Mepolizumab in severe uncontrolled CRSwNP: a real-life multicentre study in Northeast Italy

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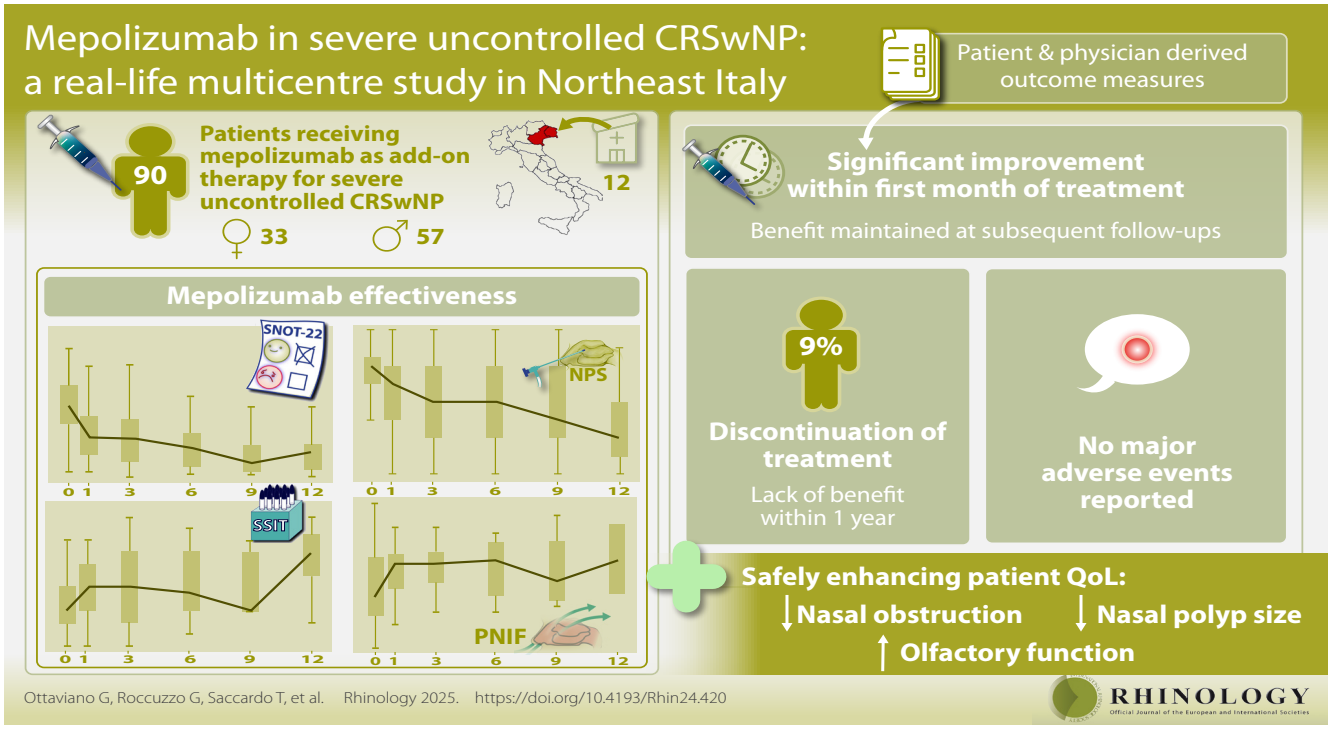

Abstract

Background: The aim of this study was to evaluate the efficacy of mepolizumab as add-on therapy to intranasal corticosteroids for the treatment of severe, uncontrolled Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) in a real-life setting in the Triveneto region of northeast Italy.

Methods: Patients with severe CRSwNP receiving mepolizumab were followed up at 1, 3, 6, 9 and 12 months from the first administration. At baseline and at each follow-up, patients underwent nasal endoscopy, completed the Sinonasal Outcome Test 22, Visual Analogue Scales for smell, nasal obstruction, rhinorrhoea and facial pain, the Nasal Congestion Score and the Asthma Control Test. Peak nasal inspiratory flow, Sniffin' Sticks Identification Test and blood eosinophil count were also evaluated.

Results: Ninety patients from twelve different rhinological units were enrolled in the study. Both patient- and physician- derived outcome measures significantly improved within the first month after biological treatment initiation, maintaining the benefit at subsequent follow-ups. Nine percent of patients discontinued the treatment due to lack of benefit within the first year. No major adverse events were reported.

Conclusions: Mepolizumab is effective in improving nasal obstruction and the sense of smell in patients with severe uncontrolled CRSwNP, based on both patient- and physician derived outcome measures.

Key words: CRSwNP, mepolizumab, NPS, PNIF, Sniffin' Sticks test

Introduction

Chronic rhinosinusitis (CRS) is a multifactorial disease characterized by prolonged inflammation of the sinonasal mucosa lasting more than 12 weeks. It is traditionally categorized by the presence or absence of a specific phenotypical aspect: the nasal polyps. Accordingly, two main phenotypes are identified: "CRS with nasal polyps" (CRSwNP), and "CRS without (sine) nasal polyps" (CRSsNP). The former can be associated with genetic disorders, immunodeficiency, anatomical abnormalities, and chronic osteomyelitis, but it can also be influenced by exposure to environmental factors such as air pollution, smoke, allergens, viruses, bacteria, and fungi [1].

CRSwNP accounts for 25–30% of all CRS cases and significantly impacts patients' quality of life (QoL) [2]. The standard management of CRSwNP involves the use of nasal steroid sprays, saline rinses, oral corticosteroids, and surgical procedures such as endoscopic sinus surgery (ESS) [3,4]. Since late 2019, CRS management has transitioned to an approach emphasizing the underlying immunopathological mechanisms, referred to as endotyping. In this perspective, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) introduced a novel classification of CRS, dividing it into primary and secondary categories, and further into localized and diffuse subtypes based on anatomical distribution. Primary CRS is further subclassified by its endotypic dominance as type 2 or non-type 2 inflammation [5].

