121, O1131, O1141, O1151, O1152, O1161, O1171, O1172, O1176, O1177, or O1182), more than once between January 1st 2010 and February 15th 2023. To assess the efficacy of biologics in the treatment of CRS, systemic steroid (pharmaceutical substance code: 170901ATB, 170906ATB, 193302ATB, 193305ATB, 193601BIJ, 217001ATB, 217034ASY, 217035ASY) use was compared in the period before and after administration of biologics. Asthma was also analysed as a comorbidity, and patients were defined as having asthma when they were diagnosed with asthma (J45) or status asthmaticus (J46) more than two times, by a physician and were treated with asthma-related medications, including inhaled corticosteroids (ICSs) or ICSs combined with long-acting β2-agonists (LABAs) (pharmaceutical substance code: 119530CSI, 162231CSS, 162231CSI, 497130CSI, 500431CSI, 542800CSI, 542900CSI, 543000CSI, 543100CSI, 543200CSI, 543400CSI, 543500CSI, 543600CSI, 543800CSI, 543900CSI, 544000CSI, 544100CSI, 544200CSI, 636700CSI, 636800CSI, 681000CSI, 698400CSI, 698500CSI, 698600CSI), or short-acting β2-agonists (SABAs) (pharmaceutical substance code: 225530-2CSI).

Table S1. Demographics of the patients not treated with biologics.

	Biologics (n = 808)	Non-biologics (n =163,272)
Age at initiating treatment (years)†	49 (36-61)	50 (39-60)
Sex (M:F)	449 : 359	108.712 : 54,560
Diagnosis of asthma	376 (46.5%)	20,316 (12.4%)

All values are represented as median (IQR). † Biologics group: age when biologics was first prescribed; Nasal polyp and CRS group: age when first surgery was done.

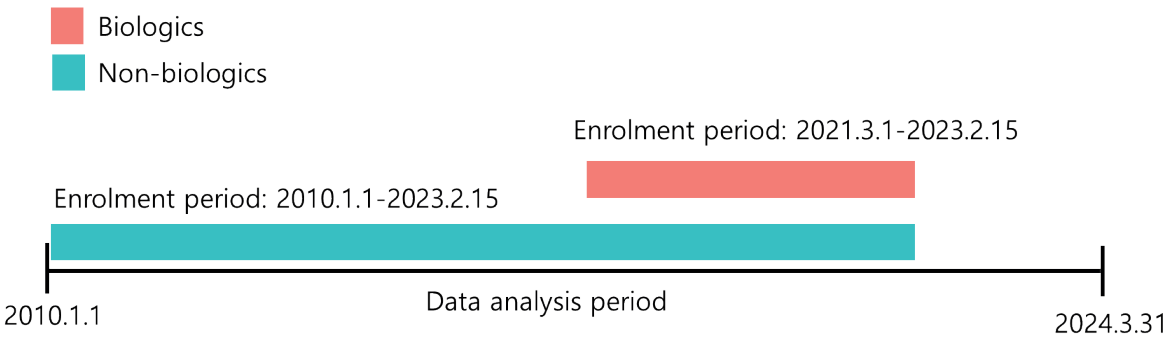

Figure S1. Enrolment and analysis periods for the participants. The red bar represents the enrolment period for the biologics group (2021.3.1–2023.2.15), while the teal bar represents the enrolment period for the non-biologics group (2010.1.1–2023.2.15). Both groups share a common analysis period (2010.1.1–2024.3.31).

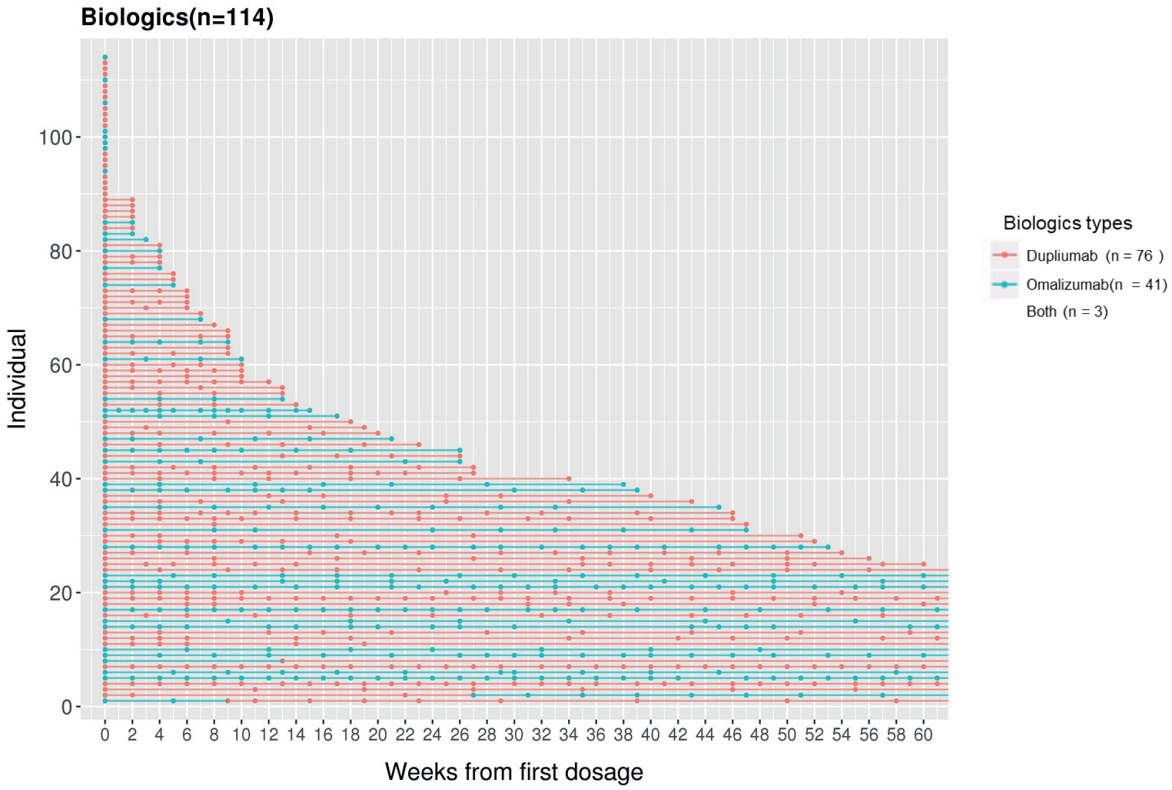

Figure S2. Individual dosing patterns in 114 patients who were prescribed biologics within 3 years after receiving surgery. Each horizontal line refers to a single patient. The numbers on the y-axis correspond to each of 114 individual patients, and the points on x-axis represent the dosing times.