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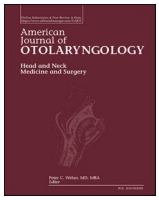

Mepolizumab in chronic rhinosinusitis with nasal polyps: Real life data in a multicentric Sicilian experience

Cosimo Galletti [a,b], Federico Sireci [c], Giovanna Stilo [d], Maria Antonietta Barbieri [e], Giuliano Messina [d], Riccardo Manzella [f], Daniele Portelli [b], Andrea Guglielmo Zappalà [d], Mariut Diana [d], Silvia Frangipane [d], Angelo Immordino [f], Francesco Lorusso [f], Francesco Dispensa [f], Francesco Ciodaro [b], Francesco Freni [b], Francesco Galletti [b], Salvatore Gallina [f], Ignazio La Mantia [d], Bruno Galletti [b,*]

[a] Faculty of Medicine and Surgery, University of Enna "Kore", 94100 Enna, Italy
[b] Department of Adult and Development Age Human Pathology "Gaetano Barresi", Unit of Otorhinolaryngology, University of Messina, Via Consolare Valeria 1, 98125 3, Italy
[c] Otorhinolaryngology Section, Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C), University of Palermo, Palermo, Italy
[d] Department of Medical-Surgical Sciences and Advanced Technologies, E.N.T. Unit, P.O. "G. Rodolico", University of Catania, Catania, Messina, Italy
[e] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[f] Otorhinolaryngology Section, Biomedicine, Neuroscience and Advanced Diagnostic Department, University of Palermo, Via del Vespro 129, 133, 90127 Palermo, Italy

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ABSTRACT

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by a type 2 pattern of inflammation. Mepolizumab was approved for the treatment of CRSwNP in 2021. However, there is a lack of real-life studies.

Aim: This work aimed to evaluate the effectiveness and safety profile of Mepolizumab during the first year of treatment in a real-life setting.

Methods: A multicentric observational cohort study was carried out. A total of 67 patients were enrolled in the Otorhinolaryngology Unit of the three University Hospitals and considered for Mepolizumab therapy. All recorder characteristics were age (at the first Mepolizumab 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 Mepolizumab therapy and number of doses of Mepolizumab and eventually, Mepolizumab'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 in 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 Mepolizumab and continued the treatment because of a reduced NPS, improved quality of life, and a reduced need for system corticosteroids.

Conclusions: This multi-centric real-life study supported the effectiveness of Mepolizumab in patients with severe uncontrolled CRSwNP in the improvement of quality of life, the severity of symptoms, polyp size reduction, and smell function. Our data also support the safety profile of monoclonal therapy with Mepolizumab.

* Corresponding author at: Department of Adult and Development Age Human Pathology "Gaetano Barresi", unit of Otorhinolaryngology, University of Messina, Via Consolare Valeria 1, 98125 Messina, ME, Italy.
E-mail address: bgalletti@unime.it (B. Galletti).

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1. Introduction

Chronic rhinosinusitis (CRS) is a disease that affects approximately 5–28 % of the world's population [1–6]. Recently, treatment algorithms have been updated with monoclonal antibodies and a focus on inflammation affecting the sinus mucosa and biomarkers such as IL-4, IL-13, IL-5, and IgE. The EUFOREA expert team published "The Biologic in CRSwNP: A Consensus Statement on Clinical Criteria to Consider Treatment" [7,8] and was reported in the EPOS (European Position Paper on Rhino-sinusitis and Nasal Polyps), which was further refined by the latest expert group proposal. In the latest EPOS, CRS consists of inflammation of the nasal mucosa and paranasal sinuses, characterized clinically by two or more symptoms, one of which is nasal congestion, nasal discharge and/or facial pain, pressure, and/or decreased/loss of sense of smell, endoscopic signs of nasal polyps and discharge or swelling of the mucosa of the middle pharynx, and nasal mucosal abnormalities and abnormalities such as bony complexes or mucosal changes of the sinuses on CT scan of the sinuses, described as persisting for at least three months [6].

Overall, CRS is a clinically based diagnosis, validated by classic nasal endoscopy and head CT scan. CRS is classified into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). CRSwNP accounts for 1–4 % of the general population, and 25–30 % of patients with CRS are evaluated. The average age of patients at diagnosis is 40–50 years, although the first symptoms often begin in their 20s and 30s. Males are more frequently affected than females. The history is an important step for two reasons. Most rhinologic symptoms, such as nasal obstruction, anterior and posterior rhinorrhea, sneezing attacks, facial heaviness, and facial pain, are present in all sinusopathies, acute and chronic.

