Screening olfaction under dupilumab in chronic rhinosinusitis with nasal polyps

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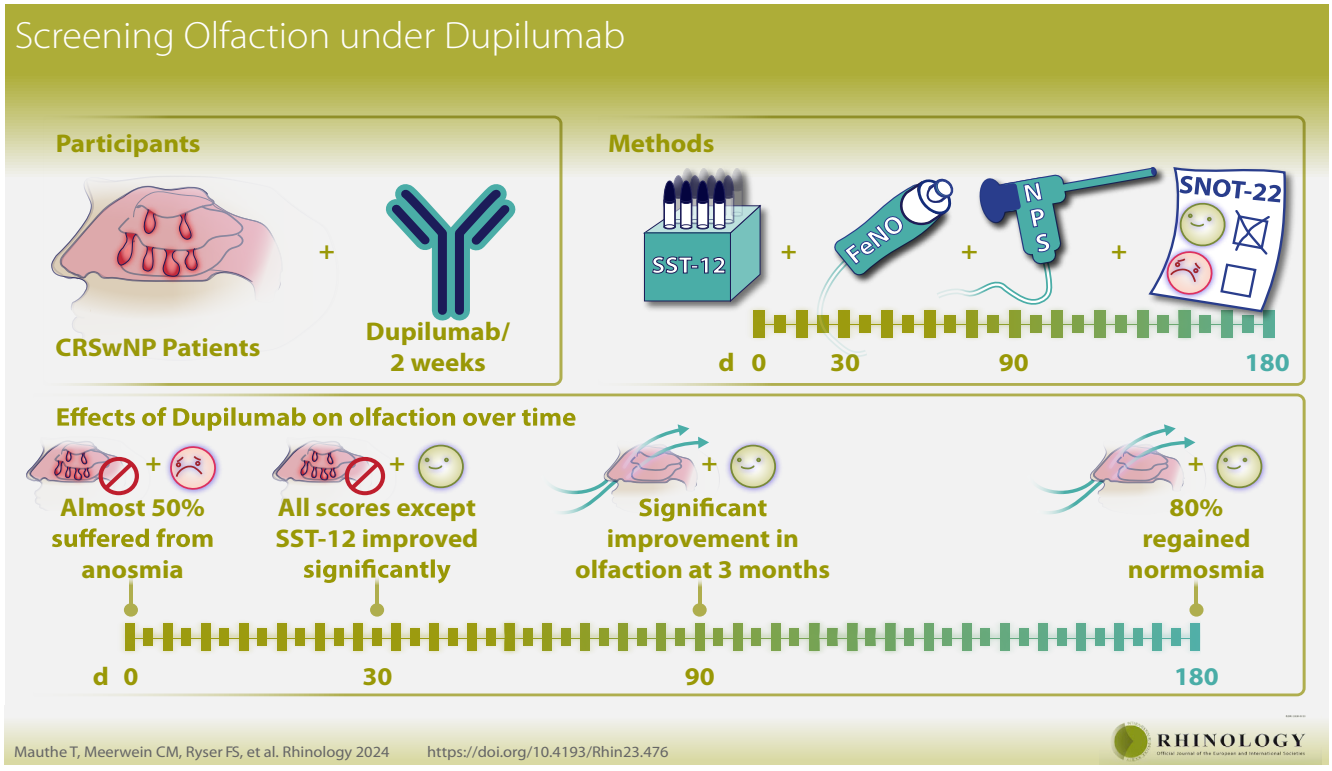


Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) frequently leads to olfactory dysfunction. This study aimed to assess the impact of dupilumab on CRSwNP patients, focusing on olfactory outcomes and potential correlations with other clinical factors.

Methods: CRSwNP patients eligible for dupilumab therapy received subcutaneous Dupixent® injections every two weeks (300mg/2ml dupilumab). The 12-item Sniffin' Sticks Test (SST-12), fractional exhaled nitric oxide (FeNO) and Nasal Polyp Score (NPS) were assessed at baseline and after one, three, and six months. Patients also completed the Sino-Nasal Outcome Test (SNOT-22) weekly.

Results: 26 CRSwNP patients were included. After one month, dupilumab led to substantial reductions in FeNO, SNOT scores, and NPS, whereas SST-12 scores improved significantly only after three months. A shift toward normosmia occurred, with 81% achieving normosmia after six months, and a drop in anosmia prevalence to 9.5%. Significant negative correlations between olfaction (SST-12) and polyp severity (NPS) at baseline and after six months were found, while no significant correlations were observed between SST-12 and FeNO or SNOT scores. Age did not correlate with olfaction.

Conclusions: Dupilumab demonstrated efficacy in restoring olfaction in CRSwNP patients. Reaching normosmia in over 80% of patients after six months of treatment underscores the drug's effectiveness in managing this challenging symptom.

