Responders to biologics in severe uncontrolled chronic rhinosinusitis with nasal polyps: a multicentric observational real-life study

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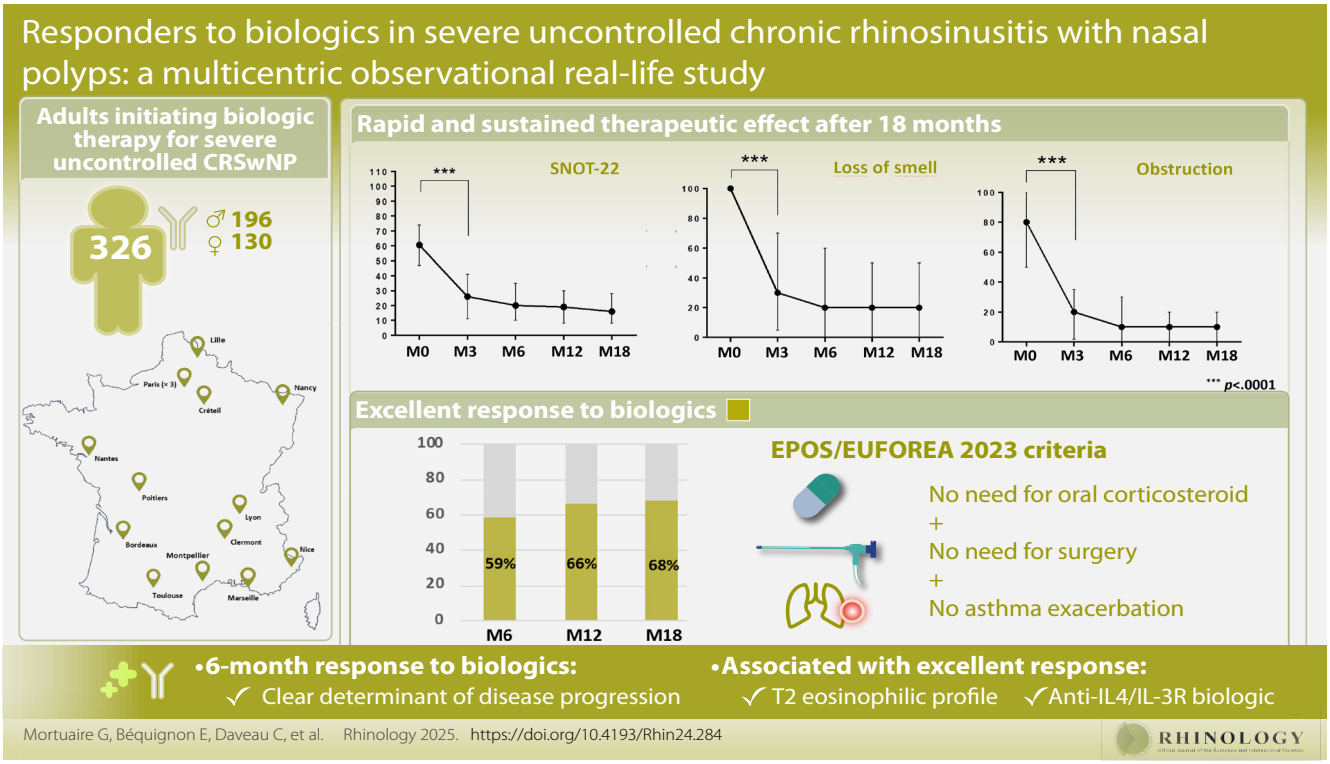

Abstract

Background: Clinical trials have demonstrated the effectiveness of biologics in treating chronic rhinosinusitis with nasal polyps (CRSwNP). However, real-world evidence regarding patient outcomes and predictors of clinical response remains limited. **Methodology**: In this multicentric 18-month follow-up study, 326 adult patients who initiated biologic therapy for severe uncontrolled CRSwNP were included. Patient characteristics, including clinical and inflammatory markers, and comorbidities were collected at baseline and at 3, 6, 12, and 18 months of follow-up. We examined success rates based on current guidelines and identified potential factors associated to clinical response at 6 months. **Results**: We observed a significant decrease of Sino-Nasal Outcomes Test-22 (SNOT-22) from a median score (interquartile range) of 60.5 (47-74) at baseline to 26.0 (11-41) at 3 months. A significant decrease of nasal symptoms and endoscopic nasal polyp score was observed at 3 months. After 6 months of biologic treatment, 59% of patients were classified as excellent responders according to the EUFOREA-EPOS 2023 criteria. Multivariate analysis revealed a suggestive association between baseline eosinophil blood count, type of biologic and an excellent response at 6 months. **Conclusions**: This real-world study confirms the effectiveness of biologics as an add-on therapy in patients with severe uncontrolled CRSwNP. Biologics lead to rapid and sustained improvement in clinical symptoms. A significant proportion of patients exhibit an excellent response, with no need for systemic corticosteroids.

