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Original article

Biologics in severe uncontrolled chronic rhinosinusitis with nasal polyps: A bicentric experience

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Abstract. *Background and aim:* The introduction of biologics in the management of chronic rhinosinusitis with nasal polyposis (CRSwNP) has allowed for new therapeutic options and dupilumab represents the first approved biological agent. Aim of this paper is to provide a bicentric study in a real-life setting of treatment with dupilumab for severe uncontrolled CRSwNP in Italy. *Methods:* A retrospective data collection was performed from the Departments of Otolaryngology of two major health institutions in Rome: San Camillo Forlanini Hospital and Tor Vergata University. Both centres contributed to the study providing information about patients affected by severe uncontrolled CRSwNP and treated with dupilumab. *Results:* A total of 83 patients were included in the study (43 males; 40 females; mean age: 55.8 years). Monitoring our patients, we observed improvement in reduction of nasal polyposis and nasal obstruction, respectively measured through NPS and PNIF. Concerning the CRSwNP symptoms and their impact on quality of life, we found an improvement in the olfaction, as measured respectively by SSIT-16 and SNOT-22. *Conclusions*: Dupilumab has demonstrated broad efficacy in CRSwNP management. Further studies are needed to confirm our results and to establish new biomarkers able to identify endotypes and predict response to biologics treatment in CRSwNP. (www.actabiomedica.it)

Key words: chronic rhinosinusitis with nasal polyps, type 2 inflammation, quality of life, biologics, dupilumab

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) represents a chronic inflammatory disorder of the nasal mucosa and paranasal sinuses (1).

Clinical symptoms of CRSwNP include nasal congestion, loss of smell, nasal discharge, and facial pain/pressure for at least 12 weeks. This debilitating disease is typically characterized by the endoscopic finding of nasal polyps in both nasal cavities and evidence of sinus disease on computed tomography (CT) (2).

Eosinophilia in these patients is referred to as type 2 inflammation and causes more severe symptoms, a high relapse rate, and a higher prevalence and severity of concomitant asthma (3).

Many studies have underlined the strong epidemiologic, pathogenetic, and clinical association between chronic rhinosinusitis and asthma, leading to the important concept of global airway disease (4, 5).

This pathological condition has a high impact on patients' health-related quality of life and productivity, with frequent recurrence despite pharmacological therapy with corticosteroids and/or surgical treatments (6).

Recently, monoclonal antibodies (Mabs), which represent biological treatments targeting specific inflammatory mediators or immune cells, have deeply

changed the therapeutic approach to chronic eosinophilic diseases such as severe asthma and atopic dermatitis. These molecules, acting on type 2 inflammation, are also proving effective on severe uncontrolled CRSwNP, and therefore, this topic is raising more and more interest among clinicians and researchers in the field (7, 8).

European guidelines on this topic are continuously updated and widely recommend the use of biologics in the treatment of uncontrolled severe CRSwNP, providing specific guidance on the patient features to be treated with Mabs and their follow-up (9, 10).

Based on this, dupilumab is largely used in several T2-related diseases, including asthma and atopic dermatitis. Moreover, this anti-IL-4/IL-13 signaling Mab is the first biological treatment approved by the Italian Agency of Drugs (AIFA) in December 2020 for adult patients with severe CRSwNP in addition to topical treatment with intranasal corticosteroids (INCS) in those cases which are uncontrolled with oral steroids and/or surgery. CRSwNP is defined as severe grade when the nasal polyp score (NPS) is greater than or equal to 5 and the Sinonasal Outcome Test 22 (SNOT-22) is greater than or equal to 50 (11).

The aim of this paper is to provide a bicentric study in a real-life setting of treatment with dupilumab for severe uncontrolled CRSwNP in Italy.

Materials and methods

Retrospective data collection was performed in the Departments of Otolaryngology and Head and Neck Surgery of two major health institutions in Rome: San Camillo Forlanini Hospital and Tor Vergata University of Rome.

Both centers contributed to the study by providing information about patients affected by severe uncontrolled CRSwNP and treated with dupilumab, administered through subcutaneous 300 mg injection every 2 weeks with an auto-injector as add-on therapy to INCS.

The overall number of patients included in the present report is 83.

Ethics committee approval was obtained (Prot. N 411/CE Lazio1 19 Apr 2022), and informed consent on privacy and utilization of clinical data was obtained from patients at the time of their collection.