Key words: dupilumab, chronic rhinosinusitis with nasal polyps, olfaction, loss of smell, correlation

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) represents a prevalent and diverse inflammatory condition, frequently entailing a pronounced subjective burden for afflicted individuals [1,2]. Patients commonly experience symptoms including nasal congestion, rhinorrhea, and impairment of the sense of smell, leading to a relevant deterioration of their quality of life [3-5]. Among these burdening manifestations, the diminishment of olfactory function emerges as a cardinal symptom and affects over 80% of all CRSwNP patients [6-8]. It is associated with a significant decline in patient-reported quality of life, notably affecting mental health and diminishing the enjoyment of food (9). It not only exhibits a significant association with the severity of the disease but also has the potential to function as an early indicator of disease relapse [10].

The precise mechanism underlying olfactory dysfunction in CRSwNP is not yet completely understood, but findings propose a dual etiology, suggesting an obstructive component resulting in conductive olfactory loss and an inflammatory process within the olfactory cleft, contributing to sensorineural olfactory impairment [11,12]. Developing effective therapeutic strategies to address the loss of smell in CRSwNP patients continues to pose a clinical challenge. Conventional treatments frequently offer transient relief but struggle to provide lasting enhancements in olfactory function [13]. These approaches typically entail saline irrigation and the application of intranasal and systemic corticosteroids [14]. However, conventional treatment is often insufficient in achieving the desired treatment outcomes, often leading to the necessity of surgical intervention, specifically endoscopic sinus surgery (ESS) [15]. While corticosteroids and ESS have demonstrated effectiveness in enhancing olfactory outcomes in CRSwNP, achieving complete resolution and long-term durability of these effects remains challenging for some patients [16,17].

Recent advances in comprehending the underlying pathophysiology of CRSwNP have highlighted the growing importance of immunomodulatory therapies with biologics for managing CRSwNP patients [18-21]. The approval of dupilumab, an anti-interleukin-4 receptor alpha monoclonal antibody, by both the US Food and Drug Administration and the European Medicines Agency in 2019 [22], represents a significant milestone in expanding therapeutic options for individuals afflicted with CRSwNP, as recent research has shown highly promising outcomes with dupilumab [23,24].

The objective of this study was to investigate the effects of dupilumab on patients with CRSwNP, particularly focusing on olfactory outcomes. Furthermore, we aimed to explore potential correlations between olfactory improvements and other outcome measures.

Materials and methods

Study design and participants

This investigation drew data from the IMMUNOPOLYP prospective observational cohort study, conducted from December 2021 to November 2022. Ethical approval was obtained from the cantonal ethics committee (BASEC-No. 2021-01213), adhering to the Declaration of Helsinki of 1975 principles and national regulations [25].

Adult patients (≥ 18 years) with refractory CRSwNP, either with a surgical history or ineligibility for surgery, were included. Eligibility criteria for biologic therapy with dupilumab followed the EUFOREA consensus [26]. Data from participants who discontinued the study prematurely were incorporated into the analysis. Participants with a non-type 2 inflammation pattern were excluded.

Intervention

All participants received subcutaneous Dupixent® (Sanofi) injections every two weeks (300mg/2ml dupilumab). The 12-item Sniffin' Sticks Test (SST-12), FeNO (fractional exhaled nitric oxide), and NPS were evaluated on the day of the initial dupilumab injection. Subsequent follow-up consultations occurred at one, three, and six months, during which all scores were reassessed. All consultations were conducted at the University Hospital of Zurich in Zurich, Switzerland.

Assessment tools

The SST-12, a validated olfactory screening tool, was administered to evaluate olfactory function. The SST-12 (Burghart Messtechnik GmbH, Germany) involves presenting participants with a series of 12 different odors, and participants were required to identify each odor from a predefined list of options. The total test score ranged from 0 to 12, reflecting the number of correctly identified odors. We categorized olfactory function based on the SST-12 scores: Normosmic (scores ≥ 11), hyposmic (7 ≤ score ≤ 10), and anosmic (score ≤ 6) [27].

FeNO measurement served as an indicator of airway inflammation. Participants exhaled into a specialized device (Vivatmo-me, Bosch Healthcare Solutions, Waiblingen, Germany), which quantifies nitric oxide concentration in parts per billion (ppb) in the exhaled breath. FeNO levels were stratified according to the ERS/ATS (European Respiratory Society/ American Thoracic Society) recommendations: High (> 50 ppb), intermediate (25-50 ppb), and low (< 25 ppb) [28].

Nasal polyp assessment was conducted systematically within each nasal cavity and documented using video recordings. Polyp extent was categorized on a scale ranging from 0 to 4. The cumulative NPS was computed by summing scores from both right and left nostrils, resulting in a composite score that spans from 0 to 8 [29].

In addition to hospital consultations, patients were directed to

Table 1. Patient characteristics and scores following dupilumab treatment.

