

Mepolizumab improves sino-nasal symptoms and asthma control in severe eosinophilic asthma patients with chronic rhinosinusitis and nasal polyps: a 12-month real-life study

Aikaterini Detoraki^{ID}, Eugenio Tremante, Maria D'Amato, Cecilia Calabrese, Claudia Casella, Mauro Maniscalco, Remo Poto, Raffaele Brancaccio, Matilde Boccia, Maria Martino, Clara Imperatore and Giuseppe Spadaro

Abstract

Background: Severe eosinophilic asthma is frequently associated to chronic rhinosinusitis and nasal polyposis (CRSwNP) that contribute to poor asthma control. Mepolizumab is an anti-IL-5 monoclonal antibody, approved for the treatment of severe eosinophilic asthma. A limited number of studies have assessed the efficacy of mepolizumab on CRSwNP in severe asthmatics. We aim to evaluate the efficacy of mepolizumab on sino-nasal symptoms, polyp growth and asthma control in severe eosinophilic asthma patients with CRSwNP in real life.

Methods: In this study 44 severe eosinophilic asthma patients with CRSwNP were treated with mepolizumab (100 mg q4w) for 1 year. The following outcomes were assessed before (T0), after 6 (T6) and 12 months (T12) of treatment: sino/nasal outcome test (SNOT-22), Total Endoscopic Nasal Polyp Score (TENPS), %FEV₁ (FEV₁/FEV₁ predicted) and Asthma control test (ACT). Blood eosinophil count, exhaled nitric oxide (FENO) and prednisone intake were measured. In a subgroup of patients, nasal cytology was performed before (T0), after 6 (T6) and after 12 months (T12) of treatment with mepolizumab.

Results: We reported a significant reduction of SNOT-22 [from 51.5 ± 21.2 at baseline (T0) to 31.70 ± 17.36 at T6 and 29.7 ± 21.5 at T12 (T0–T12 $p < 0.001$)] and a decrease of TENPS (from 2.88 ± 3.07 to 1.70 ± 2.37 and 1.77 ± 2.56 at T0, T6 and T12, respectively, T0–T12 $p = 0.99$).

A significant improvement of %FEV₁, ACT and a decrease in blood eosinophils and mean prednisone intake were also reported. No statistically significant decreasing trend was measured for FENO. Nasal cytology findings suggest a significant reduction of eosinophil percentage following mepolizumab treatment (from 16.8 ± 7.2% to 3.6 ± 6.2% and 0.8 ± 2.4% at T0, T6 and T12 respectively, T0 to T12: $p < 0.001$).

Conclusions: Mepolizumab improves sino-nasal and asthma symptoms and reduces polyp growth in patients with severe eosinophilic asthma and concomitant CRSwNP in real life.

The reviews of this paper are available via the supplemental material section.

Keywords: biologics, chronic rhinosinusitis, mepolizumab, nasal polyposis, personalized therapy, severe eosinophilic asthma

Received: 13 October 2020; revised manuscript accepted: 11 March 2021.

Introduction

Patients with severe or difficult-to-treat asthma represent a 5–10% of adult asthmatic patients but

put a strain on the national health system due to the costs of disease management.¹ Chronic rhinosinusitis with nasal polyposis (CRSwNP) presents a

Ther Adv Respir Dis

2021, Vol. 15: 1–11

DOI: 10.1177/
17534666211009398

© The Author(s), 2021.

Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

Aikaterini Detoraki
Department of Internal
Medicine, Clinical
Immunology, Clinical
Pathology and Infectious
Diseases, AOU Federico
II, Via Pansini 5, Naples,
80131, Italy.
caterina.detoraki@gmail.com

Eugenio Tremante
Division of ENT, Azienda
Ospedaliera dei Colli,
Naples, Italy

Maria D'Amato
Department of Respiratory
Medicine, Azienda
Ospedaliera dei Colli,
Naples, Italy

Cecilia Calabrese
Department of
Translational Medical
Sciences, University
of Campania "Luigi
Vanvitelli", Naples, Italy

Claudia Casella
Department of Advanced
Biomedical Sciences,
University Federico II,
Naples, Italy

Mauro Maniscalco
Pulmonary Rehabilitation
Division ICS Maugeri
IRCCS, Telesse (BN), Italy

Remo Poto
Post-Graduate Program
in Clinical Immunology
and Allergy, University
Federico II, Naples, Italy

Raffaele Brancaccio
Post-Graduate Program
in Clinical Immunology
and Allergy, University
Federico II, Naples, Italy

Matilde Boccia
Department of
Translational Medical
Sciences, University
of Campania "Luigi
Vanvitelli", Naples, Italy

Maria Martino
Department of Respiratory
Medicine, Azienda
Ospedaliera dei Colli,
Naples, Italy

Clara Imperatore
U. O. Allergology - Nasal
Cytology, P.A.T. Loreto
Crispi - District, ASL
Naples Center, Naples,
Italy

Giuseppe Spadaro
Department of
Translational Medical
Sciences, Allergy and
Clinical Immunology
Center for Basic and
Clinical Immunology
Research (CISI), University
of Naples, Italy

prevalence of 42.6% in severe asthmatic patients, as reported by the Italian severe asthma Network (SANI),¹ and it significantly impacts patients' lung function, asthma control and health-related quality of life (HRQoL).²

Severe asthma with CRSwNP sub-phenotype is frequently a "T2 high" eosinophilic endotype³ characterized by the activation of type-2 innate lymphoid cells (ILC2) releasing interleukin (IL)-5 and IL-13, and relatively small amount of IL-4. The same pattern of cytokine release, linked to the activation of ILC2, has been reported in nasal polyp tissue.^{4,5} IL-5 is the major driver of eosinophilic blood and tissue inflammation.

