Steroid responsiveness predicts olfactory function recovery in dupilumab treated CRSwNP

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Abstract

Background: There is no known predictor for olfactory function recovery with dupilumab treatment in chronic rhinosinusitis with nasal polyps (CRSwNP). This study assessed whether patient-reported recovery of olfactory function on oral corticosteroids (OCS) is a prognostic factor. **Methods**: Retrospective analysis of pre-biological OCS-responsiveness on olfactory functioning (OCS-responsive or OCS-unresponsive; OCS-r and OCR-u, respectively) as predictor for olfactory functioning after 6 months of dupilumab therapy for severe CRSwNP. **Results**: 212 CRSwNP patients treated with dupilumab were divided between OCS-r (reported improvement of olfactory function with OCS before dupilumab treatment, n = 152), and OCS-u (OCS-unresponsive; no such improvement, n = 60). Olfactory function was tested with Sniffin'Sticks Identification Test (12 pens; SSIT-12). At baseline, both groups had a median SSIT-12 score of 3 / 12 indicating anosmia. Hyposmia and normosmia rates were also comparable (5.9% and 3.3% in OCS-r, respectively; 5.0% and 1.7% in OCS-u, respectively). After 6 months of dupilumab treatment, OCS-r showed higher olfactory scores (median SSIT-12: 8/12; 52.6% hyposmia and 17.8% normosmia) than OCS-u (median SSIT-12: 5/12; 31.7% hyposmia and 3.3% normosmia). The positive predictive value of OCS-responsiveness on scoring \geq 7 (normosmia/hyposmia) on the SSIT-12 after 6 months of dupilumab treatment was 65.0%. **Conclusion**: Patients who report olfactory function improvement on OCS have a higher chance of recovery of olfactory function during the first six months of treatment with dupilumab than patients who do not.

Key words: biological treatment, olfaction disorders, nasal polyps, type-2 inflammation, smell, chronic rhinosinusitis.

Introduction

One of the leading causes of olfactory dysfunction is chronic rhinosinusitis (CRS) ⁽¹⁾. The loss of smell (LoS) can profoundly affect quality of life ⁽²⁻⁴⁾.

CRS is characterized by inflammation of the nose and paranasal sinuses with a duration of more than 12 weeks. CRS can be classified into two main phenotypes: chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) ⁽⁵⁾. Additionally, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 acknowledges the concept of endotypes in CRS. Endotypes represent distinct underlying mechanisms that contribute to the inflammation in CRS. Endotypes in primary CRS are classified as types 1, 2, or 3, or more pragmatically as type 2 and non-type 2. In particular, type 2 CRS patients struggle more often with LoS than patients with type 1 ^(6,7). Loss of smell can be classified as anosmia (total LoS) and hyposmia (partial LoS).

In CRS, olfactory dysfunction (OD) can occur due to a variety of factors. In patients with CRSwNP, inflammation, mechanical obstruction of the olfactory cleft and iatrogenic damage to the olfactory epithelium due to surgery are of particular concern⁽⁵⁾. Patients with CRS may also suffer from post-viral anosmia and age-related anosmia. One potential therapeutic option for type 2 CRS related OD lies in the treatment with biologicals. The first to be registered in the Netherlands for this diagnosis is dupilumab, a monoclonal antibody targeting interleukin-4 receptor alpha (IL-4Ra). It has been shown to improve olfactory function in patients with type 2 CRS ⁽⁸⁾. However, a significant number of patients remain anosmic even when treated with dupilumab. Therefore, it would be helpful to predict the recovery of OD at baseline. Currently, only the presence of respiratory epithelial adenomatoid hamartoma (REAH) is described as a possible predictor of dupilumab efficacy on olfactory function improvement⁽⁹⁾. Predictors of efficacy of sinonasal surgery on olfactory function improvement are described. A prospective study on olfactory outcomes after surgery found that absence of smell improvement on oral corticosteroids (OCS) predicts no benefit from functional endoscopic surgery (FESS) regarding olfactory function recovery ⁽¹⁰⁾. Conversely, two prospective studies found that subjective preoperative improvement in olfactory function after a course of oral corticosteroids was a predictor of subjective improvement in olfactory function after sinonasal surgery (11, 12). These findings suggest the possible predictive nature of the response to oral corticosteroids and the efficacy of dupilumab treatment in CRSwNP patients with olfactory dysfunction.

