MAGIERSKA, Agata, SZCZEPANIAK, Zuzanna, PTAK, Olga and GOMUŁKA, Krzysztof. Biological Therapy, Therapeutic Approaches and Future Perspectives in the Treatment of Chronic Rhinitis. Quality in Sport. 2024;18:52161. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.18.52161
https://apcz.umk.pl/QS/article/view/52161

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.06.2024. Revised: 22.07.2024. Accepted: 23.07.2024. Published: 25.07.2024.

Biological Therapy, Therapeutic Approaches and Future Perspectives in the Treatment of Chronic Rhinitis

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Abstract

Introduction: The widespread prevalence of chronic rhinitis necessitates the search for effective treatment methods. Modern type of medicine is biological treatment. Pathomechanism of AR is based on lymphocytes Th-2 reaction and connected with that

cascade of effects. Biological treatment in the form of monoclonal antibodies blocks interleukins or immunoglobulin E signaling and leads to decrease in inflammatory reaction. Mechanism of action of these drugs and short period of use in AR requires patients to meet the including criteria and is usually used after other treatment options have run out. Taking under consideration the amount of patients suffering from AR and the impact on the quality of life indicates that there is still a need for new drugs and using drugs which are useful in similar diseases.

Purpose of the work: This study aims to review and evaluate biological drugs used or having the potential to be used in the treatment of allergic rhinitis (AR), including: omalizumab, dupilumab, mepolizumab, reslizumab and the possibility of their use on a wider scale in the future.

Materials and methods: An analysis of research papers available on PubMed and Google Scholar was undertaken using the following keywords: chronic rhinitis with nasal polyps; immunotherapy; monoclonal antibodies; allergic rhinitis; Quality of Life in rhinitis; omalizumab; dupilumab; mepolizumab; reslizumab; biological treatment during pregnancy;

Results: The use of biological drugs in AR results in a significant improvement in symptom control and an increase in quality of life. This option can be an effective form of treatment for nasal polyps, reducing the risk of needing sinus surgery. However, the criteria for using these drugs are still very limiting, due to the lack of specific biomarkers that could early indicate a high chance of success. Biological drugs seem to be a great opportunity and a worthwhile possibility in the treatment of people with chronic allergic rhinitis.

Keywords: chronic rhinitis with nasal polyps; immunotherapy; monoclonal antibodies; allergic rhinitis; Quality of Life; omalizumab

1. Introduction

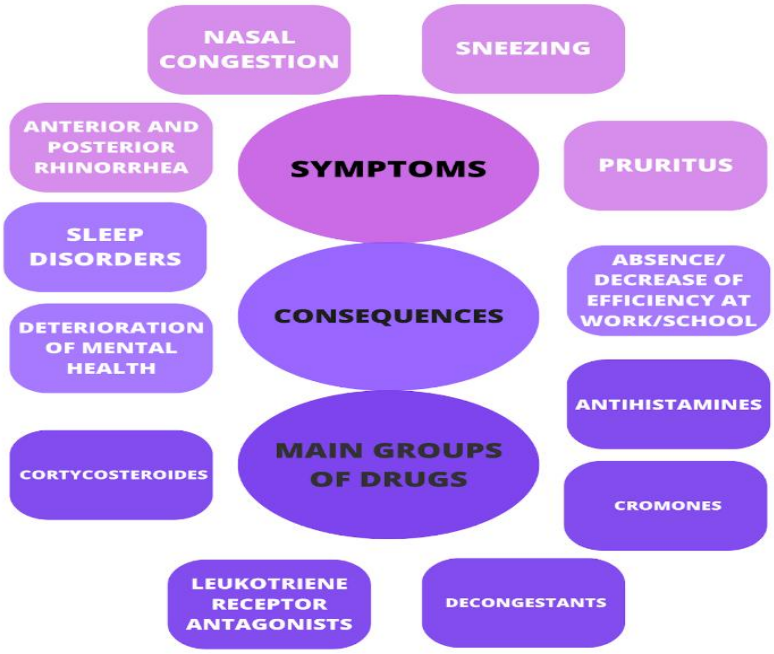
Rhinitis is an entity manifested by a group of nasal symptoms: nasal congestion, anterior and posterior rhinorrhea, pruritus, and sneezing (Figure 1) [1-4]. Additional symptoms and abnormalities relate to the mechanism that causes rhinitis [4,5]. Based on the pathophysiology, three main groups can be distinguished: infectious rhinitis, allergic rhinitis (AR), and nonallergic rhinitis (NAR). During qualification different criteria are taken into consideration,

