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ORIGINAL ARTICLE

Rhinitis, Sinusitis and Upper Airway Disease

Dupilumab in the treatment of severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP): A multicentric observational Phase IV real-life study (DUPIREAL)

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Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is associated with significant morbidity and reduced health-related quality of life. Findings from clinical trials have demonstrated the effectiveness of dupilumab in CRSwNP, although real-world evidence is still limited.

Methods: This Phase IV real-life, observational, multicenter study assessed the effectiveness and safety of dupilumab in patients with severe uncontrolled CRSwNP ($n = 648$) over the first year of treatment. We collected data at baseline and after 1, 3, 6, 9, and 12 months of follow-up. We focused on nasal polyps score (NPS), symptoms, and olfactory function. We stratified outcomes by comorbidities, previous surgery, and adherence to intranasal corticosteroids, and examined the success rates based on current guidelines, as well as potential predictors of response at each timepoint.

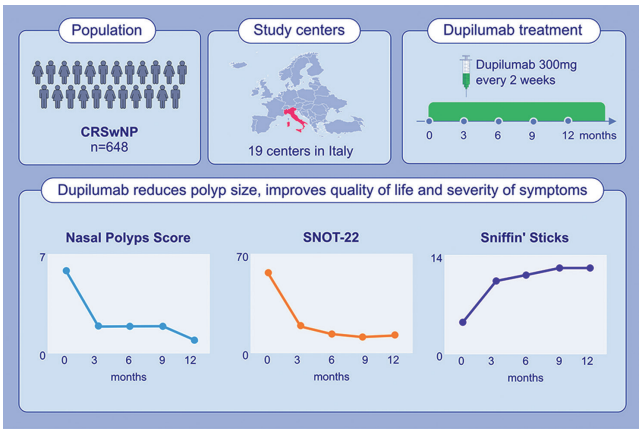
Results: We observed a significant decrease in NPS from a median value of 6 (IQR 5–6) at baseline to 1.0 (IQR 0.0–2.0) at 12 months ($p < .001$), and a significant decrease in Sino-Nasal Outcomes Test-22 (SNOT-22) from a median score of 58 (IQR 49–70) at baseline to 11 (IQR 6–21; $p < .001$) at 12 months. Sniffin' Sticks scores showed a significant increase over 12 months ($p < .001$) compared to baseline. The results were unaffected by concomitant diseases, number of previous surgeries, and adherence to topical steroids, except for minor differences in rapidity of action. An excellent-moderate response was observed in 96.9% of patients at 12 months based on EPOS 2020 criteria.

Dupireal Italian Study Group members are listed in Appendix A.

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Conclusions: Our findings from this large-scale real-life study support the effectiveness of dupilumab as an add-on therapy in patients with severe uncontrolled CRSwNP in reducing polyp size and improving the quality of life, severity of symptoms, nasal congestion, and smell.

KEYWORDS
asthma, biologics, chronic rhinosinusitis with nasal polyps, dupilumab, smell



GRAPHICAL ABSTRACT

This study assessed the effectiveness and safety of dupilumab in severe uncontrolled CRSwNP. In the first 12 months, dupilumab significantly decreased NPS and SNOT-22 and improved smell function; an excellent-moderate response was observed in 96.9% of patients. At the study end, only six patients had discontinued dupilumab due to a major adverse event.
Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; NPS, nasal polyp score; SNOT-22, sino-nasal outcomes test-22

1 | INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a sino-nasal chronic inflammatory disease that strongly affects patients' quality of life, especially in difficult-to-treat cases.[1–4] In these patients, severity is mostly driven by a Type 2 inflammatory pathway,[5–7] especially in Western World, and its management has rapidly changed over the last year thanks to the advent of biologics.[8]

The efficacy of dupilumab has been demonstrated in randomized clinical trials (RCTs),[9,10] which showed a significant improvement (starting from the fourth week of treatment) in all primary and secondary endpoints (nasal congestion/obstruction severity, nasal polyps score, sinus opacification, and loss of smell) at Weeks 24 and 52 of treatment.[9,10] Nevertheless, evidence in real-life clinical practice is still limited to few single-center series on small cohorts.

The primary aim of this study was to evaluate the effectiveness and safety of dupilumab during the first year of treatment in a real-life setting, focusing on improvement in nasal polyp score (NPS) as well as specific symptoms, quality of life, and olfactory function. In addition, we assessed side effects and reasons for discontinuation. Lastly, we studied the rate of clinical response according to EPOS2020,[1] and EUFOREA2021 criteria,[4] as well as potential predictors of response at each timepoint.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This a Phase IV real-life, observational, retrospective, multicenter study that involved 19 centers throughout Italy with specific minimal requirements to be included (Appendix S1 of Data S1) and a follow-up schedule similar to that of the coordinating center. We enrolled patients treated between November 2020 and March 2022, collecting data at baseline (V0), and at early [1 month (V1), 3 months (V2), 6 months (V3)] and late [9 months (V4) and 12 months (V5)] follow-up.

The study conformed to the 1976 Declaration of Helsinki, and was approved by the coordinating center Ethics committee (Agostino Gemelli University Hospital Foundation IRCCS) (Protocol n.0034704/21—ID-4429) and by each satellite center. All patients signed a written informed consent form for study participation. The trial was registered in ClinicalTrials.gov (No. NCT04181190).

2.2 | Inclusion and exclusion criteria

We included patients with severe uncontrolled CRSwNP who received, in the context of real-life clinical practice, self-administered subcutaneous 300 mg dupilumab every 2 weeks as an add-on therapy

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to intranasal corticosteroids (INCS), prescribed accordingly to the indications provided by Italian Agency of Drugs (AIFA),[8] as follows:

1. Age ≥18 years;
2. Diffuse CRSwNP confirmed by endoscopy and CT (performed at least 6 months prior to therapy start);
3. Severe disease stage (NPS ≥5 and/or SNOT-22 ≥50);
4. Inadequate symptom controls with INCS;
5. Failure (or intolerance) of previous medical treatments (at least two cycles of systemic corticosteroid over the last year) and/or of previous endoscopic sinus surgery (ESS).

We excluded all pregnant women, as well as patients on immunosuppressive therapy, radio-chemotherapy treatments for cancer in the 12 months before starting therapy, and concomitant long-term corticosteroid therapy for chronic autoimmune disorders.[8]

2.3 | Aims and measurements

The primary endpoint of the study was to assess the effectiveness of dupilumab in the treatment of severe uncontrolled CRSwNP, with or without asthma, considering NPS reduction over the first year of treatment. As secondary endpoints we assessed nasal congestion score (NCS), Sino-Nasal Outcomes Test-22 (SNOT-22), and visual analog scale (VAS) scales for different symptoms and olfactory outcomes measured by Sniffin' Sticks identification test with 16 odors. Sub-analyses were further performed to evaluate outcomes stratified for: surgery (number of past interventions and time since intervention), asthma, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD), and adherence to INCS (patients taking INCS <5 days/week were considered as non-adherent).

Disease control and response were evaluated according to EPOS[1] and EUFOREA[4] criteria, (summarized in Appendix S2). In addition, we assessed potential predictors of clinical response at each timepoint (1, 3, 6, 9, and 12 months) considering as main outcomes the four identified in the EUFOREA 2021 at 12 months (NPS <4, NCS <2, VAS total symptoms <5, and SNOT-22 score <30). We defined a 4-outcome response (4-OutR) when all four criteria were satisfied, in addition to no current need for surgery or systemic corticosteroids.[4] In order to establish predictors of response, we compared patients with 4-OutR to patients with no-4-OutR. We included in the predictive model both anamnestic and clinical data, as well as nasal score and VAS scales, including only the variables present at each timepoint.

