

**Smell improvement in chronic rhinosinusitis with nasal polyps with monoclonal antibodies: a systematic review**

**Running title:** Review of smell in CRSwNP with biologics

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## ABSTRACT

**Background:** Smell impairment is more commonly related to chronic rhinosinusitis with nasal polyps (CRSwNP) than without, especially given associated asthma and/or NSAID-exacerbated respiratory disease and type 2 inflammation. 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. Inclusion criteria were: adult patients with CRS treated with dupilumab, omalizumab, mepolizumab, benralizumab or reslizumab; studies published in English reporting outcomes in sense of smell using a psychophysical and/or subjective tools. Exclusion criteria covered reports that did not assess CRSwNP, smell loss evaluated with a different method according to mentioned inclusion criteria, review articles and expert opinion. No source of funding is available.

**Results:** Dupilumab has demonstrated rapid and sustained long-term improvement in smell in clinical trials and real-life. Omalizumab improves smell at 24w with a long-term maintenance but do not reach clinically relevant improvement. Mepolizumab and benralizumab improved smell at long-term measured with a subjective scale. No studies regarding the improvement of smell in patients with CRSwNP treated with reslizumab were found. Indirect comparisons by meta-analysis consistently conclude that dupilumab is the most effective biologic to improve the sense of smell.

**Conclusion:** Dupilumab may have the highest efficacy in improving sense of smell, compared to 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.

## INTRODUCTION

Chronic rhinosinusitis (CRS) is a common disease characterised by inflammation of the nose and paranasal sinuses. In adults, it is characterised by 2 or more symptoms, consisting of either nasal blockage/obstruction/congestion or discharge (anterior/posterior nasal drip)  $\pm$  facial pain/pressure  $\pm$  reduction/loss of smell lasting over 12w (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 are differentiated based on presence of associated nasal polyposis (NP) on nasal endoscopy and/or computed tomography (CT) scan: CRSwNP (with NP) and CRSsNP (without NP) [1]. The prevalence of CRSwNP in European countries is around 1.8 to 2.7% [4]. Nevertheless, most of these patients are not being referred to specialized clinics [5]. Approximately 67-78% of subjects with CRSwNP experience olfactory dysfunction [6]; which is the symptom that most affects the quality of life of these patients [1]. To evaluate the smell, subjective tests are useful but they should not be undertaken in isolation given its poor accuracy so association with psychophysical tests, which provide a more reliable assessment of olfactory function, is strongly recommended (*see Supplementary material*). A sense of smell impairment (hyposmia when partial and anosmia indicating total loss) is more commonly related to CRSwNP than CRSsNP, with asthma and/or nonsteroidal antiinflammatory 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, characterised by local eosinophilic inflammation with high production of eosinophil cationic protein, IL-4, IL-5, IL-13, and local immunoglobulin E (IgE) [7]. T2 inflammation leads to olfactory epithelium shedding and olfactory sensory neurons (OSN) degeneration as potential causes of the loss of smell [8]. Anti-inflammatory therapy potentially reduces olfactory cleft inflammation and induces basal stem cells proliferation and OSN regeneration, causing the partial or total recovery of the sense of smell [8].

Most subjects 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 low and not related to disease severity [5]. Many patients with refractory disease will require functional endoscopic sinus surgery (FESS) to alleviate their symptoms; despite this, 79% develop 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 to improve results on smell recovery.

The European Medicines Agency (EMA) and Food and Drug Administration (FDA) have approved the use of 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 do not provide adequate disease control [9]. Dupilumab (Dupixent®) is a fully human monoclonal antibody binding to the IL-4  $\alpha$  receptor, which inhibits signaling of IL-4 and IL-13, therefore blocking the pathways leading to differentiation of B cells into IgE production and eosinophil activation underlying the T2 inflammatory mechanism. Omalizumab (Xolair®) is a recombinant humanized immunoglobulin-G1 $\kappa$  monoclonal antibody that selectively binds to the C $\epsilon$ 3 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 (Fc $\epsilon$ RI) on the surface of mast cells, basophils, and dendritic cells, thereby interfering with activation. The increased local production of IgE in patients with CRSwNP indicates that this drug hold potential. Mepolizumab (Nucala®) is an IgG1 kappa monoclonal antibody that antagonizes interleukin-5, causing a decrease in airway eosinophils. Other anti-IL 5 drugs (benralizumab, reslizumab), although with potential action on CRSwNP, have not been approved with this indication.



### ***Objective of the study***

The objective of this study was to do a systematic revision to summarize current knowledge on the effect of biologics on olfaction in patients with CRSwNP.