Olfaction and dysgeusia are some of the "starter" useful symptoms for the diagnosis of chronic rhinosinusitis with nasal polyps. Symptomatology can be used to monitor the effectiveness of proposed treatments. Because sinus polyposis is a chronic airway disease, patients should be followed over time, as with any other chronic disease. To provide the best medical or surgical treatment, it is essential to regularly assess the patient's complaints and determine the effectiveness of treatment. Several quantification methods have been proposed, including visual analog scales (VAS), the DyNaChron questionnaire, severity class quantification, and quality of life questionnaires like Sinonasal Outcome Test-22 [9–12]. In addition, the medical history should include allergies, asthma, chronic cough, intolerance to aspirin, nonsteroidal anti-inflammatory drugs, sulfites (wine), and otolaryngological symptoms (recurrent otitis media, chronic otitis media).

The association between asthma and CRS is strongly reported in the scientific literature: about 25 % of patients with CRS have asthma, compared with 5 % in the general population. Specifically, in patients with CRSwNP, the association with asthma ranges from 30 % to 70 %, with NP status being associated with a more insidious pattern of more severe asthma [13–15], patients with CRS can be classified into three endotypes based on the presence of type 1, 2, and 3 inflammation, each of which regulates the expression of three different cytokine clusters [16,17]. Defects in epithelial barrier function and type 2 inflammation patterns play an important role in the pathogenesis of CRSwNP, leading to the production of several cytokines, including interleukin-4 (IL-4), IL-5, and IL-13. IL-4 and IL-13 have IL-4Rα and IL-13Rα1 chains that activate the same heterodimeric receptor composed of two subunits [17]. Thus, cytokines are pharmacological targets for biological therapies. Mepolizumab is a humanized monoclonal antibody (mAb), approved by the European Commission in 2021 for CRSwNP when systemic therapy with corticosteroids or surgery fails to provide adequate control. Mepolizumab binds to and inactivates IL-5, a cytokine involved in eosinophil proliferation, activation, and survival [18].

Mepolizumab thus significantly reduced blood eosinophil levels. Recently, a phase III study, SYNAPSE, demonstrated that eosinophil recruitment, survival, and activation are mainly promoted by IL-5 and that specific targeted therapy is beneficial for CRSwNP [7–20].

2. Materials and methods

2.1. Study population

A multicentric observational cohort study was carried out to assess the effectiveness and safety of Mepolizumab 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 Mepolizumab 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 Mepolizumab therapy, and number of doses of Mepolizumab, and eventually, Mepolizumab'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 Mepolizumab prescription during the study period was considered the "index date" for each patient. The prescription of Mepolizumab 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 the use of monoclonal therapy in patients with CRSwNP, fulfilling the EUFOREA consensus for treatment with monoclonal antibodies [1,17]. Patients were subjected every 30 days to a subcutaneous injection of Mepolizumab 100 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 Mepolizumab. The minimum follow-up period was twelve 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

Seventy-one patients were enrolled in the Otorhinolaryngology Unit of the three University Hospitals and considered for Mepolizumab therapy (Table 1). During the observational period, four patients were excluded due to a lack of adherence to the treatment following the EPOS criteria. Of all 67 patients, 40 were men (59.7 %), while 27 were women (40.3 %), with a median (Q1–Q3) age of 55 (49–66) years. Seventeen patients (25.4 %) were smokers. Moreover, 48 patients (71.6 %) had a history of allergic conditions with concomitant asthma (p-value 0.005) presented in 43 patients (64.2 %). The median value of Sino-Nasal Outcome Test 22 (SNOT-22) pretreatment was 64, with a median nasal polyps score (NPS) at pretreatment of 6. 91.0 % of the patients were under treatment with intranasal corticosteroids. Forty-three patients (64,2 %) were in treatment with oral corticosteroids in the last ear and were unresponsive or not compliant. Other comorbidities included hypertension ($n = 25$; 37.3 %), diabetes ($n = 10$; 14.9 %), cardiovascular diseases ($n = 9$; 13.4 %), obesity ($n = 7$; 10.4 %), and anxiety or depression ($n = 5$; 7.5 %).

We noted that 14 patients were intolerant to non-steroidal anti-inflammatory drugs (20.9 %) with p values < 0.05. Nine patients (13.4 %) were affected by aspirin-exacerbated respiratory disease (p-value < 0.005). Fifty-five patients (82,1 %) were previously subjected to endoscopic sinus surgery (ESS), 33 of whom were men. General characteristics of the sample size and previous ESS and naïve groups are reported in Table 1. 60 % of patients who underwent a Previous ESS resulted in treatment with oral corticosteroids in the last year *vs* 83.3 % presented in the naive patients group.

