Improvement in Smell Using Monoclonal Antibodies Among Patients With Chronic Rhinosinusitis With Nasal Polyps: A Systematic Review

Barroso B[1,2], Valverde-Monge M[1,2], Betancor D[1,2], Gómez-López A[1], Villalobos-Vilda C[1], González-Cano B[1], Sastre J[1,2]

[1]Allergy Department, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
[2]CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain

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Abstract

Background: Impairment of smell is more commonly related to chronic rhinosinusitis with nasal polyps (CRSwNP) than without, especially when asthma and/or NSAID-exacerbated respiratory disease and type 2 inflammation are also present. Therapeutic options include intranasal and systemic corticosteroids, surgery, and, more recently, biological therapy. We summarize current knowledge on the effect of biologics on olfaction in patients with CRSwNP.
Methods: We performed a systematic search of the PubMed and Cochrane databases from January 2001 to June 2022. The inclusion criteria were as follows: adult patients with CRS treated with dupilumab, omalizumab, mepolizumab, benralizumab, or reslizumab; and studies published in English reporting outcomes for sense of smell based on psychophysical and/or subjective tools. We excluded reports that did not assess CRSwNP, loss of smell evaluated with a method other than those accepted in the inclusion criteria, review articles, and expert opinions. No funding was received.
Results: Dupilumab has demonstrated rapid and sustained long-term improvement in smell in clinical trials and in real life. Omalizumab improves smell at 24 weeks. This improvement is maintained in the long-term, although it is not clinically relevant. Mepolizumab and benralizumab improved smell in the long term based on a subjective scale. No studies examining the improvement in smell in patients with CRSwNP treated with reslizumab were found. Indirect comparisons by meta-analysis consistently conclude that dupilumab is the most effective biologic for improving impaired sense of smell.
Conclusion: Dupilumab seems to be more efficacious for improving the sense of smell than omalizumab, mepolizumab, and benralizumab.

Key words: Smell. Chronic rhinosinusitis with nasal polyps (CRSwNP). Dupilumab. Omalizumab. Mepolizumab. Benralizumab. Monoclonal antibodies.

Resumen

Antecedentes: La pérdida de olfato de la rinosinusitis crónica se relaciona principalmente con el fenotipo que presenta poliposis nasal (RSCcPN), especialmente si asocia asma y/o EREA, e inflamación tipo 2. Los corticoides intranasales y sistémicos, la cirugía y, de forma más reciente, los fármacos biológicos, constituyen las principales estrategias terapéuticas. Este documento contiene una revisión sistemática del efecto de los fármacos biológicos en el olfato de pacientes con RSCcPN.
Métodos: Se realizó una búsqueda sistemática en las bases de datos PubMed y Cochrane desde enero de 2001 hasta junio de 2022. Los criterios de inclusión fueron: pacientes adultos con RSC tratados con dupilumab, omalizumab, mepolizumab, benralizumab o reslizumab; estudios publicados en inglés, con datos sobre la mejoría del olfato utilizando test psicofísicos y/o subjetivos. Los criterios de exclusión fueron: publicaciones que no incluían pacientes con poliposis nasal, la pérdida del olfato evaluada con un método diferente de los criterios de inclusión mencionados, los artículos de revisión y la opinión de expertos. No se empleó ningún recurso de financiación.
Resultados: Dupilumab ha demostrado una mejora del olfato rápida y mantenida a largo plazo en ensayos clínicos y en la práctica clínica habitual. Omalizumab mejora el olfato en la 24ª semana y lo mantiene a largo plazo, pero no alcanza una mejoría clínicamente relevante. Mepolizumab y benralizumab mejoran el olfato a largo plazo, evaluado mediante un test subjetivo. No se encontraron estudios respecto a la mejoría del olfato en pacientes con RSCcPN tratados con reslizumab. Las comparaciones indirectas mediante metaanálisis concluyen de forma consistente que dupilumab es el biológico más eficaz para mejorar el sentido del olfato.
Conclusión: Dupilumab es el biológico más eficaz en la mejoría del olfato en RSCcPN, en comparación con omalizumab, mepolizumab y benralizumab.

Palabras clave: Olfato. Rinosinusitis crónica con poliposis nasal (RSCcPN). Dupilumab. Omalizumab. Mepolizumab. Benralizumab. Anticuerpos monoclonales.

1. Introduction

Chronic rhinosinusitis (CRS) is a common disease characterized by inflammation of the nose and paranasal sinuses. In adults, it is characterized by 2 or more symptoms, consisting of either nasal blockage/obstruction/congestion or discharge (anterior/posterior nasal drip) ± facial pain/pressure ± reduction/loss of smell lasting over 12 weeks [1]. With a prevalence of 5%-12% in the general population, CRS is associated with poor quality of life due to altered social functioning [2] and comorbid depressive illnesses and is one of the 10 most costly conditions for US employers [3].

Two phenotypes of CRS can be differentiated based on the presence of associated nasal polyposis (NP) on nasal endoscopy and/or computed tomography (CT) scan, namely, CRS with NP (CRSwNP) and CRS without NP (CRSsNP) [1]. The prevalence of CRSwNP in Europe is around 1.8% to 2.7% [4]. Nevertheless, most affected patients are not referred to specialized clinics [5]. Approximately 67%-78% of persons with CRSwNP experience olfactory dysfunction [6], which is the symptom that most affects quality of life [1]. Sense of smell should be evaluated based on subjective tests, which are useful but should not be undertaken in isolation given their poor accuracy. Therefore, combination with psychophysical tests, which provide a more reliable assessment of olfactory function, is strongly recommended (see Supplementary material). Impaired sense of smell (hyposmia when partial and anosmia indicating total loss) is more commonly related to CRSwNP than CRSsNP, asthma and/or nonsteroidal anti-inflammatory drug (NSAID)–exacerbated respiratory disease (N-ERD), and type (T) 2 inflammation [7].

In the European population, >85% of patients with CRSwNP present T2 inflammation, which is characterized by local eosinophilic inflammation and high production of eosinophil cationic protein, IL-4, IL-5, IL-13, and local immunoglobulin E (IgE) [7]. T2 inflammation leads to shedding of olfactory epithelium and degeneration of olfactory sensory neurons as potential causes of loss of smell [8]. Anti-inflammatory therapy potentially reduces inflammation of the olfactory clefts and induces basal stem cell proliferation and olfactory sensory neuron regeneration, leading to partial or total recovery of the sense of smell [8].