CRSwNP symptoms, such as anterior and/or posterior nasal discharge, nasal congestion, hyposmia, facial pressure or pain and sleep disturbances, substantially affect patients' HRQoL.⁶ CRSwNP diagnosis is based on clinical symptoms supported by signs of sinus inflammation detected by a sinus computed tomography (CT) scan and/or a nasal endoscopy.⁷ According to current guidelines, topical and oral corticosteroids (OCS) are the main pharmacologic approaches for CRSwNP but provide short-term efficacy. Furthermore, the use of OCS is limited by the occurrence of adverse events. Patients with significant sino-nasal disease and/or those who fail medical management should be evaluated for functional endoscopic sinus surgery (FESS).⁸ Patients with CRSwNP and comorbid asthma have a more severe disease, repeated revision sinus surgery, frequent systemic corticosteroid dependence, and poor asthma control resulting in costly use of healthcare resources. In these patients, a therapy that directly targets T2 inflammation driving the disease may provide a valid therapeutic approach.⁸

Mepolizumab is an anti-IL-5 monoclonal antibody, approved as an add-on treatment for patients with severe eosinophilic asthma in accordance with Global Initiative for Asthma (GINA) guidelines.⁹⁻¹¹

The drug is administered subcutaneously (s.) every 4 weeks with a dosage of 100 milligrams (mg). The therapeutic potential of mepolizumab as a treatment for severe nasal polyposis has been previously evaluated in clinical trials demonstrating a reduction of nasal endoscopic polyp score (TENPS),¹² an improvement in the polyposis severity visual analog scale (VAS) score and

"Sino-nasal Outcomes Test-22" (SNOT-22) and a greater reduction in the need for surgery in patients with recurrent, severe nasal polyposis.¹³ In these studies, patients received a monthly dose of 750 mg i.v. of mepolizumab for either two or six-month period, respectively. In the SYNAPSE phase III trial, clinical efficacy and safety of 100 mg s.c. mepolizumab was assessed as an add-on to maintenance treatment in adults with severe bilateral nasal polyposis. TENPS and nasal obstruction VAS score significantly improved with mepolizumab *versus* placebo. Mepolizumab reduced nasal polyp surgery by 57%, improved SNOT-22 and VAS (overall, composite, loss of smell).¹⁴

To date, there is little real-life evidence on the effects of mepolizumab at the dosage of 100 mg s.c. administered every 4 weeks (dosage approved for the treatment of severe eosinophilic asthma) on CRSwNP, irrespective of the severity of the disease.

The aim of this study was to investigate the effect of mepolizumab in severe eosinophilic asthma patients with CRSwNP, evaluated by reduction of the SNOT-22 score and the TENPS, after 6 and 12 months of treatment with mepolizumab.

Secondary endpoints of the study were evaluation of airway obstruction improvement and asthma control by Forced Expiratory Volume at 1 s % (%FEV1: FEV1/FEV1 predicted) measurements and Asthma Control Test (ACT), respectively, exhaled nitric oxide (FENO) measurements, reduction of eosinophil blood count and prednisone intake. Asthma exacerbations were also assessed at baseline (number of exacerbations in the 6 months preceding treatment) and after 6 and 12 months of mepolizumab treatment.

Additionally, in a subgroup of patients undergoing nasal cytology, we investigated the effect of mepolizumab treatment on the reduction of eosinophils (expressed as percentage of total white cells) in the cytological sampling obtained from nasal mucosa at T0, T6 and T12.

Methods

Study design and patients

This prospective observational study involved four Italian tertiary care centers (one Allergy and

Clinical Immunology Center, two Pneumology Centers and one Head and Neck Center).

The study design comprised a 12-month treatment period with mepolizumab added to a background treatment of intranasal corticosteroids (mometasone 50 mcg spray: one spray in the morning and one spray in the evening for each nostril) for CRSwNP, and inhaled long-acting beta 2 agonists/corticosteroids (ICS) associations plus long-acting anti-antimuscarinic drugs and, in some cases, OCS, in accordance with step 5 GINA guidelines.

Throughout the study period, patients were required to maintain stable doses of their pre-treatment therapy with nasal and ICS and bronchodilators. According to the recommendations of the Italian Drug Agency for severe eosinophilic asthma, mepolizumab was administered subcutaneously every 4 weeks at doses of 100 mg for a 12-month course.

Patients aged more than 18 years with severe eosinophilic asthma and CRSwNP were included in the study. All patients were eligible for treatment with mepolizumab in accordance with GINA guidelines.

Exclusion criteria were: treatment with monoclonal antibodies for severe asthma within the previous 6 months, pregnancy, malignancies and immune-deficiencies.

Clinical evaluation, SNOT-22, TENPS, spirometry, ACT, FENO, registration of asthma exacerbation episodes, blood samples for eosinophilic count and prednisone intake were performed at baseline (T0) and after 6 (T6) and 12 months (T12) of treatment with mepolizumab. In addition, for each participant, the following information was collected at baseline (T0): demographic data [age, sex, height, weight, body mass index (BMI)], smoking status, comorbid diseases [gastrointestinal reflux disease (GERD), non-steroidal anti-inflammatory drugs (NSAIDs) hypersensitivity reactions, atopic dermatitis, total serum IgE (KU/L)] and data on previous surgical revisions for polyposis (Table 1).

Rhino-fibroscopy (with a straight forward telescope 0° and forward oblique telescope 30°, diameter 4 mm, length 18 cm; straight forward telescope 0°, diameter 3 mm, length 14 cm) was performed in order to validate a diagnosis

CRSwNP; TENPS was assessed by means of nasal endoscopy for each nostril using the sum of both unilateral scores. Each nostril was scored as follows: score 0, no polyps; score 1, small polyps in the middle meatus not reaching below the inferior border of the middle concha; score 2, polyps reaching below the lower border of the middle turbinate; score 3, large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha; score 4, large polyps causing almost complete congestion/nasal obstruction of the inferior meatus¹³ (Table 2). A patient with severe bilateral polyposis would therefore have a maximum score of 8.