It has been recognized that the most common endotype of CRSwNP in Western Countries is type 2 inflammation, characterized by elevated levels of interleukin (IL)-4, IL-5, and IL-13, as well as a significant presence of eosinophils, type 2 innate lymphoid cells, macrophages, and mast cells [2,5,6,7]. This classification enables the identification of patient subgroups more likely to benefit from targeted therapies, facilitating a personalized treatment approach. The development of monoclonal antibodies targeting type 2 inflammatory pathways has transformed the management of severe uncontrolled CRSwNP, resulting in significant QoL improvements for patients.

International rhinological guidelines [5,8,9] recommend the use of biological therapies as an add-on treatment to severe, uncontrolled CRSwNP, in patients who have undergone ESS at least once and meet three of the following five criteria: evidence of type 2 inflammation, need for systemic corticosteroids or contraindication for systemic corticosteroids, significantly impaired QoL, substantial loss of smell, and a diagnosis of comorbid asthma.

At present dupilumab, mepolizumab and omalizumab are the only three biological drugs approved as add-on therapies for severe and uncontrolled CRSwNP. These drugs consist of humanized monoclonal antibodies (mAbs), targeting different components in the type 2 inflammatory pathway. Dupilumab (IgG4 subclass mAb) selectively binds to the IL-4 receptor α subunit, shared by both IL-4 and IL-13 receptor, thereby blocking IL-4 and IL-13 signaling [10]. Omalizumab (IgG mAb) selectively binds to IgE at its Cε3 domain, inhibiting the binding of IgE to its high-affinity Fce receptor (FcεRI) on effector cells, thus reducing the amount of free IgE available for recognition by effector cells [11]. Mepolizumab (IgG1/kappa subclass mAb) selectively targets IL-5, inhibiting its activity by preventing its association with the α chain of the IL-5 receptor complex (IL-5R) [12].

Mepolizumab, previously approved for the treatment of severe eosinophilic asthma, is the most recent mAb to receive an indication specifically for severe CRSwNP treatment. It was approved by the Italian Medicines Agency (AIFA) in March 2023 for the treatment of severe, uncontrolled CRSwNP. Its safety and effectiveness have been extensively investigated by a randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial [13]. Nevertheless, there is currently only a small amount of data available in the literature regarding its real-life efficacy.

The aim of the present multicentre study is to evaluate the real-life effects of mepolizumab in patients with severe, uncontrolled CRSwNP residing in the region of Triveneto, one of the most populated areas of Italy [14].

Materials and methods

This is a non-profit, observational retrospective multicentre study. Study participants were recruited and followed in the rhinological units of 12 different hospitals in Triveneto during the first 18 months of approval of mepolizumab in Italy. Inclusion criteria were defined according to the Italian Medicines Agency (AIFA):

1) age ≥ 18 years;

2) diagnosis of severe chronic rhinosinusitis with nasal polyps (CRSwNP), defined by a nasal polyp score (NPS) ≥ 5 and/or a Sinonasal Outcome Tests-22 (SNOT-22) ≥ 50, with inadequate symptoms control despite intranasal corticosteroids (INCS) use, receiving at least 2 cycles of systemic corticosteroid in the last year and/or having undergone one or more sinonasal surgeries [endoscopic sinus surgery (ESS)];

3) administration of mepolizumab 100 mg, one sub-cutaneous injection every four weeks, indicated specifically for severe CRSwNP treatment as an add-on therapy to INCS as conventional treatment [15].

Bilateral diffuse CRS with predominance of type 2 inflammation was evident in each patient. Criteria considered for type 2 endotyping were: history of elevated blood eosinophil count (BEC) and/or high levels of eosinophil infiltrate in previous surgical biopsies [5,16], mild/moderate comorbid asthma as per GINA criteria [17], non-steroidal anti-inflammatory drugs (NSAID) intolerance and NSAID- exacerbated respiratory disease (N-ERD). For the diagnosis of N-ERD, a clear history of multiple reactions within 1-2 hours after the ingestion of an NSAID with respiratory symptoms, according to Kowalski et al. [18], was sufficient for

Table 1. Patients' main clinical characteristics at baseline for the whole group and separated for the different Hospital Units.

	Padova n=24	Udine n=10	Legnago n=10	Feltre n=9	S. Vito al Tagliamento n=9	Rovigo n=8	Venezia Mestre n=6	Verona n=5	Schiavonia n=5	ENT Units with <5 patients each* n=4	TOTAL n=90
Sex	W = 8 M = 16	W = 2 M = 8	W = 4 M = 6	W = 3 M = 6	W = 1 M = 8	W = 5 M = 3	W = 4 M = 2	W = 3 M = 2	W = 0 M = 5	W = 3 M = 1	W = 33 M = 57
Median Age, yr [IQR]	59 [52-65]	73.5 [69.5-77.8]	50 [40.8-59]	74 [58-79]	58 [49-75]	66.5 [57.3-75.8]	56.5 [44.5-69.3]	60 [52-76]	57 [56-71]	70 [68-73.5]	61 [52-74]
BMI [IQR]	25 [23.3-26.4]	23.1 [21.4-25.2]	24.7 [23.1-29.7]	25 [23.7-29.7]	28 [24.6-29.4]	28 [23.8-34]	24.4 [23.4-24.8]	28.4 [27.5-29.3]	26.4 [25.1-27.5]	22.3 [20.3-26]	25 [23-28]
Asthma, n (%)	19 (79.2)	9 (90.0)	10 (100)	9 (100)	6 (66.7)	7 (87.5)	6 (100)	5 (100)	3 (60.0)	4 (100)	78 (86.7)
N-ERD, n (%)	7 (29.2)	6 (60.0)	3 (30.0)	4 (44.4)	1 (11.1)	1 (12.5)	3 (50.0)	1 (20.0)	1 (20.0)	1 (25.0)	28 (31.1)
Allergy to inhalants, n (%)	18 (75.0)	5 (50.0)	8 (80.0)	3 (33.3)	4 (44.4)	6 (75.0)	4 (66.7)	1 (20.0)	2 (40.0)	4 (100)	55 (61.1)
Active smokers, n (%)	4 (16.7)	1 (10.0)	2 (20.0)	0	1 (11.1)	1 (12.5)	1 (16.7)	0	0	0	10 (9)
OCS short course per year [IQR]	1 [0.8-2]	0 [0-2]	3 [2-3.8]	1 [1-3]	0 [0-0]	0 [0-0]	1 [1-1]	4 [1-5]	0 [0-0]	1 [0-2.8]	1 [0-2.3]
BEC [IQR]	0.6 [0.4-0.9]	0.7 [0.6-1.2]	1.6 [0.9-1.9]	0.6 [0.6-0.8]	0.4 [0.3-0.7]	0.8 [0.3-0.8]	1.3 [0.8-1.7]	0.4 [0.4-0.6]	1.2 [1.1-1.8]	0.9 [0.7-1.2]	1 [0.4-1.1]
Previous ESS, n (%)	22 (91.7)	9 (90.0)	7 (70.0)	8 (88.9)	9 (100)	8 (100)	6 (100)	5 (100)	5 (100)	4 (100)	83 (92.2)
Median n. of previous surgeries, n [IQR]	1 [1-2]	2 [1.3-3]	3 [1.5-3]	1 [1-1.3]	2 [2-2]	1 [1-2.3]	2 [1.3-3.5]	2 [1-2]	0 [0-2]	2 [1-3.3]	2 [1-2]