2.4 | Statistical analysis

The sample was described in its clinical and demographic characteristics by the appropriate descriptive statistics indexes (i.e., absolute and relative percentage frequency, mean and standard deviation (SD) or median, and interquartile range (IQR)). Gaussian distribution was verified by Shapiro–Wilk's test. Missing values (all ≤15%; see the missing data table in the Data S1) were treated by multiple imputation (MI) with *imputeR* R package.[11] Due to the real-life study design and the acquisition of data from retrieved medical records, missing values are mainly attributable to the MAR (missing at random) class, better definable as "missing conditionally at random".[12] In fact, at the time of data collection we were in the pandemic period, and either visits were delayed or patients had a lower compliance in providing all data as they wanted to minimize time in hospital. In this sense, the package "*imputeR*" we used in our MI process has been specifically developed to provide a general framework for missing values imputation based on automated variable selection, and results are extremely useful to deal with MAR due to the referral to advanced imputation methods even based on machine learning. The strength of this package is the "Multivariate Expectation-Maximization (EM) based imputation framework", which offers several algorithms according to the type of missing data (e.g., regularization methods, tree-based models, etc...). The main function *"impute"* inputs a matrix containing missing values and returns a complete data matrix using the variable selection functions provided. Thanks to this package, we could also compute an estimate of the accuracy at each MI process, so to be sure that the selected MI method provided us the best accuracy. In our case, for all quantitative variables, we based on "ImFun" variable selection method for quantitative data (in our case Lasso regression), with the "mean" as initial step of the optimization algorithm, from which the optimal imputed values were then computed. Likewise, for categorical data, the variable selection method recalled with "cFun" was based on a decision tree classification system, with the "majority (mode)" as initial step of the optimization algorithm". The computation provided us the results of the convergence of our imputation algorithm and the output matrix of data with the imputed values.

Fluctuations over time in NPS, NCS, VAS scales, Sniffin' Sticks test, and SNOT-22 were assessed by Friedman's non-parametric test with Bonferroni correction for multiple comparisons, and pairwise comparisons evaluated by either Durbin-Conover's or Dunn's test. Repeated-measures generalized linear mixed models (GLMMRM) were used to assess the effect of group (surgery vs. non-surgery, asthma vs. no-asthma, NSAID-ERD vs. not, and INCS adherent vs. not) on NPS, SNOT-22, and smell outcomes. The model included as fixed effects the subgroup allocation (e.g. Asthma vs. No Asthma), follow-up timepoints as categorical variables (i.e. baseline, 1, 3, 6, 9, 12 months) and the interaction subgroup-time, whilst random effects were assigned to each ID. Correlations between repeated measures were modelled using a repeated effect with an unstructured covariance matrix. The same models were applied to assess mean total VAS fluctuations over time according to response to all, at least three or at least two of the four main EUFOREA criteria.[4] All models were fitted with the "*glmmTMB*" R package.[13]

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Fluctuations in the different parameters over time were further represented by "violin plots", by using R packages "*ggpubr*", "*ggstatsplot*", "*ggplot2*", "*ggprism*", and "*ggsignif*",[14–18] on both the overall sample and stratified for past surgery, asthma, NSAID-ERD, and INCS.

Potential predictors of clinical response at each timepoint were assessed by univariable and multivariable logistic regression with "*rms*" package,[19] considering clinical and anamnestic variables and scores related to the immediately previous timepoint. Statistical significance was set at $p < .05$. Suggestive p-values are also reported (≤0.05–0.10). All analyses were performed with R software v4.2.0 (CRAN®, R Core 2022, Wien, Austria).[20,21]

3 | RESULTS

3.1 | General characteristics of the study population

We enrolled 648 patients (median age: 54 years—IQR 45–63), mainly male (61.7%). Asthma was present in 56.5% and NSAID-ERD in 29.5% of patients. Regarding disease control, 85% of patients had received more than two brief cycles of OCS throughout the last year and 91.4% had undergone at least one previous ESS. Overall baseline characteristics, detailed medical treatment, and surgery are reported in Table 1. Of note, the dose of dupilumab was not modified, except for four cases in which injections were self-delayed for 2 weeks in a month due to SARS-CoV2 infection. All patients were adherent to follow-up schedules except for one who was lost to follow-up.

3.2 | Effectiveness of dupilumab on NPS reduction over 12 months of treatment

We observed a significant improvement in NPS scores over time, which decreased from a median baseline value of 6 (IQR 5–6) to 1.0 (IQR 0.0–2.0) at 12 months ($p < .001$). Significant changes were observed at all timepoints as reported in Table 2 and Figure 1A.

3.3 | Effectiveness of dupilumab on symptoms, quality of life, and olfactory function

Nasal obstruction significantly decreased at each timepoint, considering VAS nasal obstruction (see also Figure S1A). NCS improved accordingly over time, as reported in Table 2. Subjective VAS evaluation of rhinorrhea, sleep disorders, and craniofacial pain showed very similar improvements, with significant reductions in all scores ($p < .001$) over time, confirming a significant relief for all the most relevant symptoms of CRSwNP (Figures S1B and S2A,B). All data are detailed in Table 2.

TABLE 1 General characteristics of the study population.

	N = 648
Age, yr.	54 (45–63)
Age at diagnosis of CRS (yrs.), median (IQR)	37.3 (30.0–45.0)
Sex	
M	400 (61.7)
F	248 (38.3)
Smoking habit	107 (16.5)
Allergies	416 (64.2)
Number of positive allergens, median (IQR)	1 (0–2)
Familial atopia	266 (41.0)
FANS intolerance	213 (32.9)
ASA triad	191 (29.5)
Presence of asthma	366 (56.5)
Asthma control ACT score, median (IQR)	24 (19–24)
Blood eosinophils, median (IQR)	500 (300–682)
Total IgE, median (IQR)	180.0 (85.4–439.0)
Lund-Mackay score, median (IQR)	17.0 (12.0–21.0)
Previous medical treatment	
Adherence to intranasal corticosteroids	648 (100)
Mometasone furoate	542 (83.6)
Budesonide	61 (9.4)
Other	45 (6.9)
More than two brief cycle of OCS in the last years	551 (85)
Mean no. of brief cycles of OCS in the last year	2 (1–3)
Mean total no. of days of OCS in the last year	18 (6–30)
Corticosteroid inhalers	283 (43.7)
Continuative daily inhalers[b]	237 (36.6)
SABA[b]	46 (7.1)
LABA[b]	184 (28.4)
LAMA[b]	16 (2.5)
Previous biological therapy	41 (6.3)
Benralizumab[b]	19 (46.3)
Omalizumab[b]	17 (41.5)
Mepolizumab[b]	8 (19.5)
Past surgery	592 (91.4)
No. of past surgeries	
0	56 (8.6)
1	244 (37.6)
2	171 (26.4)
≥3	177 (27.3)
No. of past surgeries[a], median (IQR)	2 (1–3)
Type of surgery[b]	
Polypectomy	93 (15.7)
Anterior FESS or FESS	388 (65.5)
ESS ± Draf III frontal senotomy	111 (18.8)
Years since last surgery, median (IQR)	4.8 (2.5–8.4)

Abbreviations: ACT, asthma control test; ASA, acetylsalicylic acid; CS, corticosteroids; F, female; (F)ESS, (Functional) endoscopic sinus surgery; Ig, immunoglobulin; LABA, long-acting beta agonists; LAMA, long-acting muscarinic (LAMA); M, male; NSAIDs, non-steroidal anti-inflammatory agents; OCS, oral corticosteroids; SABA, short-acting beta agonists.