The primary objective of this study is to investigate whether olfactory (un)responsiveness to a course of OCS can predict anosmia after six months of dupilumab treatment in patients with severe uncontrolled type 2 CRS.

Patients and methods

Patient

Patients treated with dupilumab between December 2019 and January 2023 for type 2 CRS with nasal polyps (300mg s.c. every two weeks) were included, if treated for at least 6 months, and when data was available from smell tests at baseline and 6 months after start of treatment. The indication criteria for biological therapy were used as per EPOS2020 biological criteria, meaning a blood eosinophil count of >=250 cells/mL and/or a total serum IgE of >100 kU/L and/or tissue eosinophils >=10/HPF ⁽⁵⁾. 98.6% of the current study population met the type2 criterion.

Data collection

Outcomes of smell tests were collected in a prospective observational database (PolyREG ^(8, 13)). Data on smell improvement on OCS were collected retrospectively from electronic medical records. Patients were divided into two groups. The first group included patients who reported improvement of olfactory function on OCS before treatment with dupilumab (OCS-responsive), and the second group included patients who did not report such an improvement (OCS-unresponsive). Olfactory function improvement was based on patient-reported responsiveness to OCS as noted in the medical records (i.e., no smell testing was performed before, during, or shortly after OCS treatment). OCS were given any time before starting treatment with dupilumab. The duration of the OCS-course ranged from 7-10 days, 30 milligrams per day. OCS-responsiveness was evaluated by the physician asking the question: 'did your ability to smell return after the course of OCS?'. Patients were excluded (n=36) if no data were available on olfactory function improvement with OCS.

Olfactory function during dupilumab treatment was assessed using the Sniffin' Sticks-12 Identification Test (SSIT-12), a validated and standardized measure of olfactory function ^(14, 15). Scores were collected at baseline (before treatment with dupilumab) and 6 months after the start of dupilumab treatment.

Other baseline data included: age at start of therapy, gender, type2 CRS duration, history of nasal polyp surgery, SNOT-22 score, bilateral nasal polyp score, SSIT-12 score, peak nasal inspiratory flow (PNIF), blood eosinophils, total serum immunoglobulin E (IgE), need for systemic corticosteroids in the past two years or a contraindication for OCS, comorbidities like non-steroidal anti-inflammatory drugs (NSAID)-exacerbated respiratory disease (N-ERD), asthma and eosinophilic otitis media (EOM). Lund-Mackay (LM) scores were obtained for patients who had a computed tomography (CT) scan available within the past year and subsequent to their most recent functional endoscopic sinus surgery (FESS).

Table 1. baseline characteristics.

Characteristics	Total	OCS-responsive patients	OCS-unresponsive patients	p-value ^
Total number of patients (n)	212	152	60	
Age at start of therapy (years; mean (SD))	51.4 (13.7)	51.3 (14.3)	51.6 (12.3)	0.86
Gender				0.77
Male (%)	63.2	63.8	61.7	
Female (%)	36.8	36.2	38.3	
CRSwNP duration (years; median (IQR))	10.5 (6.0-18.3)	12.0 (6.3-20.0)	9.5 (6.0-15.0)	0.13
Nasal polyp surgery (n; IQR)	3 (2-4)	3 (2-4)	3 (2-4)	0.81
SNOT-22 (0-110; median (IQR))	53 (41-64)	53 (43.5-64)	53 (35-65)	0.66
Bilateral Nasal Polyp Score (median (IQR))	6 (5-6)	6 (4-6)	6 (5-6)	0.07
SSIT-12 score at baseline (median (IQR))	3 (2-4)	3 (2-4)	3 (2-4)	0.33
Lund-Mackay CT total score (0 – 24; median (IQR))	20 (16-22)	20 (16-22)	19 (16.5-22)	0.46
Peak nasal inspiratory flow (L/min; mean (SD))	97 (45)	101 (47)	89 (37)	0.08
Blood eosinophils (x10 ⁹ /L; median (IQR))	0.47 (0.30-0.71)	0.45 (0.30-0.68)	0.50 (0.30-0.75)	0.46
Total IgE (kU/L; median (IQR))	139.0 (57.2-285.5)	139.00 (58.3-295.0)	131.50 (54.5-285.3)	0.96
Need for systemic corticosteroids or contraindication (%)	60.9	62.5	56.7	0.02
N-ERD (%)	36.8	34.9	41.7	0.17
Asthma (%)	83.0	83.6	81.7	0.10
EOM (%)	15.1	15.1	15.0	0.66