for example: pattern, frequency and duration of symptoms, intensity of disease and triggering factors [1,2]. Sometimes diagnosis can be complicated, because subtypes coexist or evolve from one to the other and symptoms coincide [1,4,6]. The diagnosis can be formed based on medical history, but AR should be confirmed by allergic tests and non-infectious NAR is found after excluding other possible illnesses [6].

The estimated number of people suffering from rhinitis exceeds 200 million in the world. The most common type is AR and ranges from 10% to 40% worldwide [6]. Some studies show that the frequency of occurrence increases with each passing year [7,8]. Prevalence varies between age groups in the adult population and tends to decrease with age. KNHANES (South Korean National Health and Nutrition Examination Survey) stated it ranges from 21.1% in a group of 20-29 years old patients to 5.4% in patients over 60 years old [9]. In contrast to that, in the pediatric population, the prevalence of this disease increases with age [10]. Determining the exact epidemiology is difficult due to the unsystematized structure of research, various methods of confirming the disease in each study and differences between individual regions in the world, for example in terms of environment, pollution, allergens, genetics etc.

Rhinitis strongly affects patients' quality of life. The symptoms cause sleep disorders, absence or decrease of efficiency at work/school and deterioration of mental health (Figure 1) [1-4]. Wide dissemination and interfering with daily functioning imply high direct and indirect costs [1-3].

Figure 1. The most important symptoms of rhinitis, consequences of disease in patients' quality of life, main groups of drugs used in rhinitis.



Therapy should be highly associated with the phenotype of rhinitis. Treatment includes drugs (like intranasal corticosteroids, oral antihistamines, leukotriene receptor antagonists, cromones, decongestants) and surgical treatment - especially to remove polyps resulting in illness (Figure 1). Nowadays the meaning of biological treatment in AR grows as a new treatment option. This method uses monoclonal antibodies to block interleukin signalization and based on this, to reduce inflammatory reaction [1,4,11,12].

2. Risk and protective factors in development of AR

The first risk factor that should be mentioned is genetics, although there is no specific gene detected that is responsible for the disease. Genome-wide association studies (GWAS) stated that single nucleotide polymorphisms (SNPs) are strongly connected with AR, as well as in other allergic diseases [13].

Researchers have indicated that gene-environment interactions and epigenetic mechanisms can also risk developing AR. The following factors, which may cause changes in phenotype or gene expression, are listed:

-mother smoking during pregnancy [14],

-length of pregnancy [15],

-childhood exposure to mites, pollen, animal dander, fungal allergens [16-19],

-pollution [20,21],

-socioeconomic factors - low education, poverty, poor hand hygiene [22,23].

Among the factors that reduce the risk of allergic rhinitis prolonged breastfeeding (over 6 months) is proven by several studies [24-26]. Han et al. in prospective cohort study indicated an even longer period of breastfeeding (≥12 months) [27]. When it comes to the mother's diet, research indicates that dietary diversity increases, decreases, or even has no effect at all on allergic rhinitis in children [28-30]. There is no recommendation in guidelines regarding infant diet for early introduction of specific products for prevention of allergic rhinitis.

