One year mepolizumab outcomes in severe, uncontrolled CRSwNP: a real-life study

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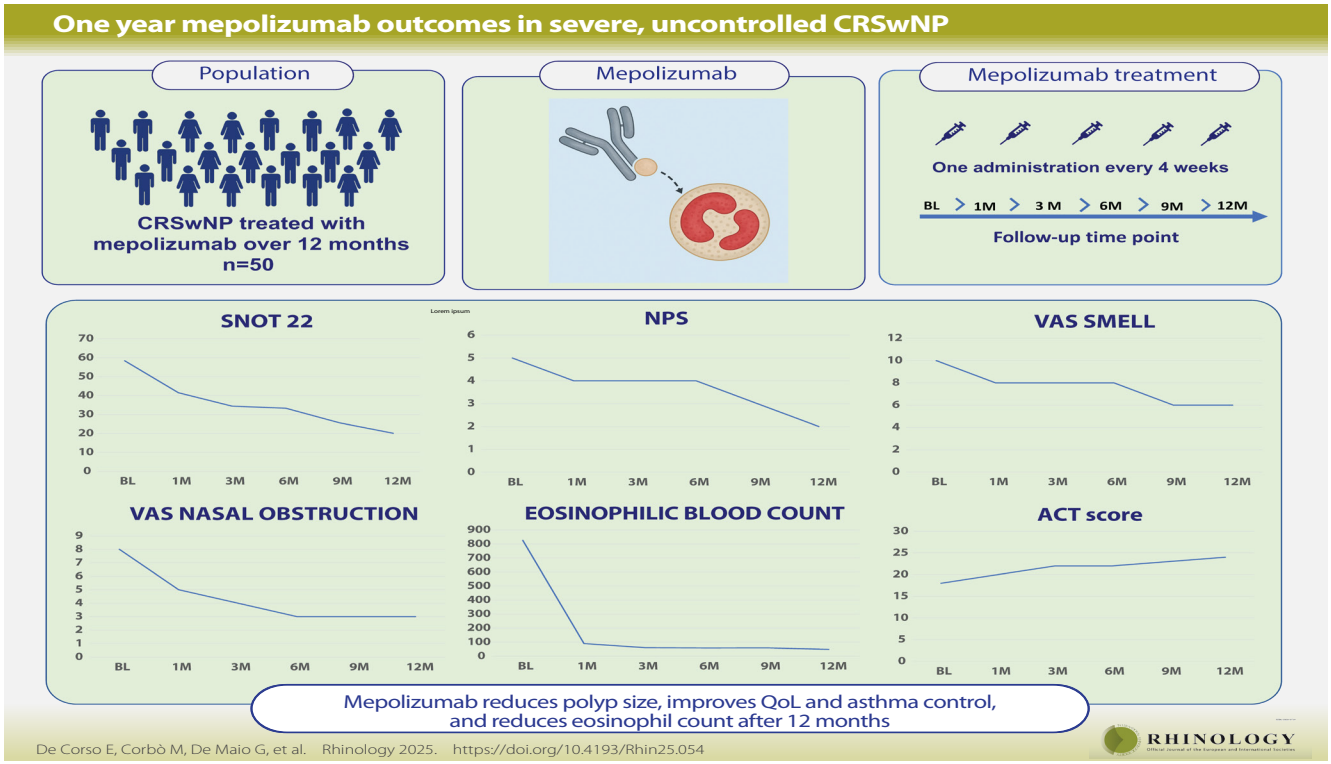

Abstract

Background: This study aimed to evaluate the effectiveness of mepolizumab in the treatment of severe, uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) as add-on therapy to intranasal corticosteroids (INCS) in a real-life setting over the first year of treatment.

Methodology: We included 50 patients (28 males; mean age: 56.4 years, range 35-77) who received mepolizumab 100 mg every 4 weeks. The primary objective of this study was to evaluate the reduction in nasal polyp size and improvement in patients' quality of life, measured through symptom-based questionnaires. The secondary objective was to evaluate improvements in smell dysfunction, severity of comorbidities, blood eosinophilia, and the need for surgery or systemic steroids.

Results: After 12 months of treatment, the median nasal polyp score (NPS) decreased from 5 to 2 and the mean sino-nasal outcome test-22 (SNOT-22) score decreased from 58.4±21 to 26.1±17.5. Olfaction only slightly improved with a median VAS score decreasing from 10 at baseline to 6 at 12 months. Seven patients remained uncontrolled and required systemic steroids and in 5 cases also endoscopic sinus surgery.

Conclusions: The results support the use of mepolizumab as an effective option in the current standard of care for patients affected by severe, uncontrolled CRSwNP especially in decreasing nasal polyps' size and improving quality of life, although a minor impact was observed on recovery of smell.

