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LITERATURE REVIEW

Efficacy and safety of monoclonal antibody therapy for chronic rhinosinusitis with nasal polyposis

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ABSTRACT

Chronic rhinosinusitis (CRS) is one of the most common chronic inflammatory syndromes reported in the general population, with high prevalence reported. It is classified in two distinct entities depending on the endotype dominance, either type 2 or non-type 2, – chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps. CRSwNP is described as a type 2 inflammatory disease, with the implication of T-helper 2 inflammation mechanisms with a secondary increase in the concentration of eosinophils and total Immunoglobulin E. CRSwNP is characterized by a high recurrence rate even after endoscopic sinus surgery. Considering the challenges associated with the treatment of CRSwNP, new medical therapies, such as monoclonal antibodies, have been developed over the years.

Biologics with anti-IL-5, anti-IgE, anti-IL-4 receptor alpha (IL-4-Rα) action have been developed and tested for the treatment of asthma, eosinophilic dermatitis, and secondarily evaluated and approved for the treatment of chronic rhinosinusitis with nasal polyps.

In this review, we make a synthesis of the monoclonal antibodies available and their efficacy and safety in the treatment of nasal polyposis.

KEYWORDS: nasal polyps, chronic rhinosinusitis, monoclonal antibodies, inflammation.

INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common chronic inflammatory syndromes reported in the general population, with a prevalence of 11% in Europe[1,2], 12% in the United States[2,3] and 8-11% in Asia[2,4,5]. European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS2020)[2] defines CRS as the inflammation of the nose and paranasal sinuses characterized by subjective and objective criteria for more than 12 weeks. It is classified in two distinct entities depending on the endotype dominance, either type 2 or non-type 2, – chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). CRSwNP is described as a type 2 inflammatory disease, with the implication of T-helper 2 inflammation mechanisms with a secondary increase in the concentration of eosinophils and total Immunoglobulin E (IgE)[2,6-8].

It is estimated that up to 4% of the population, 20% in the United States, suffer of CRSwNP[9,10], and in 20-70% of the cases asthma is associated[8,11]. The symptoms presented by the patients with nasal polyposis include nasal obstruction, anterior and/or posterior rhinorrhea, loss of smell, each of them of different severity. Current available and recommended treatment options are represented by oral and intranasal corticosteroids, saline irrigations, antihistamines, long-term antibiotics and surgery[2]. Even if in most of the cases symptoms can be managed with medical treatment, there are patients in whom nasal surgery is required even for more than one time[2,12,13]. Only in the United States, within 18 months after endoscopic sinus surgery, 40% of patients presented polyps recurrence according to a study[14].

The relapse characteristic of nasal polyposis may be related to its type 2 endotype. During a type 2 inflammation response, T helper cells increase the production of type 2 cytokines, such as interleukin (IL) 4, IL-5, IL-9, IL-13, and promote the activation of IgE antibodies[15,16]; this may also explain the common association of nasal polyposis and asthma. Considering the challenges associated with the treatment of CRSwNP, new medical therapies have been

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developed over the years. Biologics, like monoclonal antibodies, are one of the novel treatment options in case of refractory CRSwNP[2,6,8], their mechanism of action being the reduction of type 2 inflammation by targeting specific molecules, immune cells and pathways: IL-5 who mediates the eosinophils concentration, IL-4 and IL-3 involved in IgE production and eosinophils chemotaxis[8]. As a result, biologics with anti-IL-5, anti-IgE, anti-IL-4 receptor alpha (IL-4-Rα) action have been developed and tested for the treatment of asthma, eosinophilic dermatitis, and secondarily evaluated and approved for the treatment of chronic rhinosinusitis with nasal polyps.

ANTI-IGE MONOCLONAL ANTIBODIES

Immunoglobulin E (IgE) is an inflammatory mediator agent, its concentration level being associated with the presence or absence of an allergic background. It is produced by the B cells, which are stimulated by the Th2 cells. The exposure to an allergen leads to a type 2 inflammation reaction, activation of Th2 cells, with a secondary increase in the IgE concentration and activation of mast cells. All these reactions lead to a high production of histamines, prostaglandins and leukotrienes[17].

Another explanation for the high concentration of IgE in the nasal polyps seems to be due to the presence of Staphylococcus aureus enterotoxin[6,18].

Considering the high concentrations of IgE in the nasal polyp tissue, nasal secretion, blood in the patients with CRSwNP, the development of an anti-IgE therapeutic agent was just a matter of time.

Omalizumab is a humanized monoclonal antibody which binds to free IgE and blocks its adhesion to the IgE receptors found at the surface of mast cells[6]. As a secondary effect, it decreases the IgE receptors on the dendritic cells and basophils[19,20]. It was first approved by the US Food and Drug Administration in 2003 for the treatment of severe allergic asthma (Xolair®, Genentech and Novartis Pharmaceuticals Corporation, USA) and in 2020 received the approval for the treatment of nasal polyps in adult patients 18 years of age and older with inadequate response to topic intranasal corticosteroids[21]. It has the authorization for use in the European Union from the European Medicines Agency (EMA)[22]. The dose and frequency of the drug administration (subcutaneous) for CRSwNP is determined by baseline IgE (IU/ml) and body weight (kg); 75 to 600mg of omalizumab in 1 to 4 injections may be needed for each administration, every 2 or 4 weeks.

ANTI-IL-5 MONOCLONAL ANTIBODIES

Interleukine-5 (IL-5) is a proinflammatory type 2 cytokine with an important role in eosinophils production, differentiation and survival. In case of nasal polyps, it has been shown that in more than 80% of the patients with this pathology a high concentration of eosinophils is present[2]. As a result, the IL-5 levels in these patients are higher than in healthy controls. The eosinophilic inflammation and high IL-5 concentrations may be associated with the nasal polyps' post-surgical recurrence[23].

In case of allergic asthma and eosinophilic dermatitis, anti-IL-5 treatment reduces the concentration of eosinophils in both blood and tissues, by regulating the IL-5 alpha receptor. On the same basis, it seems to be the action in case of nasal polyps[24]. For the treatment of severe allergic asthma, there are three anti-IL-5 monoclonal antibodies available: mepolizumab (approved in 2015, from 12 years of age), benralizumab (2017, from 12 years of age) and reslizumab (2016, from 18 years of age).

For the treatment of nasal polyps, mepolizumab is the first anti-IL-5 monoclonal antibody approved by the FDA for adult patients (18 years of age and older) with CRSwNP in 2021 (Nucala®, GlaxoSmithKline plc), and in 2015 by EMA[25,26]. Under investigation for approval are benralizumab (Fasenra®, AstraZeneca) and reslizumab; these drugs are already used with success in patients with allergic asthma and atopic dermatitis.

ANTI-IL-4 AND IL-13 MONOCLONAL ANTIBODIES

Interleukin 4 (IL-4) is an important cytokine involved in the allergic inflammation: it increases the expression of eotaxin-1; induction of VCAM-1 (vascular cell adhesion molecule) with a secondary migration of T lymphocytes, monocytes, basophils and eosinophils at the inflammation site; it inhibits eosinophils apoptosis and of T lymphocytes; it activates the differentiation of Th0 in Th2 lymphocytes which stimulates the production of IL-4, IL-5, IL-9 and IL-13; it upregulates the expression of cysteinyl leukotriene receptors presented in the nasal polyps[27]. An interleukin with similar actions is IL-13.

The first humanized monoclonal antibody approved for the treatment of CRwNP was dupilumab (Dupixent®, Sanofi and Regeneron) which inhibits the signalling of IL-4 and IL-13 (in 2019 by FDA and EMA). Its molecule bids to the IL-4 alpha receptor. The recommended administration is an initial dose of 600mg and then 300mg every 2 weeks.

MATERIAL AND METHODS

Study design

For this review, the PubMed, Cochrane Library and Microsoft Academic databases were accessed and researched in order to identify studies that evaluate the efficacy and safety of monoclonal antibodies therapy for chronic rhi-

nosinusitis with nasal polyps (CRSwNP). The literature research was performed between January 2006 and December 2021, using the following terms: "rhinosinusitis", "nasal polyps", "dupilumab", "omalizumab", "mepolizumab", "reslizumab", "anti-IL-5", "anti-IgE". In the PubMed search we used the advanced Boolean operator [AND] and [OR] – rhinosinusitis [OR] nasal polyps [AND] dupilumab [OR] omalizumab [OR] mepolizumab [OR] reslizumab [OR] anti-IL-5 [OR] anti-IgE.

