Effect of Different Therapeutic Strategies on Olfactory Outcomes in Patients With Chronic Rhinosinusitis With Nasal Polyps: A Systematic Review

Alobid I[1,2,3,4,5], Barroso B[3,6], Calvo C[7], Ferrario MG[8], Sastre J[3,6,9]

[1]Skull Base Unit, ENT Department, Hospital Clinic, Barcelona, Spain
[2]DIBAPS, Barcelona, Spain
[3]CIBERES, Instituto de Salud Carlos III, Spain
[4]University of Barcelona, Barcelona, Spain
[5]Unidad Alergo-Rino, Centro Médico Teknon, Barcelona, Spain
[6]Department of Allergy, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
[7]Rhinology and Sleep Apnea Unit, Otolaryngology Department, Hospital Complex of Santiago de Compostela, Santiago de Compostela, Spain
[8]Medical Science Consulting, Valencia, Spain
[9]Department of Medicine, Universidad Autónoma de Madrid, Madrid, Spain

J Investig Allergol Clin Immunol 2024; Vol. 34(4): 218-224
doi: 10.18176/jiaci.0987

Abstract

Introduction: Olfactory impairment is one of the cardinal symptoms of chronic rhinosinusitis with nasal polyps (CRSwNP). However, the effect of currently available therapeutic options on the recovery of the sense of smell is not well defined. The aim of this systematic review was to compile evidence on the impact of medical, surgical, and biological treatment on olfactory outcomes in patients with CRSwNP.
Methods: This review was conducted by 2 reviewers according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The quality of evidence of all the studies included in the qualitative synthesis was evaluated using the Critical Appraisal Skills Programme (CASP).
Results: Forty-four studies were included in the qualitative synthesis. These assessed sinonasal surgery (n=23), biologics (n=15), and conventional medical treatment (n=6). The methodological quality was moderate-to-high in most. Overall, significant improvements in the sense of smell were detected with all the interventions analyzed and measured using an objective tool, a subjective tool, or both. However, most studies used different outcome measures, thus hindering comparisons between interventions, and data on clinically relevant changes were missing.
Conclusion: Oral corticosteroids, biologics, and sinonasal surgery improve the olfactory impairment associated with CRSwNP. However, the heterogeneous nature of existing studies does not allow accurate comparisons.

Key words: CRSwNP. Olfaction. Impairment. Biologics. Surgery. Corticosteroids.

Resumen

Introducción: El deterioro del olfato es uno de los síntomas cardinales de la rinosinusitis crónica con pólipos nasales (RSCcPN), pero el efecto de las opciones terapéuticas actualmente disponibles sobre la recuperación del sentido del olfato no está bien definido. El objetivo de esta revisión sistemática es recopilar datos sobre el impacto de los tratamientos médicos, quirúrgicos y biológicos en los resultados sobre el olfato de los pacientes con RSCcPN.
Métodos: La revisión se llevó a cabo de acuerdo con las directrices *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA), y el proceso fue realizado por dos revisores. La calidad de la evidencia de todos los estudios incluidos para la síntesis cualitativa se evaluó mediante el Critical Appraisal Skills Programme (CASP).
Resultados: Se incluyeron cuarenta y cuatro estudios para la síntesis cualitativa (que evaluaban la cirugía sinonasal [n=23], los productos biológicos [n=15] o el tratamiento médico convencional [n=6]), la mayoría de ellos con una calidad metodológica de moderada a alta. En general, se detectaron mejoras significativas en el sentido del olfato con todas las intervenciones analizadas medidas mediante una herramienta objetiva o subjetiva (o ambas). Sin embargo, la mayoría de los estudios utilizaron diferentes pruebas de medición de resultados, lo que dificultó las comparaciones entre intervenciones, y se ofrecían datos sobre el cambio clínicamente relevante.
Conclusion: Los corticosteroides orales, los fármacos biológicos y la cirugía sinonasal mejoran la alteración olfativa asociada a la RSCcPN, pero la elevada variabilidad entre los estudios existentes no permite realizar comparaciones precisas.

Palabras clave: RSCcPN. Olfato. Deterioro. Fármacos biológicos. Cirugía. Corticosteroides.

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a complex disorder characterized by chronic inflammation of the sinonasal mucosa and presence of nasal polyps [1], which confer a significant long-term symptom burden [2]. It affects about 4% of the population globally [3] and, in most patients, is associated with type 2 inflammation, a pathway involved in other airway diseases. For this reason, CRSwNP often co-occurs with asthma and/or nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (N-ERD) [4]. Among the range of clinical symptoms usually present in CRSwNP, olfactory impairment is a common complaint that can be troublesome and substantially impact on patients' quality of life [5].