## METHODS

This systematic review was reported in accordance to the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) [10]. The search was performed using PubMed (which includes MEDLINE) and Cochrane databases establishing a publication timeframe 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 were subjects with CRSwNP received biologic treatments (dupilumab, omalizumab, mepolizumab, benralizumab and reslizumab) and Mesh terms and keywords were mentioned in the title or abstract, it was restricted to human studies, to include only English language and 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 (see Table 1). The population was constituted by 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 the beginning of the treatment in the sense of smell measured with 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], T&T olfactometer [15]); and/or subjective test: daily diary of sense of smell, loss of smell score (LoS), visual analogue scale (VAS) or numerical analogue scale (NAS), and/or Likert scale (see Table S1, Supplementary material). The search protocol was not registered.

Studies were included if they met the following criteria: (1) population: human studies; (2) performed on adult patients ( $\geq 18$  years old) with CRS; (3) intervention and comparison: studies comparing human monoclonal antibodies (dupilumab, omalizumab, mepolizumab, benralizumab or reslizumab) with a placebo; (4) case reports or series of subjects with CRS who were treated with human monoclonal antibodies (dupilumab, omalizumab, mepolizumab, benralizumab or reslizumab); (5) meta-analysis studies; (6) written and published in English language; (7) studies reporting outcomes in sense of smell using: psychophysical (UPSIT, Sniffin' Sticks, T&T olfactometer) or psychometric instruments (daily diary of sense of smell, LoS, VAS or NAS).

Exclusion criteria covered publication languages other than English, reports that did not assess CRSwNP, did not assess smell loss, smell loss evaluated with a different method according to mentioned inclusion criteria, review articles and expert opinion. Publications where loss of smell was assessed just by Sinonasal Outcome Test (SNOT-22) test [16], which only includes a question about smell, were excluded.

For selection process and data extraction, the titles and abstracts of the retrieved articles were screened for their potential relevance by one reviewer. The full-text articles were then obtained and assessed by the three 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 (subject's 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 included studies 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 study design/methodology and outcomes/results, using the appropriate checklist depending on the type of study. The articles were classified as low, moderate, or high-quality evidence according to the type of study/design and the number of questions in the corresponding checklist that answered positive or negative. Single cases could not be evaluated with this system (see Table S2, Supplementary material).

## RESULTS

The search obtained 648 results from January 2001 to June 2022. Seventeen records were removed because they were written in another language that was not English, 437 were excluded by human review of title/abstract, 8 did not assess CRS, 96 did not assess smell loss, 8 were excluded because smell loss was evaluated with a different method according to mentioned criteria and 46 studies were removed for being review articles or expert opinion.

After the selection process, only 36 were included. *Figure 1* contains a PRISMA diagram showing in detail the workflow of the screening process [10]. 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 on CRSwNP on the smell impairment measured by one the previously mentioned tests. The details of the included studies are included in table S4 of the *Supplementary material*.

## 1. DUPILUMAB

### 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 24w, evaluated by UPSIT ( $p < 0.0001$ ) and by LoS score ( $p < 0.0001$ ) [17,18]. The proportion of patients with anosmia in the dupilumab group declined from 78% at baseline to 45% at 2week and 28% at 24w (both  $p < 0.0001$ ). In the placebo group, the proportion of patients who were anosmic was unchanged at 24w relative to baseline [18]. Post hoc analysis of SINUS-24 and SINUS-52 concluded that dupilumab produce rapid improvements in sense of smell: in 3 days if evaluated by LoS score ( $p < 0.05$ ), 2w with UPSIT ( $p < 0.0001$ ) and 8w with SNOT-22 item “decreased sense of smell/taste” ( $p < 0.0001$ ). Improvements with dupilumab continued and were sustained and it remained significantly different to placebo through 52w [19]. However, smell outcomes worsened after discontinuation of dupilumab [20]. Onset of treatment effect with dupilumab was similar regardless of prior surgery, asthma, N-ERD or allergic rhinitis [20]. Patients of SINUS-52 were stratified by eosinophilic chronic rhinosinusitis (ECRS) status according to the Japanese Epidemiological Survey of Refractory Eosinophilic Rhinosinusitis algorithm [21]. Improvement at 24w and maintained in smell (measured by UPSIT) was independent of their ECRS status [22]. See tables 2 and 3.

