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The relationship between blood eosinophilia and disease severity in chronic rhinosinusitis with nasal polyps

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Introduction Based on epidemiological data, the prevalence of chronic rhinosinusitis (CRS) is estimated to be 10.9% in Europe, 11.9% in the USA, 8% in China and 5.5% in Brazil [1].

CRS is a complex, multifactorial inflammatory disease of the nasal mucosa and paranasal sinuses, whose diagnosis is based on the criteria set out in the European Position Paper on Rhinosinusitis 2020 (EPOS) [2]. According to the EPOS 2020, CRS is divided into primary and secondary or localized and diffused, based on anatomic distribution. The primary may be related to type 2 (T2) inflammation or other types of inflammatory responses. Depending on the profile of the cytokines produced, the subpopulation of CD4+ T lymphocytes can be divided into three main effector groups protecting against various types of microbial infections (Th1, Th2, Th17) and the fourth subpopulation - follicular helper lymphocytes (Tfh) activating type B lymphocytes in peripheral lymphatic organs [3]. Type 2 immune response involves ILC2, Tc2 and Th2 cells responsible for the production of IL-4, IL-5, Il-13 affecting the production of immunoglobulin E (IgE), activation of macrophages through the alternative pathway and activation of eosinophils. This type of response engages in the fight against parasites, induces IgE-mediated allergic diseases, causes hyperplasia of the mucous glands and participates in chronic diseases involving eosinophilia [4,5].

Type 3 immune response to bacterial and fungal infections is characterized by the production of IL-17 and IL-22 by Tc17 and Th17 cells. Tfh lymphocytes are involved in the regulation of B-cell responses and antibody production. Their main cytokine is IL-21 [3].

In Caucasians and some Asians, CRS with polyps (CRSwNP) is characterized by a predominance of type 2 inflammation. Il-4 regulates the expression of the vascular cell adhesion molecule (VCAM)-1, increasing the adhesion of eosinophils to vascular endothelium, which, under the influence of eotaxins, IL-5 and IL-13, penetrate into tissues [6]. Local IgE production increases not only in response to airborne allergens, but also to Staphylococcus Aureus enterotoxins, which are superantigens that stimulate local overproduction of these antibodies. Activation of IgE-coated mast cells in the nasal mucosa

and sinuses leads to their degranulation and stimulation of further infiltration of eosinophils [7].

Eosinophils have receptors for cytokines, chemokines and adhesion molecules, which engages them in inflammatory reactions and homeostasis regulation. The presence of receptors for bacterial patterns allows them to participate in the innate response, and the presence of the receptor for the Fc molecule (FcRs) in the adaptive response. In response to stimuli, eosinophils release eosinophil cationic protein (ECP), major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil-derived neurotoxin (EDN), cytokines, cytosolic Charcot-Leyden crystal protein, galectin 10 (CLC/Gal-10), eosinophil extracellular traps (EETs) [8]. In vitro, MBP activates basophils, mast cells and neutrophils, and EDN activates dendritic cells, CLC/Gal-10, promoting the type 2 response [8]. Chronic, primary, diffuse, T2-dependent rhinosinusitis with polyps often coexists with other eosinophilic diseases such as asthma, IgE-mediated allergy or hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) [2].

Type 2 CRSwNP is a chronic disease of unclear aetiology, requiring repeated endoscopic surgery and systemic steroid therapy. The recurrence of polyps and related symptoms are not the result of poorly performed surgery or incorrect conservative treatment, but they are due to the intensification of inflammatory processes at the molecular level. Treatment with monoclonal antibodies directed against IL-4 (precisely its receptor alpha subunit) or IL-5 /IL-5 receptor can reduce eosinophilic inflammation, which will extend the time between surgical interventions and improve the patient's quality of life. The number of blood eosinophils is an easily accessible biomarker of the severity of the disease and is one of the criteria for qualifying CRSwNP patients for biological treatment. The authors of the study decided to answer the question whether blood absolute eosinophilia could be an important criterion for qualifying CRSwNP patients for biological treatment. They assessed the number

of blood eosinophils in patients with CRSwNP and chronic rhinosinusitis without nasal polyps (CRSsNP), treated as the control group, qualified for endoscopic surgery of the nasal cavity and to examine whether there is a relationship between the number of eosinophils and: 1) the extent of inflammation in the sinuses assessed according to the Lund-Mackay system (L-M), 2) multiplicity of procedures related to the presence of polyps, 3) coexistence of T2 diseases such as allergy, hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and asthma.