The prescription of dupilumab was in accordance with the treatment plan established by the AIFA: age of at least 18 years, diagnosis of CRSwNP confirmed on nasal endoscopy and CT scan performed at least 6 months before start therapy, severe disease stage assessed by NPS ≥ 5 or SNOT-22 ≥ 50, failure or refusal of previous medical therapies, and/or failure of previous surgical treatments (functional endoscopic sinus surgery [FESS] and/or endoscopic sinus surgery [ESS]).

Exclusion criteria for starting treatment were patients refusing to undergo treatment with dupilumab, pregnancy, radio-chemotherapy for a tumor in the last year, and patients refusing to undergo complete follow-up.

Patients were evaluated at baseline before starting dupilumab (Time 0 or T0), 1 month (T1), 3 months (T3), 6 months (T6), and 12 months (T12) from the first administration. After 1 year, visits occurred every 6 months.

Before starting dupilumab, each patient was systematically assessed in order to obtain a comprehensive anamnestic collection including personal information such as sex, age, and job; a clinical evaluation (comorbidities, drugs, allergies); asthma concomitance; atopic dermatitis concurrence; alcohol and tobacco consumption; autoimmune diseases; and non-steroidal anti-inflammatory drug (NSAID) intolerance. Additionally, we included an anamnestic collection about CRSwNP (year of diagnosis; past medical therapies; type, time, and number of any surgical procedures).

Thereafter, we focused on the presence and the extent of nasal polyposis objectively detected through nasal endoscopy. The nasal polyp score (NPS) proposed by Meltzer et al. was chosen as the staging system to quantify the severity of the disease at the endoscopic assessment. According to the NPS, each nasal cavity is separately evaluated and scored in a range from 0 to 4 (0 = no visible nasal polyps, 1 = small polyps limited to the middle meatus and not reaching below the lower border of the middle turbinate, 2 = polyps occupying the middle meatus and reaching below the lower border of the middle turbinate, 3 = large polyps extending beyond the middle meatus but not completely

obstructing the nasal fossa, 4 = large polyps completely obstructing the nasal fossa). The sum of the scores of each nasal fossa provides the final NPS (12).

The quality-of-life assessment was pursued through the SNOT-22, a patient-reported measure of outcome (PROM) constituting 22 individual custom-designed questions regarding symptom severity and health-related quality of life (QoL) in patients affected by CRS with or without nasal polyposis (13).

In our clinical practice, we used the validated Italian version of the SNOT-22. The outcomes measured are divided into two categories: physical symptoms (items 1-12), which include rhinological symptoms (items 1-8) and auricular and facial symptoms (items 9-12); health and QoL (items 13-22), which cover sleep function (items 13-16) and psychological problems (items 17-22). The total score can range from 0 to 110 (14).

The olfactory evaluation was performed using the Sniffin' Sticks-16 Identification Test (SSIT-16): 16 different odors of above-threshold intensity are submitted to the patient, who has to identify them by choosing from four different options. Based on the number of substances correctly identified, a result between 0 (corresponding to no identified substance) and 16 (which means that the patient recognized all the substances) is obtained. Patients are thus classified as anosmic (score from 0 to 5), hyposmic (score from 6 to 10), or normosmic (score from 11 to 16) (15).

In addition, peak nasal inspiratory flow (PNIF) was measured to assess the degree of nasal obstruction. The device used is the PNIF meter. By measuring PNIF, this instrument provides an objective value of the degree of nasal obstruction. Values are considered normal if they are between 80 L/min and 200 L/min (16).

Moreover, before starting dupilumab, a complete blood count and PRIST for IgE assay were requested for each patient.

Then, during follow–up visits, patients underwent endoscopic evaluation, quality of life assessment, evaluation of nasal obstruction and olfaction, and blood tests for monitoring, especially the eosinophilic count.

Data from the selected 83 cases were collated and processed using the Data Analysis Tool Pak loaded in Excel to calculate descriptive statistics.

Results

A total of 83 patients were included in the study. 43 (51.8%) were males and 40 (48.2%) were females, showing a slight male prevalence with an F:M of 1:1.07. The mean age was 55.8 years (range 32-84 years). 36.2% of patients were smokers, and 26.6% consumed alcohol. 78.2% of patients had concomitant asthma, and in 76.6% of cases, there were concomitant allergies, especially for dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) and pellitory. 18.8% of patients suffered from NSAID intolerance, and 19% reported atopic dermatitis as a comorbidity. The other most commonly reported comorbidities were high blood pressure and cardiovascular diseases, affecting 40.8% of all patients.