The conventional approach to improving olfactory outcomes consists of medical treatment with intranasal corticosteroids (INCS), nasal washing, antibiotics, and/or oral corticosteroids (OCS) [6]. In refractory cases, endoscopic surgical resection of nasal polyps is recommended, and biological agents were recently approved as an alternative treatment for these cases [7]. However, despite the increasing number of studies assessing olfactory outcomes in patients with CRSwNP [8], the effect of currently available therapeutic options on olfactory recovery is not well defined.

The aim of this systematic review, then, was to analyze the literature in order to compile and summarize current evidence on the effect of medical, surgical, and biological treatment of olfactory dysfunction associated with CRSwNP.

Methods

This review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [9] and the recommendations of the Cochrane handbook for systematic reviews [10]. The search protocol was entered in the International Prospective Register of Systematic Reviews (PROSPERO) of the National Institute for Health Research under number CRD42022336668.

Search Strategy

The research question was defined using the PICO structure. The population comprised patients with CRSwNP, and the interventions considered included biologic therapies, medical therapies, and surgery. Outcome was the change in the sense of smell at different timepoints after surgery or after the beginning of the treatment measured with 1 or more of the following psychophysical and/or subjective tests: Sniffin' Sticks test, Connecticut Chemosensory Clinical Research Center (CCCRC) test, Brief Smell Identification Test (BSIT), University of Pennsylvania Smell Identification Test (UPSIT), Barcelona Smell Test-24 (BAST-24), visual analog scale (VAS), Likert scale, and smell item of the 22-item Sinonasal Outcome Test (SNOT-22). The comparator was the change in outcome after the intervention, or another intervention, or placebo.

A search strategy that also included Medical Subject Heading (MeSH) terms was developed (Table S1). Searches for publications in English and/or Spanish were performed using the PubMed, Web of Science, and SCOPUS databases on April 1, 2022, with a publication timeframe that ran from January 2014 to March 2022.

Study Selection and Data Extraction

Two reviewers screened the title, abstract, and full text of all articles (one reviewer screened the records and the other checked the decisions) and applied eligibility standards based on the inclusion/exclusion criteria for selecting the studies. The final articles comprised systematic reviews with meta-analyses, clinical trials (both randomized and nonrandomized), post hoc studies of randomized trials, and observational studies focusing specifically on the effects of the medical, surgical, or biological treatment of CRSwNP on smell impairment measured using one of the previously mentioned tests. The exclusion criteria were systematic reviews without meta-analyses, case reports or case series, narrative reviews, studies on chronic rhinosinusitis without nasal polyps (CRSsNP) or mixed CRS (CRSwNP and CRSsNP), studies with patients presenting comorbidities not associated with T2 inflamation, studies with a sample size smaller than 25 patients (we estimated the sample size for between-group mean comparisons with an α level of 0.05 and a power of 80%, assuming a mean difference in the UPSIT score of 5 points and an SD of 4), publications where explicit olfactory outcomes could not be retrieved, and subanalyses of a study already included with repeated outcome data. The data extracted were recorded using a standardized Microsoft Excel® template by a single reviewer and validated by a second reviewer and included information about the study design and methodology, percentage of participants with asthma, N-ERD and previous surgery at baseline, follow-up time, outcomes before and after the intervention, data on olfactory status and clinically relevant changes when available, and conclusions.

Methodological Quality Assessment

The quality of evidence of all studies included was evaluated to determine risk of bias using the Critical Appraisal Skills Programme (CASP) (https://casp-uk.net/casp-tools-checklists/). Two independent reviewers assessed both methodology and results using the appropriate checklist depending on the type of study. In the absence of a numeric score, the articles were classified as low-, medium-, or high-quality evidence according to the type of study and the number of questions in the corresponding checklist that were answered affirmatively or negatively.

Results

A total of 1659 records were identified through the database searches. After eliminating duplicates and screening the title, abstract, and full text, we selected 44 publications for inclusion. The Figure shows the PRISMA diagram detailing the workflow of the screening process. Articles finally selected for the qualitative synthesis included clinical trials, subgroup and post hoc analyses, systematic reviews with meta-analyses, and observational studies. The methodological quality of the references reviewed is shown in Table S2a and Table S2b.

