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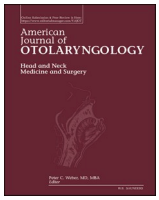

Dupilumab in chronic rhinosinusitis with nasal polyps: Real life data in a multicentric Sicilian experience

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ABSTRACT

Objective: This study aimed 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.

Methodology/principal: A multicentric observational cohort study was carried out. A total of 170 patients were enrolled in the Otorhinolaryngology Unit of the three University Hospitals and considered for dupilumab therapy. All recorder characteristics were age (at the first dupilumab application visit), sex, smoke habits, previous local and systemic corticosteroid therapy, history of endoscopic sinus surgery, number of previous endoscopic sinus surgery, concomitant asthma, history of an allergic condition, immunoglobulin E (IgE), allergy to nonsteroidal anti-inflammatory drugs (NSAIDs), Aspirin Exacerbated Respiratory Disease (AERD), other comorbidities associated, blood eosinophils, nasal polyp score, sinonasal outcome test 22 (SNOT 22), sniffin' stick test, the start date of dupilumab therapy and number of doses of dupilumab and eventually, Dupilumab's adverse events related to administration. The Wilcoxon test for dependent samples was performed to compare variables. Statistical significance was assumed for p values < 0.05.

Results: A statistically significant reduction in SNOT-22 and NPS was shown at the 6th and 12th month compared to baseline values ($p < 0.001$ for both comparisons). A statistically significant increase value at the Sniffin' sticks test was shown in the 6th and 12th month compared to baseline values ($p < 0.001$ for both comparisons).

At the 12-month follow-up, according to EUFOREA indications, all patients were considered to remain in treatment with dupilumab and continued the treatment because of a reduced NPS, improved quality of life and a reduced need for system corticosteroids.

Dupilumab seemed to be well tolerated by all patients. Any adverse effect of the drug led to the quit of biological treatment.

Conclusions: This multi-centric real-life study supported the effectiveness of dupilumab as an add-on therapy to intranasal corticosteroids in patients with severe uncontrolled CRSwNP in improvement of quality of life, severity of symptoms, polyp size reduction and smell function. Furthermore, our data support the safety profile of monoclonal therapy with dupilumab.

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1. Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease with widespread affection, approximately occurring in 5–28 % of the population worldwide [1–7]. The last European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) explains that CRS consists of inflammation of the nasal mucosa and the paranasal sinuses, clinically characterised by two or more symptoms, one of which should be either nasal congestion or nasal discharge and/or facial pain, pressure and/or reduction/loss of smell and either endoscopic signs of nasal polyps and abnormalities such as discharge and swollen mucosa in the middle meatus and mucosal changes within the osteo-meatal complex and sinuses on CT scan of the sinuses lasting at least 3 months [1]. Overall, CRS is a clinic-based diagnosis verified by a classic nasal endoscopic exam and a head CT scan. CRS is classified as chronic rhinosinusitis with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). CRSwNP is evaluated in 1–4 % of the general population and 25–30 % of patients with CRS. The mean age of patients is between 40 and 60 years at the time of diagnosis, but the first symptoms often begin between the ages of 20 and 30. The prevalence of CRSwNP increases with increasing age and is half as prevalent in men as in women, with a sex ratio of 1.3 [8,9]. Classical pharmacological therapy and nasal endoscopic surgical treatment have always represented the cornerstones of the management of patients with CRSwNP; unfortunately, over the years, it has been found that to control the progression of the disease it is necessary to intervene mainly in the Th2 inflammatory cascade. The deficient barrier function of the epithelium and the type 2 pattern of inflammation play a key role in the pathogenesis of CRSwNP, resulting in the production of some cytokines, including IL-4, IL-5 and IL-13 that induce the activation of eosinophils increasing the production of fibroblasts by eotaxin and B cells by IgE and Th2 cell differentiation and survival [10–12]. The recent advent of biological therapy for the treatment of CRSwNP has radically changed patient management with positive repercussions on disease control and, therefore, on the patient's quality of life. The quality of life of these patients is very poor due to the sensorial loss and inflammatory affection of the upper and lower respiratory airways [1,2,4]. The association between asthma and CRS is strongly reported by the scientific literature: approximately 25 % of patients with CRS compared to 5 % of the general population. In particular, in CRSwNP patients, the association with asthma rises to 30–70 %, and the NP condition is related to a more insidious pattern of asthma with higher severity [13,14]. This data once again supports the need to frame the upper and lower airways as a single morphofunctional entity, the concept of "united airway disease". Biological monoclonal therapy allows us to experiment with a type of precision and personalized medicine, improving outcomes, especially in those patients affected by uncontrolled CRSwNP. At the same time, target therapy requires careful endotyping and phenotyping of the patient, fundamental processes to make the most of the therapeutic effect [15]. It is important to underline once again how, where possible, a multidisciplinary approach with a proactive comparison between otorhinolaryngologists, pulmonologists and allergists can contribute to better a patient management. This study aims to report the results obtained with therapy in patients with CRSwNP enrolled and followed up in three third-level centers in Sicily. 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 life5 and olfactory function.