[a]Data are expressed as absolute and relative percentage frequency for qualitative variables. Median and interquartile range (IQR) were instead applied on quantitative data.

[b]Percentages were computed only on the number of patients experimenting the established condition.

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TABLE 2 Change in clinical parameters over time in the study population ($N = 648$).[a]

	Baseline	1-m	3-m	6-m	9-m	12-m	*p*
NPS	6.0 (5.0–6.0)	4.0 (2.0–5.0)	2.0 (1.0–4.0)	2.0 (0.0–3.0)	2.0 (0.0–3.0)	1.0 (0.0–2.0)	**<.001**
SNOT-22	58.0 (49.0–70.0)	26.0 (16.0–41.0)	19.0 (9.0–33.0)	13.0 (6.0–26.0)	11.0 (6.0–21.0)	12.0 (5.0–20.0)	**<.001**
Sniffin's Sticks	4.0 (2.0–7.0)	9.0 (5.0–12.0)	10.0 (7.0–12.0)	11.0 (8.0–13.0)	12.0 (9.0–13.0)	12.0 (9.0–14.0)	**<.001**
Smell (VAS)	9.0 (4.8–10.0)	5.0 (2.0–8.0)	3.0 (1.0–7.0)	2.0 (1.0–6.3)	2.0 (0.0–5.0)	2.0 (0.0–5.0)	**<.001**
Nasal obstruction (VAS)	8.0 (7.0–10.0)	4.0 (2.0–6.0)	2.0 (1.0–4.0)	2.0 (0.0–3.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	**<.001**
Rhinorrhea (VAS)	7.0 (5.0–9.0)	3.0 (1.0–5.0)	2.0 (1.0–4.0)	1.0 (0.0–3.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	**<.001**
Craniofacial pain (VAS)	5.0 (2.0–7.0)	1.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–1.3)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	**<.001**
Sleep disorders (VAS)	6.0 (4.0–8.0)	2.0 (0.0–4.0)	1.0 (0.0–3.0)	1.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	**<.001**
NCS							**<.001**
Absent	-	109 (16.8)	230 (35.5)	345 (53.2)	434 (67.0)	428 (66.0)	
Mild	47 (7.2)	292 (45.1)	286 (44.1)	235 (36.3)	167 (25.8)	155 (24.0)	
Moderate	203 (31.4)	203 (31.3)	119 (18.4)	63 (9.7)	47 (7.2)	65 (10.0)	
Severe	398 (61.4)	44 (6.8)	13 (2.0)	5 (0.8)	-	-	
INCS therapy adherence	551 (85)	603 (93.1)	592 (91.4)	603 (93.1)	600 (92.6)	599 (92.4)	**<.001**

Abbreviations: CS, corticosteroids; m, month; NCS, Nasal congestion score; NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test-22; VAS, visual analog scale.

[a]Data are expressed as absolute and relative percentage frequency for qualitative data, median and interquartile range (IQR) for quantitative. *P*-values were computed by Friedman's non-parametric test for quantitative and ordinal data, while Cochran Q test was applied on binary qualitative data. In bold significant *p*-values. Pairwise comparisons are reported in Figures 1 and 2, Figures S1 and S2.

Patients' quality of life significantly improved, as shown by a decrease in SNOT-22 scores from baseline (median 58, IQR 49–70) up to 9 months (median 11, IQR 6–21; $p < .001$) to then reach steady median values (Figure 1B). Of note, smell VAS score was significantly reduced over the six timepoints ($p < .001$), while Sniffin' Sticks score showed a significant increase over time ($p < .001$) compared to baseline (Figure 2A,B), demonstrating improved olfactory functioning.

We further assessed whether number and timing of surgery affected improvements in nasal and smell function. No significant difference emerged (Figures S4–S7), except for a 2.5-fold improvement ($p < .05$) in NCS at 12 months among patients who had undergone one intervention, as well as among those with a shorter time of recurrence of polyps (<3 years since previous surgery) (Figure S6B).

3.4 | Efficacy outcomes based on number and timing of surgeries

Over 90% of patients had undergone prior surgery (Table 1). Intragroup NPS and SNOT-22 significantly decreased over time among patients irrespective of previous surgery, both overall and at pairwise comparisons (Figure 3). Differences were observed at between-groups evaluation ($p = .008$ for NPS and $p < .001$ for SNOT-22, respectively), with a faster decrease among those who had undergone previous surgery. Of note, the extremely high variability in the "no-surgery" subgroup is mainly due to the small number of patients. Olfactory function, assessed by smell VAS scale, significantly improved in both groups over time ($p < .001$), with a faster decrease in those without previous surgery ($p = .012$). Sniffin' Sticks showed a significant increase (Figure S3) with a similar between-group behavior to that of smell VAS. Of note, all differences observed are small and may not be relevant from a clinical point of view, although statistical significance was achieved.

3.5 | Efficacy outcomes based on concomitant disease

NPS and SNOT-22 showed a significant decrease over time among patients with or without asthma, both overall and at pairwise comparisons (Figure 4). In both cases, between-groups variability over time demonstrated a significantly faster reduction among asthmatic patients ($p < .001$ and $p = .004$, respectively for NPS and SNOT-22), even though the differences, in term of absolute values, did not appear to be clinically relevant. With regards to smell, smell VAS and Sniffin' Sticks showed significant variability over time in both subgroups (Figure S8), with no between-group difference.

Considering the presence of NSAID-ERD, a significant reduction in NPS and SNOT-22 was observed in both subgroups (Figure S9A,B). Of note, between-group comparison showed a faster improvement in terms of NPS ($p < .001$), SNOT-22 ($p = .006$), and olfactory function at Sniffin' Sticks evaluation ($p = .011$) and, though weaker, at smell VAS scale ($p = .046$) in the NSAID-ERD subgroup (Figure S10A,B).

