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Severe chronic rhinosinusitis treated with dupilumab, a real-life analysis of early effectiveness

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Abstract. – OBJECTIVE: The present study evaluated the safety and efficacy of dupilumab in severe uncontrolled type 2 chronic rhinosinusitis with nasal polyps (CRSwNP).

PATIENTS AND METHODS: A retrospective analysis was conducted on a cohort of adult patients affected by severe CRSwNP treated with dupilumab. Maxillofacial computed tomography, evaluation of blood eosinophils and serum IgE levels, measurement of nasal polyp score (NPS), smell identification test (SSIT-16), sinonasal outcome test-22 (SNOT-22) and asthma control test (ACT) were performed. Follow-up was conducted at 2 weeks, and at 1, 3, and 6 months. Adverse events and the efficacy of treatment were monitored.

RESULTS: 23 patients were enrolled. After 15 days, scores of the SNOT-22, NPS and SSIT-16 significantly improved. These outcomes were also maintained after 1, 3, and 6 months ($p < 0.001$). At this latter follow-up time, SNOT-22 showed a change of -33.10 ($p < 0.001$), NPS -3.36 ($p < 0.001$) and SSIT-16 +5.60 ($p < 0.001$). In all, 26.1% of patients experienced early minor complications.

CONCLUSIONS: In the present study, dupilumab was effective in the treatment of severe uncontrolled CRSwNP, demonstrating a quick significant improvement in both questionnaires and endoscopic evaluation. Only minor complications were observed.

Key Words:
Chronic rhinosinusitis, Dupilumab, Monoclonal antibodies, Nasal polyps, Type-2 inflammation.

Introduction

Chronic rhinosinusitis (CRS) represents a wide spectrum of diseases characterized by persistent inflammation of the nose and the paranasal sinuses connoted by nasal congestion, rhinorrhea, facial pain, and reduction of smell[1]. Additionally, nasal polyps, mucopurulent discharge, and mucosal edema can be found during the endoscopic evaluation of nasal cavities. The detection of tissue remodeling has generally been employed to discriminate between chronic rhinosinusitis with and without nasal polyps (CRSwNP and CRSsNP, respectively). Nevertheless, this phenotypic categorization of CRS has recently been revolutionized in the newest European Position Paper of Rhinosinusitis and Nasal Polyps (EPOS)[1], where the endotype of inflammation (immunological alterations that lead to the development of the disease and, eventually, polyp formation) was put in focus. Three major CRS-related endotypes (type 1, 2 and 3) have been described, but CRSwNP mainly associates with type 2 inflammation, which entails the production of interleukin-4 (IL-4), IL-5 and IL-13[1-3]. Moreover, it is characterized by the recruitment of eosinophils, basophils and mast cells and is clinically related to a more severe form that is resistant to current therapies for CRS[1,4].

The difficulties encountered in the management of type-2-related CRSwNP resulted in the

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development of biological target therapies, which restrain the signaling of specific cytokines and interrupt the inflammatory cascade. Dupilumab is a fully human monoclonal antibody that, binding to the shared receptor's subunit called IL-4Rα, inhibits the IL-4 and IL-13 pathway[4]. This antibody has already shown clinical efficacy in the endotype-2 related conditions[5,6], and the latest studies evaluating its efficacy and safety in adult patients with severe CRSwNP have reported[4,7] encouraging data, improving patients' quality of life (QoL) and reducing the volume of polyps.

In this scenario, the present study assessed the safety and efficacy of dupilumab in a real-life setting in a selected cohort of patients affected by severe uncontrolled type 2 CRSwNP.

Patients and Methods

A retrospective analysis was conducted on a cohort of adult patients affected by severe CRSwNP and treated with Dupixent® (dupilumab) between May 2021 and May 2022 at the Unit of Otorhinolaryngology – Head and Neck Surgery at the IRCSS Ospedale Policlinico San Martino, Genoa, Italy. The research was conducted under the approval of the IRCCS Ospedale Policlinico San Martino Institutional Ethics Committee (CER Liguria: 384/2022-DB id 11996) following the principles of the Declaration of Helsinki.

Diagnostic Work Up

Before treatment, all patients were investigated in terms of clinical history and habits, previous endoscopic sinus surgery, use of nasal or systemic corticosteroids (SCS), and the presence of allergy to inhalant agents or intolerance to non-steroidal anti-inflammatory drugs (NSAIDs). A blood test for evaluation of blood eosinophils and serum IgE level was also performed.

Radiological Assessment

A maxillofacial computed tomography (CT) scan was performed before treatment to evaluate the radiological severity of the disease (Lund-Mackay score)[8] and the completeness of previous endoscopic surgeries, when performed, based on the degree of patency of drainage routes of the paranasal sinuses (ACCESS score)[9]. With the Lund-Mackay staging system, each sinus cavity is given a score according to radiological opacification: 0 (no opacification), 1 (partial opacification), or 2 (complete opacification). Additionally, the ostiomeatal complex is scored as 0 (not occluded) or 2 (occluded). Similarly, the ACCESS score assigns to each sinus a score based on the extent of previous surgery: 0 (no more bony structures have to be removed to free the sinus pathway drainage), 1 (there are still some bony lamellae/cells that need to be removed), or 2 (no previous surgery has been performed).