Key words: biological treatment, chronic rhinosinusitis, nasal polyps, quality of life, type -2 inflammation

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a persistent inflammatory condition characterized by various underlying inflammatory pathways. In Western countries there is a predominance of T helper 2 (Th2)-driven inflammation and elevated levels of type 2 cytokines (IL-4, IL-5, and IL-13). IL-5 plays a role in the differentiation, regulation and activation of eosinophils, contributing to their accumulation in the nasal tissues where they mediate tissue damage [1-4]. Elevated levels of IL-5 and eosinophils are commonly observed in patients with CRSwNP with or without asthma, and their presence is linked to the severity and persistence of these conditions, making them promising therapeutic targets [1-2].

Mepolizumab is an anti–IL-5 monoclonal antibody (mAb) that prevents IL-5 from binding to its receptor on eosinophils, thereby selectively inhibiting eosinophilic inflammation. The results of the phase III SYNAPSE trial demonstrated that subcutaneous administration of mepolizumab (100 mg every 4 weeks) resulted in a significant reduction in the size of nasal polyps, an improvement in nasal obstruction and sinonasal symptoms, and a decrease in the need for endoscopic sinus surgery (ESS) and systemic corticosteroids (SCS) in patients with severe CRSwNP. The study also demonstrated a favourable safety profile [5].

More recently, similar effects have been observed in the phase III MERIT trial, a randomized, double-blind, placebo-controlled, 52-week study assessing mepolizumab outcomes in patients with CRSwNP/eosinophilic CRS (ECRS) in Japan, Russia, and China. The MERIT findings highlight that, beyond the reductions in symptoms observed via endoscopic assessments, a decrease in pathological tissue was also evident when evaluated by CT scans. The main difference between the MERIT trial and the SYNAPSE trial was the percentage of patients enrolled with previous (ESS): 65% in the MERIT trial compared to 100% in the SYNAPSE trial [6].

Since mepolizumab was approved and reimbursed in Italy for severe uncontrolled CRSwNP, several real-life studies have been published, although heterogeneity in the results has been observed. To deepen the current understanding of mepolizumab effectiveness, our study aimed to evaluate its impact on severe, uncontrolled CRSwNP patients, with or without asthma, after one year of treatment in a real-life setting. The primary objective of this study was to evaluate the reduction of nasal polyp size and improvement in patients' quality of life measured through symptom-based questionnaires. The secondary objective was to evaluate improvements in smell dysfunction, comorbidities, blood eosinophilia, and the need for ESS or SCS.

Materials and methods

Population and study design

This is a real-life, prospective and retrospective study monocentric observational study including 50 patients (males: 28/50

Table 1. Patients characteristics at baseline.

Epidemiology	
Age, mean ± SD	56.4+12.2
Female, n (%)	22 /50(44%)
Male, n (%)	28/50 (56%)
BMI, mean ± SD	24.9+4.8
Phenotyping	
Asthma, n (%)	42/50 (84%)
Allergies, n (%)	32/50 (75%)
NSAID-ERD, n (%)	18/50 (36%)
Smoking	8/50 (16%)
ASA TRIAD, n (%)	18/50 (36%)
Peripheral blood eosinophils >250 cells/mm3, n (%)	39/50 (90.6%)
Blood eosinophils, mean ± SD	826+472
Control of disease	
N (%) of previous sinonasal surgery	
0	7/50 (14%)
1	27/50 (54 %)
2	12/50 (24%)
>3	4/50 (8%)
Number SCS course per year, mean ± SD	2.6± 2.2
Previous biological treatment, n	12/50
Benralizumab, n	4/50
Omalizumab, n	4/50
Dupilumab, n	4/50
Staging	
SNOT-22 score, mean ± SD	58.4 ± 21.0
NPS, median (IQR)	5 (4-5.25)
SSIT-16, median (IQR)	3 (5-2)
VAS obstruction, median (IQR)	8 (9-5)
VAS smell, median (IQR)	10 (10-8.5)
VAS rhinorrhea, median (IQR)	7 (9-4)
VAS facial pain, median (IQR)	3 (8-0)
PNIF, media ± SD	92.5 ± 39.2
NCS, median (IQR)	3 (3-2)
TNSS, median (IQR)	9 (11-7)
EQ-VAS, mean ± SD	56.3+22.4
ACT, median (IQR)	18 (22-15)

ACT: asthma control test; ASA TRIAD: aspirin-exacerbated respiratory disease; BMI: body mass index; EQ-5D-5L: EuroQol visual analogue scale; IQR: interquartile range; NCS: nasal congestion score; NPS: nasal polyp score; NSAID-ERD: non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SCS:systemic corticosteroids; PNIF: peak nasal inspiratory flow; SCS: systemic corticosteroids; SNOT-22: sinonasal outcome test-22; SSIT-16: sniffin' sticks identification test (16-item version); TNSS: total nasal symptom score; VAS: visual analog scale.