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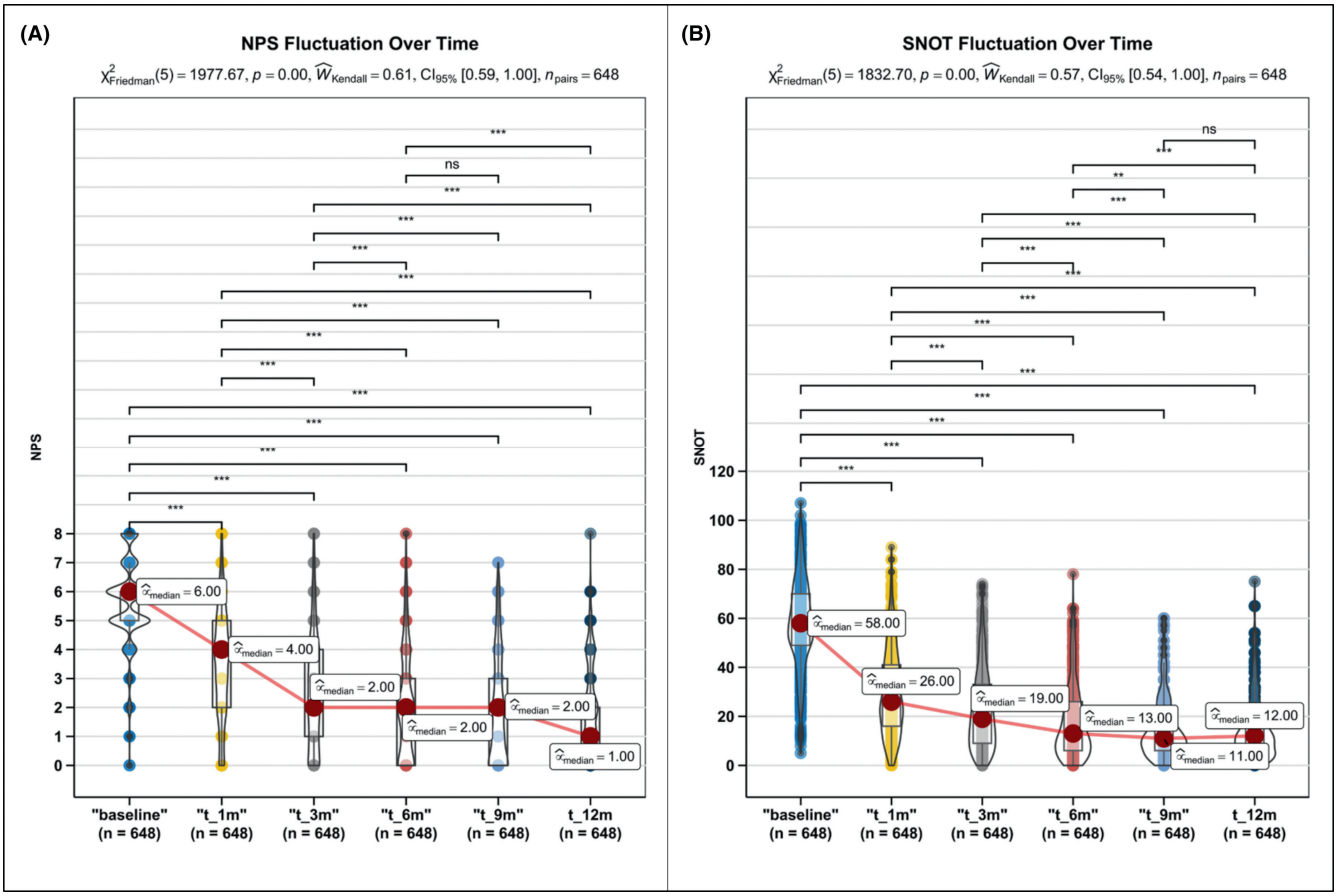


FIGURE 1 Efficacy of dupilumab on obstruction and symptoms. Nasal polyp endoscopic score (NPS) and Sino-nasal Outcome Test-22 (SNOT-22) fluctuation over time. Pairwise comparisons were computed by the Durbin-Conover's test.

3.6 | Efficacy outcomes based on adherence to INCS

Adherence to INCS was 85% ($N = 551$). Both INCS adherent and non-adherent patients showed a significant reduction in NPS over time ($p < .001$ in both cases), although it was notably faster in the INCS-adherent subgroup ($p = .001$). For SNOT-22, a slightly faster reduction was observed among non-adherent patients, even though this difference may not be clinically relevant ($p = .008$) (Figure S11). Smell VAS significantly improved only among adherent patients. Conversely, Sniffin' Sticks showed a significant improvement over time in both subgroups without any between-group significance (Figure 5).

3.7 | Predictive factors of a "4 outcomes clinical response" at each observation timepoint

At univariable analysis, among the clinical factors analyzed, asthma was positively associated with good response at 3 (OR 1.41, 95% CI: 1.03–1.93; $p = .034$), 6 (OR 1.44, 95% CI: 1.05–1.97; $p = .023$), and 9 months (OR 1.53, 95% CI: 1.11–2.12; $p = .007$). Notably, no significant association emerged for blood total IgE and eosinophil blood count at either early or late response to dupilumab.

In addition, the number of previous surgeries and the time since the last surgery did not affect the 4-Out response to dupilumab at the different timepoints, except for a very early response at 1 month (OR 2.79, 95% CI: 1.09–7.12; $p = .032$), although this finding have clinical relevance as previously mentioned. None of the other clinical factors analyzed significantly affected the 4-out response at the timepoints considered.

Among outcome parameters, lower values in almost all scores were associated with outcomes at 3, 6, 9, and 12 months at univariable analyses. The multivariable model confirmed that only NPS and SNOT-22 were independent predictors of 4-Out response at most timepoints. Finally, the following parameters were independently associated with a late 4-Out response at 12 months: NPS (OR 0.60, 95% CI: 0.54–0.68; $p < .001$), SNOT-22 (OR 0.92, 95% CI: 0.90–0.94; $p < .001$), rhinorrhea VAS (OR 0.86, 95% CI: 0.75–0.98; $p = .026$), and both mild and moderate NCS (OR 0.52, 95% CI: 0.33–0.83; $p = .006$ and OR 0.07, 95% CI: 0.03–0.20; $p < .001$, respectively) (Tables S1–S5).

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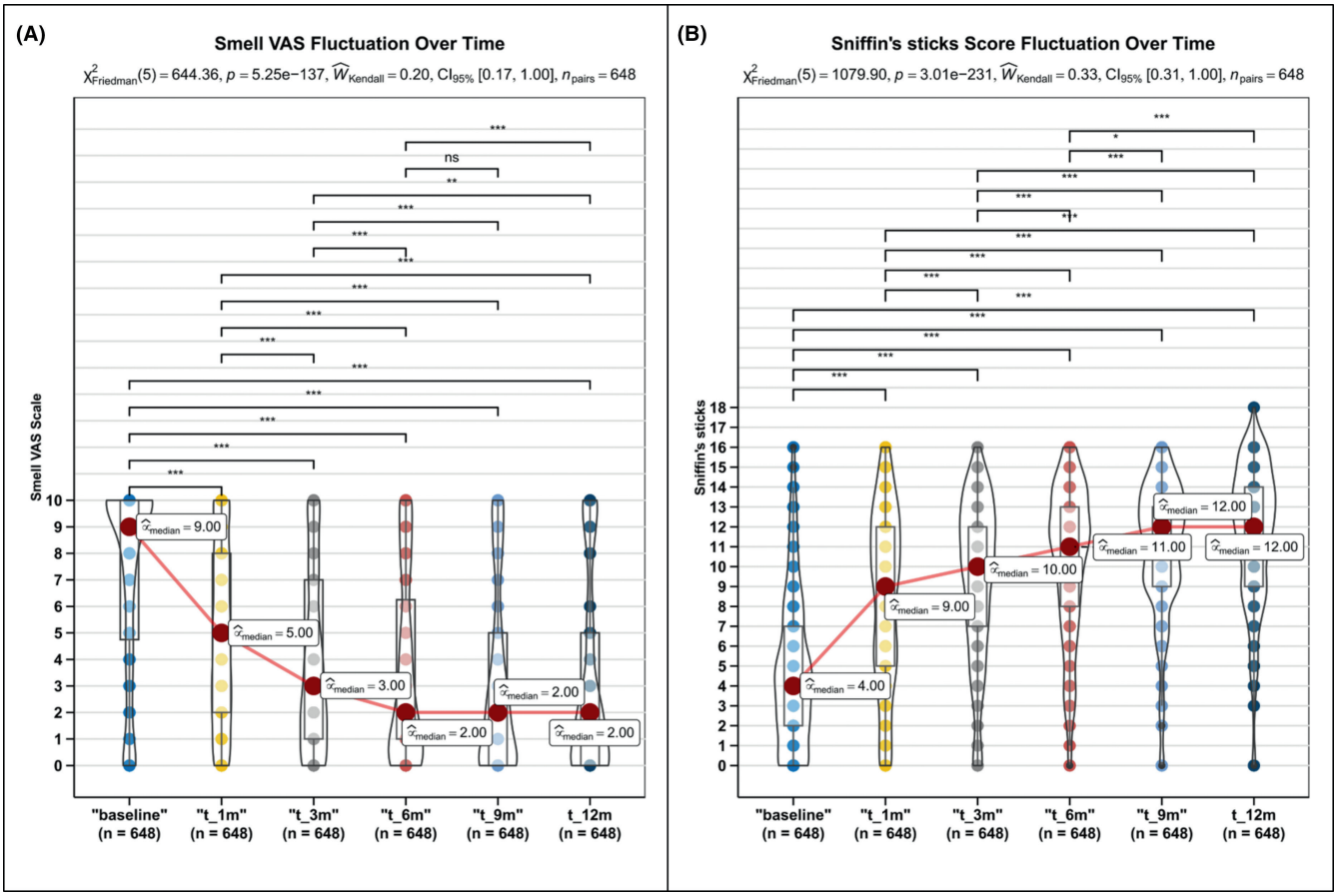


FIGURE 2 Efficacy of dupilumab on restoration of smell. Sniffin' Sticks test and smell visual analogue scale (VAS) scores fluctuations over time. Pairwise comparisons were computed by the Durbin-Conover's test.