Key words: biologics, chronic rhinosinusitis, real-life, excellent responder, eosinophil

Introduction

The treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) is currently undergoing significant changes, particularly for the subset of patients who have already exhausted traditional therapeutic options, including medical interventions (intranasal corticosteroids (INCS), systemic oral corticosteroids (OCS)) and endoscopic sinus surgery (ESS). In the recent years, phase III trials have established biological therapy targeting Type-2 (T2) inflammatory mediators as a viable add-on treatment for patients with severe uncontrolled CRSwNP, changing the paradigm of management [1–4]. Studies conducted in real-life clinical practice provide essential complementary insights to validate the effectiveness of biologics in CRSwNP.

The latest updates from EUFOREA-EPOS 2023 guidelines have defined key endpoints of biologic response, including improvement in nasal polyp (NP) size, OCS use, quality of life (QoL), sense of smell, and impact of comorbidities. The EUFOREA-EPOS report also highlights the lack of data predicting the time until improvement with biologic therapies [5].

A real-world national registry BIOPOSE (BIOlogics in severe nasal POlyposis SurvEy) has been established to address these clinically relevant questions. In this article, we present the results of this multicentric observational cohort study regarding the effectiveness of biologics during the first 18 months of treatment in a real-life setting, focusing on improvements in QoL, nasal symptoms, and NP size. Additionally, we examine the rate of clinical response according to current guidelines under stringent conditions to identify "excellent responders", with no need for OCS.

Materials and methods

Study design and population

A phase IV real-life, observational, prospective cohort study was conducted in 15 tertiary care centers in France. It was integrated into the routine patient care of participating centers with a standardized follow-up schedule. We enrolled patients treated with biologics for severe chronic rhinosinusitis with nasal polyps (CRSwNP) between August 2021 to December 2022. We collected pseudonymized data at baseline (M0), 3 months (M3), 6 months (M6), 12 months (M12), and 18 months (M18).

The study conformed to the 1976 Declaration of Helsinki and was conducted in compliance with the French Public Health Code, European Union Good Clinical Practice (GCP) and applicable regulatory requirements. All patients signed a written informed consent form for study participation. The trial was approved by the French Committee for the Protection of Individuals and registered on the public database ClinicalTrials.gov (No NCT05228041). The study protocol was designed following the EQUATOR guidelines and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist as previously described [6].

Inclusion and exclusion criteria

We included patients who received biologics for CRSwNP in the context of real-life clinical practice. Dupilumab or mepolizumab were prescribed accordingly to the indication provided by their marketing approval in France: age ≥ 18 years, severe CRSwNP that are uncontrolled despite appropriate medical treatment (intranasal corticosteroids (INCS) and at least 2 to 3 cycles of systemic oral corticosteroid (OCS) over the last year) and endoscopic sinus surgery (ESS). The severity of CRSwNP is defined by symptoms perceived as debilitating by the patient and a quality of life they consider to be significantly impaired. In France, the initiation of biologic therapy is not contingent on specific threshold values for symptom visual analogic scale (VAS) scores or a predefined level of quality of life as assessed by questionnaires. Additionally, no specific surgical procedure or defined time since the last surgery is required to determine the failure of endoscopic sinus surgery. The choice between dupilumab and mepolizumab was left to the clinician's discretion, based on their individual prescribing preferences.

We excluded patients with other immunosuppressive therapy or long-term corticosteroid therapy for chronic autoimmune diseases, patients who received any other biologic for inflammatory diseases in the previous 6 months apart from ongoing biologics for severe asthma. We also excluded pregnant or breast-feeding women, patients with hypersensitivity to humanized antibodies. Patients with any documented SARS-Cov2 infection in the last 3 months with persistent olfactory disorders related to COVID were not recorded in the survey for smell assessment purpose.

Measurements

A 4-week washout period for systemic corticosteroids (OCS) was required before recording baseline symptoms.

The primary and secondary endpoints of the study were selected from patient- and physician-reported outcomes, as defined by the EUFOREA-EPOS 2023 guidelines, to meet the requirements of the French National Health Authority for evaluating biologics in real-world settings. The primary endpoint was to assess the effectiveness of biologics using the Sino-Nasal Outcomes Test-22 (SNOT-22) questionnaire over the first 18 months of treatment. Each item is scored from 0 (no problem) to 5 (problem as bad as it can be) with two-week recall, resulting in a total score ranging from 0 to 110 points [7].