Inclusion criteria: adult patients (18+ years); patients diagnosed with CRSwNP; randomized controlled trials comparing the therapy with monoclonal antibodies with placebo/other therapy; full text articles, written in English language; evaluation made by the CT score, nasal endoscopic polyps score, olfaction status, quality of life, nasal airflow measurement, cellular inflammation.

Exclusion criteria: patients with chronic rhinosinusitis without nasal polyps; paediatric patients; patients diagnosed with allergic fungal rhinosinusitis; patients with other comorbidities usually associated with nasal polyps, such as cystic fibrosis, ciliary dyskinesia, Churg-Strauss syndrome, Kartagener's syndrome.

We also searched for eligible clinical trials evaluating the question of interest on ClinicalTrials.gov website.

Evaluated parameters

From each eligible article the following data was ex-

Table 1. Characteristics of the randomized controlled studies included in the review.

Study	Country	No. of patients	Treatment group	Placebo group	Diagnosis	Monoclonal antibody	Treatment protocol	Follow-up period
Gevaert et al.[34] (2006)	Belgium Austria	24	16	8	CRSwNP	Anti-IL-5 (Reslizumab)	1mg/kg or 3mg/kg or placebo i.v. single dose	36 weeks
Pinto et al.[28] (2010)	USA	14	7	7	CRSwNP	Anti-IgE (Omalizumab)	0.016mg/kg per IU total serum IgE/mL s.c. at enrolment and every 4 weeks for 6 months or placebo	24 weeks
Gevaert et al.[36] (2011)	Belgium	30	20	10	CRSwNP	Anti-IL-5 (Mepolizumab)	2 single i.v. injections of 750mg or placebo (28 days apart)	48 weeks
Gevaert et al.[29] (2013)	Belgium	23	15	8	CRSwNP Asthma	Anti-IgE (Omalizumab)	Maximum 375mg s.c. (every 2 weeks/8 injections in total or every month/4 injections in total) or placebo	20 weeks
Bachert et al.[30] (2016)	USA Belgium Spain Sweden	60	30	30	CRSwNP	Anti-IL-4Rα (Dupilumab)	600mg loading dose s.c. followed by 15 weekly doses of 300mg and MFNS 100µg in each nostril twice daily or placebo	16 weeks
Bachert et al.[35] (2017)	Belgium Netherlands UK	105	54	51	CRSwNP	Anti-IL-5 (Mepolizumab)	Six doses (one every 4 weeks) of mepolizumab 750mg i.v. or placebo	25 weeks
Jonstam et al.[31] (2019)	Sweden USA France Belgium Germany	60	30	30	CRSwNP	Anti-IL-4Rα (Dupilumab)	600mg loading dose followed by 16 weeks of 300mg dupilumab or placebo and MFNS	16 weeks
Bachert et al.[32] (2019)	Belgium Sweden USA France Spain	35	16	30	CRSwNP	Anti-IL-4Rα (Dupilumab)	300 mg s.c. dupilumab weekly or placebo plus MFNS for 16 weeks	16 weeks
Fujieda et al.[33] (2021)	Japan	49	33	19	CRSwNP Asthma	Anti-IL-4Rα (Dupilumab)	300mg dupilumab every 2 weeks for 52 weeks, 300mg dupilumab every 2 weeks for 24 weeks followed by every 4 weeks for 28 weeks or placebo plus MFNS	52 weeks

CRSwNP – chronic rhinosinusitis with nasal polyps; i.v. – intravenous; s.c. – subcutaneous; MFNS – mometasone furoate nasal spray; IgE – immunoglobulin E; IL-5 – interleukin-5; IL-4Rα – interleukin-4 receptor α subunit; IU – international unit

Table 2. Baseline clinical and evaluated parameters characteristics in the randomized controlled studies included in the review.

	Gevaert et al.[34] (2006)			Pinto et al.[28] (2010)		Gevaert et al.[36] (2011)		Gevaert et al.[29] (2013)		Bachert et al.[30] (2016)		Bachert et al.[35] (2017)		Jonstam et al.[31] (2019)		Bachert et al.[32] (2019)		Fujieda et al.[33] (2021)		
	SG1	SG2	PG	SG	PG	SG	PG	SG	PG	SG	PG	SG	PG	SG	PG	SG	PG	SG1*	SG2*	PG
Female/male sex	2/6	4/4	2/6	4/3	0/7	6/14	2/8	3/12	4/4	12/18	14/16	13/41	17/34	12/18	14/16	9/7	12/7	4/12	9/8	6/10
Asthma	7/8	5/8	6/8	7/7	7/7	10/20	3/10	15/15	8/8	16/30	19/30	44/54	38/51	16/30	19/30	5/16	8/19	8/16	12/17	11/16
Allergy	NR	NR	NR	NR	NR	10/20	4/10	7/15	6/8	18/26	20/28	NR	NR	NR	NR	NR	NR	12/16	12/17	10/16
Aspirin intolerance	NR	NR	NR	NR	NR	5/20	0/10	8/15	4/8	6/30	9/30	NR	NR	NR	NR	5/16	8/19	5/16	4/17	5/16
TNPS	6(4.5-7) range	5(3.5-6.75)	6(4.5-8)	1.5(0.5-3) (mean, range)	1.25 (0.8-2.5)	5.2(1.74) (mean (SD))	5.5(1.65)	6(4-6) (median (IQR))	6(6-8)	5.9(1.0) (mean (SD))	5.7(0.9)	6.28 (0.88) (mean (SD))	6.31 (0.88)	5.63 (1.19)	6.25 (0.50)	5.94 (0.85) (mean (SD))	5.53 (1.02)	5.6(1.1) (mean (SD))	6.6(1.2)	5.6 (1.6)
LMK-CT score	NR	NR	NR	NR	NR	NR	NR	17.5 (14.5-21) (median (IQR))	16.5 (15.3-21.3)	18.6 (5.0) (mean (SD))	18.7 (5.5)	NR	NR	18.13 (4.76) (mean (SD))	18.25 (3.95)	19.07 (4.23) (mean (SD))	19.95 (5.65)	19.0 (3.1) (mean (SD))	19.7 (3.9)	17.3 (3.0)
UPSIT	NR	NR	NR	13±2.8 (mean ± sem)	19±3.4	NR	NR	12(10-23) (median (IQR))	12(10-13)	12.8 (8.3) (mean (SD))	15.6(7.9)	NR	NR	14.38 (8.60) (mean) SD))	12.00 (2.16)	NR	NR	13.3 (7.6) (mean (SD))	14.2 (8.0)	12.2 (8.4)
NPIF	NR	NR	NR	93.3 (53.3-173.3) (mean, range)	133.3 (113.3-156.7)	NR	NR	NR	NR	98.4 (48.5) (mean (SD), L/min)	109.2 (46.8)	101(67) (mean (SD), L/min)	102(65)	108.38 (66.18) (mean (SD), L/min)	108.21 (88.57)	NR	NR	83.0 (40.4) (mean (SD), L/min)	64.2 (40.4)	80.7 (53.1)
SNOT-22	NR	NR	NR	45.7 ± 5.6 (mean ± sem)	46±11	NR	NR	NR	NR	41.4 (18.2) (mean (SD))	40.6 (19.9)	51.5 (17.0) (mean (SD))	49.5 (19.0)	45.50 (13.61) (mean (SD))	42.50 (25.89)	40.63 (16.26) (mean (SD))	43.63 (20.66)	37.7 (15.1) (mean (SD))	40.1 (21.2)	45.9 (26.7)