3.8 | Disease control and safety of dupilumab in real life

Table 3 details control of disease applying EPOS2020 criteria.[1] Of note, after 3 months of treatment 50.3% of patients were "excellent" responders (326/648) and 46.5% (301/648) "moderate". The number of excellent and moderate responders continued to increase until reaching a peak of 69.6% and 27.3%, respectively, at 12 months. Only 3.2% of patients (20/648) were poor responders or non-responders and were treated according to their level of satisfaction. In particular, two patients withdrew early treatment at 3 months and underwent surgery; another two underwent salvage treatments (surgery in one case and a cycle of OCS in the second) at 6 months and continued dupilumab; seven discontinued at 6 months, of whom six underwent surgery and one switched to another biologic; and nine patients stopped at 12 months to undergo surgery.

The application of EUFOREA[4] criteria revealed a much different scenario. In fact, at 12 months of treatment only 426 of 648 (65.7%) patients showed a "4-outcome response (4-OutR)", fulfilling all criteria (NPS <4, SNOT <30, NCS <2, VAS total symptoms <5) for eligibility to treatment continuation, whereas 222 patients should have been considered as "non-responders" and theoretically withdrawn from the therapeutic program.

Due to this reason, we decided to assess whether 12-month EUFOREA criteria were too restrictive. First, we looked at how many patients satisfied the criteria individually, and observed that SNOT-22 was <30 in 133 (59.9%); NCS was <2 in 157 (70.7%); NPS was <4 in 109 (49.1%) and total VAS was <5 in 97.7% of patients, thus providing a good level of satisfaction in the group in whom treatment was prolonged (196/222).

In addition, mean/median VAS for the major symptoms of CRSwNP further supported to our hypothesis. In particular, non-4-OutR compared to 4-OutR patients had significantly higher values of VAS for smell [median 2.0 (IQR 0–6) vs. 2 (IQR 0–5); $p = .012$], nasal obstruction [median 2.0 (IQR 1–3) vs. 1 (IQR 0–2); $p < .001$], rhinorrhea [mean 1.7 ± 2.1 vs. 1.1 ± 1.5; $p < .001$], pain [median 0.0 (IQR 0–1) vs. 0 (IQR 0–0); $p = .019$], and sleep disorders [mean 1.4 ± 1.9 vs. 0.9 ± 1.5; $p = .003$]. Despite these differences, mean/median values among "non-4-OutR" were always suggestive of high symptomatic satisfaction by patients. Our data thus show that the 12-month EUFOREA[4] criteria might lead clinicians to wrongly discontinue the treatment at 12 months even if patient satisfaction is acceptable.

Finally, we tried to simulate different potential scenarios created from the modification of EUFOREA 2021 criteria,[4] considering two options: at least three of four criteria or at least two of four criteria satisfied at 12 months of follow-up. We further performed

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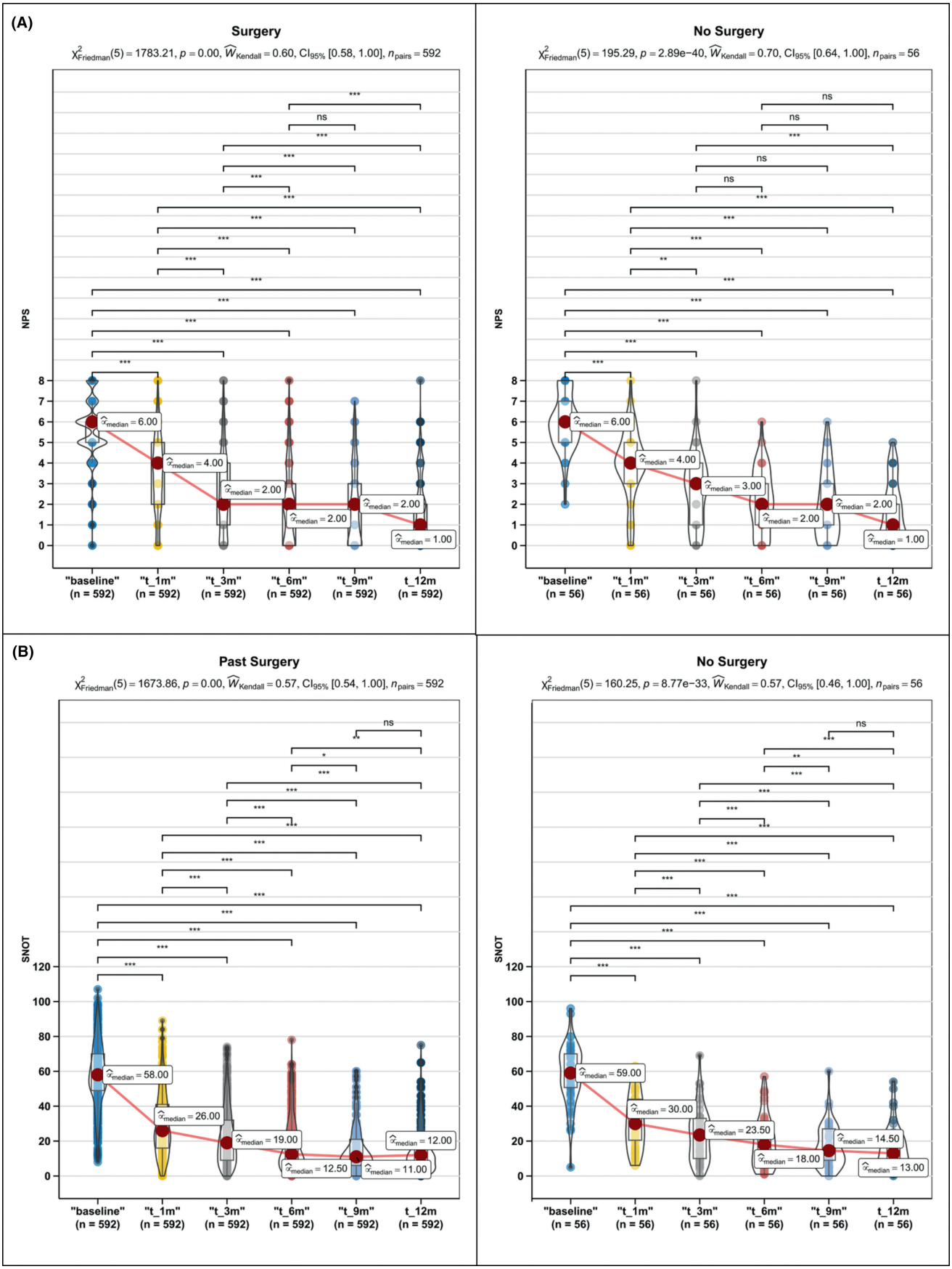


FIGURE 3 Impact of previous surgery on dupilumab efficacy. Nasal polyp endoscopic score (NPS) and Sino-Nasal Outcome Test (SNOT-22) modifications over time, stratified for surgical intervention. Pairwise comparisons were computed by the Durbin-Conover's test.