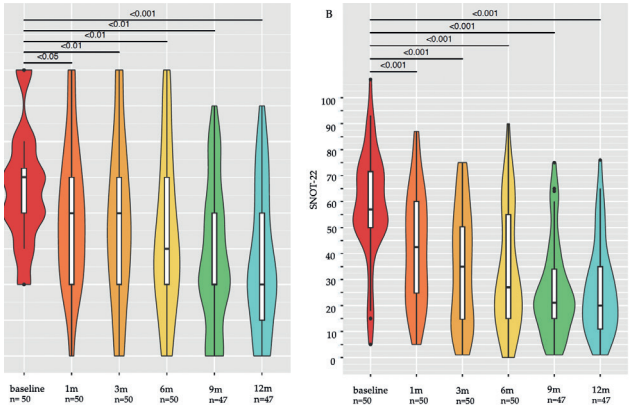

Figure 1. Violin plots representing changes in NPS (A) and SNOT-22 scores (B) over mepolizumab treatment period.

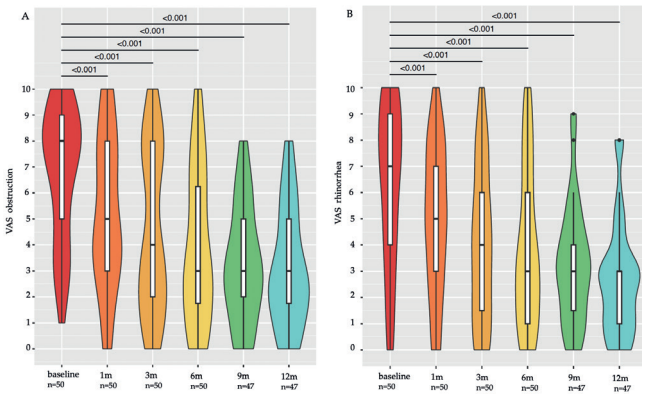

Figure 2. Violin plots representing changes in VAS nasal obstruction scores (A) and rhinorrhea scores (B) over mepolizumab treatment period.

[56%]; mean age: 56.4 ± 12.2 years; range 35-77) affected by severe, uncontrolled CRSwNP who received mepolizumab at the dose of 100 mg every 4 weeks. Most patients had concomitant asthma (42/50, 84%) and underwent previous surgeries (43/50, 86%).

Mepolizumab was administered subcutaneously with an auto-injector as add-on therapy to intranasal corticosteroids (INCS), as indicated by the Italian National Agency for Medicines (AIFA) [7].

Patients were enrolled between March 2023 and December 2024 at the Rhinology Service of A. Gemelli Hospital Foundation-IRCCS, Catholic University of Sacred Heart, Rome, Italy. Table 1 summarizes the baseline characteristics of the cohort.

To participate in this study, patients had to meet the following inclusion criteria: 1) diffuse diagnosis of CRSwNP in adults confirmed by endoscopy/computer tomography (CT) scan performed at least 6 months prior to mepolizumab treatment; 2) severe disease stage, defined by nasal polyp score (NPS) ≥5 and/or sino-nasal outcome test-22 (SNOT-22) ≥50; 3) inadequate symptom control despite maintaining INCS therapy; 4) at least 2 brief cycles of systemic corticosteroids in the previous year and/or failure of previous endoscopic sinus surgery. In this manuscript, we have included only the patients who completed the 12-month follow-up period. Exclusion criteria included: 1) pregnancy; 2) radio-chemotherapy treatments for cancer in the previous 12 months; 3) concomitant immunosuppressive therapy; 4) long-term corticosteroid therapy for chronic autoimmune disorders.

At our center, CRSwNP patients undergoing biologics treatment are usually evaluated at baseline, re-assessed at 1 month and followed up at 3, 6, 9, and 12 months during the first year of treatment. At baseline, we gathered socio-demographic and clinical information including sex, age, smoking habit, presence of concomitant asthma, allergies, previous surgery for CRSwNP, and use of SCS.

The study was approved by the local ethics committee (Number of protocol:ID 6231). Informed consent about privacy and utilization of clinical data was obtained from all patients at the time of original data collection. Clinical data were anonymously analyzed.

Assessment of clinical outcomes

Nasal polyp size was evaluated by NPS (score range: 0-8) according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines [8]. Quality of life was assessed using the validated Italian version of SNOT-22 (score range: 0–110) [9].

Patients were also asked to complete the EQ-5D-5L, a health-related quality of life questionnaire that includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels of severity; patients are asked to choose the level that best describes their health in each of these dimensions. Additionally, the EuroQol Visual Analogue Scale (EQ-VAS) was used to assess the patient's overall current health. The scale ranges from 0 to 100, where 100 represents "The best health you can imagine" and 0 represents "The worst health you can imagine" [10].

Overall symptoms were evaluated by Total Nasal Symptom Score (TNSS) (score range: 0–15) [11]. Severity of main sino-nasal symptoms (nasal obstruction, smell, rhinorrhea, facial pain) was measured by a visual analogue scale (VAS) of 10-cm length [12].

Nasal obstruction was also assessed using the Nasal Congestion Score (NCS) and peak nasal inspiratory flow (PNIF), which provides an objective measure of the degree of nasal obstruction [12].