### 1.2 Real-life studies of dupilumab

The first real-life experience with dupilumab was published in 2021. A 65-year-old male with asthma and CRSwNP who had undergone 7 FESS experienced a partial but persistent recovery of the loss of smell (UPSIT of 25) after 6 months of treatment [23]. Napolitano et al. demonstrated a significant



reduction in LoS score after 24w in 19 patients with both atopic dermatitis (AD) and CRSwNP treated with dupilumab [24]. In 2022, Lans et al. published findings from a prospective observational 131-patient cohort treated with dupilumab. Sniffin' Sticks was performed, showing significant improvement in smell at 24w and 48w [25]. In a multicenter Italian prospective study, who followed 82 patients with CRSwNP treated with dupilumab for 16w, a significant impact in LoS ( $p<0.001$ ) and olfaction VAS ( $p<0.001$ ) was demonstrated [26]. Another prospective observational study was performed for 16w to observe the evolution of subjects with AD and CRSwNP. Improvement in LoS ( $p<0.05$ ) was demonstrated [27]. See table 4.

## 2. OMALIZUMAB

### 2.1. Clinical trials with omalizumab

In 2013, a phase 2 trial with dupilumab vs placebo found a significant decrease in LoS ( $p=0.004$ ) in 24 patients with CRSwNP and comorbid asthma after 16w 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 vs placebo in CRSwNP. Sense of smell significantly improved at 24w vs placebo, evaluated by LoS score (POLYP-1:  $p=0.0161$ ; and POLYP-2:  $p=0.0024$ ) and by UPSIT (POLYP-1:  $p=0.024$ ; and POLYP 2-  $p=0.0011$ ). Although there was significant improvement of smell, patients did not achieve normosmia [29]. Further analysis of POLYP-1 and POLYP-2 patients revealed that improved smell at 24w was superior with omalizumab than placebo, independent of their blood eosinophil count ( $\leq 300$  or  $>300$  cells/ $\mu$ L), previous FESS, asthma or N-ERD status [30]. In 2022, an open-label extension (OLE) study was performed with an additional 28w (a total of 52w), including 123 patients who continued omalizumab and 126 patients who switched treatment (from placebo to omalizumab). Improvements in UPSIT score were maintained through 52w in patients who continued with omalizumab. In patients who switched to omalizumab, improvements in UPSIT scores peaked at 3.88 points at 52w. However, these scores are still within the range of anosmia. Omalizumab was withdrawn after the treatment period, and patients were observed for an additional 24w. UPSIT scores gradually worsened [31]. See tables 2 and 3.

## 2.2 Real-life studies of omalizumab

In 2020, Ruiz-Hornillos et al. found, under real-life conditions, no significant differences for smell (evaluated by question about smell of the Rhinosinusitis Disability Index -RSDI- questionnaire) after 12 months of treatment with omalizumab in 16 patients who received it for asthma with associated NP [32]. Also in 2020, a multicenter, non-interventional, retrospective, observational, real-life study was performed on 24 patients with severe allergic asthma and CRSwNP treated with omalizumab. After 6 months of treatment, loss of smell improved significantly, evaluated by VAS ( $p < 0.001$ ) [33]. See table 4.

## 3. MEPOLIZUMAB

### 3.1 Clinical trials with mepolizumab

In 2011, Gevaert et al. described an improvement in the VAS score of loss of smell, in 20 subjects treated with mepolizumab vs placebo for 8w, although this parameter did not reach statistical significance ( $p = 0.079$ ) [34]. After that, a randomized placebo-controlled trial was performed on 105 subjects with severe recurrent bilateral NP treated with mepolizumab during 24w. An improvement was observed in the VAS for loss of smell ( $p < 0.001$ ) but not with Sniffin' Sticks Screening-12 test score ( $p = 0.23$ ) [35]. SYNAPSE is the phase 3 trial with mepolizumab for CRSwNP. At 52w the mean loss of smell VAS symptom score revealed a statistically significantly reduction of in the mepolizumab group in comparison with placebo ( $p = 0.02$ ). However, this improvement was not found when evaluating olfaction with UPSIT. Of note, greater improvements in loss of smell were found in patients with fewer previous surgeries [36]. See tables 2 and 3.

### 3.2. Real-life studies of mepolizumab

The first real-life report with mepolizumab was about a 62-year-old female with severe uncontrolled atopic asthma and CRSwNP who recovered her sense of smell (patient assessment) after 4 months with treatment [37]. In Israel, Kassem et al. prospectively followed 11 subjects presenting severe eosinophilic asthma and CRSwNP (10 with anosmia). After 17.4 ( $\pm 5.5$ ) months of treatment with mepolizumab, 4 patients ceased to be anosmic [38]. A retrospective study including 16 subjects with

asthma and CRSwNP who received mepolizumab reported reduced NAS regarding loss of smell ( $p>0.05$ ) after 24w[39]. See table 4.

