Dupilumab for chronic rhinosinusitis with nasal polyps: real-life retrospective 12-month effectiveness data*

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Abstract

Background: Dupilumab, an IL-4/13 receptor inhibitor, is approved for the treatment of uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP).

Methodology: We evaluated the effectiveness and safety of dupilumab for CRSwNP based on retrospective 12-month follow-up data of 41 patients. We analysed nasal endoscopy scores, patient-reported outcome measures (PROMs), 12-item Sniffin'-Sticks odor identification test (SSIT-12), total serum IgE, serum Eosinophilic Cationic Protein (ECP), and total blood eosinophil count (BEC). We performed statistical analysis using non-parametric ANOVA-type models and Spearman's correlation.

Results: At month 1, endoscopy scores, PROMs and SSIT-12 showed meaningful improvements that were maintained until month 12. Initial elevations in both median ECP and BECs returned to near baseline levels by month 12. The percentage of patients with BEC ≥0.6 remained increased at month 12 (42.1%) compared to baseline (19.5%). Total serum IgE levels decreased progressively and correlated with nasal polyp scores at month 12. "Adequate response" was reached in 86.8% of our cohort.

Conclusions: Our data suggest that dupilumab is effective for the treatment of CRSwNP. The potential for short- and long-term BEC elevations in some CRSwNP patients should be carefully monitored.

Key words: biologicals, CRSwNP, dupilumab, nasal polyps, chronic rhinosinusitis, eosinophils

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a phenotype of chronic rhinosinusitis (CRS), characterized by polypoid inflammatory outgrowths from the nasal mucosa. The cardinal symptoms of CRS are chronic nasal congestion, nasal discharge, loss of smell, and facial pressure. Despite first-line therapy with topical corticosteroids, systemic corticosteroids and/or surgery, CRSwNP frequently recurs. In Europe, CRSwNP is estimated to affect 2.11% to 4.3% of the population, with 0.027% suffering from uncontrolled severe CRSwNP [(1)]. Nasal polyps coexist with type-2-driven diseases such as asthma, NSAID-exacerbated respiratory disease (N-ERD), and aeroallergen sensitization. The type-2 inflammatory endotype predominates in western nasal polyps and correlates with more severe disease and higher recurrence rates. The appreciation of inflammatory CRS-endotypes has led to the development of targeted therapies such as dupilumab, a human monoclonal IgG4 antibody that blocks IL-4 and IL-13 downstream signaling by binding to the IL-4 receptor alpha subunit. Dupilumab is approved as add-on treatment to intranasal corticosteroids (INCS) in adults with uncontrolled, severe CRSwNP [(2)].

Our study adds to the existing body of real-world evidence on dupilumab for CRSwNP [(3–11)], by providing 12-month follow-up with safety and effectiveness data, scrutinizing BEC development, and performing correlation analysis of baseline and 12-month parameters.

Materials and methods

This study was approved by the ethics committee of the University of Lübeck (AZ 20-490). We gathered consent for the utilization of clinical data for research from all patients at their first visit to our clinic. We retrospectively reviewed the records

of adult patients with bilateral CRSwNP initiated on dupilumab 1x300mg s.c. biweekly as an add-on to INCS at the Department of Otorhinolaryngology of the University Medical Center Lübeck in 2019-2020. Diagnosis of CRSwNP was based on the EPOS2012 criteria [12]. Patients with uncontrolled CRSwNP despite prior surgery and long-term use of INCS were considered for dupilumab. Indication for dupilumab treatment was based on the EUFOREA-2019 [13] / EPOS2020 criteria [14]. Patients who underwent sinus surgery or were transferred from another biological drug prescribed for CRSwNP within three months before initiation of dupilumab did not need to present with bilateral nasal polyps if bilateral CRSwNP had been previously documented. Exclusion criteria for dupilumab in real-life were concomitant therapy with other biologicals, pregnancy, and cystic fibrosis. After a baseline visit before the first dupilumab injection, follow-up visits were scheduled at months 1, 3, 6, 9, and 12. For the effectiveness analysis, we included all patients with a minimum follow-up time of >3 months and included data up to month 12.

Study outcome parameters

We recorded age, sex, clinical history including coexisting type-2 inflammatory diseases, medication use, and number of prior sinus surgeries. N-ERD was diagnosed according to the EACCI position paper criteria [15]. For grading of nasal polyps, we video-recorded nasal endoscopies of both nasal cavities at each visit. To limit the risk for observer bias, we (R.B., M.H) independently assessed the Nasal Polyp Score (NPS) according to Gevaert [16,17] and the modified Lund-Kennedy score (MLKS; 1-12 points) [18]. In case of discrepancies between the two observers, a consensus was reached through discussion. Laboratory work-up included complete blood count, serum Eosinophilic Cationic Protein (ECP), serum total IgE and specific serum IgE levels (ImmunoCAP panels "sx1", "rx2", "mx2"; ThermoFisher Scientific, USA). We recorded general and specific CRS symptoms on paper forms with validated patient-reported outcome measures (PROMs) [19], including visual analogue scales (VAS; 0-10cm) for both rhinosinusitis disease severity and nasal obstruction, and 22-item Sino-Nasal Outcome Test (SNOT-22 German adapted version) [20]. The minimal clinically important difference (MCID) for the SNOT-22 is 8.9 points. We assessed four SNOT-22 subdomains that have been validated to reflect sleep (MCID=4), nasal (MCID=4), ear/facial pain (MCID=2), and emotional symptoms (MCID=1) [21,22]. For screening of olfactory function, we used the 12-item Sniffin' Sticks odor identification test kit (SSIT-12; Burghart Messtechnik, Germany). We tested each nostril individually and used the total score of the better-performing side to classify anosmia (score 0-6), hyposmia (7-10), and normosmia (11-12) [23].

To categorize levels of disease control and treatment response, we explored various published assessment scores: Rhinosinusitis disease severity VAS score (well controlled = VAS ≤ 2; partly controlled = VAS >2 ≤5; uncontrolled = VAS >5) [24], SNOT-22 (<35 controlled, ≥35 uncontrolled), EUFOREA-2021 criteria [1], and EPOS2020 criteria. In both EUFOREA-2021 and the EPOS2020 criteria, we replaced parameters that were not recorded in our cohort with comparable converted symptoms-specific SNOT-22 items (Tables S1-S3).

We performed data analysis in "R" (Version 4.2.2) [25]. We handled missing outcome variables with multiple imputation methods assuming data to be "missing at random". A missing data analysis is provided in Table S4. Incomplete variables were imputed under fully conditional specification using the default settings of the mice 3.14.0 package [26]. We created 50 multiply imputed datasets. The parameters of substantive interest were estimated in each imputed dataset separately and combined using Rubin's rules. We used the LD-F1 model of the R package "nparLD" (Version 2.2) [27] for non-parametric statistical analysis of longitudinal data. We applied the model separately to each imputed dataset and present the estimated medians of ANOVA-type test statistics and relative treatment effects (RTE). RTE values can take values between 0 and 1. An RTE value of, e.g., 0.77 indicates that a randomly chosen value from the whole dataset is with an estimated 77% probability lower than a randomly chosen value from the timepoint analysed. We determined the main RTE across the observed 12-month observation period, and in the case of a statistically significant main RTE, we compared values from single follow-up visits to baseline. We calculated Spearman's rho statistics to estimate rank-based measures of association between individual variables at baseline and month 12. To control for the false-discovery rate, we applied Benjamini-Hochberg adjustments [28] and report the adjusted p-values. We analysed count data in Fisher's exact test. We set the statistical significance level to α=0.05. We generated plots in "R" with "ggplot2" (Version 3.4.0) [29].

Results

We screened 45 records and excluded four records of subjects lost to follow-up ≤3 months after initiation of dupilumab-treatment. Our final analysis included 41 subjects, of which 38 (92.7%) completed ≥12 months follow-up. Prior to the initiation of dupilumab-treatment, five subjects had received other biologicals ≤3 months earlier: 4 (9.75%) subjects had received omalizumab and 1 (2.44%) mepolizumab. We treated 2 (4.89%) patients with a combination of dupilumab as induction therapy and revision surgery performed 1 and 2 months after initiation of dupilumab, respectively. Four (9.75%) subjects started dupilumab-treatment within 3 months after undergoing sinus surgery.