	Overall (mean (SD))	p-value (Ref. group d0)
n	26	
age	51.57 (11.80)	
sex = f (%)	6 (23.08)	
sex = m (%)	20 (76.92)	
SST-12 d0	5.44 (3.10)	
SST-12 d28	6.28 (3.55)	0.38
SST-12 d90	9.17 (2.63)	<0.001
SST-12 d180	9.29 (2.88)	<0.001
FeNO d0	84.96 (65.55)	
FeNO d28	28.00 (15.84)	<0.001
FeNO d90	27.80 (17.50)	<0.001
FeNO d180	28.33 (17.28)	<0.001
SNOT d0	48.39 (16.63)	
SNOT d28	24.26 (16.90)	<0.001
SNOT d90	14.56 (15.94)	<0.001
SNOT d180	12.72 (18.37)	<0.001
TNPS d0	5.00 (2.00)	
TNPS d28	3.71 (1.94)	0.02
TNPS d90	2.50 (2.06)	<0.001
TNPS d180	1.95 (1.70)	<0.001

SD: Standard Deviation, SST-12: 12-item Sniffin' Sticks Test, FeNO: Fraction of Exhaled Nitric Oxide, SNOT: Sinonasal Outcome Test, NPS: Nasal Polyp Score. Statistical analysis employed Student's paired t-test, using SNOT 0 as the reference group.

complete the Sino-Nasal Outcome Test (SNOT-22) on a smartphone weekly. Only SNOT scores recorded within ±7 days of consultations were evaluated to ensure temporal alignment of patient-reported outcome measures (PROMs) with objective score assessments. Symptom severity is categorized as mild (8-20 points), moderate (21-50 points), and severe (> 51 points) [30].

Statistical analyses

Descriptive statistics were used to evaluate the baseline characteristics of the included patients. Mean differences were assessed using Student's paired t-test. Linear associations were assessed using Spearman's rank correlation, and 95% confidence intervals (CI) were computed to estimate the precision of the correlation coefficients. These results were further validated through linear regression modeling. Significance was set at $p < 0.05$. All analyses were computed using R and R-Studio software (version 4.2.2) [31].

Results

Patient characteristics

A total of 26 patients initially enrolled in the IMMUNOPOLYP study were eligible for inclusion in the present analyses. Among the participants included in the study, there were 20 males (76.92%) and 6 females (23.08%). The mean age at the initiation of therapy was determined to be 51.57 years (SD ± 11.80), ranging from 31 to 68 years. Among the 26 patients included, four had not undergone any prior surgical procedures. Among the 22 patients with a history of previous endoscopic sinus surgery, the majority (n=15) had undergone a single intervention, whereas three patients had experienced two such surgeries. Additionally, four patients had received more than two surgical interventions. Of note, unrelated to the study, four patients chose to prematurely discontinue their participation in the study, with reasons including unclear causes (n=2), relocation abroad (n=1), and psychological stress (n=1).

Effects of dupilumab therapy on scores

The levels of FeNO, SNOT, and NPS experienced a significant reduction after one month of dupilumab therapy (-67.1% $p < 0.001$, -49.9% $p < 0.001$, -25.8% $p = 0.02$, respectively). Notably, the SST-12 score was the only measure that displayed a non-significant improvement after one month (+13%, $p = 0.38$). However, a notable improvement in all scores was evident after three months (all $p < 0.001$). The precise scores are provided in Table 1 and visually represented in Figure 1a-d, exhibiting the dynamic improvement in SST-12 scores, FeNO levels, SNOT scores, and NPS under dupilumab therapy.

Regarding FeNO, no significant difference was observed between the 1-month and 6-month time points ($p = 0.95$). Similarly, for SNOT, there was a non-significant improvement between the 1-month and 6-month outcomes ($p = 0.06$). In contrast, both SST-12 and NPS continued to exhibit significant improvement after 1 month compared to 6 months (SST-12: $p = 0.003$, NPS: $p = 0.002$), suggesting that the full therapeutic effect of dupilumab may not have been reached by the 1-month mark. Notably, none of the scores demonstrated statistically significant enhancement between the 3-month and 6-month time points.

At the initial assessment (d0), only 24% of the participants had a normal sense of smell, while the majority (44%) reported anosmia. The remainder were hyposmic. However, a shift emerged after a 6-month course of dupilumab therapy: 81% of the subjects reached normosmic values, and the prevalence of anosmia decreased to 9.5%.