#### 4. BENRALIZUMAB

##### 4.1 Clinical trials with benralizumab

Tversky et al. performed a randomized, placebo-controlled clinical trial with benralizumab in CRSwNP, with no significant change in UPSIT score compared with placebo at 20w ( $p=0.530$ ) [40]. In 2021, a phase 2 trial with benralizumab in CRSwNP was conducted in Japan, in which there was no change in smell assessed by VAS at 24w of treatment [41]. OSTRO is the phase 3 trial with benralizumab in CRSwNP. Sense of smell was assessed using mean daily LoS score and UPSIT. At 40w, LoS showed significant improvement against placebo ( $p=0.003$ ), though changes in sense of smell measured by UPSIT were not appreciably different between treatment groups [42]. See tables 2 and 3.

##### 4.2 Real-life studies of benralizumab

Shimizu et al. described a 52-year-old woman with asthma, eosinophilic otitis media, and recurrent eosinophilic CRSwNP with self-reported anosmia who experienced partial improvement in sense of smell following therapy with benralizumab [43]. Bagnasco et al. performed a real-life study of 34 patients with asthma and CRSwNP treated with benralizumab (26 reported having anosmia). Anosmia disappeared in 31% patients ( $p=0.0034$ ) [44]. See table 4.

#### 5. RESLIZUMAB

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

## 6. COMPARISONS BETWEEN BIOLOGICS

### 6.1. Meta-analysis

Peters et al. carried out a Bucher indirect comparison (ITC) of the efficacy of dupilumab and omalizumab vs placebo. In the intent to treat population, dupilumab had significantly greater improvements from baseline to 24w vs omalizumab across LoS score and UPSIT [45].

In 2021, another systematic review and network meta-analysis (NMA) was conducted by Wang et al. to evaluate the efficacy of anti-IL-5 vs placebo in CRSwNP. Seven randomized controlled trials (RCTs) assessing anti-IL-5 treatments. Benralizumab improved the UPSIT score but not mepolizumab [46]. Wu et al. conducted a NMA comparing 3 different biologics (dupilumab, omalizumab, and mepolizumab) vs placebo for CRSwNP. Dupilumab had the best efficacy in terms of UPSIT for surface under the cumulative ranking curve (SUCRA value of 1.000), followed by omalizumab (SUCRA 0.500) [47].

Oykhman et al. conducted a NMA to compare effects of biologics (dupilumab, omalizumab, mepolizumab, benralizumab) and aspirin desensitization (ASA-D) for treatment of CRSwNP. Compared to placebo, as measured by UPSIT, there was moderate certainty evidence that dupilumab likely improves smell compared to omalizumab, mepolizumab, benralizumab, and ASA-D. [48].

In 2022, Cai et al. performed a Bucher indirect treatment comparison involving 7 RCTs with four biologics (dupilumab, omalizumab, mepolizumab and benralizumab.). Dupilumab demonstrated better effects in improving loss of smell and UPSIT score compared to the other 3 biologics at 24w of treatment and at the end of follow-up (more than 48w) [49].

### 6.2 Studies in real-life conditions

In 2021, Meier et al. 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 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% benralizumab, and 26% with omalizumab [50].

In 2021, Tiotiu et al. performed a binational, multicenter, observational, real-life study, retrospectively analyzing data from 72 patients with severe asthma and CRSwNP treated with omalizumab, benralizumab, or mepolizumab for at least 6 months. Data analyzed included patient-assessed loss of smell in each treatment group. The study showed a statistically significant decrease in the subjects with loss of smell before and after all treatments: mepolizumab (18 to 12,  $p=0.008$ ), benralizumab (16 to 11,  $p=0.001$ ), and omalizumab (33 to 21,  $p<0.001$ ) [51].

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

In 2021, a multicenter, non-interventional, retrospective, observational study was performed, including 206 patients with severe asthma and CRSwNP undergoing biological treatment: 81 (39.3%) omalizumab, 65 (31.6%) mepolizumab, 14 (6.8%) reslizumab, and 46 (22.3%) benralizumab [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). A total or partial improvement in loss of smell was found after treatment with all monoclonal antibodies: omalizumab (35.8%), mepolizumab (35.4%), reslizumab (35.7%), and benralizumab (39.1%), with no differences between groups. Partial smell improvement (anosmia to hyposmia) was observed in subjects administered omalizumab (16%), mepolizumab (22%), reslizumab (22%), and benralizumab (17%), with no differences between groups. Total smell improvement was reached in therapy with omalizumab (20%), mepolizumab (14%), reslizumab (14%), and benralizumab (22%), also with no inter-group differences. A comparison of total improvement, partial improvement, and no improvement between subjects with high vs low blood eosinophil count ( $500/\mu\text{L}$ ) showed no statistical differences. The proportion of patients with improved olfaction was similar between the N-ERD (37%) and non-N-ERD (35.7%) groups [53].