At baseline, the mean age was 52.12 (range 27-79) years. 40 (97.6%) patients had evidence of type-2 inflammation, 28

Table 1. Baseline patient characteristics.

Characteristic	Value
No. patients treated with dupilumab (n)	41
Sex: male/female, n (%)	23/18 (56/44)
Age at start of therapy, mean (range)	52.12 (27-79)
Evidence of type-2 inflammation, n (%)	40 (97.6)
Patients with asthma, n (%)	28 (68.3)
Patients with NSAID-exacerbated respiratory disease, n (%)	17 (41.5)
sIgE against inhalant allergens (ImmunoCAP ≥1), n (%)	26 (63.4)
Atopic dermatitis, n (%)	2 (4.9)
Coexisting type-2 inflammatory diseases, n (%)	36 (87.8)
Current Smoker, n (%)	4 (9.8)
Previous sinus surgery, n (%)	
0 previous surgery, n (%)	0 (0)
≥1 previous surgery, n (%)	41 (100)
≥2 previous surgeries, n (%)	33 (80)
≥3 previous surgeries, n (%)	18 (43.9)
≥4 previous surgeries, n (%)	8 (19.5)
Time since last sinus surgery (months), median (Q1, Q3)	36.00 (21.00, 84.00)
OCS long-term use or ≥ 2 courses in previous year, n (%)	12 (29.2)
Total endoscopic Nasal Polyp Score (scale 0–8), median (Q1, Q3)	5.00 (4.00, 6.00)
NPS 0, n (%)	3 (7.3)
NPS 1-3, n (%)	4 (9.8)
NPS 4-8, n (%)	34 (82.9)
Modified Lund-Kennedy score (scale 0-12), median (Q1, Q3)	8.00 (6.00, 10.00)
Rhinosinusitis disease severity VAS score (scale: 0–10), median (Q1, Q3)	8.00 (7.00, 10.00)
Nasal obstruction VAS score (scale: 0–10), median (Q1, Q3)	7.00 (4.00, 9.00)
SNOT-22 total score (scale: 0–110), median (Q1, Q3)	48.00 (37.00, 68.00)
Sniffin' Sticks Identification Test-12 total score (SSIT-12; scale: 0–12), median (Q1, Q3)	3.00 (2.00, 4.00)
Normosmia, n (%)	0 (0)
Hyposmia, n (%)	1 (2.4)
Anosmia, n (%)	40 (97.6)
Serum total IgE (IU/mL), median (Q1, Q3)	111.26 (39.73, 240.08)
Eosinophilic Cationic Protein (ECP; µg/L), median (Q1, Q3)	38.15 (23.96, 62.29)
Blood eosinophil count, median (Q1, Q3)	0.44 (0.28, 0.58)
Number of EPOS2020 indication criteria met per patient, n (%)	
1	0
2	4 (9.8)
3	17 (41.5)
4	12 (29.3)
5	8 (19.5)
≥3	37 (90.2)
Specific IgE (ImmunoCAP >1)	
Dermatophagoides pteronyssinus (d1), n (%)	13 (31.7)
Dermatophagoides farinae (d2), n (%)	13 (31.7)
Cat dander (e1), n (%)	8 (19.5)
Dog dander (e5), n (%)	2 (4.9)
Horse dander (e3), n (%)	1 (2.4)
Timothy grass pollen (g6), n (%)	11 (26.8)
Cultivated rye (g12), n (%)	13 (31.7)
Cladosporium herbarum (m2), n (%)	1 (2.4)
Birch pollen (t3), n (%)	12 (29.3)
Mugwort pollen (w6), n (%)	4 (9.8)
Aspergillus fumigatus (m3), n (%)	0 (0)
Candida albicans (m5), n (%)	4 (9.76)
Alternaria alternata (m6), n (%)	2 (4.9)
Setomelanomma rostrata (m8), n (%)	0 (0)

(68.3%) asthma, 17 (41.5%) N-ERD, and 2 (4.9%) atopic dermatitis, respectively. Complete baseline characteristics and demographics are shown in Table 1.

Thirty-seven (90.24%) subjects met the EPOS2020 inclusion criteria for biologicals with at least 3 criteria fulfilled.

Effectiveness assessments

Our analysis of the follow-up data revealed significant relative treatment effects (RTE) for all parameters analysed (Table 2). The comparisons between the baseline and follow-up visits are presented below and are summarized in Table S5. Since all endoscopic scores, PROMs and SSIT-12 significantly improved as early as the first assessment time point at month 1 and continued to improve through to month 12, we only present the values for baseline, month 1 and month 12 to enhance the manuscript's readability.

Nasal polyp score and modified Lund-Kennedy score

Median total nasal polyp scores (NPS) decreased from 5.00 (IQR 2.00) at baseline to 3.00 (IQR 3.00) at month 1 ($p < 0.001$), and further to 1.00 (IQR 3.00) at month 12 ($p<0.001$) (Figure 1A). Severe nasal polyps (NPS ≥4) were present in 82.9% (34/41) of the subjects at baseline and 15.8% (6/38) at month 12 (Figure 2A). Median modified Lund-Kennedy scores (MLKS) decreased from 8.00 (IQR 4.00) at baseline to 5.00 (IQR 3.00) at month 1 ($p<0.001$), and further to median 4.00 (IQR 3.00) at month 12 ($p<0.001$) (Figure 1B). At month 12, 92.1% (35/38) of the subjects