Concomitantly, during the initial assessment, only 13% of the participants exhibited a low level of eosinophilic inflammation in the lower respiratory tract, as determined by FeNO measurement, contrasting with 56.5% exhibiting high levels of inflamma-

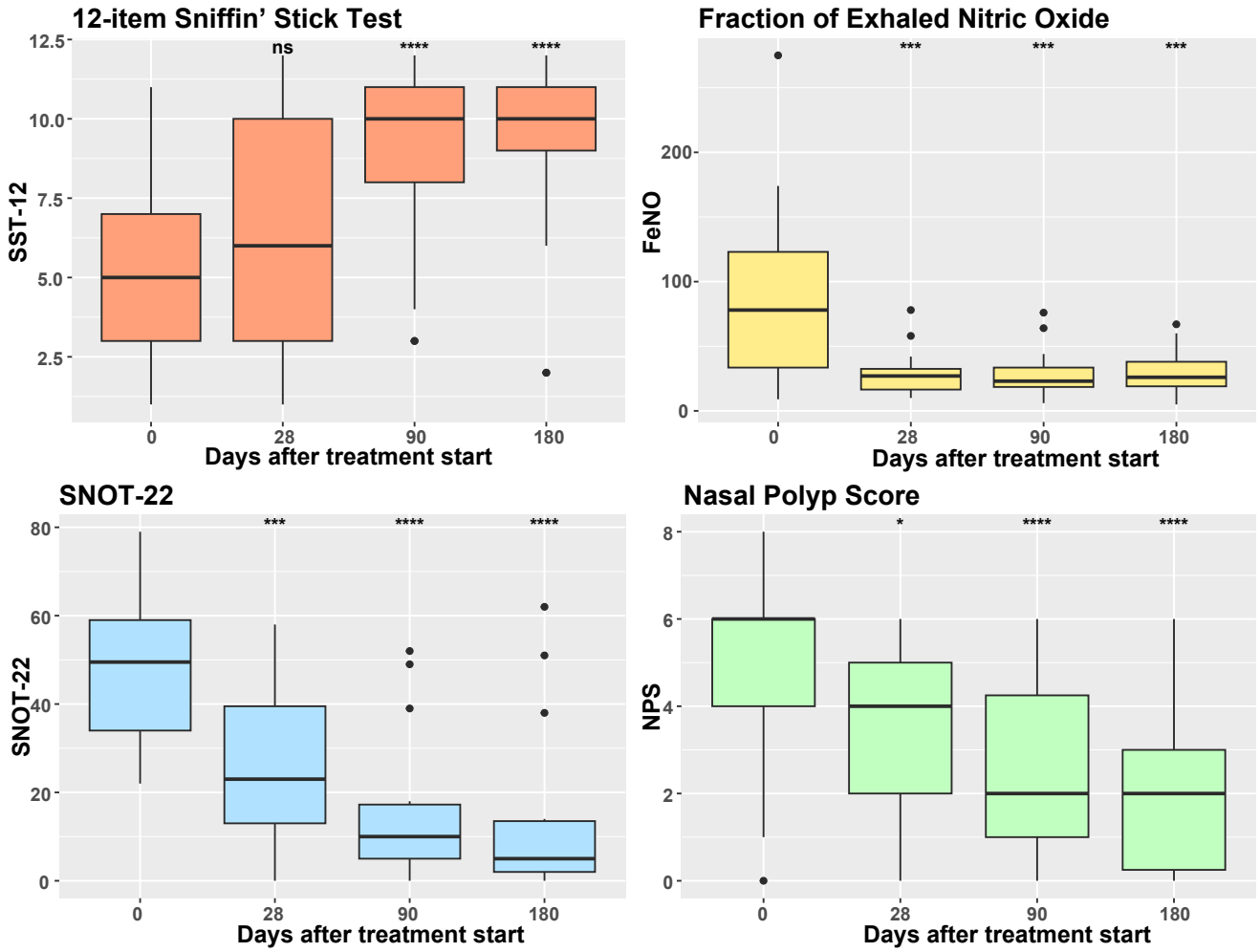


Figure 1a-d. Boxplots representing the scores at days 0, 28, 90, and 180 after the initiation of dupilumab therapy. The color scheme signifies different scores. Red: 12-item Sniffin' Sticks Test (SST-12) scores, yellow: Fraction of Exhaled Nitric Oxide (FeNO) levels, blue: Sinonasal Outcome Test (SNOT) scores, and green: Nasal Polyp Score (NPS). The boxplots showcase variations in means or medians compared to the day 0 reference group. Levels of significance are indicated by symbols (*p<0.05, **p<0.01, ***p<0.001), with "ns" indicating no significance.

tion. However, following the intervention of dupilumab therapy for 6 months, the cohort displaying low FeNO levels increased to 47.6%, while a notable reduction occurred, with only 14.3% maintaining elevated levels.

Parallel observations were recorded with respect to the SNOT score. None of the participants reported mild symptoms (due to inclusion criteria), whereas a substantial 50% reported severe symptoms. Conversely, an amelioration was apparent following a 6-month dupilumab treatment, where 83.3% experienced mild sinonasal symptoms, leaving a mere 11.1% enduring a profile marked by severe symptomatology.