Smell dysfunction was semi-objectively evaluated by the Sniffin' Stick-16 identification test (SSIT-16); based on this score, patients were categorized as anosmic (score between 0 and 5), hyposmic (score between 6 and 10), or normosmic (score between 11 and 16) [13,14].

In patients with asthma, we evaluated disease control using the asthma control test (ACT), a self-reported patient tool for identifying individuals with poorly controlled asthma. The score ranges from 5 (poor control of asthma) to 25 (complete control

Table 2. Patients' clinical outcomes over the treatment period.

	Baseline (n=50)	1 month (n=50)	3 months (n=50)	6 months (n=50)	9 months (n=47)	12 months (n=47)
Mean SNOT-22* ± SD	58.4±21.0	41.5±20.5	34.4±21.9	33.3±22.8	25.6±17.8	26.1±17.5
Median NPS (IQR)	5 (4-5.25)	4 (5-2)	4 (5-2)	4 (5-2)	3 (4-2)	2 (4-1)
Mean PNIF* ± SD	92.5±39.2	104.9±34.8	102.7±28.6	110.0±32.9	107.5±35.5	118.8±38.0
Median NCS (IQR)	3 (3-2)	2 (2-1)	1.5 (2-1)	2 (2-1)	1 (2-1)	1 (2-0)
Median SSIT-16 (IQR)	3 (5-2)	5 (8-3)	6 (10-3)	6 (11-3)	7 (11-4)	7 (11-4)
Median TNSS (IQR)	9 (11-7)	7.5 (9.75-4.25)	5 (8.3)	4 (7-3)	4 (7-2)	3 (6-2)
Mean eosinophilic blood count ± SD	826±472	89±41	60±29	58±17	59±30	48±23
Median VAS smell (IQR)	10 (10-8.5)	8 (10-5)	8 (10-5)	8 (10-3)	6 (10-2)	6 (9-2)
Median VAS obstruction (IQR)	8 (9-5)	5 (8-3)	4 (8-2)	3 (6.25-1.75)	3 (5-2)	3 (5-1.75)
Median VAS rhinorrhea (IQR)	7 (9-4)	5 (7-3)	4 (6-1.5)	3 (6-1)	3 (4-1.5)	3 (3-1)
Median VAS facial pain (IQR)	3 (8-0)	2 (6-0)	1 (7-0)	0 (4.5-0)	0 (2-0)	0 (2-0)
Median VAS sleep disorder (IQR)	6 (8-1)	2 (6-0)	2 (5.5-0)	2 (6-0)	1 (3.25-0)	1 (4-0)
Mean EQ-VAS ± SD	56.3±22.4	66.7±16.1	70.4±16.5	71.8±15.5	72.5±14.5	76.7±11.6
Median ACT (IQR)	18 (22-15)	20 (23-17)	22 (24-17.5)	22 (25-18)	23 (25-18)	24 (25-20.5)

Variables were normally distributed, so they are expressed as mean +DS and tested using Student T test for paired samples. ° Only the first timestep resulted significant for asymmetry but almost normally distributed, the other timestep resulted normally distributed so the entire variable was considered as normal. All significances are plotted Bonferroni corrected (5x). ACT: asthma control test; EQ-5D-5L: EuroQol 5-dimension 5-level; IQR: interquartile range; NCS: nasal congestion score; NPS: nasal polyp score; PNIF: peak nasal inspiratory flow; SD: standard deviation; SNOT-22: sinonasal outcome test-22; SSIT-16: sniffin' sticks identification test (16-item version); TNSS: total nasal symptom score; VAS: visual analog scale.

of asthma), with higher scores reflecting greater asthma control. An ACT score >19 indicates a well-controlled asthma [16].

Response to biologics was measured according to European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS)/European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) 2023 criteria, based on which patients are classified into 3 groups: "non responders" (0 criteria met); "poor-moderate responders" (1-3 criteria met); " and "good-excellent responders" (4-5 criteria met). In this study, we slightly modified this classification for normosomic patients and/or patients without comorbidities. Briefly, for normosomic patients (who could never improve their sense of smell) or in absence of asthma, we applied the following classification: "non responders" (0 criteria met), "poor-moderate response" (1-3 criteria met), and "good-excellent response" (4 criteria met). For patients who were normosmic and had no comorbidities (who could not improve either aspect), we applied the following modified classification: "non responders" (0 criteria met); "poor-moderate responders" (1-2 criteria met), and "good-excellent responders" (3 criteria met) [17].

Clinical outcomes were measured at each follow-up visit (1-3-6-9-12 months). For patients who underwent ESS at 6 months, post-ESS outcomes were excluded from the analyses. For patients who underwent surgery or switched to dupilumab at 12 months, outcomes before surgery/switch were included in the analyses. Data after SCS use were included in the analyses, as they were only used in non-responder patients.