As secondary endpoints, we assessed subjective VAS for nasal symptoms (nasal obstruction or blocking, rhinorrhea, facial pain, dysosmia) and VAS for overall symptoms burden (from 0 (no problem) to 100 (problem as bad as it can be). Nasal polyp score (NPS) was measured at each timepoint by endoscopy and scored according to Meltzer staging from 0 to 4 (0 = no polyps, 1 = small polyps in the middle meatus not reaching below the inferior border of the middle turbinate, 2 = polyps reaching below the lower border of the middle turbinate, 3 = large polyps

Table 1. Clinical characteristics of patients at baseline.

Characteristics	n = 326
Clinical characteristics	
Age (yr), median (IQR)	52 (42-59)
Sex: male, %	60.3
Active smoker, %	9.1
Asthma, %	76.1
ACT, median (IQR)	21 (17-24)
Allergy, %	38.6
N-ERD, %	30.9
Previous treatment	
Ongoing INCS, %	89.8
More than two brief cycles of OCS in the last year, %	76.1
1-yr cumulative dose of OCS before biologics (gr), median (IQR)1	900 (480-1500)
Past surgery, %	100
Type of surgery	
• Polypectomy, %	35.5
• ESS, %	88.4
Previous biological therapy for asthma, %	3.9
• Benralizumab, n	3
• Omalizumab, n	8
• Mepolizumab, n	2
Biological markers	
Blood eosinophils (cell/µL), median (IQR)	480 (300-700)
Blood total IgE (KU/L), median (IQR)	141 (60.7-289)
Biologics for CRSwNP	
Duration of CRSwNP prior to initiation of biologic (yr), median (IQR)	12 (7-20)
Time between last surgery and biologic initiation (yr), median (IQR)	5 (2-9)
Type of biologics prescribed for CRSwNP,	
• Dupilumab, %	89.9
• Mepoluzumab, %	10.1

Abbreviations: ACT, Asthma Control Test; ESS, endoscopic sinus surgery; INCS, intranasal corticosteroid; OCS, oral corticosteroid; N-ERD, Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease. 1 OCS dose is provided as prednisone-equivalent for patients who received OCS in the last year. Data are expressed as absolute percentage frequency for qualitative variables. Median and interquartile range (IQR) were applied on quantitative data.

reaching the lower border of the inferior turbinate, and 4 = large polyps causing complete obstruction of the inferior nasal cavity; total score 0-8) [8].

Definition of responders

Response to biologics was evaluated according to EUFOREA-EPOS 2023 guidelines at M6, M12 and M18. Patients were considered "good to excellent" responders if they met 4 to 5 of the following criteria: reduced NP size, reduced need for OCS, improved QoL, improved sense of smell, and reduced impact of comorbidities [5]. We also applied the quantitative thresholds proposed by the EUFOREA expert board in 2021 [9]. Consequently, "excellent" responders were defined in our study as follows: decrease of NPS by ≥ 1/8 by nasal endoscopy, smell VAS increase of ≥ 16.7/100, SNOT-22 reduction of ≥ 8.9 (minimal clinically important difference) with a total score ≤ 40/110 and VAS total symptoms reduction of ≥ 20/100, no need for OCS, no need for surgery and complete control of comorbidities (no asthma exacerbation) between each visit.

To identify potential clinical or biological parameters associated with an excellent therapeutic response at 6 months , we also recorded : age, sex, comorbid asthma, allergy or N-ERD (Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease), active smoking habit, time from CRSwNP diagnosis to initiation of biologic therapy, time from last surgery to initiation of biologic therapy, blood eosinophil count at baseline, blood total IgE at baseline, 1-year cumulative dose of OCS prior to biologic and type of biologics prescribed for CRSwNP (dupilumab or mepolizumab).

Statistical analysis

Quantitative data were described as median and interquartile range (IQR) as Gaussian distribution was not observed by Shapiro-Wilk normality test for each variable. Qualitative data were defined by absolute percentage frequency. Fluctuations over time in SNOT-22 scores, VAS symptoms scores, and NPS were assessed by Kruskal-Wallis's non-parametric test for multiple comparisons and Dunn's test for pairwise comparisons. Statistical significance was set at $p < 0.05$. The association between baseline parameters and the occurrence of an excellent response to biologics at 6 months was assessed using univariable Wilcoxon, Chi-squared, or Fisher's exact tests when applicable. All variables with a p-value < 0.2 in the univariate analysis were included in the multivariate analysis. The model employed logistic regression with a binary covariate defined as "excellent responder (yes/no)", optimized with Fisher scoring. The Wald Chi-square test was applied to the logistic procedure. Results are reported as odds ratio (OR) estimates along with 95% Wald Confidence Intervals (95% CI). All analyses were performed with Graphpad Prism 10 software (Boston, MA, USA).