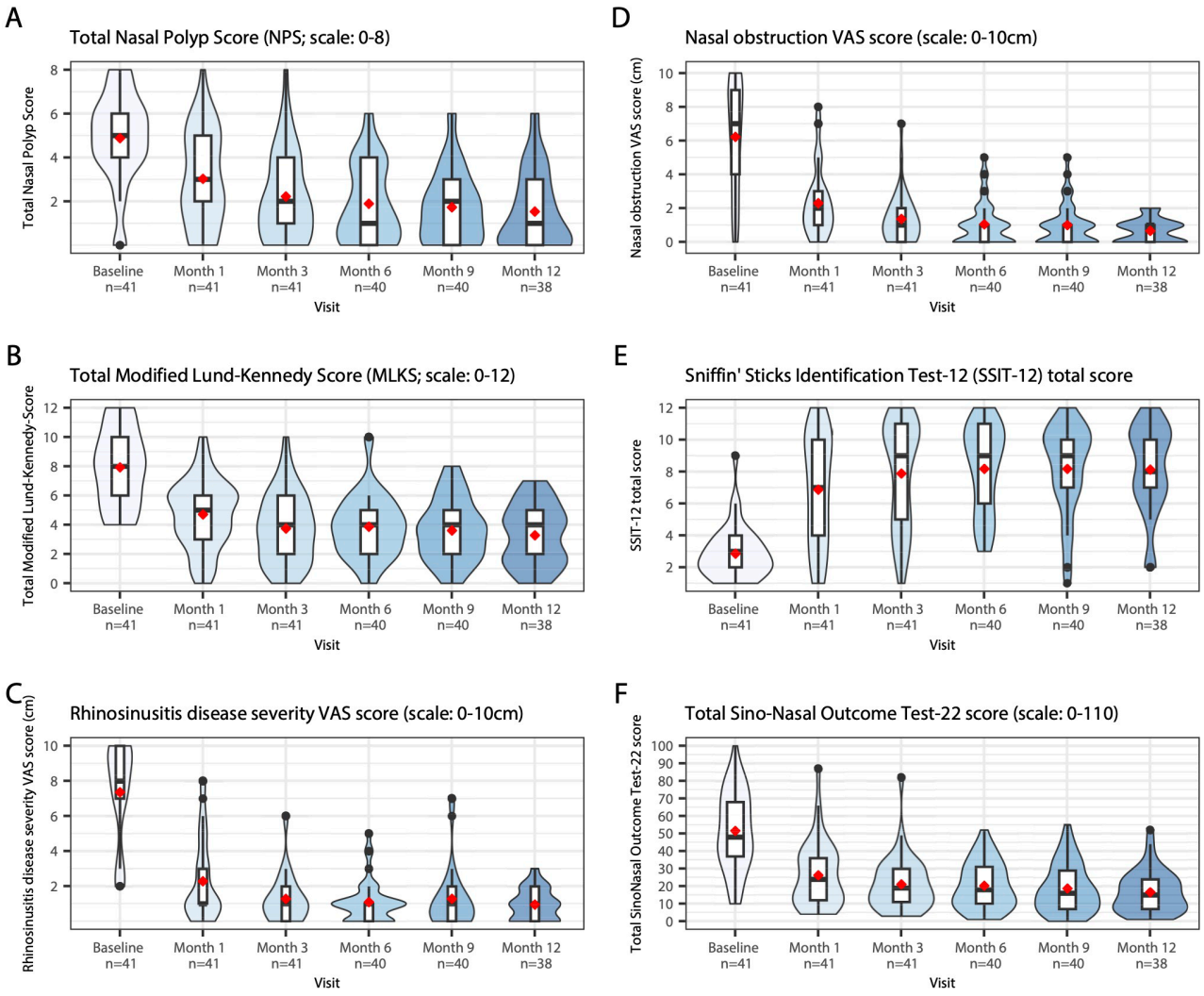

Figure 1. Violin plots with included boxplots. The red diamonds indicate the statistical mean. Shown are the baseline visit and visits at months 1, 3, 6, 9, 12. A) Total Nasal Polyp Score; B) Total modified Lund-Kennedy score; C) Rhinosinusitis disease severity VAS score; D) Nasal obstruction VAS score; E) 12-item Sniffin' Sticks oder identification test total score, F) Total Sino-Nasal Outcome Test-22 (SNOT-22) score.

had an MLKS score ≥1, indicating the presence of mucosal pathology.

Rhinosinusitis disease severity and nasal obstruction VAS scores

The median rhinosinusitis disease severity VAS scores improved from median 8.00 (IQR 3.00) at baseline to 1.00 (IQR 2.00) at month 1 ($p<0.001$) and remained at 1.00 (IQR 2.00) at month 12 ($p<0.001$) (Figure 1C). Nasal obstruction VAS scores significantly decreased from a median of 7.00 (IQR 5.00) at baseline to 2.00 (IQR 2.00) at month 1 ($p<0.001$), and median 1.00 (IQR 1.00) at month 12 ($p<0.001$) (Figure 1D). Baseline rhinosinusitis disease severity VAS scores were associated with baseline NPS ($r=0.44$, $p=0.03$). Baseline nasal obstruction VAS scores were associated with both baseline NPS ($r=0.51$, $p=0.005$) and baseline MLKS ($r=0.51$, $p=0.006$; Figure 3) scores.

Sino-Nasal Outcome Test-22

Total SNOT-22 scores decreased from a median value of 48.00 (IQR 31.00) at baseline to 23.00 (IQR 25.00) at month 1 ($p<0.001$), and 15.00 (IQR 16.00) at month 12 ($p<0.001$), respectively (Figure 1F). At 12 months, 86.8% (33/38) of the subjects recorded a clinically meaningful improvement in SNOT-22 scores, defined as a reduction of ≥8.9 points. In addition, we examined the SNOT-22 subdomains of sleep, nasal, ear/facial pain, and emotional symptoms. The median scores of all SNOT-22 subdomains demonstrated clinically meaningful improvements starting at month 1 ($p<0.001$) and these improvements were sustained through month 12 ($p<0.001$; Table S5). At month 12, MCIDs were met for the SNOT-22 nasal subdomain in 97.7% (37/38) of the subjects, for the SNOT-22 ear/facial pain subdomain in 69.2% (27/38), for the SNOT-22 sleep subdomain in 71% (27/38), and for the SNOT-22 emotional subdomain in 71% (27/38), respecti-

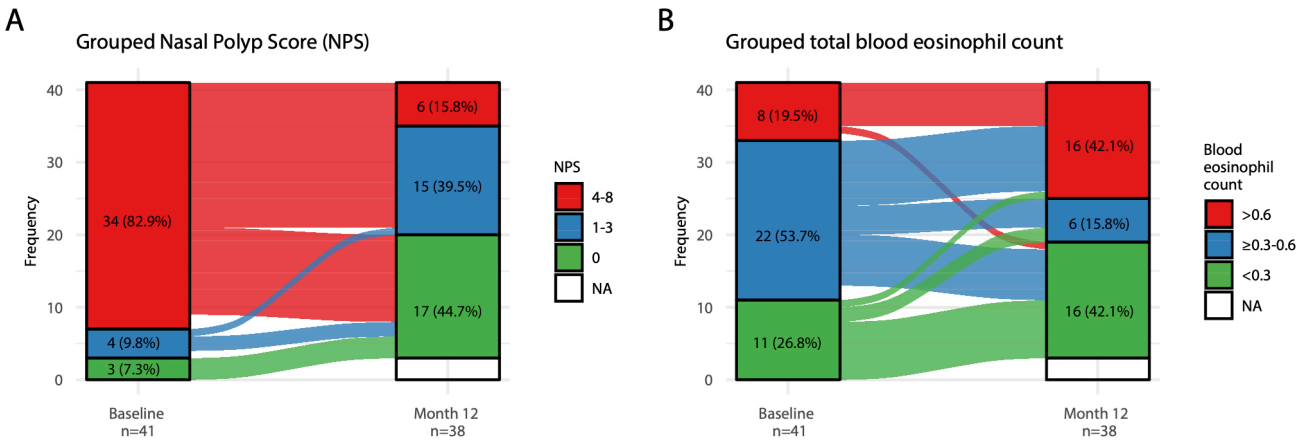

Figure 2. Alluvial plots for A) grouped Nasal Polyp Score (NPS) and B) grouped blood eosinophil count (BEC). Each stratum of the stacked bar plots indicates the aggregated count of each group. The coloured ribbons depict the development from baseline to month 12. Both grouped NPS and BECs were significantly different at month 12 compared to baseline (both p<0.001).