SNOT-22, the most commonly used instrument for patient-reported chronic rhinosinusitis outcomes, was administered.¹⁵ It rates 22 different symptoms from 0 (no problem) to 5 (problem as bad as it can be) related to rhinological, ear, facial, general, physical and psychological domains. The scores range from 0 to 110 with high scores indicating greater symptoms, and change of 8.9 or more points represents a minimally importance difference.¹⁶ ACT is a validated five-item questionnaire for assessing asthma control. Each item is scored on a five-point Likert scale from 1 to 5 (1 = worst; 5 = best), with a total score of 5–19 and 20–25 points describing uncontrolled and well-controlled asthma, respectively.¹⁷

Spirometry (model “Quark PTF”, COSMED) before and after salbutamol 400 mcg, was performed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines;¹⁸ FEV₁, Forced Vital Capacity (FVC), FEV₁/FVC were measured and the best of three forced maneuvers was recorded. Results were expressed both as absolute values and as a percentage of the predicted values referred to ERS 1993 reference values.

FENO was measured using an electrochemical analyzer (HypairFeNOMedisoftExp’air, 2010) according to ATS/ERS recommendations for online measurement of exhaled NO in adults.¹⁹

Peripheral blood eosinophil counts were measured using an automated hematology analyzer. Prednisone intake was registered (mg/day) at T0 (baseline), T6 and T12 (after 6 and 12 months of mepolizumab therapy, respectively). The mean prednisone intake of all 44 patients was calculated for the aforementioned time points.

Table 1. Baseline characteristics of patients (T0).

Age (years), no.	44
Mean (SD)	54 (12)
Sex, no.	44
Male, no. (%)	24 (55)
BMI (kg m ²), no.	44
Mean (SD)	26 (4.4)
Smoker, no.	44
Yes, no. (%)	2 (5)
No, no. (%)	28 (64)
Former, no. (%)	14 (32)
GERD, no.	44
Yes, no. (%)	20 (46)
NSAID hypersensitivity reactions, no.	44
Yes, no. (%)	10 (23)
Polyposis surgery, no.	44
Yes, no. (%)	39 (89)
No, no. (%)	5 (11)
Atopic dermatitis, no. (%)	28 (64)
Yes, no. (%)	5 (14)
No, no. (%)	24 (55)
Eosinophilis (cell/mcl), no.	41
Mean (SD)	863 (900)
%FEV1 (FEV1/FEV1predicted) no.	38
Mean (SD)	69 (23)
ACT, no.	43
Mean (SD)	12 (4)
Total IGE, no.	37
Mean (SD) (KU/L)	483 (723)
Prednisone intake, no.	44
Mean (SD)	9 (11)
SNOT-22 no.	44
Mean (SD)	51.55 (21.2)
TENPS no.	44
Mean (SD)	2.8 (3.1)
Asthma exacerbations no.	44
Mean (SD)	5.40 (2.3)

ACT, asthma control test; BMI, body mass index; FEV1%, forced expiratory volume at 1 s (%); GERD, gastro-esophageal reflux disease; NSAID, non-steroidal anti-inflammatory drugs; SNOT-22, sino-nasal outcomes test; TENPS, total endoscopic polyp score.

Nasal scraping and nasal cytologic evaluation was performed as a sub-study, carried out by two of the centers that participated in the real-life study. Nasal cytology was performed by anterior rhinoscopy using a speculum and adequate lighting. Sampling was carried out at the average portion of the lower turbinate. After sampling, the cellular material present in the nasal scraping is fixed by May–Grunwald–Giemsa (MGG) on a glass slide. This coloring method is capable of coloring all cellular components of the nasal mucosa and inflammatory cells (neutrophils, eosinophils, lymphocytes and mast cells), bacteria, fungal spores and fungal hyphae, and indirect signs of viral infection. The observation of the slide is carried out through the use of an optical microscope, equipped with a lens capable of zooming up to 1000×. For the analysis of the rhinocytogram we proceed with a reading for fields (not less than 50), in order to find the elements important cells for diagnosis (eosinophils, mast cells, neutrophils, bacteria, spores, etc.), calculating, at end of reading, the percentage of them.²⁰

All procedures complied with the Helsinki Declaration of 1964, subsequently revised in 2013. The study protocol was approved by the ethical committee of Naples University Hospital, Italy (approval number PT: 51/19). Informed consent was obtained from all patients who agreed to participate to this study.

Values of SNOT-22, TENPS, ACT, % FEV₁, FENO, eosinophil blood count, asthma exacerbations and prednisone intake as well as nasal cytology samples, were collected at T0, T6 and T12 for statistical elaboration.

Study endpoints

The primary efficacy endpoints included mean change in SNOT-22 and TENPS from baseline (T0) to respective values at 6 (T6) and 12 (T12) months of mepolizumab therapy.

Secondary efficacy outcomes included the variation in blood eosinophil count, prednisone intake, ACT score, FEV₁%, FENO, from T0 to T6 and T12. Registration of asthma exacerbation episodes was also assessed at T0, T6 and T12. In a subgroup of 16 patients, the variation of eosinophils in the nasal cytology samples was assessed at T0, T6 and T12. Safety was evaluated by monitoring and recording frequency and severity of adverse events (AEs).

Table 2. Endoscopic nasal scoring.

TENPS is the sum of both unilateral scores.