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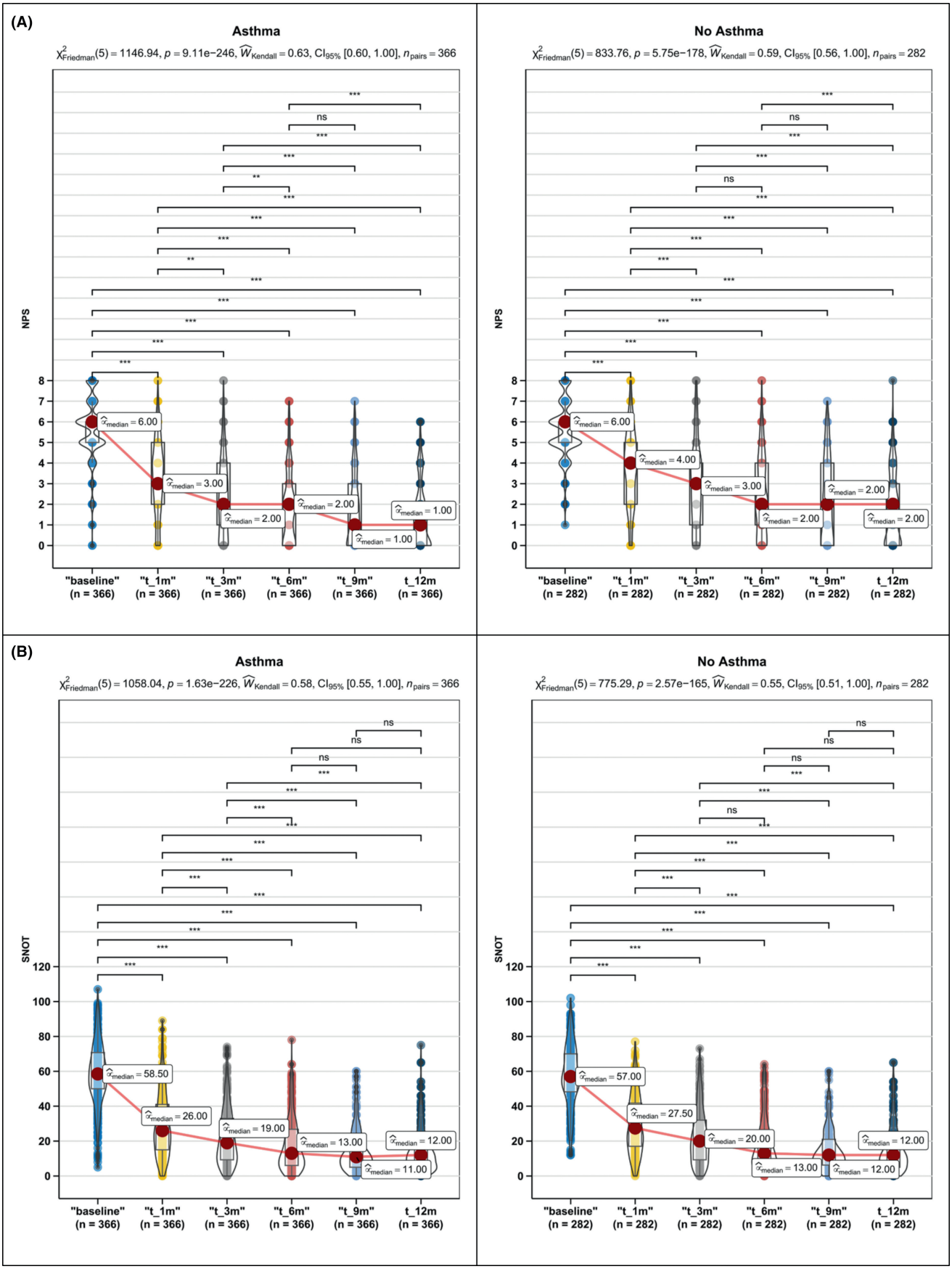


FIGURE 4 Impact of asthma on dupilumab efficacy. Nasal polyp endoscopic score (NPS) and Sino-Nasal Outcome Test (SNOT-22) modifications over time, stratified for presence of asthma. Pairwise comparisons were computed by the Durbin-Conover's test.

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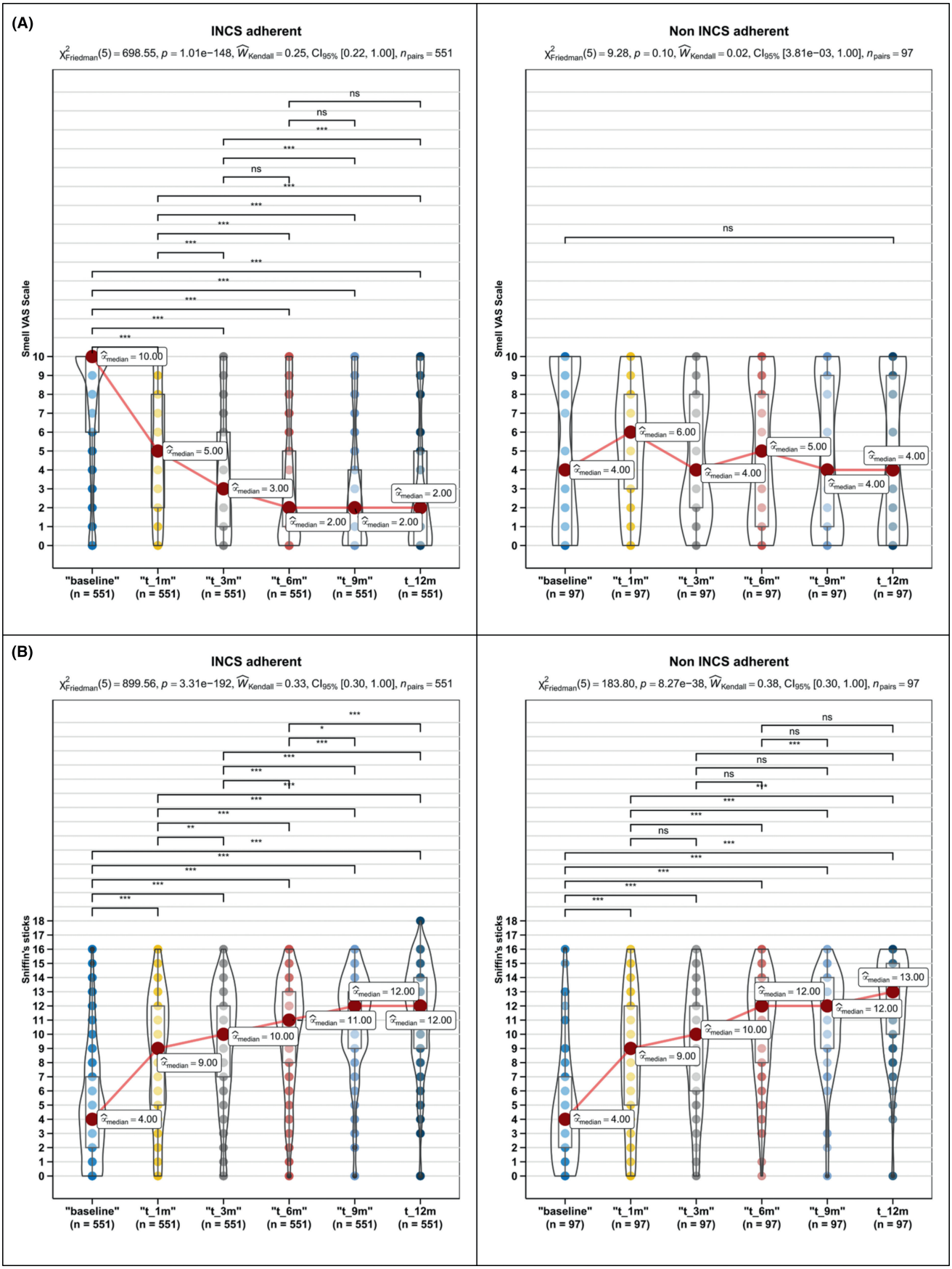