Material and method This single-centre retrospective observational case-control study included patients treated at the Department of Laryngology and Laryngological Oncology of the Upper Silesian Medical Centre in Katowice between 2021 and 2022.The patients admitted to the department for endoscopic surgery had NSAID hypersensitivity and asthma. The data on the CRS phenotypes, comorbidities such as IgE-mediated inhalant allergy, NSAID hypersensitivity, and asthma, and absolute blood eosinophilia, were retrospectively analysed. The data on previous surgical procedures involving the nasal cavity and sinuses were obtained from the patients' records and medical history.

The diagnosed IgE-mediated inhalant allergy was confirmed by a skin test or the presence of specific IgE antibodies to seasonal (tree, grass, weed) and/or perennial allergens (mites and mould spores, cat and dog allergens) conducted on an outpatient basis. Pharmacological treatment was introduced by an allergist. Patients with allergic reactions by other immune mechanisms (non-IgE-dependent allergies) were not included here.

NSAID hypersensitivity was confirmed based on medical anamnestic data, i.e. clinical signs involving the mucous membranes of the respiratory and digestive systems and/or the skin induced by one or more NSAIDs [9]. Asthma was diagnosed and treated on an outpatient basis according to the Global Initiative for Asthma (GINA) [10]. Sinus computed tomography was performed in each patient, on the basis of which the severity of inflammatory lesions was

assessed according to the L-M score. The degree of opacity in the maxillary, anterior and posterior ethmoid, frontal and sphenoid sinuses, as well as the ostiomeatal complex obstruction were assessed (on both sides) on a scale from 0 to 2 with a maximum of 24 points. All patients underwent endoscopic examination of the nasal cavity. The Nasal Polyp Score (NPS by The Meltzer Clinical Scoring System) was used for the polyp phenotype. The Meltzer Clinical Scoring System is a 0–4 polyp grading system (0 = no polyps, 1 = polyps confined to the middle meatus, 2 = multiple polyps occupying the middle meatus, 3 = polyps extending beyond middle meatus, 4 = polyps completely obstructing the nasal cavity) [11]. Absolute eosinophilia was assessed in each treated patient during routine morphology tests using the Sysmex XN-1000 Haematology Analyzer.

Patient baseline characteristics were summarized using descriptive statistics. The results were expressed as median values with interquartile ranges because they were not normally distributed. The nonparametric Mann-Whitney U rank sum test was used for comparisons between the two subgroups. The comparisons between frequencies were performed using the Z-test for proportions. The linear regression model was performed with age, sex, occurrence of asthma, inhalant allergy, NSAID hypersensitivity and L-M score to determine the relationship with peripheral blood eosinophil numbers in both groups. In CRSwNP, the number of previous Functional Endoscopic Sinus Surgery (FESS) procedures was also included. Cut-off analysis was based on ROC analysis and Youden's index. All analyses were performed with a software package (The STATISTICA 13.3, StatSoft Poland). *P* values less than 0.05 were considered significant. The study had a retrospective design. The patients consented to the proposed routine procedures upon admission to hospital. The consent of the Bioethics Committee was not required.

Results In the period from 01/01/2021 to 31/12/2022, 701 patients were treated due to CRS, of which 407 (58.1%) were men. The median age of the patients was 49 (IQR 38–62