## 7. RISK OF BIAS

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

Risk of bias of the 6 phase III trials included in this revision [dupilumab (SINUS-24 and SINUS-52), omalizumab (POLYP-1 and POLYP-2), mepolizumab (SYNAPSE) and benralizumab (OSTRO)] were 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 just high in attrition bias among SINUS-52 and OSTRO, where there was disproportionately more discontinuations in the placebo arm.

## **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 24w with a long-term maintenance but do not reach clinically relevant improvement. Mepolizumab and benralizumab improved smell at long-term measured with a subjective scale. No studies regarding the improvement of smell in patients with CRSwNP treated with reslizumab were found.

Loss 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 severe and unresponsive subgroup of individuals with 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 provide rapid (within 1w) and lasting (up to 52w) [18, 19] improvement in sense of smell in patients with severe CRSwNP, regardless of NP duration, blood eosinophil count, serum total IgE, prior FESS, comorbid asthma, N-ERD or allergic rhinitis [20], and ERSC status [22]. Therefore, it gets a clinically relevant improvement, with more than 60% of patients with anosmia achieving improvement in sense of smell by 24w [19]. The improvement stops when dupilumab is withdrawn. The results of real-life studies with dupilumab are consistent with those of RCTs [23-27]. The largest cohort, with 131 patients, finds smell improvement at 24w evaluated with a psychophysical test, Sniffin' Sticks-12 [25].

Omalizumab improves smell evaluated by UPSIT and LoS score at 24w, 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 patients persist in anosmia range (UPSIT <19). UPSIT scores gradually worsened after discontinuation of omalizumab [31]. Experiences in real-life are scarce and inconclusive [32-33].

Mepolizumab has demonstrated improved smell with a subjective scale (VAS) at 24w and at long-term (52w) but it has not demonstrated improvement in smell assessed with a psychophysical test [36]. Real-life experiences include few patients (n=11-16), and find improvement in smell (assessed only with subjective tests) in the long term [37-39].

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

NMA including the 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 24w of the treatment and end of follow-up [49]. Oykhman et al. also conclude in

their NMA that among biologics and ASA-D, dupilumab likely improves smell compared to the others therapies [48]. The overall risk of bias of the RCTs included in this revision was low (Table S2). However, the comparison between them cannot be totally conclusive. The evaluation of smell was carried out through different tests and in 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. Further, the methodology of all these studies does not allow comparing the results in smell. Furthermore, although all these RCTs have included patients with severe CRSwNP, they have 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. Prevalence of comorbid asthma, which is associated with greater severity of 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 compared with 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. All this prevents making a direct comparison or obtaining completely conclusive data on the improvement of smell with biologics.

There is no real-life direct comparison which includes all biologics in CRSwNP. The largest cohort describes an improvement in smell after treatment with all monoclonal antibodies: 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 that assesses smell improvement with reslizumab. In addition, it is one of the few studies in which changes in anosmia, hyposmia, and normormia before and after treatment are assessed. For all treatments, only 20% of patients went from anosmia to smell recovery [53]. However, in this study, the evaluation of smell was performed only by subjective test, only includes Spanish population and does not include patients treated with dupilumab, so more studies are needed in real-life with direct comparison of the biologics that include dupilumab, that includes international population and that uses, in addition to a subjective test, a psychophysical tool. The only real-life



cohort that includes dupilumab is that of De Corso et al., which finds a smell improvement assessed by Sniffin stick test-16 in 8 patients affected by refractory eosinophilic otitis media, asthma and CRSwNP in treatment with dupilumab (5), omalizumab (1), mepolizumab (1) and benralizumab (1) but, due to the small sample size, no comparison between biologics is described [52].

The smell recovery observed in these trials support the key role of T2 inflammatory processes in smell loss in CRSwNP, and suggests that loss of smell may be reversible with biologics. The fact that not all patients improve seems to mean that there may also be factors other than T2 inflammation that contribute to the loss of smell. Dupilumab is the only one biologic which achieves a relevant clinical improvement, reducing the percentage of anosmic patients (60% at 24w) [19], that remains similar (61%) at 48w, showing that the longer the treatment time there is no greater improvement in smell. With the other biological, reduction in anosmic patients is not described. Even so, it appears that the improvement from 24w to 52w with omalizumab and mepolizumab is also not progressive, since UPSIT values remain similar. For both, dupilumab and omalizumab, a worsening in smell after discontinuation of treatment is described.