Most individuals with CRSwNP experience symptom relief with intranasal corticosteroids (INCS), the first line of treatment [1]. However, it has been shown that adherence to INCS in patients with CRSwNP is poor and not related to disease severity [5]. Many patients with refractory disease require functional endoscopic sinus surgery (FESS) to alleviate their symptoms, although 79% have recurring NP at 12 years of follow-up [9].

Biologic treatments present an opportunity to address this severe, unresponsive subgroup of individuals with CRSwNP. Biological drugs are a new option for improvement of outcomes in recovery of the sense of smell.

The European Medicines Agency and the United States Food and Drug Administration have approved dupilumab (2019), omalizumab (2020), and mepolizumab (2021) in CRSwNP as an add-on therapy with INCS for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery does not provide adequate disease control [9]. Dupilumab (Dupixent) is a fully human monoclonal antibody that binds to the IL-4α receptor, thus inhibiting signaling of IL-4 and IL-13 and blocking the pathways leading to differentiation of B cells into the production of IgE and activation of eosinophils underlying the T2 inflammatory mechanism. Omalizumab (Xolair) is a recombinant humanized immunoglobulin-G1κ monoclonal antibody that selectively binds to the Cε3 domain of the Fc region of human IgE in blood and interstitial fluid, blocking its action and preventing it from binding to the high-affinity receptor (FcεRI) on the surface of mast cells, basophils, and dendritic cells, thereby interfering with activation. The increased local production of IgE in patients with CRSwNP points to the potential of this drug. Mepolizumab (Nucala) is an IgG1κ monoclonal antibody that antagonizes IL-5, causing a decrease in airway eosinophils. Other anti–IL-5 drugs (benralizumab, reslizumab) can potentially act against CRSwNP, although they have not been approved for this indication.

We performed a systematic review to summarize current knowledge on the effect of biologics on olfaction in patients with CRSwNP.

2. Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) statement [10]. The search was performed using the PubMed (which includes MEDLINE) and Cochrane databases with a publication timeframe running from January 2001 to June 2022. The search strategy was designed using a combination of MeSH terms with keywords and Boolean operators to obtain as many records as possible where patients with CRSwNP received biologic treatments (dupilumab, omalizumab, mepolizumab, benralizumab, and reslizumab) and MeSH terms and keywords were mentioned in the title or abstract. The search was restricted to human studies and articles in English. Abstracts were excluded.

The research question was structured using the PICO methodology in order to assess the impact of biologic treatment on olfactory impairment in patients with CRSwNP (Table 1). The study population comprised patients with CRSwNP. The interventions considered included treatment with biologic therapies (dupilumab, omalizumab, mepolizumab, benralizumab, or reslizumab) compared or not with placebo. The outcome was the change after initiation of treatment in the sense of smell measured using a psychophysical test (University of Pennsylvania Smell Identification Test [UPSIT] [11], Sniffin' sticks [12], Barcelona Smell Test 24 [BAST-24] [13], Barcelona Olfactory Test [BOT-8] [14], or T&T olfactometer [15]) and/or a subjective test (daily diary of sense of smell, loss of smell score [LoS], visual analog scale [VAS], numerical analog scale [NAS], and/or Likert scale) (Table S1, Supplementary material). The search protocol was not registered.

Studies were included if they met the following criteria: (*1*) human study population; (*2*) performed on adult patients with CRS (≥18 years old); (*3*) intervention and comparison, ie, studies comparing human monoclonal antibodies (dupilumab,

Table 1. Search Strategy.

Code	Term	Synonyms
#1	Chronic rhinosinusitis with nasal polyps	("Nasal Polyps"[Mesh] OR "nasal polyp*"[tiab] OR "Sinusitis"[Mesh:NoExp] OR "sinusiti*"[tiab] OR "sinus infection*"[tiab] OR "Rhinitis"[Mesh:NoExp] OR "rhiniti*"[tiab] OR "nasal catarrh*"[tiab] OR CRSwNP[Title/Abstract] OR "chronic rhinosinusitis"[Title/Abstract])
#2	Smell impairment	("smell*"[tiab] OR "olfaction*"[tiab] OR "nasal polyp*"[tiab]) AND ("impairment*"[tiab] OR "dysfunction*"[tiab] OR "alteration*"[tiab] OR "disorder*"[tiab] OR "loss*"[tiab])
#3	Biological treatment	("Omalizumab"[Mesh] OR "omalizumab"[tiab] OR "benralizumab" [Supplementary Concept] OR "benralizumab"[tiab] OR "reslizumab" [Supplementary Concept] OR "reslizumab"[tiab] OR "mepolizumab" [Supplementary Concept] OR "mepolizumab"[tiab] OR "dupilumab" [Supplementary Concept] OR "Dupilumab"[tiab])
#4		#1 OR #2
#5		#4 AND #3

omalizumab, mepolizumab, benralizumab, or reslizumab) with a placebo; (*4*) case reports or series of patients with CRS who were treated with human monoclonal antibodies (dupilumab, omalizumab, mepolizumab, benralizumab, or reslizumab); (*5*) meta-analyses; (*6*) written and published in English; (*7*) studies reporting outcomes in sense of smell using psychophysical instruments (UPSIT, Sniffin' Sticks, T&T olfactometer) or psychometric instruments (daily diary of sense of smell, LoS, VAS, or NAS).

We excluded articles published in languages other than English, reports that did not assess CRSwNP, reports that did not assess loss of smell, reports in which loss of smell was evaluated with a method other than those in the inclusion criteria, review articles, and expert opinions. We also excluded publications where loss of smell was assessed using the Sinonasal Outcome Test (SNOT-22) only [16], since this test asks only 1 question about smell.

For the selection process and data extraction, the titles and abstracts of the articles retrieved were screened for their potential relevance by 1 reviewer. The full-text articles were then obtained and assessed by all 3 reviewers to determine whether they met the inclusion criteria for this review. Any differences were resolved by discussion with a fourth author. Six reviewers read the full-text articles and extracted data (patient characteristics, study methods, blood eosinophils, asthma and N-ERD population, the primary endpoint, and changes in smell outcome data).