years). The CRSwNP phenotype was found in 300 (42.8%) subjects (Table 1). CRSwNP patients differed from the CRSsNP group in several respects. There were more men in the CRSwNP group, the patients were older, asthma and NSAID hypersensitivity were diagnosed more often, inhalant allergy was less common. CRSwNP patients had more severe radiological lesions in the sinuses according to the L-M scoring system and underwent more laryngological procedures (polypectomy and/or FESS). In this group, the absolute number of peripheral blood eosinophils was higher (Table 1). In the entire group of patients the cut-off value of the absolute blood eosinophil count for CRSwNP diagnosis was 150/µl, for NSAID hypersensitivity it was 190 cells/µ, for asthma - 250 cells/µl, and for repeated sinus surgery - 250 cells/µl. The regression analysis showed that a higher absolute number of eosinophils in the CRSwNP group was documented in younger patients (for age standardized regression coefficient beta was -0.13; 95%CI: -0.25–(-0.02); $P = 0.02$), with more intense severity of sinus lesions according to the L-M scoring system (beta: 0.13; 95%CI: 0.01–0.25; $P = 0.02$), and in those with asthma (beta: 0.19; 95%CI: 0.06–0.32; $P = 0.004$; $P < 0.001$ for regression analysis). In the CRSsNP group, the number of eosinophils was higher in patients with more severe sinus lesions according to the L-M scoring system (beta: 0.3; 95%CI: 0.2–0.4; $P < 0.001$).

Discussion In this study, the authors assessed the number of eosinophils in two main different phenotypes of CRS in relation to the co-existing diseases such as asthma, atopy and NSAIDs hypersensitivity, and with regard to the intensity of sinus inflammation and the number of sinus procedures. It was found that the higher absolute number of blood eosinophils, the more advanced the inflammatory process according to the L-M scoring system, regardless of the phenotype (with or without polyps). However, in the CRSwNP group, significantly higher numbers of eosinophils were documented in younger patients with concomitant asthma and higher L-M scores. Our results are concordant with the study by

Bachert et al. They revealed that higher eosinophilia, concomitant asthma and NSAID hypersensitivity were more frequent in CRSwNP patients compared to the patients with lower baseline eosinophilia. The patients with higher baseline eosinophilia had a lower risk of reoperation or systemic steroid use during biological treatment compared to the patients with lower baseline eosinophil counts [12].

Taking into account the qualification criteria for biological treatment, based on the EPOS 2020 guidelines [2], the European Forum for Allergy and Airway Diseases guidelines (EUFOREA) [13], the POLINA 2.0 consensus [14] and the SYNAPSE III phase [12] research on CRSwNP patients, as well as the results of our observations, absolute eosinophilia seems to be of equal or greater importance than the criterion of the number of procedures or the use of systemic steroid therapy. The criterion of the presence of asthma, mentioned in EPOS and EUPHOREA [2,13], is reflected in the eosinophilia level observed in the study group. CRSwNP is severe when it affects the patient's quality of life, which can be assessed with the Sino-Nasal Outcome Test (SNOT-22) or Visual Analogue Scale (VAS) test. On the other hand, uncontrolled CRSwNP is evidenced by restricted nasal patency, mucopurulent discharge, facial pain, weakening or loss of smell, sleep disorders and fatigue requiring long-term administration of antibiotics or systemic steroids [15]. Within the polyp phenotype, endotypes with concomitant asthma and NSAIDs exacerbated respiratory disease (N-ERD) are particularly difficult to treat. In these endotypes, there are no doubts about the type of inflammation taking place in the mucous membranes of the respiratory tract. In cases without concomitant asthma, the type of inflammation should be confirmed by evaluating at least one biomarker. It can be absolute blood eosinophilia, tissue eosinophilia tested, for example, in a cytological smear from the nasal mucosa or the level of total IgE in atopic patients. The EPOS guidelines give values of eosinophilia ≥250, EUPHOREA ≥150, whereas according to the Polish Society of Otolaryngologists, Head and Neck Surgeons and the Polish Society of

Allergology, biological treatment should be considered when at least three criteria are fulfilled: the disease is T2 dependent, poorly controlled, VAS ≥5 or SNOT-22 ≥40, there is concomitant asthma or atopic dermatitis. The required cut-off value of blood eosinophilia is ≥150 [16].