Polyp score by each nostril	Polyp size
Score 0	No polyps
Score 1	Small polyps in the middle meatus not reaching below the inferior border of the middle concha
Score 2	Polyps reaching below the lower border of the middle turbinate
Score 3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha
Score 4	Large polyps causing almost complete congestion/nasal obstruction of the inferior meatus

Statistical analysis

Data as demographic, clinical and other disease-related variables were statistically described with the use of frequencies (percentages when appropriate) for categorical variables and the mean and range for quantitative variables. Bonferroni's multiple comparisons test was adopted to compare means for continuous variables. The relationship between the improvement in SNOT-22 and ACT score was performed by means of the Pearson's correlation. All *p*-values were two-sided and values less than 0.05 were considered significant. The calculations were performed using IBM SPSS Statistics, v.20.0 software (IBM Corp. Armonk, NY).

Results

A total of 44 severe eosinophilic asthma patients, eligible for mepolizumab treatment, were enrolled (Table 1).

A diagnosis of gastrointestinal reflux disease was made in 46% of the patients whereas only 23% had (NSAIDs)-exacerbated respiratory disease diagnosis; 39 out of 44 patients had already undergone surgery for nasal polyposis.

Figure 1a depicts the effect of mepolizumab on SNOT 22. Mean SNOT-22 score decreased from 51.5 ± 21.2 at baseline (T0) to 31.70 ± 17.36 at T6 (T0 to T6: $p < 0.001$) and 29.7 ± 21.5 at T12 (T6 to T12: $p > 0.1$) suggesting that the SNOT-22 score reduction is maintained throughout the study period (T0 to T12, $p < 0.001$).

Mean TENPS value decreased from 2.88 ± 3.07 at T0 to 1.70 ± 2.37 at T6 and was 1.77 ± 2.56 at

T12 (T0 to T6: $p = 0.0024$, T6 to T12: $p = 0.358$, T0 to T12: $p = 0.99$) (Figure 1b).

Mean ACT score significantly increased from 12.1 ± 4.4 at T0, to 20.9 ± 4.4 at T6 (T0 to T6: $p < 0.001$) and 22.3 ± 4.5 at T12 (T6 to T12: $p > 0.1$) (T0 to T12: $p < 0.001$) (Figure 1c). This clinical improvement was paralleled by a considerable improvement in airflow limitation, expressed by mean % FEV1: $68.1 \pm 22.8\%$ at T0, $77.4 \pm 22.5\%$ at T6, and $82.1 \pm 22.5\%$ at T12 (T0 to T6: $p = 0.295$, T6–T12: $p = 0.9$, T0–T12: $p = 0.044$) (Figure 1d).

A drastic drop of eosinophil blood count was observed throughout the study (863.9 ± 899.6 cell/ μ l at T0, 102.2 ± 106.7 cell/ μ l at T6 and 73.7 ± 72.9 cell/ μ l at T12; T0 to T6 $p < 0.001$, T6 to T12: $p = 0.5$, T0 to T12 $p < 0.001$) (Figure 1e).

Mean prednisone intake significantly reduced from 8.6 ± 11.2 mg/day at T0 to 2.0 ± 4.9 mg/day at T6 (T0 to T6: $p < 0.001$) and 1.1 ± 3.7 mg/day at T12 (T6 to T12: $p = 0.7$, T0 to T12 $p < 0.001$) (Figure 1f).

No statistically significant decreasing trend was measured for FENO 58.8 ± 37.1 ppb at T0, 56.3 ± 52.2 ppb at T6 and 54.7 ± 42.0 ppb at T12 (always $p > 0.1$).

Figure 2a shows the relationship between the improvement in SNOT-22 and ACT score.

A sharp decrease in the number of asthma exacerbations was observed from 5.40 ± 2.3 at T0, to

