Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

STUDY PROTOCOL.

EFFECTIVENESS ON SINO-NASAL SYMPTOMS OF MEPOLIZUMAB 300 IN PATIENTS AFFECTED BY EGPA AND CONCOMITANT SEVERE AND UNCONTROLLED CRSwNP: ITALIAN MULTICENTRIC "REAL-LIFE" OBSERVATIONAL STUDY

Acronym: MEPO300REAL

Principal Investigator: Dr. Eugenio De Corso, Complex Operative Unit of Otorhinolaryngology, Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Largo Francesco Vito 1, 00168, Rome (Italy).

Sub-investigators:

- Prof Jacopo Galli
- Dott.ssa Spanu Camilla
- Dott. Corbò Marco

- Dott. Montuori Claudio
- Dott. D'Auria Leandro
- Dott.ssa Rizzuti Alberta
- Dott.ssa Serena Pisciottano

Sponsor Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Francesco Vito 1, 00168, Rome (Italy)

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Background and rationale

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare necrotizing vasculitis affecting small and medium-sized vessels, histologically characterized by an extensive eosinophilic infiltrate, responsible for inflammation and tissue ischemia.

The disease presents with various clinical manifestations, with multiple organs and systems involved (respiratory, skin, heart, kidney, nerve, etc). The main characteristic are asthma and peripheral eosinophilia, but it also involves the head and neck district. In most cases it presents with chronic rhinosinusitis associated with diffuse nasal polyposis (CRSwNP), but the appearance of otologic symptoms, particularly eosinophilic otitis media, is not uncommon. The development of EGPA is classically divided into 3 phases. The first phase is the prodromal phase, characterized by bronchial asthma, allergic rhinitis, and chronic rhinosinusitis, and lasts approximately 3 to 10 years. The second stage is the eosinophilic stage, during which we can see eosinophilia in the blood and eosinophilic infiltrate in tissues and organs. The third stage is the vasculitic stage, characterized by the clinical manifestations of vasculitic disease, then with purpura or erythematous papules and peripheral neuropathy.

In patients with EGPA, CRSwNP has a negative impact on the quality of life, it is often unresponsive to standard therapies, which include intranasal corticosteroids, short courses of systemic corticosteroids and endoscopic nasosinus surgery.

Although EGPA is a relatively rare disease, its treatment is constantly progressing, and a variety of therapeutic approaches are emerging and improving the traditional treatment model, based on the use of glucocorticoids and immunosuppressants to control the

symptoms. Glucocorticoids are the main treatment for EGPA, Cyclophosphamide is recommended as an immunosuppressant in patients who do not respond well to GC therapy or have poor prognostic factors. In patients refractory or intolerant to cyclophosphamide, rituximab, mycophenolate mofetil, and azathioprine are alternatively used. A variety of immune cells and mediators are involved in the development of diseases, and this is why drugs targeting specific immune cells or mediators are applied and help reduce the dosage of glucocorticoids to achieve better disease control on symptoms and recurrence.

Biological treatments that mainly target type 2 inflammatory pathways are widely used in clinical practice for remission induction and maintenance of EGPA: in particular, anti-interleukin 5 (IL5) strategies are an important component of treatment.

Mepolizumab 300 represents one of the treatment options for patients with EGPA. It is a humanised monoclonal antibody targeting interleukin-5 (IL-5), a cytokine involved in the activation, differentiation, and survival of eosinophils. By inhibiting IL-5 signaling, Mepolizumab significantly reduces eosinophil levels and the eosinophilic inflammation associated to EGPA.

Mepolizumab 300 is primarily used in combination with GCs for remission induction in non-severe EGPA or as an adjunct to maintain remission, with notable efficacy in reducing GC usage and improving respiratory symptoms

Mepolizumab 300 proved to be an effective treatment for eosinophilic granulomatosis with polyangiitis (EGPA) at a dose of 300 mg every 4 weeks in the multicenter, double-blind, phase III MIRRA trial (ClinicalTrials.gov NCT02020889), which demonstrated that patients treated with mepolizumab (300 mg every 4 weeks for 52 weeks) had significantly higher rates of disease remission, with a prolonged duration of remission, fewer relapses, and a reduced need for glucocorticoids, compared to those receiving a placebo.