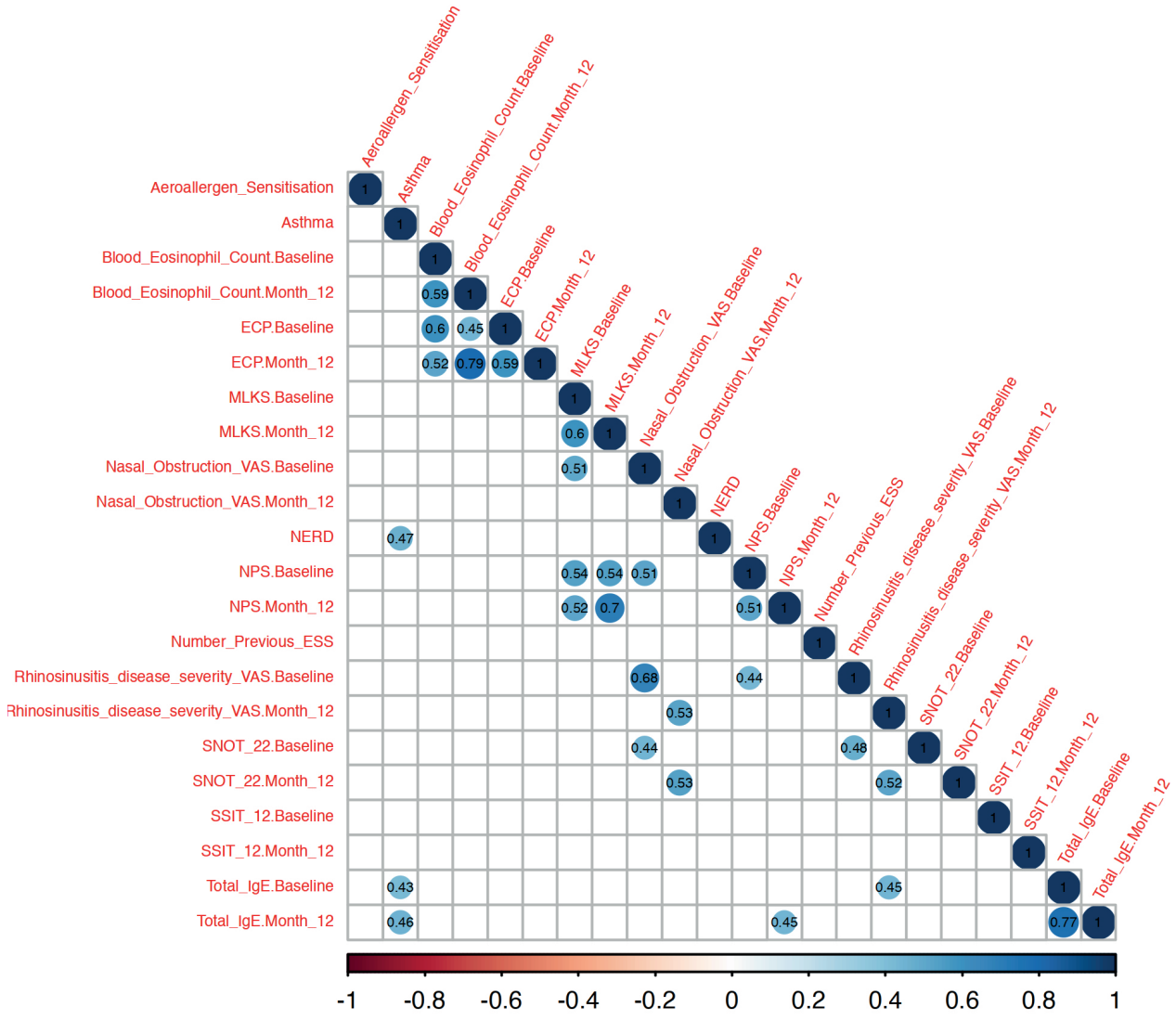

Figure 3. Correlation matrix plot of patient characteristics and variables at baseline and month 12. Statistically significant Spearman's correlation coefficients (FDR-adjusted p-values <0.05) are shown as colored circles. The color intensities are proportional to the correlation coefficients.

Table 2. Relative treatment effects and ANOVA-type test statistics (LD-F1 model).

	Relative Treatment Effect (RTE)						ANOVA-type test statistic	
	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12	F (1.00, ∞)	FDR-adjusted p-value
Total Nasal Polyp Score	0.77	0.57	0.46	0.42	0.41	0.36	54.06	$3.45x10^{-36}$ ***
Modified Lund-Kennedy Score	0.81	0.54	0.43	0.44	0.42	0.38	51.51	$1.01x10^{-42}$ ***
Rhinosinusitis symptom severity VAS score	0.88	0.53	0.42	0.39	0.40	0.38	44.18	$3.76x10^{-39}$ ***
Nasal obstruction VAS score	0.82	0.58	0.46	0.40	0.39	0.35	31.76	$1.64x10^{-23}$ ***
SSIT-12	0.16	0.48	0.58	0.59	0.59	0.59	42.04	$2.64x10^{-31}$ ***
Total SNOT-22 score	0.81	0.52	0.45	0.44	0.40	0.37	41.93	$3.36x10^{-30}$ ***
SNOT-22 ear/facial pain	0.73	0.49	0.47	0.45	0.45	0.41	17.23	$1.09x10^{-13}$ ***
SNOT-22 emotional symptoms	0.73	0.49	0.46	0.48	0.42	0.43	19.60	$2.48x10^{-14}$ ***
SNOT-22 nasal symptoms	0.84	0.52	0.47	0.44	0.39	0.35	38.73	$3.36x10^{-30}$ ***
SNOT-22 sleep	0.75	0.54	0.44	0.45	0.43	0.40	24.80	$4.78x10^{-18}$ ***
Total serum IgE (IU/mL)	0.66	0.61	0.53	0.46	0.40	0.36	37.59	$5.67x10^{-21}$ ***
Eosinophilic Cationic Protein (ECP; µg/L)	0.41	0.61	0.57	0.54	0.46	0.41	11.13	$1.78x10^{-08}$ ***
Total Blood Eosinophil Count (Giga/L)	0.41	0.54	0.58	0.54	0.49	0.44	4.46	$1.84x10^{-03}$ **

* adj. p <0.05; ** adj. p <0.01; *** adj. p <0.001; n.s.= not significant; n.a.= not applicable

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Sniffin' Sticks odor identification test

The SSIT-12 smell test showed significant improvements, with a median score of 3.00 (IQR 2.00) at baseline increasing to 7.00 (IQR 6.00) at month 1 (p<0.001) and 8.00 (IQR 3.00) at month 12 (p<0.001) (Figure 1E). 97.6% (40/41) of the subjects had anosmia at baseline and 21.0% (8/38) at month 12, respectively.

Total serum IgE

Total serum IgE levels decreased progressively from median 111.26 IU/mL (IQR 200.35) at baseline to 79.27 (IQR 109.28) at month 1 (p<0.001) and 27.78 (IQR 35.65) at month 12 (p<0.001; Figure 4A). Total serum IgE levels at baseline were associated with 12-month rhinosinusitis disease severity VAS scores (r=0.45, p=0.04). Month-12 total serum IgE levels correlated with month-12 NPS scores (r=0.45, p=0.04). Both baseline and month-12 total serum IgE levels were associated with asthma comorbidity (r=0.43, p=0.04; r=0.46, p=0.02).

Eosinophilic Cationic Protein

Median ECP levels increased significantly from a median value of 38.15 µg/L (IQR 38.33) at baseline to 75.20 (IQR 118.54) at month 1 (p<0.001). ECP levels remained elevated at month 3 (60.29 (IQR 118.77); p=0.003) and month 6 (52.39 (IQR 98.53); p=0.002) but normalized at month 9 (39.14 (IQR 59.85); p=0.34) and month 12 (28.87 (IQR 80.62); p=0.84) (Figure 4B), respectively.

Blood eosinophil count

Median blood eosinophil counts (BEC) increased from 0.44 (IQR 0.30) Giga/L at baseline to 0.59 (IQR 0.66) at month 1 (p=0.01). BEC levels remained elevated at month 3 (0.73 (IQR 0.91; p=0.004) and month 6 (0.59 (IQR 0.80; p=0.007), but decreased towards baseline levels at month 9 (0.46, IQR 0.64; p=0.14) and month 12 (0.50, IQR 0.68; p=0.56) (Figure 4C). When grouping the BEC into three strata (<0.3 ≥0.3-0.6, >0.6 Giga/L), we found significant differences between baseline and month 12 (p<0.001). At month 12, 42.1% (16/38) of the patients had an elevated BEC ≥0.6, compared to 19.5% (8/41) at baseline (Figure 2B). Conversely, the percentage of patients with normal BEC <0.3 Giga/L increased from 26.8% (11/41) at baseline to 42.1% (16/38) at month 12. Hypereosinophilic BEC >1.5 Giga/L occurred in 6/41 (14.6%) subjects at any time point throughout the observation period, and in 3 subjects in more than two blood exams without signs of organ damage.