In the European population, >85% of patients with CRSwNP present T2 inflammation [7]. Subjects with CRSwNP who have a T2 endotype frequently present asthma or N-ERD and have a more severe, symptomatic, and recurrent disease. Borish et al. suggest that if a study has a higher prevalence of the T2 endotype, positive outcomes could be influenced by a difficult-to-treat disease [54]. Nevertheless, subsequent subgroup analysis of the improvement in sense of smell of 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]. Another issue related to type T2 vs non-T2 endotype and how this could influence the response to dupilumab was assessed in the Japanese subgroup population: a comparison of outcomes between non/mild eosinophilic disease and moderate/severe disease did not cause a better response to dupilumab [22].

Another feature considered as a possible biomarker of improvement after treatment with biologics is blood eosinophilia. SINUS-52 showed that the improvement in smell during dupilumab treatment was unaffected by blood eosinophil count [19]. Similarly, POLYP-1 and POLYP-2 demonstrated that omalizumab improves UPSIT score independently of baseline eosinophil counts [30]. Therefore,

blood eosinophil level may not be a suitable biomarker for dupilumab or omalizumab efficacy in CRSwNP. In SYNAPSE, no comparison was performed between subjects with different cut-offs for blood eosinophils, but the study does mention a predictive model for calculating the median change for nasal obstruction VAS, predicting that subjects with higher blood eosinophils could show a larger predictive effect, though the authors recognize the need for further analysis [36]. No mention is made of blood eosinophils and outcomes in sense of smell [36]. The subgroup analyses in the OSTRO study did not assess this outcome [42].

On the other hand, the data of SINUS-24/SINUS-52 and POLYP-1/POLYP-2 indicate that the improvement of smell with dupilumab and omalizumab does not depend on previous FESS. SYNAPSE does not evaluate as such the differences between operated and non-operated patients because 100% of the included patients had had previous nasal surgery.

Currently, new molecules with the potential to improve smell are under development in CRSwNP. Tezepelumab is a human IgG2 $\lambda$  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 an important factor in the pathophysiology of chronic inflammatory airway diseases, promoting eosinophilic (allergic and non-allergic) inflammation, non-eosinophilic inflammation, and airway structural changes through its effects on a variety of adaptive and innate immune cells and epithelial cells. Tezepelumab received its first approval on 2021 as an add-on maintenance treatment for patients aged  $\geq 12$  years with severe asthma in the USA and it is undergoing clinical development for the treatment of CRSwNP.

## CONCLUSION

To date, 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 but the methodology of these studies does not allow comparing the results in smell. 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.

Despite the overall risk of bias of the studies included in this revision was low, the included evidence is highly diverse due to the variability in enrollment criteria, varied methods to assess baseline disease characteristics and the different tests used in the evaluation of smell so the comparison between them cannot be totally conclusive. Furthermore, it is important to note that this review only includes publications up to June 2022 therefore it may not include all the evidence available at the time of its publication.

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### **Conflict of interest**

J.S. reports having served as a consultant to Thermofisher, MEDA, Novartis, Sanofi, Leti, FaesFarma, Mundipharma, and GSK; having been paid lecture fees by Novartis, GSK, Stallergenes, Leti, Sanofi, and FaesFarma; as well as having received grant support for research from Thermofisher, Sanofi, and ALK. B.B. reports having received personal lecture fees from Roxall outside of 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 honoraries for lectures from GSK and Astra Zeneca. The other authors declare no conflicts of interest.