^ p-value for comparison between the OCS-responsive and OCS-unresponsive groups. SD: standard deviation; IQR: interquartile range

Data analysis

Data were analyzed using descriptive statistics to summarize patient characteristics and outcomes of the SSIT-12. Baseline characteristics of the two groups were compared using independent t-test, Mann-Whitney U test or Chi-square test. The independent t-test was used to compare mean age and the PNIF. The Mann-Whitney U test was used for the following variables: CRS duration, amount of FESS, NPS at baseline, SSITscore at baseline, LMK score, baseline eosinophils and IgE and SNOT-22 scores due to outliers. Chi-square tests were used for the variables OCS use in the past 2 years/contraindication for OCS, N-ERD, asthma and EOM.

The primary outcome was olfactory function scores from the follow-up visit after six months. SSIT-12 scores were compared between the two groups, but as a minimal clinically important difference for the SSIT-12 is lacking, further analyses were performed over the categories of olfactory function (i.e., anosmia (SSIT-12 \leq 6), hyposmia (SSIT-12 \geq 7 – \leq 10) and normosmia (SSIT-12 \geq 11)). These categories were compared between the two groups using Chi-square analysis or Fisher Exact test when cells had counts less than 5. The positive and negative predictive value were calculated using the above-mentioned categories of olfactory function. Different cut-offs were used: not scoring anosmia (SSIT-12 \geq 7) and scoring normosmia (SSIT-12 \geq 11).

Since olfactory function declines after the age of 55, the PPV and NPV without patients above the age of 55 were calculated as well ⁽¹³⁾. Statistical analysis was conducted using SPSS version 28.0.

Ethical considerations

Informed consent was obtained from all patients before starting dupilumab treatment. Assessment of the institutional Medical Ethical Review Committee of the PolyREG registry deemed it not to be subject to the Dutch Medical Research Involving Human Subjects Act (MREC ID: W21_030#21.034).

Results

In total, 212 patients were included in the analysis, predominantly male (63.2%) and with a mean age (\pm SD) of 51.4 \pm 13.7 years. Common comorbidities were asthma (83.0% of study population), NSAID-exacerbated respiratory disease (N-ERD) (36.8%) and eosinophilic otitis media (15.1%).

There were 152 patients in the OCS-responsive group, and 60 in the OCS-unresponsive group. At baseline, the olfactory function as measured with the SSIT-12 was comparable, with a median score (IQR) of 3 (2-4) and 3 (2-4), respectively. This is also reflected in the categorical division of olfactory functioning which was comparable between groups at baseline (Figure 1).



Figure 1. Categorical olfactory functioning at baseline and 6 months after start of dupilumab treatment in OCS-responsive and OCSunresponsive patients. OCS = oral corticosteroids. OCS-responsive: patients whose olfactory function recovered during treatment with OCS. OCS-unresponsive: patients whose olfactory function did not recover during treatment with OCS.

After 6 months, the median SSIT-12 score in the OCS-responsive patients rose to 8 (6-10), which was significantly higher than those in the OCS-unresponsive group (5 (3-8)), p < 0.001). Now, the olfactory functioning categories also showed significant differences (Figure 1). Anosmia was 29.6% in the OCS-responsive group and 65.0% in the OCS-unresponsive group. Hyposmia was 52.6% in the OCS-responsive group and 31.7% in the OCS-unresponsive group and 3.3% in the OCS-unresponsive group (Figure 1).

The positive predictive value (PPV) of OCS-responsiveness was 70.4%. The negative predictive value (NPV) of OCS-unresponsiveness was 65.0% (Table 2). Using the cut-off of normosmia, the PPV of OCS-responsiveness is 17.8%. The NPV of OCS-unresponsiveness is 96.7% (Table 3).

The age distribution was similar for the OCS-responsive group compared to the OCS-unresponsive group. Ninety-one patients in the study population were aged over 55 years old (69 in the OCS-responsive group, 22 in the OCS-unresponsive group).