The quality of evidence of all studies included was evaluated to determine risk of bias using the Critical

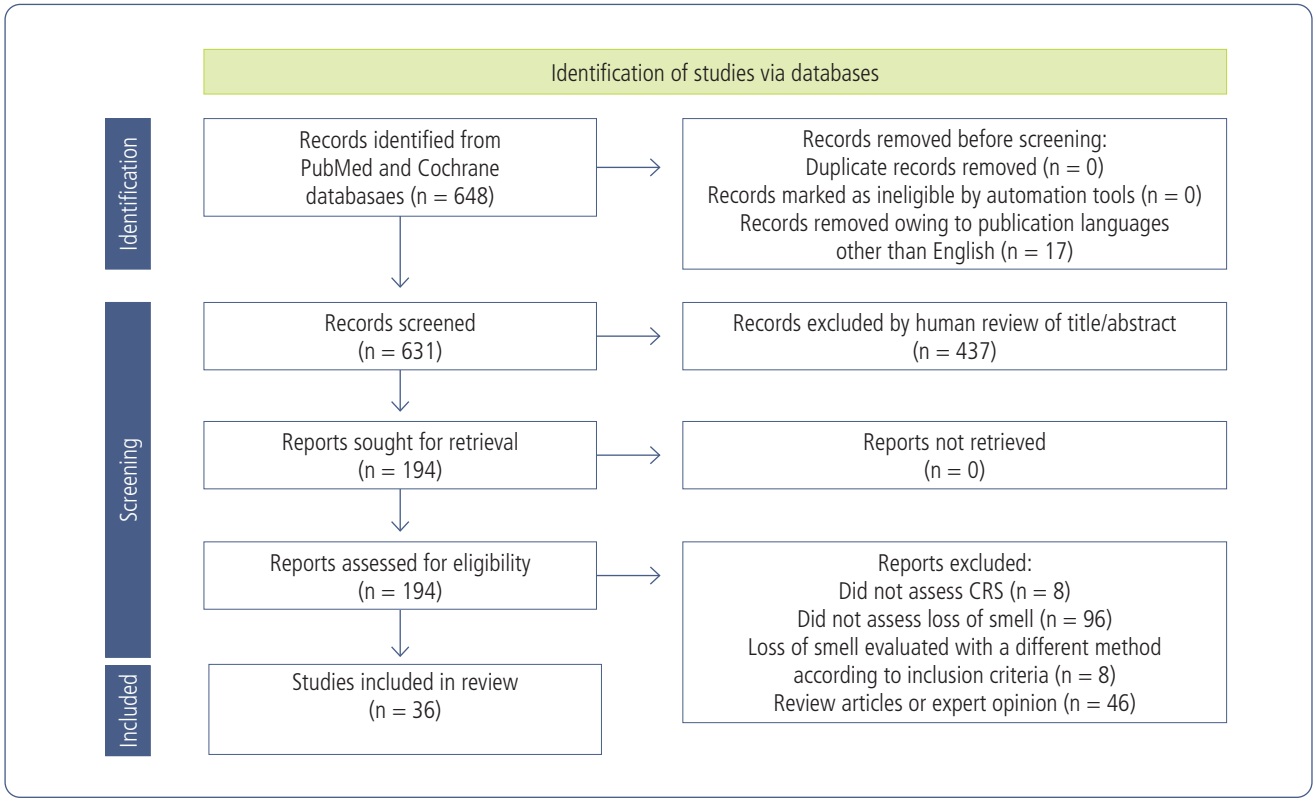

Figure. PRISMA flow diagram for the systematic review. CRS indicates chronic rhinosinusitis.

Appraisal Skills Programme (https://casp-uk.net/casp-tools-checklists/). Two independent reviewers assessed both study design/methodology and outcomes/results using the appropriate checklist depending on the type of study. The articles were classified as providing low-, moderate-, or high-quality evidence according to the type of study/design and the number of questions in the corresponding checklist with a positive or negative response. Single cases could not be evaluated with this system (Table S2, Supplementary material).

Table 2. Baseline Characteristics of Patients Enrolled in Phase 3 Clinical Trials of Biologic-Treated CRSwNP Patients.

Biologic	Dupilumab		Omalizumab		Mepolizumab	Benralizumab
Phase 3 study	SINUS-24	SINUS-52	POLYP 1	POLYP 2	SYNAPSE	OSTRO
Design	Placebo vs dupilumab 300 mg q2w (1:1)	Placebo vs dupilumab 300 mg q2w vs dupilumab 300 mg q2w until week 24 and 300 mg q4w until week 52 (1:1:1)	Placebo vs omalizumab 75-600 mg q2-4w (depending on the pretreatment serum total IgE level and body weight)	Placebo vs omalizumab 75-600 mg q2-4w (depending on the pretreatment serum total IgE level and body weight)	Placebo vs mepolizumab 100 q4w	Placebo vs benralizumab 30 mg q4w for the first 3 doses then 30 mg q8w
Population, No.	n=133 vs n=143	n=153 vs n=150 vs n=145	n=66 vs n=72	n=72 vs n=62	n=201 vs n=206	n=206 vs n=207
Follow-up time, wk	24	52	24	24	52	40
Asthma, %	59% vs 57%	59% vs 63% vs 57%	48.5% vs 58%	60% vs 61%	74% vs 68%	67% vs 69%
AERD, %	29% vs 32%	29% vs 28% vs 23%	17% vs 22%	32% vs 39%	31% vs 22%	29% vs 30%
NP surgery	≥1 previous surgery: 74% vs 69%; ≥3 previous surgeries: 22% vs 23%	1 previous surgery: 58% vs 59% vs 59%; ≥3 previous surgeries: 12% vs 6% vs 15%	1 previous surgery: 36% vs 32%; ≥2 previous surgery: 24% vs 22%	1 previous surgery: 23% vs 35.5%; ≥2 previous surgery: 38.5% vs 27%	0 Previous nasal surgery: 0%; ≥1 Previous nasal surgery: 100%; ≥2 Previous nasal surgery: 48%; ≥3 Previous nasal surgery: 25%; ≥4 Previous nasal surgery: 12%; ≥5 Previous nasal surgery: 5%	Prior NP surgery: median (range): 2 (1.15) vs 2 (1.40)
Bilateral endoscopic NP score* (scale 0-8); mean (SD)	5.86 (1.31) vs 5.64 (1.23)	5.96 (1.21) vs 6.29 (1.20) vs 6.07 (1.22)	6.3 (0.9) vs 6.2 (1.0)	6.1 (0.9) vs (0.9)	5.6 (1.4) vs 5.4 (1.2)	6.13 (1.13) vs 6.15 (1.19)
Smell at baseline	77.6 % anosmia (UPSIT <19) / 20.7% hyposmia (UPSIT 19-34)	Normosmia 1.7% (UPSIT > 34)	Unavailable	Unavailable	Mean (SD) loss of smell VAS score (range 0-10): 10.0 (9.6-10.0) vs 10.0 (9.6-10.0)	84.4% vs 82.6% anosmia (UPSIT <19)
Baseline blood eosinophils, cells/L	440 (310.0) vs 0.440 (350.0)	450 (360.0) vs 400 (300.0) vs 450 (390)	358.6 (305.2) vs 334.4 (264.7)	357.4 (196.2) vs 310.8 (176.6)	400 (910) vs 390 (880)	448.3 (364.6) vs 445 (245.1)
Baseline total IgE, IU/mL	222.55 (269.11) vs 202.06 (282.37)	282.28 (463.72) vs 210.82 (256.78) vs 229.21 (318.13)	162.0 (141.2) vs 159.9 (139.0)	196.1 (200.6) vs 184.1 (201.9)	Unavailable	251 (549) vs 214 (344)
Anosmia (UPSIT<18) decreased	From 74% to 24% at week 24	From 79% to 30% at week 24	Unavailable	Unavailable	Unavailable	Unavailable