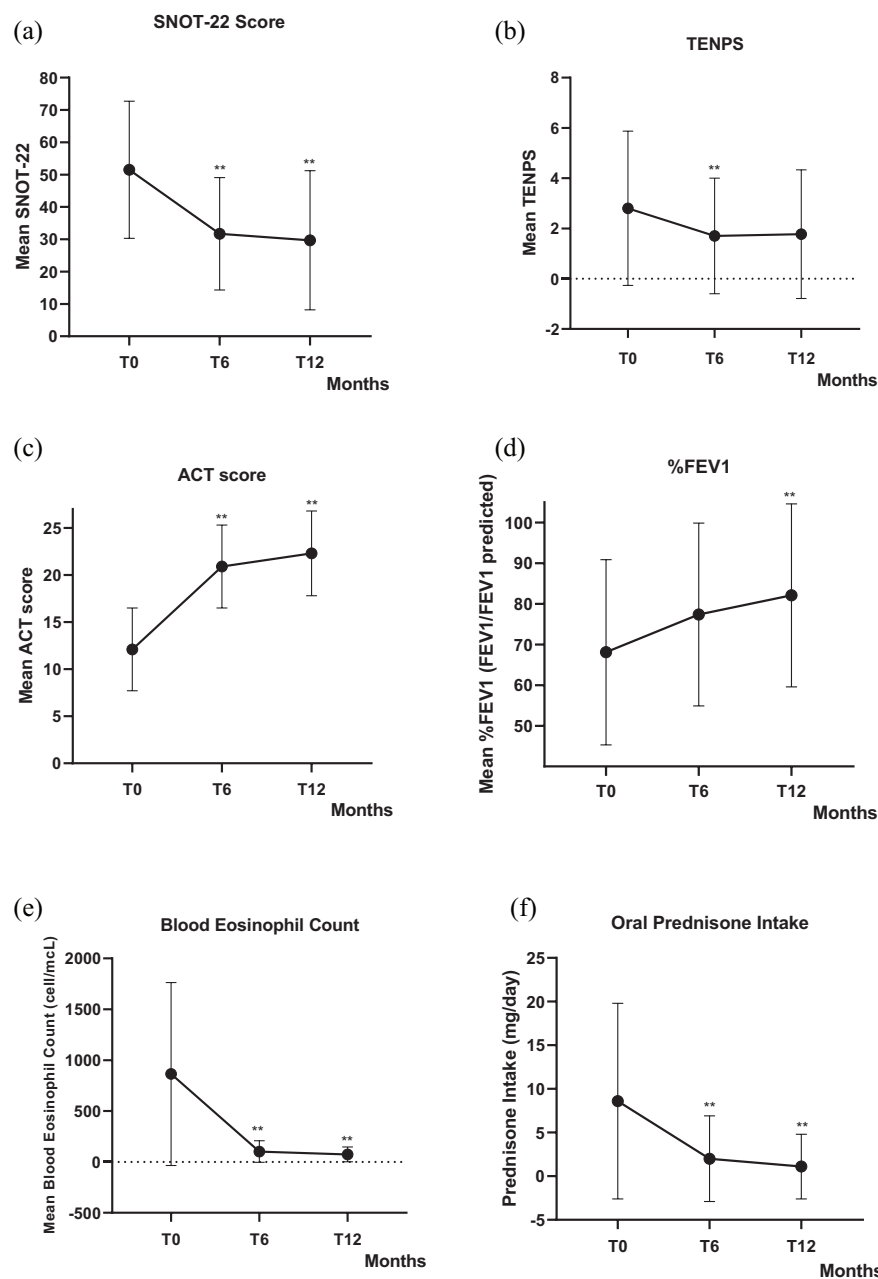


Figure 1. (a) Sino-Nasal Outcome Test (SNOT-22) score at baseline (T0), at 6 (T6) and 12 months (T12) of treatment with mepolizumab (Bars represent 95% CIs). ***p* < 0.01 versus T0. (b) Total endoscopic nasal polyp score (TENPS) measured at T0, T6 and T12 (Bars represent 95% CIs). (c) Asthma Control Test (ACT) at T0, T6 and T12 (Bars represent 95% CIs). (d) Mean % Forced Expiratory Volume at T0, T6 and T12 (Bars represent 95% CIs). (e) Peripheral eosinophil reduction (cells/ μ l) observed at T6 and T12 after treatment (Bars represent 95% CIs). (f) Prednisone intake (mg/day) at T0, T6 and T12 (Bars represent 95% CIs).

0.26 \pm 0.65 at T6 and 0.21 \pm 0.46 at T12. (T0 to T6 *p* < 0.001, T6–T12 *p* > 0.1, T0–T12 *p* < 0.001) (Figure 2b). In the subgroup of 17 patients who underwent analysis of the nasal cytology with nasal scraping, there was a significant reduction in

the mean percentage of the eosinophil count from 15.8 \pm 7.2%, to 3.7 \pm 6.2% and 0.8 \pm 2.4% at T0, T6 and T12 respectively (T0 to T6 *p* < 0.001, T6 to T12 *p* > 0.1, T0 to T12 *p* < 0.001) (Figure 3a and b).

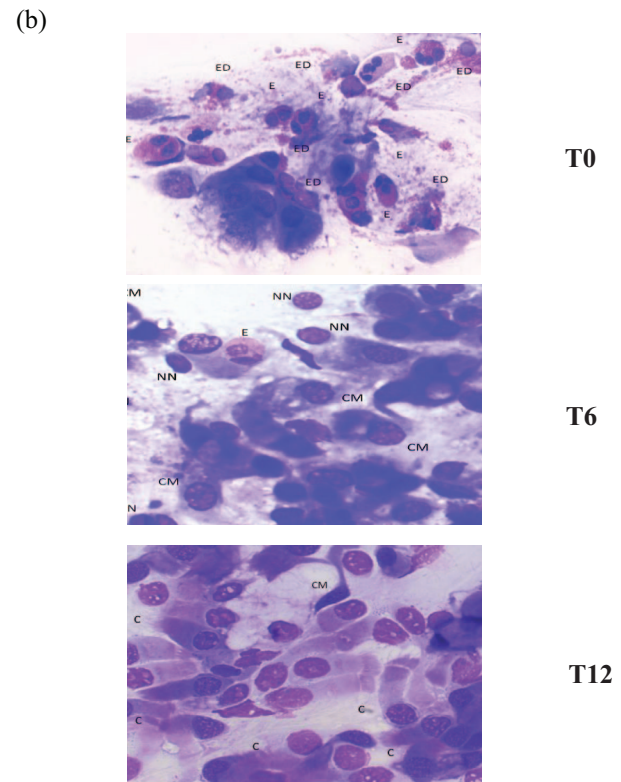
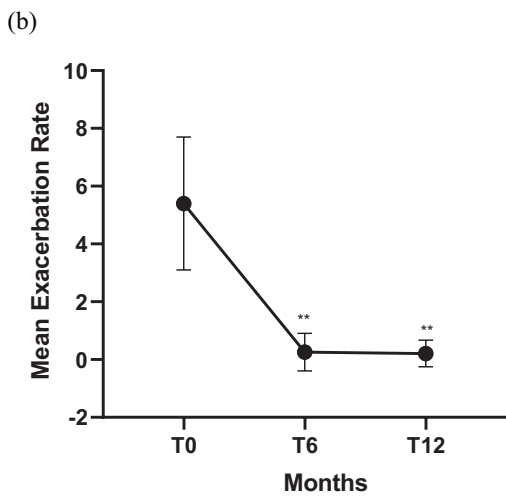
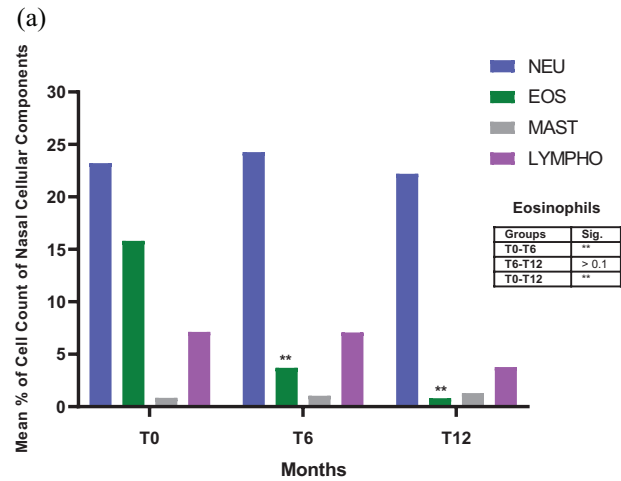
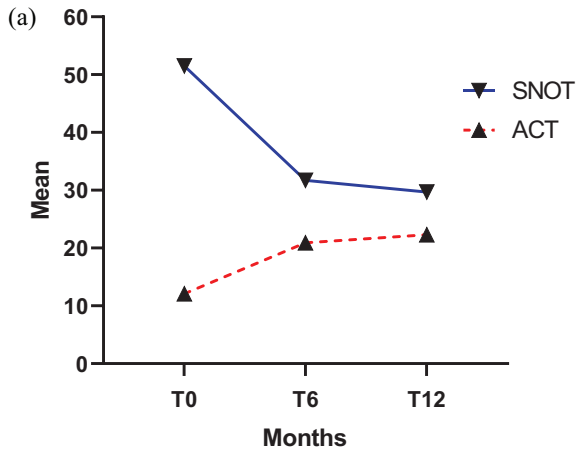