Despite the promising results, its efficacy in patients with acute severe manifestations, including organ-threatening cardiomyopathy and gastrointestinal involvement, remains under investigation. Additionally, while the efficacy of mepolizumab in ANCA-negative EGPA has been suggested by some studies, the MIRRA trial did not show a significant association between efficacy and ANCA status.

From March 2023, Mepolizumab 300 mg administered subcutaneously every 4 weeks has been approved in Italy as adjunctive therapy for patients aged 6 years and older with relapsed/remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

In clinical practice, the role of the otorhinolaryngologist is crucial in assessing the evolution of symptoms and naso-sinus signs in patients with EGPA and concomitant severe and uncontrolled CRSwNP.

Studies conducted in clinical practice, or 'real-life' studies, represent a fundamental tool for assessing the effectiveness of a therapeutic treatment. Our study aims to be one of the first to investigate the efficacy on the sino-nasal region of Mepolizumab 300 mg administered subcutaneously every 4 weeks in a real-life setting, thus contributing to an improvement in knowledge on the use of this drug in the management of EGPA.

OBJECTIVES

The *primary objective* of this study is evaluating the reduction of dimension of nasal polyps measured with Nasal Polyp Endoscopic Score (NPS)

The *secondary objective* is to evaluate the improvement in nasal symptoms and quality of life in the patient measured through symptom questionnaires, the improvements in terms of smell dysfunction and symptomatology related to eosinophilic otitis media;evaluate the need of surgery or systemic corticosteroids.

ENDPOINTS

Primary endpoint

The primary endpoints will be the Improvement of NPS score (indicative of polyps score reduction) at 12 months after start of therapy.

Secondary endpoints

- Improvement of SNOT-22 score (indicative of an improvement in quality of life)
- Improvement of VAS score for nasal obstruction
- Improvement of Nasal Congestion Score (NCS)
- Improvement of VAS score for smell;
- Improvement of sniffin' sticks score;

- Evaluate adherence to drug therapy with Mepolizumab 300, any suspension of the same and reasons for discontinuing treatment (lack of efficacy, complications reported, safety profile);
- Assess how many patients require FESS surgery and/or systemic steroids for sino-nasal symptoms during treatment;
- Evaluate the improvement of symptoms of any associated comorbidities and in particular chronic eosinophilic otitis media.

Study design

Observational, retrospective/prospective, non-profit and national multicenter real-life study.

Population.

We will collect data from patients affected by EGPA and concomitant severe chronic rhinosinusitis with nasal polyps (CRSwNP) not controlled by local and systemic corticosteroids and/or surgery, who have received indication, during normal clinical practice, to therapy with Mepolizumab 300mg every 4 weeks (self-administered at home with subcutaneous autoinjector), in addition to topical nasal corticosteroids.

For the retrospective cohort, the start of observation is from 01 March 2023

We be enrolled 65 patients.

Duration of the study

The foreseen study duration is of 18 months since the approval of the present protocol by the Local Ethics Committee.

Inclusion criteria

Eligible patients will be:

- Patients over 18 years of age who can sign a written informed consent;
- Confirmed diagnosis of EGPA by rheumatologist and in treatment with Mepolizumab 300 mg every 4 weeks, according to clinical pratice;
- Confirmed clinical / radiological diagnosis of chronic rhinosinusitis with diffuse naso-sinusal polyposis by nasal endoscopy and/or massive facial CT scan without contrast medium carried out within 6 months prior to the start of therapy;
- Severe disease stage, defined by Nasal Polyp Score (NPS) ≥ 5 or nasal obstruction symptom visual analogue scale (VAS) score of >5 and/or SNOT-22 ≥ 50);
- Inadequate symptom control with intranasal local corticosteroid therapy;
- Failure of previous medical treatments (at least 2 cycles in the last year of systemic corticosteroid) or failure of previous surgical treatment through nasal endoscopic surgery (FESS), with no clinical benefit or postoperative complications.