W: Women; M: Men; Yr: years; IQR: interquartile range; BMI: body mass index; n: number of patients; N-ERD: non-steroidal anti-inflammatory drugs exacerbated respiratory disease; OCS: oral corticosteroids; BEC: blood eosinophil count (cells x109/L); ESS: endoscopic sinus surgery. * The included ENT Units were from Cittadella Hospital, Montebelluna "San Valentino" Hospital, Belluno Hospital and Bassano del Grappa "San Bassiano" Hospital.

most of the patients with adult-onset asthma. In a few unclear cases, a challenge test with aspirin or culprit drug was performed at the Allergy Unit and Asthma Centre of Verona University Hospital, according to EAACI criteria [19].

We collected data at baseline (before starting the biological treatment) (T0) and at subsequent follow-up visits [1 month (T1), 3 months (T3), 6 months (T6), 9 months (T9) and 12 months (T12)]. Anthropometric and demographic data, surgical history, respiratory allergens sensitivity, active smoking habit, and number of oral coticosteroids (OCS) short courses in the previous 12 months [5] were collected before starting the treatment. At each timepoint, patients were assessed by means of the Sinonasal Outcome Test 22 (SNOT 22) [20], and by means of a nasal endoscopy (using 0° and/or 30° rigid endoscope) to assess both the Nasal Polyp Score (NPS) and the modified Lund Kennedy Score (LKS) [21,22]. The sino-nasal symptoms were also collected using the Visual Analogue Scale (VAS) scores for nasal obstruction (VAS-NO), smell (VAS-smell), rhinorrhoea (VAS-rhinorrhoea) and facial pain (VAS-facial pain) [23] together with the Nasal Congestion Score (NCS) [20] and, whenever comorbid asthma was present, the Asthma Control Test (ACT) score [10].

Physician-outcome derived measures were also collected. In particular, olfaction was measured by means of the Sniffin' Sticks identification sub-test (SSIT) (12 odours) (Burghart Messtechnik GmbH, Holm) [25] and nasal airflow was assessed by means of Peak Nasal Inspiratory Flow (PNIF - Clement Clarke International)

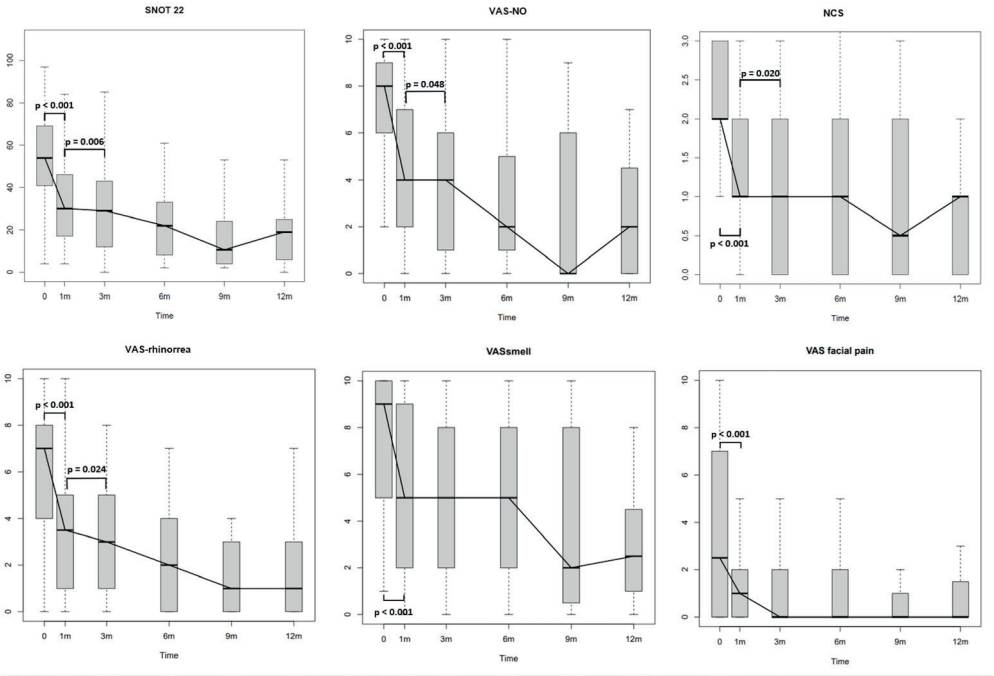

Figure 1. Patient derived outcome measures changes during the study period. Paired Wilcoxon test was used to compare measures between time-points. SNOT-22: Sinonasal Outcome Test-22; NO: Nasal Obstruction; VAS: Visual Analogue Scale; NCS: Nasal Congestion Score; m: months.