Table 1. 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, 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 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) (Tables 2 and 3).

Table 1
Patients' main clinical characteristics and endoscopic and symptom evaluations at baseline for the whole group and for the post-surgical and naïve groups separately.

Variable	Post-surgical ($n = 55$)	Naive ($n = 12$)	p_value	Total
Age, years (Median [Q1–Q3])	55 [49.5–66]	53.5 [35.25–66]	0,2802	55
Sex, Males, (N [%])	33 (60 %)	7 (58.3 %)	1,0000	40 (59,7 %)
Smokers, N (%)	13 (23.6 %)	4 (33.3 %)	0,7389	17 (25,4 %)
Allergic conditions, N (%)	38 (69.1 %)	10 (83.3 %)	0,5233	48 (71,6 %)
Concomitant asthma, N (%)	36 (65.5 %)	7 (58.3 %)	0,8935	43 (64,2 %)
Hypertension, N (%)	19(34.5 %)	6 (50 %)	0,5006	25 (37,3 %)
Obesity, N (%)	5 (9.1 %)	2 (16.7 %)	0,7975	7 (10,4 %)
Diabetes, N (%)	6 (10.9 %)	4 (33.3 %)	0,1265	10 (14,9 %)
Cardiovascular disease, N (%)	5 (9.1 %)	4 (33.3 %)	0,0777	9 (13,4 %)
Anxiety/Depression, N (%)	5 (9.1 %)			5 (7,5 %)
Celiac disease, N (%)	2 (3.6 %)			2 (3 %)
Dyslipidemia, N (%)	3 (5.5 %)	1 (8.3 %)	10,000	4 (6 %)
Other comorbidities, N (%)	4 (7.3 %)	1 (8.3 %)	10,000	5 (7,5 %)
CCS intranasal, N (%)	50 (90.9 %)	11 (91.7 %)	10,000	61 (91 %)
OCS last year, N (%)	33 (60 %)	10 (83.3 %)	0,2320	43 (64,2 %)
FANS intolerance, N (%)	11 (20 %)	3 (25 %)	10,000	14 (20,9 %)
ASA triad, N (%)	6 (10.9 %)	3 (25 %)	0,4067	9 (13,4 %)
SNOT-22 (Median [Q1–Q3])	64 [64–64]	63.5 [63.5–63.5]	0,9218	64
NPS (Median [Q1–Q3])	6 [6–6]	6 [6–6]	0,4289	6
Sniffin' Stick Test Score (Median [Q1–Q3])	2 [2–2]	2 [2–2]	0,8990	2
Blood eosinophil count cells/L (Median [Q1–Q3])	0.7 [0.7–0.7]	0.895 [0.895–0.895]	0,0469	1

Mepolizumab seemed to be well tolerated by all patients, however, during the length of the study, nine patients reported that they had some adverse reaction to the treatment: eight patients reported pain at the site of the injection, referring to rubor, calor, and dolor during the first three-four days after the injection. The patients were treated with local application, two times a day, of betamethasone di-propionate and gentamicin sulfate until the resolution of symptoms Moreover, one patient experienced a reactivation of Herpes zoster infection treated with anti-viral therapy and therapy to control the pain. Any adverse effect of the drug led to the quit of biological treatment.

4. Discussion

The research group presents data on mepolizumab treatment and real-life data, given the growing interest in monoclonal therapies and

Table 2
Median value variatons 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.