2. Materials and methods

2.1. Study population

A multicentric observational cohort study was carried out to assess the effectiveness and safety of dupilumab in patients affected by CRSwNP who were followed by the Otorhinolaryngology Unit of the University Hospital of Messina "G.Martino", Otorhinolaryngology Unit of the University Hospital of Palermo "P.Giaccone" and by the Otorhinolaryngology Unit of the University Hospital of Catania "G.Rodolico", all centers situated in Sicily, Italy. The study population was collected from January 2021 to May 2023. The sample size included all patients ≥18 years with a diagnosis of CRSwNP and a minimum NPS of 4 who had received systemic and/or topical corticosteroids in the preceding two years, previous sinonasal surgery, or not. The exclusion criteria were low adherence to drug use, radio-chemotherapy treatment in the last 12 months, concomitant long-term systemic corticosteroid therapy for chronic autoimmune disease, and pregnancy. As criteria of low adherence to drug use, we referred to all patients who are uncompliant with the posology of drug administration or all those patients who quit from follow-up visits programmed spontaneously. A patient-encrypted code was used to maintain the anonymity of patients in agreement with the Declaration of Helsinki.

2.2. Clinical evaluation

All recorder characteristics were age (at first visit for dupilumab application), sex, smoke habits, previous local and systemic corticosteroid therapy, history of endoscopic sinus surgery, number of previous endoscopic sinus surgery, concomitant asthma, history of an allergic condition, immunoglobulin E (IgE), allergy to non-steroidal anti-inflammatory drugs (NSAIDs), Aspirin Exacerbated Respiratory Disease (AERD), other comorbidities associated, blood eosinophils, nasal polyp score, sinonasal outcome test 22 (SNOT 22), sniffin' stick test, the start date of dupilumab therapy, and number of doses of dupilumab, and eventually, Dupilumab's adverse events related to administration. Patients were evaluated before starting the biological therapy and every six months with a general anamnesis, calculating the SNOT-22 questionnaire, and performing an endoscopic sinonasal evaluation to determine the NPS. A blood test with complete blood counts to evaluate the total serum immunoglobulin E (IgE) and eosinophil count was performed before starting the treatment and every six months and sniffing sticks test. The date of the first dupilumab prescription during the study period was considered the "index date" for each patient. The prescription of dupilumab followed the criteria validated by the Italian Medicines Agency (AIFA) for CRSwNP treatment. The adherence to therapy was evaluated following EPOS 2020 criteria [1] in which the panel advises to use of dupilumab in patients with CRSwNP fulfilling the EUFOREA consensus for treatment with monoclonal antibodies [1,17]. Patients were subjected every 14 days to an injection of dupilumab 300 mg and underwent scheduled follow-up visits with the evaluation of clinical scores to establish the state of activity of CRSwNP, evaluating the reduction of NPS by endoscopic exam, and considering the subjective perception of the disease by SNOT-22. An endoscopic exam was performed evaluating each nasal fossa separately following NPS 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 reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate, and 4 = large polyps causing complete obstruction of the inferior nasal cavity). The total for both nasal cavities was registered as the NPS. The subjective perception of the disease was calculated using the Italian version of the SNOT-22 with a possible total score range from 0 to 110. Moreover, all AEs were collected during the follow-up period every three months. Each patient informed the clinician of any new symptoms they may be experiencing since the start of dupilumab. The minimum follow-up period was six months.