[26]. BEC was evaluated before starting the treatment and during the follow-up.

The minimal clinical importance difference (MCID) was calculated to assess the relevance of changing in the patient- and physician-derived outcome measures.

The study was conducted in accordance with the 1996 Helsinki Declaration and was approved by each hospital's ethical committee (AOP3240). Informed consent on personal data collection and use for research purposes was obtained from each subject before starting mepolizumab treatment.

Statistical analysis

Descriptive statistics are presented by median and interquartile range [IQR] for continuous variables, and absolute values and percentage (%) for categorical variables. Sample quantiles were used to describe the effect of all relevant variables in time and Bravais–Pearson correlation coefficient to measure the relations between the different indicators. Paired Wilcoxon test was also used to compare quantities between timepoints.

Multiple linear regression with selection of variable based on Akaike's information criterion (hybrid backward stepwise) was executed to identify the effects of the available variables on the QoL improvement as per SNOT-22.

For all tests, p-values were calculated, and 5% was considered as the critical level of significance. The R statistical package (R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses [27].

Results

A cohort of 90 consecutive patients (57 males and 33 females, median age 61 [52-74] years) who received mepolizumab as add-on therapy were considered for the present study. Specifically, 24 patients from the Rhinological Unit of Padova University Hospital, 10 patients from the ENT Unit of Udine "Santa Maria della Misericordia" Hospital, 10 patients from the ENT Unit of Legnago "Mater Salutis" Hospital, 9 patients from the ENT Unit of San Vito al Tagliamento Hospital, 9 patients from the ENT Unit of Feltre Hospital, 8 patients from the ENT Unit of Rovigo "Santa Maria della Misericordia" Hospital, 6 patients from the ENT Unit of Venezia Mestre "dell'Angelo" Hospital, 5 patients from the ENT Unit of Schiavonia "Madre Teresa di Calcutta" Hospital, 5 patients from the Allergy Unit and Asthma Centre of Verona University Hospital. All the subjects who were followed by ENT Units with fewer than 5 patients each, were grouped as one centre. Patients' main clinical characteristics at baseline (T0) are reported in Table 1. All the patients are having regular check-ups at the various territorial units and have reached different timepoints. All the subjects completed the 1- and 3-month follow-up (T1 and T3, respectively), while 40 of them (44%) completed the 6-month follow-up (T6) and 18 of them (20%) the 12-month follow-up (T12). Comorbid asthma and non-steroidal anti-inflammatory drugs (NSAID) intolerance were present in 86.7% (78 patients) and 33.3% (30 patients) of the population, respectively. N-ERD was present in 31.1% of the population (28 patients). Seven patients had no history of prior ESS as they were not fit for surgery, while all the others had a history of at least one

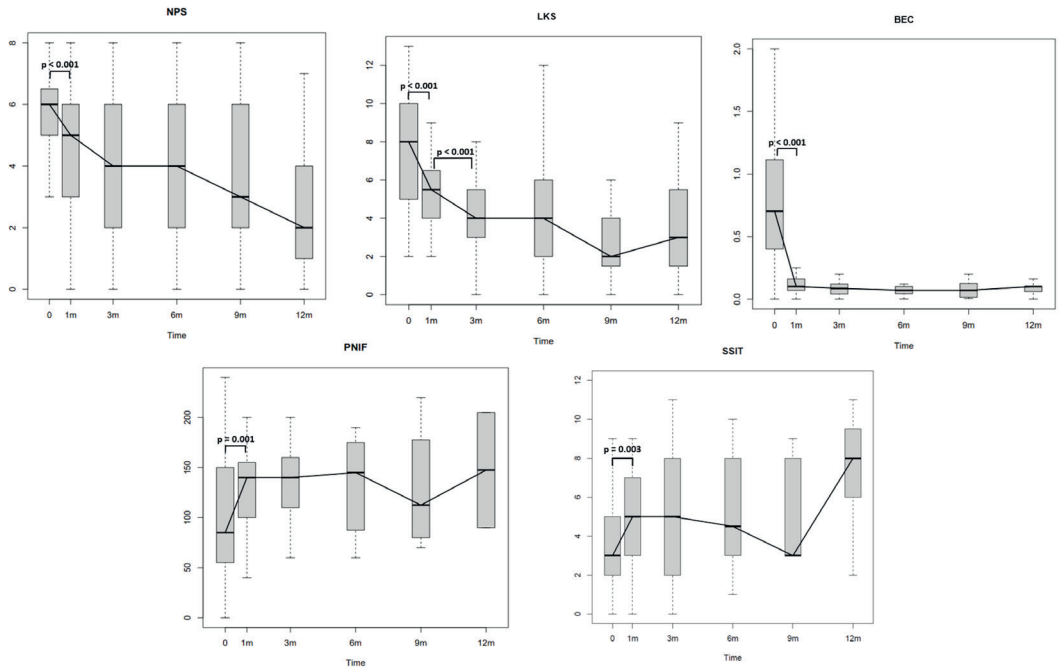

Figure 2. Physician derived outcome measures and blood test results changes during the study period. Paired Wilcoxon test was used to compare parameters between timepoints. NPS: Bilateral Nasal Polyp Score; LKS: Bilateral Lund-Kennedy score; BEC: blood eosinophil count (cells x109/L); PNIF: Peak Nasal Inspiratory Flow (L/min); SSIT: Sniffin' Sticks Identification Test; m: months.

previous ESS and suffered from nasal polyps' recurrence. In the post-surgical group (n=83), the median number of previous ESS was 2 [1-2], while the median interval since the last surgery was 84 [36.8-131.5] months.