Results

Characteristics of the population

We enrolled 326 patients (median age: 52 years – IQR 42-59), mainly male (60,3%). Asthma was present in 76,1% of patients with a median Asthma Control Test of 21/25 (IQR 17-24). Allergy was reported in 38,6% and N-ERD in 30,9% of patients. Active smoking was observed in 9,1% of patients. Regarding disease

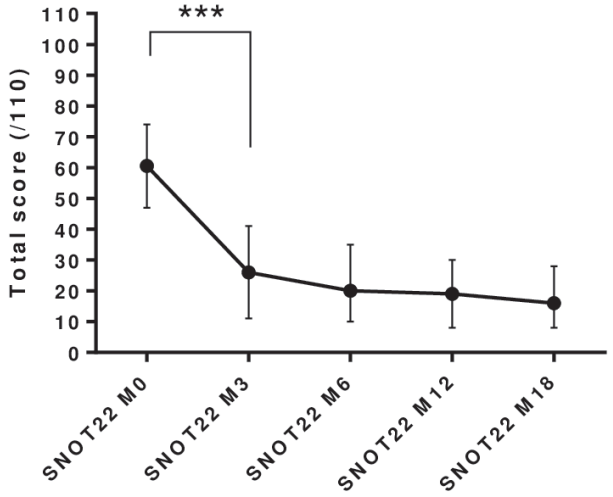

Figure 1. Efficacy of biologics on quality of life measured by Sino-nasal Outcome Test (SNOT-22) over 18 months. Pairwise comparisons were computed by Dunn's test. *** $p < 0.0001$.

control with medical therapy, 89,8% of patients used daily INCS and 76,1 % had received more than two courses of OCS throughout the last year for a median 1-year cumulative dose of 900 gr (prednisone-equivalent) (480-1500). As required for biologic reimbursement, all patients had undergone at least one sinus surgery (35,5 % by at least polypectomy and 88,4% by ESS). The median time between the last surgical procedure and the initiation of biologics was 5 years (IQR 2-9). Overall baseline characteristics are reported in Table 1. Dupilumab (300 mg every two weeks) was prescribed in 293 patients and mepolizumab (100 mg every month) in 33 patients.

Effectiveness of biologics on quality of life

Quality of life significantly improved from baseline to M3 with SNOT- 22 median scores of respectively 60.5 (IQR 47-74) and 26.0 (IQR 11-41) (p 0.0001). SNOT-22 scores stayed low at each time point from M3 to M18 without significant change beyond M3 (Figure 1).

Effectiveness of biologics on nasal symptoms and NPS reduction

The same profile of improvement was observed considering each nasal symptom and NP size. We observed significant changes for VAS scores and NPS from baseline to M3 ($p < 0.0001$). No significant reduction between subsequent timepoints beyond M3 was observed, as illustrated in Figure 2.

Prevalence of excellent responders over 18 months of treatment

Clinical parameters used to define excellent response to biologics at 6 months were partially missing in 54 patients leading to their exclusion for the analysis. For the other 272 patients,

Table 2. Relationship between the clinico-biological parameters of CRSwNP and the presence of an excellent response to biologics at six months.

Parameters	Uni-variate analysis	Multivariate ***	
	p value	p value	OR [95% CI]
Gender	0.35 *	-	-
Age	0.11 **	0.45	-
Active smoking	0.74*	-	-
Allergy	0.13 *	0.56	-
Asthma	0.45 *	-	-
N-ERD	0.36 *	-	-
Type of biologic	0.01 **	0.01	4.03 [1.37-13.17]
Time between last surgery and the initiation of biologic	0.61**	-	-
CRSwNP duration prior to the initiation of biologic	0.01 **	0.06	-
Blood eosinophil count at baseline	0.05 **	0.02	1.001 [1.000-1.002]
Blood total IgE at baseline	0.60 **	-	-
1-yr cumulative dose of OCS before biologics	0.35 **	-	-

The results described here correspond to those obtained for the 272 patients for whom all clinical and biological data were available at 6 months. Abbreviations: N-ERD, Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease; OCS, oral corticosteroid. * Chi square test, ** Wilcoxon Test, *** p value with Wald testing (Pr > ChiSq) against the global null hypothesis for logistic regression with one binary covariate "excellent responder" (beta=0) was 0.02.

