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COMITATO ETICO
TERRITORIALE
AREA NORD VENETO

OBSERVATIONAL STUDY PROTOCOL

Study Title: Real-world simultaneous remission in asthma and CRSwNP after dupilumab treatment

Protocol Code: NA

Version: 6

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1. Background and Rationale

Asthma is a heterogeneous chronic inflammatory airway disease affecting approximately 300 million people globally. Roughly 5–10% of patients suffer from Severe Asthma (SA), leading to significant clinical impact and high resource consumption (emergency visits, hospitalizations, and intensive care).

Patients with SA often present with comorbidities driven by Type 2-high (T2-high) inflammation, characterized by persistent blood hypereosinophilia and increased tissue expression of Interleukin-5 (IL-5). The most frequent comorbidity is Chronic Rhinosinusitis with Nasal Polyps (CRSwNP). This is often explained by the "unified airway theory," suggesting that the upper and lower airways function as a single unit subjected to similar inflammatory insults.

While biologic therapies like dupilumab (targeting IL-4/13R) have revolutionized treatment, the goal has shifted toward achieving Clinical Remission (CR). According to the Severe Asthma Network Italy (SANI), CR in asthma is defined by:

Absence of Oral Corticosteroids (OCS) use.

No exacerbations.

Stable lung function.

Absence of symptoms, measured by an Asthma Control Test (ACT) score of 20–25 or an Asthma Control Questionnaire (ACQ) score < 1.5.

For CRSwNP, the EUFOREA (European Forum for Research and Education in Allergy and Airway Diseases) defines remission as a condition with a Nasal Polyp Score (NPS) < 4, Nasal Congestion Severity (NCS) < 2, and no need for surgery or systemic corticosteroids after 12 months.

2. Study Objectives

Primary Objective:

To evaluate the clinical efficacy of dupilumab after 12 months of treatment in patients with comorbid asthma and CRSwNP regarding:

Percentage of patients in complete CR for asthma (SANI criteria).

Percentage of patients in complete CR for CRSwNP (EPOS/EUFOREA criteria).

Percentage of patients achieving simultaneous complete CR for both conditions.

Secondary Objectives (at 1, 6, and 12 months):

Partial CR rates.

Improvement in disease control scores (ACT and SNOT-22 [22-Item Sino-Nasal Outcome Test]).

Stabilization of spirometric parameters (e.g., FEV1 [Forced Expiratory Volume in 1 second]).

Reduction in OCS use and annual exacerbation rates.

Improvement in smell via Sniffin' Sticks.

3. Study Design and Population

This is a no-profit, observational, retrospective, multicenter study.

Setting: Adult patients (≥18 years) with asthma and CRSwNP treated with dupilumab for at least 12 months in outpatient hospital settings.

Sample Size: Approximately 280 patients across 14 centers.

Inclusion Criteria: Diagnosis of CRSwNP (EPOS 2020 [European Position Paper on Rhinosinusitis and Nasal Polyps]) and asthma (ERS/ATS 2014 [European Respiratory Society/American Thoracic Society]).

Exclusion Criteria: Conditions contraindicating dupilumab (e.g., helminth infections), clinically significant bronchiectasis, pregnancy, or breastfeeding.

4. Data Management and Statistical Plan

Data will be collected at four timepoints: Baseline, 1 month, 6 months, and 12 months.

Key Variables:

Blood Biomarkers: Blood eosinophils and total IgE (Immunoglobulin E).

Functional Tests: FeNO (Fractional exhaled Nitric Oxide) and plethysmography (FEV1, FVC [Forced Vital Capacity], TLC [Total Lung Capacity], DLCO [Diffusing Capacity for Carbon Monoxide]).

Clinical Scores: NPS, SNOT-22, and ACT.

Statistical Analysis:

Continuous variables will be presented as medians and interquartile ranges (IQRs), while categorical variables are reported as counts and percentages. Comparison between independent groups will be performed with the Mann-Whitney test for numerical variables or with the Fisher test for categorical variables. Longitudinal comparisons across time points (e.g., baseline vs 12 or 24 months) will be conducted using mixed-effects models. In longitudinal figures, remission rates will be presented as estimated probabilities with 95% confidence intervals (95% CI). Comparisons between independent groups (severe vs mild-to-moderate asthma) will be conducted to evaluate differences in remission proportions at baseline and their evolution over time. A p-value < 0.05 was considered statistically significant across all analyses.

5. Ethical and Administrative Considerations

Ethics: Conducted according to the Declaration of Helsinki.

Privacy: Data will be pseudonymized. Patients are identified by a 2-digit center code and a 3-digit progressive number (e.g., 01-001).

Informed Consent: Required from all living participants.

Conflict of Interest: None reported by researchers.

Data Ownership: Property of the Sponsor (San Valentino Hospital, AULSS2 Marca Trevigiana, Treviso, Italy).