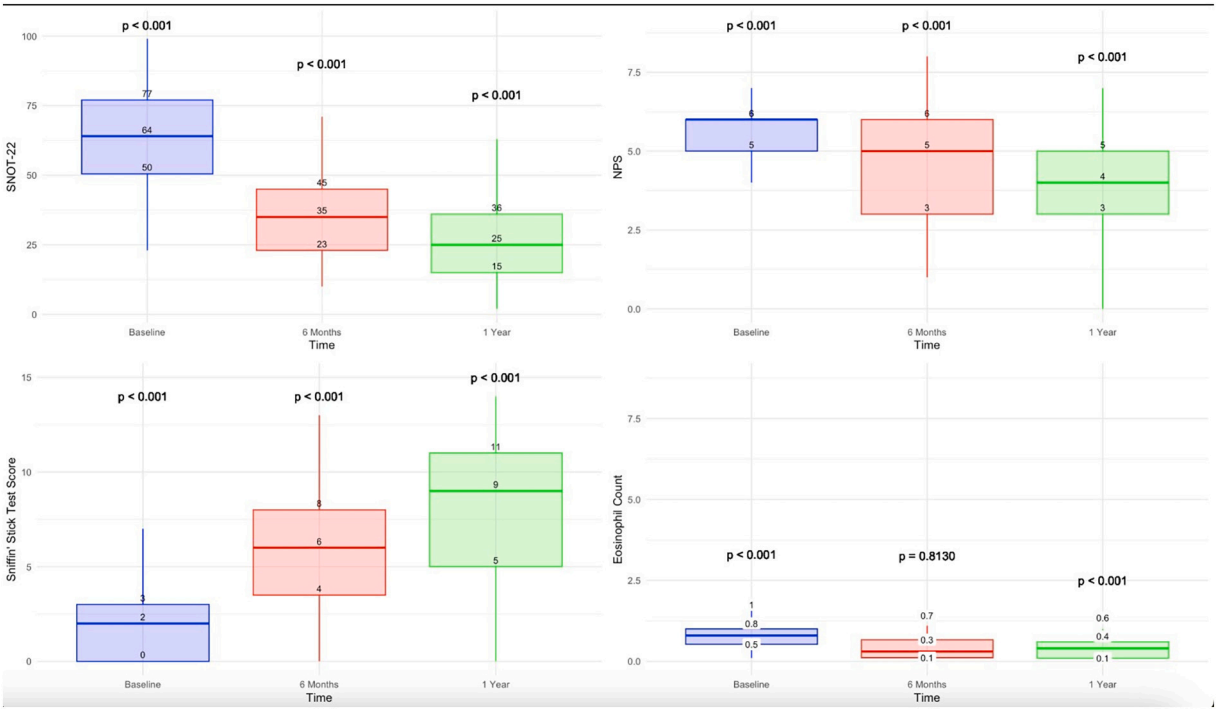

Table 3
Differences from baseline to each follow-up for SNOT-22, NPS, sniffin' sticks test, and blood eosinophil count.

	6th month vs. baseline	P value	12th months vs. baseline	P value
SNOT-22, median (Q1–Q3)	−29	<0.001	−39	<0.001
NPS, median (Q1–Q3)	−1	<0.001	−2	<0.001
Sniffin' sticks test, median (Q1–Q3)	4	<0.001	7	<0.001
Blood eosinophil count, median (Q1–Q3)	−0,40	<0.001	−0,30	<0.001

CRSwNP [16–23]. These data come from three referral centers to examine the efficacy and safety profile of mepolizumab in the treatment of CRSwNP in a large population sample. Mepolizumab is a humanized monoclonal antibody (mAb) against IL-5, a cytokine that promotes eosinophil development and survival. Mepolizumab 100 mg subcutaneously every four weeks has been approved since 2015 as adjunctive maintenance therapy for adult patients with severe eosinophilic asthma (SEA) [24–29]. After phase 3 studies demonstrated subjective and objective efficacy, the FDA approved mepolizumab for CRSwNP in July 2021, according to the guidelines for CRSwNP and monoclonal therapy, when systemic therapy with corticosteroids and/or surgery fails to adequately control the disease [19]. Subcutaneous mepolizumab was administered as an adjunctive treatment to topical corticosteroids and was well tolerated. Mepolizumab specifically binds to and inactivates IL-5, a cytokine involved in eosinophil proliferation, activation, and survival [18]. Mepolizumab thus significantly reduced blood eosinophil levels. Recently, the phase III SYNAPSE study showed that eosinophil recruitment, survival, and activation are mainly promoted by IL-5 and that specific targeted therapy is useful in CRSwNP [7–19].

Our study confirms the efficacy of a 100-mg dose of mepolizumab injected every 4 weeks, as well as clinical trials conducted in specific populations [7–19] and in a real-world research setting [30-32], with consistent results as early as 6 months after treatment initiation. Diagnosis of CRSwNP, the patient's quality of life worsens due to loss of sensation and inflammatory effects on the upper and lower airways [1,2,4], and because CRSwNP is a chronic airway disease, patients are followed for a long period, similar to other chronic diseases with a disease burden associated with significant health care costs [24]. We observed a significant improvement in patients' quality of life, with SNOT-22 values of −29 and −39 at 6 and 12 months, respectively, compared with baseline values. We also found that the group that had previously undergone endoscopic sinus surgery left with higher baseline SNOT-22 values than the Naive group. One of the most important data was the recovery of olfactory function, which showed +4 and +7 compared with baseline values at 6 and 12 months, respectively. This is one of the first signs of response to treatment seen by patients after starting mepolizumab therapy.