Statistical analyses

Data were anonymized and collected using REDCap (Research Electronic Data Capture, ver.12.3 2023). Statistical analyses were performed using SPSS 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, USA). The normality of continuous variables was verified with the Shapiro-Wilk test (normal for $p>0.05$).

All timesteps were compared with baseline using paired samples test: student T-test was used for normally distributed data (SNOT-22 and PNIF) whereas Wilcoxon signed-rank test was used for non-normally distributed data. Normally distributed variables (SNOT-22, PNIF, mean eosinophilic blood count, EQ-VAS) are reported as mean ± standard deviation (SD); non-normally distributed variables (NPS, NCS, VAS, SSIT-16, ACT) are plotted as median (interquartile range, IQR); dichotomic data are expressed as absolute values (percentage). Violin plots were obtained using R software (R:A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria) with GGsigni package. Multiple comparisons for time series were corrected using the Bonferroni method; significance in text is intended as already corrected. Statistical significance was defined by p-values <0.05.

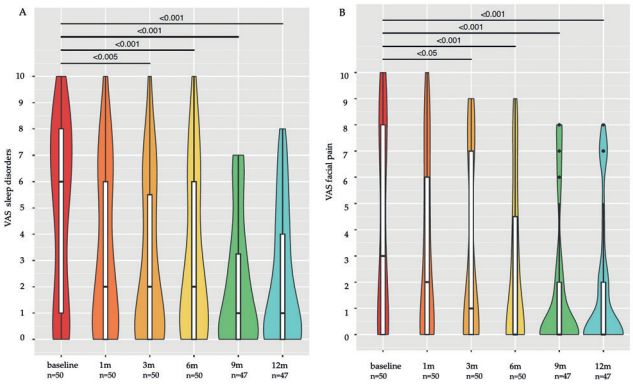

Figure 3. Violin plots representing changes in VAS facial pain scores (A) and sleep disturbances (B) over mepolizumab treatment period.

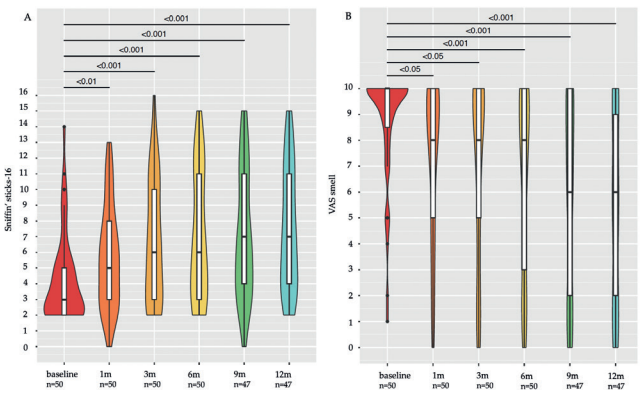

Figure 4. Violin plots representing changes in SSIT-16 scores (A) and VAS smell score (B) over mepolizumab treatment period.

Results

Effectiveness of mepolizumab in reducing NPS score and improving quality of life

The median NPS score decreased significantly over the course of treatment, from 5 (IQR 4-5.25) at baseline, to 4 (IQR 5-2) at 3 months (p <0.001), 4 (IQR 5-2) at 6 months (p <0.001) and 2 (IQR 4-1) at 12 months (p <0.001) (Figure 1A). Additionally, we observed a significant improvement in quality of life, as evidenced by a reduction in SNOT-22 score from an average of 58.4±21.0 at baseline to 34.4±21.9 at 3 months (p <0.001), 33.3±22.8 at 6 months (p <0.001) and 26.1±17.5 at 12 months (p <0.001) (Figure 1B). The mean values of NPS and SNOT-22 scores over time are shown in Table 2. Patients also reported an improvement in the perception of good health and well-being, as measured with EQ-VAS; the mean composite score improved from 56.3±22.4 at baseline to 71.8±15.5 at 6 months (p <0.001), and 76.7±11.6 at 12 months of treatment (p <0.001) (Table 2).

Effectiveness of mepolizumab on nasal obstruction

The median NCS score significantly decreased from 3 (IQR 3-2) at baseline to 2 (IQR 2-1) at 6 months (p <0.001), and further to 1 (IQR 2-0) at 12 months (p <0.001) (Table 2). Similarly, the median VAS nasal obstruction score improved significantly, decreasing from 8 (IQR 9-5) at baseline to 3 (IQR 6.2-1.7) at 6 months (p <0.001) and 3 (IQR 5-1.7) at 12 months (p <0.001) (Table 2 and Figure 2A). A significant improvement was also found in objective measures of nasal obstruction, with mean PNIF values increasing from 92.5±39.2 L/min at baseline to 118.8±38.0 at 12 months (p <0.001) (Table 2).

Effectiveness of mepolizumab on other symptoms, including loss of smell

The overall impact of mepolizumab on symptoms was assessed using the TNSS. The median TNSS decreased from 9 (IQR 11-7) at baseline to 4 (IQR 7-3) at 6 months (p <0.05), and further to 3 (IQR 6-2) at 12 months of treatment (p <0.001) (Table 2).