2.3. Data analysis

A descriptive analysis was performed using StatPlus: mac. Medians with interquartile ranges (Q1–Q3) were estimated for continuous variables, while absolute and percentage frequencies were estimated for

categorical variables. The normality of variables was verified with the Kolmogorov–Smirnov test for normality. Since a non-normal distribution of some of the numerical variables was verified, a nonparametric approach was adopted. Groups of post-surgical and naïve patients were compared for baseline characteristics. All endoscopic evaluations by NPS and subjective perception comparisons by SNOT-22 were made between data obtained at different follow-up times (e.g., 6 and 12 months after the beginning of therapy) and baseline. The Wilcoxon test for dependent samples was performed to compare continuous variables, while Fisher's exact test was used for qualitative variables. The Mann-Whitney *U* test for independent samples was performed to compare continuous variables, while the Pearson Chi-square test was used for qualitative variables. Statistical significance was assumed for p values $<$ 0.05.

3. Results

A total of 170 patients were enrolled in the Otorhinolaryngology Unit of the three University Hospitals and considered for dupilumab therapy (Table 1). During the observational period, eight patients were excluded due to a lack of adherence to the treatment in accordance with the EPOS criteria. Of all 170 patients, 109 were men (64.1 %) while 61 were women (35.9 %), with a median (Q1–Q3) age of 54 (45–63) years. Thirty free patients (19.4 %) were smokers. Moreover, 100 patients (58.8 %) had a history of allergic conditions with concomitant asthma (p-value 0.005) presented in 66 patients (85.7 %). The median value of Sino-Nasal Outcome Test 22 (SNOT-22) pretreatment was 70 (54–80), with a median nasal polyps score (NPS) at pretreatment of 6 (5–7). 95.3 % of the patients were under treatment with intranasal corticosteroids. 140 patients (82,4 %) were in treatment with oral corticosteroids and were unresponsive or not compliant. We noted that 47 patients were intolerant to non-steroidal anti-inflammatory drugs (27.6 %) with p values $<$ 0.05. 37 patients (21.8 %) results affected by aspirin-exacerbated respiratory disease (p value $<$ 0.005). 134 patients (78.8 %) were previously subjected to endoscopic sinus surgery (ESS), 86 of whom were men. General characteristics of the sample size and previous ESS and naïve groups are reported in Table 2. In the previous ESS group, a higher percentage of males and the elderly was shown without any statistically significant differences compared to naïve patients, while a statistically significantly higher median baseline value of SNOT-22 was reported for previous ESS patients compared to naive patients (52–79 vs 53–65 SNOT value, $p = 0.005$). 79.1 % of patients who underwent a Previous ESS resulted in treatment with oral corticosteroids in the last year vs 94.4 % presented in the naive patients group ($p = 0.05$).

In Fig. 1 we study the median value variations over time about the NPS, SNOT-22, Sniffin' sticks test, and eosinophil count. The median (Q1–Q3) NPS score at baseline was 6 (7–5), in the 6th month, was 3 (4–2), and in the 12th month was 2 (3–1). The median (Q1–Q3) SNOT-22 baseline was 66 (78–54), in the 6th month was 27 (35–15), and in the 12th month was 21 (31−11). The median (Q1–Q3) Sniffin' sticks test at baseline was 2 (4–0), in the 6th month was 9 (12–7), and in the 12th month was 12 (14–9). The median (Q1–Q3) Eosinophil blood count at baseline was 0.6 (0.7–0.3), in the 6th month 0.6 (0.9–0.4) and in the

Table 1
Patients' main clinical characteristics and endoscopic and symptom evaluations at baseline for the whole group and for the asthma and non-asthma patients, separately.