89.5% of patients underwent at least one surgical management before starting dupilumab. In 41.5% of cases, patients underwent a FESS procedure before starting biological therapy; in 31.4% of cases, dupilumab was the therapeutic choice after two FESS procedures; finally, in 27.1% of cases, dupilumab represented the therapeutic option after three or more FESS procedures.

A summary of all described anamnestic patients' features can be found in Table 1.

Table 1. Patients' Features.

Feature	Result
M/F	43 (51.8%) / 40 (48.2%)
Mean age	55.8 yrs (32-84)
Asthma Allergy Smoke Alcohol consumption	78.2% 76.6% 36.2% 26.6%
NSAIDs intolerance	18.8%
Atopic dermatitis	19%
Surgical treatment	89.5% Y / 10.5% N
Single FESS procedure Two FESS procedures > than two FESS procedures	41.5% 31.4% 27.1%

*NSAID intolerance: non-steroidal anti-inflammatory drug intolerance; yrs: years; Y: yes; N: no; FESS: functional endoscopic sinus surgery.

During follow-up, we found a significant improvement in NPS, SNOT-22, sense of smell, and nasal obstruction.

Concerning the nasal polyposis evaluated through a periodically performed nasal endoscopy, we found a gradual improvement of the NPS. The mean value before starting dupilumab was 5.5; after 1 month of therapy, the score improved, dropping to 3.4; after 3 months, the value was 2.9; after 6 months, we observed a further improvement, with a value of 2.4; and after 1 year, the mean value reached 1.3.

Consequently, the degree of nasal obstruction measured through PNIF also improved: the mean PNIF increased from 103.4 L/min at baseline to 134.3 L/min at 1 month of treatment, 138.7 L/min at 3 months, 143.2 L/min at 6 months, and 144.4 L/min at 12 months of biological therapy.

The improvement of mean NPS and PNIF values over the first year of biological therapy is shown respectively in Figures 1a and 1b.

Focusing on the quality of life measured through SNOT-22, the mean value before starting dupilumab was 59.5; after 1 month of therapy, it improved, reaching a value of 27.1; after 3 months, the value continued to decrease to 22.8; at 6 months, the recorded value was 19.4; and after 1 year, the mean value was 13.3.

Concerning olfaction, the SSIT-16 mean score improved from 4.4 at baseline to 8.1 at 1 month of treatment. This improvement was confirmed at 3 months, with an increase in olfactory performance to 8.8, at 6 months with a further increase to 10.2, and finally at 1 year of treatment with an SSIT-16 mean score value of 10.8.

Figures 1c and 1d report respectively the SNOT-22 mean value and the SSIT-16 mean value over the first year of treatment.

We performed statistical analysis using one-tailed paired t-test and it resulted statistically significant (<0.01) in all the parameters analyzed.