QoL and Asthma Control Assessment

A smell identification test on 16 samples (Burghart Odofin Sniffin' 16-Stick Identification Test®)[10], sinonasal outcome test- 22 (SNOT-22), and asthma control test (ACT) questionnaires were performed before treatment and at each visit to monitor the quality of life and presence and control of asthma. The smell 16-stick identification test (SSIT-16) is performed by the administration of 16 odors in which the patient must choose between four different options; depending on the number of correct answers, patients were stratified as anosmic (score between 0 and 5), hyposmic (score between 6 and 10) and normosmic (score between 11 and 16). SNOT-22 is a questionnaire that assigns a score (min. 0, max. 5) to 22 items, that focuses on major CRS symptoms of the nasal domain and additional otolaryngologic, psychological, and emotional symptoms[11]. The ACT is used to understand the burden of the patient's asthma and clinical control. This latter is a patient self-administered tool that measures the frequency of asthma symptoms, use of rescue medications and the effect of asthma on daily functioning. It is represented by a 5-item scoring system, with a 5-point scale that results in total scores ranging from 5 (poor control) to 25 (complete control of the disease)[12].

Endoscopic Evaluation

A nasal rigid endoscopy with 0-30° and 45° rod lenses (Karl Storz® endoscope, Tuttlingen, Germany) was performed to evaluate both nasal cavities and to measure the nasal polyp score (NPS) on a scale from 0 to 8 (0 = no polyps, 1 = 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 = 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)[13].

Dupilumab Treatment Eligibility Criteria

Based on the therapeutic plan established by the Italian Medicines Agency (AIFA), patients

with the following characteristics were considered eligible for treatment: age ≥ 18 years; endoscopic diagnosis of severe CRSwNP; NPS > 5 or SNOT-22 > 50; failure of prior medical treatments due to complications or inefficacy (at least 2 cycles of systemic corticosteroid in the last year); failure of previous surgical treatment (ascertained by the onset of postoperative complications or by lack of therapeutic response).

Dupilumab Administration and Follow-Up

Dupilumab was administered with a pre-filled syringe through a subcutaneous injection at a dose of 300 mg once every two weeks. The first injection was carried out under medical control at the Unit of Otorhinolaryngology-Head and Neck Surgery at the IRCSS Ospedale Policlinico San Martino, Genoa, Italy. Adverse events were monitored and defined as early or late, if the onset was before or after 30 days of treatment, respectively. Therefore, follow-up visits were conducted at 2 weeks, and 1, 3 and 6 months after the start of the therapy. Follow-up of all these patients is still ongoing. QoL assessments, ACT, nasal endoscopy, and eosinophilic count were investigated at each follow-up visit.

Efficacy of Treatment

To assess the efficacy of treatment, the indications proposed by the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) were followed. Therapy was carried on after 6 months if at least one of the following criteria were satisfied: improvement of smell from anosmia to hyposmia/normosmia; NPS reduction ≥ 1, SNOT-22 reduction ≥ 8.9[14]. Moreover, the disease control was evaluated by the criteria proposed by the latest EPOS guidelines[1], dividing patients according to clinical response as follows: NPS reduction (at least 1 point); SNOT-22 reduction (at least 8.9 points); SCS need reduction; SSIT-16 improvement (at least 4 points); reduced impact of comorbidities (at least ACT > 19). Based on the abovementioned criteria, patients were divided into 4 groups: "Non-responder" (0 criteria met); "Poor responder" (1-2 criteria met); "Moderate responder" (3-4 criteria met); and "Excellent responder" (5 criteria met).

Statistical Analysis

Age, gender, presence of allergy, NSAID intolerance, asthma, need for SCS in the previous year and previous surgery were correlated with the onset of complications in the cohort. NPS, ACT, SNOT-22, SSIT-16 mean results and eosinophilic count were compared at different follow-up times. The impact of previous surgery was investigated and correlated with the previous parameters. A paired *t*-test was used for matched group analyses. In these cases, as data were paired, missing data were removed pairwise from the analysis. In case of numerous matched group comparisons, a one-way ANOVA test was used. Therefore, a post-hoc test (Bonferroni test) was used to understand significant associations between groups. Differences in the distribution of categorical data between groups were tested by χ^2 or Fisher's exact test, as appropriate. Statistical significance was assumed for *p*-values < 0.05. Statistical analysis was performed using SPSS Statistics v. 29.0.0 for Mac (IBM Corp., Armonk, NY, USA).

Results

Twenty-three patients (9 males) were retrospectively enrolled, with a female-to-male ratio of 1.6. The mean age was 55.8 ± 14.8 years. In all, 17 (73.9%) patients included in the study had undergone previous endoscopic sinus surgery. The mean follow-up was 5.1 ± 1.7 months.

Twelve patients (52.2%) had performed at least two cycles of SCS therapy in the previous year, and 19 (82.6%) had comorbid asthma. Fourteen (60.9%) patients were intolerant to NSAIDs, and all of these presented Samter's triad consisting of the simultaneous presence of nasal polyps, asthma, and NSAID intolerance. General data are presented in Table I**,** while Table II shows the clinical and radiological scores, blood test results, and endoscopic assessment of NPS collected before starting biological therapy.

Follow-Up and Adverse Events

Of the 23 patients included, 21 (91.3%) completed the 15-day follow-up, 20 (87.0%) 1-month follow-up, 19 (82.6%) the 3-month follow-up and 15 (65.2%) the 6-month follow-up. Missing patients interrupted the follow-up spontaneously for reasons unrelated to the therapy.