Disease control

We further assessed disease control based on the EPOS2020 criteria, total SNOT-22 score and rhinosinusitis severity VAS score. At baseline, uncontrolled CRSwNP was present in 82.9% (34/41)

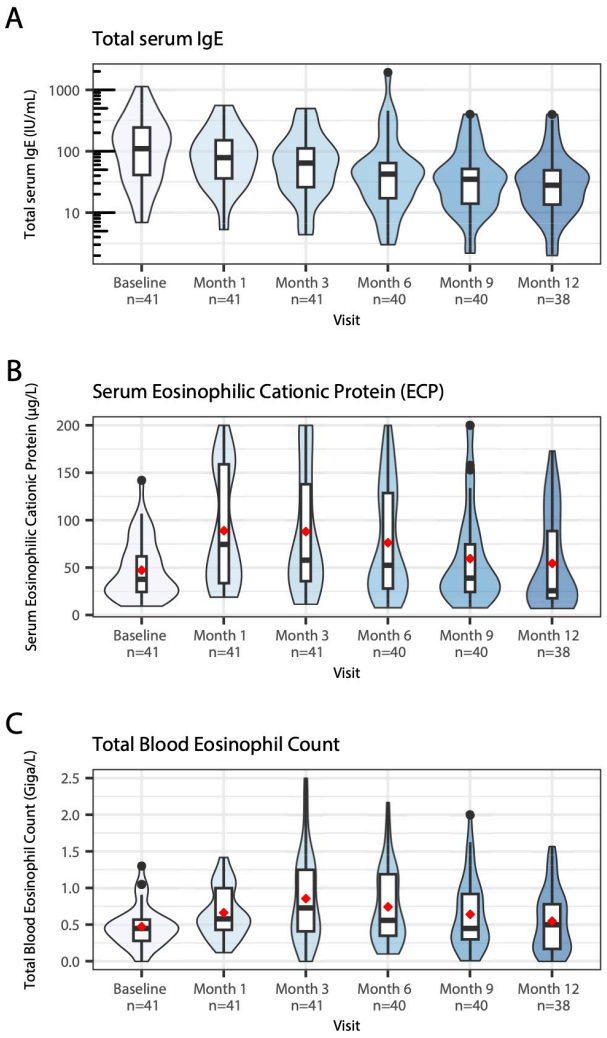

Figure 4. Violin plots with included boxplots. Red diamonds indicate the statistical mean. Shown are the baseline visit and visits at months 1, 3, 6, 9, 12. A) Total IgE (log10 scale); B) Eosinophilic Cationic Protein (ECP); C) Total Blood Eosinophil Count.

of the subjects according to the EPOS2020 criteria, 75.6% (31/41) based on total SNOT-22 score ≥35, and 78.0% (32/41) based on rhinosinusitis disease severity VAS score >5, respectively. At month 12, "uncontrolled" CRSwNP was seen in 15.8% (6/38) of the subjects based on the EPOS2020 criteria, 7.9% (3/38) based on total SNOT-22 score ≥35, and 0% (0/38) based on rhinosinusitis disease severity VAS score >5 (Figures 5A-C). Based on the EUFOREA-2021 criteria [1], uncontrolled severe disease was present in 56.1% (23/41) subjects at baseline. The EUFOREA-2021 clinical response criteria at month 6 recommended continuation of biological treatment in 95% (38/40) of the subjects. The remaining two subjects who did not meet the EUFOREA-2021 criteria had a baseline total NPS score of 0 due to recent sinus surgery, and therefore were unable to achieve the required reduction in NPS score for the criteria to be met. EUFOREA-2021 "adequate response" was met by 86.8% (33/38) of the subjects (Figure 5D) at month 12.

Two patients underwent planned sinus surgery after "induction" therapy with dupilumab. Both patients had severe nasal polyps before undergoing surgical intervention and, at month 12, showed an NPS of 0 and "adequate control" based on the EUFOREA-2021 criteria.

No patient required rescue surgery, and no systemic corticosteroids or antibiotics were prescribed by indication of CRSwNP.

Safety

We did not observe any severe treatment-emergent adverse events. Frequent treatment-emergent adverse events were transient injection site reaction in 9 patients (22%) and ocular side effects in 4 subjects (9.8%). Ocular side effects included mild xerophthalmia in 3 subjects and keratoconjunctivitis/blepharitis in one female subject with comorbid atopic dermatitis. Keratoconjunctivitis/blepharitis in this subject regressed within four days with ciclosporin eye drops and periorbital application of tacrolimus ointment. One male patient reported arthralgia at month 3 and was lost to follow-up after being referred to a rheumatologist. Three patients permanently discontinued treatment. One male patient discontinued treatment after ten months due to nausea and diarrhoea that he believed were caused by dupilumab. A female patient with suspected hypereosinophilic syndrome (HES), uncontrolled CRSwNP, asthma, and N-ERD discontinued dupilumab after 9 months of treatment. Upon starting dupilumab, the patient had chosen to discontinue methotrexate treatment for hypereosinophilic syndrome. At baseline her BEC was 0.60 Giga/L. After one month of treatment with dupilumab, the patient's PROMs had improved significantly, and SSIT-12 results improved from anosmia to hyposmia. At month 3, however, olfaction had deteriorated to anosmia and BECs were 2.77 Giga/L, with otherwise general well-being. We added a short course of oral corticosteroids and, in collaboration with her rheumatologist, changed medication to methotrexate/mepolizumab.

Discussion

Biological drugs, such as dupilumab, have greatly improved the treatment options for chronic rhinosinusitis with nasal polyps (CRSwNP). The phase 3 trials for dupilumab as an add-on treatment for uncontrolled CRSwNP, LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52, demonstrated compelling efficacy data and a good safety profile. In the LIBERTY NP SINUS-24 trial, nasal polyps recurred after treatment with dupilumab was stopped [2], indicating that it may be an effective maintenance therapy, but is unlikely to be a curative treatment.

Consistent with previous real-world studies of dupilumab in CRSwNP [3–11], our real-life effectiveness data show that dupilumab treatment resulted in rapid, sustained improvements