2.1. Quality of Life with chronic rhinitis

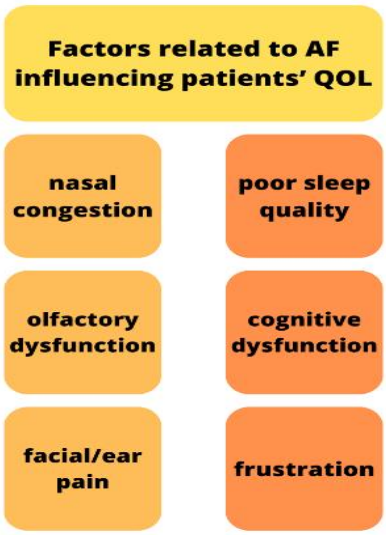
Chronic allergic rhinitis is considered a common disease that might be complicated by other respiratory diseases, both upper and lower level, such as asthma, sinusitis and otitis media. It has been proven to significantly decrease the quality of life (QOL) [31] with a wide array of symptoms that have an impact on patients' everyday functioning. That includes nasal congestion, olfactory dysfunction, chronic facial and otological pain, reduced quality of sleep and mental health repercussions.

The symptoms may be divided into two categories: strictly rhinosinus-related (nasal congestion, olfactory dysfunction, facial/ear pain) and other (poor sleep quality, cognitive dysfunction, frustration). Nasal congestion is the key symptom while diagnosing AR and its severity correlates with reduced QOL. Recently, the impact on QOL of olfactory dysfunction has received more attention because of its prevalence during COVID-19 pandemic. Patients reported reduced food enjoyment, difficulty while performing basic household chores such as cooking, cleaning, and recognizing rotten food and smoke. All of which lead to poorer emotional well-being, depression, and anxiety [4]. Pain and discomfort in the facial area has an impact on many aspects of patients' lives. From constant mild discomfort to severe pain that may exclude the patient from daily tasks. Sleep impairment may result from many mechanisms that relate to AR such as nasal obstruction, chronic pain, and general discomfort from rhinorrhea. Nevertheless, the result is reduced sleep quality from snoring, fragmented sleep, and even obstructive sleep apnea [32,33] which leads to sleepiness, loss of productivity and lowering of cognitive function. The patients suffering from chronic rhinitis with olfactory loss may be more prone to anxiety, phobia, and depression [34]. Patients' mental health might be affected by the social repercussions they experience from constant sneezing, rhinorrhea, and lower productivity.

The most popular way of documenting severity of symptoms experienced by patients is the SNOT-22 (Sino-nasal Outcome Test) survey that usually correlates with their clinical symptomatology. Not only the presence of rhinitis but also its management has an impact on

the QOL [31,35]. Mainly, the significant improvement of QOL was noticed with better sleep and better rhinosinusitis-associated pain management [36].

Figure 2. Symptoms and effects of AR strongly affect patients' QOL.



2.2. Biological treatment

2.2.1. Including criteria

Biological treatment is dedicated to patients with rhinitis, who passed through bilateral nasal polyps' removal or were disqualified from this procedure. Patients have to fulfill at least 3 of the 5 criteria: confirmed presence of type 2 inflammation (tissue eosinophils ≥10/hpf or blood eosinophils ≥250 or total IgE ≥100), loss of smell (anosmic or appropriately bad score in one of the tests created for assessing the smell), present, active asthma (needing regular use of corticosteroids - inhaled one), significantly impaired quality of life (score in SNOT-22 ≥40 points), need for systemic corticosteroids (≥2 courses/year or long term - >3 months curation of low dose steroids) or contraindication to systemic steroids [6].

Table 1 – Including criteria for biological treatment in AR.