None of the variables analyzed (age, gender, presence of allergy, NSAID intolerance, asthma, need for SCS in the previous year and previous surgery) showed a significant correlation with complications. Overall, 6 patients (26.1%) experienced an early complication. One (4.3%), despite a remarkable reduction of NPS after 15 days of treatment (from

Table I. Demographic data of patients included in the study. Results represent the mean ± standard deviation and number of events (%) for continuous and categoric variables, respectively. SCS: systemic corticosteroid; NSAID: non steroid anti-inflammatory drug.

Variable	Value
Patients	23 (100.0%)
Age	55.8 ± 14.8
Gender	
Male	9 (39.1%)
Female	14 (60.9%)
Previous endoscopic sinus surgery	
Yes	17 (73.9%)
No	6 (26.1%)
Patients using SCS in the previous year	
Yes	16 (69.6%)
No	7 (30.4%)
Number of cycles of SCS in the previous year	5.0 ± 6.9
Allergy	
Yes	17 (73.9%)
No	6 (26.1%)
Asthma	
Yes	19 (82.6%)
No	4 (17.4%)
NSAID intolerance	
Yes	15 (65.2%)
No	8 (34.8%)

6 to 0), experienced progressive headache, ocular pain, and worsening of nasal symptoms after two drug administrations, without evidence of hyper-eosinophilia. Thus, dupilumab was interrupted after 1 month, and the patient continued intranasal steroid therapy with nasal rinses only. The remaining 5 patients suffered from minor symptoms: one complained of headache; two reported mild myalgia and arthralgia; one referred to stomach pain; lastly, one patient reported conjunctivitis. None of these five patients needed to stop the therapy as symptoms were transient and resolved spontaneously. No patient showed late complications.

Table II. Quality of life and asthma assessment, radiological evaluation and eosinophilic count before starting therapy. SSIT-16: Sniffin' Sticks-16 Identification Test; SNOT-22: Sinonasal Outcome Test-22; ACT: Asthma Control Test; NPS: Nasal Polyp Score.

Variable	Mean value	Standard deviation
SSIT-16	4.00	2.72
SNOT-22	62.70	18.61
ACT	15.94	5.17
NPS	6.09	1.31
Lund-Mackay score	19.21	3.78
Eosinophil count (*10^9 U/L)	0.68	0.51

Steroid Treatment

All patients continued long-term nasal therapy consisting of intra-nasal corticosteroid (INCS) and nasal irrigation with saline during the study period. Before starting therapy, 16 patients (69.6%) had undergone at least 1 cycle of SCS, and 12 (52.2%) had at least 2 cycles of SCS in the previous year. After starting dupilumab, no patients required SCS. Similarly, none of the patients were submitted to surgical revision.

Impact on QoL, Endoscopic and Biochemical Outcomes, and ACT

After 15 days, SNOT-22 and NPS values reduced significantly from 62.90 ± 17.45 to 38.05 ± 20.75 and from 5.95 ± 1.35 to 3.95 ± 2.17, respectively ($p < 0.001$). Similarly, outcomes of the SSIT-16 changed significantly from 3.75 ± 2.69 to 7.90 ± 2.87 ($p < 0.001$). ACT showed a positive trend without achieving statistical significance (Table III). Therefore, the impact of dupilumab therapy at 1, 3, and 6 months and its correlation with QoL, endoscopic and biochemical measures was investigated (Table IV). As presented in

Table III. Impact of dupilumab at 15 days after treatment. SD: Standard Deviation; SNOT-22: Sinonasal Outcome Test-22; NPS: Nasal Polyp Score; ACT: Asthma Control Test; SSIT-16: Sniffin' Sticks-16 Identification Test.

	Pre-treatment		15 days			
Variables	Mean	SD	Mean	SD	Delta	*p*-value
SNOT-22	62.9	17.4	38.0	20.7	-24.9	**< 0.001**
NPS	5.95	1.35	3.95	2.17	-2.00	**< 0.001**
ACT	16.13	5.45	19.38	5.08	3.25	0.059
SSIT-16	3.75	2.69	7.80	2.87	4.05	**< 0.001**

Table IV. Impact of dupilumab administration at 1, 3 and 6 months. SD: Standard Deviation; SNOT-22: Sinonasal Outcome Test-22; NPS: Nasal Polyp Score; ACT: Asthma Control Test; SSIT-16: Sniffin' Sticks-16 Identification Test.

	Pre-treatment		1 month		3 months		6 months		
Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*-value
SNOT-22	62.70	18.60	30.45	22.23	22.11	10.99	29.60	17.56	**< 0.001**
NPS	6.09	1.31	3.35	2.41	2.88	2.59	2.73	2.31	**< 0.001**
ACT	15.94	5.33	20.93	4.04	22.10	10.99	23.09	1.92	0.054
Eosinophilic count (*10^9/L)	0.68	0.50	0.72	0.60	1.14	0.65	0.67	0.53	0.198
SSIT-16	4.00	2.72	8.95	2.66	8.26	3.54	9.60	3.54	**< 0.001**

Figure 1, the SNOT-22 score showed a significant reduction with a mean change of -32.25 ($p < 0.001$) from baseline at 1 month, -40.59 ($p < 0.001$) from baseline at 3 months, and -33.10 ($p < 0.001$) from baseline at 6 months. There was no significant mean difference between 1, 3, and 6 months.