SF-36	NR	NR	NR	61.8 ± 15.2 (mean ± sem)	67.6± 10.5	NR	NR	48(45-52) (median (IQR))	50(45.5-52.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nasal obstruction (mean (SD))	NR	NR	NR	NR	NR	2.15 (0.75)	2.4 (0.70)	NR	NR	AM 1.7(0.7) PM 1.6(0.8)	AM 1.7(0.7) PM 1.6(0.7)	7.90 (7.23-8.56)	8.01 (7.32-8.69)	1.82 (0.57)	1.61 (0.66)	1.43 (0.73)	1.67 (0.74)	2.2 (0.5)	2.3 (0.5)	2.2 (0.5)
Loss of smell (mean (SD))	NR	NR	NR	NR	NR	2.65 (0.59)	2.4 (0.84)	NR	NR	AM 2.4 (0.9) PM 2.4 (0.9)	AM 2.8 (0.5) PM 2.8 (0.5)	9.06 (8.43-9.69)	9.10 (8.45-9.75)	NR	NR	2.47 (0.96)	2.93 (0.24)	2.7 (0.5)	2.7 (0.4)	2.7 (0.6)
Anterior rhinorrhea	NR	NR	NR	NR	NR	1.5 (0.89) (mean (SD))	1.8 (0.79)	NR	NR	AM 1.0 (0.9) PM 1.0 (0.9)	AM 1.1 (0.8) PM 1.2 (0.7)	6.24 (5.57-6.91) (mean (95%CI)	6.19 (5.50-6.87)	NR	NR	NR	NR	1.6 (0.8) (mean (SD))	2.0 (0.6)	1.7 (0.7)
Blood eosinophils	0.21 (0.18-0.35) (103/mL)	0.24 (0.18-0.46)	0.17 (0.13-0.28)	NR	NR	NR	NR	390 (313-698) (/µL, median (IQR))	475 (365-630)	0.36 (0.25-0.47) (x109/L, median (IQR))	0.32 (0.18-0.49)	NR	NR	0.32 (0.20) (x109/L, mean (SD))	0.29 (0.18)	0.51 (0.25) (x109/L)	0.55 (0.83)	0.4 (0.3)	0.6 (0.4)	0.7 (0.8)
Serum ECP (µg/L)	15.8 (11.2-35.7)	13.5 (9.9-31.6)	10.7 (5.2-34.7)	NR	NR	NR	NR	31 (14-56)	32 (20-91)	NR	NR	NR	NR	NR	NR	35.38 (26.27)	37.26 (48.33)	NR	NR	NR
Serum IL-5-Rα (pg/mL)	464.6 (384-695)	737 (436-2263)	547 (406-756)	NR	NR	NR	NR	258 (207-332)	292 (249-413)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Serum total IgE (IU/mL)	NR	NR	NR	NR	NR	NR	NR	108 (39-130)	84 (71-148)	87 (47-185)	101 (37-254)	NR	NR	142.50 (119.29)	151.75 (125.84)	167.13 (153.77)	233.06 (300.44)	268.3 (236.4)	292.3 (294.5)	364.4 (349.0)
Nasal ECP (µg/L)	350.7 (76.6-1519.6)	283.1 (196.8-932.1)	344.1 (74.2-867.3)	NR	NR	NR	NR	362 (176-653)	994 (591-1888)	NR	NR	NR	NR	NR	NR	41.80 (43.44)	16.47 (11.49)	NR	NR	NR
Nasal IL-5-Rα (pg/mL)	2243 (779-6461)	2198 (592-7103)	1385 (677-3766)	NR	NR	NR	NR	494 (169-1128)	1199 (757-2771)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

SG – study group; SG1 – study group with Reslizumab 1mg/kg; SG2 – study group with Reslizumab 3mg/kg; PG – placebo group; SG1* - Dupilumab 300mg every 2 weeks; SG2* - Dupilumab 300mg every 2 weeks for 24 weeks and every 4 weeks for 28 weeks; NP- not reported; CI – confidence interval; ECP - eosinophil cationic protein; IL-5 - Interleukin-5; IU – international unit; TNPS – total nasal polyp score; LMK-CT – Lund Mackay CT score; UPSIT - University of Pennsylvania Smell Identification Test; PNIF - peak nasal inspiratory flow; SNOT-22 - Sino-nasal Outcome Test; SF-36 - 36-Item Short Form Survey; SD – standard deviation.

tracted: first author name, year of publication, country, study design, sample study, treatment protocol, following period, primary and secondary outcomes, treatment side effects.

For the primary outcomes, a point of interest was the endoscopic nasal polyp score which was evaluated for each nostril during every visit performed by the patients included in the study. The total nasal polyp score (TNPS) was graded between 0 and 4 and included the sum of both nostrils: grade 0 – no polyps; grade 1 – small polyps in the middle meatus, not reaching the inferior border of the middle turbinate; grade 2 – polyps reaching below the inferior border of the middle turbinate; grade 3 – large polyps reaching below the inferior border of the inferior turbinate / polyps medial to the middle turbinate; grade 4 – large polyps with complete obstruction of the nasal cavity.

For the second outcome, of interest were: the Lund-Mackay CT score (evaluates the grade of sinus opacification bilaterally from 0 to 2, score range between 0 and 24); quality of life (QoL) measured by the Sino-nasal Outcome Test (SNOT-22; assesses 22 symptoms – nasal symptoms, sleep quality, otologic symptoms, emotional symptoms, scored between 0 - 5), 36-Item Short Form Survey (SF-36), University of Pennsylvania Smell Identification Test (UPSIT, 40 items); peak nasal inspiratory flow (PNIF); serum eosinophils and interleukin E (IgE); serum and nasal anti-interleukin-5 (anti-IL-5) and eosinophil cationic protein (ECP).

The safety of monoclonal antibodies treatment was assessed by identifying the side effects reported in the evaluated studies.

Articles selection

The total search identified a number of 620 publications. After applying the inclusion criteria, eliminating duplicates and those articles which presented the results of the clinical trials, 9 articles remained[28-36]. In total, there were 400 patients (37.25% female, 62.75% male), 221 of them receiving monoclonal antibodies treatment and 179 placebo. Of all the patients included in the study, 264 had asthma (66%; 145 in the study groups and 119 in the placebo groups), 99 were diagnosed with allergy (24.75%; 59 in the study groups, 40 in the placebo groups) and 59 with aspirin intolerance (14.75%; 33 in the study groups, 26 in placebo). The patients included in the studies were randomly distributed to receive anti-IgE treatment with omalizumab in 2 studies[28,29], anti-interleukin-4 receptor α subunit (anti-IL4Rα) treatment with dupilumab in 5 studies[30-33] and anti-IL5 (mepolizumab or reslizumab) in 3 studies[34-36]. In Table 1, Table 2 are presented the characteristics of the randomized controlled studies included in the review.

Separately, we reviewed the results of 6 completed clinical trials performed for dupilumab (SINUS-52, NCT02898454, and SINUS-24, NCT02912468)[37,38], omalizumab (POLYP 1, NCT03280550, and POLYP 2, NCT03280537)[39,40], mepolizumab (SYNAPSE, NCT03085797)[41], benralizumab (OSTRO, NCT03401229)[42]. All six clinical trials included 1806 patients, 985 of them receiving the treatment with a

Table 3. Characteristics of the Clinical Trials included in the review.

Clinical Trials. gov Identifier	No. of patients	Age	Treatment group	Placebo group	Diagnosis	Monoclonal antibody	Treatment protocol	Follow-up period
NCT02912468 (SINUS-24)[38]	276	18+ years	143	133	CRSwNP	Dupilumab (Anti-IL-4Rα)	Dupilumab 300mg s.c. every 2 weeks for 24 weeks + MFNS vs placebo + MFNS	52 weeks
NCT02898454 (SINUS-52)[37]	448	18+ years	295	153	CRSwNP	Dupilumab (Anti-IL-4Rα)	Dupilumab 300mg s.c. every 2 weeks for 24 weeks then 300mg every 4 weeks until week 52 + MFNS vs Dupilumab 300mg s.c. every 2 weeks for 52 weeks + MFNS vs placebo + MFNS	52 weeks
NCT03280550 (POLYP 1)[39]	138	18 - 75 years	72	66	CRSwNP	Omalizumab (Anti-IgE)	Omalizumab s.c. once every 2 weeks or every 4 weeks (dose 75-600mg; depending on serum total IgE and body weight) + MFNS vs placebo + MFNS	28 weeks
NCT03280537 (POLYP 2)[40]	127	18 - 75 years	62	65	CRSwNP	Omalizumab (Anti-IgE)	Omalizumab s.c. once every 2 weeks or every 4 weeks (dose 75-600mg; depending on serum total IgE and body weight) + MFNS vs placebo + MFNS	28 weeks
NCT03085797 (SYNAPSE)[41]	407	18+ years	206	201	NP	Mepolizumab (Anti-IL-5)	Mepolizumab s.c. 100mg/mL every 4 weeks to week 52 + MFNS vs placebo + MFNS	52 weeks
NCT03401229 (OSTRO)[42]	410	18 - 75 years	207	203	NP	Benralizumab (Anti-IL-5)	Benralizumab 30mg s.c. every 4 weeks the first 3 doses and every 8 weeks + MFNS vs placebo + MFNS	56 weeks

CRSwNP – chronic rhinosinusitis with nasal polyps; s.c. – subcutaneous; MFNS – mometasone furoate nasal spray; IgE – immunoglobulin E; IL-5 – interleukin-5; IL-4Rα – interleukin-4 receptor α subunit; NP – nasal polyps; vs – versus.

monoclonal antibody and 821 placebo. Also, we found an ongoing study on benralizumab (NAPPREB, NCT04185012) which estimated completion date on July 30, 2022[43]. In Table 3 are presented the characteristics of the clinical trials included in the review.