Criteria	**Detailed description**
Type 2 of inflammation	Tissue eosinophils ≥10/hpf / blood eosinophils ≥250 / total IgE ≥100
Loss of smell	Anosmic on smell test (score depending on test)
Present astma	Asthma needing regular inhaled corticosteroids

Significantly impaired quality of life	SNOT-22 ≥ 40
Need for systemic corticosteroids / contraindication to systemic steroids	≥ 2 courses per year / long term (>3 months) low dose steroids

SNOT - Sino-nasal Outcome Test

2.2.2. Dupilumab

Dupilumab is a recombinant IgG4 monoclonal antibody directed against the IL-4Rα chain, presented on receptors for interleukin 4 (IL-4) and 13 (IL-13). Blocking receptors results in a lack of signal transmission usually caused by these cytokines. In this mechanism dupilumab inhibits type 2 response, connected with type 2 helper T lymphocytes [11,37,38].

Dupilumab is an approved method of treatment in atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP). Indication for this medicine in CRSwNP is not achieving enough efficiency of treatment with systemic corticosteroids and/or chirurgical methods. In some European countries dupilumab is reimbursed in this diseae [11,37,38].

Stated effects of dupilumab are better quality of life (as seen in SNOT-22 questionnaire and VAS scale), reduction of nasal polyps' size (endoscopy), reduction of inflammation of sinuses (CT scan) and improving smell (UPSIT test) [11].

In 2018 randomized, double-blind, placebo-controlled SINUS-24 and SINUS-52 studies, patients received 300 mg of dupilumab (subcutaneously or matching placebo every 2 weeks) for appropriately 24 or 52 weeks. Dupilumab improved perception in LoS (Loss of smell), effect observed from 3rd day of study (least squares mean difference vs placebo −0.07 [95% CI −0.12 to −0.02]; nominal $P < 0.05$ at day 3, and −1.04 [−1.17 to −0.91]; $P < 0.0001$ at week 24). Dupilumab influenced positively on University of Pennsylvania Smell Identification Test (UPSIT) mean by 10.54 (least squares mean difference vs placebo 10.57 [9.40–11.74]; $P < 0.0001$) at week 24 from baseline (score 13.90) [39].

In studies performed in Japan, the effects of using dupilumab were well demonstrated. There were significant differences in Nasal Polyps Score (NPS), Nasal Congestion (NC) and LMK-CT compared to placebo at week 24 in all patients despite their ECRS status (Eosinophilic Chronic Rhinosinusitis) - $p < 0.001$. Effect of treatment was maintained or increased in all subgroups measured at the end of week 52 ($p < 0.001$). The only disparity was proved at week 24 for LMK-CT ($p = 0.0275$) - indicating that dupilumab shows greater results in

moderate/severe ERCS subgroup treatment than in non-/mild ones. Similar outcomes were seen for the secondary endpoints [40].

Disadvantage of using dupilumab is a necessity of long-term use and undergoing withdrawal relates to reversal of treatment effects. Therapy can be also blocked by antibodies produced against dupilumab and steroids cannot be set aside during treatment. Also, high costs of this medication may be an obstacle to the use of dupilumab [11,41].

2.2.3. Mepolizumab

Mepolizumab is a humanized monoclonal IgG1 class antibody that specifically binds to and neutralizes interleukin-5. Interleukin 5 (IL-5) is a cytokine produced by T-cells and plays a major role in proliferation, maturation, activation, and survival of eosinophils. Mepolizumab prevents binding between IL-5 and IL-5 receptors localized on the cell surface of eosinophils.

Mepolizumab is an approved method of treatment in severe, drug resistant eosinophilic asthma. In addition to that, it may be considered as an add-on treatment to other type 2 inflammatory diseases such as: eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome (HES), and CRSwNP.

In randomized clinical trials regarding therapeutic benefits of mepolizumab in patients suffering from CRSwNP, the results show decreased need of surgical intervention in a group receiving medication in contrast to the group receiving placebo [42].

In recent studies from January 2023 mepolizumab provided a significant increase in quality of life and relief from CRSwNP symptoms. In placebo-controlled, double blind and randomized clinical trials patients received 100 mg of mepolizumab or placebo every 4 weeks for 52 days, while still administering their standard treatment consisting of nasal sprays containing corticosteroids and saline nasal irrigations. Overall, patients that received medicine noted improvement with symptoms management and quality of life [43].