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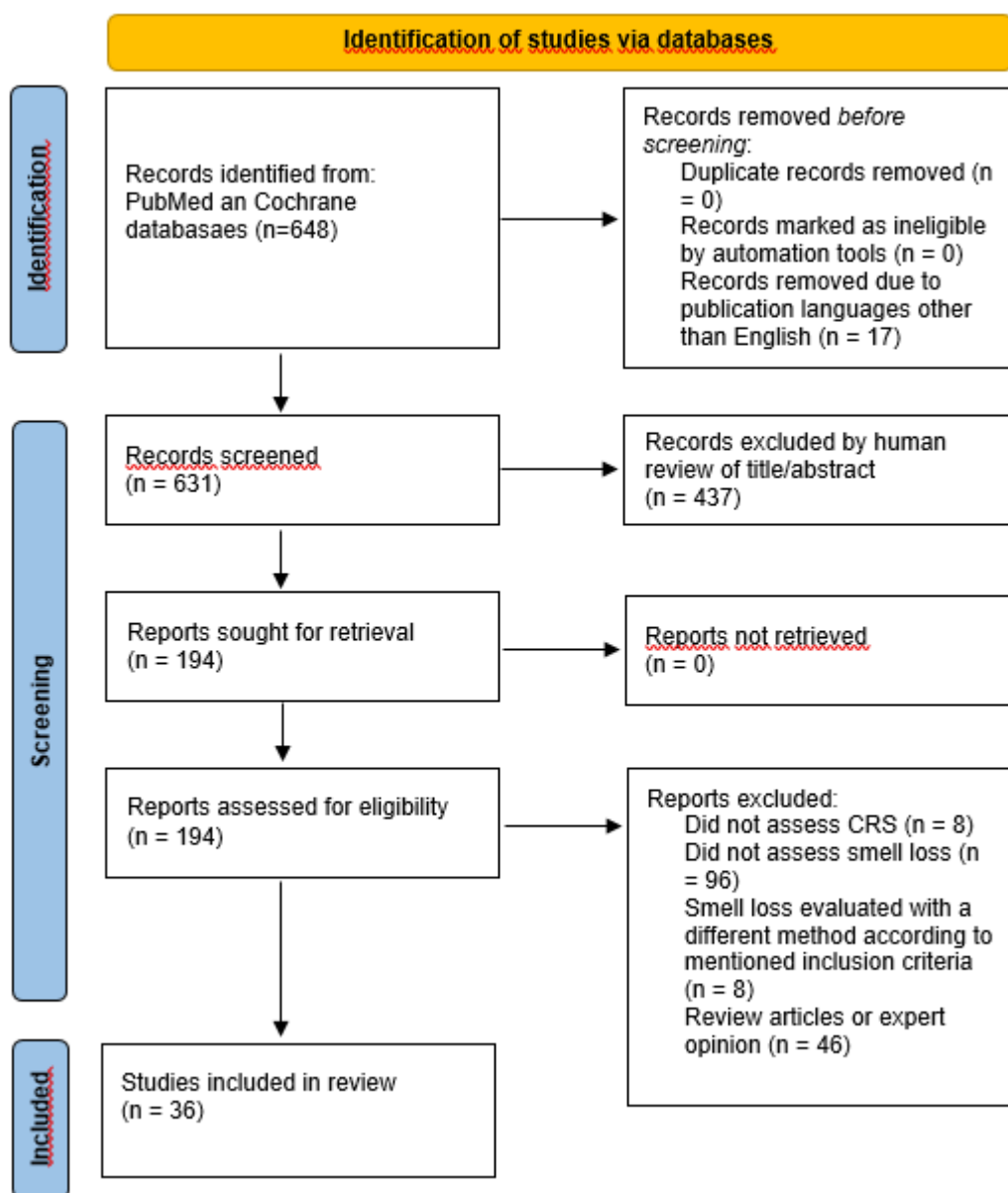
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Figure. PRISMA flow diagram for the systematic review





**Table 1. Search strategy.**

<b>Search strategy: #1 AND #2 AND #3</b>		
<b>Code</b>	<b>Term</b>	<b>Synonyms</b>
<b>#1</b>	Chronic rhinosinusitis with nasal polyps	Nasal Polyps OR nasal polyp OR Sinusitis OR sinusitis OR sinus infection OR Rhinitis OR rhinitis OR nasal catarrh OR Chronic Rhinosinusitis with nasal polyp OR CRSwNP OR nasal polypos OR chronic rhinosinusitis OR smell
<b>#2</b>	Smell impairment	OR olfaction OR nasal polyp AND impairment OR dysfunction OR alteration OR disorder OR loss
<b>#3</b>	Biological treatment	Omalizumab OR benralizumab OR reslizumab OR mepolizumab OR dupilumab

**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 300mg q2w (1:1)	Placebo vs dupilumab 300mg q2w vs dupilumab 300mg q2w until week 24 nd 300mg q4w until week 52 (1:1:1)	Placebo vs Omalizumab 75-600mg q2-4w (depending on the pretreatment serum total IgE level and body weight)	Placebo vs Omalizumab 75-600mg q2-4w (depending on the pretreatment serum total IgE level and body weight)	Placebo vs Mepolizumab 100 q4w	Placebo vs Benralizumab 30mg q4w for the first 3 doses then 30mg q8w
Sizepopulation (n)	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 (weeks)	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%; ≥ 2previous surgery: 24% vs 22%	1 previous surgery: 23% vs 35.5%; ≥ 2previous 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)