	Asthma ($n = 77$)	Non-asthma ($n = 93$)	*P* value	All ($n = 170$)
Sex, male *n* (%)	46 (59.7)	63 (67.7)	0.279	109 (64.1)
Age, years median (Q1–Q3)	53 (45–62)	55 (46–64)	0.749	54 (45–63)
Smokers, *n* (%)	17 (22.1)	16 (17.2)	0.424	33 (19.4)
Allergic conditions, *n* (%)	66 (85.7)	34 (36.6)	<0.001	100 (58.8)
Hypertension, *n* (%)	23 (29.9)	27 (29.0)	0.905	50 (29.4)
Obesity, *n* (%)	5 (6.5)	15 (16.1)	0.052	20 (11.8)
Diabetes, *n* (%)	3 (3.9)	4 (4.3)	0.895	7 (4.1)
Cardiovascular disease, *n* (%)	1 (1.3)	3 (3.2)	0.409	4 (2.4)
Anxiety/depression, *n* (%)	5 (6.5)	3 (3.2)	0.317	8 (4.7)
Dyslipidemia, *n* (%)	2 (2.6)	2 (2.2)	0.848	4 (2.4)
Other comorbidities*(Celiac, Churg Strauss disease o EGPA, other autoinmune diseases), *n* (%)	11 (14.3)	5 (5.4)	0.048	16 (9.4)
SNOT-22, median (Q1–Q3)	70 (54–80)	65 (52–76)	0.235	66 (53–78)
NPS, median (Q1–Q3)	6 (5–7)	6 (5–7)	0.171	6 (5–7)
Blood eosinophil count, median (Q1–Q3)	0.6 (0.4–0.8)	0.5 (0.3–0.7)	0.126	0.6 (0.3–0.7)
Previous ESS, *n* (%)	62 (80.5)	72 (77.4)	0.622	134 (78.8)
Intranasal CCS treatment, *n* (%)	75 (97.4)	87 (98.5)	0.238	162 (95.3)
Oral CCS treatment in the last year, *n* (%)	65 (84.4)	75 (80.6)	0.521	140 (82.4)
NSAID intolerance, *n* (%)	31 (40.3)	16 (34.0)	0.001	47 (27.6)
Aspirin exacerbated respiratory disease, *n* (%)	30 (39.0)	7 (7.5)	<0.001	37 (21.8)

CCS = corticosteroid; ESS = endoscopic sinus surgery; NSAID = non-steroidal anti-inflammatory drugs; SNOT-22 = Sino-Nasal Outcome Tests-22; NPS = nasal polyps score.
The Mann-Whitney *U* test for independent samples was performed to compare continuous variables, while Pearson Chi-square test was used for qualitative variables. Statistical significance was assumed for p values $<$ 0.05.

Table 2
Patients' main clinical characteristics and endoscopic and symptom evaluations at baseline for the whole group and for the post-surgical and naïve groups separately.