However, the other study showcases that the most notable clinical improvement was observed in patients that have never undergone sinus surgery and it was achieved at both week 24 and week 52 of 52 weeks of clinical trial [44].

2.2.4. Reslizumab

Reslizumab is also a humanized monoclonal antibody that targets IL-5 and is already approved for severe, drug resistant eosinophilic asthma [45]. In a double-blind, placebo-controlled, randomized trial, 24 patients with bilateral nasal polyps received single doses of reslizumab at 1 or 3 mg/kg or adequate dose of placebo. Medication lasted 4 weeks and showed that this treatment is safe and effective. Blood eosinophil number was reduced and

stayed decreased up to 8 weeks after treatment both in serum and nasal secretions. Only half of the group achieved polyps size reduction, but correlation between increased baseline nasal IL-5 levels (>40 pg/mL) and response to reslizumab gives a chance to predict effectiveness of anti-IL-5 treatment [46].

2.2.5. Omalizumab

Omalizumab is a monoclonal anti-IgE antibody - it binds to free IgE and therefore prevents them from binding to the receptor FcεRI on mast cells and basophils [47]. This agent restrains the immune response regardless of the allergen because of its ability to integrate with non-allergen-specific regions of these receptors [48]. Moreover, the agent causes downregulation of density of FcεRI receptors on basophils, dendritic cells, and mast cells [49-51]. This results in inhibition of antigen presentation to T cells, their differentiation, activation, proliferation, production of cytokines and at the end inhibits the inflammatory cascade [48-52].

Omalizumab was already introduced in 2003 by the FDA and in 2005 by EMA as an adjuvant drug in the treatment of uncontrolled, moderate, and severe allergic asthma (in patients over 6 years of age) which pathogenesis is associated with IgE immunoglobulin [53,54]. EPOS 2020 stated using monoclonal anti-IgE antibodies as promising in chronic sinusitis - category of evidence Ib - due to unfinished clinical trials [41]. Presently omalizumab is recommended in:

-severe CRSwNP - adjuvant therapy alongside intranasal corticosteroids (patients >18 years of age)

-severe, chronic allergic asthma - adjuvant treatment (patients >6 years of age) [55];

-chronic spontaneous urticaria (off-label indication) [56,57].

Clinical trials showed positive results in CRS treatment using this agent.

In 2010 randomized, double-blinded, placebo-controlled trial (n = 14, serum total IgE 30 - 700 IU/ml, primary CRS, despite severity of disease) Pinto et al treated patients using omalizumab for 6 months. The study demonstrated a statistically significant decrease of inflammation in the group treated with omalizumab ($p < 0,043$) with no significant difference in the group receiving placebo ($p < 0,463$). However, effect “pre-treatment minus post-treatment” was insignificant ($p < 0,391$) - omalizumab 11,9% and placebo 5,9% [52].

Gevaert et al conducted in 2013 a randomized, double-blind, placebo-controlled study (n = 24). The trial showed a significant difference in total nasal endoscopic polyp scores after 16 weeks of omalizumab treatment ($p = 0,001$) confirmed by CT scan, soothed subjective symptoms of inflammation and improved quality of life [58].

In 2020 Gevaert et al carried out two randomized trials - POLYP 1 (n = 138) and POLYP 2 (n = 127) in patients with CRSwNP and incomplete response to intranasal CCS. In both studies mean differences were statistically significant (table 2) [59]:

Table 2 – Comparison of results between the omalizumab and placebo groups in POLYP-1 and POLYP-2 studies.