Mepolizumab significantly reduced SNOT-22 after the first month of treatment and between T1 and T3. Also, VAS-NO, NCS, and VAS-rhinorrhoea showed a similar trend within the first 3 months of treatment. VAS-smell and VAS-facial pain showed a significant improvement only within the first month (Table 2 and Figure 1). Furthermore, NPS significantly improved between T0 and T1, as well as PNIF and SSIT (Table 2 and Figure 2). In the same study period, BEC showed a significant reduction. LKS improved significantly between T0 and T1 and between T1 and T3 (Table 2 and Figure 2). The percentage of patients who met the MCID after the first month of treatment and at the last follow-up was 65.2% and 78% for SNOT-22, 79% and 92% for VAS-NO, 77.4% and 89.4% for VAS-rhinorrhoea, 60% and 84.9% for VAS-smell, 54% and 68.2% for NCS, 54.8% and 94.6% for VAS-facial pain, 60.6% and 63.4% for NPS, 78.9% and 73.7% for PNIF, 61.1% and 60.1% for SSIT.

Focusing on the correlations between patient- and physician-derived outcome measures, PNIF and VAS-NO showed no significant correlation. On the contrary, VAS-smell and SSIT significantly correlated both at baseline and at almost every follow-up visit. NPS significantly correlated with both SSIT and SNOT-22, but did not correlate with PNIF neither at baseline nor at any follow-up visit. Similarly to NPS, LKS did not correlate with PNIF, while it significantly correlated with SNOT-22 at almost every follow-up visit and with SSIT only at T9. Significant correlations were also observed between LKS and BEC at T0 and T1 (Table 3).

At the multivariate analysis, higher baseline SNOT-22 and LKS emerged as independent positive prognostic factors for mepolizumab response in terms of sino-nasal symptom reduction (measured as SNOT-22 reduction). On the contrary, inhalant allergic and N-ERD patients, as well as those with a less impaired sense of smell at baseline, experienced a significantly and independently inferior reduction in SNOT-22 (Table 4).

All patients continued their long-term nasal therapy consisting of INCS and nasal douches with saline during the study period [28] and none of them required either OCS courses or sinonasal surgery during the follow-up period. Eight patients (8.8% of the whole cohort) stopped the biological treatment between the 6th and the 9th month of follow-up due to no response to the therapy according to Euforea 2023 criteria [8].

No serious adverse events were observed during the treatment period. The only reported events were tiredness (1 patient), injection site dermatitis (2 patients), and transient musculoskeletal pain (2 patients). There was no need for discontinuation of the biological therapy due to adverse events.

Discussion

The present multicentre study provides valuable insights on the efficacy and safety of mepolizumab 100 mg as an add-on therapy in the management of severe and uncontrolled CRSwNP.

Table 2. Changes of the main clinical outcomes during the study period.

	T1vsT0		T3vsT1		T6vsT3		T9vsT6		T12vsT9	
	Difference*	p	Difference*	p	Difference*	p	Difference*	p	Difference*	p
VAS-NO	-2.8	<0.001	-0.6	0.048	-0.7	0.3	0.0	1.0	-0.3	1. 0
VAS-rhinorrhea	-2.7	<0.001	-0.7	0.024	-0.5	0.3	-0.4	0.4	0.17	1.0
VAS-facial pain	-2.0	<0.001	0.2	0.7	-0.1	0.7	-0.2	0. 6	-0.3	1.0
VAS-smell	-1.9	<0.001	0.3	0.5	0.1	0.7	0.0	0.9	-0.3	0.6
SNOT22	-20.3	<0.001	-5.2	0.003	-1.1	0.3	-0.2	0.8	5.1	1.0
ACT	2.5	0.003	0.5	0.3	-0.6	0.5	0.9	0.3	0.0	1.0
NCS	-0.7	<0.001	-0.3	0.020	0.0	0.9	-0.3	0.3	-0.2	0.8
NPS	-1.3	<0.001	-0.1	0.3	-0.3	0.9	-0.3	0.2	0.4	0.6
PNIF	37.4	<0.001	16.8	0.07	10.0	0.5	-18.8	0.7	-15.0	1.0
SSIT	1.1	<0.003	-0.09	0.7	0.2	0.7	0.4	0.3	2.0	0.6
BEC	-0.87	<0.001	-0.05	0.1	-0.04	0.4	-0.04	0.2	-0.02	0.4

Difference*: difference in mean score between the two timepoints. Paired Wilcoxon test was used to compare measures between timepoints. VAS: Visual Analogue Scale; NO: Nasal Obstruction; SNOT-22: Sinonasal Outcome Test-22; ACT: Asthma Control Test; NCS: Nasal Congestion Score; NPS: Nasal Polyp Score; PNIF: Peak Nasal Inspiratory Flow; SSIT: Sniffin' Sticks Identification Test; p: p-value; BEC: blood eosinophil count (cells x109/L). T0: baseline; T1: 1 month after the first administration; T3: 3 months after the first administration; T6: 6 months after the first administration; T9: 9 months after the first administration; T12: 12 months after the first administration.

In the absence of clear biomarkers to guide clinicians towards one biological therapy or another, in this population mepolizumab was preferred over dupilumab or omalizumab in consideration of the patients' clinical history. Most of these patients had demonstrated elevated BEC before starting the biological therapy (as demonstrated by the baseline BEC shown in Table 1) and/or showed mild-moderate adult-onset comorbid asthma (86.7% of the patients included in the study). Notably, the prevalence of asthma among our patients was higher than that reported in the phase 3 trial of mepolizumab (68.6%) [13] and other real-world studies involving patients with severe CRSwNP treated with dupilumab [24]. Specifically, in the DUPIREAL study, the largest real-world investigation to date, this prevalence was 56.5%, consistent with findings from smaller studies [10,28]. In a minority of cases during patient counselling, mepolizumab was chosen because of its single monthly administration and its manageability.