Abbreviations: AERD, aspirin-exacerbated respiratory disease; CRSwNP, chronic rhinosinusitis with nasal polyposis; NP, nasal polyposis; UPSIT, University of Pennsylvania Smell Identification Test (0-40); VAS, visual analog scale.

3. Results

The search yielded 648 results from January 2001 to June 2022. Seventeen records were removed because they were written in a language that was not English, 437 were excluded after human review of the title/abstract, 8 did not assess CRS, 96 did not assess loss of smell, 8 evaluated loss of smell using a method other than those accepted in the inclusion criteria, and 46 were removed because they were review articles or expert opinions.

After the selection process, only 36 were included. The Figure shows the PRISMA diagram, which details the workflow of the screening process [10]. The PRISMA checklist is described in the Supplementary material (Table S3). The articles finally selected included case reports, case series, observational studies, clinical trials, post hoc studies of randomized trials, and systematic reviews with meta-analysis focusing on the effects of biological treatments for CRSwNP on impaired smell measured according to one of the previously mentioned tests. The details of the studies included are presented in Table S4 of the Supplementary material.

3.1. Dupilumab

3.1.1. Clinical trials with dupilumab

Phase 3 clinical trials (SINUS-24 and SINUS-52) demonstrated improvement in smell in patients with CRSwNP treated with dupilumab vs placebo at 24 weeks, evaluated using UPSIT (P<.0001) and the LoS score (P<.0001) [17,18]. The proportion of patients with anosmia in the dupilumab group declined from 78% at baseline to 45% at 2 weeks and 28% at 24 weeks (both P<.0001). In the placebo group, the proportion of patients who were anosmic remained unchanged at 24 weeks relative to baseline [18]. Post hoc analysis of SINUS-24 and SINUS-52 concluded that dupilumab produces rapid improvements in sense of smell: in 3 days according to the LoS score (P<.05), 2 weeks according to UPSIT (P<.0001), and 8 weeks according to the SNOT-22 item "decreased sense of smell/taste" (P<.0001). Improvements with dupilumab

Table 3. Comparison Between UPSIT and Loss of Smell Score in Phase 3 Studies.

	Dupilumab			Omalizumab		Mepolizumab	Benralizumab
Phase 3 study	**SINUS-24**	**SINUS-52 (q2w)**	**SINUS-52 (q2w-q4w)**	**POLYP-1**	**POLYP-2**	**SYNAPSE**	**OSTRO**
Mean (SD) UPSIT, score	14.68 (8.7)	13.50 (8.20)	13.60 (7.60)	12.8 (7.9)	12.8 (7.6)	13.0 (6.8)[a]	NM
Mean (SD) UPSIT score, 24 wk	25.39 (9.49)	23.89 (9.21)	23.89 (9.21)	17.24 (0.84)	17.11 (0.83)	–	–
Mean (SD) UPSIT score, 40 wk	–	–	–	–	–	–	NM
Mean (SD) UPSIT score, 52 wk	–	–	–	–	–	NM	–
MD points (95%CI) vs placebo group	10.56 (8.79-12.34)	10.52 (8.98-12.07)	NM	3.81 (1.38-6.24)	3.86 (1.57-6.15)	0.4 (–1.49 to 2.28)[b]	NM
P Value	<.0001	<.0001	NM	.024	.0011	.30	NM
Mean (SD) LoS	2.70 (0.57)	2.73 (0.59)	2.81 (0.46)	2.5 (0.8)	2.6 (0.8)	9.60 (0.80)	NM
Mean (SD) LoS, 24 wk	1.35 (0.99)	1.55 (1.02)	NM	1.94 (0.09)	2.02 (0.10)	–	–
Mean (SD) LoS, 40 wk	–	–	–	–	–	6.80 (3.61)	NM
Mean (SD) LoS, 52 wk	–	–	–	–	–	–	–
MD points (95% CI) vs placebo group	–1.12 (–1.31 to –0.93)	–0.98 (–1.15 to 0.81)	NM	–0.33 (–0.6 to –0.06)	–0.45 (–0.73 to –0.16)	–0.37 (–0.65 to 0.08)	–0.22 (–0.36 to –0.07)
P value	<.0001	.0001	NM	.0161	.0024	.020	.0030

Abbreviations: LoS, loss of smell score (0-3); LoS VAS: loss of smell with visual analog scale (0-10); MD, mean difference; NM, not mentioned; UPSIT, University of Pennsylvania Smell Identification Test (0-40).
[a]UPSIT was performed on a subset of the population included (54 patients).
[b]At 52 weeks.

continued and were sustained, differing significantly from placebo through 52 weeks [19]. However, smell outcomes worsened after discontinuation of dupilumab [20]. Onset of the treatment effect with dupilumab was similar regardless of prior surgery, asthma, N-ERD, or allergic rhinitis [20].