Our results, like those of SYNAPSE and other studies, show that neither surgical history nor asthma comorbidities or NSAID-ERDs influenced the improvement of olfaction with mepolizumab [17,18,24,27,29,31].

In addition, data suggest that patients who underwent extended endoscopic sinus surgery (ESS) respond earlier to biologic therapy based on the Amsterdam Access Score evaluation. Furthermore, according to results reported in the literature, blood eosinophil counts showed statistically significant reductions at 6 and 12 months [24,33-36]. This condition is attributed to the mechanism of action of mepolizumab, which reduces its concentration by inhibiting Il-5, failing eosinophil activation, preservation, and survival [15]. Our real-world clinical studies are consistent with the reduction in nasal symptoms described in the literature [35,36], particularly the improvement in QoL due to the restoration of the sense of smell, one of the most important parameters of QoL. In addition, mepolizumab appears to be more effective in terms of reducing eosinophilia and nasal symptom severity in the presence of coexisting respiratory disease or aspirin-exacerbated asthma [38,39]. In

patients with such comorbidities, decisions about continued treatment should be made in close collaboration with rheumatologists and respiratory specialists [40,41].

All patients achieved 1-year follow-up and continued treatment with mepolizumab due to reduced NPS, improved quality of life, reduced need for corticosteroids, and improved CRSwNP-associated comorbidities. Given the safety profile established in the premarketing studies, mepolizumab appears to be well tolerated without serious adverse events (AEs); in the CRSwNP studies, the most frequently reported AEs were nasopharyngitis, pain, and erythema at the injection site, nosebleed, headache, and sinusitis [18,22,42–45]. Safety analyses confirmed that mepolizumab was well tolerated in our series, and AEs were few; the choice of biologic for the treatment of CRSwNP depends on the patient's superior phenotype and endotype, so refinement of patient selection will ensure efficacy and safety. Treatment of CRSwNP with biologics would yield the best results in terms of efficacy and safety. This study has several strengths and limitations. The first is the prospective nature of data collection in actual clinical practice, as already known from previous studies [22,27,37,42,43].

Monoclonal treatment with mepolizumab is effective in controlling type 2 inflammation, leading to CRSwNP, supporting the AIFA indication for biologic therapy with monoclonal antibodies. A strength of this study is the use of real-world clinical data, which plays a key role in the overall evaluation of the efficacy and safety of biologics. It provides valuable insights beyond clinical trials to guide informed medical decisions and ensure the well-being of patients. The indication criteria, treatment protocols, and follow-up criteria established for all patients reinforce this methodology. In addition, an education program was conducted with patients during the first month of treatment, explaining how to administer self-injections at home. Adherence rates have been very high. No changes were made to the dosing schedule during the first year of treatment, allowing the focus to be on efficacy and safety. However, patients were followed in tertiary care, including the most severe and difficult-to-treat CRSwNP with a significant history of rebellious and uncontrolled nasal polyposis.

Further studies with larger numbers of real patients enrolled and longer observation periods are needed to make efficacy and safety profiles in these patients, especially long-term in real-world settings.

5. Conclusion

This multicenter, real-world clinical trial showed promising results in terms of quality of life, symptom severity, reduction in polyp size, and improvement in olfactory function in poorly controlled CRSwNP when 100 mg of mepolizumab was administered every four weeks as adjunctive therapy to intranasal corticosteroids (INCS). The results are promising in terms of quality of life, symptom severity, reduction in polyp size, and improvement in olfactory function. Finally, our data support the safety profile of mepolizumab in the treatment of patients with severe uncontrolled CRSwNP in real life.

CRediT authorship contribution statement

Cosimo Galletti: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Federico Sireci:** Supervision, Data curation, Conceptualization. **Giovanna Stilo:** Validation, Data curation, Conceptualization. **Maria Antonietta Barbieri:** Validation, Formal analysis. **Giuliano Messina:** Data curation, Conceptualization. **Riccardo Manzella:** Data curation, Conceptualization. **Daniele Portelli:** Visualization, Supervision. **Andrea Guglielmo Zappalà:** Visualization. **Mariut Diana:** Visualization. **Silvia Frangipane:** Visualization. **Angelo Immordino:** Visualization. **Francesco Lorusso:** Visualization. **Francesco Ciodaro:** Visualization, Validation, Supervision. **Francesco Freni:** Visualization, Supervision. **Francesco Galletti:** Validation, Supervision. **Salvatore Gallina:** Visualization, Validation, Supervision. **Ignazio La Mantia:** Visualization, Validation, Supervision. **Bruno Galletti:** Visualization, Validation, Supervision.

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.

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Declaration of competing interest

All authors declare no conflict of interest.

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