Similarly, NPS and SSIT-16 showed a significant variation across follow-up times, with a mean difference of -2.74 ($p < 0.001$) and +4.95 ($p < 0.001$) from baseline to 1 month, -3.21 ($p < 0.001$) and +4.26 ($p < 0.001$), from baseline to 3 months, -3.36 ($p < 0.001$) and +5.60 ($p < 0.001$) from baseline to 6 months, respectively. The results did not change significantly between 1, 3, and 6 months. The variation of mean NPS and SSIT-16 over time is shown in Figure 1. Mean ACT values improved during follow-up compared to baseline values, showing a trend towards significance without reaching statistically significant values ($p = 0.054$): +4.99 at 1 month, +6.16 at 3 months, and +7.15 at 6 months (Figure 2). Blood eosinophil count showed no significant variation when compared before treatment and at 1, 3, and 6 months.

No patients included in the study were categorized as a "non-responder", according to EPOS 2020 criteria[1]. Figure 3 shows the rate of response over time.

Impact of Previous Surgery on QoL and Endoscopic Outcomes

In Table V, the analysis of QoL and endoscopic outcomes at 15 days, and at 1, 3 and 6 months after treatment in patients with or without a history of previous endoscopic sinus surgery (ESS) is reported. No significant association was found during follow-up, except for SNOT-22 at 3 months, which was significantly lower in patients who were previously submitted to surgery (19.14 ± 9.99 *vs.* 30.40 ± 10.13, p=0.041).

The same analysis was performed, taking into account allergy, NSAID intolerance, or asthma as independent variables and no significant differences in the two subgroups were found. Moreover, taking in consideration the ACCESS score[9], no significant differences were noted dividing the entire cohort in patients submitted to a "correct" or "incorrect" surgery (considering values of ACCESS score ≤ 10 as representative of "correct" surgeries).

Discussion

In the present real-life study, dupilumab was effective in the treatment of severe and uncontrolled CRSwNP. Indeed, both the questionnaires and endoscopic evaluation showed rapid and significant improvement that was noticeable after only 15 days from the start of the therapy (Table III**)**. Moreover, significant improvements in SNOT-22, SSIT-16, and NPS were documented over the entire follow-up period of up to 6 months. On the other hand, the ACT results did not improve significantly but only showed a positive trend. Asthmatic patients, however, were not the entirety of the cohort (82.6%), and therefore the statistical power of this correlation may have been undermined. Indeed, as already pointed out in the literature[15,16], dupilumab improves the ACT in these patients, and thus a larger asthmatic group is necessary to statistically demonstrate this finding in our cohort. Furthermore, as a confirmation of the disease control achieved, none of the patients needed SCS or revision surgery in addition to regular treatment (INCS + saline irrigations + dupilumab).

At present, only a few studies[16-18] have investigated the efficacy dupilumab in CRSwNP patients in a real-life setting. Notably, Van der Lans et al[17], in their preliminary findings on 131 patients, reported a mean NPS reduction of 3.67 at 6 months of follow-up. The same study describes a significant improvement in SNOT-22 (from 52.4