	Previous ESS ($n = 134$)	Naïve ($n = 36$)	*P* value	All ($n = 170$)
Sex, male *n* (%)	86 (64.2)	23 (63.9)	0.974	109 (64.1)
Age, years median (Q1–Q3)	55 (46–64)	50 (41–58)	0.197	54 (45–63)
Smokers, *n* (%)	25 (18.7)	8 (22.2)	0.631	33 (19.4)
Allergic conditions, *n* (%)	77 (57.5)	23 (63.9)	0.487	100 (58.8)
Asthma, *n* (%)	62 (46.3)	15 (41.7)	0.622	77 (45.3)
Hypertension, *n* (%)	38 (28.4)	12 (33.3)	0.561	50 (29.4)
Obesity, *n* (%)	16 (11.1)	4 (11.9)	0.891	20 (11.8)
Diabetes, *n* (%)	6 (4.5)	1 (2.8)	0.649	7 (4.1)
Cardiovascular disease, *n* (%)	4 (3.0)	–	–	4 (2.4)
Anxiety/depression, *n* (%)	7 (5.2)	1 (2.8)	0.538	8 (4.7)
Dyslipidemia, *n* (%)	2 (1.5)	2 (5.6)	0.153	4 (2.4)
Other comorbidities*(Celiac, Churg Strauss disease or EGPA and Other Autoinmune diseases), *n* (%)	12 (9.0)	4 (11.1)	0.694	16 (9.4)
SNOT-22, median (Q1–Q3)	70 (52–79)	59 (53–65)	0.017	66 (53–78)
NPS, median (Q1–Q3)	6 (5–7)	6 (5–7)	0.832	6 (5–7)
Blood eosinophil count, median (Q1–Q3)	0.6 (0.4–0.7)	0.5 (0.3–0.8)	0.540	0.6 (0.3–0.7)
Intranasal CCS treatment, *n* (%)	126 (94.0)	36 (100)	–	162 (95.3)
Oral CCS treatment in the last year, *n* (%)	106 (79.1)	34 (94.4)	0.032	140 (82.4)
NSAID intolerance, *n* (%)	37 (27.6)	10 (27.8)	0.984	47 (27.6)
Aspirin exacerbated respiratory disease, *n* (%)	30 (22.4)	7 (19.4)	0.704	37 (21.8)

CCS = corticosteroid; ESS = endoscopic sinus surgery; NSAID = non-steroidal anti-inflammatory drugs; SNOT-22 = Sino-Nasal Outcome Tests-22; NPS = nasal polyps score.
The Mann-Whitney *U* test for independent samples was performed to compare continuous variables, while Pearson Chi-square test was used for qualitative variables. Statistical significance was assumed for p values $<$ 0.05.