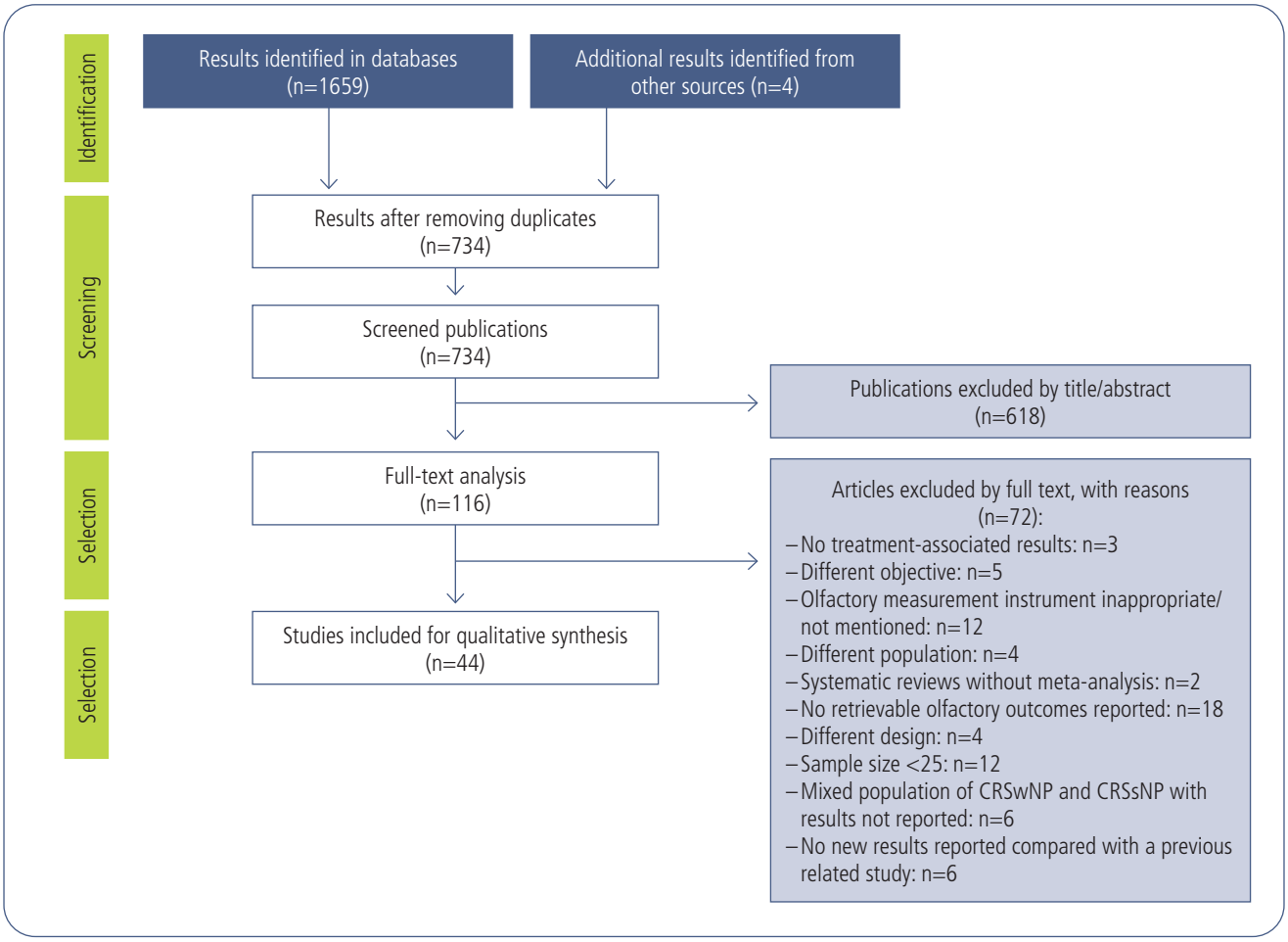

Figure. PRISMA diagram showing the selection flow of identified references. PRISMA indicates Preferred Reporting Items for Systematic reviews and Meta-Analyses; CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyps.

Effect of Biological Treatment on Olfaction

Fifteen articles addressed biological treatment with dupilumab, mepolizumab, omalizumab, benralizumab, or reslizumab. Of these, 10 were randomized controlled trials (RCTs) and 5 were systematic reviews with meta-analyses. The population sample in most studies comprised patients with noncontrolled CRSwNP and an inadequate response to INCS and/or previous endoscopic surgery.

The UPSIT was used in almost all articles that addressed the efficacy of either dupilumab or omalizumab (n=13) and in the meta-analyses that included several biologics. In general terms, significant improvements in the UPSIT scores were detected after treatment with biologics (ranging from 16 to 52 weeks), and all the studies showed a statistically significant mean change from baseline (Table). In studies where the comparator was placebo, the least square mean difference (95%CI) in the UPSIT scores between the 2 arms at 24 weeks of follow-up ranged from 3.81 (1.38-6.24) (*P*=.0024) for omalizumab (POLYP 1 trial) [11] to 10.56 (8.79-12.34) (*P*=.0001) for dupilumab (LIBERTY NP SINUS 24 trial) [12]. According to 3 network meta-analyses and indirect comparisons, the mean difference in UPSIT scores (95%CI) for dupilumab versus omalizumab was 6.70 (4.67-8.73) [13], 7.21 (5.20-9.23) [14], and 6.70 (4.59-8.80) [15], all favoring dupilumab. The latter was also superior to mepolizumab, with a mean (95%CI) difference of 4.83 (2.43-7.22), and to benralizumab, with a mean (95%CI) difference of 8.01 (5.73-10.29). Besides the UPSIT test, the Sniffin' Sticks test was the only nonsubjective smell test used, in only 1 study, revealing a mean difference of 0.7 (–0.5 to 1.9) between mepolizumab and placebo at 24 weeks of treatment (*P*=.233) [16].