59% were excellent responders at M6. Physicians decided at M6 to stop biologics in 5 cases for lack of subjective beneficial, to switch between biologics in 9 cases and to increase dupilumab interdose interval every 4 weeks in 13 cases. No patient underwent endoscopic surgery after this follow-up visit. At M12 and M18, the proportion of excellent responders was respectively 66% and 68% in the 184 patients with all clinical data available for the analysis. Biologics were stopped at M12 and M18 in respectively 5 and 1 patient. Switch between biologics was observed at M12 and M18 in respectively 4 and 2 patients. Off-label interdose interval of 4 weeks for dupilumab was applied at M12 and M18 in respectively in 12 and 31 patients. No patient underwent endoscopic surgery between and after the visits.

Association between baseline parameters and the occurrence of an excellent response to biologics at 6 months

In the univariable analysis, five parameters were identified as potentially associated with an excellent response at six months:

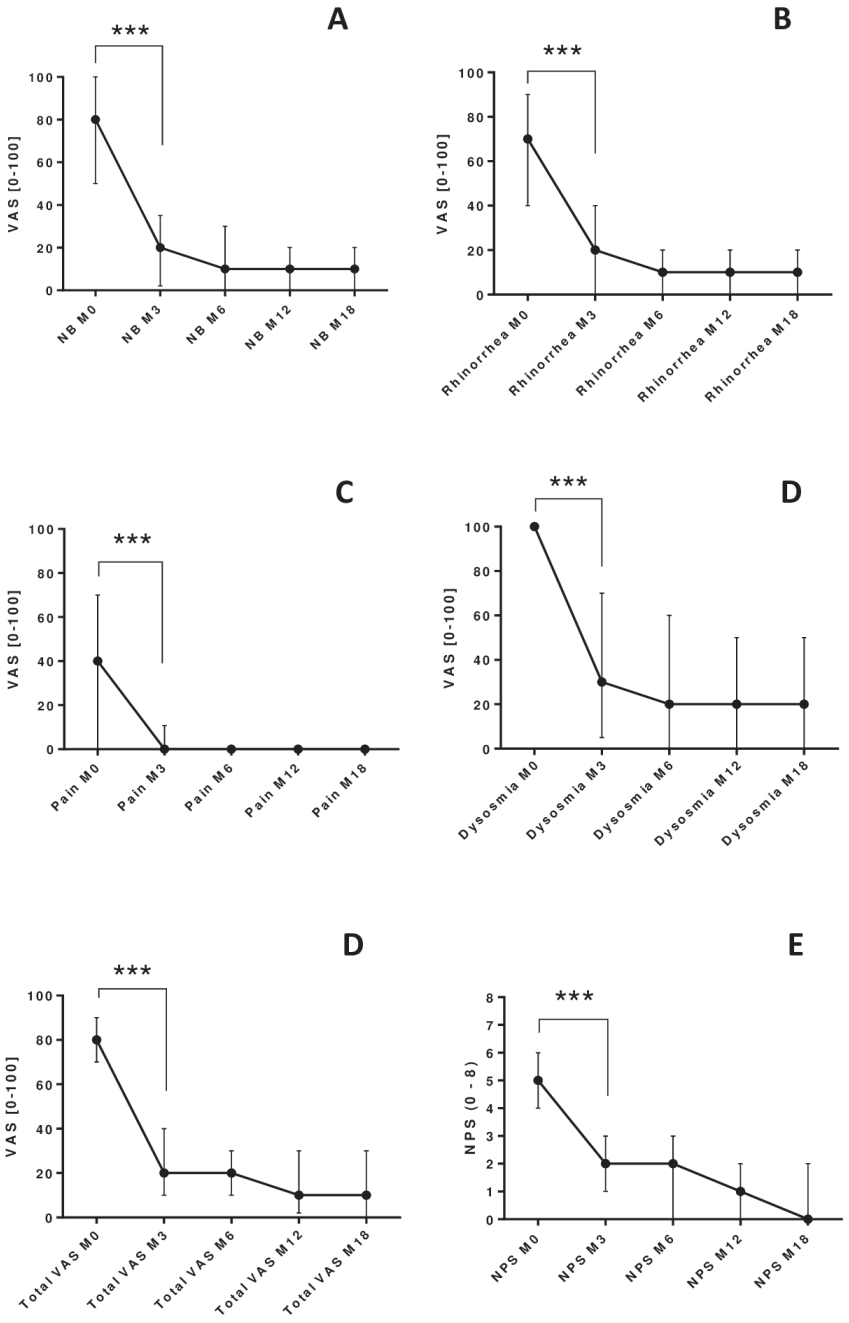

Figure 2. Efficacy of biologics on nasal symptoms and nasal polyp score (NPS) over 18 months. A) Visual analog scale (VAS) for nasal obstruction or blocking (NB); B) VAS for rhinorrhea; C) VAS for facial pain. D) VAS for smell disorder or dysosmia; E) VAS for overall symptoms score; F) Nasal polyp score (NPS). Pairwise comparisons were computed by Dunn's test. *** $p < 0.0001$.