Patients in SINUS-52 were stratified by eosinophilic chronic rhinosinusitis (ECRS) status according to the Japanese Epidemiological Survey of Refractory Eosinophilic Rhinosinusitis algorithm [21]. Improvement in smell was recorded at 24 weeks and persisted (measured by UPSIT), independent of ECRS status [22] (Tables 2 and 3).

3.1.2. Real-life studies of dupilumab

The first real-life experience with dupilumab was published in 2021. A 65-year-old man with asthma and CRSwNP who had undergone 7 FESS procedures experienced a partial but persistent recovery of his sense of smell (UPSIT of 25) after 6 months of treatment [23]. Napolitano et al [24] demonstrated a significant reduction in LoS score after 24 weeks in 19 patients with both atopic dermatitis and CRSwNP treated with dupilumab. In 2022, van der Lans et al [25] published findings from a prospective observational 131-patient cohort treated with dupilumab. The Sniffin' Sticks test was performed, showing significant improvement in smell at 24 weeks and 48 weeks. In a multicenter Italian prospective study of 82 patients with CRSwNP treated with dupilumab for 16 weeks, a significant impact was demonstrated in the LoS score (P<.001) and olfaction VAS (P<.001) [26]. Another prospective observational study performed over 16 weeks to observe the progress of patients with atopic dermatitis and CRSwNP revealed improvement in LoS (P<.05) [27] (Table 4).

3.2. Omalizumab

3.2.1. Clinical trials with omalizumab

In 2013, a phase 2 trial comparing dupilumab with placebo found a significant decrease in LoS (P=.004) in 24 patients with CRSwNP and comorbid asthma after 16 weeks of treatment, irrespective of allergy status [28]. In 2020, 2 replicated phase 3, randomized placebo-controlled trials (POLYP-1 and POLYP-2) evaluated the efficacy and safety of omalizumab and placebo in

Table 4. Real-life Studies of CRSwNP Patients Treated With Biologics.

	Dupilumab					Omalizumab		Mepolizumab			Benralizumab		Resli-zumab
Study [reference]	[23]	[24]	[25]	[26]	[27]	[32]	[33]	[37]	[38]	[39]	[43]	[44]	Not found
Number of patients	1	19	131	82	9	16	24	1	11	16	1	31	
Treatment, mo	6	4 and 6	6 and 12	4	4	12	6	4	17 (5)	6	Not defined	6	
Significant improvement in smell by scale	UPSIT (from 9 to 25)	LoS (from 1.9 (0.8) to 0.78 (0.8) at 16 wk and 0.46 (0.65) at 24 wk)	Sniffin' Sticks-12 (from 3.6 (2.1) to 7.3 (2.8) at 24 wk and 8.3 (3.2) at 48 wk)	LoS and VAS olfaction (from 3.0 (1.0) to 1.0 (2) and from 9.0 (2.0) to 2.0 (4.0)	LoS (from 1.6 (1) to 0.2 (0.4)	No improvement in smell (evaluated by question number 20 of the RSDI questionnaire)	VAS olfaction (from 8.50 (1.58) to 5.08 (3.42)	Patient assessment-method not defined	Method not described (from to 10 to 4 patients diagnosed as anosmic)	NAS olfaction (from 4 [5.1] to 2.4 [4.2])	Self-reported anosmia ("partial improvement in sense of smell") -method not defined	Patient's subjective perception of anosmia (yes/no) (anosmia disappeared in 31% patients)	
Comorbidities	100% Asthma	100% AD	Not defined	62% Asthma; 32% N-ERD	100% AD	100% Asthma	100% Asthma; 37% N-ERD	100% Asthma	100% Asthma	100% Asthma	100% Asthma; 100% eosinophilic otitis media	100% Asthma	

Abbreviations: AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyps; LoS, loss of smell score; N-ERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease; RSDI, Rhinosinusitis Disability Index.

CRSwNP. Sense of smell improved significantly at 24 weeks compared with placebo based on the LoS score (POLYP-1, *P*=.0161; and POLYP-2, *P*=.0024) and by UPSIT (POLYP-1, *P*=.024; and POLYP-2, *P*=.0011). Despite a significant improvement in smell, patients did not achieve normosmia [29]. Further analysis of POLYP-1 and POLYP-2 patients revealed that smell at 24 weeks had improved more with omalizumab than with placebo, independent of blood eosinophil count (≤300 or >300/μL), previous FESS, asthma, or N-ERD status [30]. In 2022, an open-label extension study was performed with an additional 28 weeks (total of 52 weeks), including 123 patients who continued omalizumab and 126 patients who switched treatment (from placebo to omalizumab). Improvements in the UPSIT score were maintained through 52 weeks in patients who continued with omalizumab. In patients who switched to omalizumab, improvements in UPSIT scores peaked at 3.88 points at 52 weeks. However, these scores are still within the range of anosmia. Omalizumab was withdrawn after the treatment period, and patients were observed for an additional 24 weeks. UPSIT scores gradually worsened [31] (Tables 2 and 3).

3.2.2. Real-life studies of omalizumab

In their real-world study performed in 2020, Ruiz-Hornillos et al [32] found no significant differences for smell (evaluated based on the question about smell of the Rhinosinusitis Disability Index questionnaire) after 12 months of treatment with omalizumab in 16 patients who received the drug for asthma with associated NP. Also in 2020, a multicenter, noninterventional, retrospective, observational, real-life study was performed in 24 patients with severe allergic asthma and CRSwNP treated with omalizumab. After 6 months of treatment, loss of smell improved significantly according to a VAS (*P*<.001) [33] (Table 4).

3.3. Mepolizumab

3.3.1. Clinical trials with mepolizumab

In 2011, Gevaert et al [34] reported an improvement in the VAS score for loss of smell in 20 patients treated with mepolizumab compared with placebo for 8 weeks, although this parameter did not reach statistical significance (*P*=.079). A subsequent randomized placebo-controlled trial of 105 patients with severe recurrent bilateral NP treated with mepolizumab for 24 weeks revealed an improvement in the VAS for loss of smell (*P*<.001) but not with the Sniffin' Sticks Screening-12 test score (*P*=.23) [35]. SYNAPSE is a phase 3 trial of mepolizumab for CRSwNP. At 52 weeks, the mean VAS symptom score for loss of smell revealed a statistically significantly reduction in the mepolizumab group compared with placebo (*P*=.02). However, this improvement was not found when olfaction was evaluated with UPSIT. Of note, greater improvements in loss of smell were found in patients with fewer previous surgeries [36] (Tables 2 and 3).