Turning attention to the baseline assessment of the NPS, it was found that 11.5% of participants fell within the NPS range of 0-2, while a majority of 61.5% registered an NPS of 5 or higher. However, after 6 months of dupilumab therapy, a noteworthy transformation ensued: 71.4% of participants attained an NPS within the favorable 0-2 range, with only 4.5% retaining an NPS of 5 or above (Figure 2a-d).

Olfaction analysis stratified by gender revealed the following: At baseline (d0), there was no significant difference between the two groups. After one month, the mean SST-12 scores for men and women were 6.8 and 4.2, respectively (p-value = 0.02). This suggests a potentially faster response among women compared to men. However, the observed difference between sexes diminished after three months (p-value = 0.96). There were no other significant gender-related differences in outcome measures, except for FeNO values at day 180, where women exhibited a mean value of 13.3 and men exhibited a mean value of 31.9 (p-value = 0.01)

Correlation between olfaction and FeNO, SNOT, and NPS

Pearson's correlation analyses demonstrated significant associations between olfactory function (SST-12) and polyp severity

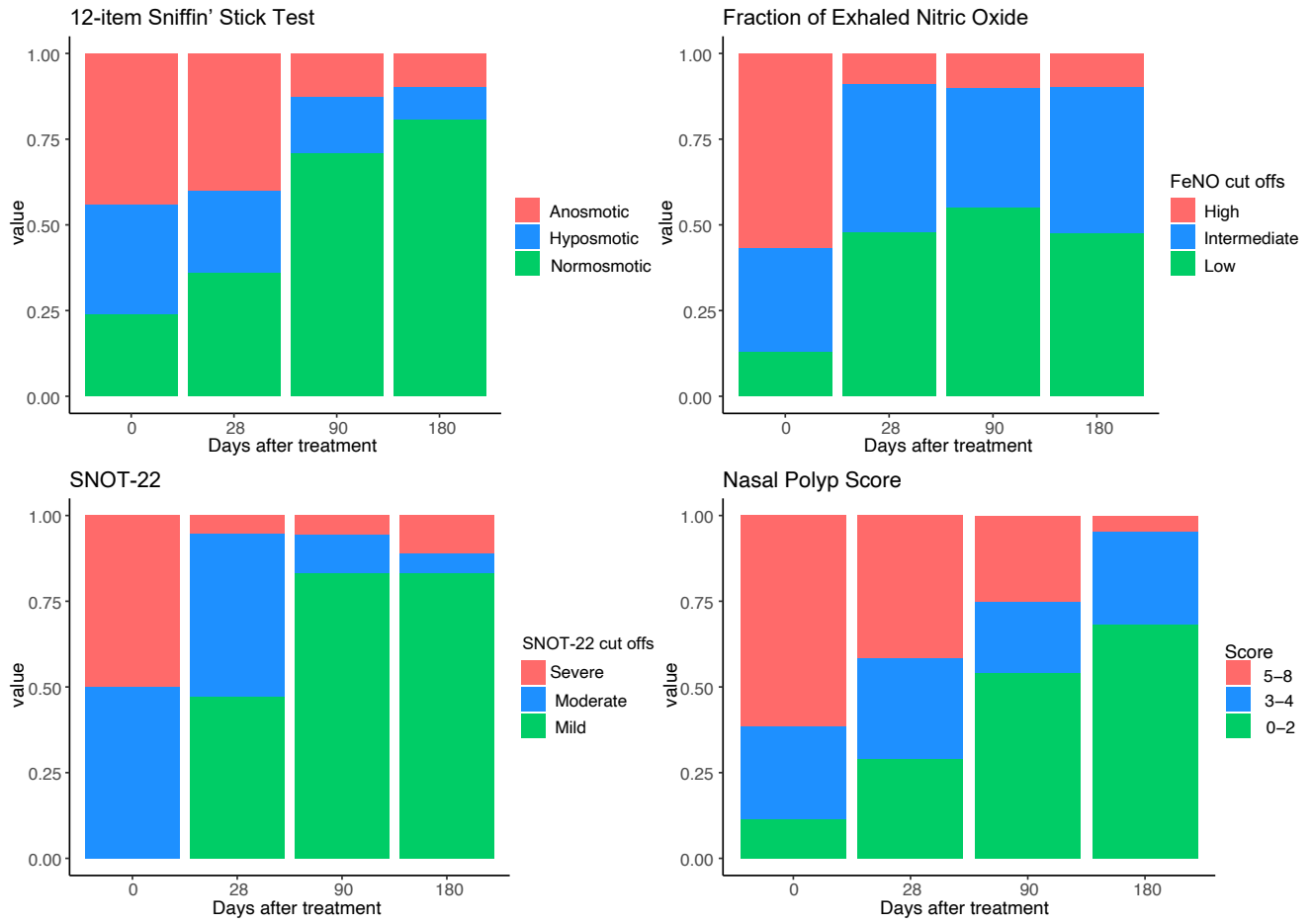


Figure 2a-d. Percentage plots illustrating alterations in severity proportions over time. The plots illustrate the following categories for each score:

- Olfaction: Normosmic (scores ≥ 11), Hyposmic (7 ≤ score ≤ 10), and Anosmic (scores ≤ 6).
- FeNO Cut-offs: High (FeNO > 50 ppb), Intermediate (FeNO 25-50 ppb), and Low (FeNO < 25 ppb).
- SNOT: Mild (8-20 points), Moderate (21-50 points), and Severe (51 points or above).
- NPS: Classified as 0-2, 3-4, and 5-8.