	POLYP - 1			POLYP - 2		
	omalizumab	placebo	p	omalizumab	placebo	p
NPS	-1.08	0.06	< 0,0001	-0,90	-0,31	0.0140
NCS	-0.89	-0.35	0.0004	-0.70	-0.20	0.0017
SNOT-22	-24,7	-8.6	<0.0001	-21.6	-6.6	<0.0001

NPS - Nasal Polyp Score, NCS - Nasal Congestion Score, SNOT - Sino-nasal Outcome Test

Patients from POLYP-1 and POLYP-2 studies were further treated with omalizumab and nasal mometasone for 28 weeks, then observed for 24 weeks and evaluated. Subjects who received omalizumab therapy for 52 weeks had greater results, ones who switched the placebo for the agent experienced favorable results and those who discontinued drug intake gradually worsened during the follow-up (table 3) [59].

Table 3 – Comparison of outcome - 52 week in POLYP-1 and POLYP-2 studies (mean results).

	Omalizumab - 52 weeks	Placebo + 28 weeks of omalizumab	Difference (95% CI)	p
NCS	-1.12	-0.99	-0.14	0.234
NPS	-1.31	-0.97	-0.34	0.0954
TNSS	-3.83	-3.01	-0.82	0.0195
SNOT	-28.47	-22.39	-6.07	0.0056

NCS - Nasal Congestion Score, NPS - Nasal Polyp Score, TNSS - Total Nasal Symptom Score, SNOT - Sino-nasal Outcome Test

Table 4 – Comparison of outcome between 24 and 52 weeks of omalizumab treatment (mean results).

	Week 24	Week 52	Difference (95% CI)	p
NCS	-0,85	-1.12	-0.27	0.0001
NPS	-1.01	-1.31	-0.30	0.0236
TNSS	-2.82	-3.83	-1.01	<0.0001
SNOT-22	-23.56	-28.47	-4.91	0.0009

NCS - Nasal Congestion Score, NPS - Nasal Polyp Score, TNSS - Total Nasal Symptom Score, SNOT - Sino-nasal Outcome Test

Haxel et al in a randomized, controlled trial from 2022 compared dupilumab (n = 49) and omalizumab treatment (n = 21). Moderate to excellent results were observed in both groups and there was no difference between them [60].

2.2.6. Benralizumab

Benralizumab is a humanized, afucosylated monoclonal antibody directed against the IL-5 receptor (IL-5Rα). This receptor is on the surface of eosinophils and basophils and presence of this agent leads to apoptosis of these cells. In this mechanism benralizumab causes relief of eosinophilic inflammation. Benralizumab is recommended as a supportive, adjuvant treatment in patients with uncontrolled, severe, eosinophilic asthma and so far 4 studies have been conducted to evaluate the effectiveness of the use of this antibody in CRSwNP [11,61].

Three randomized studies tested benralizumab - two of them showed statistically significant improved Nasal Polyps score (NPS). One study confirmed a better effect in nasal blockage score (P=<0.005). One indicated improvement in difficulty in sense of smell score (P =0.003). Almost half of benralizumab-treated patients had some improvements in all major outcomes (polyp score, CT, SNOT-22, and smell test). The ratio of baseline blood eosinophil count positivity correlated with polyp reduction [11,61-63].

2.3. Special situations

2.3.1. Biologics in CRS patients with comorbid COVID-19

Although both above-mentioned diseases do not share similar pathophysiology, they may have similar symptoms e.g. they are connected with anosmia which is progressive in CR and suden in COVID-19, cough, nasal obstruction and it is sometimes hard to distinguish one illness from another [64-66]. There was one study that focused on the severity of symptoms in patients with chronic rhinosinusitis who contracted the coronavirus. Akhlaghi et al indicated that COVID-19 may not have a negative effect in patients with CRS. Sino-Nasal Outcome Test-22 was used and no differences between groups of patients (CRS with and without COVID-19) were observed [67]. A few different studies also showed that CRS has a neutral effect on coronavirus infection. [68, 69] In some studies it was even stated that CRS may be a protective factor [70, 71]. When it comes to the treatment of CRS patients who have contracted COVID-19, they can use intranasal corticosteroids [72], but systemic CS as well as biologics should not be used. Antibodies used in CRS therapy may increase the risk of infection. The European Academy of Allergy and Clinical Immunology stated that biologics should be discontinued until full recovery from COVID-19 [73, 74].