3.3.2. Real-life studies with mepolizumab

The first real-life report with mepolizumab involved a 62-year-old woman with severe uncontrolled atopic asthma and CRSwNP who recovered her sense of smell (patient assessment) after 4 months of treatment [37]. In Israel, Kassem et al [38] prospectively followed 11 patients presenting severe eosinophilic asthma and CRSwNP (10 with anosmia). After 17.4 (5.5) months of treatment with mepolizumab, 4 patients ceased to be anosmic. A retrospective study including 16 patients with asthma and CRSwNP who received mepolizumab reported reduced NAS in terms of loss of smell (*P*>.05) after 24 weeks [39] (Table 4).

3.4. Benralizumab

3.4.1. Clinical trials with benralizumab

Tversky et al [40] performed a randomized, placebo-controlled clinical trial with benralizumab in CRSwNP, with no significant change in UPSIT score compared with placebo at 20 weeks (*P*=.530). In 2021, a phase 2 trial with benralizumab in CRSwNP conducted in Japan revealed no change in smell assessed by VAS at 24 weeks of treatment [41]. OSTRO is a phase 3 trial that assessed benralizumab in CRSwNP. Sense of smell was assessed using the mean daily LoS score and UPSIT. At 40 weeks, the LoS score improved significantly against placebo (*P*=.003), although changes in sense of smell measured by UPSIT were not appreciably different between treatment groups [42] (Tables 2 and 3).

3.4.2. Real-life studies with benralizumab

Shimizu et al [43] reported the case of a 52-year-old woman with asthma, eosinophilic otitis media, recurrent eosinophilic CRSwNP, and self-reported anosmia who experienced partial improvement in sense of smell following therapy with benralizumab. Bagnasco et al [44] performed a real-life study of 34 patients with asthma and CRSwNP treated with benralizumab (26 reported having anosmia). Anosmia resolved in 31% (*P*=.0034) (Table 4).

3.5. Reslizumab

We found no placebo-controlled studies analyzing improvement of smell in patients with CRSwNP treated with reslizumab (Cinqair).

3.6. Comparisons Between Biologics

3.6.1. Meta-analyses

Peters et al [45] carried out a Bucher indirect treatment comparison of the efficacy of dupilumab and omalizumab vs placebo. In the intent-to-treat population, dupilumab led to significantly greater improvements from baseline to 24 weeks compared with omalizumab in the LoS score and UPSIT.

In 2021, Wang et al [46] performed a systematic review and network meta-analysis (NMA) to compare the efficacy of anti–IL-5 against placebo in CRSwNP. Seven randomized controlled trials (RCTs) assessed anti–IL-5 treatments. Unlike mepolizumab, benralizumab improved the UPSIT score [46]. Wu et al [47] conducted an NMA comparing 3 different biologics (dupilumab, omalizumab, and mepolizumab) with placebo for CRSwNP. Dupilumab had the best efficacy in terms of UPSIT for the surface under the cumulative ranking curve (SUCRA value of 1.000), followed by omalizumab (SUCRA 0.500).

Oykhman et al [48] conducted an NMA to compare the effects of biologics (dupilumab, omalizumab, mepolizumab, and benralizumab) and aspirin desensitization (ASA-D) for treatment of CRSwNP. Based on UPSIT the authors reported moderately certain evidence that, compared with placebo, dupilumab improved smell more than omalizumab, mepolizumab, benralizumab, and ASA-D.

In 2022, Cai et al [49] performed a Bucher indirect treatment comparison involving 7 RCTs with 4 biologics (dupilumab, omalizumab, mepolizumab, and benralizumab,). Dupilumab was more effective for improving loss of smell and UPSIT score than the other 3 biologics at 24 weeks of treatment and at the end of follow-up (more than 48 weeks).

3.6.2. Real-world studies

In 2021, Meier et al [50] retrospectively analyzed 29 patients with CRSwNP who received a biologic between 2014 and 2020 (6 benralizumab, 19 mepolizumab, and 20 omalizumab). Smell was evaluated based on the medical history and the most recent consultation and was classified into 5 categories: –2 (strong worsening), –1 (slight worsening), 0 (no change), +1 (slight improvement), and +2 (strong improvement). Sense of smell improved in 58.8% with mepolizumab, 34% with benralizumab, and 26% with omalizumab.

In 2021, Tiotiu et al [51] performed a binational, multicenter, observational, real-life study to retrospectively analyze data from 72 patients with severe asthma and CRSwNP treated with omalizumab, benralizumab, or mepolizumab for at least 6 months. The data analyzed included patient-assessed loss of smell in each treatment group. The study showed a statistically significant decrease in patients with loss of smell before and after all treatments, as follows: mepolizumab, 18 to 12 (P=.008); benralizumab, 16 to 11 (P=.001); and omalizumab, 33 to 21 (P<.001).

In 2022, a retrospective real-life observational study analyzed 8 patients with refractory eosinophilic otitis media, asthma, and CRSwNP in treatment with biologics (5 dupilumab, 1 omalizumab, 1 mepolizumab, and 1 benralizumab). A statistically significant difference was found with the Sniffin' Sticks 16-pen identification test (0-5 anosmia, 6-11 hyposmia, and 12-16 normosmia) (from 5.75 [4.62] to 11.13 [3.04] after 6 months of treatment) [52].

A multicenter, noninterventional, retrospective, observational study performed in 2021 included 206 patients with severe asthma and CRSwNP undergoing biological treatment with the following: omalizumab, 81 (39.3%); mepolizumab, 65 (31.6%); reslizumab, 14 (6.8%); and benralizumab, 46 (22.3%) [53]. Olfaction was evaluated before and after biological treatment (mean time of treatment, 1.9 to 5.8 years) according to 3 possible values: "partial improvement" (change from anosmia to hyposmia), "total improvement" (anosmia or hyposmia to normosmia), and "no improvement" (no improvement or deteriorated olfaction). Total or partial improvement in loss of smell was reported after treatment with all monoclonal antibodies (omalizumab [35.8%], mepolizumab [35.4%], reslizumab [35.7%], and benralizumab [39.1%]), and no differences between the groups were recorded. Partial improvement in smell (anosmia to hyposmia) was observed in patients who received omalizumab (16%), mepolizumab (22%), reslizumab (22%), and benralizumab (17%), with no differences between groups. Smell improved completely with omalizumab (20%), mepolizumab (14%), reslizumab (14%), and benralizumab (22%), again with no intergroup differences. A comparison of total improvement, partial improvement, and no improvement between patients with a high blood eosinophil count and patients with a low blood eosinophil count (500/μL) showed no statistical differences. The proportion of patients with improved olfaction was similar for the N-ERD group (37%) and the non–N-ERD group (35.7%) [53].