Figure 2. (a) Relation between the improvement in SNOT-22 and ACT score at T0, T6 and T12. (b) Mean asthma exacerbation at T0, T6 and T12. Bars represent 95% CIs. ***p* < 0.01 versus T0.

Figure 3. (a) Detection of percentage of nasal cellular components (neutrophils, eosinophils, lymphocytes, mast cells) at T0, T6 and T12. (b) Nasal cytology shows many eosinophils (E) with abundant degranulation (ED) in A (T0); in B (T6) only one eosinophil surrounded by nude nuclei (NN), neutrophils (N), and muciparous cells (CM); in C (T12): many ciliate cells (C), absence of eosinophils.

With regards to drug safety, mepolizumab was well tolerated: local irritation at the injection site, fatigue, back pain and myalgia were the most frequent AEs (Table 3).

Discussion

Nasal symptoms in CRSwNP (rhinorrhea, nasal congestion, loss of smell), and symptoms derived from lower airway inflammation (cough, chest tightness, dyspnea)⁷ cause negative effects on patients’ HRQoL including physical and mental health, social and emotional functioning, sleep disturbance and work absenteeism. These symptoms contribute to poor asthma control in patients with

severe eosinophilic asthma.² Meaningful clinical improvement in CRSwNP is typically measured in terms of patient-reported outcomes. Thus, the most significant outcome measure is how patients

Table 3. Adverse events in the study population (44 patients) during mepolizumab treatment.

Adverse events	44
Site injection reactions	4
Fatigue	3
Back pain	2
Myalgia	2

feel after treatment. This type of subjective reporting of improvement is best captured with patient-reported outcome measures: SNOT-22 is the most commonly used instrument and appears to have the highest quality of developmental methodology and psychometric performance.¹⁵ In our study, a statistically significant change in the SNOT-22 score was achieved after 6 months and was maintained after 12 months of mepolizumab therapy. This reflects one of the positive effects of mepolizumab treatment on disease severity and HRQoL. Our real-life experience with mepolizumab in severe eosinophilic asthma patients with CRSwNP is in line with the results achieved from previous randomized controlled trials (RCTs) where patients responded favorably to mepolizumab treatment in terms of CRSwNP disease severity assessed by SNOT-22.^{12–14} In addition, the first open-label, 48-week pilot study of subcutaneous administration of mepolizumab showed safely improvements on nasal symptoms, CT scan findings of the paranasal sinuses and lung function in severe asthmatics with chronic rhinosinusitis.²¹ Interestingly, previous data from a *post hoc* analysis of the MUSCA study and a meta-analysis of MUSCA and MENSA studies highlighted that clinical improvements with mepolizumab were greater in patients with severe eosinophilic asthma and nasal polyps than in those without nasal polyps.²¹

About 25% of patients with type 2 high CRSwNP endotype may relapse after oral OCS or sinus surgery and often need more surgeries in lifetime; more than 60% of these patients have late-onset asthma.⁸ In our study population 39/44 of severe asthmatic patients with CRSwNP had already undergone surgery for nasal polyposis in the last 1–5 years. These patients had refractory disease with new formation of nasal polyps. TENPS score at baseline was low (TENPS at T0 = 2.8 ± 3.1) and decreased during the study, suggesting that

mepolizumab treatment may reduce or delay polyp growth. Mepolizumab treatment has been assessed in patients with CRSwNP in two phase II RCTs where intravenous administration of 750 mg q4w reduced polyp size or the need for FESS. The dose was considerably higher than the standard subcutaneous 100 mg q4w dose used in a real-life setting for the treatment of severe eosinophilic asthma.^{11,12} In the SYNAPSE study 100 mg s.c. of mepolizumab improved TENPS and reduced nasal polyp surgery in adults with severe CRSwNP. In a recent publication of a series of six retrospective cases a “disconnection” in mepolizumab response between upper and lower airways was observed in severe eosinophilic asthma patients with concomitant CRSwNP treated with 100 mg of the drug s.c. every 4 weeks for a mean duration of 9 months: standard doses of mepolizumab significantly improved asthma control but patients overall had an appreciable nasal polyposis burden based on nasal endoscopic scoring.²²

The incidence of asthma in CRSwNP is 66% and it is further increased in patients with refractory disease.²³ Suboptimal control of CRSwNP and the presence of nasal polyps reduce asthma control. In our study, a 12-month treatment with mepolizumab in patients with severe eosinophilic asthma and comorbid CRSwNP induced a better asthma control in terms of clinical (ACT test) and functional (FEV1%) evaluation. Moreover, a sharp reduction of asthma exacerbation frequency was observed.