(NPS) at baseline (d0) and after six months (d180), indicating a linear negative correlation. Specifically, a higher NPS was associated with a poorer SST-12 score (d0: r = -0.47, p = 0.018, 95% CI -0.73 to -0.09; d180: r = -0.54, p = 0.012, 95% CI -0.79 to -0.14). These findings are displayed in Figure 3a-b. In contrast, correlations at one month (d28) and three months (d90) were not significant (d28: p = 0.39; d90: p = 0.79). To further explore and confirm these relationships, linear regression analyses were conducted. The results revealed that a decrease in NPS was associated with increased SST-12 at baseline (Day 0: β = -0.3066, p = 0.018) and after six months (Day 180: β = -0.3144, p = 0.012). The adjusted r-values of -0.43 and -0.5 for Day 0 and Day 180, respectively, indicated that these regression models accounted for a moderate proportion of the variability in NPS at each time point.

It's important to highlight that no significant correlations were observed between SST-12 scores and FeNO levels or SNOT scores. Furthermore, the analysis revealed that olfactory function (SST-12) did not exhibit any significant correlation with age at any of the examined time points.

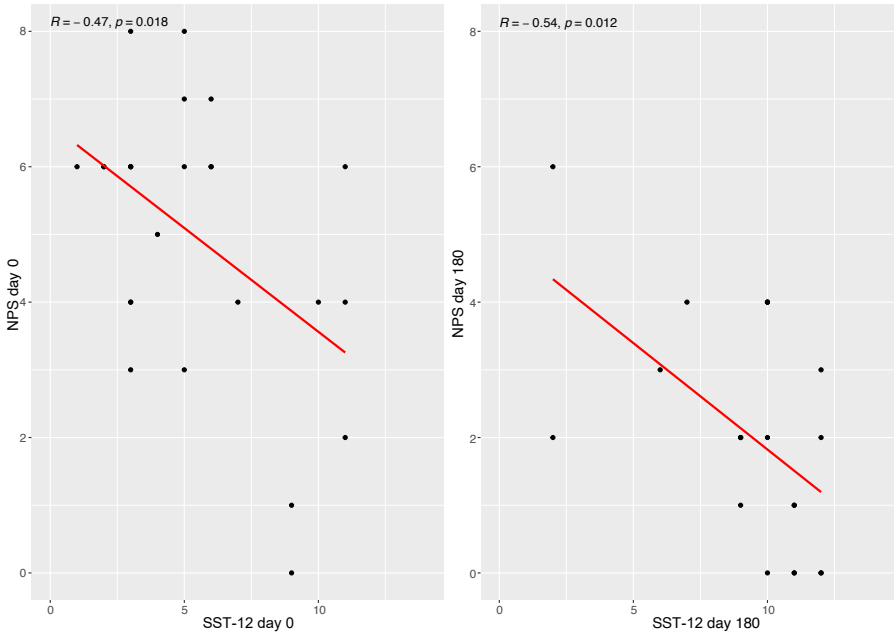
Discussion

Main results

This study showed an impressive improvement of psycho-physically measured olfaction in type 2 CRSwNP patients treated with dupilumab. However, when employing the SST-12 as a screening test, the improvement did not seem to become evident until 3 months after initiation of treatment. Other symptoms and scores improved much more rapidly, represented be the SNOT, NPS and FeNO values after one month. Correlation analysis revealed associations between olfactory function (SST-12) and polyp severity (NPS).

Loss of smell

Studies have shown that approximately 50% of patients with



igure 3a-b. Correlation analysis between SST-12 and NPS at day 0 and day 180. NPS: Nasal Polyp Score, SS: 12-item Sniffin' Sticks Test, R = Spearman's Rho, p = p-value.

CRSwNP who undergo surgery achieve olfactory restoration comparable to healthy controls [32,33]. Olfactory scores typically peak one month post-surgery but decline by three months [34]. Nonetheless, a study examining the long-term effects of ESS on olfactory function found that five years after ESS, 53% of the patients showed improvement in the psychophysical measurements, and a total of 79% of patients reported an improvement in their subjective sense of olfaction using a visual analog scale [35]. These findings emphasize that achieving a permanent restoration of the sense of smell presents a significant challenge, and it is not always attainable through surgical intervention [36]. While ESS holds potential for ameliorating olfactory conditions in some CRSwNP patients, dupilumab is a valuable treatment option, for patients with uncontrolled CRSwNP despite appropriate medical treatment and sinus surgery [15]. The assessment of olfaction under dupilumab therapy is crucial, as an improved sense of smell is a criterion to evaluate the effectiveness of biologics according to the recent EPOS/EUFOREA update on the indication of biologics [37].