The exclusion of patients aged above 55 years of age resulted in a PPV of OCS-responsiveness on scoring \geq 7 on the SSIT-12 of 68.7%, and a NPV of OCS-unresponsiveness on scoring <7 on the SSIT-12 of 73.7% (Table 4). In addition, the same exclusion resulted in a PPV of OCS-responsiveness on scoring \geq 11 on the SSIT-12 of 16.9%, and an NPV of OCS-unresponsiveness on scoring <11 on the SSIT-12 of 97.4% (Table 5). Sensitivity and specificity rates are also shown (Tables 2-5).

Discussion

Olfactory dysfunction in CRSwNP is known to improve during treatment with dupilumab for most patients, but conclusive predictors are not described yet. The present study aimed to investigate the predictive value of past improvement in olfactory function with oral corticosteroids in these patients. Patients who showed an improvement in their sense of smell with oral corticosteroids had a higher chance of experiencing an improvement in olfactory function during the first six months of dupilumab treatment. In other words, OCS-responsiveness appears to be a strong indicator that normosmia or hyposmia is likely to be achieved. However, it is important to note that non-responsiveness of olfactory dysfunction to dupilumab treatment does not mean (complete) non-response to dupilumab treatment since its evaluation encompasses other aspects as well (reduced nasal polyp size, reduced need for systemic corticosteroids, improved quality of life, and reduced impact of co-morbidities) ^(5, 17). However, it might help in managing patient expectations when addressing the option of dupilumab treatment.

The two groups were comparable in terms of baseline variables (i.e. presence of comorbidities, disease-specific health-related quality of life (SNOT-22), nasal polyp score, SSIT-12 scores, PNIF, blood eosinophils and serum IgE). The only significant difference found was the need for or contraindication to systemic corticosteroids (62.5% vs. 56.7%, Table 1), which is clinically irrelevant. This small difference in the use of OCS between the two groups might be explained by the OCS response itself: those who respond to OCS are expected to be more likely to get one or more prescriptions of an OCS course.

Olfactory function declines after the age of 55 ^(16, 18, 19). The results of the SSIT-12 are not corrected for age, so this may have underestimated the results of the test. However, excluding patients over the age of 55 from the NPV and PPV calculations did not relevantly change the percentage of the PPV and NPV calculated (Table 4 and 5). OCS-responsiveness remains a strong predictor regardless of age.

Another cause of no improvement of olfactory function after six months of dupilumab treatment may be irreversible damage to the olfactory cleft imposed by surgery. It may appear that the OCS-unresponsive patients are also the ones who are more likely to have permanent damage to their olfactory cleft. Either way, the nature of their unresponsiveness to OCS does not affect the outcome. It may still serve as a predictor of the efficacy of dupilumab in improving olfactory function.

The low specificity of whether or not olfactory function had

Table 2. Positive and negative predictive value, sensitivity and specificity of OCS-responsiveness on anosmia at 6 months of dupilumab treatment.

T = 6 months	SSIT-12 score ≥7 (normosmia and hyposmia) (N)	SSIT-12 score ≤6 (anosmia) (N)	
OCS-responsive patients	107	45	PPV = 70.4%
OCS-unresponsive patients	21	39	NPV = 65.0%
	Sensitivity = 83.6%	Specificity =46.4%	

SSIT-12 = Sniffin' Sticks Identification Test 12 pens, OCS = oral corticosteroids, T = time point.

Table 3. Positive and negative predictive value, sensitivity and specificity of OCS-responsiveness on normosmia at 6 months of dupilumab treatment.

T = 6 months	SSIT-12 score ≥11 (normosmia) (N)	SSIT-12 score ≤10 (anosmia and hyposmia) (N)	
OCS-responsive patients	27	125	PPV = 17.8%
OCS-unresponsive patients	2	58	NPV = 96.7%
	Sensitivity = 93.1%	Specificity = 31.7%	

SSIT-12 = Sniffin' Sticks Identification Test 12 pens, OCS = oral corticosteroids, T = time point.

Table 4. Positive and negative predictive value, sensitivity and specificity of OCS-responsiveness on anosmia at 6 months of dupilumab treatment. Excluding patients aged >55.