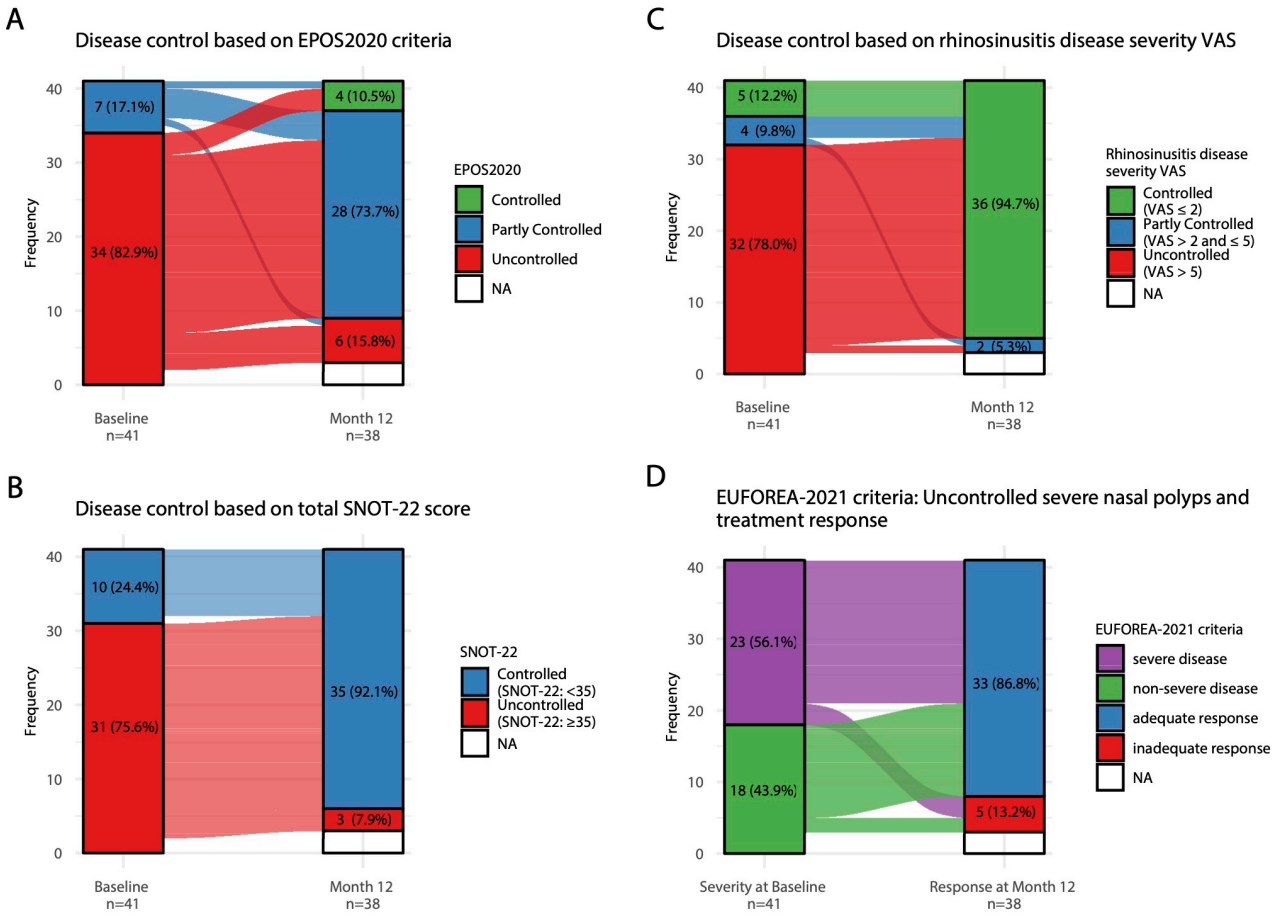

Figure 5. Alluvial plots of assessments of disease control for CRS. Each stratum of the stacked bar plots indicates the aggregated count for each disease control level. The colored ribbons depict the development of disease control levels from baseline to month 12. A) EPOS2020 disease control criteria, B) Disease control based on rhinosinusitis disease severity VAS score, C) Disease control based on total SNOT-22 <35 and ≥35, D) EUFOREA-2021 criteria: CRSwNP severity at baseline and treatment response at month 12.

in nasal endoscopy scores, patient reported outcome measures, and olfactory performance. In real-life studies with 12-13 months follow-up [3–5], total NPS scores decreased from 4.3-5.7 at baseline to 1.0-1.75 at ~1 year. SNOT-22 scores improved from 52.4-60.0 to 10.8-20.8, and SSIT-12 scores increased from 3.2-3.6 to 7.8-8.3 at ~1 year.

Several potential limitations exist for our data. The data was retrospectively collected with a limited sample size. There was no placebo control group or blinding of patients or observers. Intervals of dupilumab application and adherence to INCS may have been varied by the patient without our knowledge. The retrospective character led to missing values due to omitted blood tests and questionnaires. Missingness of data was mainly caused by omitted visits due to the first COVID-19 lockdown in Germany. The strengths of this analysis are the real-life setting, regular blood tests, and a fixed 12-month follow-up schedule completed by all but three subjects.

We applied our follow-up data to various published recommendations for the assessment of CRS disease control. Disease control is the goal of any treatment for chronic disease and can be defined as the extent to which manifestations of a disease are within acceptable limits [30]. We found a high level of treatment response, with a substantial reduction in the number of subjects classified as "uncontrolled". To use the EPOS2020 and EUFOREA-2021 criteria, we converted symptoms-specific SNOT-22 scores into the scoring systems used in these criteria, based on the assumption that a SNOT score ≥3 is predictive of VAS >5 [31].

In our cohort, most patients (86.8%) experienced clinically meaningful improvements in their CRS-related quality of life, as reflected by total SNOT-22 scores. In all four SNOT-22 subdomains, median improvements exceeded the MCID of each subdomain. Previous research has shown that the SNOT-22 subdomains of sleep and ear/facial pain significantly impact overall quality of life [32]. The nasal SNOT-22 subdomain has been reported to be

most strongly linked to patient-reported control of CRS (32). Patients typically define disease control as the alleviation of symptoms [31], while practitioners use endoscopy findings as a surrogate marker for treatment success. We continued to see residual mucosal pathology in most patients at month 12 even though PROMs indicated controlled disease in most patients. This suggests that with dupilumab treatment, endoscopy scores may not always accurately predict the patients' impairment [33]. At baseline, NPS correlated with rhinosinusitis disease severity VAS and nasal congestion VAS scores, but not with total SNOT-22 total scores. This finding suggests that disease-specific VAS scores may be more closely related to nasal polyp size than the total SNOT-22 score.

Previous research has shown that CRSwNP is associated with both elevated serum and local polyclonal IgE levels. Local IgE drives mucosal inflammation by triggering the release of inflammatory mediators from mast cells and basophils [34]. In our study, total serum IgE levels continuously decreased over the course of the observation period, similar to previous studies showing a reduction in both serum and mucosal IgE formation in CRSwNP patients treated with dupilumab [2,35]. At month 12, we found that serum total IgE levels were associated with month-12 NPS scores, which highlights the relevance of IgE for CRSwNP severity [36].

Median ECP levels and BECs increased significantly in the early stages of treatment, but regressed at months 9 and 12. However, it is noteworthy that the percentage of patients with BECs >0.6 Giga/L remained increased at month 12 compared to baseline. Transient elevations of BECs have been previously reported in the pivotal trials as well as in other real-world studies [3,4,37], and patients with higher baseline BECs seem to be at greater risk for dupilumab-induced BEC elevations [38]. A possible explanation for dupilumab-induced hypereosinophilia is a decreased migration of eosinophils into the tissue due to the downregulation of eotaxin-3, VCAM-1, and TARC, with unaffected eosinophilopoiesis in the bone marrow [2,39]. While dupilumab-induced eosinophilia is benign in most cases, the rare possibility of hypereosinophilic syndrome or eosinophilic granulomatosis with polyangiitis should be scrutinized [40]. In case of dupilumab-induced hypereosinophilia without signs of organ damage, short-term oral corticosteroids (OCS) can be considered to reduce the number of blood eosinophils [37]. For patients with a history of hypereosinophilia, i.e., BECs >1-1.5 Giga/L, anti-IL-5 biologicals can be considered as an alternative to dupilumab to circumvent the risk of an acute surge in BECs [41,42].

Consistent with previous studies, olfactory dysfunction improved quickly in the majority of patients in our study [2,43]. Olfactory dysfunction can considerably affect quality of life [44] and is one of the most intractable symptoms of CRSwNP. Based on the rapid improvements in olfactory function following the use of anti-inflammatory dupilumab treatment, we propose that olfactory dysfunction in CRSwNP is primarily caused by inflammatory mediators and tissue eosinophilia-related neurotoxic effects rather than mechanical obstruction of the olfactory cleft [45,46].

We treated two patients in our cohort with dupilumab as induction therapy before scheduled "full-house" sinus surgery. From our data, we cannot determine if concomitant sinus surgery has any additional benefit for patients receiving biological treatment. Based on the fast-acting nature of dupilumab, it may be more advisable to reassess the need for surgery after several months of dupilumab treatment, rather than using it as a pre-surgical induction therapy [1].

Subgroup analyses were beyond the scope of this study. In previous clinical trials, dupilumab demonstrated comparable efficacy in patients with or without comorbid asthma, N-ERD, and baseline eosinophilic status [43,47–49]. To date, no validated predictive biomarkers for response to dupilumab treatment have been established. One study reported that high levels of serum osteoprotegrin (OPG) were strongly associated with a positive response to dupilumab treatment [50].

Conclusion

Our analysis of real-world data on the effectiveness of dupilumab for uncontrolled CRSwNP suggests that the treatment resulted in rapid and sustained improvements in endoscopy scores, PROMs, and olfaction. However, we observed residual mucosal pathology in most patients. Initial median BEC elevations normalized over time, but a higher proportion of patients had elevated BECs at month 12 compared to baseline. Given that dupilumab is a maintenance therapy that requires long-term use, the potential for short- and long-term BEC elevations in some CRSwNP patients should be carefully monitored.

Authorship contribution

RB: drafting of the study, acquisition and analysis of the data, write up of the manuscript. MH: acquisition and critical interpretation of the data, critical revision of the manuscript. KLB: critical revision of the manuscript.