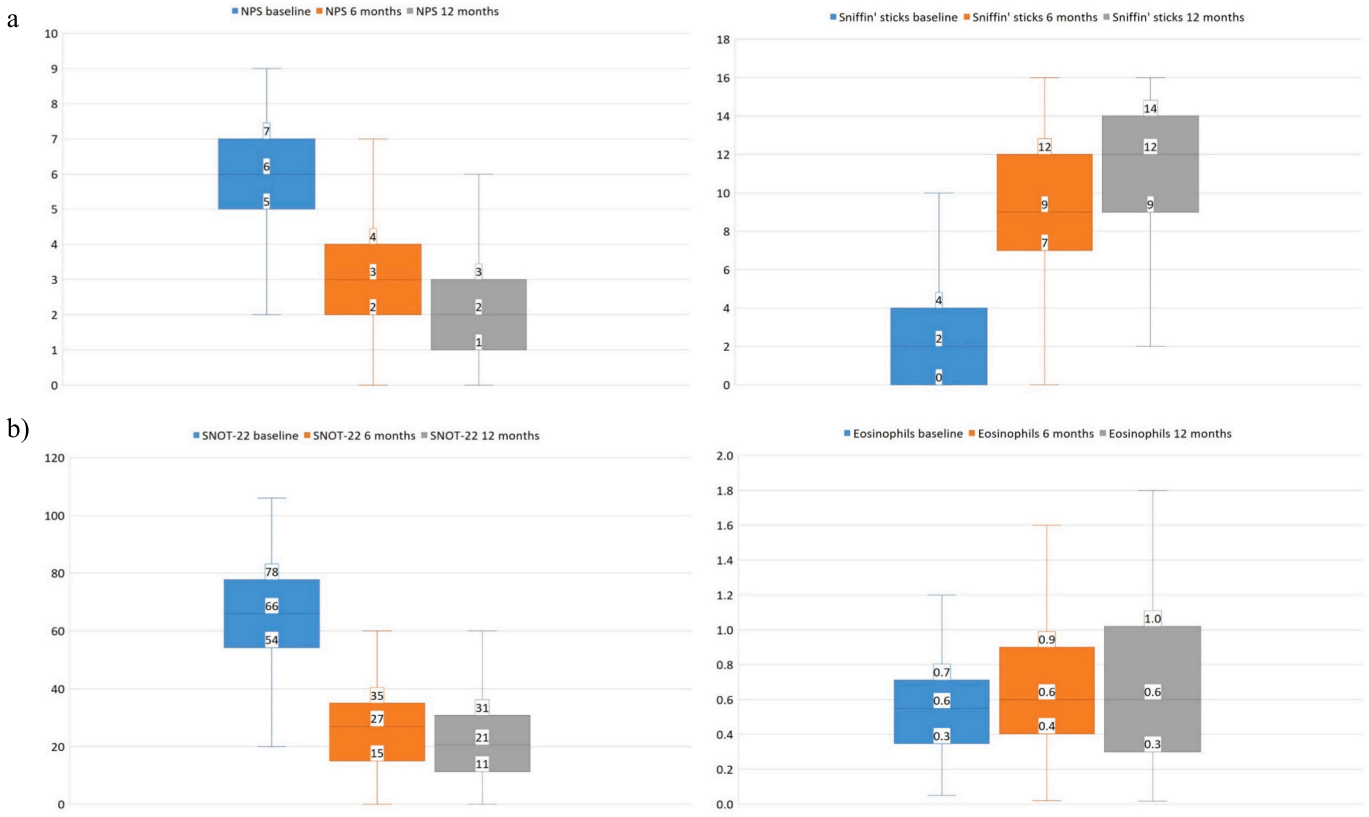

Fig. 1. Median value variations over time: (a) NPS, (b) SNOT-22, (c) Sniffin' sticks test, (d) eosinophil count.
SNOT-22 = Sino-Nasal Outcome Test 22; NPS = nasal polyps score.

12th month was 0.6 (1.0–0.3).

A statistically significant reduction in SNOT-22 and NPS was shown at the 6th and 12th months compared to baseline values (SNOT-22, −39 and −45, $p < 0.001$ for both comparisons; NPS, −3 and −4, $p < 0.001$ for both comparisons). A statistically significant increase value at the Sniffin' sticks test was shown in the 6th and 12th month compared to baseline values, +7 and +10 respectively ($p < 0.001$ for both comparisons) (Table 3).

3.1. Safety profile

Dupilumab seemed to be well tolerated by all patients however, during the follow-up period, twenty-four patients reported that they had some adverse reactions: eight patients had pain at the site of injection referring to rubor, calor and dolor during the first 3 days after the injection. The patients were treated with betamethasone di-propionate and gentamicin sulfate, with a local application two times a day until the end of symptomatology. Moreover, five patients experimented with transient hypereosinophilia confirmed by an increase in blood eosinophil count with stabilization and/or resolution with any further implications, four patients experimented with arthralgia in the subsequent day after the injection, two patients had epiphora ceasing spontaneously, a patient had headache associated of 24 h of duration after the second injection, a patient experimented a dermic rash with an erythematous rash on the homolateral arm where patient performed the injection, while one patient reported pyrexia on the third day after the second injection and, a patient had various episodes of itching in all body solving with a common antihistaminic oral treatment. Any adverse effect of the drug led to the quit of biological treatment.

Table 3
Differences from baseline to each follow-up for SNOT-22, NPS, sniffin' sticks test, and blood eosinophil count.