In caucasian CRSwNP patients 80–90% of nasal polyps are characterized by prominent eosinophilia.^{8,24} Eosinophils mediate tissue damage and polyp growth due to the release of toxic products. Eosinophilic infiltration and activation are potentiated by IL-5 and eotaxin. High levels of IL-5 have been measured in patients with nasal polyps at the m-RNA and protein level: IL-5 is a potent indicator of eosinophilic chemotaxis, activation and survival.^{25,26} Moreover, high local eosinophilia is a strong predictor of disease recurrence.²⁷ Following IL-5-mediated activation, delayed apoptosis and the presence of other triggers, eosinophils might undergo extracellular DNA trap cell death (EETosis) with epithelial damage and formation of Charcot–Leyden crystals.²⁸ These crystals enhance pro-inflammatory cytokine production from the epithelium and other inflammatory cells²⁹ leading to a secondary neutrophilic inflammation and NETosis with further tissue damage and resistance to corticosteroid therapy.

In our study, peripheral blood eosinophil count at baseline was considerably high and drastically dropped after 6 and 12 months of mepolizumab treatment. Interestingly, in the subgroup of patients undergoing nasal cytology assessment, a significant reduction of local eosinophilic infiltration was observed after 6 and 12 months of treatment, suggesting that mepolizumab may target local IL-5 release and therefore inhibit tissue eosinophilic activation. Eosinophil decrease was paralleled by a significant reduction in prednisone intake from baseline to T6 and T12.

It is well known that OCS treatment is linked to an extensive range of potential AEs (diabetes, osteoporosis, cardiovascular AEs, infections etc.).³⁰ Unfortunately, in clinical practice, OCS are used more frequently and for long periods. The steroid-sparing effect of mepolizumab treatment in patients with severe eosinophilic asthma has already been described in previous studies.³¹ A single real-life study³² showed short-term efficacy of mepolizumab treatment on OCS-dependent severe eosinophilic asthma patients with CRSwNP. The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) consensus on biologics for CRSwNP highlights the need for real-life studies to measure the cumulative exposure to OCS in patients with asthma and comorbid CRSwNP and determine the OCS effects.³²

The preliminary evidence of a significant reduction in mean eosinophil percentage assessed by nasal cytology after 6 months of mepolizumab treatment may suggest the drug's efficacy at tissue level: eosinophils orchestrate nasal inflammation in patients with CRSwNP and their reduction may easily correlate to SNOT-22 score improvement and reduced polyp growth in patients treated with an anti-IL5 drug.

In severe asthmatic patients with CRSwNP, the high burden of uncontrolled disease, the recurrence of nasal polyps after sinus surgery and the side effects associated with repeated courses of OCS have a significant adverse impact on patients' HRQoL and underline the need for novel therapies. Clinical trials with biological therapies (anti-IgE, anti-IL-5/anti-IL-5 receptor, and anti-IL-4/IL13 receptor alpha) revealed an innovative therapeutic potential in CRwNPs patients.⁸ As biologics come with a high cost for the healthcare system, careful selection of patients is highly recommended.

The EPOS 2020 steering group advises use of mepolizumab in CRSwNP, in patients who had FESS and bilateral polyps and present three out of five from the following criteria: (1) evidence of type 2 inflammation; (2) need for systemic corticosteroids or contraindication to systemic steroids; (3) significantly impaired quality of life; (4) significant loss of sense of smell; (5) diagnosis of comorbid asthma. The EPOS 2020³³ suggests initial treatment evaluation response after 16 weeks and final evaluation after 1 year. In our study, clinical efficacy was shown at T6 (24 weeks: 6 months), but we may consider earlier evaluation of mepolizumab effectiveness in patients with CRSwNP.

We are aware that the present study has some limitations. Firstly, it is a non-controlled study and it relies on a small number of subjects. However, the aim of our study was to evaluate the effect of mepolizumab in a real-life setting. Secondly, most of our patients had undergone surgery for nasal polyposis. The TENPS score at baseline was low and the possible effect of mepolizumab was not explicit.

A limited number of studies has been published so far on the effect of mepolizumab in patients affected by recalcitrant CRSwNP and severe eosinophilic asthma. The real-life setting of this research makes it an interesting addition to the currently available data. Mepolizumab effectiveness on sino-nasal outcomes (TENPS, SNOT-22), asthma outcomes (FEV1%, ACT), asthma exacerbations, oral corticosteroid tapering and blood eosinophil count, as well as on cellular components obtained by nasal scraping have not been addressed collectively in previous reports in a real-life setting.

In conclusion, our study provides evidence that a well-tolerated, standard subcutaneous 100mg q4w dose of mepolizumab used in a real-life setting for the treatment of severe eosinophilic asthma improves sino-nasal and asthma outcomes, decreases polyp growth and exerts a steroid-sparing effect in patients with concomitant CRSwNP.

Acknowledgements

We thank Prof. Giuseppe Quaremba from the Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy, for his precious support for statistical analysis of the present study.


Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Aikaterini Detoraki  <https://orcid.org/0000-0002-3692-1384>

Supplemental material

The reviews of this paper are available via the supplemental material section.