T = 6 months	SSIT-12 score ≥7 (normosmia and hyposmia) (N)	SSIT-12 score ≤6 (anosmia) (N)	
OCS-responsive patients	57	26	PPV = 68.7%
OCS-unresponsive patients	10	28	NPV = 73.7%
	Sensitivity = 85.1%	Specificity = 51.9%	

SSIT-12 = Sniffin' Sticks Identification Test 12 pens, OCS = oral corticosteroids, T = time point.

Table 5. Positive and negative predictive value, sensitivity and specificity of OCS-responsiveness on normosmia at 6 months of dupilumab treatment. Excluding patients aged >55.

T = 6 months	SSIT-12 score ≥11 (normosmia) (N)	SSIT-12 score ≤10 (anosmia and hyposmia) (N)	
OCS-responsive patients	14	69	PPV = 16.9%
OCS-unresponsive patients	1	37	NPV = 97.4%
	Sensitivity = 93.3%	Specificity = 34.9%	

SSIT-12 = Sniffin' Sticks Identification Test 12 pens, OCS = oral corticosteroids, T = time point.

improved shows that even in patients who were OCS-responsive a significant number are still anosmic or hyposmic after six months of dupilumab treatment (29.6% and 52.6%, respectively). Naturally, the study population does not have an a priori probability to reach normosmia of 100% because other causes of olfactory dysfunction are likely to be seen as well, such as permanent post-surgical and post-viral olfactory dysfunction. Even in the general population, the a priori probability of normosmia is not 100%. Two studies ^(20, 21) have reported that only 78-80% of the general population will achieve a normosmia score on the SSIT-12. Still, the use of the SSIT-12 which in itself is especially useful as a short screening test, is a limitation of the current study and might contribute to the low specificity. In detail, assessing olfactory function can be achieved by evaluating three different aspects: threshold, discrimination, and identification (TDI) ⁽¹⁶⁾. The SSIT-12 used in this study focuses solely on the identification aspect. The test may not capture the full complexity of olfactory function. Identification of odours can

be challenging for patients, especially for those who have been living with anosmia or hyposmia for an extended period of time. Therefore, the scores of the Sniffin' Sticks-12 Identification test may be an underestimation of the patients' real ability to have olfactory awareness. It is possible that more rigorous testing with threshold and/or discrimination tests shows better performance in the OCS-unresponsive group as well. On the other hand, this is not very likely, given the magnitude of differences at identification tests between the two groups. In addition, the study of Bogdanov et al. ⁽¹⁰⁾ used TDI scores and found that olfaction did not improve after surgery if the patients' olfaction did not improve after glucocorticosteroids. Our studies' conclusions are in line with these findings.

Another limitation of the study is that the improvement of smell before treatment with dupilumab was solely determined by asking patients whether their sense of smell returned upon treatment with oral corticosteroids which could have caused recall bias. In addition, studies have shown that it can be challenging for healthy individuals to estimate their olfactory function by patient reported olfactory measures. This could be explained by the fact that judging olfactory function is related to the feeling of nasal patency (22). However, Ottaviano et al. (23) found a general moderate correlation between SSIT and Visual Analogue Scale for assessing smell in patients with CRSwNP treated with dupilumab. Additionally, Alobid et al. (24) also found a significant correlation between the VAS score and the Barcelona Smell Test (BAST-24) and between SNOT-22 item 21 (loss of smell) and the BAST-24 in CRSwNP patients. These findings suggests that CRSwNP patients may be better at subjectively assessing their olfactory function or at least its improvement than healthy individuals might be. Unfortunately, smell test data was lacking to evaluate olfactory function before and after treatment with oral corticosteroids to corroborate the reported patient history.

Conclusions

In patients with severe CRSwNP, pre-biological olfactory functi-

on recovery on OCS is predictive for olfactory function recovery in the first six months of dupilumab treatment. This knowledge helps optimizing personalized treatment strategies and setting realistic expectations for patients regarding their potential for olfactory function recovery.

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Authorship contribution

GA, LB, VV and RH contributed to resources and writing - review and editing. WF, SR and RL contributed to conceptualization, methodology, resources, supervision, and writing - review and editing. JO contributed to writing - original draft, data curation, formal analysis, and visualization.