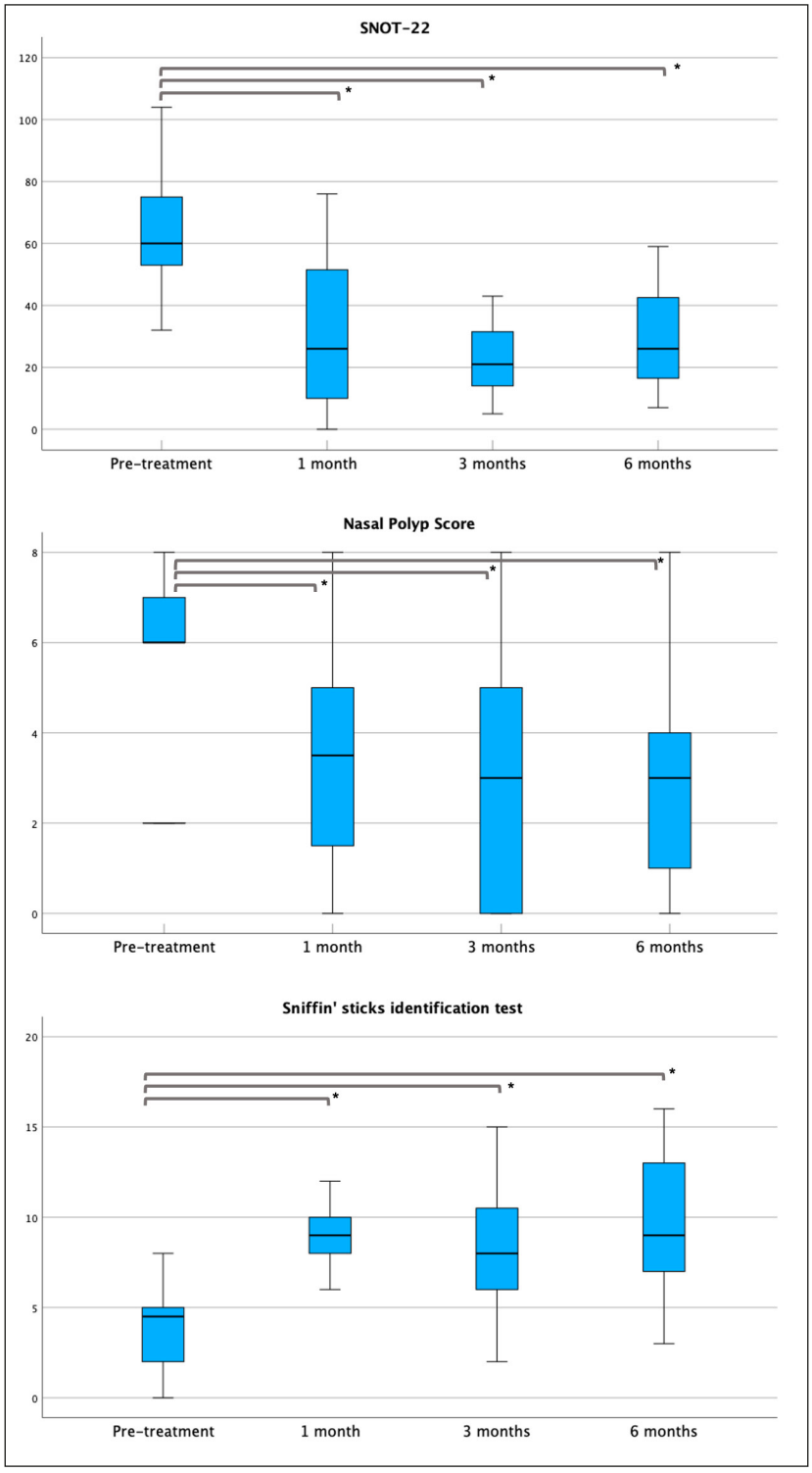

Figure 1. Box-plots representing mean values of sinonasal outcome test -22 (SNOT-22), Nasal Polyp Score and smell identification test at different follow-up times. The horizonal bold line represents the median value, while the upper and the lower limit of the box represent the first and the third quartile so that the box contain 50% of the values distribution. Asterisks represent significant differences (p-value <0.001).

Table V. Impact of previous surgeries on quality of life and endoscopic outcomes at 15 days, and at 1, 3 and 6 months of treatment. Results are reported as mean values ± standard deviation. NPS: Nasal Polyp Score; SNOT-22: Sinonasal Outcome Test-22; ACT: Asthma Control Test; SSIT-16: Sniffin' Sticks-16 Identification Test.

		15 days		1 Month		3 Months		6 Months	
	Previous surgery		*p*-value		*p*-value		*p*-value		*p*-value
NPS	No	4.00 ± 2.55	0.962	4.60 ± 1.51	0.123	4.00 ± 2.70	0.274	2.75 ± 1.89	0.641
	Yes	3.93 ± 2.12		2.93 ± 2.54		2.54 ± 2.57		2.73 ± 2.53	
SNOT-22	No	44.80 ± 16.58	0.432	42.60 ± 26.00	0.190	30.40 ± 10.13	**0.041**	39.00 ± 11.74	0.117
	Yes	35.94 ± 21.93		26.40 ± 20.17		19.14 ± 9.99		26.18 ± 18.49	
ACT	No	22.33 ± 1.52	0.310	20.75 ± 4.57	0.693	21.25 ± 2.75	0.193	23.67 ± 1.52	0.055
	Yes	18.69 ± 5.40		21.00 ± 4.07		20.64 ± 6.45		22.88 ± 2.10	
SSIT-16	No	10.00 ± 2.94	0.116	10.80 ± 2.58	0.093	10.20 ± 4.20	0.549	12.50 ± 3.31	0.602
	Yes	7.25 ± 2.67		8.33 ± 2.46		7.57 ± 3.15		8.55 ± 3.11	

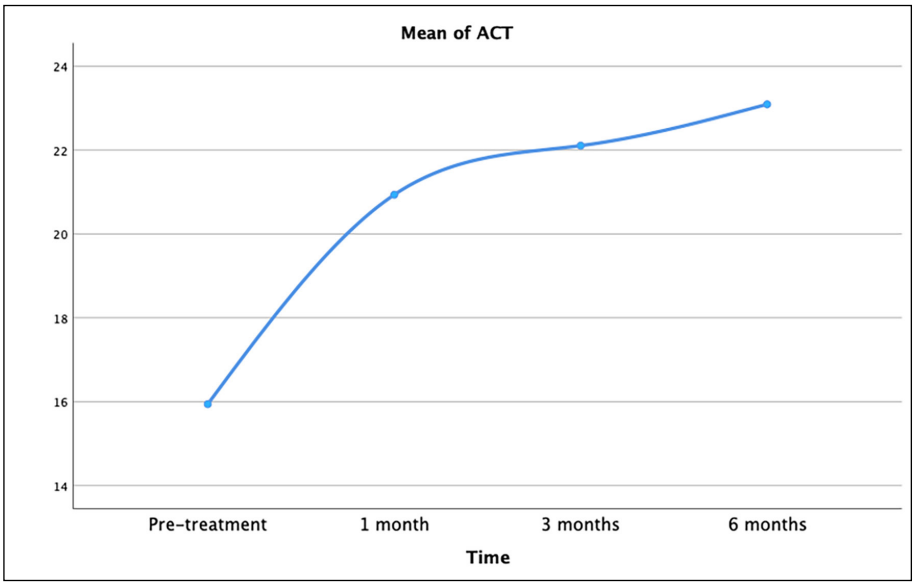

Figure 2. Plot showing mean values of asthma control tests in asthmatic patients before starting treatment and at 1, 3 and 6 months.