In 10 of the 15 publications, 1 or more subjective outcome measures of olfaction were used. These outcomes were usually in line with those derived from the objective tests (Table). However, none of the studies included provided complete data on the clinically relevant change based on the olfactory condition, evaluated as the percentage of patients who were normosmic, hyposmic, and anosmic before and after treatment. Only a pooled analysis of the LIBERTY NP SINUS-24 and SINUS-52 phase 3 trials reported that 77.6% of 724 patients were anosmic at baseline, compared with 28% after treatment with dupilumab [17]. Detailed data for all outcomes and studies included are shown in the Table.

Effect of Surgical Treatment on Olfaction

In 23 of the references included, the study intervention was sinus surgery, and most were prospective observational studies (n=17). The remaining articles were systematic reviews with meta-analyses (n=2), randomized or nonrandomized clinical trials (n=3), and a retrospective study (n=1). An objective olfactory test was used in 12 studies, whereas a subjective test was used in 11 studies. Six studies combined the use of an objective and subjective tool, and 8 included data on the percentage of patients with each clinical olfactory status before and after the intervention. Globally, all studies concluded that sinus surgery significantly improved the CRSwNP patient's perceived and measured sense of smell. The follow-up time ranged from 6 weeks to 12 years, and the population analyzed comprised mostly patients with CRSwNP refractory to medical treatment (Table S3). One study showed very long-term postoperative improvement in olfaction according to the BAST-24 test: at baseline, the median percentage (IQR) of smell detection, smell memory, and smell identification were 0 (0-5), 0 (0-5), and 0 (0-0), respectively, while at a 12-year follow-up, they were 65 (0-100) (*P*=.001), 15 (0-46.2) (*P*=.031), and 30 (0-55) (*P*=.001).

Two studies that reported separate CRSwNP and CRSsNP data observed a more pronounced response to surgery in patients with CRSwNP [18,19]. From the analyses including data on clinical olfactory status, 1 study reported a change in the proportion of anosmic patients, falling from 36.6% before surgery to 17.1% at 6 months after surgery. Almost half (46.5%) were hyposmic both before surgery and 6 months after surgery, while the proportion of normosmic patients rose from 17.1% before surgery to 36.6% at 6 months after surgery [20]. According to Bardaranfar et al [21], combined surgical and medical treatment had a better effect (CCCRC mean [SD] score: 1.10 [0.344] pretreatment vs CCCRC 7.0 [0.0] posttreatment) than surgery alone (CCCRC 1.33 [0.32] pretreatment vs CCCRC 6.37 [0.24] posttreatment), and these results correlated with clinical olfactory status (Table). In a different study, CRSwNP patients were significantly more likely to report complete restoration of smell or taste following sinus surgery than with medical management (23.8% vs 4.0%; *P*=.026) [22]. One trial compared the difference in olfactory outcomes between extensive endoscopic sinus surgery (EESS) and functional endoscopic sinus surgery (FESS). The mean (SD) difference in the VAS score 1 year after surgery was 6.00 (3.67) in the EESS group (n=23) and 3.30 (3.44) in the FESS group (n=24) (*P*=.015).

Effect of Medical Treatment on Olfaction

Of the 44 references included in the qualitative synthesis, only 6 reported a medical intervention other than surgery or biologics, and all 6 were RCTs. Thus, 1 of these trials assessed the administration of oral prednisone for 2 weeks (30 mg daily for 4 days followed by a 2-day reduction of 5 mg) plus intranasal budesonide spray twice daily (400 µg) for 12 weeks. The control group did not receive the 2-week treatment with oral prednisone [23]. The combination of OCS and INCS improved smell and nasal congestion while decreasing nasal inflammation compared with the control group (*P*=.05). These results were in line with those of another study, in which recovery of olfaction was better when initial medical treatment consisted of a short course of oral dexamethasone and intranasal budesonide compared with INCS alone (*P*=.001) (Table) [24].

Kern et al [25] performed a sham-controlled trial with a sample of 300 refractory CRSwNP patients. Patients who received absorbable mometasone-eluting furoate 200 µg nasal spray combined with a mometasone nasal implant (1350 µg) experienced sustained olfactory improvement (*P*=.0470) compared with placebo (Table) after 90 days of follow-up. A first-in-human study with 30 patients reported a statistical improvement in the CCCRC test (Table) between baseline and 24 weeks with 0.1% tretinoin added to intranasal budesonide compared to the latter alone [26]. Poletti et al [27] compared the efficacy of a specific device for endonasal aerosol delivery of corticosteroid (AMSA®) with that of a conventional nasal spray. The clinically relevant olfactory improvement was limited, and this device was not superior to the conventional spray according to the Sniffin' Sticks test results (Table). Lastly, a prospective randomized open-label trial compared the efficacy of montelukast as an add-on treatment to INCS in postoperative CRSwNP patients (n=72) with INCS alone. The mean change in BAST-24 and VAS scores after 1 year was similar between the 2 treatment groups (Table). Therefore, the addition of montelukast to INCS in the treatment of postoperative CRSwNP patients is not recommended [28].