<b>Bilateral endoscopic NP score* (scale 0–8); mean (SD)</b>	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)
<b>Smell at baseline</b>	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)
<b>Baseline blood eosinophils (× 10<sup>9</sup> cells per L)</b>	0.44 (0.31) vs 0.44 (0.35)		0.45 (0.36) vs 0.40 (0.30) vs 0.45 (0.39)	358.6 (305.2) vs 334.4 (264.7)	357.4 (196.2) vs 310.8 (176.6)	400 (0.91) vs 390 (0.88)	400.0 (80. 1710) vs 375.0 (40. 3670)
<b>Baseline total IgE (IU/mL)</b>	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
<b>Anosmia (UPSIT&lt;18) decreased</b>	From 74% to 24% at week 24		From 79% to 30% at week 24	unavailable	unavailable	unavailable	unavailable

**Table 3. Comparison in UPSIT and loss of smell score (LoS) between phase 3 studies.**

Phase 3 study	Dupilumab			Omalizumab		Mepolizumab	Benralizumab
	SINUS-24	SINUS-52 (q2w)	SINUS-52 (q2w-q4w)	POLYP 1	POLYP 2	SYNAPSE	OSTRO
<b>UPSIT, score mean (SD)</b>	14.68 (8.7)	13.50 (8.20)	13.60 (7.60)	12.8 (7.9)	12.8 (7.6)	13.0* (6.8)	N.M
<b>24w UPSIT score mean (SD)</b>	25.39 (9.49)	23.89 (9.21)	23.89 (9.21)	17.24 (0.84)	17.11 (0.83)	-	-
<b>40w UPSIT score mean (SD)</b>	-	-	-	-	-	-	N.M.
<b>52w UPSIT score mean (SD)</b>	-	-	-	-	-	N.M	-
<b>MD points, (95% CI) vs placebo group</b>	10.56 (8.79 to 12.34)	10.52 (8.98 to 12.07)	N.M	3.81 (1.38 to 6.24)	3.86 (1.57 to 6.15)	0.4** (-1.49 to 2.28)	N.M
<b>p value</b>	<0.0001	<0.0001	N.M.	0.024	0.0011	0.30	N.M
<b>LoS mean (SD)</b>	2.70 (0.57)	2.73 (0.59)	2.81 (0.46)	2.5 (0.8)	2.6 (0.8)	9.60 (0.80)	N.M
<b>24w LoS mean (SD)</b>	1.35 (0.99)	1.55 (1.02)	N.M	1.94 (0.09)	2.02 (0.10)	-	-
<b>40w LoS mean (SD)</b>	-	-	-	-	-	6.80 (3.61)	N.M
<b>52w LoS mean (SD)</b>	-	-	-	-	-	-	-
<b>MD points, (95% CI) vs placebo group</b>	-1.12 (-1.31 to -0.93)	-0.98 (-1.15 to 0.81)	N.M.	-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)
<b>p value</b>	<0.0001	0.0001	N.M	0.0161	0.0024	0.020	0.0030

\*UPSIT was performed on a subset of the population included (54 subjects)

\*\*at 52w

CI: coefficient interval; LoS: loss of smell score (0-3); LoS VAS: loss of smell with visual analogue scale (0-10); MD: mean difference; N.M.: not mentioned; N.S.: non-significant; SD: standard deviation; UPSIT score: University of Pennsylvania Smell Identification Test (0-40); w: weeks.

Table 4. Real life studies with patients with CRSwNP treated with biologics.

Study [reference]	DUPILUMAB					OMALIZUMAB		MEPOLIZUMAB			BENRALIZUMAB		RESLIZUMAB
	[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 (months)	6	4 and 6	6 and 12	4	4	12	6	4	17±5	6	N.D.	6	
Smell significant improvement scale	UPSIT (from 9 to 25)	LoS (from 1.9±0.8 to 0.78 ± 0.8 at 16w and 0.46±0.65 at 24w)	Sniffin 'Sticks-12 (from 3.6±2.1 to 7.3±2.8 at 24w and 8.3±3.2 at 48w)	LoS and VAS olfaction (from 3.0±1.0 to 1.0±2.0, and from 9.0±2.0 to 2.0±4.0)	LoS (from 1.6±1 to 0.2±0.4)	Not found 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 N.D-	Method not described (from 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 N.D-	Subjective patient's perception of anosmia (yes/no) (anosmia disappeared in 31% patients)	
Comorbidities	100% Asthma	100% AD	N.D.	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	

AD = atopic dermatitis; LoS = loss of smell score; N.D= not defined; N-ERD = NSAID exacerbated respiratory disease;w = week.