± 19.6 to 16.8 ± 12.4) and smell identification test (from 3.6 ± 2.1 to 8.3 ± 3.2) after the same period. The results of De Corso et al[16] are concordant with these outcomes, reporting that SNOT-22 and SSIT-16 improved significantly after 6 months. Furthermore, evaluating the endoscopic outcomes in their cohort (57 patients), they found a mean change in NPS of -3.2 after 6 months of therapy. Accordingly, a recent real-life analysis by Cantone et al[18] came to the same conclusions, describing a significant reduction in SNOT-22 and NPS after 3 and 6 months of dupilumab therapy, and a parallel improvement in SSIT-16 outcomes at the same follow-up times. These results are in accordance with our findings since we observed significant improvement in every parameter analyzed (SNOT-22, SSIT-16, and NPS) at 1, 3 and 6 months of therapy, as reported in Table III.

On the other hand, no significant difference was found in blood eosinophil count at baseline *vs.* 1, 3, and 6 months of follow-up. In reality, transient eosinophilia was observed in most cases, but only 2 of 23 patients (8.7%) reached values consistent with hyper-eosinophilia (eosinophils >1.5*10^9/L). Of note, these patients continued the biologic therapy without experiencing any adverse events or the necessity of introducing SCS. Interestingly, this finding has already been reported in the literature by several authors[15,19]. Indeed, in a study conducted by Hamilton et al[19], a subset of patients receiving dupilumab for CRSwNP experienced transient eosinophilia that subsequently resolved autonomously. Pelaia et al[15], using dupilumab in patients affected by CRSwNP and severe asthma, reported that the blood eosinophil count fluctuated from baseline to 4 weeks of treatment, without changing significantly. Furthermore, it is known that eosinophils have multiple biological functions, including the maintenance of homeostasis and host defense against infections, as well as anti-inflammatory and anti-tumorigenic activities. Moreover, murine models[20] have shown that eosinophils from lung tissue can phenotypically belong to two distinct subtypes: tissue-resident and tissue-recruited eosinophils, which are involved in the inflammatory cascade. This suggests the existence of distinct different subpopulations of eosinophils with heterogenous features, which is supported by the findings of Matucci et al[21] who demonstrated that eosinophils in CRSwNP patients can exhibit different phenotypes of surface expression molecules. Of note, those recruited with nasal polyps more frequently showed a $CD62L^{low}$ phenotype (presenting surface expression molecules involved in the inflammatory cascade) compared with peripheral blood eosinophils. These findings could justify the asymptomatic transient hypereosinophilia that developed in some of our patients, but further studies are needed to determine the true significance of eosinophils subpopulations and temporary hypereosinophilia observed during biologic treatment of CRSwNP.

Among the entire cohort, one patient did not show improvement in smell or reduction of NPS or SNOT-22 at 6 months of follow-up. Notably, before starting dupilumab, he underwent two surgical procedures and currently refuses a new intervention. Moreover, another patient unfit for surgery interrupted the therapy after 2 injections despite improvement of NPS, because of the onset of headache, conjunctivitis, and the worsening of nasal congestion. According to EUFOREA criteria[14], these patients could benefit from the switch to another biologic drug, since both surgical and medical therapy failed in controlling the disease and no additional surgeries can be performed. In this context, both mepolizumab and omalizumab (which target IL-5 and IgE, respectively) have already been approved by the Food and Drug Administration (FDA) and the European Medicines Agency's (EMA) for the treatment of severe uncontrolled CRSwNP. Notably, both drugs were superior to the placebo, and current evidence[22,23] shows that mepolizumab performs best in terms of efficacy while omalizumab has a better safety profile. Certainly, the switch from one biologic drug to another should be cautiously weighed in such complicated patients, and their management should be performed in a multi-disciplinary way. Indeed, it is our belief that the management of severe uncontrolled CRSwNP must be shared between the otolaryngologist, allergologist and pneumologist to cover every aspect of such a challenging disease.

In light of this, it is paramount to monitor the patient's response to the drug, because non-responders are expected to be 25% to 50% of total cases, according to EUFOREA guidelines[14]. Moreover, considering these latter, the therapeutic response should be evaluated 6 months after initiating treatment. Conversely, we found that 100% of patients who completed the 3-month follow-up already fulfilled the criteria to continue the therapy, while 95.0% (19/20) did it at 1 month, and 90.5% (19/21) at 15 days. These findings lead us to reasonably think that these patients could show their response well before the temporal cut-off of 6 months proposed by the EUFOREA guidelines[14]. Moreover, we believe that the high response rate observed in our cohort is the result of accurate and thorough case selection, which should always represent a cornerstone in the management of these patients[24].