Exclusion criteria

- Age <18 years;
- Patients with EGPA with organ impairment or at risk of death;
- Patients undergoing radio/chemotherapy treatments for cancer in the 12 months before the start of therapy.

Procedures

All patients eligible for biological therapy will require adiagnostic work-up" according to the current guidelines (EPOS2020 and EUFOREA). According to clinical practice, patients first must have performed a CT and/or endoscopic examination to confirm the diagnosis of severe diffuse chronic rhinosinusitis with nasal polyps and allow for a staging of the disease through the application of specific and validated endoscopic scores (e.g., Nasal Polyps Score) and radiological scores (e.g., Lund Mackay score). EPOS and EUFOREA also recommend an accurate medical history collection, focusing on the main clinical features

(family history of chronic rhinosinusitis, concomitant respiratory diseases, intolerance to NSAIDs, allergies, blood hyper-eosinophilia) before starting therapy, as clinical practice.

The medical history should be sensitized by administration of questionnaires specific for nasal symptoms and quality of life and, in particular, SNOT-22 administration is largely recommended. SNOT-22 is world-wide used in common clinical practice for patients with diffuse nasal polyposis during the evaluation to the eligibility for biological therapy. It consists of two parts, one more specific for the assessment of nasal symptoms, and a second focused on the quality of life and any comorbidities associated with nasal polyps. As for the evaluation of nasal symptom (i.e. nasal obstruction, rhinorrhea, craniofacial pain, etc.) the visual analogue scale (VAS) can alternatively be used, with a score ranging from 0 to 10.

Other questionnaires widely used in clinical practice are the one on nasal congestion symptoms (NCS – Nasal congestion score) and the visual analogue scale related to the subjective loss of smell. The guidelines also recommend to routinely assess the olfactory sensitivity in a semi-objective manner. To this aim, the test currently used at national level is the subjective olfactometry using "Sniffin' Sticks", and in particular the identification test, which consists of 16 sticks filled in with odorous substances.

For the evaluation of asthma and its symptoms, the guidelines instead recommend to use of ACT (Asthma Control Test) questionnaire.

Patients receiving Mepolizumab 300 are generally evaluated in normal clinical practice at baseline and 30 days after first administration for an early re-evaluation. Subsequently, follow-up is continued with clinical re-evaluation every 3 months in the first year of treatment. Due to this reason, all participating centers will be asked to retrieve the clinical data of the visits performed at 30 days since the beginning of therapy and at 3,6,9 and 12 months.

As well, all centers will be required to provide data about any discontinuation of Mepolizumab due to adverse effects, intolerance to the drug, or related to its inefficacy. We will finally record any sino-nasal surgical treatment during treatment.

Variables

Data from the baseline clinical evaluation and follow-up visits will include a complete sensitized medical history and radiological or laboratory data carried out as normal practice.

In depth, we will collect:

- Anthropometric characteristics (age, height, gender, body mass index);
- Clinical characteristics (occupational exposure to particulate, exposure to cigarette smoke, allergies and sensitization to various allergens, presence of comorbidities, need for hospitalization for asthma and/or access to the emergency room in recent years);
- Assessment of symptoms and quality of life through validated questionnaires such as SNOT-22, Total Nasal-Symptom Score-VAS and Nasal Congestion Score (NCS);
- Nasal endoscopic staging: Nasal Polyp Score (NPS);
- Radiological extension of the CRSwNP: Lund-MacKay Score (LMS);
- Laboratory data (differential count of peripheral leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils), determination of total and specific IgE;
- Type of inflammation gathered from the result of non-invasive tests such as nasal cytology;
- Medications regularly taken by the patient for CRSwNP, and for comorbidities

(asthma, allergic rhinitis, etc.);

- Surgical history and any surgical treatment carried out before and during Mepolizumab therapy;
- Adverse reactions reported during drug treatment.