FIGURE 5 Impact of adherence to local corticosteroids on restoration of smell provided by dupilumab. Subjective (smell VAS scale) and objective (Sniffin' Sticks) olfactory function changes over time, stratified for the baseline adherence to corticosteroids therapy. Pairwise comparisons were computed by the Durbin-Conover's test.

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TABLE 3 Response to biologics according to EPOS2020 criteria at different timepoints ($N = 648$)[a].

	NONE	POOR	MODERATE	EXCELLENT
1 month	8 (1.2)	16 (2.5)	427 (65.9)	197 (30.4)
3 months	8 (1.2)	13 (2.0)	301 (46.5)	326 (50.3)
6 months	8 (1.2)	12 (1.9)	254 (39.2)	374 (57.7)
9 months	8 (1.2)	12 (1.9)	210 (32.4)	418 (64.5)
12 months	8 (1.2)	12 (1.9)	177 (27.3)	451 (69.6)

[a]Data are reported as absolute and relative percentage frequency for qualitative data, median and interquartile range (IQR) for quantitative variables. Suggestive *p*-values are expressed in italic ($0.10 < p < 0.05$), significant in bold ($p < 0.05$).

a repeated measures analysis for each option. Of note, the achievement of at least three criteria at 12 months was likely the best compromise, as supported by the significant differences after Month 3 and by the overall number of patients at 12 months (607; 93.7%), which better mirrors real-life data (Table 4).

Discontinuation of treatment was also due to adverse events. Four patients interrupted due to severe arthralgia (two within the first month, one at 3 months follow-up, and one after 1 year). Another two patients withdrew due to persistent severe hypereosinophilia (>1500 cells/μL), one at 9 months with asthma exacerbation, and the other experienced eosinophilic pneumonia. At study end, 26 patients had discontinued dupilumab, 20 due to either "no" or "poor" response" and 6 for major adverse events.

4 | DISCUSSION

RCTs represent a fundamental step in clinical drug development. However, it is crucial to evaluate the effectiveness of biologics in clinical practice, even considering the heterogeneity of the general population and factors which may affect clinical outcomes. This is the first multicenter real-life experience assessing the effectiveness and safety of dupilumab in the treatment of severe uncontrolled CRSwNP in a large population, as the most recent literature arises from a small number of single-center studies.[22–25]

Our findings confirm that subcutaneous 300 mg dupilumab home-administered by auto-injector every 2 weeks is highly effective in improving all efficacy scores over 12 months of treatment. We also confirmed the rapidity of action of dupilumab, with significant changes in all outcomes measured within 1 month of treatment. Consistent with previous real-life evidence,[23–25] we observed that the therapeutic effects of dupilumab were more favorable in "real-life" compared to LNPS-trials.[10] As for quality of life, SNOT-22 significantly improved, consistent with recent real-life studies.[26,27] Similar data were also observed in the LNPS-52 RCT[10]; however, in our population real-life findings were slightly better. Moreover, we observed a significant improvement in olfactory function using both Sniffin' Sticks and subjective smell VAS. This was among the earliest changes observed, after only 1 month of treatment, consistent with the results of Mullol and colleagues.[28] Similar to another study,[28] as well as post hoc analyses of SINUS-24 and SINUS-52,[29–31] we further observed that neither prior surgery, comorbid asthma, or NSAID-ERD affected smell improvement with dupilumab.

Interesting insights emerged from the analyses of the effects on outcomes of concomitant diseases, the number and timing of previous surgeries, and INCS adherence. NPS and SNOT-22 showed a significant decrease regardless of the presence of asthma or NSAID-ERD, with a significantly faster score reduction among asthmatic patients and in the presence of NSAID-ERD. However, despite the statistical significance obtained, these findings do not seem clinically relevant due to the remarkably small change between scores. Similarly, outcomes decreased over time both with and without previous surgery, with a significantly faster decrease in those who had surgery, in spite of the very small differences. Finally, at 12 months a 2.5-fold improvement ($p < .05$) in NCS was observed among patients who underwent one surgical intervention, as well as in case of a shorter time of recurrence (<3 years). Conversely, olfactory function, despite a significant improvement in both smell VAS scale and Sniffin' Stick scores, showed a faster response in those who had not undergone surgery ($p = .012$).

Some intriguing results were observed for adherence to INCS. In fact, adherence seems to determine a slightly faster decrease in NPS, even though this difference may not be clinically relevant in terms of absolute values. In addition, an interesting relationship between smell dysfunction and adherence to INCS was observed. Non-adherent patients ($n = 97$) had lower baseline median VAS (4 vs. 10). Moreover, the score significantly decreased only among adherent patients. Subjective data were not confirmed at Sniffin' Sticks test, which significantly improved in both subgroups, with no between-groups difference. These data should be interpreted with caution, considering that patients may misestimate the olfactory impairment with VAS evaluation, while the almost identical improvement at the semi-objective test is of interest.

We furthermore tried to identify factors that may affect a full 4-outcome response (all criteria fulfilled: NPS <4; NCS <2; VAS total symptoms <5; SNOT-22 score <30). We documented that asthma was significantly associated with a 4-Out response at 3, 6, and 9 months. Moreover, baseline biomarkers levels (blood total IgE and eosinophil blood count) and previous surgeries (number and the time since the last intervention), did not affect the 4-Out response to dupilumab at the different timepoints. Among outcomes, levels of NPS and SNOT scores were confirmed as independent factors able to predict the 4-Out response at most observation timepoints.

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TABLE 4 Definition of clinical response based on EUFOREA2021 criteria ($n = 648$)[a].