The 18 patients who completed the 1st year of follow-up (T12) showed an excellent to moderate response to the biological therapy, as per 2023 EUFOREA criteria [8]. Nevertheless, mepolizumab administration was interrupted in 8 patients (8.9% of the whole cohort) between the 6th and the 12th month of treatment, due to poor or no sinonasal response [29], like what was already observed in the phase 3 study [13].

The most significant improvements of both patient- and physician-derived outcome measures were observed mainly within the first month of treatment (T1) (Table 2, Figures 1-2) with subsequent long-term maintenance in the first 12 months. Differently from what was previously observed in the post hoc analysis of the SYNAPSE study [30], in our cohort not only VAS-smell significantly improved, but also the smell test, namely SSIT, significantly improved from baseline measures. Additionally, a significant correlation between VAS-smell and SSIT was found (Table 3). Similarly to other studies on biological therapies for severe uncontrolled CRSwNP [28], we also found a significant correlation between NPS and both SNOT-22 (T1, T3 and T9) and SSIT (T1 and T6), showing how nasal polyps' shrinkage not only positively impacts symptom burden, but also improves the olfactory function, probably because of the olfactory cleft airflow increase [31]. The latter correlation also highlights how smell impairment in CRSwNP is a multifactorial event, probably resulting from a combination of improved olfactory pathway patency and enhanced control of mucosal inflammation. Further research is required to deepen our understanding of the factors influencing the olfactory epithelium changes during biological therapy [32,33].

When considering nasal airflow, no significant correlation was observed between PNIF and both VAS-NO and NPS, probably because nasal polyp volume reduction is not the only factor impacting the global nasal airflow [26,28,34]. Similar results were obtained when adopting LKS instead of NPS as endoscopic score. In fact, LKS did not correlate with PNIF at any timepoint, while significantly correlated with both SNOT-22 (at all the follow-up visits, except T6) and SSIT (at T6 and T9). These results are not surprising as both NPS and LKS are systems to endoscopically

Table 3. Correlation between the main parameters studied.

Correlation	T0	T1	T3	T6	T9	T12
PNIF and VAS-NO	-0.015 (p>0.05)	0.369 (p>0.05)	-0.005 (p>0.05)	-0.611 (p>0.05)	-0.780 (p>0.05)	-0.015 (p>0.05)
SSIT and VAS-smell	-0.52 (p<0.001)	-0.59 (p<0.001)	-0.69 (p<0.001)	-0.398 (p>0.05)	-0.9 (p=0.007)	-0.8 (p=0.032)
NPS and PNIF	-0.286 (p>0.05)	-0.168 (p>0.05)	-0.333 (p>0.05)	-0.302 (p>0.05)	-0.276 (p>0.05)	1.000 (p>0.05)
NPS and SNOT-22	0.182 (p>0.05)	0.42 (p<0.001)	0.51 (p<0.001)	0.254 (p>0.05)	0.72 (p=0.006)	-0.157 (p>0.05)
NPS and SSIT	-0.0099 (p>0.05)	-0.47 (p=0.003)	-0.352 (p>0.05)	-0.5 (p=0.025)	-0.563 (p>0.05)	-0.564 (p>0.05)
NPS and BEC	-0.013 (p>0.05)	0.119 (p>0.05)	0.423 (p>0.05)	0.116 (p>0.05)	-0.372 (p>0.05)	-0.208 (p>0.05)
NPS and LKS	0.182 (p>0.05)	0.418 (p<0.001)	0.513 (p<0.001)	0.254 (p>0.05)	0.715 (p<0.001)	-0.157 (p>0.05)
LKS and PNIF	-0.2 (p>0.05)	0.4 (p>0.05)	-0.4 (p>0.05)	-0.3 (p>0.05)	-0.2 (p>0.05)	1 (p>0.05)
LKS and SNOT-22	0.16 (p>0.05)	0.48 (p<0.001)	0.54 (p<0.001)	0.3 (p>0.05)	0.7 (p<0.001)	-0.14 (p<0.001)
LKS and SSIT	-0.19 (p>0.05)	-0.26 (p>0.05)	-0.15 (p>0.05)	-0.57 (p=0.08)	-0.9 (p=0.02)	-0.7 p>0.05
LKS and BEC	0.26 (p=0.02)	0.29 (p=0.03)	0.13 (p>0.05)	0.16 (p>0.05)	0.11 (p>0.05)	0.01 (p>0.05)

VAS: Visual Analogue Scale; NO: Nasal Obstruction; SNOT-22: Sinonasal Outcome Test-22; NPS: Nasal Polyp Score; PNIF: Peak Nasal Inspiratory Flow; SSIT: Sniffin' Sticks Identification Test; p: p-value; BEC: blood eosinophil count; LKS: Lund-Kennedy Score. T0: baseline; T1: 1 month after the first administration; T3: 3 months after the first administration; T6: 6 months after the first administration; T9: 9 months after the first administration; T12: 12 months after the first administration.

Table 4. Multivariate analyses to identify the effects of the variables on the symptoms control (SNOT-22) during the follow-up.

	Estimate	Std. Error	t-value	p-value
(Intercept)	-36.054	18.291	-1.971	0.055
Weight	0.386	0.192	2.013	0.051
Allergy to inhalants	-12.929	5.476	-2.361	0.023
N-ERD	-14.922	5.992	-2.490	0.017
SNOT-22	0.471	0.121	3.897	<0.001
SSIT	-2.327	1.064	-2.187	0.034
BEC	7.597	4.115	1.846	0.072
LKS	4.158	1.193	3.485	0.001

N-ERD: non-steroidal anti-inflammatory drugs exacerbated respiratory disease; SNOT-22: Sinonasal Outcome Test-22; SSIT: Sniffin' Sticks Identification Test; BEC: blood eosinophil count; LKS: Lund-Kennedy Score.

evaluate the severity of the disease and in our study showed a significant correlation at each timepoint, except T6 (Table 3). Although LKS should provide a more accurate assessment of the disease severity as it considers not only the nasal polyps volume (as NPS does), but also the mucosal oedema and the nasal secretions, in our study these scores showed similar results.