Discussion

Among the cardinal symptoms of CRSwNP, olfactory impairment is usually described by patients as one of the most bothersome, severely impacting on their quality of life [5]. This is the first systematic review to evaluate the 3 currently available therapeutic approaches to CRSwNP (biologics, surgery, and conventional medical treatment). In general, very few studies compare these approaches directly. Significant olfactory improvements were detected with all the interventions assessed. In terms of conventional medical treatment, better olfactory outcomes were achieved in more than 1 study with the combination of OCS and INCS than with the latter alone [23,24], although evidence is very limited and inconclusive for other combinations [26-28]. Comparisons between the outcomes retrieved with different biologics when using the same measurement tool reveal dupilumab to be the most beneficial in terms of recovery of olfaction [1,12,17,29,30]. In all these studies, the comparator was placebo or the medical standard of care. The findings are supported by the network meta-analysis [2,13-15], although they are based on indirect treatment comparisons. As a result, samples may not be comparable, and results may be subject to selection bias; hence the need for head-to-head comparisons between biologics with longer follow-up times and real-world evidence to draw more reliable conclusions. With respect to surgery, most publications included also reported a significant response to ESS and better olfactory function based on both subjective and objective measurements. However, there is some disagreement in this regard: Lind et al [31] stated that

certain patients are less likely to benefit from surgery and that 7%-10% of the patients may experience deterioration in their sense of smell after surgery.

Although the outcomes of medical interventions (mostly corticosteroids) show an improvement in olfaction, the results do not seem as clear as those obtained with surgery or biologics. According to DeConde et al [22], patients with CRSwNP were significantly more likely to report complete resolution of smell following surgery than following medical treatment. However, it is difficult to compare the 3 interventions globally owing to the heterogeneity of the olfactory tests applied and the characteristics of the study population. In general terms, the methodological design of studies assessing biologics or medical treatment is more robust, as most are RCTs with large samples, whereas studies analyzing surgery tend to be observational and include significantly fewer patients. Besides, in some of the studies included in this review, the authors performed subgroup analyses within the CRSwNP population. These revealed significant improvements in olfaction for dupilumab regardless of prior sinonasal surgery or prior systemic corticosteroids [1]. Furthermore, among patients with anosmia at baseline, the proportions of patients who regained some sense of smell (UPSIT >18) at week 24 with dupilumab were comparable among those with and without N-ERD [30]. However, patients with N-ERD are more frequently anosmic and have more severe and difficult-to-treat disease, which might result in better outcomes in this subpopulation than in patients without N-ERD.

It is important to emphasize that most studies to date only include information on olfactory outcomes expressed as objectively measured and/or patient-reported scores, and do not include data on the percentage of anosmic or hyposmic patients who recover their sense of smell, a variable that reflects the clinically relevant change. Only a few studies incorporate these qualitative criteria. According to these results, biological treatments, including dupilumab, seem to be the most effective intervention in terms of improved olfaction, suggesting that the design of studies should include more qualitative parameters for measuring recovery of the sense of smell.

Measurement of olfaction must be standardized in order to establish common criteria for studies that compare treatments in terms of efficacy or effectiveness. Nevertheless, the phenotyping of respiratory diseases with an underlying pathophysiologic mechanism, such as T2 inflammation, is becoming the cornerstone of accurate patient management [32], helping patients to benefit from the best treatment option depending on the primary goal of therapy. This classification is often omitted in current clinical practice, thus hindering the choice of the most suitable first-line therapeutic option to achieve the desired outcomes.

This work is limited by the broadly based research question, which gave rise to considerable heterogeneity between studies, including patient cohorts that differ in severity, number of previous surgeries, and type and location of polyps. Additionally, the severity of olfactory impairment may vary depending on the endotype, which was not assessed in all studies. Likewise, in patients with the same endotype, the degree of improvement in olfaction may vary according to the degree of impairment, which is not well defined in many publications. Therefore, while these samples are not always easily comparable, our results may guide the design of future studies. In contrast, a major strength of our work is that the studies selected are high-quality and recent and used validated measurement tools. Another asset of this review is that it brings together all the evidence on the effect of the 3 current therapeutic interventions in olfactory loss in CRSwNP.

In conclusion, this review of the literature reveals that treatments targeting CRSwNP, such as OCS, biologics, and ESS, improve not only other markers and symptoms of the disease, but also the loss of smell. However, given that the currently available evidence is highly diverse due to the variability in outcome measurements, establishing standardized criteria would be desirable. Further research with real-world data that include results on clinically relevant changes measured by qualitative parameters is needed to gain in-depth knowledge on the optimal management of olfactory impairment.