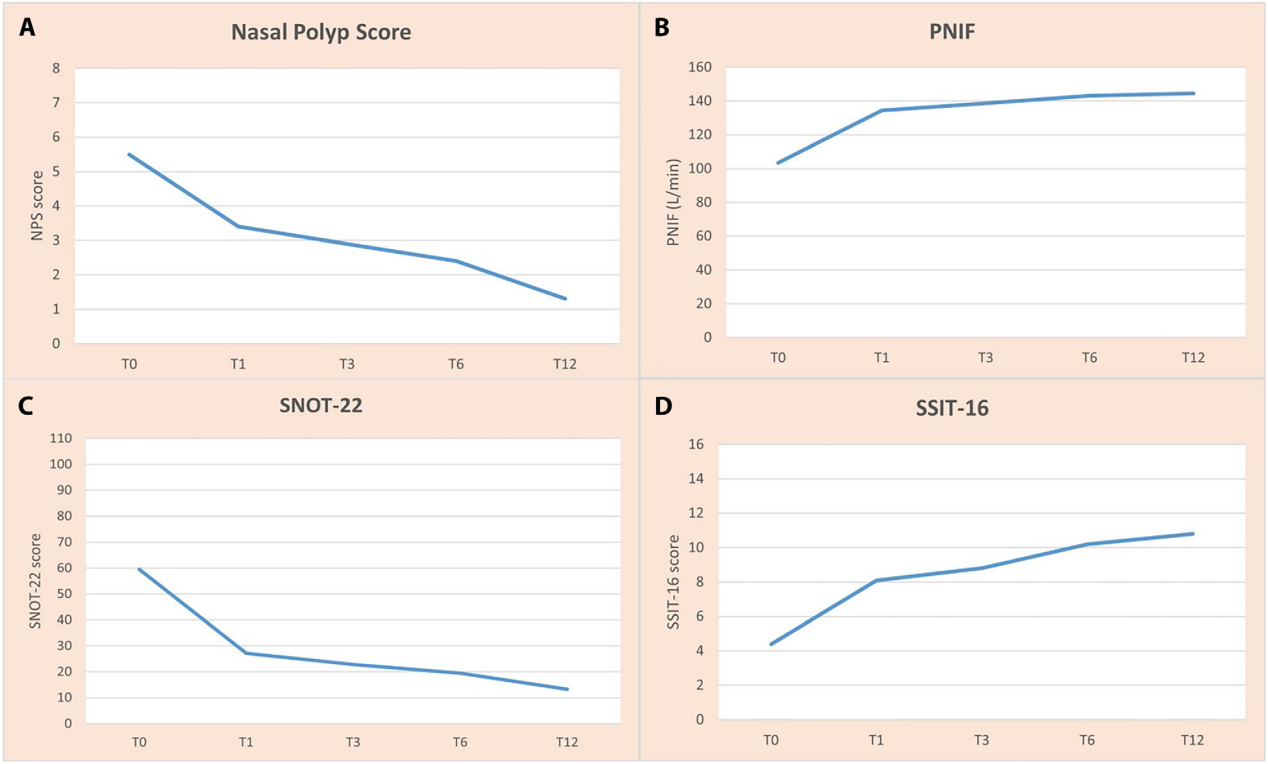

Figure. 1a NPS; 1b PNIF score; 1c SNOT-22 score; 1d SSIT-16 score. * T0: baseline or Time 0; T1: 1 month from the first administration of dupilumab; T3: 3 months; T6: 6 months; T12: 12 months.

Five patients completed 18 months of treatment; the average value of their NPS was 0.6, the mean PNIF was 139.8, the mean SNOT-22 value was 12.1, and the SSIT-16 mean score reached 11.2.

With regard to the safety profile of dupilumab, only 13 patients (15.7%) showed side effects, mostly mild and transient, such as irritation and pain at the injection site, fever, asthenia, headache, and joint pain. No severe adverse reactions were observed. Three subjects reported eye dryness, which occurred within the first 3 months of treatment and presented spontaneous resolution.

A transient increase in blood eosinophils was found in most cases, but only in 4 patients out of 83 (4.8% of all cases) were eosinophils > 1.5 x 109/L, thus being consistent with a condition of hypereosinophilia. Rapid and spontaneous resolution occurred in these cases without the need for any steroid treatment or dupilumab discontinuation, as suggested in the recent literature proposals (17).

Discussion

In our cohort, the mean age was 55.8 years, and men were more affected than women, in line with data available in the literature (18).

In our retrospective series, most of the collected patients suffered from concomitant asthma (78.2% of cases) and allergies (76.6% of cases).

It is widely known that CRSwNP and asthma often coexist in the same patient, since inflammation of the nasal mucosa is directly related to lower airway inflammation. With regard to this point, the united airways concept, some authors have found a significant correlation between the inflammatory profiles of nasal polyps and bronchial biopsies (19, 20).

In addition, there are studies supporting the possible pathophysiological role that allergy plays in CRSwNP; in fact, allergic inflammation of the nasal mucosa can lead to mucosal swelling and decreased mucociliary clearance, with consequently reduced clearance of pro-inflammatory agents allowing the development of chronic rhinosinusitis (21, 22).

On these premises, closer collaboration among otolaryngologists, pulmonologists, and allergists/immunologists is desirable in the management of these patients (23).

In accordance with the EPOS 2020 guidelines, before starting dupilumab, most of our patients (89.5%) underwent at least one previous surgery, while the few cases who did not undergo previous FESS were those not fit for surgery.

The classical treatment of CRSwNP consists of local therapeutic approaches, with the use of INCS and nasal irrigation with saline and, in case of failure to respond, short courses of oral corticosteroids (OCS), with or without antibiotics. If medical therapy fails, endoscopic surgical treatment is a viable option to improve nasal obstruction, restore normal ventilation, and improve access to future local follow-up treatment (24).

However, some patients do not find relief with these therapeutic strategies, showing persistence or recurrence of the disease. These patients have recently been identified as having "severe uncontrolled CRSwNP" (9).