	6th months vs. baseline	*P* value	12th months vs. baseline	*P* value
SNOT-22, median (Q1–Q3)	−39	<0.001	−45	<0.001
NPS, median (Q1–Q3)	−3	<0.001	−4	<0.001
Sniffin' sticks test, median (Q1–Q3)	+7	<0.001	+10	<0.001
Blood eosinophil count, median (Q1–Q3)	0		0	

The Wilcoxon test for dependent samples was performed to compare variables. Statistical significance was assumed for p values < 0.05.
At the 12-month follow-up, according to EUFOREA indications, all patients were considered to remain in treatment with dupilumab and continued the treatment because of a reduced NPS, improved quality of life, and a reduced need for system corticosteroids (good response 3–4 criteria).

4. Discussion

This research group based on the studies in the literature on therapy with dupilumab and real-life [16–21] presents data from three reference centers aimed at studying the efficacy and safety profile of dupilumab in the treatment of CRSwNP in a large population sample. Our study confirms that the administration of dupilumab 300 mg by injection every 2 weeks is highly effective, with already consistent results 6 months after the start of treatment that are much more optimistic than in trials performed in selected populations. The diagnosis of CRSwNP leads to a worsening in patients' quality of life due to sensory loss and inflammatory effects on the upper and lower respiratory airways [1,2,4]. Since CRSwNP is a chronic disease of the airways, the patient will be followed up long-term as with any chronic disease with a burden of disease that has significant healthcare-related costs [22]. We observed a substantial improvement in the quality of life of our patients, recording a

SNOT-22 value which was −39 and −45 compared to the baseline value at 6 months and 12 months respectively. In addition we report that the group who underwent endoscopic sinus surgery previously started from a higher baseline value of SNOT-22 vs the Naive group. One of the most significant data is certainly the recovery of the olfactory function at the Sniffin' Sticks test, finding a +7 and a +10 compared to the baseline values respectively at the 6th and 12th month. It is one of the earliest signs of treatment efficacy that patients experience once Dupilumab therapy is started [22]. The results that we have, similar to another study [23], as well as post hoc analyses of SINUS-24 and SINUS-52 studies [24–26], indicate that neither prior surgery, comorbid asthma, nor NSAID-ERD affected smell improvement with dupilumab. Moreover, we have data suggesting that patients undergoing excellent ESS, according to the Access Score, respond earlier to biologic therapy; also about asthmatic patients and/or NSAID-ERD, we register a significant decrease of NPS and SNOT-22. We also studied, as suggested in the literature [5,27], the trend of plasma eosinophils resulting in non-significant statistical changes during the follow-up period compared to the baseline value, in contrast with the data presented in the literature [28]. An increased eosinophil blood value was not associated with clinical symptoms or sequelae and had no observable impact on treatment efficacy. This condition is attributable to the dupilumab mechanism of action, which transiently increases blood eosinophil concentrations by inhibiting eotaxin-3, resulting in a lack of migration of eosinophils from peripheral blood to polyp tissue. Although these increases are mostly temporary, clinic discretion should be used to monitor patients suspected of having an eosinophilic clinical state, and stronger collaboration with rheumatologists and pulmonologists should be evaluated to implement decisions regarding therapy continuation [28,29].

All patients arrived at 1 year of observation and continued the treatment with dupilumab because of the reduced NPS, improved quality of life, reduced need for system corticosteroids and improved comorbidities related to the CRSwNP; the evaluation of the treatment corresponded to three criteria and it was considered as a good response following the EUFOREA response criteria [15].

5. Conclusion

This multi-centric real-life study supported the 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 the improvement of quality of life, severity of symptoms, polyp size reduction and smell function. Finally, our data support the safety profile of dupilumab treating patients with severe uncontrolled CRSwNP in real life.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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CRediT authorship contribution statement

Conceptualization, C.G., M.R, F.S.; methodology, C.G, M.A.B.; validation, F.C., B.G.; formal analysis, C.G.; data curation, C.G.; writing—original draft preparation, C.G.; writing—review and editing, C.G.; visualization, M.A.B., G.G., E. G., A. I., F.L., F.D., F.F.; supervision, B.G., F.G., S.G. I.L.M.

All authors have read and agreed to the published version of the manuscript.

Conflict of interest

No conflict of interest exists.

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