Acknowledgments

The authors would like to thank Dr. Laura Hidalgo (Medical Science Consulting; Valencia, Spain) for technical and medical writing support.

Funding

This project was funded by Sanofi. The sponsor had no role in the article's content or wording. Writing and editorial assistance was provided by Laura Hidalgo, PhD (Medical Science Consulting, Valencia, Spain).

Conflicts of Interest

IA declares receiving consulting fees and honoraria for lectures, presentations, speakers bureaus, educational events, and expert testimony, as well as support for attending meetings and/or travel from Menarini, Metronic, Olympus, Salvat, Novartis, Sanofi, GSK, AstraZeneca, Galenus Health, and Viatris. BB declares receiving honoraria for lectures, presentations, speakers bureaus, educational events for Chiesi and Roxall, as well as support for attending meetings and/or travel from Sanofi, GSK, Allergopharma, Allergy, and Roxall. CC declares receiving consulting fees from Forwardontics, honoraria for lectures, presentations, speakers bureaus, educational events from Sanofi, GSK, Mylan, Forwardontics, and Cinfa and for expert testimony from Audifon, as well as support for attending meetings and/or travel from Sanofi, GSK, Mylan, Forwardontics, and Cinfa. MGF is an employee of Medical Statistics Consulting, SL and declares no other conflicts of interest. JS declares receiving grants from Sanofi paid to the Fundación Jimenez Diaz, consulting fees from Sanofi, AbbVie, and Novartis, honoraria for lectures, presentations, speakers bureaus, or educational events from Sanofi, GSK, FAES Farma, as well as support for attending meetings and/or travel from Sanofi. JS also declares having an unpaid leadership or fiduciary role in the Spanish Society of Allergology and Clinical Immunology (SEAIC), the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Allergy, Asthma & Immunology (AAAAI).