In the multivariate analyses, patients with higher baseline SNOT-22 and LKS scores demonstrated a better response to biological therapy, as reflected by greater reductions in sinonasal symptom severity (SNOT-22). This finding suggests that individuals with a higher clinical and inflammatory burden have more substantial benefits from mepolizumab, consistent with the previous observations obtained in the phase 3 SYNAPSE trial [13]. Conversely, patients with less impaired olfaction at baseline experienced a lower improvement in quality of life (QoL) with the treatment. Given that olfactory dysfunction is a marker of type 2 inflammation [35], this observation further indicates that patients with less pronounced nasal Th2 inflammation may exhibit lower responses to biological therapy. Interestingly, type 2 inflammation-associated comorbidities, such as inhalant allergies and N-ERD, were independently associated with a less significant QoL improvement following mepolizumab therapy. This may suggest that in the case of allergies as comorbidity, it would be necessary to comprehensively manage this comorbidity with condition-specific treatments (i.e, allergy therapies) together with biological therapy. In the case of mepolizumab, similar findings were reported in the SYNAPSE registration study [13] and in a recent real-life study [36].

Regarding tolerability, no major adverse events were observed during the treatment period. Minor adverse events were reported in six patients (6.7%), consistent with the favourable safety profile of mepolizumab as established in the SYNAPSE phase 3 trial [13].

Currently, within the scope of biologic therapies for CRSwNP, numerous studies have demonstrated the efficacy of dupilumab in managing severe CRSwNP [37-39]. However, in the absence of head-to-head comparison studies, it remains challenging to ascertain whether mepolizumab is more effective than dupilumab in treating these patients. Nonetheless, meta-analyses have indicated the superiority of dupilumab in symptom control and nasal polyp size reduction [40,41]. Further studies comparing the effects of dupilumab, mepolizumab and omalizumab in real-life

setting are warranted to elucidate this complex and clinically significant topic.

The present study has some limitations. The first one could be the retrospective design of the study. A more important one could be that patients were treated by different ENT doctors in different ENT Units. Nevertheless, the hospitals involved in the study comply with high-quality standards of care of patients' evaluation and management according to ISO 9000 certification (International Organization for Standardization, Geneva, Switzerland) [42] guaranteeing a comparable practice across the different Units. Additionally, all participating ENT specialists had undergone specialised training in diagnostic rhinology during a series of shared meetings held at the University of Padua.

Conclusion

This multicentre study highlights the potential efficacy and safety of mepolizumab as an add-on therapy in patients with uncontrolled diffuse type 2 CRS, in a real-life setting. Significant improvements in symptom control, nasal polyp size, and olfactory function were observed, particularly in patients with higher baseline severity and more pronounced type 2 nasal inflammation. While mepolizumab demonstrated a favourable safety profile, the presence of comorbid conditions like inhalant allergies and N-ERD may reduce its overall impact.

Further research, including head-to-head comparisons with other biologics available for the treatment of severe CRSwNP patients, is indeed needed to refine treatment strategies for this complex condition.

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Authorship contribution

The first two co-authors equally contributed to the manuscript. All authors participated in data collection. All authors gave final approval for submission.

Conflict of interest

We have no conflicts of interest to declare.

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References

1. Ottaviano G, Cappellesso R, Mylonakis I, et al. Endoglin (CD105) expression in sinonasal polyposis. Eur Arch Otorhinolaryngol. 2015;272(11):3367-3373.
2. Bayar Muluk N, Cingi C, Scadding GK, Scadding G. Chronic rhinosinusitis-could phenotyping or endotyping aid therapy? Am J Rhinol Allergy. 2019;33(1):83-93.
3. De Corso E, Pipolo C, Cantone E, et al. Survey on use of local and systemic corticosteroids in the management of chronic rhinosinusitis with nasal polyps: identification of unmet clinical needs. J Pers Med. 2022;12(6):897.
4. Ottaviano G, Marioni G, Giacomelli L, et al. Smoking and chronic rhinitis: effects of nasal irrigations with sulfurous-arsenical-ferruginous thermal water: A prospective, randomized, double-blind study. Am J Otolaryngol. 2012;33(6):657-662.
5. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1-464.
6. Vlastos I, Gkouskou K, Doulaptsi M, Karatzanis A, Prokopakis EP. Precision Medicine in Rhinosinusitis. Curr Allergy Asthma Rep. 2019;19(2):12.
7. De Corso E, Bellocchi G, De Benedetto M, et al. Biologics for severe uncontrolled chronic rhinosinusitis with nasal polyps: a change management approach. Consensus of the Joint Committee of Italian Society of Otorhinolaryngology on biologics in rhinology. Acta Otorhinolaryngol Ital. 2022;42(1):1-16.
8. Fokkens WJ, Viskens AS, Backer V, et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. Rhinology. 2023;61(3):194-202.
9. Roland LT, Smith TL, Schlosser RJ, et al. Guidance for contemporary use of biologics in management of chronic rhinosinusitis with nasal polyps: discussion from a National Institutes of Health-sponsored workshop. Int Forum Allergy Rhinol. 2020;10(9):1037-1042.
10. Ottaviano G, Roccuzzo G, Lora L, et al. The impact of dupilumab on work productivity and emotional health in CRSwNP: a multicentric study in Northeast Italy. J Pers Med. 2024;14(5):468.
11. Fritscher L, Chapman KR. Omalizumab for asthma: pharmacology and clinical profile. Expert Rev Respir Med. 2009;3(2):119-127.
12. Smith DA, Minthorn EA, Beerahee M. Pharmacokinetics and pharmacodynamics of mepolizumab, an anti-interleukin-5 monoclonal antibody. Clin Pharmacokinet. 2011;50(4):215-227.
13. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9(10):1141-1153.
14. Caminati M, Guarnieri G, Marchetti P, et al. COVID-19 pandemic and environment: not only air pollution. Allergy. 2022;77(12):3699-3701.
15. De Corso E, Pipolo C, Caminati M, et al. Multidisciplinary decision-making-ITAlian consensus after two years of real practice on the management of severe uncontrolled CRSwNP by biologics (ITACA study). Curr Allergy Asthma Rep. 2024;24(3):143-154.
16. Toro MDC, Antonio MA, Alves Dos Reis MG, de Assumpcao MS, Sakano E. Achieving the best method to classify Eosinophilic Chronic Rhinosinusitis: a systematic review. Rhinology. 2021 Aug 1;59(4):330-339.
17. Venkatesan P. 2023 GINA report for asthma. Lancet Respir Med. 2023 Jul;11(7):589.
18. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013 Oct;68(10):1219-1232.
19. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper. Allergy. 2019 Jan;74(1):28-39.
20. Mozzanica F, Preti A, Gera R, et al. Cross-cultural adaptation and validation of the SNOT-22 into Italian [published correction appears in Eur Arch Otorhinolaryngol. 2022 Jul;279(7):3753-3754]. Eur Arch Otorhinolaryngol. 2017;274(2):887-895.
21. Gevaert P, De Craemer J, Bachert C, et al. European Academy of Allergy and Clinical Immunology position paper on endoscopic scoring of nasal polyposis. Allergy. 2023;78(4):912-922.
22. Psaltis AJ, Li G, Vaezeafshar R, Cho KS, Hwang PH. Modification of the Lund-Kennedy endoscopic scoring system improves its reliability and correlation with patient-reported outcome measures. Laryngoscope. 2014;124(10):2216-2223.
23. Rimmer J, Hellings P, Lund VJ, et al. European position paper on diagnostic tools in rhinology. Rhinology. 2019;57(Suppl S28):1-41.
24. De Corso E, Pasquini E, Trimarchi M, et al. Dupilumab in the treatment of severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP): a multicentric observational