3.7. Risk of Bias

The quality of evidence in all the studies included was evaluated to determine the risk of bias. The articles were classified as being of low-, moderate-, or high-quality evidence according to the type of study/design and the number of questions in the corresponding checklist that were answered positive or negative using the Critical Appraisal Skills Programme approach. Single cases could not be evaluated with this system (see results in Table S2, Supplementary material).

Risk of bias for the 6 phase 3 trials included in this review (dupilumab [SINUS-24 and SINUS-52], omalizumab [POLYP-1 and POLYP-2], mepolizumab [SYNAPSE], and benralizumab [OSTRO]) was assessed by Cai et al [49] using the Cochrane Risk of Bias Tool for methodologic quality, which demonstrated that the overall risk was low in selection, performance, and reporting bias and high in attrition bias only in SINUS-52 and OSTRO, where there were disproportionally more discontinuations in the placebo arm.

4. Discussion

The biologic treatments approved for uncontrolled CRSwNP with INCS are dupilumab, omalizumab, and mepolizumab. Indirect comparisons by meta-analysis consistently conclude that dupilumab may have the highest efficacy in improving sense of smell. Dupilumab has demonstrated rapid and sustained long-term improvement in smell in clinical trials and real life. Omalizumab improves smell at 24 weeks, and the improvement is maintained in the long term, although it is not clinically relevant. Mepolizumab and benralizumab improve smell in the long term, as measured with a subjective scale. We found no studies regarding the improvement in smell in patients with CRSwNP treated with reslizumab.

Loss of or reduction in sense of smell is one of the most troublesome and difficult-to-treat symptoms in CRSwNP. Biologic treatments present an opportunity to address a subgroup of individuals with severe, nonresponsive CRSwNP, given that they act on targets of the T2 scale of inflammation, which is predominant in NP, especially when associated with asthma and/or N-ERD. Sense of smell has been included in criteria for both patient selection and response to biologics in recent international expert consensus statements from the European Forum for Allergy and Airway Diseases (EUFOREA) [9] and the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [1]. However, no

specific criteria have been established for the indication of one or the other biologic in CRSwNP.

Dupilumab provides a rapid (within 1 week) and lasting improvement in sense of smell (up to 52 weeks) [18,19] in patients with severe CRSwNP, regardless of the duration of NP, blood eosinophil count, serum total IgE, prior FESS, comorbid asthma, N-ERD or allergic rhinitis [20], and eosinophilic chronic rhinosinusitis status [22]. Therefore, it leads to a clinically relevant improvement, with more than 60% of patients with anosmia achieving an improvement in sense of smell by 24 weeks [19]. The improvement stops when dupilumab is withdrawn. The results of real-life studies with dupilumab are consistent with those of RCTs [23-27]. A study of the largest cohort to date (131 patients) revealed an improvement in smell at 24 weeks, as evaluated using a psychophysical test, the 12-item Sniffin' Sticks test [25].

Omalizumab improves smell evaluated by UPSIT and LoS score at 24 weeks, regardless of peripheral eosinophilia, prior FESS, asthma, and N-ERD [29,30]. However, although it produces an improvement in these smell scales, it does not achieve a clinically relevant improvement, and anosmia persists (UPSIT <19). UPSIT scores gradually worsened after discontinuation of omalizumab [31]. Experiences in real life are scarce and inconclusive [32-33].

Improved smell has been reported with mepolizumab based on a subjective scale (VAS) at 24 weeks and in the long term (52 weeks), although no improvement was recorded after a psychophysical test [36]. Real-life experiences include few patients (n=11-16) and report improvement in smell (assessed only with subjective tests) in the long term [37-39].

Benralizumab led to a significant improvement in smell based only on a subjective tool (LoS) and in the long term (40 weeks) [42]. The only relevant real-life study with this biologic includes 31 patients, of whom 31% ceased to be anosmic after treatment (as evaluated by the patient) [44]. No placebo-controlled studies regarding the improvement in smell in patients with CRSwNP treated with reslizumab were found.

An NMA including all the phase 3 trials of dupilumab, omalizumab, mepolizumab, and benralizumab conclude that dupilumab is the most effective and safe treatment route for CRSwNP when compared with the others at 24 weeks of treatment and at the end of follow-up [49]. Oykhman et al [48] also conclude in their NMA that dupilumab is more likely to improve smell than the other biologics and ASA-D. The overall risk of bias of the RCTs included in this review was low (Table S2). However, the comparison between them cannot be totally conclusive. Smell was evaluated using different tests with a different time interval for each biologic. None of the RCTs had as its primary goal to assess or extensively study the sense of smell. In addition, the methodology of all these studies does not allow the results for smell to be compared. Furthermore, although all these RCTs included patients with severe CRSwNP, they used different enrollment criteria and varied methods to assess baseline disease characteristics [54]. As expected, the differences in eligibility criteria led to differing baseline populations across the trials. The prevalence of comorbid asthma, which is associated with more severe loss of smell, was higher in SYNAPSE than in the SINUS, POLYP, and OSTRO trials. Blood eosinophil counts were also higher in SINUS, SYNAPSE, and OSTRO than in POLYP. These baseline discrepancies in disease characteristics complicate comparisons between the trial outcomes. Ideally, future studies need to use head-to-head comparisons, or, in the absence of this approach, will need to include comparable patient populations and standardized outcome measures [54]. The baseline characteristics of these phase 3 clinical trials can be consulted in Table 2. The abovementioned problems prevent direct comparison or completely conclusive data on improvement in smell with biologics.