In our study, in the CRSwNP group, the median value of peripheral blood eosinophils was 250 cells/µl, which indicates that in the case of this phenotype, 75% of patients would meet the EUPHOREA criteria and 50% the EPOS criteria. Therefore, it seems that the diagnosis of CRSwNP with eosinophilia ≥250 cells/µl will confirm the T2-dependent endotype of rhinosinusitis and, in combination with additional criteria, will facilitate the qualification of patients for biological treatment. Moreover, the same cut-off values of the absolute number of blood eosinophils were revealed for asthma and repeated sinus surgery, and lower for the presence of nasal polyps and NSAID hypersensitivity. All these data support the above suggestion that patients with an absolute blood eosinophil count of 250 cells/µl may suffer from bronchial asthma or may have undergone previous sinus surgery and may be candidates for biological treatment if they have nasal polyps.

Knowing the mechanism of inflammation occurring in the mucous membrane of the nasal cavity and sinuses, we can use new instruments in the treatment of CRSwNP. Dupilumab and mepolizumab are currently registered in Poland for the treatment of CRSwNP. Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 signaling via the type I receptor (IL-4Rα/γc) and both IL-4 and IL-13 signaling via the type II receptor (IL-4Rα /IL-13Rα). As a consequence, recruitment and activation of eosinophils are inhibited [17,18]. Mepolizumab is a monoclonal antibody of the IgG1 kappa class, directed against IL-5,-thereby inhibiting IL-5 signaling and reducing the production and survival of eosinophils. The Synapse study found that the baseline number of eosinophils ≥150 or ≥300 cells/microL may be a useful biomarker of response to mepolizumab treatment in patients with severe

CRSwNP [12]. High baseline blood eosinophil values may be a risk factor for the development of transient hypereosinophilia in patients treated with dupilumab and requires monitoring of the eosinophil level during treatment [18]. The results from the asthma study (VENTURE) suggest that other factors, such as systemic steroid therapy, may interfere with the regulation of the blood eosinophil level, which should also be taken into account in the case of CRSwNP patients with high baseline eosinophil counts [19]. However, it should be kept in mind that values ≥1500 require extended diagnostics towards hypereosinophilic syndrome (HES) or eosinophilic granulomatosis with polyangiitis (EGPA) [20].

The results of our study indicate a relationship between the absolute number of blood eosinophils and the intensity of inflammation in paranasal sinuses. Blood eosinophils numbers were higher in patients with CRSwNP, higher L-M scores and asthma. In patients with CRSsNP, blood eosinophil numbers were related only to the L-M score.

Blood absolute eosinophilia in CRSwNP patients is an important biomarker that may be used in the qualification for biological treatment.

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Table 1 Clinical characteristics of patients with the group of patients with chronic rhinosinusitis and nasal polyps and the group of patients with chronic rhinosinusitis and without nasal polyps

	CRSwNP N = 300	CRSsNP N = 401	*P* value
Men, n (%)	202 (67%)	205 (51%)	<0.001
Age (years), median (IQR)	54.5 (44–65)	45 (36–58)	<0.001
Inhalant allergy, n (%)	119 (39.7%)	270 (60.3%)	<0.001
NSAID hypersensitivity, n (%)	54 (18%)	9 (2.2%)	<0.001
Asthma, n (%)	121 (40.3%)	37 (9.2%)	<0.001
Peripheral blood eosinophil number (median, IQR)	250 (160–380)	135 (75–240)	<0.001
Number of surgeries, n (%)			
0	1 (0,3)	5 (1.2)	n.d
1 x	137 (45.7)	329 (82)	<0.001
2 x	84 (28)	55 (13.7)	<0.001
>2 x	78 (26)	12 (3)	<0.001
Number of FESS, n (%)			
0	1 (0,3)	7 (1.7)	n.d.
1 x	194 (64.7)	340 (84.8)	<0.001

2 x	75 (25)	47 (11.7)	<0.001
>2 x	30 (10)	7 (1.7)	<0.001
L-M score, (median, IQR)	16 (14–20)	9 (6–12)	<0.001

Z-test for proportions and Mann-Whitney U rank sum test for comparisons between two groups)

Abbreviations: CRSsNP, the group of patients with chronic rhinosinusitis and without nasal polyps; CRSwNP, the group of patients with chronic rhinosinusitis and nasal polyps; FESS, functional endoscopic sinus surgery; L-M, Lund-Mackay score; n.d., not done; NSAIDs, non-steroidal anti-inflammatory drugs

Short title: Blood eosinophilia in chronic rhinosinusitis with polyps