2.3.2. Biological treatment during pregnancy

Monoclonal antibodies are transported across the placenta to a fetus and can potentially affect it, especially during the second and third trimesters of pregnancy [75-78].

There were two articles about using biologics during pregnancy published in 2014 and 2019, in which outcomes of the Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy (EXPECT) were interpreted. Both works apply to the treatment of asthma in pregnant women, not the AR, but they give information about the impact of omalizumab exposure on unborn children [79, 80].

Article from 2014 described 191 pregnant women treated with omalizumab. The median duration of omalizumab exposure during pregnancy was 8.8 months for the 169 pregnancies with a known outcome. Among this group noted:

- 156 live births with 160 babies (4 cases of twins),
- 1 fetal death/stillbirth,
- 11 spontaneous abortions,
- 1 elective termination.

Among 152 singleton infants, 14.5% were born prematurely. Of 147 singleton infants with weight data, 10.9% were small for gestational age. Among 125 singleton full-term infants, 3.2% had low birth weights.

Overall, 20 fetuses were found with confirmed congenital anomalies, 7 of them had one major defect. No pattern of anomalies was observed [79].

The second “EXPECT” based article published in 2019 concerned 250 women with asthma exposed to omalizumab during pregnancy. In this case, a disease-matched external comparator cohort of women with moderate-to-severe asthma (n = 1153), termed the Quebec External Comparator Cohort (QECC), was created.

Table 5 - A comparison of results in the group exposed to omalizumab and the control group.

Group	Women with asthma exposed to omalizumab during pregnancy	QECC
Prevalence of major congenital anomalies	8.1%	8.9%
Live births	99.1%	99.3%
Premature birth	15.0%	11.3%
Small for gestational age	9.7%	15.8%

QECC - Quebec External Comparator Cohort

Study did not reveal an increased risk of major congenital anomalies connected with exposure to omalizumab during pregnancy. There was no evidence of an elevated risk of major congenital anomalies among women with asthma treated with omalizumab during pregnancy compared to Quebec External Comparator Cohort [80].

In addition, among pregnant animals exposed to omalizumab, no evidence of fetal harm was observed [75]. Despite those results, the teratogenic effect of omalizumab on fetuses cannot be excluded, because of insufficient data [75, 79, 80].

Every other monoclonal antibody highlighted in this article, i.e.: dupilumab, mepolizumab, reslizumab and benralizumab, were examined during studies with animals and no evidence of fetal harm caused by these agents was observed [76-79, 81].

Several case reports of pregnant women exposed to the above-mentioned drugs can be found, but based on them, no teratogenic effect of these drugs on the fetus can be established [82-85].

2.3.3. Probiotics as a potential adjuvant therapy in biological therapy

Probiotics are live microorganisms that are administered to the patient's body for their intended beneficial role in maintaining health and homeostasis. In recent years, there have been an increase in studies proving that probiotics might be an useful option as an adjuvant therapy in numerous medical conditions that mainly include gut related disorders but many researchers consider the applicability of targeted microbiome transplantation for other inflammatory diseases, among those - CRS. The chronic inflammation changes nasal microbiota, causing it to be impoverished [86, 87]. The intranasal administration of probiotics bacteria changes the pathological microbiota in nasal passages for a more beneficial one but the long-term results on the CRS improvement are yet to be researched [86]. The general usefulness of probiotics as a treatment option is a heavily debated topic. Although, there is not a solid proof that it is an effective form of therapy, many researchers see potential in improving patients' quality of life, sleep quality and SNOT questionnaire [88-90]. All of the above-mentioned points lead to the conclusion that there is a need for properly performed clinical trials that may show future directions for clinical utilization of probiotics and as an effect further improve patients' quality of life.