THE INFLUENCE OF MONOCLONAL ANTIBODY THERAPY ON TOTAL NASAL ENDOSCOPIC POLYP SCORE

Nasal endoscopy is a reliable tool in the evaluation of the clinical local status of the rhinosinusal disease, including in the treatment of nasal polyposis. The total nasal endoscopic polyp score (TNPS) was an important parameter for the primary outcomes in all nine randomized controlled studies and all six clinical trials, being considered the most important indicator for the efficacy of the treatment with monoclonal antibodies.

An important reduction in TNPS values was observed in all evaluated studies and clinical trials compared to baseline (Table 4, Table 5), except Pinto et al.[28] who reported no significant difference between the study group and placebo in the case of omalizumab treatment (p= .58) and Jonstram et al.[31] in the case of dupilumab (p= .3391).

Evaluating the treatment with reslizumab, Gevaert et al.[34] (2006) compared placebo with 1mg/kg and 3mg/kg reslizumab. They reported an improvement in the total nasal endoscopic polyp score from baseline to week 12 in 5/12 patients who received 1mg/kg and in 4/8 at 4 weeks in patients with 3mg/kg. However, at 12 weeks of treatment, in those cases who received 3mg/kg reslizumab, there was no change in 3/8 patients, improvement in 1/8 patients and worse in 4/8 patients. In the placebo group, 3 patients felt better and 3 had worse TNPS and 2 patients required nasal surgery.

In the case of mepolizumab, another anti-IL-5 antibody treatment, Gevaert et al.[36] (2011) identified a significant difference compared to baseline (p = .028) and between the two groups at 8 weeks, with 60% improvement in the TNPS in the study group compared to 10% in the placebo cases (p= .018). For the same monoclonal antibody, Bachert et al.[35] (2017) and the SYNAPSE[41] clinical trial reported the same significant decrease (p = .031 in week 9, p = .025 in week 25[35], and p < .001 respectively[41]).

The OSTRO clinical trial evaluated another anti-IL-5 antibody, benralizumab, its effect on TNPS being statistically significantly different between the two groups up to 40 weeks and 56 weeks of treatment (p < .0001 and p = .0048 respectively)[42] (Table 5).

For omalizumab, while Pinto et al.[28] showed no significant difference between the study and the placebo group at week 24, Gevaert et al.[29] (2013) reported a statistically important reduction in the TNPS in the study group compared to the placebo from baseline to week 16 (the study group -2.67, p = .001; placebo group -0.12, p = .99). Between the two groups, the difference became statistically significant from the eighth week of treatment, with p = .03 at 8 weeks and p = .005 at 16 weeks[29]. The positive impact of omalizumab on the total nasal endoscopic polyp score is also sustained by POLYP 1 and POLYP 2 clinical trials (Table 5), with p < .0001 and p = .0140, from baseline to week 24[39,40].

Concerning dupilumab, Jonstam et al.[31] did not show any significant change between treatment group and placebo (p = .3391) from baseline to week 16. The important influence of dupilumab on TNPS reduction is sustained by Bachert et al.[30] (2016) (p < .001), Bachert et al.[32] (2019) (p < .001) and Fujieda et al.[33] (p = .0011 in those patients who received 300mg dupilumab every 2 weeks for 52 weeks, and p = .0002 in dupilumab 300mg every 2 weeks for 24 weeks and every 4 weeks for 28 weeks) (Table 4).

Comparing the reported effects of all three types of monoclonal antibodies on the evolution of TNPS, one can see that all clinical trials (performed on a higher number of patients compared to the randomized-controlled studies) report a statistically significant improvement in the nasal total endoscopic polyp score in the treatment groups (compared to baseline and placebo groups)[37-42].

THE INFLUENCE OF MONOCLONAL ANTIBODY THERAPY ON THE CT SCORE

The Lund-Mackay CT (LMK-CT) score is used for the radiologic staging of chronic rhinosinusitis by evaluating the paranasal sinuses (0 – no abnormality, 1 – partial opacification, 2 – complete opacification) and the ostiomeatal complex (0 – not obstructed, 2 – obstructed). A score of up to 24 can be obtained[44].

For the evaluation of the efficacy of monoclonal antibody therapy in nasal polyposis, the changes from baseline in LMK-CT scores was a second outcome parameter. Also, the status of sinus mucosa inflammation as seen on the CT scans was evaluated. Tables 4 and 5 summarize the changes in this parameter.

For dupilumab, a reduction in the LMK-CT scores was identified by several studies[30-33] (Table 4). Fujieda et al.[33] compared the efficacy of dupilumab administered every 2 weeks for 52 weeks (Arm A) and every 2 weeks for 24 weeks and every 4 weeks for the subsequent 28 weeks (Arm B). They reported a significant improvement in sinus LMK-CT score at all times in patients who received 300mg every 2 weeks for 52 weeks (p < .0001 Arm A, p = .0371 Arm B) (Table 4).

Gevaert et al.[36] (2011) admitted an improvement in CT scan scores in more than 50% of patients who received mepolizumab and less than 20% of the placebos compared to baseline (results according to three observers: A with p = .058, B with p = .024, C with p = .049). The same significant improvement was reported by Gevaert et al.[29]

Table 4. Randomized controlled studies results.

Study	TNPS	Lund-Mackay CT score	SNOT-22	SF-36	PNIF
Gevaert et al.[34] (2006)	SG1 – decrease in 5/8 patients up to 12w; SG2 – decrease in 4/8 patients up to 4w	NR	NR	NR	NR
Pinto et al.[28] (2010)	No significant difference SG vs PG (p = .58)	NR	Significant improvement in SG (-1.05) and not clinically significant in the PG (-0.20) SG vs PG p < 0.78	No significant difference SG vs PG (p > .05), except vitality (p < .05)	No significant difference SG vs PG (p = .47)
Gevaert et al.[36] (2011)	Significant decrease at 8w compared to baseline – SG -1.30 (SD, 1.72) vs PG 0.00 (SD, 0.94) (p=.0.28). Improvement of 60% vs 10% (p=.018)	Improvement in more than half of the SG and less than 20% in PG	NR	NR	Better values in the SG vs PG (p=.095)
Gevaert et al.[29] (2013)	From baseline to w16 SG -2.64, p = .001 PG -0.12, p = .99	SG 17.6 to 13.6, p = .02 PG 17.8 to 18.3, p = .10 SG vs PG p = .04	NR	SG p = .02 PG p = .75	NR
Bachert et al.[30] (2016)	-1.6 [95%CI, -24 to -0.7] p < .001	-8.8 [95%CI, -11.1 to -6.6] p < .001	-18.1 [95%CI, -25.6 to -10.6] p < .001	NR	33.1L/min [95%CI, 12.7 to 53.5 L/min] p = .002
Bachert et al.[35] (2017)	Significant reduction in SG vs PG w9 (OR, 5.6; p = .031) to w25 (OR, 6.6; p = .025)	NR	Significant improvement in SG vs PG (p = .005)	NR	Significant difference SG vs PG (mean 26.7; 95% CI, 3.1-50.2; p = .027)
Jonstam et al.[31] (2019)	-1.06 [95%CI, -3.43 to 1.31] p = .3391	-10.62 [95%CI, -14.70 to -6.54] p = .0005	-31.52 [95%CI, -55.12 to -7.91] p = .0177	NR	57.25 [95%CI, -2.05 to 116.54] p = .0568
Bachert et al.[32] (2019)	Improvement SG vs PG p < .001	Improvement in SG vs PG p < .001	Improvement in SG vs PG p < .001	NR	NR
Fujieda et al.[33] (2021)	SG1* vs PG w24 -3.1 [95%CI, -4.3 to -1.8] p <.0001 w52 -2.1 [95%CI, -3.4 to .08] p = .0011 SG2* vs PG w24 -3.5 [95%CI, -4.8 to -2.3] p < .0001 w52 -2.4 [95%CI, -3.7 to -1.1] p = .0002	SG1* vs PG w24 -5.1 [95%CI, -8.2 to -2.0] p = .0005 w52 -7.5 [95%CI, -1.9 to -4.0] p < .0001 SG2* vs PG w24 -2.8 [95%CI, -5.9 to 0.3] p = .0425 w52 -3.6 [95%CI, -7.1 to -0.2] p = .0371	SG1* vs PG w24 -16.1 [95%CI, -25.8 to -6.5] p = .0011 w52 -18.9 [95%CI, -29.1 to -8.8] p = .0002 SG2* vs PG w24 -11.4 [95%CI, -20.8 to -1.9] p = .0186 w52 -11.5 [95%CI, -21.4 to -1.6] p = .0077	NR	NR