References

1. Desrosiers M, Mannent LP, Amin N, Canonica GW, Hellings PW, Gevaert P, et al. Dupilumab reduces systemic corticosteroid use and sinonasal surgery rate in CRSwNP. Rhinology. 2021;59(3):301-11.
2. Tsetsos N, Markou K, Konstantinidis I. Effect of monoclonal antibodies on olfactory dysfunction caused by chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis. Int Forum Allergy Rhinol. 2020;10(7):893-900.
3. De Corso E, Pipolo C, Cantone E, Ottaviano G, Gallo S, Canevari FRM, et al. Survey on Use of Local and Systemic Corticosteroids in the Management of Chronic Rhinosinusitis with Nasal Polyps: Identification of Unmet Clinical Needs. J Pers Med. 2022;12(6):897.
4. Bachert C, Bhattacharyya N, Desrosiers M, Khan AH. Burden of Disease in Chronic Rhinosinusitis with Nasal Polyps. J Asthma Allergy. 2021;14:127-34.
5. Mullol J, Mariño-Sánchez F, Valls M, Alobid I, Marin C. The sense of smell in chronic rhinosinusitis. J Allergy Clin Immunol. 2020;145(3):773-6.
6. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012;50(1):1-12.
7. Tsetsos N, Goudakos JK, Daskalakis D, Konstantinidis I, Markou K. Monoclonal antibodies for the treatment of chronic rhinosinusitis with nasal polyposis: a systematic review. Rhinology. 2018;56(1):11-21.
8. Barroso B, Valverde-Monge M, Betancor D, Gómez-López A, Villalobos-Vildas C, González-Cano B, et al. Smell improvement in chronic rhinosinusitis with nasal polyps with monoclonal antibodies: a systematic review. J Investig Allergol Clin Immunol. 2023;33(6):419-30.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
10. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:Ed000142.
11. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol. 2020;146(3):595-605.
12. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638-50.
13. Cai S, Xu S, Lou H, Zhang L. Comparison of Different Biologics for Treating Chronic Rhinosinusitis with Nasal Polyps: A Network Analysis. J Allergy Clin Immunol Pract. 2022;10(7):1876-86.
14. Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: A systematic review and network meta-analysis. J Allergy Clin Immunol. 2022;149(4):1286-95.
15. Peters AT, Han JK, Hellings P, Heffler E, Gevaert P, Bachert C, et al. Indirect Treatment Comparison of Biologics in Chronic Rhinosinusitis with Nasal Polyps. J Allergy Clin Immunol Pract. 2021;9(6):2461-71 e5.
16. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. J Allergy Clin Immunol. 2017;140(4):1024-31 e14.
17. Mullol J, Bachert C, Amin N, Desrosiers M, Hellings PW, Han JK, et al. Olfactory Outcomes With Dupilumab in Chronic Rhinosinusitis With Nasal Polyps. J Allergy Clin Immunol Pract. 2022;10(4):1086-95 e5.
18. Andrews PJ, Poirrier AL, Lund VJ, Choi D. Outcomes in endoscopic sinus surgery: olfaction, nose scale and quality of life in a prospective cohort study. Clin Otolaryngol. 2016;41(6):798-803.
19. Kohli P, Naik AN, Farhood Z, Ong AA, Nguyen SA, Soler ZM, et al. Olfactory Outcomes after Endoscopic Sinus Surgery for Chronic Rhinosinusitis: A Meta-analysis. Otolaryngol Head Neck Surg. 2016;155(6):936-48.
20. Haxel BR, Boessert P, Weyer-Elberich V, Fruth K. Course of olfaction after sinus surgery for chronic rhinosinusitis. Laryngoscope Investig Otolaryngol. 2017;2(5):269-75.
21. Bardaranfar MH, Ranjbar Z, Dadgarnia MH, Atighechi S, Mirvakili A, Behniafard N, et al. The effect of an absorbable gelatin dressing impregnated with triamcinolone within the olfactory cleft on polypoid rhinosinusitis smell disorders. Am J Rhinol Allergy. 2014;28(2):172-5.
22. DeConde AS, Mace JC, Alt JA, Soler ZM, Orlandi RR, Smith TL. Investigation of change in cardinal symptoms of chronic rhinosinusitis after surgical or ongoing medical management. Int Forum Allergy Rhinol. 2015;5(1):36-45.
23. Alobid I, Benitez P, Cardelus S, de Borja Callejas F, Lehrer-Coriat E, Pujols L, et al. Oral plus nasal corticosteroids improve smell, nasal congestion, and inflammation in sino-nasal polyposis. Laryngoscope. 2014;124(1):50-6.
24. Papadakis CE, Chimona TS, Chaidas K, Ladias A, Zisoglou M, Proimos EK. Effect of oral steroids on olfactory function in chronic rhinosinusitis with nasal polyps. Eur Ann Otorhinolaryngol Head Neck Dis. 2021;138(5):343-8.
25. Kern RC, Stolovitzky JP, Silvers SL, Singh A, Lee JT, Yen DM, et al. A phase 3 trial of mometasone furoate sinus implants for chronic sinusitis with recurrent nasal polyps. Int Forum Allergy Rhinol. 2018;8(4):471-81.
26. Antonio MA, Marson FAL, Toro MDC, Sampaio MH, Barreto IS, Dertkigil SSJ, et al. Topical tretinoin in chronic rhinosinusitis with nasal polyps: a randomized clinical trial. Int Forum Allergy Rhinol. 2021;11(8):1187-96.
27. Poletti SC, Batashev I, Reden J, Hummel T. Olfaction in chronic rhinosinusitis: comparing two different endonasal steroid application methods. Eur Arch Otorhinolaryngol. 2017;274(3):1431-5.
28. Van Gerven L, Langdon C, Cordero A, Cardelus S, Mullol J, Alobid I. Lack of long-term add-on effect by montelukast in postoperative chronic rhinosinusitis patients with nasal polyps. Laryngoscope. 2018;128(8):1743-51.
29. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial. JAMA. 2016;315(5):469-79.