Several authors have highlighted that the pathophysiology of this type of CRSwNP is mostly driven by type 2 inflammation, with eosinophilia, associated T-helper cell cytokines 2, and IgE formation. Therefore, the biological therapy used in the management of type 2 inflammatory diseases, such as asthma and atopic dermatitis, may also be used for type 2 CRSwNP by targeting specific immunologic mediators: anti-IL-4/IL-13 (dupilumab), anti-IgE antibodies (omalizumab), and anti-IL-5 (mepolizumab, benralizumab) (25, 26).

Our results showed that dupilumab therapy, administered according to AIFA guidelines, is rapidly effective in uncontrolled severe CRSwNP. Specifically, we observed a clinical improvement, with a reduction of nasal polyposis and nasal obstruction, respectively measured through NPS and PNIF.

Focusing on CRSwNP symptoms and their impact on quality of life, we found an improvement, especially in olfaction, as measured respectively by SSIT-16 and SNOT-22.

These results are in line with recent real-life studies confirming the efficacy and safety of dupilumab in treating severe CRSwNP (27-30).

Table 2. Comparison of real-life studies about biologics.

Drug	Author	Year	n. of patients	FUP (months)	NPS		SNOT-22		PNIF (L/min)		SSIT16	
					T_b	T_f	T_b	T_f	T_b	T_f	T_b	T_f
Dupilumab	Bellocchi et al.	2023	83	12	5.5	1.3	59.5	13.3	103.4	144.4	4.4	10.8
	De Corso et al.	2023	648	12	6.0	1.0	58.0	12.0	n.a.	n.a.	4.0	12.0
Mepolizumab	Domínguez-Sosa et al.	2023	55	6	4.0	1.0	76.0	10.0	n.a.	n.a.	n.a.	n.a.
	Gallo et al.	2022	45	12	3.0	2.0	54.8	31.5	n.a.	n.a.	n.a.	n.a.
Benralizumab	Santomasi et al.	2023	17	12	4.2	2.9	61.5	21.5	n.a.	n.a.	n.a.	n.a.
	Cavaliere et al.	2022	11	12	5	2	45	14	n.a.	n.a.	n.a.	n.a.

*FUP: Follow-up; T_b: Time at baseline; T_f: Time at last follow-up; n.a.: Not available

The most common adverse events described in the literature are nasopharyngitis, injection site reactions, headache, asthenia, arthralgia, and conjunctivitis (31).

In our collection, just a low percentage of patients suffered from transient side effects, which were irritation and pain at the injection site, fever, asthenia, headache, and joint pain. Three subjects reported eye dryness with spontaneous resolution.

Dupilumab has been associated with possible ocular side effects such as conjunctivitis, blepharitis, keratitis, ocular itching, and dry eye. In particular, there is an increased incidence of conjunctivitis in patients with atopic dermatitis (32, 33).

In our cohort, most cases reported a transient increase in blood eosinophils with spontaneous resolution. Many studies dealing with dupilumab have described transient increases in eosinophil counts. Usually, such an increase occurs in the first few weeks of therapy and is followed by a subsequent return to baseline or an even lower value by the end of the treatment period. Even though these increases are typically transient, clinicians should carefully monitor all patients (34).

In table 2 we present a comparison of the latest real-life studies in terms of NPS, SNOT-22, PNIF and SSIT-16 among dupilumab, mepolizumab and benralizumab (35-39).

There are several limitations to our series as follows: first of all is the retrospective nature of this study; secondly, the number of patients, even though considerable if compared to other series published, is not sufficient to draw any conclusive evidence; finally, the duration of the follow-up period is limited in most cases to 12 months.

There are still unresolved critical issues about the use of biologic treatment such as the best duration and the upcoming challenge to select the best biologic agent for each individual case according to the endotyping (40).

Conclusions

Based on our preliminary observations, dupilumab has demonstrated broad efficacy in the management of patients with CRSwNP, with benefits in terms of improved quality of life and reduction of nasal polyps and disease-related symptoms, especially for the sense of smell.

Further studies are needed to confirm our results and to establish new biomarkers able to identify endotypes and predict the response to biologic treatment in CRSwNP.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership,

equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: AL, FMP and SM have given substantial contributions to study conception and design; GV and MP to data acquisition, analysis and interpretation; AL and LDM to manuscript writing; GB and SDG to review and editing the paper. All authors read and approved the final version of the manuscript.

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