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Conflict of interest

RB has participated in advisory boards for and/or received

speaker's honoraria and travel cost compensation from Sanofi, Novartis, and GSK. MH received speaker's honoraria and travel cost compensation from Sanofi and GSK. KLB has participated in advisory boards for Sanofi and GSK.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Table S1. EUFOREA-2021 definition of uncontrolled, severe CRSwNP [1].

Uncontrolled: "Persistent or recurring CRSwNP despite long-term INCS and having received at least one course of systemic corticosteroids in the preceding 2 years and/or previous sinonasal surgery."

Severe: "Bilateral CRSwNP with a NPS of ≥4, and persistent symptoms despite long-term INCS with the need for add-on treatment."

EUFOREA-2021	Our study
Bilateral polyposis (by nasal endoscopy)	Bilateral polyposis (by nasal endoscopy)
NPS ≥4 out of 8	NPS ≥4 out 8
Presence of persistent symptoms assessed by: • Loss of smell score (scale 0-3) ≥ 2 points • Nasal Congestion Score (NCS; scale 0-3): ≥2 points • SNOT-22 ≥35 • Rhinosinusitis disease severity VAS ≥ 5 out of 10cm	Presence of persistent symptoms assessed by: • **SNOT-22 item #12 "Decreased Sense of Smell/Taste" ≥3** • **Nasal obstruction VAS score ≥5 out of 10cm** • SNOT-22 ≥35 • Rhinosinusitis disease severity VAS ≥5 out of 10cm

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Table S2. EUFOREA-2021: Evaluation of the clinical response to a biologic within 6 months of treatment: "continue or stop" suggestions [1].

Improvement of at least one symptom/score:

EUFOREA-2021	Our study
Sense of smell: from anosmia to hyposmia/normosmia	Sense of smell: from anosmia to hyposmia/normosmia
Nasal Congestion Score (NCS; scale 0-3): decrease by ≥0.5 or objective testing	**Nasal obstruction VAS score decrease by ≥2cm**
• NPS: decrease by ≥ 1 by nasal endoscopy	• NPS: decrease by ≥ 1 by nasal endoscopy
• SNOT-22: reduction of ≥8.9 (minimal clinically important difference)	• SNOT-22: reduction of ≥8.9 (minimal clinically important difference)
• Rhinosinusitis disease severity VAS: reduction of ≥ 2cm	• Rhinosinusitis disease severity VAS: reduction of ≥ 2cm

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Table S3. EPOS2020 criteria for assessment of current clinical control of CRS [(1)].

EPOS 2020: Assessment of current clinical control of CRS (in the last month)

	Controlled (all of the following)	Partly controlled (at least 1 present)	Uncontrolled (3 or more present)	Criteria used in our study for items in "Partly controlled" and "Uncontrolled"
Nasal blockage[1]	Not present or not bothersome[2]	Present on most days of the week[3]	Present on most days of the week[3]	SNOT-22 item #1 "Need to blow nose" ≥ 3
Rhinorrhoea / Postnasal drip[1]	Little and mucous[2]	Mucopurulent on most days of the week[3]	Mucopurulent on most days of the week[3]	SNOT-22 item #4 "Runny nose" and/or SNOT-22 item #6 "post-nasal discharge" ≥ 3
Facial pain / Pressure[1]	Not present or not bothersome[2]	Present on most days of the week[3]	Present on most days of the week[3]	SNOT-22 item #11 "Facial pain/pressure" ≥ 3
Smell[1]	Normal or only slightly impaired[2]	Impaired[3]	Impaired[3]	SNOT-22 item #11 "Decreased Sense of Smell/ Taste" ≥3
Sleep disturbance or fatigue[1]	Not present[2]	Present[3]	Present[3]	SNOT-22 #14 "Wake up at night" ≥3
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa[4]	Diseased mucosa[4]	MLKS ≥1
Rescue treatment (in last 6 months)	Not needed	Need of 1 course of rescue treatment	Symptoms (as above) persist despite rescue treatment(s)	Rescue treatment (in last 6 months)

[1] Symptoms of CRS; [2] VAS ≤ 5; [3] VAS > 5; [4] Showing nasal polyps, mucopurulent secretions or inflamed mucosa.

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Table S4. Missing data analysis.

	Nasal obstruction VAS	NPS	MLKS	SNOT-22	Rhinosinusitis disease severity VAS	SSIT-12	Total serum IgE	Blood eosinophil count	ECP	
206	1	1	1	1	1	1	1	1	1	0
9	1	1	1	1	1	1	1	1	0	1
5	1	1	1	1	1	1	1	0	1	1
1	1	1	1	1	1	1	0	1	1	1
3	1	1	1	1	1	1	0	1	0	2
29	1	1	1	1	1	1	0	0	0	3
2	1	1	1	1	1	0	1	1	1	1
1	1	1	1	1	1	0	0	0	0	4
3	1	1	1	1	0	1	1	1	1	1
2	1	1	1	1	0	1	1	0	1	2
4	1	1	1	0	1	1	1	1	1	1
2	1	0	0	1	1	0	0	0	0	6
1	0	1	1	1	0	0	1	1	1	3
1	0	0	0	1	0	0	0	0	0	8
2	0	0	0	0	0	0	0	1	0	8
6	0	0	0	0	0	0	0	0	0	9
	10	11	11	12	15	15	45	46	53	218

The variables are ordered according to the frequency of missing data. Columns are either 0 (missing) or 1 (observed). The first column provides the frequency of each pattern. The last column lists the number of missing entries per pattern. The bottom row provides the number of missing entries per variable, and the total number of missing cells [1].

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Table S5. Comparisons between the baseline and follow-up visits: Relative treatment effects and ANOVA-type test statistics (LD-F1 model).

	Visit	Estimated mean (SD)	Estimated median (Q1, Q3)	ANOVA-type test statistic		
				F (1.00, ∞)	FDR-adjusted p-value	
Total endoscopic Nasal Polyp Score (scale: 0–8)	Baseline	4.88 (2.06)	5.00 (4.00, 6.00)	n.a.	n.a.	
	Month 1	3.03 (2.20)	3.00 (2.00, 5.00)	64.66	1.81×10^{-15}	***
	Month 3	2.23 (2.02)	2.00 (1.00, 4.00)	115.37	2.82×10^{-26}	***
	Month 6	1.88 (1.80)	1.00 (0.00, 4.00)	125.81	1.99×10^{-28}	***
	Month 9	1.74 (1.63)	2.00 (0.00, 3.00)	134.18	4.05×10^{-30}	***
	Month 12	1.52 (1.75)	1.00 (0.00, 3.00)	126.39	1.83×10^{-28}	***
Modified Lund-Kennedy Score (scale: 0-12)	Baseline	7.93 (2.62)	8.00 (6.00, 10.00)	n.a.	n.a.	
	Month 1	4.66 (2.39)	5.00 (3.00, 6.00)	90.92	4.82×10^{-21}	***
	Month 3	3.75 (2.38)	4.00 (2.00, 6.00)	157.88	4.78×10^{-35}	***
	Month 6	3.86 (2.17)	4.00 (2.00, 5.00)	155.92	9.52×10^{-35}	***
	Month 9	3.63 (2.10)	4.00 (2.00, 5.00)	196.46	4.03×10^{-43}	***
	Month 12	3.27 (2.04)	4.00 (2.00, 5.00)	199.60	1.66×10^{-43}	***
Rhinosinusitis disease severity VAS score (scale: 0–10)	Baseline	7.33 (2.87)	8.00 (7.00, 10.00)	n.a.	n.a.	
	Month 1	2.37 (2.39)	1.00 (1.00, 3.00)	85.00	7.72×10^{-20}	***
	Month 3	1.27 (1.48)	1.00 (0.00, 2.00)	157.65	4.78×10^{-35}	***
	Month 6	1.09 (1.20)	1.00 (0.00, 1.00)	126.04	1.96×10^{-28}	***
	Month 9	1.28 (1.76)	1.00 (0.00, 2.00)	138.93	4.28×10^{-28}	***
	Month 12	0.94 (0.93)	1.00 (0.00, 2.00)	186.09	5.11×10^{-41}	***