The median VAS rhinorrhea was 7 (IQR 9-4) at baseline, decreased to 3 (IQR 6-1) at 6 months (p <0.001) and was stable at 3 (IQR 3-1) at 12 months (p <0.001) (Table 2 and Figure 2B). The median VAS facial pain was 3 (IQR 8-0) at baseline and declined to 0 at both 6 months (IQR 4.5-0, p <0.001) and 12 months (IQR 2-0, p <0.001) (Table 2 and Figure 3A). The median VAS sleep disorder was 6 (IQR 8-1) at baseline and decreased to 2 (IQR 6-0) at 6 months (p <0.001) and 1 (IQR 4-0) at 12 months (p <0.001) (Table 2 and Figure 3B).

Regarding the results on olfaction, we observed a modest overall improvement which, although statistically significant, may be considered of limited clinical relevance. The median VAS smell score decreased from 10 (IQR 10-8.5) at baseline to 8 (IQR 10-3) at 6 months (p <0.001) and 6 (IQR 9-2) at 12 months (p <0.05). Similarly, the SSIT-16 median score improved from 3 (IQR 5-2) at baseline to 6 (IQR 11- 3) at 6 months (p <0.001) and further improved to 7 (IQR 11-4) at 12 months (p <0.001). The temporal changes of mean SSIT-16 and VAS smell scores over the first year of treatment are shown in Table 2 and Figure 4A-B.

According to SSIT-16 scores at baseline, 76% of patients were classified as anosmic, 18% as hyposmic, and 6% as normosmic. At 12 months, the percentages of anosmic, hyposmic and normosmic patients were 36%, 40% and 24%, respectively (Table 3).

Blood eosinophilia during treatment and associated comorbidities.

Regarding blood eosinophil count, we observed a reduction in eosinophils number, from a mean value of 826±472 cells/mm^3 at baseline to 48±23 cells/mm^3 at 12 months (p <0.001) (Table 2). The treatment also improved asthma control, as demonstrated by a significant increase in ACT score. At baseline, patients had a median ACT score of 18 (IQR 22-15), which progressively improved to 22 (IQR 25-18) (p <0.01) and 24 (IQR 25-20.5) (p <0.01) at 6 and 12 months, respectively (Table 2). We also report the cases of 2 patients with eosinophilic otitis media who experienced significant improvements, including enhanced hearing and no

Table 3. Patient distribution based on SSIT-16 results over time.

	Baseline (n=50)	1 month (n=50)	3 months (n=50)	6 months (n=50)	9 months (n=47)	12 months (n=47)
Anosmic	38 (76%)	27(54%)	25 (50%)	23 (46%)	20(20%)	18 (36%)
Hyposmic	9 (18%)	19 (38%)	18 (36%)	17(34%)	20(40%)	20 (40%)
Normosmic	3 (6%)	4 (8%)	7 (14%)	10 (20%)	10 (20%)	12 (24%)

SSIT-16: SSIT-16: sniffin' sticks identification test (16-item version).

further need for antibiotics and systemic steroids.

Rescue treatments and rate of treatment success evaluated by EPOS/EUFOREA 2023 criteria

Basing on EPOS/EUFOREA 2023 criteria after 3 months of treatment, we observed an "excellent/good "response in 9/50 patients (18%), a "moderate/poor " response in 28/50 patients (56%) and "no response" in 13/50 patients (26%). At 6 months, 14/50 patients (28%) met the "excellent/good" response criteria, 26/50 patients (52%) showed a "moderate/poor " response, and 10/50 patients (20%) had "no response". After 1 year of treatment, 24/50 patients (48%) had an "excellent" response, 19/50 patients (38%) had a "moderate" response, and 7/50 patients (14%) had "no response" (Figure 5).

In the non-responder group, all 7/50 patients (14%) required systemic corticosteroids (SCS) during treatment but remained uncontrolled despite their use. They were managed as follow:

- 3 patients underwent ESS at 6 months, and maintained mepolizumab, because of effective asthma control (2 patients had a markedly elevated eosinophilic profile, and 1 had a history of incomplete prior surgery).
- 2 patients discontinued mepolizumab at 12 months (They were not responder a Dupilumab in the past) and subsequently underwent ESS.
- 2 patients were discontinued mepolizumab and switched to dupilumab at 12 months.

Safety

Mepolizumab was generally well tolerated, except for 2 patients (4%) who experienced severe adverse events (AEs) requiring treatment discontinuation. One patient developed severe arthralgia, necessitating rheumatologic evaluation and medical intervention. Another patient experienced fever after the first two mepolizumab injections, followed by fever and a skin rash after the third injection, leading to the discontinuation of treatment. Furthermore, 6 patients (12%) reported minor AEs, including arthralgia in 4 patients and psoriasis in 2 patients.