There is no real-life direct comparison including all biologics in CRSwNP. Data from the largest cohort point to an improvement in smell after treatment with all monoclonal antibodies, namely, omalizumab (35.8%), mepolizumab (35.4%), reslizumab (35.7%), and benralizumab (39.1%), with no differences between groups, independent of the blood eosinophil count and the presence of N-ERD [53]. This is the only study to assess improvement in smell with reslizumab. In addition, it is one of the few studies in which changes in anosmia, hyposmia, and normosmia before and after treatment are assessed. For all treatments, only 20% of patients went from anosmia to recovery of the sense of smell [53]. However, in this study, smell was evaluated using only subjective tests, only Spanish patients were included, and no patients had been treated with dupilumab. Therefore, more real-life studies are needed to directly compare biologics, including dupilumab, based on an international population, and using a psychophysical tool in addition to subjective tests. The only real-life cohort that includes dupilumab is that of De Corso et al [52], who reported an improvement in smell, as assessed using the 16-pen Sniffin' Stick Test in 8 patients affected by refractory eosinophilic otitis media, asthma, and CRSwNP in treatment with dupilumab (5), omalizumab (1), mepolizumab (1), and benralizumab (1). However, given the small sample size, no comparison between biologics is described.

The recovery of smell observed in these trials supports the key role of T2 inflammatory processes in loss of smell in CRSwNP and suggests that this may be reversible with biologics. The fact that not all patients improve indicates that factors other than T2 inflammation contribute to the loss of smell. Dupilumab is the only biologic to achieve a relevant clinical improvement, reducing the percentage of anosmic patients to 60% at 24 weeks [19]. A similar percentage was maintained at 48 weeks (61%). However, no greater improvement in smell was observed with longer treatment times. No reduction in anosmic patients is reported with the other biologic. Even so, it appears that, again, the improvement from 24 weeks to 52 weeks with omalizumab and mepolizumab is not progressive, since UPSIT values remain similar. For both dupilumab and omalizumab, smell worsens after discontinuation of treatment.

In the European population, >85% of patients with CRSwNP present T2 inflammation [7]. Patients with CRSwNP who have a T2 endotype frequently present asthma or N-ERD and have more severe, symptomatic, and recurrent disease. Borish et al [54] suggest that if a study reports a higher prevalence of the T2 endotype, positive outcomes could be influenced by difficult-to-treat disease. Nevertheless, subsequent subgroup analysis of the improvement in sense of smell in the population treated with

dupilumab and omalizumab showed that the favorable outcomes in sense of smell were unaffected by the presence of comorbid asthma and/or N-ERD [19,20,30]. The effect of the type T2 vs non-T2 endotype on the response to dupilumab was assessed in a Japanese subgroup: a comparison of outcomes between noneosinophilic/mild eosinophilic disease and moderate/severe disease did not reveal a better response to dupilumab [22].

Blood eosinophilia is yet another feature considered a possible biomarker of improvement after treatment with biologics. SINUS-52 showed that the improvement in smell during treatment with dupilumab was unaffected by blood eosinophil count [19]. Similarly, POLYP-1 and POLYP-2 demonstrated that omalizumab improves the UPSIT score independently of baseline eosinophil counts [30]. Therefore, blood eosinophil level may not be a suitable biomarker of the efficacy of dupilumab or omalizumab in CRSwNP. In SYNAPSE, no comparison was made between patients with different cut-offs for blood eosinophils, although the study does mention a predictive model for calculating the median change in the VAS score for nasal obstruction, predicting that a larger predictive effect could be seen in patients with higher blood eosinophil values; however, the authors recognize the need for further analysis [36]. No mention is made of blood eosinophils or outcomes in sense of smell [36]. The subgroup analyzed in the OSTRO study did not assess this outcome [42].

Data from SINUS-24/SINUS-52 and POLYP-1/POLYP-2 indicate that the improvement in smell with dupilumab and omalizumab does not depend on previous FESS. SYNAPSE did not evaluate as such the differences between patients who had and had not undergone surgery because all the patients included had previously undergone nasal surgery.

New molecules with the potential to improve smell are currently under development in CRSwNP. Tezepelumab is a human IgG2λ monoclonal antibody that inhibits the action of thymic stromal lymphopoietin (TSLP), a cytokine primarily expressed by airway epithelium and released in response to environmental factors, triggering various inflammatory processes. Evidence suggests that TSLP is a key factor in the pathophysiology of chronic inflammatory airway diseases, promoting eosinophilic (allergic and nonallergic) inflammation, noneosinophilic inflammation, and airway structural changes through its effects on a variety of adaptive and innate immune cells and epithelial cells. Tezepelumab was first approved in 2021 as add-on maintenance treatment for patients aged ≥12 years with severe asthma in the USA and is undergoing clinical development for the treatment of CRSwNP.

5. Conclusion

Currently approved biologics for combination with INCS in uncontrolled CRSwNP comprise dupilumab, omalizumab, and mepolizumab. Indirect comparisons by meta-analysis consistently conclude that dupilumab may have the highest efficacy in improving sense of smell. However, the methodology of these studies does not enable comparison of smell outcomes. Ideally, future studies should be head-to-head comparisons, or, in the absence of this approach, should include comparable patient populations and standardized outcome measures.

While the overall risk of bias affecting the studies included in this review was low, the evidence included remains highly diverse owing to the variability in enrollment criteria, the different methods to assess baseline disease characteristics, and the numerous tests used in the evaluation of smell. Consequently, any comparison between them cannot be totally conclusive. Furthermore, it is important to note that this review only includes publications up to June 2022, with the result that it may not include all the evidence available at the time of publication.

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Conflicts of Interest

J.S. reports the following: having served as a consultant to Thermo Fisher, MEDA, Novartis, Sanofi, Leti, FaesFarma, Mundipharma, and GSK; having been paid lecture fees by Novartis, GSK, Stallergenes, Leti, Sanofi, and FaesFarma; and having received grant support for research from Thermo Fisher, Sanofi, and ALK. B.B. reports having received personal lecture fees from Roxall, outside the submitted work. D.B. reports having received grant support for research from Instituto Carlos III and having served as a consultant to Astra Zeneca. M.V.M. has served as a consultant for Organon and has received fees for lectures from GSK and Astra Zeneca. The remaining authors declare that they have no conflicts of interest.

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Diana Betancor
Allergy Department
Hospital Universitario Fundación Jiménez Díaz
Avenida Reyes Católicos, 2
28040, Madrid, Spain
E-mail: diana.betancor@quironsalud.es