Study	UPSIT	Total blood eosinophils	Serum IL-5-Rα	Serum ECP	Nasal IL-5-Rα	Nasal ECP
Gevaert et al.[34] (2006)	NR	Significant decrease in SG1 SG2 compared to PG up to 8w; returned to baseline values at 12w; rebound at 24w in SG1 and 32w in SG2	Significant decrease up to 4w of treatment compared to placebo		Significant decrease up to 8w of treatment compared to placebo	
Pinto et al.[28] (2010)	No significant difference SG vs PG (p = .31)	NR	NR	NR	NR	NR
Gevaert et al.[36] (2011)	NR	Decrease SG vs PG at 8w p < .001	Decrease SG vs PG at 8w p < .001	Decrease SG vs PG at 8w p = .022	Decrease SG vs PG at 8w p = .010	Decrease SG vs PG at 8w p = .260
Gevaert et al.[29] (2013)	NR	NR	NR	NR	NR	NR
Bachert et al.[30] (2016)	14.8 [95%CI, 10.9 to 18.7] p < .001	-4.4 [95%CI, -36.1 to 27.2] p = .78	NR	NR	NR	NR
Bachert et al.[35] (2017)	NR	Decrease from 500 cells/µl at baseline to 50 cells/µl at 25w in the SG	NR	NR	NR	NR
Jonstam et al.[31] (2019)	12.11 [95%CI, 1.74 to 22.48] p = .0277	-0.07 [95%CI, -0.38 to 0.24] p = .5199	NR	NR	NR	NR
Bachert et al.[32] (2019)	NR	0.09 [95%CI, -0.34 to 0.51] p = .682	NR	21.25 [95%CI, -3.70 to 46.20] p = .094	NR	-9.55 [95%CI, -35.84 to 16.80] p = .472
Fujieda et al.[33] (2021)	SG1* vs PG w24 12.7 [95%CI, 7.5 to 17.9] p < .0001 w52 12.7 [95%CI, 7.8 to 17.7] p < .0001 SG2* vs PG w24 7.6 [95%CI, 2.4 to 12.7] p = .0038 w52 8.5 [95%CI, 3.6 to 13.4] p = .0006	Negative median percentage change by w52 in the SG	NR	NR	NR	NR

SG – study group; SG1 – study group with Reslizumab 1mg/kg; SG2 – study group with Reslizumab 3mg/kg; PG – placebo group; SG1* - Dupilumab 300mg every 2 weeks; SG2* - Dupilumab 300mg every 2 weeks for 24 weeks and every 4 weeks for 28 weeks; NP- not reported; CI – confidence interval; ECP - eosinophil cationic protein; IL-5 - Interleukin-5; IU – international unit; TNPS – total nasal polyp score; LMK-CT – Lund Mackay CT score; UPSIT - University of Pennsylvania Smell Identification Test; PNIF - peak nasal inspiratory flow; SNOT-22 - Sino-nasal Outcome Test; SF-36 - 36-Item Short Form Survey; SD – standard deviation; w – week

Table 5. Clinical Trials results.

	NCT02912468 (SINUS-24)[38]		NCT02898454 (SINUS-52)[37]		NCT03280550 (POLYP 1)[39]	NCT03280537 (POLYP 2)[40]	NCT03085797 (SYNAPSE)[41]	NCT03401229 (OSTRO)[42]	
	w0 to w24	w0 to w48	w0 to w24	w0 to w52	w0 to w24	w0 to w24	w0 to w52	w0 to w40	w0 to w56
TNPS LS Mean (95%CI)	PG 0.17 (0.15) SG -1.89 (0.14) SG vs PG -2.06 (-2.43 to -1.69) p < .0001	PG 0.14 (0.13) SG -0.66 (0.13)	PG 0.10 (0.14) SG -1.71 (0.11) SG vs PG -1.80 (-2.10 to 1.51) p < .0001	PG 0.16 (0.15) SG1 -2.05 (0.15) SG2 -2.24 (0.15) p < .0001	PG 0.06 (-0.27 to 0.38) SG -1.08 (-1.40 to -0.77) SG vs PG -1.14 (-1.59 to -0.69) p < .0001	PG -0.31 (-0.63 to 0.01) SG -0.90 (-1.23 to -0.57) SG vs PG -0.59 (-1.05 to -0.12) p = .0140	PG 0.0 (-5 to 3) SG -1.0 (-6 to 3) (median) SG vs PG -0.73 (-1.11 to -0.34) p < .001	PG 0.17 (1.18) SG -0.36 (1.66) (mean, SD) SG vs PG -0.570 (-0.852 to -0.289) p < .0001	PG 0.18 (1.44) SG -0.22 (1.76) (mean, SD) SG vs PG -0.475 (-0.810 to -0.141) p = .0048
Lund-Mackay score LS Mean (SE) (95%CI)	PG -0.74 (0.37) SG -8.18 (0.34) SG vs PG -7.44 (-8.35 to -2.17) p < .0001	PG -0.82 (0.38) SG -2.62 (0.36)	PG -0.09 (0.31) SG -5.21 (0.24) SG vs PG -5.13 (-5.80 to -4.46) p < .0001	PG 0.11 (0.37) SG1 -5.60 (0.37) SG2 -6.83 (0.37)	NR	NR	NR	NR	PG -0.20 (4.20) SG -0.93 (5.06) (mean, SD) SG vs PG -0.856 (-2.281 to 0.570) p = .2375
Nasal congestion/ obstruction LS Mean (95%CI) (SE)	PG -0.45 (0.07) SG -1.34 (0.07) SG vs PG -0.89 (-1.07 to -0.71) p = .0001	PG -0.52 (0.08) SG -0.77 (0.07)	PG -0.38 (0.07) SG -1.25 (0.06) SG vs PG -0.87 (-1.03 to -0.71) p < .0001	PG -0.37 (0.08) SG1 -1.48 (0.08) SG2 -1.36 (0.07) p < .0001	PG -0.35 (-0.56 to -.03) SG -0.89 (-1.10 to -0.69) SG vs PG -0.55 (-0.84 to -0.25) p = .0004	PG -0.20 (-0.42 to 0.01) SG -0.70 (-0.92 to -0.48) SG vs PG -0.15 (-0.80 to -0.19) p = .0017	PG -0.82 (-9.23 to 2.58) SG -4.41 (-9.90 to 1.54) (median) SG vs PG -3.14 (-4.09 to -2.18) p < .001	PG -0.41 (0.89) SG -0.68 (1.02) (mean, SD) SG vs PG -0.270 (-0.458 to -0.083) p = .0048	PG -0.38 (0.91) SG -0.68 (1.03) (mean, SD) SG vs PG -0.287 (-0.477 to -0.096) p = .0032
Sense of smell LS Mean (95%CI)	PG -0.29 (0.07) SG -1.41 (0.07) SG vs PG -1.12 (-1.31 to -0.93) p < .0001	PG -0.30 (0.07) SG -0.71 (0.06)	PG -0.23 (0.08) SG -1.21 (0.06) SG vs PG -0.98 (-1.15 to -0.81) p < .0001	PG -0.18 (0.09) SG1 -1.49 (0.09) SG2 -1.29 (0.08)	PG -0.23 (-0.42 to -0.04) SG -0.56 (-0.74 to -0.38) SG vs PG –0.33 (-0.60 to -0.6) p = .0161	PG -0.13 (-0.33 to 0.06) SG -0.58 (-0.78 to -0.38) SG vs PG -0.45 (-0.73 to -0.16) p = .0024	PG 0.00 (-9.97 to 1.94) SG -0.53 (-10.00 to 1.27) (median) SG vs PG -0.37 (-0.65 to -0.08) p = .003	PG -0.16 (0.65) SG -0.34 (0.79) (mean, SD) SG vs PG -0.218 (-0.361 to -0.074) p = .0029	PG -0.21 (0.65) SG -0.39 (0.79) (mean, SD) SG vs PG -0.237 (-0.389 to -0.084) p = .0023
Rhinorrhea LS Mean (95%CI)	PG -0.42 (0.06) SG -1.04 (0.06)	PG -0.45 (0.07) SG -0.58 (0.07)	PG -0.40 (0.07) SG -0.99 (0.05)	PG -0.35 (0.07) SG1 -1.19 (0.07) SG2 -1.15 (0.07)	PG -0.34 (-0.54 to -0.15) SG -0.77 (-0.96 to 0.58) SG vs PG -0.43 (-0.70 to -0.16) p = .0023	PG -0.08 (-0.17 to 0.11) SG -0.70 (-0.90 to -0.51) SG vs PG -0.63 (-0.90 to -0.35) p < .0001	NR	NR	NR
TNSS LS Mean (95%CI)	PG -1.17 (0.17) SG -3.77 (0.16) SG vs PG -2.61 (-3.04 to -2.17) p < .0001	PG -1.28 (0.19) SG -2.05 (0.18)	PG -1.00 (0.20) SG -3.45 (0.15) SG vs PG -2.44 (-2.87 to -2.02) p < .0001	PG -0.93 (0.20) SG1 -4.17 (0.20) SG2 -3.79 (0.20)	PG-1.06 (-1.74 to -0.38) SG -2.97 (-3.61 to -2.32) SG vs PG -1.91 (-2.85 to -0.96) p = .0001	PG -0.44 (-1.07 to 0.19) SG -2.53 (-3.08 to -1.89) SG vs PG -2.09 (-3.00 to -1.18) p < .0001	NR	PG -1.38 (6.29) SG -3.20 (6.90) (mean, SD) SG vs PG -1.854 (-3.101 to -0.608) p = .0036	NR
SNOT-22 LS Mean (95%CI)	PG -9.31 (1.62) SG -30.43 (1.54) SG vs PG -21.12 (-25.17 to -17.06) p < .0001	PG -8.36 (1.88) SG -17.66 (1.80)	PG -10.40 (1.61) SG –27.77 (1.26) SG vs PG -17.36 (-20.87 to -13.85) p < .0001	PG -9.06 (1.61) SG1 -30.42 (1.65) SG2 -29.79 (1.64) p < .0001	PG -8.58 (-12.71 to -4.46) SG -24.70 (-28.67 to -20.73) SG vs PG -16.02 (-21.86 to -10.38) p < .0001	PG -6.55 (-10.88 to -2.23) SG -21.59 (-26.05 to -17.14) SG vs PG -15.04 (-21.26 to -8.82) p < .0001	PG -14.0 (-86 to 38) SG -30.0 (-93 to 42) (median) SG vs PG -16.49 (-23.57 to -9.42) p = .020	PG -10.7 (31.64) SG -15.2 (30.47) (mean, SD) SG vs PG -5.212 (-11.087 to 0.664) p < .0821	PG -7.9 (33.22) SG -15.1 (33.55) (mean, SD) SG vs PG -7.492 (-13.741 to -1.243) p = .0188
UPSIT LS Mean (95%CI)	PG 0.70 (0.71) SG 11.26 (0.67) SG vs PG 10.56 (8.79 to 12.34) p < .0001	PG 0.21 (0.77) SG 4.20 (0.73)	PG -0.81 (0.71) SG 9.71 (0.56) SG vs PG 10.52 (8.98 to 12.07) p < .0001	PG -0.78 (0.71) SG1 9.99 (0.73) SG2 9.53 (0.72)	PG 0.63 (-1.12 to 2.39) SG 4.44 (2.77 to 6.12) SG vs PG 3.81 (1.38 to 6.24) p = .0024	PG 0.44 (-1.15 to 2.04) SG 4.31 (2.66 to 5.95) SG vs PG 3.86 (1.57 to 6.15) p = .0011	NR	Males PG 0.09 (8.05) SG -0.20 (10.29) (mean, SD) p = .5833 Females PG -1.32 (7.66) SG 1.66 (8.86) p = .0619	NR
PNIF LS Mean (SE) (95%CI)	PG 14.09 (3.97) SG 54.50 (3.73)	NR	PG 18.65 (3.95) SG 55.29 (3.08)	NR	NR	NR	NR	NR	NR