3. Therapeutic Approaches

Biological treatment is not a basic way of treatment of rhinitis. After using all conventional methods this kind of medication should be considered. Firstly, it is needed to define which type of rhinitis the patient has. Monoclonal antibodies are indicated for patients suffering from rhinitis with bilateral polyps and type 2 inflammation. Including criteria contains surgery of bilateral nasal polyps or contraindications for surgeries in the past. With other including criteria, the list of potential candidates for medical treatment is strictly selected. Additionally, evaluation criteria for using monoclonal antibodies in CRSwNP exist. Based on it, treatment should be stopped, when the patient does not meet any of the criteria in evaluation after 16 weeks or 1 year. Patients are examined and evaluated in 5 sections: sense of smell (improvement), size of nasal polyps (reduction), quality of life (improved), need for systemic corticosteroids (reduced), impact of comorbidities (reduced: allergy, asthma, and GORD etc.). Based on that, 4 types of response can be separated: excellent (patient fulfill 5 criterias), moderate (patient fulfill 3 or 4 criterias), poor (patient fulfill 1 or 2 criterias) and no response (patient fulfill any criteria). Evaluation helps to analyze effects of treatment and avoid side effects in the event of unjustified drug administration [41].

4. Conclusions

Biological treatments are relatively new and should be further researched in the future as it holds huge opportunities for chronic rhinitis management. This therapy is another chance for patients who had at least once performed endoscopic sinus surgery, for those in whom such surgery is contraindicated or who has severe comorbidities (such as asthma, aspirin-exacerbated respiratory disease). The effectiveness of therapy is measured, among other things, by subjective questionnaires, which can sometimes give uncles results. Another challenge is the fact that treatment of chronic rhinitis, especially with comorbidities, requires the cooperation of specialists in various fields - including pulmonologists, immunologists, and allergologists. In the future, the focus should be on understanding the immunological mechanism involved in the development of chronic sinusitis, because the multitude of them makes target therapy difficult [91,92].

The overall conclusion from the studies regarding the use of biological treatment in chronic rhinitis indicates that there is a notable improvement in symptom control and increase in quality of life. This option can be an effective form of treatment for nasal polyps lowering the risk of needing sinus surgery. Still, there is a glaring lack of recommendations for physicians to help guide the choice of biological medication. that is connected to lack of specific biomarkers that may indicate an early high chance of success. Also, in a special case such as pregnancy, there is a great potential for the therapeutic use of biological treatment, while in other special situations, such as Covid-19, it is worth refraining from using this treatment. There is also the potential to use probiotics as an adjuvant therapy, but in each of these cases further research is necessary on the long-term effects and, above all, on the safety of biological treatment in AR.

5. Future directions

Many other diseases with similar pathophysiology, such as asthma, allergic rhinitis, atopic dermatitis etc., are treated with biologic agents or these drugs are under evaluation [91].

Some potential targets in CRS:

-OX40L and TSLP - which are under development in treatment Th2-mediated diseases; their concentration also increasing in nasal polyp tissue [93];

-Eosinophils - drugs against them are used for example in severe asthma; can be target in eosinophilic CRS [94];

-Th1 pathway cytokines - drugs used for example in rheumatoid arthritis and psoriasis can potentially be used in CRSsNP due to similar pathophysiology [95,96];

-Th1 and Th17 pathway cytokines - drugs against them are used in rheumatoid arthritis and Crohn disease [97-99].

Further investigation is also needed in CRS endotypes that have not overlapping immunology with above-mentioned diseases and find potential targets for biologics [91,94]. Moreover, in the future researchers should focus on drugs such as synthetic peptides and JAK inhibitors as well as on sinusal microbiome [100]. It is suggested that even vitamin D3 can be an immune modulator for dendritic cells, which are taking part in developing CRS, and should be further tested [101-103].

Author Contributions: Conceptualization, Z.S., A.M., O.P. and K.G.; writing—original draft preparation, Z.S., A.M., O.P.; visualization, Z.S. A.M. and O.P.; supervision, K.G.

All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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