Conflict of interest

SR further reports grants, consulting fees and honoraria from Sanofi and Novartis and GSK. RL further reports consulting fees from GSK.JO has acted as a consultant member for Sanofi. RL has acted as a consultant and/or advisory board member for GSK. WF is an advisory board member of and received consulting fees from Sanofi, GSK, and Dianosic. SR has acted as a consultant and/or advisory board member for Sanofi, GSK, and Novartis. The department of Otorhinolaryngology and Head/ Neck Surgery of the Amsterdam UMC has received research funding from Sanofi, GSK, and Novartis. VV has acted as a consultant and/or advisory board member for GSK.

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References

- Qureshi HA, Lane AP. Olfaction now and in the future in CRSwNP. Am J Rhinol Allergy. 2023;37(2):168-74.
- Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. Rhinol Suppl. 2017;54(26):1-30.
- Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life--an updated review. Chem Senses. 2014;39(3):185-94.
- Liu DT, Prem B, Sharma G, Kaiser J, Besser G, Mueller CA. Depression symptoms and olfactory-related quality of life. Laryngoscope. 2022;132(9):1829-34.
- 5. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis

and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1-464.

- Thompson CF, Price CP, Huang JH, et al. A pilot study of symptom profiles from a polyp vs an eosinophilic-based classification of chronic rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(5):500-7.
- Hao D, Wu Y, Li P, et al. An integrated analysis of inflammatory endotypes and clinical characteristics in chronic rhinosinusitis with nasal polyps. J Inflamm Res. 2022;15:5557-65.
- van der Lans RJL, Fokkens WJ, Adriaensen G, Hoven DR, Drubbel JJ, Reitsma S. Real-life observational cohort verifies high efficacy of dupilumab for chronic rhinosinusitis with

nasal polyps. Allergy. 2022;77(2):670-4.

- Bogdanov V, Walliczek-Dworschak U, Whitcroft KL, Landis BN, Hummel T. Response to glucocorticosteroids predicts olfactory outcome after ESS in chronic rhinosinusitis. Laryngoscope. 2020;130(7):1616-21.
- van der Lans RJL, Otten JJ, Adriaensen G, et al. Two-year results of tapered dupilumab for CRSwNP demonstrates enduring efficacy established in the first 6 months. Allergy. 2023;78(10):2684-97.
- Boesveldt S, Verbaan D, Knol DL, van Hilten JJ, Berendse HW. Odour identification and discrimination in Dutch adults over 45 years. Rhinology. 2008;46(2):131-6.

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- van Spronsen E, Ebbens FA, Fokkens WJ. Olfactory function in healthy children: normative data for odor identification. Am J Rhinol Allergy. 2013;27(3):197-201.
- Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol. 2007;264(3):237-43.
- Kondo K, Kikuta S, Ueha R, Suzukawa K, Yamasoba T. Age-related olfactory dysfunction: epidemiology, pathophysiology, and clinical management. Front Aging Neurosci. 2020;12:208.
- Oleszkiewicz A, Schriever VA, Croy I, Hahner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol. 2019;276(3):719-28.
- Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol. 2007;264(3):237-43.

- Fokkens WJ, Lund V, Bachert C, Mullol J, Bjermer L, Bousquet J, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. Allergy. 2019;74(12):2312-9.
- Kondo K, Kikuta S, Ueha R, Suzukawa K, Yamasoba T. Age-Related Olfactory Dysfunction: Epidemiology, Pathophysiology, and Clinical Management. Front Aging Neurosci. 2020;12:208.
- Oleszkiewicz A, Schriever VA, Croy I, Hahner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol. 2019;276(3):719-28.
- 20. Vennemann MM, Hummel T, Berger K. The association between smoking and smell and taste impairment in the general population. J Neurol. 2008;255(8):1121-6.
- 21. Landis BN, Konnerth CG, Hummel T. A study on the frequency of olfactory dysfunction. Laryngoscope. 2004;114(10):1764-9.
- Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. Chem Senses. 2003;28(8):691-4.
- Ottaviano G, De Corso E, Cantone E, Ciofalo A, Saccardo T, Bernardi R, et al. Measuring Nasal Patency and the Sense of Smell in CRSwNP Patients Treated with Dupilumab. J

Pers Med. 2023;13(2).

 Alobid I, Calvo-Henriquez C, Viveros-Diez P, Lopez-Chacon M, Rojas-Lechuga MJ, Langdon C, et al. Validation of Visual Analogue Scale for loss of smell as a quick test in chronic rhinosinusitis with nasal polyps. J Investig Allergol Clin Immunol. 2023:0.

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