Our findings demonstrated a significant improvement in olfactory function, assessed using the SST-12. After six months of dupilumab treatment, over 80% of patients achieved normosmia, with fewer than one in ten patients still experiencing anosmia. These findings align with other investigations using the SST, which also highlight the remarkable efficacy of dupilumab in improving olfaction, a key symptom of CRSwNP [23,38,39]. Additionally, subjective assessments of smell by other authors yielded similar results, with over 80% of CRSwNP patients reporting improved smell within six to twelve months under dupilumab treatment [40].

Restoration of olfaction

Mullol et al. found that dupilumab rapidly enhanced olfactory function. Statistically significant improvements were evident within three days through daily patient-reported Loss of Smell scores, and at the first assessment after two weeks with the University of Pennsylvania Smell Identification Test (UPSIT) [41]. However, our findings exhibited divergence from these results. In comparison to other concurrently assessed scores such as FeNO, SNOT, and NPS, which displayed faster improvements, we observed that a statistically significant improvement in SST-12 scores was only evident after three months. In a recent study, we demonstrated that NPS and SNOT improved significantly after just one week of treatment [24], suggesting that, although clinical response in other parameters can be observed very early during therapy, olfaction restoration takes more time.

This observation may be indicative that the SST-12 lacks the sensitivity required to detect potential early alterations in olfaction during the initial phases of treatment. The considerable overlap between anosmic and hyposmic patients may occurs because anosmic patients occasionally succeed in identification tasks by chance (one out of four), leading to consistent scores despite changes in olfactory function. On the other hand, there is also some unreliability in distinguishing between normosmia and mild hyposmia [42]. Hummel et al. suggest that to differentiate between them, patients who score close to threshold levels may require a more detailed olfactory investigation [27].

Another explanation for the delayed recovery of smell compa-

red to other outcome measures is the resulting bulb hypotrophy after smell deprivation, as evidenced by studies showing a significant reduction in olfactory bulb volume among patients with severe CRSwNP [43,44]. According to a 2022 systematic review, patients undergoing surgical procedures typically require 3-6 months before experiencing a statistically significant increase in olfactory bulb volume [45]. This aligns with our observations as we first noticed an improvement in olfaction after 3 months. Moreover, in the presence of uncontrolled chronic inflammation, researchers have noted a decline or complete cessation in the regenerative capacity of stem cells within the olfactory epithelium, resulting in anosmia that may be irreversible [46]: Prolonged exposure to chronic inflammation induces scarring in the olfactory cleft's epithelium. The development of fibrous tissue may account for the persistent anosmia observed in some of our patients (9.5%), even after six months of Dupilumab treatment. Conversely, other researchers discovered that the impressive regenerative capacity of neurons in the sensory system enables the complete reversal of extensive damage linked to inflammation. Notably, dramatic histopathologic changes of the olfactory epithelium were reversed entirely upon discontinuation of cytokine induction [47]. Thus, a more extended period may be necessary for complete recovery.
As noted by Bachert et al. in their LIBERTY NP SINUS-52 study, the maximum effects of dupilumab may not be achieved by week 52, making it unclear what the complete treatment effect of dupilumab might be [48]. However, a prospective observational cohort study, spanning a follow-up period of two years, revealed a decline in olfactory function over this duration, transitioning from 33% of patients exhibiting anosmia at one year to 40% at the end of the second year under dupilumab treatment [49]. To acquire insights into the long-term outcomes of dupilumab on olfaction exceeding five or even ten years, continued research is imperative.

Gender-related differences

Our study initially demonstrated a significant difference in mean SST-12 scores between men and women after one month of treatment, indicating a potential faster response among women. However, this difference appeared to diminish after three months. Nevertheless, an RCT investigating dupilumab's impact on olfactory outcomes in CRSwNP found no gender-related differences [41]. Additionally, a multicenter study evaluating dupilumab's efficacy in CRSwNP patients found no disparities in SST scores when stratified by sex. The only gender-related distinctions indicated that females exhibited a negative influence on Peak Nasal Inspiratory Flow (PNIF) values, hinting at a potentially reduced effectiveness of dupilumab in women [50].
Population-based research has indicated that olfactory impairment prevalence is higher in males [51]. One study encompassing almost 2,000 individuals identified a correlation between female sex, education, cognitive speed, verbal fluency, and vocabulary with improved odor identification [52]. Although these findings suggest that women might have an advantage in odor identification due to superior semantic memory, they don't necessarily account for our observed results, as there were no gender-based differences at baseline. Further research is needed to explore how gender may affect dupilumab's impact on clinical scores.