age, history of allergy, type of biologic, duration of CRSwNP prior to the initiation of biologic therapy, and baseline blood eosinophil count (Table 2). In the multivariable analysis (Wald test for logistic regression with one binary covariate) applied to these five parameters, two were suggestively associated with an excellent response at 6 months: the blood eosinophil count at baseline (OR:1.001 95% CI: 1.000-1.002; p=0.02) and the treatment with dupilumab vs mepolizumab (OR:4.03 95% CI: 1.37-13.17; p=0.01) (Table 2).

Discussion

Pivotal randomized clinical trials with biologics targeting T2 inflammation consistently showed beneficial effect on QoL, nasal symptoms and NPS in severe, uncontrolled CRSwNP over a 24 to 52-week period [1–4]. With their market approval and reimbursement by regulatory administrations, it is critical to control their effectiveness in routine practice, even considering the heterogeneity of the population and other clinical factors which may affect outcomes [10]. This is the first national cohort in France to

follow patients with CRSwNP undergoing biologic therapy. It allows for the analysis of follow-up data up to 18 months from a substantial number of patients. Additionally, it provides the opportunity to study patients who are excellent responders, for whom no systemic corticosteroids were prescribed between follow-up visits, indicating an optimal level of disease control. Our findings confirm that biologics are highly effective in improving all efficacy scores over 18 months of treatment in CRSwNP refractory to medical and surgical treatment. We also showed the rapidity of action with significant changes in all outcomes within 3 months of treatment.

Our results are consistent with previous real-life studies [10–13]. De Corso et al. observed similar outcomes in a cohort of 648 patients treated with dupilumab over a 12-month period [10]. The ranges of improvement in SNOT-22 scores, VAS for nasal symptoms, and NPS in their cohort were comparable to those observed in our study between baseline and M3. However, 8.6% of their patients never underwent surgery. The rapidity of symptoms recovery was even reported within 1 month in a real life prospective controlled study comparing 60 patients treated with dupilumab and 60 with INCS and OCS [14]. In our study, we observed a less pronounced improvement in symptoms after 6 months, consistent with findings from other real-world cohorts [10,15].

International guidelines from joint committee EUFOREA-EPOS 2023 provide a framework of eligibility criteria for biologic treatments [5]. The population characteristics in our study adhered to these recommendations, with a prominent smell disorder and a prior history of sinus surgery in 100% of cases. Median time to last surgery was 5 years [2-9] which is comparable to an Italian multicentric retrospective study enrolling 145 patients treated with dupilumab in real-life settings [15]. Surgery is mandatory in our country to comply with regulatory administrations. However there is still debate regarding the type of surgery to perform before considering biologic in uncontrolled CRSwNP [15]. In our cohort, more or less complete ESS was applied in 88.4 % of patients without a clear consensus. A significant proportion of our patients had a history of asthma (76.1%), accompanied by a blood eosinophilic profile (median blood count at baseline: 480 cell/μL (300-700)), indicating evidence of type 2 inflammation. In a study using computer data from 121 patients treated with dupilumab, Schmale et al. showed that 29% of the patients did not follow EUFOREA-EPOS guidelines, highlighting the deviations in the prescription of biologics in real life [16]. One explanation is the diverse prescribing patterns of biologics by different specialists, including otolaryngologists, allergists, and immunologists, based on varying indications. In BIOPOSE, biologics were exclusively initiated by rhinologists leading to a more standardized care pathway. In a cohort of 98 patients who were given dupilumab, Van der Lans et al. suggested that using EUFOREA-EPOS criteria to initiate biologic therapy resulted in comparable or slightly more favorable outcomes compared to the LIBERTY trials [17].