	1 month		3 months		6 months		9 months		12 months	
	N (%)	Median VAS (IQR)	N (%)	Median VAS (IQR)	N (%)	Median VAS (IQR)	N (%)	Median VAS (IQR)	N (%)	Median VAS (IQR)
4-outcome response	132 (20.4)	2.0 (1.0–2.8)	281 (43.4)	1.8 (1.0–2.6)	375 (57.9)	1.4 (0.8–2.4)	412 (63.6)	1.2 (0.6–1.8)	427 (65.9)	1.0 (0.6–2.0)
Yes	516 (79.6)	3.4 (2.4–4.6)	367 (56.6)	2.8 (1.8–3.8)	273 (42.1)	2.4 (1.4–3.4)	236 (36.4)	(1.0–2.8)	221 (34.1)	1.6 (1.0–2.4)
No										
	Estimate (95% CI); *p*		**Estimate (95% CI); *p***		**Estimate (95% CI); *p***		**Estimate (95% CI); *p***		**Estimate (95% CI); *p***	
Time	-		**−0.77 (−0.90; −0.63); <0.001**		**−1.18 (−1.33; −1.04); <0.001**		**−1.78 (−1.92 (−1.64); <0.001)**		**−1.88 (−2.04; −1.73); <0.001**	
*Time*Response*			**0.46 (0.18; 0.74); 0.001**		**0.55 (0.27; 0.82); <0.001**		**0.79 (0.52; 1.06); <0.001**		**0.86 (0.59; 1.14); <0.001**	
At least three of four	354 (54.6)	2.4 (1.6–3.4)	495 (76.4)	2.0 (1.2–2.8)	570 (88.0)	1.6 (0.8–2.6)	606 (93.5)	1.2 (0.6–2.0)	607 (93.7)	1.2 (0.6–2.0)
Yes	294 (45.4)	4.2 (3.2–5.4)	153 (23.6)	3.4 (2.4–5.0)	78 (12)	3.5 (2.2–5.0)	42 (6.5)	2.8 (2.0–3.5)	41 (6.3)	2.0 (1.4–3.4)
No										
	Estimate (95% CI); *p*		**Estimate (95% CI); *p***		**Estimate (95% CI); *p***		**Estimate (95% CI); *p***		**Estimate (95% CI); *p***	
Time	-		**−0.91 (−1.11; −0.71); <0.001**		**−1.31 (−1.54; −1.07); <0.001**		**−2.00 (−2.25; −1.76); <0.001**		**−2.14 (−2.40; −1.88); <0.001**	
*Time*Response*			**0.53 (0.27; 0.78); <0.001**		**0.58 (0.30; 0.86); <0.001**		**0.87 (0.58; 1.15); <0.001**		**0.95 (0.65; 1.25); <0.001**	
At least two of four	514 (79.3)	2.8 (1.8–3.8)	599 (92.4)	2.2 (1.2–3.0)	627 (96.8)	1.8 (1.0–2.6)	641 (98.9)	1.4 (0.6–2.2)	640 (98.8)	1.2 (0.6–2.0)
Yes	134 (20.7)	5.4 (3.8–6.2)	49 (7.6)	5.2 (3.6–6.2)	21 (3.2)	5.2 (4.4–6.0)	7 (1.1)	3.6 (3.1–5.3)	8 (1.2)	3.0 (2.4–3.2)
No										
	Estimate (95% CI); *p*		**Estimate (95% CI); *p***		**Estimate (95% CI); *p***		**Estimate (95% CI); *p***		**Estimate (95% CI); *p***	
Time	-		**−0.85 (−1.17; −0.53); <0.001**		**−1.16 (−1.55; −0.76); <0.001**		**−2.26 (−2.74; −1.77); <0.001**		**−2.80 (−3.31; −2.29); <0.001**	
*Time*Response*			*0.31 (−0.04; 0.66); 0.083*		0.24 (−0.18; 0.65); 0.260		**0.91 (0.41; 1.41); <0.001**		**1.40 (0.88; 1.92); <0.001**	

Abbreviations: CI, confidence interval; 4-OutR, 4-outcome response; SD, standard deviation.

[a]Data are reported as absolute and relative percentage frequency for qualitative data, median and interquartile range (IQR) for quantitative variables. Suggestive *p*-values are expressed in italic ($.10 < p < .05$), significant in bold ($p < .05$).

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Provided the fact that dupilumab is a chronic therapy, a long-standing issue concerns the definition of the best criteria applicable for the establishment of clinical success at 6 and 12 months. Currently, EPOS2020[1] and EUFOREA2021[4] represent the two main criteria. As shown in Tables 3 and 4, EUFOREA2021,[4] seems to be more restrictive at 12 months, leading to the risk of ruling out the therapy after 1 year in many more patients than those experiencing significant symptoms. Due to this reason, we tried to simulate different potential scenarios of modified EUFOREA 2021 criteria,[4] taking into consideration two options: at least three of four criteria or at least two of four criteria satisfied at 12 months of follow-up. The analysis of subjective symptomatology, that is, mean total VAS scale in each group, disclosed observed that choosing at least any three of four criteria satisfied was the best option mirroring our real life data. In this group, in fact symptoms significantly improved (median total VAS scale <5) starting since the first month after treatment till at 12 months of therapy. Based on this approach, 93.7% of patients would be considered eligible to pursue the treatment at 12 months, hence excluding from therapy only a remarkably small number of patients, better simulating our real-life scenario. In our series, in fact, only 26 patients interrupted dupilumab. Even though CRSwNP is a chronic disease and, as such, therapy must be long-term, monitoring of clinical response over time is helpful to better predict the time-window of response of each patient. Actually, although the success rate with dupilumab seems very high since the first months of therapy, a small proportion of patients may show a later response. It would be worthy to tailor the therapy on an individual basis by finding which factors modulate the response over time. In such a way, we would be able to foresee the best time in which to decide to perform salvage surgery. Interestingly, in real life some few patients underwent salvage surgery only after 3 months of therapy and this seems quite early considering the general trend of the data. In this sense, multiple repeated measures joint modelling would represent a potential method to investigate this issue and potentially develop a predictive algorithm.

However, our study is not without limitations. Due to its real-life nature, data on eosinophil counts were not available at all time-points, which did not allow to better focus on their potential role in clinical response. Furthermore, some of the intergroup comparisons in the subgroup analyses (surgery vs. non-surgery and adherent vs. non-adherent) involved a small number of patients, with a risk of high variability. As such, future studies are required to confirm our findings.

5 | CONCLUSION

In conclusion, this large real-life study confirmed effectiveness of dupilumab 300 mg self-administered subcutaneously every 2 weeks as add-on therapy to intranasal corticosteroids (INCS) in patients with severe uncontrolled CRSwNP in polyp size reduction, improvement of quality of life, severity of symptoms, nasal congestion, and smell function. Clinical outcomes improvement in the clinical practice seems consistent with that from the main RCTs and from the limited real-life evidence. The observed improvements obtained with dupilumab in the real-life setting appears even better if compared with findings from RCTs, as previously documented in smaller series.[22–24] Finally, our data support definite inclusion of dupilumab to treat patients with severe uncontrolled CRSwNP in real life.

AUTHOR CONTRIBUTIONS

EDC: conceptualization, project administration, investigation, data collection, formal analysis, methodology, writing—original draft, final approval, full access to all the data. PCP, CM, SS: software, data curation, formal analysis, methodology, full access to all the data, writing, review and editing, final approval of the manuscript. EP, MT, ILM, FP, GO, MG, CP, ST, VS, EC, AC, DL, GLF, FA, GP, AG, CC, MM, FB, SG, FRMC: investigation, data collection, supervision, review and editing, final approval of the manuscript. GP, JG: review and editing, supervision, final approval.

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CONFLICT OF INTEREST STATEMENT

EDC, CC, VS, ST: Lecture fees and participations in experts board meeting of GSK, Novartis, Sanofi, Astrazeneca. CP: Lecture fees and participations in experts board meeting of GSK, Novartis, Sanofi, Firma, Deca. EC: Lecture fees and participations in experts board meeting of GSK, Novartis, Sanofi, NOOS. ILM: Lecture fees and participations in experts board meeting of GSK, Novartis, Sanofi, Chiesi. FA, AG, GO: Lecture fees and participations in experts board meeting of GSK, Novartis, Sanofi. GLF: Lecture fees and participations in experts board meeting of Astrazeneca, Sanofi. SS: Lecture fees and participations in experts board meeting of GSK. FB, AC, PCP, JG, GP, FRMC, SG, DL, MG, MM, CM, FP, GP, EP, MT: none.

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SUPPORTING INFORMATION

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APPENDIX A

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