Sample size calculation

Based on the most recent literature, retrieved from the findings of preliminary phase III studies on Mepolizumab in the treatment of severe CRSwNP, a significant reduction NPS and SNOT-22 was observed. We therefore expect in our real-life experience a significant mean decrease at 12 months. Hence, hypothesing to assess a similar small effect size [d = (μ1 - μ1) / σ].

Considering NPS as a primary outcome a sample size of 52 patients achieves 80% power to reject the null hypothesis of zero effect size when the population effect size is 0.40 and the significance level (alpha) is 0.05. Anticipating a 20% drop-out rate, 65 patients should be enrolled to obtain the final sample size of 52 subjects. The sample size calculation was performed with a two-tailed Student's t test for paired data with PASS2025 statistical software v25.0.2.

Statistical Analysis.

The sample will be described in its clinical and demographic characteristics by descriptive statistics techniques. In depth, qualitative data will be expressed as absolute and relative percentage frequency, whilst quantitative variables by either mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. To verify the Gaussian distribution of quantitative variables, the Shapiro-Wilk test will be applied.

Fluctuations over time of NPS, NCS, VAS related to nasal obstruction, smell, sleeping disorders, rhinorrhea and craniofacial pain, nasal identification test by Sniffin' sticks, SNOT-22 questionnaire, will be assessed by repeated measurement analysis of variance or Friedman's nonparametric test, as appropriate. Correction for multiple pairwise comparisons will be performed by the Bonferroni test.

Fluctuations of the different parameters over time will be further represented by "violin plots" for quantitative variables or bar plots for qualitative/ordinal data, by using R packages "*ggpubr*", "*ggstatsplot*", "*ggplot2*", "*ggprism*" and "*ggsignif*", on both the overall sample and stratified for past surgery, asthma or ASA triad.

Potential predictors of clinical response at each time point will instead be assessed by univariable and multivariable logistic regression models with the "*rms*" R package. We will consider clinical and anamnestic variables and scores related to the immediately previous time-point (e.g., for 3-months model we will consider scores at 1-month visit).

Statistical significance will be set at a p-value <0.05. Suggestive p values will be also reported (0.05≤p<0.10). All analyses will be performed with R software version 4.2.0 (CRAN ®, R Core 2022, Wien, Austria).

SAFETY / REGULATORY MANAGEMENT OF ADVERSE EVENTS

Definitions for medicinal product(s)

Adverse event: any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

Adverse reaction: a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors.

Serious adverse reaction: any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

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Regulatory management of adverse

events

Any adverse event will be collected, recorded and assessed for seriousness and relatedness with study drug(s) or any other medicinal products in use, in order to identify suspected adverse reactions (ADRs).

All ADRs, regardless of the seriousness and expectedness, will be reported to National Competent Authority - AIFA, via the National Pharmacovigilance Network through the figure of Local Pharmacovigilance Responsible, as requested by the applicable law for the post-marketing pharmacovigilance activities (DM 30.04.2015 and GVP, module VI) and to the EC per local applicable rules. For the retrospective study with secondary analysis of clinical data, there is no further need of ADR reporting to national Competent Authority - AIFA, since all the reporting obligations have been fulfilled at the time of ADR presentation (DM 30.04.2015 and GVP module VI, section C 1.2.1.2.).

Ethical aspects

The study will be conducted conforming to the principals of Declaration of Helsinki. The study protocol is designed and will be conducted to ensure adherence to the principles and procedures of Good Clinical Practice and to comply with Italian laws, as described in the following documents and accepted, with their signature, by the study investigators.

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