References

1. Heffler E, Blasi F, Latorre M, *et al.* The severe asthma network in Italy: findings and perspectives. *J Allergy Clin Immunol Pract* 2019; 7: 1462–1468.
2. Novelli F, Bacci E, Latorre M, *et al.* Comorbidities are associated with different features of severe asthma. *Clin Mol Allergy* 2018;16: 25.
3. Yılmaz I, Bahçecioğlu SN, Türk M, *et al.* Last station in the eosinophilic asthma with chronic rhinosinusitis and/or nasal polyposis march: eosinophilic asthma with radiological findings associated with blood eosinophilia. *J Asthma* 2019; 56: 111–117.
4. Stevens WW, Ocampo CJ, Berdnikovs S, *et al.* Cytokines in chronic rhinosinusitis role in eosinophilia and aspirin-exacerbated respiratory disease. *Am J Respir Crit Care Med* 2015; 192: 682–694.
5. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. *Annu Rev Pathol Mech Dis* 2017; 12: 331–357.
6. Sahlstrand-Johnson P, Ohlsson B, von Buchwald C, *et al.* A multi-centre study on quality of life and absenteeism in patients with CRS referred for endoscopic surgery. *Rhinology* 2011; 49: 7.
7. Hopkins C. Chronic rhinosinusitis with nasal polyps. *N Engl J Med* 2019; 381: 55–63.
8. Ren L, Zhang N, Zhang L, *et al.* Biologics for the treatment of chronic rhinosinusitis with nasal polyps - state of the art. *World Allergy Organ J* 2019; 12: 100050.
9. Global Initiative for Asthma. *Global strategy asthma management and prevention (2019 update)*. GINA, 2019.
10. Ortega HG, Liu MC, Pavord ID, *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198–1207.
11. Albers FC, Hozawa S, Bratton DJ, *et al.* Update: mepolizumab treatment in patients with severe eosinophilic asthma and prior omalizumab use. *Allergy* 2020; 75: 942–946.
12. Gevaert P, Van Bruaene N, Cattaert T, *et al.* Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 2011; 128: 989–995.e1–e8.
13. Bachert C, Sousa AR, Lund VJ, *et al.* Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol* 2017; 140: 1024–1031.e14.
14. Hopkins C, Bachert C, Fokkens W, *et al.* Late breaking abstract - add-on mepolizumab for chronic rhinosinusitis with nasal polyps: SYNAPSE study. *Eur Respir J* 2020; 56: 4616.
15. Rudmik L, Hopkins C, Peters A, *et al.* Patient-reported outcome measures for adult chronic rhinosinusitis: a systematic review and quality assessment. *J Allergy Clin Immunol* 2015; 136: 1532–1540.e2.
16. Hopkins C, Gillett S, Slack R, *et al.* Psychometric validity of the 22-item sinonasal outcome test. *Clin Otolaryngol* 2009; 34: 447–454.
17. Nathan RA, Sorkness CA, Kosinski M, *et al.* Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004; 113: 59–65.
18. Graham BL, Steenbruggen I, Barjaktarevic IZ, *et al.* Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 2019; 200: e70–e88.
19. American Thoracic Society and European Respiratory Society. *ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005*. *Am J Respir Crit Care Med* 2005; 171: 912–930.
20. Gelardi M, Luigi Marseglia G, Licari A, *et al.* Nasal cytology in children: recent advances. *Ital J Pediatr* 2012; 38: 51.
21. Kurosawa M, Ogawa K and Sutoh E. Favorable clinical efficacy of mepolizumab on the upper

- and lower airways in severe eosinophilic asthma: a 48-week pilot study. *Eur Ann Allergy Clin Immunol* 2019; 51: 213–221.
22. Chan R, RuiWen Kuo C and Lipworth B. Disconnect between effects of mepolizumab on severe eosinophilic asthma and chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract* 2020; 8: 1714–1716.
 23. Bachert C, Hellings PW, Mullol J, *et al.* Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. *Allergy* 2020; 75: 148–157.
 24. Stoop AE, van der Heijden HA, Biewenga J, *et al.* Eosinophils in nasal polyps and nasal mucosa: an immunohistochemical study. *J Allergy Clin Immunol* 1993; 91: 616–622.
 25. Gevaert P, Bachert C, Holtappels G, *et al.* Enhanced soluble interleukin-5 receptor alpha expression in nasal polyposis. *Allergy* 2003; 58: 371–379.
 26. Sanderson CJ. Interleukin-5, eosinophils, and disease. *Blood* 1992; 79: 3101–3109.
 27. Vlamincck S, Vauterin T, Hellings PW, *et al.* The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: a 3-year prospective observational study. *Am J Rhinol Allergy* 2014; 28: 260–264.
 28. Gevaert E, Delemarre T, De Volder J, *et al.* Charcot-Leyden crystals promote neutrophilic inflammation in patients with nasal polyposis. *J Allergy Clin Immunol* 2020; 145: 427–430.e4.
 29. Wu D, Yan B, Wang Y, *et al.* Charcot-Leyden crystal concentration in nasal secretions predicts clinical response to glucocorticoids in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol* 2019; 144: 345–348.e8.
 30. Hox V, Lourijsen E, Jordens A, *et al.* Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. *Clin Transl Allergy* 2020; 10: 1.
 31. Nair P, Pizzichini MMM, Kjarsgaard M, *et al.* Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360: 985–993.
 32. Fokkens WJ, Lund V, Bachert C, *et al.* EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy* 2019; 74: 2312–2319.
 33. Fokkens WJ, Lund VJ, Hopkins C, *et al.* European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology* 2020; 58: 1–464.

Visit SAGE journals online
[journals.sagepub.com/
 home/tar](https://journals.sagepub.com/home/tar)

 SAGE journals