30. Mullol J, Laidlaw TM, Bachert C, Mannent LP, Canonica GW, Han JK, et al. Efficacy and safety of dupilumab in patients with uncontrolled severe chronic rhinosinusitis with nasal polyps and a clinical diagnosis of NSAID-ERD: Results from two randomized placebo-controlled phase 3 trials. Allergy. 2022;77(4):1231-44.
31. Lind H, Joergensen G, Lange B, Svendstrup F, Kjeldsen AD. Efficacy of ESS in chronic rhinosinusitis with and without nasal polyposis: a Danish cohort study. Eur Arch Otorhinolaryngol. 2016;273(4):911-9.
32. Damask CC, Ryan MW, Casale TB, Castro M, Franzese CB, Lee SE, et al. Targeted Molecular Therapies in Allergy and Rhinology. Otolaryngol Head Neck Surg. 2021;164(1_suppl):S1-s21.
33. Gevaert P, Saenz R, Corren J, Han JK, Mullol J, Lee SE, et al. Long-term efficacy and safety of omalizumab for nasal polyposis in an open-label extension study. J Allergy Clin Immunol. 2022;149(3):957-65 e3.
34. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9(10):1141-53.
35. Naclerio RM, Hamilos DL, Ferguson BJ, Bachert C, Hellings PW, Mullol J, et al. Dupilumab Improves Sense of Smell and Reduces Anosmia Among Patients with Nasal Polyposis and Chronic Sinusitis: Results from a Phase 2a Trial. J Allergy Clin Immunol. 2017;139(2):AB90-AB.
36. Wang Q, Sun Q, Chen Q, Li H, Liu D, Wu Q. Efficacy and Safety of Anti-Interleukin-5 Therapies in Chronic Rhinosinusitis with Nasal Polyps: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Int Arch Allergy Immunol. 2022;183(7):732-43.
37. Arancibia C, Langdon C, Mullol J, Alobid I. Twelve-year long-term postoperative outcomes in patients with chronic rhinosinusitis with nasal polyps. Rhinology. 2022;60(2):109-17.
38. Baradaranfar MH, Ahmadi ZS, Dadgarnia MH, Bemanian MH, Atighechi S, Karimi G, et al. Comparison of the effect of endoscopic sinus surgery versus medical therapy on olfaction in nasal polyposis. Eur Arch Otorhinolaryngol. 2014;271(2):311-6.
39. Beswick DM, Smith TL, Mace JC, Alt JA, Farrell NF, Ramakrishnan VR, et al. Ethmoid-to-maxillary opacification ratio: a predictor of postoperative olfaction and outcomes in nasal polyposis? Int Forum Allergy Rhinol. 2021;11(1):48-57.
40. 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.
41. Chen FH, Deng J, Hong HY, Xu R, Guo JB, Hou WJ, et al. Extensive versus functional endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps and asthma: A 1-year study. Am J Rhinol Allergy. 2016;30(2):143-8.
42. Dadgarnia M, Rahmani A, Baradaranfar M, Atighechi S, Zand V, Meybodian M, et al. The relationship between endoscopic and radiologic findings and olfactory status of patients with chronic rhinosinusitis with nasal polyps before and after the endoscopic sinus surgery. Eur Arch Otorhinolaryngol. 2019;276(2):397-400.
43. Djukic V, Dudvarski Z, Arsovic N, Dimitrijevic M, Janosevic L. Clinical outcomes and quality of life in patients with nasal polyposis after functional endoscopic sinus surgery. Eur Arch Otorhinolaryngol. 2015;272(1):83-9.
44. Galletti B, Gazia F, Freni F, Sireci F, Galletti F. Endoscopic sinus surgery with and without computer assisted navigation: A retrospective study. Auris Nasus Larynx. 2019;46(4):520-5.
45. Haxel BR, Fischer L, Pade J, Reden J, Hummel T. Nasal polyp load determines the recovery of olfaction after surgery for chronic rhinosinusitis. Rhinology. 2022;60(2):102-8.
46. Hema V, Rebekah G, Kurien R. Reversibility of mucociliary clearance and olfaction impairment following endoscopic sinus surgery: a prospective observational study. J Laryngol Otol. 2021;135(2):147-52.
47. Levy JM, Mace JC, Sansoni ER, Soler ZM, Smith TL. Longitudinal improvement and stability of olfactory function in the evaluation of surgical management for chronic rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(11):1188-95.
48. Lötsch J, Hintschich CA, Petridis P, Pade J, Hummel T. Machine-Learning Points at Endoscopic, Quality of Life, and Olfactory Parameters as Outcome Criteria for Endoscopic Paranasal Sinus Surgery in Chronic Rhinosinusitis. J Clin Med. 2021;10(18):4245.
49. Nguyen DT, Bey A, Arous F, Nguyen-Thi PL, Felix-Ravelo M, Jankowski R. Can surgeons predict the olfactory outcomes after endoscopic surgery for nasal polyposis? Laryngoscope. 2015;125(7):1535-40.
50. Nguyen DT, Bonfort G, Arous F, Felix-Ravelo M, Nguyen-Thi PL, Jankowski R. Evaluation of residual symptoms: A method to assess surgical outcomes for nasal polyposis. Am J Rhinol Allergy. 2016;30(2):e36-41.
51. Paksoy ZB, Cayonu M, Yucel C, Turhan T. The treatment efficacy of nasal polyposis on olfactory functions, clinical scoring systems and inflammation markers. Eur Arch Otorhinolaryngol. 2019;276(12):3367-72.
52. Szaleniec J, Wrobel A, Strek P, Kowalczyk M, Bylica E, Przeklasa M, et al. Smell impairment in chronic rhinosinusitis - evaluation of endoscopic sinus surgery results and review of literature concerning olfactory function predictors. Otolaryngol Pol. 2015;69(1):33-44.
53. Zhao R, Chen K, Tang Y. Olfactory changes after endoscopic sinus surgery for chronic rhinosinusitis: A meta-analysis. Clin Otolaryngol. 2021;46(1):41-51.

Manuscript received June 21, 2023; accepted for publication December 19, 2023.

Joaquín Sastre

https://orcid.org/0000-0003-4689-6837
Department of Allergy
Hospital Universitario Fundación Jiménez Díaz
Av. Reyes Católicos
28040 Madrid, Spain
E-mail: jsastre@fjd.es

Isam Alobid
https://orcid.org/0000-0003-2557-6017
Blanca Barroso
https://orcid.org/0000-0003-2695-8439
Christian Calvo
https://orcid.org/0000-0003-3580-0967
Maria Giovanna Ferrario
https://orcid.org/0000-0003-4415-3722