Discussion

Mepolizumab is a monoclonal antibody targeting IL-5, which prevents its interaction with its receptor and inhibits eosinophilic inflammation. It has been approved and reimbursed in Italy for the treatment of severe uncontrolled CRSwNP since March 2023. Since then, several real-life studies have confirmed its efficacy and safety, although the results have shown variability in the main outcome measures [18-22]. Indeed, most studies are single-center experiences with a limited number of patients, various endpoints and different follow-up schedules. In the study by Detoraki et al., mepolizumab reduced both SNOT-22 (from 51.5±21.2 at baseline to 29.7±21.5) and NPS score (from 2.88±3.07 to 1.77±2.56) in patients with severe asthma and comorbid CRSwNP after 52 weeks of treatment [23]. In a similar cohort of 43 severe asthmatic patients with CRSwNP, Gallo et al. showed a median change of -22(IQR 31) points in SNOT-22 score and a median change of -1(IQR 2.5) points in NPS score after 52 weeks of treatment [24]. In a different population consisting of 55 severe CRSwNP patients, Domínguez-Sosa et al. reported median decreases of 4 points (CI: ±4) and 63 points (CI: -68; -58) in NPS and SNOT-22 scores, respectively, after 24 weeks of treatment [25]. Studies of patients with CRSwNP, with or without asthma, have begun to emerge with the approval of prescriptions for nasal polyps in Italy. Galletti et al. showed similar results in a cohort of 30 patients treated for 12 months, where median NPS decreased from 6 (IQR 4–6) to 3 (IQR 2–4) and median SNOT-22 score improved from 65 (IQR 46–77) to 22 (IQR 10-33) (26). In a study involving 20 patients, Cavaliere et al. demonstrated a gradual improvement in mean NPS, which decreased from 5.11±1.05 to 1.89±1.73 after one year of treatment. In parallel, the mean SNOT-22 score significantly improved from 48.32±13.20 at baseline to 16.59±8.49 at 12 months [27]. In a 6-month follow-up study, Cantone and colleagues reported an improvement in both NPS and SNOT-22 in 20 patients (from 5.2±3.2 to 2.5±1.4, and from 61.33±24.1 to 19.5±8.4, respectively) [28].

In this study, we report the results from 50 severe, uncontrolled CRSwNP patients, mostly with comorbid asthma, treated with mepolizumab and followed up for at least 12 months at our center. The high percentage of asthma patients is linked to the significant proportion of complex, multimorbid cases referred to our center, managed within a multidisciplinary framework, and

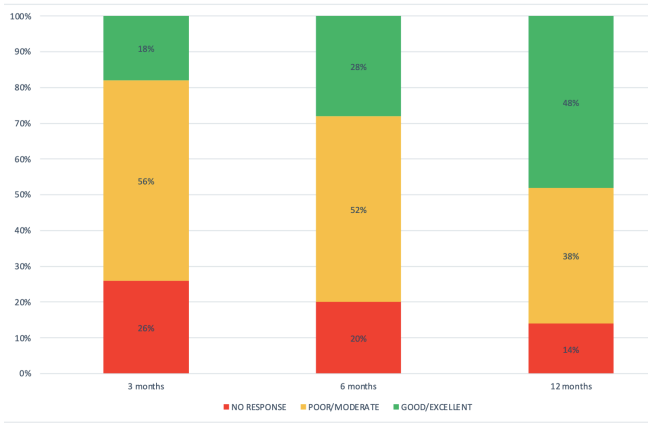

Figure 5. Evaluation of disease control at 3, 6 and 12 months of treatment with mepolizumab. Response was defined by EPOS criteria.

Mepolizumab has been frequently considered during multidisciplinary meetings, particularly for patients presenting with both high eosinophilic asthma and nasal polyps.

We observed that mepolizumab administered every 4 weeks with an auto-injector as an add-on therapy to INCS was effective in reducing several outcomes. The improvement in SNOT-22 score (from an average of 58.4±21.0 at baseline to 26.1±17.5 at 12 months) is like that obtained in the SYNAPSE study, and slightly different compared to other real-life studies, confirming the high heterogeneity of real-life results until now. Furthermore, we recorded a significant change in the median NPS value [from 5 (IQR 4-5.25) at baseline to 2 (IQR 4-1) at 12 months, $p<0.001$], showing a greater downtrend compared to NPS reduction in the SYNAPSE study.

In our study the administration of mepolizumab was associated with statistically significant improvements in sinonasal symptoms, including nasal obstruction, rhinorrhea and facial pain, as indicated by reduction in VAS scales. Regarding olfaction, however, we have observed less impactful results. Although we observed a significant reduction of VAS smell its median value remains above 5 at 12 months of observation indicating still a negative impact on the quality of life. Accordingly, there was a statistically significant improvement in median SSIT-16 score, although it was clinically not relevant for many patients. Indeed, we observed a very heterogeneous response in olfactory recovery. Based on sniffing sticks results by 12 months, the percentage of anosmic patients decreased from 76% to 36%, hyposmic patients remained stable at 40%, while the percentage of normosmic patients increased from 6% to 24%. While some patients experienced substantial improvement, others remained hyposmic, highlighting the variability in treatment response and the complexity of olfactory dysfunction in CRSwNP.