Furthermore, with respect to the timing of response, 46.7% of our cohort reached an excellent response (considering EPOS criteria[1]) after 6 months of therapy. Moreover, this kind of response was shown by 28.6% of patients at 15 days of follow-up, and by 45.0% 1 month after the first injection, as shown in Figure 3. These findings are in line with the results published by De Corso et al[16], who described that 43.0%

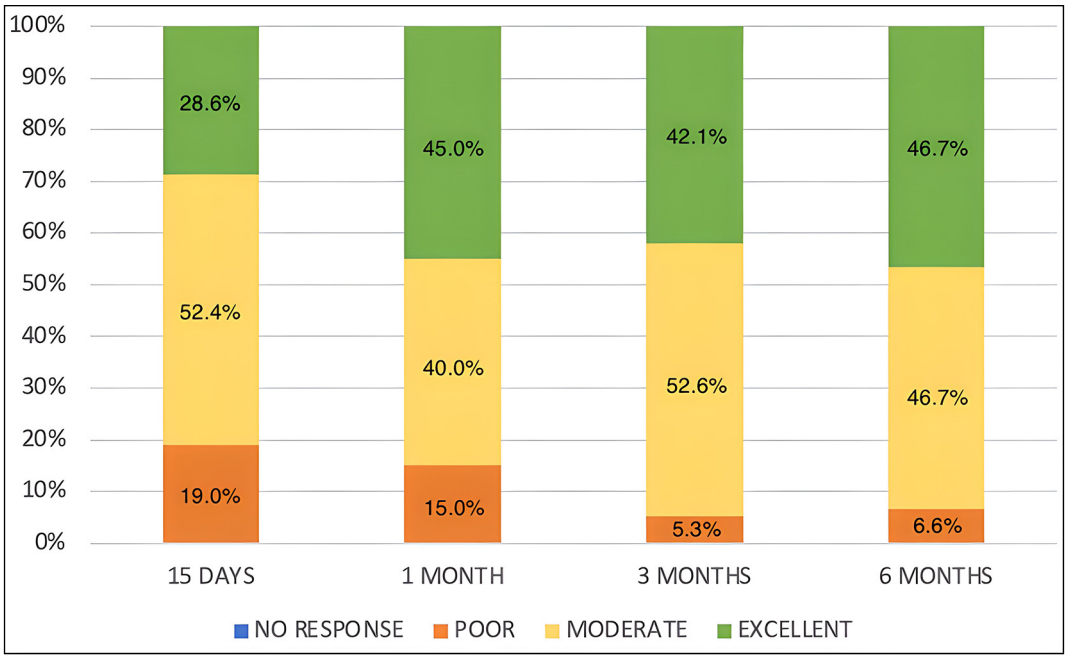

Figure 3. Rate of response according to European Position Paper on Rhinosinusitis and Nasal Polyps 2020 criteria[1] during follow-up.

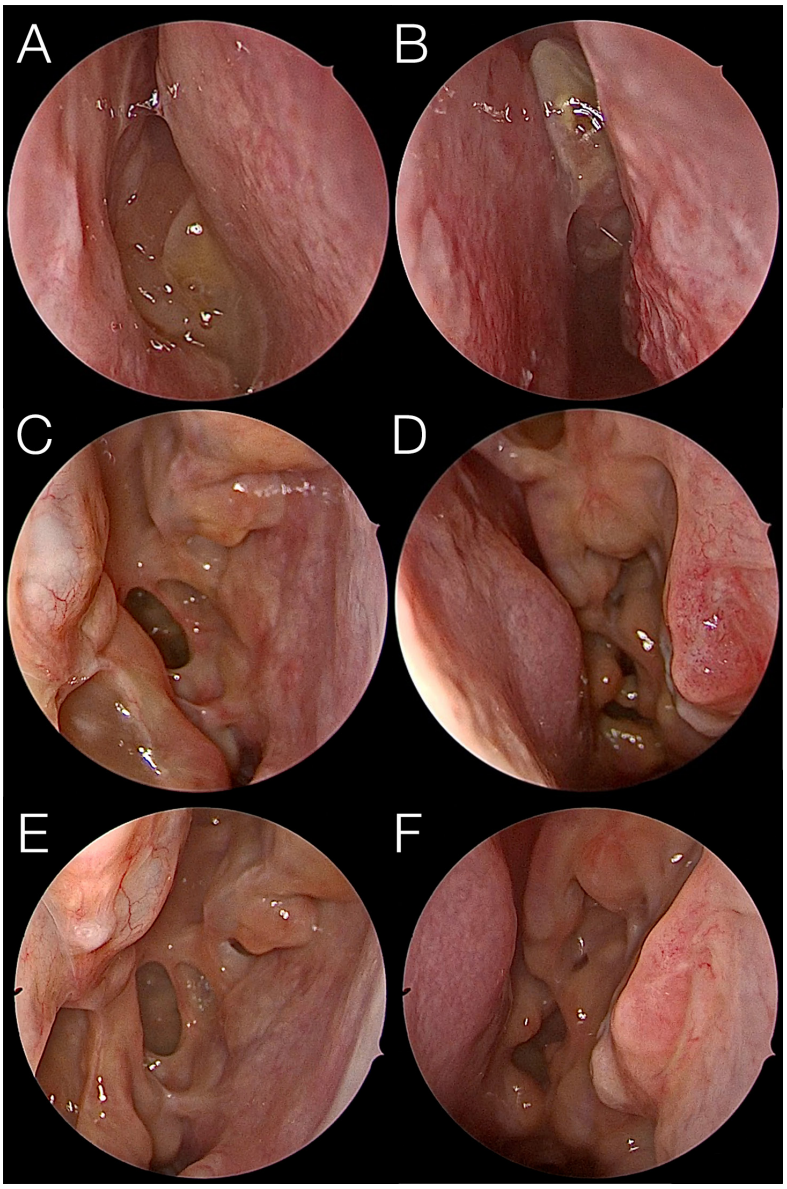

Figure 4. Panel highlighting the endoscopic outcomes of a patient categorized as a "super early responder". In the upper panels (**A**,**B**), the pre-treatment endoscopic appearance is shown, nasal polyps reaching the inferior turbinate bilaterally are evident (Nasal Polyp Score = 6). In panels **C** and **D**, the results at 15 days of treatment are reported, no residual polyps are visible. Lastly, in panels **E** and **F**, the endoscopic outcomes are maintained at the 1-month follow-up visit.