Correlation of olfactory function with polyp severity

Our correlation analyses revealed significant associations between olfactory function (SST-12) and polyp severity (NPS), while no significant correlations were observed between SST-12 scores and FeNO levels or SNOT scores. These findings align with the pathophysiological theory that the obstructive component contributing to conductive olfactory loss is a major underlying cause of anosmia [11]. Supporting this theory, other studies have reported a negative correlation between quantitative olfactory test scores and volumetric olfactory cleft opacification [53]. Especially, opacification of the ethmoid, sphenoid, and frontal sinuses were associated with olfactory impairment [54].
Conversely, some authors argue that olfaction recovery following dupilumab treatment is independent of nasal polyp reduction in CRSwNP, proposing that the improvement in olfactory function primarily depends on the anti-inflammatory effects of the medication [55]. This viewpoint is reinforced by studies indicating correlations between olfactory dysfunction and blood parameters. Specifically, olfactory dysfunction was found to correlate with blood eosinophil count [56] and mucus cytokine levels in the olfactory cleft [57], underscoring the significance of the inflammatory etiology in anosmia. Bringing these perspectives together, it is plausible that both components, including obstructive factors and anti-inflammatory effects, likely interact and contribute to olfactory function.
Remarkably, the correlations between olfactory function (SST-12) and polyp severity (NPS) exhibited statistical significance exclusively at baseline and after a six-month interval. Conversely, the correlations at one month and three months did not reach statistical significance. This suggests the possibility of a variable relationship between the observed scores over time. However, other investigators have observed significance of a consistent negative correlation between SST and NPS, both at baseline and throughout the follow-up period [58]. Nevertheless, additional research is needed on this subject, as divergent findings have been reported by other researchers who did not observe any significant correlations between alterations in olfaction and changes in polyp size among CRSwNP patients undergoing dupilumab treatment [59].

Correlation of olfactory function with other parameters

Researchers observed a significant link between inflammation in the upper and lower airways in patients with asthma presenting

with olfactory impairment [60]. Moreover, another study identified a correlation between sinus opacification and FeNO levels in CRSwNP patients [61]. Considering these findings and given the inflammatory etiology in anosmia, along with the established correlation between SST-12 and NPS, one could postulate a potential link between olfactory function and FeNO levels. Nevertheless, our investigation did not reveal any significant correlations between SST-12 and FeNO scores.

Furthermore, we observed an absence of significant correlations between SST-12 scores and SNOT scores, consistent with findings reported by other researchers [55,62]. It has been hypothesized that this may be partly attributed to the fact that the SNOT-22 only contains one question related to chemosensory function and seeks to assess both the sense of smell and taste simultaneously [63].

Strenghts and limitations

Even though there is no gold standard for measuring olfactory dysfunction [15], it should ideally encompass threshold, discrimination, and identification tests [64]. The SST is recommended as an assessment of olfactory dysfunction [65], as it comprises 3 subtests, resulting in 4 scores: T threshold score, D discrimination score, I identification score, and TDI global olfactory score [66]. However, we exclusively utilized the 12-item screening test, which assesses olfactory identification, within only four minutes [27]. This limitation could potentially introduce bias into our assessment, as it may not fully capture the complexity of olfactory dysfunction. Nevertheless, our findings are valuable given the widespread use of the SST-12, highlighting the need for assessment tools that balance easy administration with the retention of clinically essential information, such as olfactory threshold values [5]. Furthermore, it's important to note that we did not conduct separate testing for each nostril. Additionally, it should be noted that the small sample size limits the generalizability of our results. Nonetheless, this research is valuable as it contributes to the growing knowledge on the effect of dupilumab on olfaction and other scores in a real-life setting.

Conclusion

While the restoration of olfactory function may necessitate a longer duration compared to other clinical scores, our findings revealed that dupilumab led to normosmia in more than 80% of patients after six months of treatment, with the prevalence of anosmia decreasing to less than 10%. This highlights the efficacy of dupilumab in addressing a challenging symptom among individuals with CRSwNP.

Acknowledgement

None.

Authors' contributions

FSR, CB, and TM managed all aspects of data collection, specifically during patient consultations.TM was responsible for data extraction, statistical analyses, and drafted the manuscript. CMM and AY provided essential support throughout the project and contributed to the manuscript's editing process. MBS and UCS initiated the study's conceptualization, providing valuable insights during discussions and conducting thorough reviews of the study. All authors reviewed and edited the final version of the manuscript.

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Conflicts of interest

MBS is a consultant for Sanofi, GSK, Novartis, Astra Zeneca, and MSD unrelated to this study. UCS is a consultant for Sanofi, GSK, TAKEDA, BioCryst unrelated to this study. All other researchers involved assure that there are no conflicts of interest.

Data availability

The data analyzed during the current study are available from the corresponding author upon reasonable request.

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