EUFOREA-EPOS proposed clinical criteria for a "good to excellent" response in 2023 to better identify patient populations who would benefit most from biologic therapy. The authors of these recommendations suggested conducting an initial assessment of the therapeutic response at 6 months and then repeating this evaluation every 6 months as long as the biologics treatment is maintained. We combined EUFOREA-EPOS 2023 qualitative criteria (reduced NP size, improved sense of smell, improved QoL, reduce need for OCS, reduced impact of comorbidities) with a quantitative evaluation of the relevant outcome parameters defined by EUFOREA 2021(VAS, SNOT-22 and NPS). In the context of managing asthma with biologics, the status of "super responder" has been established to identify patients whose symptoms are fully controlled without the need for OCS [18]. In CRSwNP, such a definition has yet to be established. The EUFOREA-EPOS 2023 criteria for an excellent response at 6 months help identify a subgroup of patients most likely to benefit from biologics. In our study design, we assigned the status of "excellent responder" to CRSwNP patients who achieved symptom control without the use of OCS or, if applicable, without asthma exacerbations during the first 6 months of follow-up. An excellent response to biologic was observed in 59% of patients after 6 months of treatment with biologic. At 12 and 18 months, the proportion of excellent response was slightly higher (respectively 66 and 68%). By only applying EUFOREA 2021 criteria (based on NPS, SNOT-22, nasal congestion score and VAS for total symptoms), De Corso et al. reported 57.9% and 65.7% of excellent responder at respectively 6 and 12 months of treatment with dupilumab [10]. Comparable results were also observed by Haxel et al. in a cohort of 70 patients treated with dupilumab or omalizumab [19]. Comparing the proportions of excellent responders at each timepoint beyond 6 months is challenging due to variations in treatment discontinuation, switching between biologics, and the reported off-label extension of dosing intervals for dupilumab. In the context of a real-world multicenter study, the dose tapering procedure for dupilumab is not currently standardized and cannot be mandated for the different prescribers involved. The minimal improvement observed between 12 months and 18 months aligns with the improvement kinetics for each outcome parameter described in figures 1 and 2. It appears that the primary therapeutic effect was rapidly achieved, with only a slight margin for further improvement after 6 months. Thus, evaluating the therapeutic response at 6 months enables rapid guidance for subsequent management strategies. In the case of an excellent response, biologic therapy can be continued with an anticipated maintenance of its effectiveness based on our findings. In the absence of an excellent response, management could be tailored according to the assessed parameters. A patient who remains anosmic with

a high polyp size score may potentially benefit from salvage surgery. An anosmic patient without significant polyp size is presumably at high risk of not recovering olfactory function. Some experts suggest this may be due to scar fibrosis of the olfactory cleft related to prior surgical interventions (20). In this context, Otten et al. proposed that responsiveness to OCS could serve as a predictor for the recovery of olfactory function when treated with biologics [21]. For a patient without an excellent response who frequently requires OCS or experiences recurrent bronchial exacerbations, switching biologic therapies could be considered. All these therapeutic options should be evaluated based on further real-world data and require validation through multidisciplinary consensus conferences. The patient's perceived therapeutic benefit should also be considered in the management strategy with biologic therapies. Questions persist regarding the management of patients who report subjective benefits without achieving significant improvement in SNOT-22 or NPS scores according to EUFOREA-EPOS 2023 criteria. The accumulation of real-world data on biologics through registries will undoubtedly guide a more tailored approach for these patients with seemingly dissociated responses. The concept of remission that could justify discontinuing biologic therapy remains uncertain and was not adequately addressed in our study.

Identifying relevant parameters or biomarkers of response to biologics is a crucial issue in CRSwNP management. With multivariate analysis applied to our population, the blood eosinophil count at baseline was identified as poorly associated with an excellent response (OR:1.001 95% CI: 1.000-1.002; p=0.02). Van der Lans demonstrated that blood eosinophil count was the primary T2 marker associated with biological treatment [22]. De Corso et al. found no significant association between baseline blood eosinophil count and treatment response, whereas asthma was associated with good response at 6 months in univariate analysis [10]. Thus, the high prevalence of asthma in our population may partially bias the role of baseline blood eosinophil levels, which are often elevated in this clinical context. In a retrospective study, Baird et al. compared the histopathologic findings of 237 CRSwNP patients who underwent ESS alone and 20 CRSwNP who underwent ESS after the failure of biologic therapy. The authors suggested that reduced tissue eosinophilia was associated with biologic non-responders (20). This finding should be interpreted with caution, as most patients received OCS in the weeks leading up to surgery. Moreover, it can be hypothesized that T2 biologics were primarily responsible for reducing the eosinophil count in the nasal polyps. Indeed, 14 of the 20 patients who did not respond to biologic therapy had received dupilumab, which targets the IL-4 receptor and inhibits the tissue migration of circulating eosinophils [23,24]. This hypothesis is supported by a study conducted on 57 patients treated with dupilumab for severe CRSwNP. The authors observed a significant reduction in the proportion of eosinophils in the cytological analysis of nasal secretions collected after one year of treatment [25]. Similarly, a cross-sectional study by Png et al. on CRSwNP patients at 6 months post-surgery, who had preexisting biologic therapy and subsequently underwent ESS, showed that a reduction in tissue eosinophils predicts poorly controlled disease. They also found that increased serum neutrophil count was associated with a poor disease control [26]. These results underscore the heterogeneity of cellular profiles in CRSwNP, which can lead to varied therapeutic responses. Prior to the advent of T2 biologics, analyses of inflammatory markers in nasal secretions from patients in Europe, Asia, and Australia with CRSwNP already revealed a diversity of T1, T2, and T17 cytokine profiles [27]. Enhancing the prediction of therapeutic response will require integrating this analysis into routine clinical practice.