CRSwNP – chronic rhinosinusitis with nasal polyps; i.v. – intravenous; s.c. – subcutaneous; MFNS – mometasone furoate nasal spray; IgE – immunoglobulin E; IL-5 – interleukin-5; IL-4Rα – interleukin-4 receptor α subunit; IU – international unit

(2013) in the case of omalizumab in the study group (p = .02) and between the two groups (p = .04) compared to baseline and week 16. However, in the placebo groups, the CT scan images worsened (p = .10). The significant reduction of inflammation was found also by Pinto et al.[28] in the omalizumab-treated group (p < .043). They compared the changes across treatment groups and the difference was not significant from the statistical point of view (p < .391)[28].

The Lund-Mackay CT score was one of the second outcome parameters evaluated in 3 Clinical Trials included in this review[37,38,42]. In the case of dupilumab (SINUS-24, SINUS-52)[37,38], the evaluation performed after 16 weeks of treatment revealed a statistically significant improvement in LMK-CT score in the study group versus placebo (p < .001); 59% for dupilumab-treated patients and only 3% for placebo[45]. Better results were identified in total bilateral scores and for each sinus. As for the ostiomeatal obstruction, it was present more than 81% in the patients who received placebo and more than 40% in dupilumab-treated patients[46].

In the OSTRO clinical trial[42] and in the articles related to it[47,48], benralizumab treatment determined a reduction in LMK-CT scores versus placebo, but the difference between groups was not significant (p = .2375).

THE INFLUENCE OF MONOCLONAL ANTIBODY THERAPY ON SYMPTOMS

Parameters such as nasal congestion/obstruction, rhinorrhea, sense of smell, were symptoms evaluated in almost all randomized-controlled studies and clinical trials included in this review (Table 4, Table 5). They are usually associated with CRSwNP. The symptoms were assessed as entity scores, but also with different types of objective tests. Olfaction was evaluated by UPSIT[28,30,31,33] and the nasal obstruction by the nasal airflow measured by the peak nasal inspiratory flow (PNIF)[29-31,35,36]. UPSIT (University of Pennsylvania Smell Identification Test), one of the most used smell identification tests for the assessment of the olfactory function, is a 40-item subjective smell test able to identify different grades of smell disorders[49]. PNIF is a rapid, inexpensive test, which objectively measures the maximum nasal airflow.

Evaluating the influence of omalizumab treatment upon CRSwNP symptoms, one can see a significant decrease in symptom intensity in both randomized-controlled studies (nasal congestion p = .002, rhinorrhea p = .003, loss of smell p = .004)[29] and clinical trials[39,40]. In POLYP 1 (NCT03280550)[39] and POLYP 2 (NCT03280537)[40] trials, performed on 138 subjects and 127 respectively, nasal symptoms significantly improved when comparing baseline with week 24 (Table 5). The same results were seen when evaluating the evolution of TNSP (omalizumab versus placebo – POLYP 1 with p = .0001, and POLYP 2 with p < .0001).

Analysing the results of UPSIT, an improvement was seen in the sense of smell in both clinical trials (p = .0024 in POLYP 1[39], p = .0011 in POLYP 2[40]).

The study performed by Pinto et al.[28] showed no significant difference between the study groups and placebo in UPSIT (p < .31), PNIF (p < .31), total nasal symptoms score (p < .21) (Table 5). Their results might be influenced by the small number of patients included in the study (n = 14 patients).

The positive influence of the monoclonal antibody therapy upon CRSwNP symptoms can be corelated with the significant improvement the treatment has also upon the total nasal endoscopic polyp scores and Lund-Mackay CT scores.

THE INFLUENCE OF MONOCLONAL ANTIBODY THERAPY ON PATIENTS' QUALITY OF LIFE

A very important parameter in evaluating the efficacy of any treatment is the patients' quality of life (QoL). Different questionnaires can be used.

In most of the statistics we reviewed, the following scoring methods were used: SNOT-22, SF-36, the 31-item Rhinosinusitis Outcome Measuring Instrument (RSOM-31), Asthma Quality of Life Questionnaire (AQLQ), 5-item Asthma Control Questionnaire (ACG-5).

Analysing all the results, one can conclude that after the treatment with dupilumab[30-33,37,38] and mepolizumab[35,41], the SNOT-22 scores improved significantly (Table 4, Table 5). For omalizumab, both Clinical Trials (POLYP 1, POLYP 2), conducted on a clinical and scientifical significant number of patients, identified an important improvement in SNOT-22 values after treatment in the omalizumab group versus placebo (p < .0001)[39,40]. However, Pinto et al.[28] showed that although omalizumab improved the SNOT-22 scores in the study group (-1.05) and no important change in the placebo (-0.20) (Table 4), the difference between the two groups at the end of the treatment was not statistically significant (p < .78). The same observation can be made in the case of SF-36 (p > .05), except the vitality parameter (p < .05). Gevaert et al.[29] (2013) concluded that omalizumab changed in better the SF-36 of physical health for the patients who received the monoclonal antibody (p = .02 versus p = .75), in the RSOM-31 (sleep with p = .03, general symptoms with p = .01) and for AQLQ scores (p = .003).

The ACQ-5 for dupilumab presented a clinically important improvement (p < .001)[32].