Comparing our data on the sense of smell with those of other studies in real life, differences emerge in the outcomes at 12 months. Specifically, in the study by Galletti et al., an improvement in the SSIT-16 score was observed, rising from 2 (IQR 2-3) to 11 (IQR 10-13) after one year of treatment, whereas in our study, the score improved from 3 (IQR 5-2) at baseline to 7 (IQR 11-4). In Cavaliere et al., the VAS olfactory score showed an improvement, from 8.47±1.31 at baseline to a mean of 2.71±1.38 at 12 months, the median VAS smell score decreased from 10 (IQR 10-8.5) to 6 (IQR 9-2) at 12 months. Several factors (i.e., number of patients, number and type of previous surgeries, CRSwNP endotype, rate of comorbidities, etc.) are likely to influence outcomes in real-life studies and may have contributed to the observed heterogeneity in results [27,28]. Therefore, we believe that future multicentric studies with a larger number of patients are necessary to clarify the magnitude of loss of smell improvement with mepolizumab in real world. It should be emphasized that, currently, the sense of smell is considered one of the most important outcomes in the treatment of nasal polyps. In some patients, if there is no improvement in smell, a change in treatment may be considered. This decision should be made in discussion with the patient, considering the possibility of adjusting the approach based on their expectations.

The safety profile of mepolizumab was consistent with that observed in previous studies, with no new safety concerns identified [27,28].

Our study confirms the effectiveness of mepolizumab in the treatment of CRSwNP, with good/excellent and poor/moderate response rates of 48% and 38% at 12 months, respectively, based on the EPOS/EUFOREA 2023 criteria [17]. Finally, 14% of patients showed no response to treatment and required systemic corticosteroids but remained uncontrolled despite their use. In that cases salvage surgery was mainly preferred in patients with prior failure to biologics, inadequate or incomplete previous sinus surgery, markedly elevated eosinophilic profiles and well controlled asthma. A shift to dupilumab was considered in all the other cases also considering the preliminary data of superiority of dupilumab versus omalizumab [29]. It is important to emphasize that treatment decisions in real-world clinical practice are complex and multifactorial. They depend on a range of elements, including the available therapeutic options, previous treatments, potential contraindications, safety considerations, and access to treatments, which may vary between different countries.

It is important to note that the need for rescue treatments, rather than olfactory recovery, may negatively influences the definition of remission. However, in this cohort, it was not possible to determine the remission rate due to an insufficient follow-up period to draw definitive conclusions.

Our results should be interpreted in the light of the limitations of the study. This was an observational, real life, single-centre study without a control group. In addition, because the study was conducted in a tertiary referral centre, the initial cohort of patients likely included individuals with more severe and

treatment-resistant CRSwNP. Patients who underwent surgery at 6 months were excluded from the analyses, but data after SCS use were included because they were only used in poor responders and were therefore considered to have minimal impact on the final outcomes.

Future multicentric study including also non-academic patient cohorts will help determine whether differences emerge on a larger national scale. Research on larger populations could provide valuable insights into identifying the best responders to treatment. Future studies should focus on uncovering predictive factors for optimal response and determine patients' response window, ultimately improving patient management and therapeutic outcomes.

Conclusion

This study supports the use of mepolizumab as an effective option in the current standard of care for patients affected by severe, uncontrolled CRSwNP. Indeed, our preliminary findings on mepolizumab indicate that this mAb is effective in managing CRSwNP, as it reduces nasal polyp size, lowers blood eosinophil levels, improves disease-related symptoms and enhances quality of life. Nevertheless, worldwide experience with mepolizumab shows some differences in the magnitude of clinical benefits, implying variability in individual patient responses, especially in smell improvement. For this reason, the authors believe that additional multicentric studies with larger patient cohorts are necessary to expand current knowledge on mepolizumab effectiveness in treating patients with severe, uncontrolled CRSwNP.

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Authorship contribution

EDC: conception and design of the study, acquisition of the data, analysis, and interpretation of the data; drafted the article and revised it for important intellectual content; gave final approval of the version to be submitted; agree to be accountable for all aspects of the work. MC: drafted the article and revised it for important intellectual content; CM, GDM, RM, LMD, AR, CS, SP, GDA, AO, MCP, AR: acquisition of the data, analysis and interpretation of the data; gave final approval of the version to be submitted; agree to be accountable for all aspects of the work. JG: final approval of the version to be submitted.

Conflict of interest

EDC: Lecture fees and participations in experts board meeting of GSK, Novartis, Sanofi, Astrazeneca. AO: lecture fees or consultations fee from Abbvie, Astra Zeneca, GSK, Novartis, Lilly, Johnson and Johnson, UCB. MC, CM: Lecture fees from Sanofi and GSK. GDM, RM, LMD, AR, CS, SP, GDA, MCP, AR, JG declare no conflicts of interest.

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