In our cohort study, dupilumab tends to be associated with better outcomes at 6 months (OR:4.03 95% CI: 1.37-13.17; p=0.01). This result should be interpreted with caution. First, the majority of our patients were treated with dupilumab, as reimbursement for mepolizumab only began in 2022. While the multivariate analysis was statistically suggestive, it does not allow for definitive long-term conclusions. Indirect treatment comparison (ITC) studies suggests that dupilumab (targeting interleukin (IL)-4 cell receptor) may be superior to mepolizumab (targeting soluble IL-5) to improve symptoms control and QoL outcomes [28,29]. One hypothesis would be the upstream role of IL-4 in the T2 inflammation cascade; its blockade leading to a larger effect in the immune response compared to a downstream target as IL-5 [30]. Heterogeneity in terms of inclusion criteria, endpoints selection, methodology (specific questionnaire, olfactory test, VAS) and data extraction are important limitations of ITCs as reported in a recent systematic review [31]. True head-to-head clinical trials of biologics in CRSwNP are needed before definitive conclusions can be drawn [32]. Our real-world experience with mepolizumab remains limited. Phase 3 trials with mepolizumab indicated a significant clinical response from baseline to the end of the study at 52 weeks, even regarding perceived olfaction, as measured by VAS and the sense of smell item score from the SNOT-22 [3,33]. It is possible that the therapeutic effect of mepolizumab is more gradual [34]. Consequently, it is essential to inform patients about the expected timeline for clinical benefits when initiating treatment.

Several limitations of this study should be considered: the cohort was predominantly recruited from tertiary referral centers, which may bias the sample towards patients with the most severe and refractory CRSwNP. In this context, the observed trend toward a negative impact of long-standing CRSwNP on the 6-month response to biologics might reflect a population of patients who are at the end of their therapeutic course, with multiple prior surgeries. In some of these patients, bone and mucosal scarring could potentially hinder the anti-inflammatory effects of the biologic. BIOPOSE is expected to enroll more pa-

tients from non-academic centers to enhance national representativeness. A selection bias in prescribing the type of biologic therapy may be present, considering the blood eosinophil count at baseline. The concern about hypereosinophilia associated with dupilumab, as reported in clinical trials [35,36], prompted the initial prescription of mepolizumab in these patients. However, perfect randomization of treatment allocation is not feasible in a real-world study. In such settings, only the prescriber has the authority to determine therapeutic choices.

Conclusion

In real-world settings, the efficacy of biologics in CRSwNP is confirmed with a very early therapeutic response. Identifying excellent responders at 6 months allows for a rapid adjustment of therapeutic strategies. The role of surgery under biologic therapy, tapering protocols for doses and switching between biologics still needs to be refined [37]. Better defining the endotypic profiles of patients is essential for optimizing the use of biologics beyond the conventional T2 phenotypic characterization, which typically relies on measuring blood eosinophil levels and identifying associated asthma. The heterogeneity of T2 and non-T2 biological profiles in CRSwNP underscores the necessity for a comprehensive biological approach, incorporating tissue analysis of inflammatory markers and their relative expression in blood and nasal secretions.

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Authorship contribution

GM: search, study design, data collection, data analysis, drafting the article, and final approval. CD, JBL, VF, LG, CV, LC, NS, BV, FC, CR, RJ, JM, GB, VE, AC: search and data collection. JFP: search, study design, and data collection. GL: study design and data analysis. OM: search, data collection, data analysis, and final approval.

Conflict of interest

All authors report receiving personal fees as expert consultants for advisory boards from Sanofi and GlaxoSmithKline.

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