MONOCLONAL ANTIBODY THERAPY AND SEROLOGIC AND NASAL MARKERS

The monoclonal antibody therapies are directed towards specific biomarkers, such as IgE, IL-5, IL-4, IL-13,

type 2 inflammation agents[50,51]. Blocking one of these markers, the biologic agents reduce the concentration of eosinophils, ECP, IL-5-Rα or serum and nasal secretions IgE.

Omalizumab

As an IgE blocker, reducing the free IgE, omalizumab produces no significant difference after treatment in any serum and nasal secretion of the evaluated parameters[28,29] (Table 4).

Reslizumab, mepolizumab

For reslizumab, it has been seen a significant decrease in serum eosinophils in the treatment group versus placebo at 8 weeks, with a return to baseline values at week 12[34]. However, a rebound was reported at week 24 after receiving 1mg/kg treatment and at week 32 after 3mg/kg treatment[34]. Also, there was a significant decrease in nasal and serum IL-5-Rα and ECP at 8 weeks of treatment and 4 weeks, respectively, compared to placebo.

The treatment with mepolizumab gave a significant decrease in the total blood eosinophil count compared to the placebo group ($p < .001$)[35,36], with no signs of rebound. The same effect was seen on the level of nasal ($p = .010$) and serum ($p < .001$) IL-5-Rα and serum ($p = .022$) ECP[36]. An exception was the nasal ECP with $p = .260$.

Dupilumab

The patients treated with dupilumab showed an important decrease in the levels of total serum IgE, eotaxin-3 and ECP compared to baseline. In the case of eotaxin-3, the decrease was seen as early as the second week and remained reduced until the end of the treatment ($p < .001$)[30]. A valuable information is that the low levels of IgE progressed over the 16 treatment weeks, according to Bachert et al.[30] in 2016.

The blood eosinophils presented no significant variation in both groups at week 16 compared to baseline[30].

Evaluating the influence of dupilumab upon both nasal and serum inflammatory markers, one can conclude that this monoclonal antibody acts on organ and systemic type 2 inflammation.

MONOCLONAL ANTIBODY THERAPY AND THE NEED FOR RESCUE TREATMENT

An essential information in the benefit of monoclonal antibodies is the need for nasal polyps' surgery in patients who receive biologic treatment. The reviewed Clinical Trials indicated the need for rescue treatment (medication and/or surgery) in all treated patients, no matter the used biologic[37-42].

Omalizumab

POLYP 1 clinical trial[39] evaluated the need for rescue medication, systemic corticosteroids, for more than 3 consecutive days through week 24. 3 patients in the placebo group (4.5%) and 2 patients in the omalizumab-treated group (2.8%) received systemic corticotherapy, with no difference from a statistical point of view between the groups ($p = .6716$). The need for nasal polyp surgery up to week 24 was identified in 1 patient who received placebo treatment. No patients included in the study group needed surgical intervention, but there was no difference between the two groups ($p = .4815$).

In the case of patients included in POLYP 2 clinical trial[40], up to week 24, 6 patients needed rescue medication (1 patient in the study group (7.7%), 5 patients in the placebo group (1.6%); $p = .1594$) and 1 patient who received placebo needed nasal polyps' surgery.

Mepolizumab, benralizumab

SYNAPSE clinical trial[41] evaluating the effect of mepolizumab in severe bilateral nasal polyps showed that, up to week 52 of treatment, 37 patients who received placebo and 25 patients who received 100 mg mepolizumab needed at least one course of systemic corticosteroids ($p = .020$). The percentage of participants with nasal surgery over time increased from week 8 (placebo: 1.0, 95%CI 0.3 to 3.9; mepolizumab: 0.5, 95%CI 0.1 to 3.4) to week 52 (placebo: 23.6, 95%CI 18.3 to 30.3; mepolizumab: 9.2, 95%CI 5.9 to 14.2) ($p = .003$).

While analysing the efficacy and safety of benralizumab for nasal polyposis treatment, the OSTRO clinical trial[42] concluded that 70 patients needed nasal surgery for nasal polyposis and 118 patients needed systemic corticosteroids up to week 56. From the patients needing surgery, 33 patients received benralizumab (15.9%) and 37 were placebo patients (18.2%); a parameter with no statistical importance, with $p = .5419$. Systemic corticosteroids were given to 52 patients (25.1%) from the benralizumab group and 66 patients (32.5%) from the placebo group, with a $p = .0913$ between groups. Counting the time from baseline to the first rescue treatment (in months), in the study group, the time for the first surgery was 16.6 months and for corticosteroids and/or surgery 35.5 months. In the placebo-treated patients, the time to the first nasal surgery was 19.5 months and for corticotherapy and/or surgery 46.5 months.

Dupilumab

SINUS-24 clinical trial[38] evaluated the need for surgery and/or systemic corticosteroids up to week 24 and week 48. The percentage of subjects who needed nasal polyps' surgery up to week 24 was of 7.5 (95%CI, 3.7 to 13.2) in the placebo patients and 2.1 (95%CI, 0.6 to 5.6) in the study group. Regarding systemic corticosteroids, the percentage was 18.9 (95%CI, 12.7 to 26.0) in the placebo group and 6.5 (95%, 3.2 to 11.5) in the dupilumab group. Evaluating the same parameters up to week 48, the results were as follows: for the study group – need for surgery 6.3 (95%CI, 2.9 to 11.4), need for corticosteroids 21.4 (95%CI, 15.0 to 28.5); for placebo – need for surgery 12.5 (95%CI, 7.5 to 18.9), systemic corticosteroids 28.8 (95%CI, 21.4 to 36.7).

SINUS-52 clinical trial[37] concluded that, up to week 52 of treatment, the percentage of subjects who needed nasal

polyp surgery was 28.3 (95%CI, 21.2 to 35.7) in the placebo group and 5.5 (95%CI, 2.9 to 9.4) in the dupilumab group, while the need for systemic corticosteroids was of 42.5 (95%CI, 34.5 to 50.2) in the placebo group and 13.1 (95%CI, 9.0 to 18.0) in the dupilumab group.

Reslizumab

In the case of reslizumab, the randomized-controlled study who evaluated its effect upon nasal polyposis reported that nasal surgery was needed in 2 patients from the placebo group during week 2 and week 8, respectively. In their cases, the total nasal polyp score compared to baseline worsened[34].

SAFETY OF MONOCLONAL ANTIBODY NASAL POLYP THERAPY

An important parameter in evaluating a new drug is the evaluation of its safety and adverse events.

For all three types of monoclonal antibodies, a variety of adverse events were reported by the Clinical Trials[37-42] (Table 6). Only in the case of dupilumab, there was reported one case of mortality (SINUS-52 clinical trial)[37].

Serious adverse events were defined as medical events which put the patient in danger or require medical and/or surgical intervention to prevent patient's death, are not life-threatening or do not require hospitalization[37-42]. These types of adverse events were reported in both evaluated groups. Omalizumab treatment led to 3 severe adverse reactions (2.22%), the most frequent being fractures (hand) (0.74%)[39,40] (Table 6). 2 patients (1.53%) from the placebo group presented cardiac disorders (1 patient, 0.77%) and pneumonia (1 patient, 0.77%).

In the case of dupilumab, 26 patients (5.91%) from the study group and 35 patients (12.41%) from placebo presented serious adverse events[37,38]. The most frequent were infections such as pneumonia, sinusitis, diverticulitis (dupilumab group vs placebo, 1.36% vs 1.77%), gastrointestinal disorders (0.91% vs 0.35%), injuries (fractures) (1.13% vs 1.77%), nervous system disorders (0.22% vs 1.06%) (Table 6).

Twenty-five benralizumab-treated patients (12.08%) presented serious adverse effects, the most frequently reported being gastrointestinal disorders (3.38%), infections (bronchitis, pneumonia, sinusitis) (1.93%), nervous system disorders (1.45%)[42] (Table 6), while 12 patients (5.83%) treated with mepolizumab[41] presented cardiac disorders (angina pectoris, coronary artery stenosis, myocardial infarction, myocardial ischaemia) (2.91%), injuries (contusions, fractures) (2.42%) or nervous system disorders (1.45%) (Table 6).

The incidence of neoplasms, benign or malignant, was low for all four biologics, with no statistically significant difference compared to placebo: 0.22% versus 0.35% for dupil-

Table 6. Reported adverse events in the Clinical Trials.