Phase IV real-life study (DUPIREAL). Allergy. 2023;78(10):2669-2683.
25. Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol. 2019;276(3):719-728.
26. Ottaviano G, Pendolino AL, Nardello E, et al. Peak nasal inspiratory flow measurement and visual analogue scale in a large adult population. Clin Otolaryngol. 2019;44(4):541-548.
27. R Core Team. R: A Language and Environment for Statistical Computing 2020. R Foundation for Statistical Computing; Vienna, Austria: 2020.
28. Ottaviano G, Saccardo T, Roccuzzo G, et al. Effectiveness of dupilumab in the treatment of patients with uncontrolled severe CRSwNP: a "real-life" observational study in naïve and post-surgical patients. J Pers Med. 2022;12(9):1526.
29. Fokkens WJ, De Corso E, Backer V, et al. EPOS2020/EUFOREA expert opinion on defining disease states and therapeutic goals in CRSwNP. Rhinology. 2024;62(3):287-298.
30. Mullol J, Lund VJ, Wagenmann M, Han JK, Sousa AN, Smith SG, Mayer B, Chan RH, Fokkens WJ. Mepolizumab improves sense of smell in severe chronic rhinosinusitis with nasal polyps: SYNAPSE. Rhinology. 2024 Jun 1;62(3):320-329.
31. Nishijima H, Kondo K, Yamamoto T, et al. Influence of the location of nasal polyps on olfactory airflow and olfaction. Int Forum Allergy Rhinol. 2018;8(6):695-706.
32. Saraswathula A, Liu MM, Kulaga H, Lane AP. Chronic interleukin-13 expression in mouse olfactory mucosa results in regional aneuronal epithelium. Int Forum Allergy Rhinol. 2023;13(3):230-241.
33. Cantone E, De Corso E, Ricciardiello F, et al. Olfaction Recovery following Dupilumab Is Independent of Nasal Polyp Reduction in CRSwNP. J Pers Med. 2022;12(8):1215.
34. Araújo-Martins J, Brás-Geraldes C, Neuparth N. The potential role of peak nasal inspiratory flow to evaluate active sinonasal inflammation and disease severity. Sci Rep. 2020;10(1):12674.
35. Soler ZM, Patel ZM, Mullol J, et al. association between smell loss, disease burden, and dupilumab efficacy in chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy. 2024 Sep 19:19458924241274501.
36. Orlando P, Vivarelli E, Minzoni A, et al. Effects of Mepolizumab in the treatment of type 2 CRSwNP: a real-life clinical study. Eur Arch Otorhinolaryngol. 2025 Jan;282(1):265-272.
37. Kiricsi A, Bella Z, Kraxner H, et al. Real-life effectiveness of dupilumab in chronic rhinosinusitis with nasal polyps. Results from eight Hungarian centres with 12-month follow-up. Rhinology. 2024 Aug 1;62(4):410-420.
38. Boscke R, Heidemann M, Bruchhage KL. Dupilumab for chronic rhinosinusitis with nasal polyps: real-life retrospective 12-month effectiveness data. Rhinology. 2023 Jun 1;61(3):203-213.
39. Ottaviano G, De Corso E, Cantone E, et al. Measuring nasal patency and the sense of smell in CRSwNP patients treated with dupilumab. J Pers Med. 2023;13(2):234.
40. Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: a systematic review and network meta-analysis. J Allergy Clin Immunol. 2022 Apr;149(4):1286-1295.
41. Hopkins C, Han JK, Fokkens WJ, et al. Dupilumab versus mepolizumab for chronic rhinosinusitis with nasal polyposis: an indirect treatment comparison. J Allergy Clin Immunol Pract. 2024 Sep 24:S2213-2198(24)00941-3.
42. Moore LM. High standards: ISO 9000 comes to health care. Trustee. 1999;52(2):10-14.

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