	Visit	Estimated mean (SD)	Estimated median (Q1, Q3)	ANOVA-type test statistic		
				F (1.00, ∞)	FDR-adjusted p-value	
Nasal obstruction VAS score (scale: 0–10)	Baseline	6.22 (3.25)	7.00 (4.00, 9.00)	n.a.	n.a.	
	Month 1	2.33 (2.09)	2.00 (1.00, 3.00)	50.80	$1.74x10^{-12}$	***
	Month 3	1.37 (1.50)	1.00 (0.00, 2.00)	59.94	$1.87x10^{-14}$	***
	Month 6	1.06 (1.27)	1.00 (0.00, 1.00)	74.50	$1.36x10^{-17}$	***
	Month 9	1.01 (1.20)	1.00 (0.00, 1.00)	71.49	$5.85x10^{-17}$	***
	Month 12	0.70 (0.71)	1.00 (0.00, 1.00)	90.87	$4.35x10^{-21}$	***
SSIT-12 total score (scale: 0-12)	Baseline	2.86 (1.64)	3.00 (2.00, 4.00)	n.a.	n.a.	
	Month 1	6.77 (3.50)	7.00 (4.00, 10.00)	48.36	$6.10x10^{-12}$	***
	Month 3	7.85 (3.27)	9.00 (5.00, 11.00)	80.94	$5.80x10^{-19}$	***
	Month 6	8.14 (2.71)	9.00 (6.00, 11.00)	125.66	$1.99x10^{-28}$	***
	Month 9	8.17 (2.80)	9.00 (7.00, 10.00)	99.39	$7.08x10^{-23}$	***
	Month 12	8.16 (2.75)	8.00 (7.00, 10.00)	102.81	$1.32x10^{-23}$	***
Total SNOT-22 score (scale: 0-110)	Baseline	51.59 (22.16)	48.00 (37.00, 68.00)	n.a.	n.a.	
	Month 1	26.27 (18.40)	23.00 (12.00, 37.00)	48.70	$1.52x10^{-11}$	***
	Month 3	21.21 (15.18)	19.00 (11.00, 30.00)	82.34	$7.17x10^{-18}$	***
	Month 6	20.30 (13.27)	18.00 (10.00, 31.00)	82.00	$6.21x10^{-19}$	***
	Month 9	18.79 (13.90)	16.00 (7.00, 29.00)	121.68	$3.29x10^{-26}$	***
	Month 12	16.59 (11.92)	15.00 (7.00, 23.00)	108.74	$1.42x10^{-22}$	***
SNOT-22 ear/ facial pain (scale: 0-20)	Baseline	6.05 (5.02)	4.00 (2.00, 10.00)	n.a.	n.a.	
	Month 1	2.14 (3.12)	1.00 (0.00, 4.00)	27.83	$2.18x10^{-07}$	***
	Month 3	1.78 (3.18)	1.00 (0.00, 3.00)	35.63	$1.25x10^{-09}$	***
	Month 6	1.42 (1.97)	0.00 (0.00, 2.00)	41.70	$1.66x10^{-10}$	***
	Month 9	1.71 (2.51)	0.00 (0.00, 3.00)	39.75	$4.08x10^{-10}$	***
	Month 12	1.06 (1.61)	0.00 (0.00, 2.00)	47.64	$2.10x10^{-11}$	***
SNOT-22 emotional symptoms (scale: 0-10)	Baseline	3.24 (2.43)	3.00 (1.00, 5.00)	n.a.	n.a.	
	Month 1	1.40 (1.82)	1.00 (0.00, 2.00)	24.53	$3.90x10^{-06}$	***
	Month 3	1.18 (1.82)	1.00 (0.00, 1.00)	39.77	$6.11x10^{-08}$	***
	Month 6	1.23 (1.62)	1.00 (0.00, 1.00)	37.57	$1.32x10^{-09}$	***
	Month 9	0.90 (1.34)	0.00 (0.00, 1.00)	61.52	$8.63x10^{-15}$	***
	Month 12	0.93 (1.29)	0.00 (0.00, 2.00)	48.98	$1.83x10^{-14}$	***
SNOT-22 nasal symptoms (scale: 0-40)	Baseline	22.93 (7.64)	23.00 (18.00, 29.00)	n.a.	n.a.	
	Month 1	12.19 (6.97)	12.00 (8.00, 17.00)	58.40	$2.04x10^{-13}$	***
	Month 3	10.64 (4.97)	10.00 (7.00, 15.00)	107.74	$2.81x10^{-22}$	***
	Month 6	9.89 (5.35)	9.00 (6.00, 13.00)	113.51	$2.68x10^{-25}$	***
	Month 9	8.84 (5.12)	9.00 (5.00, 12.00)	127.11	$5.20x10^{-28}$	***
	Month 12	8.21 (5.09)	7.00 (5.00, 11.00)	141.12	$8.08x10^{-27}$	***
SNOT-22 sleep (scale: 0-40)	Baseline	19.37 (11.19)	22.00 (10.00, 30.00)	n.a.	n.a.	
	Month 1	10.00 (9.20)	8.00 (2.00, 15.00)	26.30	$5.31x10^{-07}$	***
	Month 3	7.15 (8.25)	4.00 (0.00, 12.00)	49.17	$1.51x10^{-11}$	***
	Month 6	7.37 (8.15)	6.00 (0.00, 12.00)	46.33	$1.69x10^{-11}$	***
	Month 9	6.83 (8.15)	4.00 (0.00, 10.00)	55.90	$1.37x10^{-13}$	***
	Month 12	5.98 (7.61)	2.00 (0.00, 9.00)	58.28	$7.13x10^{-14}$	***
Total serum IgE (IU/mL)	Baseline	189.17 (229.59)	111.26 (39.73, 240.08)	n.a.	n.a.	
	Month 1	117.02 (123.68)	79.72 (34.00, 143.28)	19.27	$1.33x10^{-05}$	***
	Month 3	94.69 (115.02)	63.25 (24.73, 104.42)	35.93	$2.78x10^{-09}$	***
	Month 6	120.54 (309.41)	41.54 (16.23, 73.68)	26.84	$2.88x10^{-07}$	***
	Month 9	61.44 (88.68)	34.61 (13.60, 51.10)	73.02	$2.80x10^{-17}$	***
	Month 12	52.07 (80.01)	27.78 (13.25, 48.90)	95.83	$3.75x10^{-22}$	***
Eosinophilic Cationic Protein (µg/L)	Baseline	48.04 (31.70)	38.15 (23.96, 62.29)	n.a.	n.a.	
	Month 1	92.11 (63.49)	75.20 (32.68, 151.22)	19.88	$1.02x10^{-05}$	***
	Month 3	90.03 (68.50)	60.29 (31.43, 150.20)	9.07	$2.91x10^{-03}$	**
	Month 6	77.01 (56.98)	52.39 (29.03, 127.56)	10.09	$1.70x10^{-03}$	**
	Month 9	61.06 (52.51)	39.14 (24.73, 84.58)	0.92	0.34	n.s.
	Month 12	58.60 (50.65)	28.87 (18.62, 99.24)	0.06	0.84	n.s.
Total Blood Eosinophil Count (Giga/L)	Baseline	0.48 (0.28)	0.44 (0.28, 0.58)	n.a.	n.a.	
	Month 1	0.68 (0.40)	0.59 (0.34, 1.00)	6.40	0.01	*
	Month 3	0.87 (0.63)	0.73 (0.37, 1.28)	8.83	$4.32x10^{-03}$	**
	Month 6	0.75 (0.52)	0.59 (0.35, 1.15)	7.42	$6.98x10^{-03}$	**
	Month 9	0.64 (0.48)	0.46 (0.28, 0.92)	2.24	0.14	n.s.
	Month 12	0.57 (0.44)	0.50 (0.16, 0.84)	0.36	0.56	n.s.

* adj. p <0.05; ** adj. p <0.01; *** adj. p <0.001; n.s.= not significant; n.a.= not applicable