Adverse events (study group / placebo patients)	Omalizumab[39,40] (135 / 130)	Dupilumab[37,38] (440 / 282)	Benralizumab[42] (207 / 203)	Mepolizumab[41] (206 / 201)
All-cause mortality	0 / 0	1 (0.23%) / 0	0 / 0	0 / 0
Serious adverse events	3 (2.22%) / 2 (1.53%) Most frequent: Cardiac disorders (0 / 0.77%) Pneumonia (0 / 0.77%) Fracture (0.74% / 0)	26 (5.91%) / 35 (12.41%) Most frequent: Infections (1.36% / 1.77%) Gastrointestinal disorders (0.91% / 0.35%) Neoplasms (0.22% / 0.35%) Injuries (1.13% / 1.77%) Nervous system disorders (0.22% / 1.06%)	25 (12.08%) / 19 (9.36%) Most frequent: Blood and lymphatic system disorders (0.96% / 0.98%) Gastrointestinal disorders (3.38% / 0) Neoplasms (0.96% / 0.98%) Nervous system disorders (1.45% / 0) Infections (1.93% / 1.97%)	12 (5.83%) / 14 (6.97%) Most frequent: Cardiac disorders (2.91% / 0) Nervous system disorders (1.45% / 0.49%) Injuries (2.42% / 0) Gastrointestinal disorders (0.97% / 0.99) Neoplasms (0.48% / 0.49%)
Other (not serious) adverse events	29 (21.48%) / 36 (27.69%) Most frequent: Injection site reaction (3.70% / 1.54%) Headache (8.14% / 5.38%) Nasopharyngitis (3.70% / 6.92%)	240 (54.54%) / 172 (60.99%) Most frequent: Injection site reaction (9.54% / 9.22%) Nasopharyngitis (18.86% / 20.56%) Sinusitis (7.5% / 11.70%) Headache (8.63% / 10.28%) Epistaxis (7.27% / 8.51%)	64 (30.92%) / 83 (40.89%) Most frequent: Nasopharyngitis (17.87% / 21.18%) Headache (3.38% / 7.88%)	139 (67.48%) / 141 (70.15%) Most frequent: Nasopharyngitis (25.24% / 22.89%) Sinusitis (4.85% / 10.95%) Headache (17.96% / 21.89%) Epistaxis (8.25% / 8.96%) Oropharyngeal pain (7.77% / 4.98%) Back pain (7.28% / 6.97%)
Total number	31 / 38	266 / 207	89 / 83	151 / 155

umab (anal cancer in 1 placebo patient, 1 patient with nasal benign tumor in the treated group)[37,38], 0.96% versus 0.98% for benralizumab (2 patients in the benralizumab group – appendix adenocarcinoma, salivary gland mucoepidermoid carcinoma; 2 patients treated with placebo – lymphoma, uterine leiomyoma)[42], 0.48% versus 0.49% for mepolizumab (1 patient in the study group with benign valvular tumor, 1 patient in the placebo group with rectal adenoma)[41]. In the case of mepolizumab, the 6-month follow-up performed after the treatment revealed zero neoplasms incidence for all subjects included in the clinical trial.

The Clinical Trial evaluating the omalizumab treatment reported not a single case of benign or malignant tumors as adverse events[39,40].

Any other (not serious) adverse event was defined as event that "does not result in death, is not life-threatening, does not require inpatient hospitalization or extend a current hospital day, does not result in an ongoing or significant incapacity or interfere substantially with normal life functions, and does not cause a congenital anomaly or birth defect; il also does not put the participant in danger and does not require medical or surgical intervention to prevent one of the results listed above"[37-42]. The number of adverse events was higher compared to serious adverse reactions: 29 patients (21.48%) for omalizumab (36 patient, 27.69%, in placebo group)[39,40], 240 patients (54.54%) for dupilumab (172 patients, 60.99%, in placebo group)[37,38], 64 patients (30.92%) for benralizumab (83 patients, 40.89%, in placebo group)[42], 139 patients (67.48%) for mepolizumab (141, 70.15%, in placebo group)[41]. The most frequently reported were nasopharyngitis, headache and injection site reactions (Table 6).

For reslizumab, Gevaert et al.[34] (2006) reported that 23 (95.8%) of the 24 subjects included in the study presented at least 1 adverse reaction. The most frequent adverse event reported was upper respiratory tract infection in 14 patients (58.3%, 10 in the reslizumab-treated group and 4 in the placebo group). Only one patient who received 300mg/kg of reslizumab did not have an adverse reaction to the treatment.

DISCUSSIONS

The management of chronic rhinosinusitis with nasal polyps refractory to both medical and surgical treatment is a challenge for every ENT specialist.

The development and approval of humanized monoclonal antibodies for the treatment of CRSwNP represent an important step in treating these patients by improving their quality of life, avoiding high rates of recurrence and the need for surgery.

In 2018, the European Forum for Research and Education in Allergy and Airway Disease (EUFOREA) released the indications for the use of biologics in patients with CRSwNP with and without comorbid asthma. Later, in 2020, the European Position paper on Rhinosinusitis and Nasal Polyps (EPOS) elaborated a revised guideline.

According to EUFOREA and EPOS2020, the treatment with biologics is indicated in CRSwNP patients with bilateral nasal polyposis, who had an endoscopic sinus surgery or had contraindication for surgery, plus three of the following criteria[2,52]:

- ✓ Evidence of type 2 inflammation (tissue eosinophils ≥10/hpf OR blood eosinophils ≥25u/l OR total IgE≥1000IU/ml
- ✓ Need for systemic corticosteroids or contraindication to systemic steroids (≥2 courses per year OR long term (more than 3 months) low dose steroids
- ✓ Significantly impaired QoL (SNOT-22 ≥ 40)
- ✓ Significant loss of smell (anosmic on smell test)
- ✓ Diagnosis of comorbid asthma (asthma needing regular inhaled corticosteroids).

Also, there have been established criteria for the response to monoclonal antibody therapy: reduced nasal polyp size, reduced need for systemic corticosteroids, improved QoL, improved sense of smell and reduced impact of co-morbidities[2,52]. Three categories of response will be registered at 16 weeks and 1 year of treatment: excellent (5 criteria), moderate (3-4 criteria), poor (1-2 criteria), no response (0 criteria)[2,52]. If no response in any criteria during the follow-up, the treatment is stopped.

All clinical trials included in this review guided the follow-up according to all above mentioned criteria.

EPOS2020 provides a grade of recommendation and level of evidence for the biologic treatment of CRSwNP patients[2]. Anti-IL5 and anti-IgE have a level of evidence Ib and they should be used when approved. Anti-IL-4/IL-13 (dupilumab) should be used in all patients fulfilling the criteria for treatment with monoclonal antibodies, with an Ia level of evidence.

All trials identified a certain percentage of adverse effects, most of them being no serious adverse events: 21.48% for omalizumab[39,40], 54.54% for dupilumab[37,38], 30.92% for benralizumab[42], 67.48% for mepolizumab[41]. The long-term safety profile is an aspect which needs further investigations.

Another aspect which needs attention is the cost-benefit of the biologic treatment, which seems to be in favour of nasal surgery. Several reports state that in the US the cost for endoscopic sinus surgery ranged between $8200 and $10,500, while for biologics between $30,000 and $40,000 depending on the type used[53-55]. In Romania, there are 3 biologicals available, 2 of them (dupilumab and omalizumab) indicated also for CRSwNP, and benralizumab indicated only for asthma and dermatitis. Considering the cost of the treatment, only one administration costs between 323€ and 1,979€, considering that none of them is compensated by the Ministry of Health and the National Health Insurance House for nasal polyposis.

Due to the continuous research, new potential biologics are studied for the treatment of nasal polyposis: anti-

IL-33 and anti-TSLP[6]. IL-33 is part of the IL-1 cytokines family, being expressed in epithelial cells, dendritic cells, macrophages, endothelial cells. It activates the production of Th2 cells, eosinophils, mast cells and basophils, leading to an inflammation response[56]. At the same time, IL-33 has an important role in the production of IL-5 and IL-3. TSLP (thymic stromal lymphopoietin) is an epithelial cell-derived cytokine which regulates Th2 inflammation, being involved in some inflammatory diseases, among which nasal polyposis, atopic dermatitis[57]. For both biologics, there are level 3b of evidence studies which evaluated their treatment efficacy in patients with CRSwNP[57-60], but future randomized clinical trials are needed in order to evaluate and understand the role of anti-IL-33 and anti-TSLP drugs in CRSwNP.

CONCLUSIONS

Based on the available data, monoclonal antibody therapy seems to be beneficial for the patients diagnosed with chronic rhinosinusitis with nasal polyps and with or without comorbid asthma. The approval of two biologics with different mechanism of action raises patients' accessibility to the treatment.

The development of new treatments challenges the otorhinolaryngologists to carefully identify the patients who meet the criteria for the initiation of monoclonal antibody therapy.

Nonetheless, further studies are needed regarding the log-time effect of this drugs and their integration in the CRSwNP treatment algorithm.

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