of their cohort exhibited an excellent response after 1 month and defined those patients as "early responders". Furthermore, they report that 34.0% of patients had an excellent response after 15 days of treatment. Accordingly, we found a non-negligible subpopulation (28.6%) that showed the same rate of response at 15 days, thus making us believe there may be a subset of "very early responders". The endoscopic outcomes of a patient belonging to this particular category are presented in Figure 4. Regardless, in our limited series, we could not identify variables that are significantly associated with the rate of response, preventing us from identifying an accurate prognosticator. Future studies on larger cohorts are needed to confirm these data and better understand the characteristics that can play a role in identifying "early responders" or "very early responders".

Regarding adverse events related to therapy, we observed 6 cases of early complications and no late complications. These patients suffered from minor symptoms, which only in one case

(progressive headache and worsening of nasal congestion) led to the interruption of the therapy. A similar finding was also reported in the study by Van der Lans et al[17], where 2 of 131 patients ceased treatment due to the onset of complications (hypereosinophilia and pericarditis). Moreover, the authors reported that adverse events occurred in about half of patients but were mild and resolved spontaneously[17]. On the other hand, De Corso et al[16] described minor complications in 7.0% of their cohort, and dupilumab was considered well tolerated by all patients. Additionally, in a recent review from Nettis et al[25] where the safety of dupilumab in 88 comorbid CRSwNP patients was evaluated, the frequency of adverse events was similar to our experience (33.8%), and no patients needed to stop treatment. Finally, the safety of dupilumab in treating severe CRSwNP was demonstrated in a clinical trial by Bachert et al[4], where adverse events were more frequent in the placebo group. In conclusion, dupilumab appears to be safe and well-tolerated, even if adverse events can occur. Monitoring side effects is crucial but might not always be easy, since frequent adverse treatment events (headache, eye disorders, nasopharyngitis) can overlap symptoms of CRS itself, and could mislead both the patient and the clinician.

Lastly, we analyzed QoL and endoscopic outcomes in our cohort, considering patients previously submitted to surgery. We tried to stratify our surgical cohort through the analysis of ACCESS score[9], considering values ≤ 10 as representative of "adequate" surgeries. Unfortunately, due to the low numerosity of the subpopulation (ACCESS score was assessable in only 14 patients), no significant differences between the two groups were seen. Notwithstanding, taking into account SNOT-22, NPS, SSIT-16 and ACT, we observed a significant difference of SNOT-22 values at 3 months of follow-up (19.14 ± 9.99 *vs.* 30.40 ± 10.13, $p = 0.041$) in favor of surgical patients. This finding highlights the tendency of this group to better respond subjectively to biologic therapy compared to patients who were never treated surgically. This result may be related to the altered anatomy consequent to previous surgery. Indeed, the improved ventilation of nasal mucosa and paranasal sinuses derived from the surgery may translate in a favorable response at tissue remodeling and consequently a more significant reduction of polyposis. On the other hand, patients who underwent surgery may psychologically experience the clinical outcomes of biologic treatment in a better way compared to never treated patients. Indeed, perceiving the benefits of the therapy without the stress of the already experienced surgery may have influenced positively those patients in addressing the psychological and emotional domains of SNOT-22.

Limitations

The present study has limitations that must be acknowledged, including its retrospective nature, the small number of patients included, and the short follow-up. Larger cohorts of patients, preferably in a multicenter setting, are needed to confirm our data and identify specific subgroups of patients affected by severe type 2 CRSwNP that could benefit most from this biologic treatment.

Conclusions

Dupilumab was effective and safe in patients affected by severe and uncontrolled CRSwNP. A significant improvement in SNOT-22, SSIT-16 and NPS was documented after 15 days of therapy, which were maintained after 1, 3, and 6 months. Accurate patient selection is paramount since different subpopulations of patients with distinct response patterns seem to exist. In this light, previous surgery and ACCESS score should be evaluated as possible prognosticators of response.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contributions

Conceptualization, D.M., A.I., F.R.M.C.; Data curation, D.M., A.I., M.B., A.P., A.T., G.G., F.R.M.C.; Formal analysis, A.I.; Investigation, A.I., D.M., M.B., A.P., A.T., G.G., F.R.M.C; Methodology, A.I., D.M.; Supervision, F.R.M.C., G.Pe., L.G., D.B., G.P., Writing-original draft, A.I., D.M.; Writing-review and editing, A.I., D.M., A.L.C.C, F.R.M.C., G.Pe., L.G.

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Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The research was conducted under the approval of the IRCCS Ospedale Policlinico San Martino institutional ethics committee (CER Liguria: 384/2022-DB id 11996) following the principles of the Declaration of Helsinki.

Informed Consent

No informed consent was needed since this was a retrospective analysis.

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